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Predicting left ventricular functional recovery in ischaemic cardiomyopathy: needs and challenges

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Left ventricular (LV) systolic function is an essential parameter for the evaluation of patients with ischaemic heart disease, and therapeutic choices are significantly driven by LV ejection fraction (LVEF) in the early stage of the disease and during follow-up. After an acute coronary syndrome, ventricular dysfunction may be reversible when caused by transient myocardial stunning. Therefore, the identification of clinical, laboratory, and instrumental predictors of improvement in LV systolic function (in addition to LVEF) is essential for an adequate prognostic stratification. In the setting of chronic ischaemic heart disease, there is no evidence that an improvement in LV systolic function is invariably associated with a better prognosis and LVEF is only one of many parameters that should be considered for the risk stratification. This state-of-the-art review will critically analyse the scientific evidence regarding known predictors of LVEF recovery, trying to elucidate their pathophysiological principles and clinical value.

The pathophysiological basis of myocardial injury

Protracted ischaemia occurring during acute myocardial infarction (AMI) causes cardiomyocytes' necrosis and their permanent replacement with fibrotic tissue. However, transient myocardial ischaemia may lead to reversible damage, resulting in a dysfunctional but viable myocardium.[1]

Historically, myocardial viability has been defined as myocardial dysfunction that improves after revascularization. This definition implies that the diagnosis of 'viable myocardium' is possible only afterwards, after the improvement of left ventricular (LV) contractile function following revascularization. Furthermore, the assumption that only percutaneous or surgical revascularization can improve LV systolic function has been overcome. Indeed, recent evidence suggest that also medical therapy may lead to LV systolic recovery.[1]

The concept of myocardial viability includes both the so-called 'stunned' and 'hibernating' myocardium. Myocardial stunning occurs when transient ischaemia results in acute dysfunction persisting despite restoration of perfusion, and it takes over hours to days. On the other hand, when the ischaemic insult is transient but repeated over time, a series of chronic, metabolic, and structural adaptations allows the myocardium to remain viable, albeit dysfunctional (this pathophysiological phenomena is also known as hibernating myocardium).[2]

Left ventricular dysfunction after acute myocardial infarction

Left ventricular dysfunction secondary to AMI is partly due to irreversible damage and also to myocardial stunning, which may be reversible. The persistence of severe LV

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dysfunction after AMI represents the strongest predictor of increased cardiovascular morbidity and mortality.[3]

International guidelines recommend implantation of implantable cardioverter defibrillator whenever severe LV systolic dysfunction [i.e. left ventricular ejection fraction (LVEF) ≤35%] persists over 40 days after the acute event or for 90 days in case of myocardial revascularization. An earlier implantation, in fact, has not demonstrated any correlation with increased survival.[4]

The identification of possible predictors of systolic function improvement is therefore essential to allow adequate risk stratification and appropriate therapeutic management.

First-line clinical, laboratory, and imaging predictive indicators

Predictors of LV functional recovery were investigated in the Predicting Persistent Left Ventricular Dysfunction Following Myocardial Infarction (PREDICTS) study,[1,4] which enrolled 231 patients with severe LV dysfunction following AMI (mean LVEF 28.8%±6.6). The patients enrolled were predominantly men (71%), with a mean age of 60 ± 11 years, 25% of whom had already had an AMI in the past. 81% of cases were ST-elevation MIs and the most frequent regional wall motion abnormalities were apical (78%) and anterior (73%) ones. Nearly 20% of the patients presented with cardio-respiratory arrest (CRA) or ventricular fibrillation (VF), and 40% required ventilatory and/or circulatory support. 84% of patients underwent percutaneous revascularization. During follow-up (mean follow-up: 81 days after discharge), among the 231 patients enrolled, 57% had LVEF >35% and 26% had ≥50%. The predictors of LVEF recovery identified in the PREDICTS study are listed in *Figure 1*.

Further, the authors developed two different predictive models to assess the probability of LVEF recovery above 35 and 50%, respectively. Each evaluated parameter was assigned a score, according to its predictive power, and, as shown in *Table 1*, LVEF at presentation was the strongest predictor of systolic function recovery.

Interestingly, presentation with CRA/VF emerged as an independent predictive factor of LVEF recovery ≥50%, for which the authors suggested two pathophysiological

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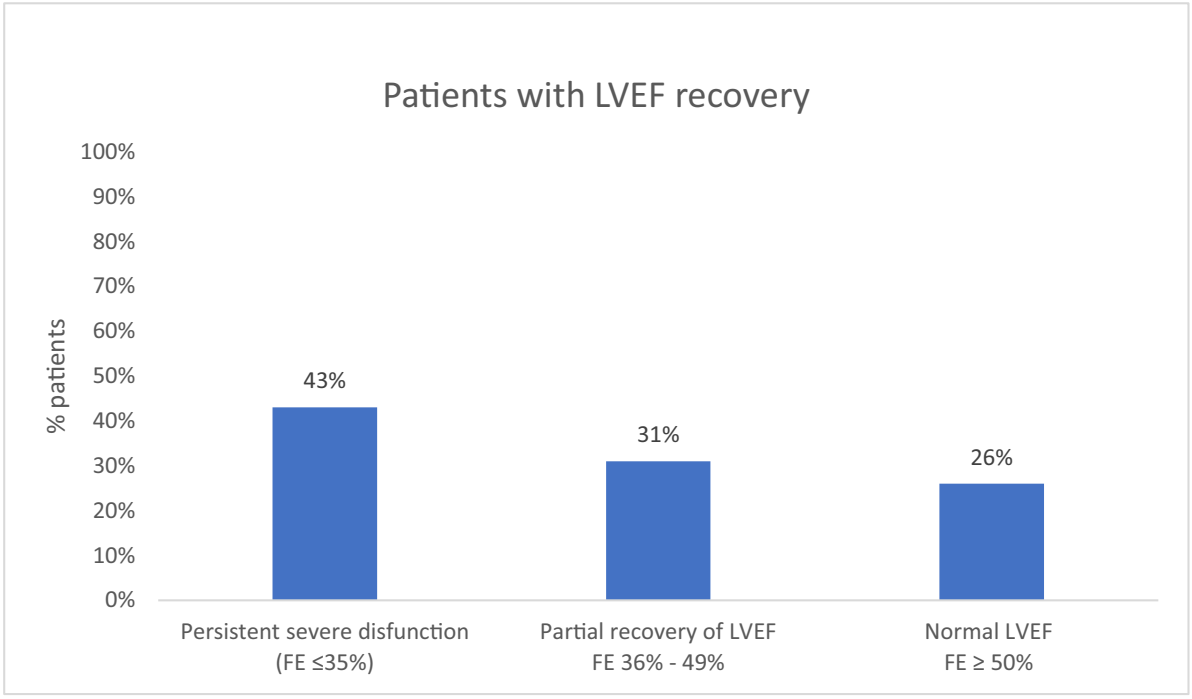

Figure 1 Predictors of ventricular function recovery.

Table 1 Model for calculating the probability of recovery of left ventricular ejection fraction ≥35% (Panel A) and ≥50% (Panel B)

Panel A		Panel B	
	Points		Points
EF at presentation	4	EF at presentation	4
31–35%	2	31–35%	1
26–30%		26–30%	
Hospital stay <4 days	1		
No previous AMI	1	No previous AMI	1
No abnormalities of lateral kinetics	1	Maximal troponin level <550ULN	4
Maximal troponin level <550ULN	4	Penetration with VF or CRA	2

Probability of LVEF recovery ≥35%: 9% if 0 points, 31.9% if 1–3 points, 57.9% if 4–5 points, 78.6% if 6 points, and 87.2% if > 7 points. Probability of LVEF recovery ≥ 50%: 4.4% if 0–2 points, 2.3% if 3–4 points, 10.3% if 5–6 points, 27.1% if 7–8 points, 48, 7% if ≥9 points 4.
ULN, upper limit of normal.

hypotheses. The first one attributed the recovery to an initial condition of myocardial stunning. However, patients with CRA/VF at presentation were also those with the greatest troponin release, which emerged as a negative predictive factor. The second hypothesis suggested that VF represented a marker of spontaneous reperfusion, which was associated with a greater risk of arrhythmias in animal models when compared with ischaemia alone.[4]

A Korean study[3] sought to identify predictors of systolic function recovery in patients with a first episode of AMI and echocardiographic evidence of LVEF ≤45%. In this study, patients were selected from the Korea Acute Myocardial Infarction Registry (KAMIR), a prospective observational registry. At a median follow-up of 7.4 months, LVEF recovery to >45% occurred in ~50% of patients ($n = 663$). In the multivariate analysis, the variables associated with LV functional recovery were:

(1) Clinical markers of less severe heart failure: Killip Classes I and II at presentation, LVEF 30–45%;
(2) Markers suggesting a smaller myocardial injury: non-ST-segment elevation myocardial infarction (NSTEMI), monovessel coronary artery disease, culprit vessel other than the left anterior descending artery, lower troponin peak;
(3) Therapy with statins and not needing diuretics at discharge.

In an another analysis,[5] only patients with initial LVEF ≤40% successfully undergoing primary angioplasty were selected. Among these 656 patients, 28% had ≥10% improvement in LV function with LVEF > 40% at 1 year after hospitalization. The predictors of systolic function improvement were: previous MI, greater leucocytosis and greater troponin release, pre-procedural thrombolysis in MI 0–1 score, and multi-vessel coronary artery disease. Moreover, the predictors of LVEF recovery were right coronary artery as culprit vessel and assumption of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers at discharge.

Finally, the extent of revascularization is one of the predictors of systolic function recovery. Although there are no dedicated studies, in the Prospective, Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 vs. Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention (PROTECT II) trial, patients undergoing extensive revascularization had a higher probability or reverse remodelling when compared with single-vessel treatment.[6]

Recently, the Ejection Fraction Improvement Following Contemporary High-Risk Percutaneous Coronary Intervention (RESTORE EF) trial has evaluated the impact of percutaneous revascularization on LVEF in high-risk surgical patients treated with Impella-supported non-emergent primary percutaneous coronary intervention (PCI; median baseline LVEF 35%, interquartile range 25–50%, SYNTAX Median pre-PCI 53, interquartile range 42–64). There was a significant improvement in LVEF in patients with at least moderate LV dysfunction and a greater improvement in LVEF in patients who underwent complete revascularization, identified as a post-PCI residual SYNTAX Score of 0.[7]

Second-line predictive indicators: imaging

In the last decades, improvement of imaging techniques such as stress echocardiography, cardiac magnetic resonance (CMR), positron emission tomography (PET), and single photon emission computed tomography (SPECT) permitted the identification of additional predictors of post-AMI LV functional recovery. Examples are the presence of myocardial viability within a few days after AMI, documented by stress echocardiography[8,9] and parameters such as infarct size or myocardial salvage index, obtained with CMR or SPECT.[10,11]

Recovery of left systolic ventricular function as a marker of minor myocardial injury

A multi-parametric evaluation including clinical, laboratory, and integrated imaging data is essential during the 40–90 days post-AMI to identify patients with extensive irreversible myocardial injury. Coherently, these patients present with greater signs of heart failure, higher troponin release, worse systolic function impairment with more extensive regional wall motion abnormalities, as well as more severe coronary artery disease.[3,4]

The clinical value of left ventricular systolic dysfunction and myocardial viability in the setting of chronic ischaemic heart disease

The presence of myocardial viability has been shown to be a valid predictor of LVEF recovery in chronic ischaemic heart disease. However, solid evidence of an association between improvement in LV systolic function and increased survival is lacking. In the Surgical Treatment of Ischemic Heart Failure (STICH) trial,[12] which enrolled 1212 patients with ischaemic heart disease and LVEF

≤35% randomized to medical therapy or coronary artery bypass graft, the presence of viable myocardium was associated with an improvement in LVEF, with both surgical and medical treatment, but only treatment with surgical revascularization was shown to increase survival. Furthermore, this survival improvement did not appear to depend upon the presence of myocardial viability at baseline. Finally, increased survival has not been associated with LV systolic function improvement. However, according to a 24-month analysis, a better prognosis seems to be associated with a >10% LVEF improvement (which occurred in <20% of patients in the STICH trial).[13] This suggests that the survival improvement following surgical reperfusion also depends on mechanisms other than LVEF improvement, such as the reduction of malignant arrhythmias or the prevention of future ischaemic events.[1] Furthermore, a positive viability test does not seem enough to decide whether to proceed with an invasive revascularization. A multi-parametric evaluation is fundamental, also accounting for consistency between the area of viable myocardium and the coronary anatomy, as well as the technical feasibility of reperfusion of the segments involved.[14]

Even the PET and Recovery Following Revascularization-2 study (PARR-2),[15] a prospective randomized study in which the indication for revascularization in patients with severe ventricular dysfunction was guided by the presence of viability on PET, did not show a correlation between the presence of viable myocardium and a reduction in the composite outcome of cardiac death, AMI, and re-hospitalizations at 1-year follow-up.[1]

However, some limitations of STICH and PARR-2 trial should be highlighted. In the STICH trial, a viability test was mandatory only in the first phase and was subsequently performed at the discretion of the clinician. Furthermore, the viable myocardium detected with SPECT did not need to be dysfunctional at rest, so healthy, non-hibernating segments could have been counted as viable myocardium. Instead, in the PARR-2 trial, surgical revascularization should have been guided by the presence of viability, but in as many as 25% of cases, the clinical decision was discordant with the radiological recommendation.[1]

Left ventricular ejection fraction evolution is undoubtedly an important element to consider during the follow-up of a patient affected by chronic ischaemic heart disease; however, these are often complex clinical pictures, whose trend over time cannot be intersected only by the trajectory of a single value.

American and European Guidelines recommend surgical revascularization in cases of severe ventricular dysfunction and multi-vessel coronary artery disease (Level of evidence I, Grades of recommendation A and B, respectively). Percutaneous revascularization was recommended by the 2018 European guidelines in patients with single- or two-vessel coronary artery disease when complete revascularization was feasible (Level of evidence 2, Grade of recommendation A).

In 2022, the results of the Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction (REVIVED-BCIS2) trial were published, the first prospective study evaluating the efficacy of percutaneous revascularization in patients with severe LV dysfunction[16]: percutaneous revascularization associated with optimal medical therapy did not reduce the composite endpoint of all-cause death and hospitalizations for heart failure vs. medical therapy alone, after a median follow-up of 41 months.[16] In this context, the role of medical therapy in the improvement of LVEF should be emphasized. The effect of Sacubitril/Valsartan on reverse remodelling has been demonstrated in several studies, including the Reverse Cardiac Remodeling Observed With Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure with reduced Ejection Fraction (PROVE-HF) trial and the Effect of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction (EVALUATE-HF) trial, which respectively enrolled ~40 and 60% of ischaemic patients with severe LV dysfunction.[17,18]

Imaging techniques to assess myocardial viability

Numerous imaging techniques are able to identify patients with LV dysfunction but viable myocardium who are most likely to improve systolic function with revascularization and medical therapy.

Dobutamine stress echocardiogram represents a reliable and readily method. In the case of hibernating myocardium, myocardial contractility increases at low doses of dobutamine and then decreases at high doses. This 'biphasic' response represents the best echocardiographic predictor of systolic function recovery after revascularization (sensitivity 74%, sensitivity 89%). A significant LVEF improvement following dobutamine infusion could underlie a non-transmural AMI, which has a lower probability of recovery (specificity 70%).[2,19] Advanced echocardiographic techniques, such as the use of contrast, strain, and 3D echocardiography, are useful complementary tools for assessing myocardial viability.[19]

Cardiac magnetic resonance is a method that has been widely used in the last decade for the study of viability. The most used method involves the evaluation of the late distribution of gadolinium (late gadolinium enhancement, LGE). In fact, the gadolinium accumulates in areas with increased extracellular space, such as those with replacement fibrosis. The myocardium is defined as viable when LGE is <50% of the myocardial thickness. In reality, despite this cut-off, it is rather a continuum, in which the higher the transmurality, the lower the probability of functional recovery and *vice versa*.

With both CMR and echocardiography, the probability of myocardial viability can be estimated by observing end-diastolic wall thickness. When the wall thickness is <5.5–6 mm, the myocardium is likely irreversibly injured and defined as nonviable. However, it has been shown that even akinetic segments <5.5 mm thick can actually be viable in the absence of LGE.[19] Like for echocardiography, dobutamine CMR can be used to better identify viable myocardial regions, increasing its specificity and, consequently, its positive predictive value.[19]

Table 2 Acute and 1 year (range 3–24 months) left ventricular ejection fraction in patients with acute myocardial infarction from 1 January 2017 to 31 December 2021

LVEF at admission AMI	LVEF after 1 year of follow-up	
	LVEF ≤40% ($n = 348$; 13.1%)	LVEF 41–49% ($n = 384$; 14.5%)
LVEF ≤40% ($n = 605$; 22.8%)	252 (41.7%)	161 (26.6%)
LVEF 41–49% ($n = 604$; 22.8%)	59 (9.8%)	141 (23.3%)
LVEF ≥50% ($n = 1441$; 54.4%)	37 (2.6%)	82 (5.7%)

Nuclear medicine techniques, such as SPECT and PET have the limitation of use of ionizing radiation. SPECT exploits the distribution of radionuclides in the myocardium, which depends both on myocardial perfusion and cellular integrity (of the sarcoplasmic membrane for technetium or of the mitochondrial membrane for thallium). PET allows to study both myocardial metabolism (with ^{18}F-FDG) and perfusion (with 82-Rubidium, N-13 ammonia, or O-18 water).[2] The hibernated myocardium is characterized by reduced perfusion, but preserved metabolism (mismatch pattern). On the contrary, in the case of stunning, a dysfunctional myocardium is observed but with normal perfusion and preserved metabolism. Instead, in the case of replacement fibrosis, both perfusion and metabolism are reduced (match pattern). PET is the imaging technique with the greatest sensitivity and therefore with the highest negative predictive value.[19]

Data from the cardiovascular observatory of Friuli Venezia Giulia

From 2017 to 2021, 2650 patients with myocardial infarction defined according to Italian 'Programma Nazionale Esiti' criteria were included and evaluated by echocardiogram at baseline and at 1-year follow-up. *Table 2* shows the LVEF data broken down according to the severity of systolic dysfunction at admission and at follow-up. In the acute phase, 22.8% of patients had LVEF ≤40% and 22.8% had LVEF between 41 and 49%. At 1 year, one-third of patients with LVEF ≤40% in the acute phase and 2/3 of cases with LVEF in the acute phase between 41 and 49% normalized LVEF.

Conclusions

Severe LV dysfunction documented in the acute phase of AMI improves in >50% of cases and normalizes in about 25% of cases. In this context, multi-parametric evidence of extensive myocardial damage indicates a lower probability of dysfunction recovery and a worse prognosis, and it suggests to the clinician the need for a more vigilant and attentive follow-up.

In chronic ischaemic heart disease, LV dysfunction represents a key element for the correct prognostic stratification of the patient, albeit not the only one. The demonstration of myocardial viability is a predictor of the improvement in heart contractile function, even if not necessarily associated with a reduction in mortality, given the extreme complexity of these clinical pictures.

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Data availability

No new data were generated or analysed in support of this research.

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