Non Invasive Assessment for Left Ventricular Function after Primary Percutaneous Coronary Intervention

Ahmed Mohammed Al Zayat, Kamel Hassan Ghazal, Alaa Walid Al-Aawar, Alaa El Sayed Salama

Cardiology Department, Faculty of Medicine, Zagazig University

Corresponding author: Alaa Walid Al-Aawar

Abstract:

Myocardial function can be assessed noninvasively by echocardiography and radionuclide techniques. M-mode echocardiography provides important clues to ventricular volumes, wall thickness, wall motion, ejection fraction, and shortening velocities. The relative movements of posterior wall and septum can be ascertained and several specific cardiomyopathies recognized. M-mode echocardiography gives a limited "ice-pick" view of the left ventricle. Two-dimensional techniques give additional information. Echocardiography is done during rest, while radionuclide procedures are done during rest and exercise. First-pass radionuclide angiocardiography can estimate ventricular ejection fractions independently of geometric assumptions. Equilibrium gated blood pool imaging by multiple gated acquisition techniques allows repeated visual assessment of overall and regional ventricular function. Thallium-201 imaging provides insight into regional myocardial perfusion during rest and exercise but is limited by its resolution and isotope persistence. Newer techniques using $^{13}NH_3$ promise better approaches to perfusion with tomographic identification of regional changes.

Keywords: Left Ventricular function, Primary Percutaneous Coronary Intervention, MI.

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Introduction:

It is estimated that nowadays well over 90% of patients hospitalized with myocardial infarction (MI) survive the acute hospital phase. Management of these patients poses several clinical challenges, such as diagnosing and managing heart failure, identifying persistent or inducible ischemia, estimating the need for anticoagulation, and assessing overall cardiovascular risk. Cardiac imaging plays a prominent role in all of these tasks, and therefore choice and quality of cardiac imaging are of paramount importance in the management of these patients **(1)**.

Assessment of structural and functional cardiac damage

Left ventricular structure and function**In the acute phase of MI, left ventricular function undergoes rapid changes influenced by the extent and reversibility of ischemia, use of**

reperfusion therapy, presence of edema, extent of passive myocardial stretch, load conditions, and other factors. In response to loss of contractile tissue, the left ventricle acutely responds by hyperkinesia of remote myocardial areas and dilates over the course of days and weeks dilates, thus recruiting preload reserve. This process, compounded by the development of mitral regurgitation due to ventricular dilatation and accompanied by complex biochemical and neuro-endocrine changes, is at the core of the vicious cycle termed 'infarct remodeling'. Cardiac imaging in the acute (0–48 h) and subacute (Day 3–7) phase is the domain of echocardiography. Primary goals of imaging are the assessment of segmental and overall left ventricular systolic function, intracavitary thrombus formation, and other mechanical complications of MI. Thus, an echo is recommended within(24–48 h)of MI.(4–7 To provide a post-infarction baseline assessment of function, an additional echo is recommended within the first 3 months after infarction . (2).

Using magnetic resonance imaging (MRI), it is now possible to directly image the size of acute MI within 30 min of its inception by detecting myocardial edema. Because clinical experience with this technique is still sparse, and its main application seems to be in the early hours of infarction.

Post-infarction remodeling of the left ventricle

Infarct remodeling has been variably defined, but is usually understood to entail a progressive increase in systolic and diastolic left ventricular volumes in the weeks and months after MI and indicating an impaired prognosis. Owing to parallel increase in both end-systolic and end-diastolic-volume, at least initially, ejection fraction may be much less affected than volumes alone. depending on the time of imaging, may already be affected by early remodeling. About 30% of patients undergo infarct remodeling after MI, and these patients fare considerably worse than those do not, more often developing clinical heart failure and suffering from increased mortality. Factors associated with remodeling are size of infarction per se, anterior location of infarction, late or unsuccessful (or altogether lacking) reperfusion therapy both at the epicardial vessel level and at the microvasculature level. Gender also affects post-infarction remodeling, with a higher incidence and more aggressive course in men, possibly due to a higher rate of myocyte apoptosis in the peri-infarction zone(3).

Assessment of left ventricular volumes and systolic and diastolic function

Volumes and ejection fraction

The prognostic importance of left ventricular ejection fraction and its implications with regard to heart failure therapy and primary prevention of ventricular tachyarrhythmias are well established. Ejection fraction usually is assessed by echo either by eye-balling or by the monoplane or biplane method of discs. Echo determination of ejection fraction, however, in spite of many technical improvements, is still fraught with large inter-observer and test–retest variabilities(4). Left heart

echo contrast enhancement can be helpful if the endocardial border of several wall segments cannot be visualized by native echocardiography. Three-dimensional echo, if image quality is sufficient and close attention is paid to the reliability of endocardial border tracking algorithms, including manual corrections, is superior to 2D assessment, since it foregoes geometrical assumptions and avoids long-axis foreshortening. Ejection fraction can also be calculated by **nuclear imaging**, either by radionuclide angiography, or, as currently is standard, from ECG-gated myocardial perfusion single-photon emission computed tomography (SPECT) as a by-product of a myocardial perfusion exam. It is also obtainable with high reliability from **MRI** or **cardiac computed tomography (CT)**, although these techniques are rarely applied to primarily study left ventricular pump function **(1)**.

Wall motion score index

A related parameter that has additional independent prognostic value as to mortality and later hospitalization for heart failure is the echo wall motion score index. This is an average of the wall motion score in all left ventricular wall segments, where the score is **1** for normokinesia, **2** for hypokinesia, **3** for akinesia, and **4** for dyskinesia; a completely normal left ventricle would therefore have a wall motion score index of 1, and higher values denote more abnormalities. Reasons cited for its better performance compared with ejection fraction are that it may better reflect mild wall motion abnormalities 'swallowed' by global ejection fraction and is not affected by compensatory hyperkinesia of remote segments**(5).**

Speckle tracking

Recent developments in echo have led to relatively robust algorithms able to quantify regional left ventricular myocardial deformation. The most commonly adopted method tracks myocardial echo scatterers ('speckle tracking') in space over time to measure regional deformation in several directions ('2D strain'); from these semi-automated measurements, a global average of segmental strain can be calculated; most commonly, longitudinal strain is used ('global longitudinal strain).. Global longitudinal strain has been reported to be more robust than classic ejection fraction and to be at the same time non-inferior in prognostic power, although broad experience with its utility is not yet available. Moreover, absolute global longitudinal strain early (<48 h) after infarction in was reported to correlate with the potential for later recovery of ejection fraction **(6).**

Assessment of right ventricular function

Right ventricular infarction is well recognized as a grave complication of inferior MI. Right ventricular infarction typically is identified by ECG signs (e.g. on V3R or V4R leads) or by echocardiography. Impaired right ventricular function after MI, measured as fractional area shortening of the right ventricle <32% 1 year after infarction, was predictive independently from ejection fraction of long-term prognosis with regard to mortality and heart failure over the ensuing

years .Similar findings using tricuspid annular systolic excursion as a parameter of right ventricular function (with a cut-off of ≤14 mm) were found in patients presenting with ST elevation infarction and cardiogenic shock. The importance of right ventricular function has been confirmed by a MRI study that found that a right ventricular ejection fraction <40% conferred an elevated mortality in patients after MI, independent of left ventricular ejection fraction (7).

Complications of myocardial infarction

Myocardial necrosis due to infarction may cause catastrophic complications early after infarction, including left ventricular free wall rupture, which leads either to tamponade or to pseudoaneurysm formation, ischemic ventricular septal defect, and papillary muscle rupture. Emergency echocardiography (often including transoesophageal imaging) is the diagnostic modality of choice. Thus, sudden clinical deterioration of the post-infarction patient, especially hypotension, shock, or a new murmur, mandate immediate echocardiography.

Thrombus

Arterial embolism to the brain and other organs is a well-recognized complication of MI. Although current treatment of the acute coronary syndrome routinely involves intense anticoagulation and anti-aggregatory therapy in the acute phase, the rationale for long-term anticoagulation is less clear. The detection of thrombi after a recent MI is an indication for long-term anticoagulation, in particular if thrombi are protruding or mobile. Such thrombi are usually first detected during routine echo evaluation of patients after MI. The echocardiographic search for thrombi may be aided by intravenous injection of left-heart contrast, which improves both positive identification and exclusion especially in the artefact-prone apical regions. Both MRI and CT excellently detect and define thrombus and MRI has been shown to detect small mural apical thrombi in apical aneurysms better than contrast echo(8).

(A) Apical thrombus (arrow) in a patient difficult to image by native echocardiography, brought out by application of left heart contrast (Sonovue, Bracco, Milano, Italy). See Supplementary Data. (B) Computed tomography two-chamber view of same patient with visualization of partially calcified (arrows) apical aneurysm and extensive thrombus formation.

Mitral regurgitation

Truly ‘ischemic’ mitral regurgitation by partial or complete papillary muscle rupture due to ischemic necrosis is a rare and catastrophic acute complication of MI, typically accompanying inferior or posterior infarct location and necessitating emergency surgery. Likewise, acute ischemic mitral regurgitation due to a reversible ischemic wall motion abnormality is a relatively rare, although well-described finding, in some cases leading to ‘flash’ pulmonary oedema.

By far a more common, and a well-recognized harbinger of adverse events, is the subacute development of functional mitral regurgitation as a consequence of left ventricular dilatation and eccentric pull of the subvalvular apparatus, preventing the valve leaflets tips from sufficient apposition. The mitral leaflets assume a characteristic 'tent' shape, with the line of apposition displaced into the left ventricle. Indeed, the distance of the line of mitral leaflet tip apposition to the annular level has been used as a parameter of severity of functional mitral regurgitation ('tenting height'), and similarly the tenting area or volume can be measured. Functional mitral regurgitation is well imaged and assessed by echo, although MRI may be used alternatively. Post-infarction mitral regurgitation because of its insidious evolution may best be evaluated after the first week post-MI. An important and long underestimated aspect of post-infarction mitral regurgitation is that it can have a dynamic component which can be elicited by physical exertion in the absence of signs of acute ischemia **(9)**.

Guidance of revascularization strategies and prognostic stratification

Inducible ischemia

Often, acute MI and not angina is the first manifestation of coronary artery disease in a patient. The question of the extent of coronary disease and the presence of inducible ischemia in other territories than the infarcted one is one of the crucial clinical questions after MI. Invasive coronary angiography with the intention of acute revascularization is recommended by current guidelines in essentially all patients presenting early with a MI, with or without ST elevation. Besides detection and treatment of the culprit lesion, this strategy often discloses coronary lesions unrelated to the acute event. Furthermore, if the patient was hospitalized late or did not undergo invasive angiography for other reasons, functional assessment of inducible ischemia is also recommended to guide further management, in particular revascularization. This is the classic field of stress tests, with a clear advantage for imaging stress tests over treadmill (Bruce protocol) or bicycle exercise tests. Both nuclear perfusion imaging and stress echo have an extensively proven track record in the field, notably by allowing risk stratification as to cardiac death or re-infarction according to the presence, extent, and severity of inducible ischemia and of scar, and both techniques are recommended by MI management guidelines. Stress tests seem to be safe if performed in clinically stable patients in the subacute phase of MI (>48 h). Of note, post-MI patients with a negative stress test can be safely discharged early**(10)**.

Stress magnetic resonance imaging with pharmacological stress (adenosine or dobutamine) competes in this field, although experience in the post-infarction patient so far is limited. MRI stress tests are performed with either inotropic or vasodilator pharmacological agents . Both tests had similar predictive accuracy, with negative tests predicting a low yearly rate of death or MI of <1%, very similar to the rates in patients with negative nuclear perfusion or stress echo tests. A MRI dobutamine stress test—similar to a dobutamine stress echo—besides evaluating inducible

ischemia also provides information about contractile response from dysfunctional, but viable myocardial regions. Dobutamine–atropine protocol (stepwise up to 40 µg/kg/min dobutamine and additional atropine if needed to get up to target heart rate), with evaluation of new wall motion abnormalities in standard views of T1-weighted, steady-state free-precession images, without contrast. At low dobutamine doses (e.g. 10 µg/kg/min), contractile reserve of dysfunctional myocardium can be evaluated. One hundred and forty microgram per kilogram per minute adenosine protocol over 6 min with gadolinium contrast, evaluating first-pass perfusion by steady-state free-precession or other sequences in three short-axis slices; reduced regional myocardial blood flow is visible and measurable as a perfusion defect matching the territory of a stenosed coronary vessel(**11**).

Myocardial viability

In acute ischemia, the myocardium ceases to contract. This is initially reversible within hours and days if perfusion is restored (myocardial stunning). If ischemia persists or occurs repetitively without being so severe as to lead to myocardial necrosis, the cardiomyocytes may stop contracting, but remain viable, with the potential to recover their contractile function after perfusion is restored. This state has been termed hibernation. Hibernation in the long term seems to be an unstable condition leading to cell death and fibrosis due to the unfavorable metabolic conditions and repetitive ischemic episodes, but may for months have the potential of functional recovery. If sufficient revascularization is achieved in time, reverse remodeling of the left ventricle may take place, with reduction in volumes, increase in ejection fraction, as well as improvement in diastolic function. Hibernation per se should not be confounded with non-transmural MI, although the relations between these two concepts are not well elucidated.

Transmurality of MI (the fraction of wall thickness made up by subendocardial necrotic tissue) has become an important issue because contrast **MRI** is able to depict the extent of scar with remarkable spatial resolution and high signal-to-noise ratio. This so-called delayed enhancement is due to the presence of contrast in myocardial scars 'late' (10–15 min) after intravenous injections, which appear brighter than intact myocardial tissue (bright is dead). While scars taking up >50% of wall thickness indicate that the myocardium will not recover contractility in over 90% of such segments, for transmural scar fractions of 25–50% the predictive power of this technique is quite limited. Of note, infarction scars contract over time and become significantly thinner in absolute and relative terms after several months than in the first days after MI; therefore, the absolute and relative degree of scar transmurality decreases over time **(1)**.

Early post-infarction contrast-enhanced MRI images can also detect myocardial no-reflow by showing non-enhanced (dark) areas, usually in the subendocardium, which are completely surrounded by late-enhanced (bright) myocardium . These areas do not exhibit late enhancement because the contrast agent cannot arrive there due to microvascular obstruction, and this pattern

is associated with lack of functional recovery and adverse outcomes independently from infarct size**(1)**..

Delayed enhancement in scar tissue is also detectable by **contrast-enhanced CT**. CT imaging can be performed shortly after coronary angiography without new injection of contrast **(12).**

The classic methodological gold standard for detecting myocardial viability has been **positron emission tomography (PET)**. This technique, which ideally requires on-site availability of a cyclotron to generate short-lived isotopes such as 13N or 11C, allows regional, quantitative myocardial blood flow measurements and also quantitative assessment of regional metabolism. Hibernating myocardium has been diagnosed by showing a regional 'perfusion-metabolism mismatch': reduced perfusion (measured by uptake of 13N ammonia, 15O water, or 82Rubidium) in the presence of normal or increased metabolism (measured by 18Fluorodeoxyglucose or 11C acetate uptake), while a concordant reduction in perfusion and metabolism would indicate predominant scar. The most accurate results are achieved under stimulation of glucose metabolism by simultaneous glucose and insulin infusion ('hyperinsulinaemic euglycaemic clamp'). Since the technique is costly and not widely available, PET has found only limited application in cardiology, often in research contexts**(13).**

The most widely applied technique to evaluate viability has long been **single-photon emission computed tomography (SPECT)** utilizing the tracers201Thallium, 99mTechnetium sestamibi, or 99mTechnetium tetrofosmin. These tracers reflect both perfusion and viability (metabolism); rest-redistribution protocols are preferred for 201Thallium and rest imaging before and after nitroglycerine application .The typical finding indicating viability on thallium imaging is a regional uptake defect that fills in after redistribution **(13).**

Besides nuclear studies, the most widespread technique to assess regional myocardial viability and the potential for functional recovery has been **dobutamine echocardiography.** Contractile reserve of chronically ischemic, hibernating myocardium is best elicited at relatively low dobutamine doses of ~7.5 μg/kg/min. The test should include a high-dose stage, since the biphasic response, where initial contractile improvement is followed by deterioration at higher dobutamine doses, is much more specific (although less sensitive) for functional recovery after revascularization. A contractile reserve can also be elicited by low-workload bicycle exercise echocardiography. Echocardiographic deformation imaging at rest, based either on **tissue Doppler or speckle tracking algorithms**, has been evaluated in several modestly sized studies with regard to predicting recovery of contractile function. In experienced hands, deformation imaging aids detection of contractile reserve under dobutamine stimulation. Moreover, strain measured by Doppler or by speckle tracking at rest correlates fairly well with the size of myocardial scar on contrast-enhanced MRI and seems to have similar predictive power for contractile recovery as MRI**(14).**

Identification of non-coronary vascular disease and secondary prevention

Myocardial infarction is proof of advanced atherosclerosis and thus a clear indication for vigorous secondary prevention. Along with identifying treatable risk factors, signs of atherosclerosis should be evaluated in vascular territories other than the heart, especially the carotids, the kidneys and lower limb circulation, and therapeutic measures considered where appropriate. The evaluation of the carotids for plaques with risk features for stroke such as irregularity or echo-lucent zones, and for carotid stenosis is the domain of duplex ultrasound scanning, with CT or MRI angiography as the next step if stenosis is severe enough to be evaluated for surgical or percutaneous intervention(15).

Whom, how, and when to image

In the acute phase of MI, an echo should be obtained as early as possible to assess regional and global left and right ventricular function and to rule out acute mechanical complications; urgent echocardiography is mandatory for patients who experience sudden deterioration, hypotension or shock, acute heart failure, a new murmur, or otherwise experience sudden deterioration. Cardiac imaging after the acute phase of MI has a wealth of valuable information to offer to inform and guide patient management. The clinical choice will therefore differ depending on local expertise and resources, patient characteristics and, last but not least, individual experience of the physician.

The following recommendations are therefore based on and perhaps to some degree biased by our practice:

1-An echo should be performed as quickly as possible in every patient with the acute coronary syndrome. Besides documenting global systolic function (ejection fraction), regional wall motion abnormalities and mitral regurgitation, signs of increased left ventricular filling pressures should be identified, in particular the restrictive mitral inflow pattern. Global strain measurements may be a useful . If large akinetic or dyskinetic left ventricular regions are present, thrombi and spontaneous echo contrast should be identified or excluded.

2-Ejection fraction with some evidence of a lower observer variability. Subtle markers of increased diastolic pressures such as an increase in left atrial size, of the E/e′ ratio or of systolic pulmonary pressure may indicate that the patient perhaps needs more aggressive treatment and a closer follow-up. If large akinetic or dyskinetic left ventricular regions are present, thrombi and spontaneous echo contrast should be identified or excluded.

3-If identification of inducible ischemia is clinically warranted, typically in a patient who did not undergo coronary angiography or who has intermediate coronary non-culprit lesions on the acute coronary angiogram, a stress test should be performed after the acute phase of MI once the patient is stable. Imaging stress tests offer substantial advantages over classic ECG and symptom-based

exercise tests, which. The most important point, though, is local availability and expertise, outweighing the modest differences in diagnostic accuracy.

4-If identification of viable myocardium is of concern, typically in a patient with impaired global left ventricular systolic function and coronary anatomy which is either unknown or amenable to revascularization, the choice is between MRI (with late contrast-enhancement and/or wall motion assessment under dobutamine stimulation), nuclear perfusion imaging, and (usually dobutamine) stress echocardiography. The interpretation of these tests in conjunction with the coronary angiogram to arrive at the decision whether to revascularize or not is frequently very difficult, unless findings are clear cut (transmural scar/no contractile reserve or minimal scar/well-preserved contractile reserve).

5- The test should be performed after the acute phase of MI. In the infarct area, especially after reperfusion therapy, stunned myocardium may be present which will recover spontaneously over the following days and weeks; however, there seems to be a fluid transition between repetitive stunning and classic myocardial hibernation, and the ideal timing of the test is unclear. Similar to the detection of ischemia, the most crucial issue is local availability and expertise, again outweighing the differences in diagnostic accuracy of the individual test **(1).**

Table 1

Strengths and weaknesses of different imaging techniques for typical goals after myocardial infarction

Technique	Goal	Strengths	Weaknesses
Echocardiography	Left and right ventricular function, morphological abnormalities (e.g. thrombus)	Very high spatial (<1 mm if image quality is sufficient) and temporal resolution (with restricted image sector >100 frames per second); can be deployed everywhere and anytime at the bedside; low cost	Quality of images and data varies and depends on operator skills and patient characteristics
	Inducible ischaemia (with physical or	Slightly more specific than nuclear imaging;	Very operator dependent; slightly less sensitive than

Technique	Goal	Strengths	Weaknesses
	pharmacological stress)	well-documented prognostic value	nuclear imaging and MRI techniques
	Myocardial viability (with pharmacological or physical stress)	Higher specificity than nuclear and MRI techniques	
Nuclear imaging (SPECT)	LV function (gated SPECT)	Well standardized, largely observer-independent	Radiation exposure; limited spatial resolution (better than PET, but less than all other techniques); low temporal resolution; slightly less specific than stress echo for myocardial ischemia and viability; emergency access limited in most places
	Inducible ischaemia (with pharmacological stress)	Standardized, quantifiable interpretation; slightly more sensitive than stress echo; very well documented prognostic value	
	Myocardial viability	Higher sensitivity than stress echo	
	Left and right ventricular function,	High spatial resolution including perfusion imaging	Not safe in the presence of pacemaker/ICD leads; small risk of nephrogenic

Technique	Goal	Strengths	Weaknesses
Magnetic resonance imaging (MRI)	morphological abnormalities (e.g. thrombus)	(higher than nuclear techniques); moderately high temporal resolution	systemic fibrosis in patients with severely impaired renal function; arrhythmia or tachycardia deteriorates image quality; in some patients claustrophobia or inability to hold still; emergency access limited in most places
	Inducible ischemia (with pharmacological stress)	High sensitivity and specificity, both wall motion and perfusion assessment possible; documented prognostic value	
	Myocardial viability (with contrast)	Excellent definition of myocardial scar, combination with perfusion assessment possible	
Computed tomography (CT)	Left and right ventricular function, morphological abnormalities (e.g. thrombus)	Very high spatial (<1 mm), low temporal resolution with excellent depiction of cardiac morphology; can image coronary arteries	Radiation and X-ray contrast exposure; arrhythmia or tachycardia deteriorates image quality; emergency access limited in most places
	Myocardial viability	Limited and preliminary	

Technique	Goal	Strengths	Weaknesses
		experience with late enhancement imaging promising	
Positron emission tomography (PET)	Myocardial viability	Separate assessment of metabolism and perfusion, with local absolute, quantitative measurements	Low spatial resolution (3–4 mm), no temporal resolution unless gated; radiation exposure; limited availability due to short-lived radioisotopes
	Inducible ischaemia (with pharmacological stress); used only if other techniques are unavailable or equivocal	Separate assessment of metabolism and perfusion, with local absolute, quantitative measurements	

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