Assessment of myocardial viability after the STICH trial: still viable?

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Summary

Ischaemic heart disease predominantly accounts for the majority of patients with heart failure symptoms. The prevalence of ischaemic cardiomyopathy (CMP) is continuously increasing owing to an increasingly elderly population and improved survival of acute coronary syndrome patients. Coronary revascularisation may improve left ventricular function, heart failure symptoms and cardiovascular outcome in those high-risk patients who have evidence of a sufficient degree of myocardial viability subtended to the target epicardial lesion. Optimal assessment of myocardial viability, therefore, remains essential for an optimal medical decision-making process in these patients. Recently, the STICH (Surgical Treatment for Ischemic Heart Failure) trial was performed, in which 1,212 ischaemic CMP patients were randomly assigned to receive medical therapy alone or medical therapy plus coronary artery bypass grafting. Although in these intermediate-risk patients the presence of viable myocardium was associated with a greater likelihood of survival, in patients with coronary artery disease and left ventricular dysfunction, this relationship did not hold after adjustment for other baseline clinical variables. At first glance, these observations may be surprising and contradictory to previous retrospective or observational investigations in the assessment of myocardial viability in ischaemic CMP patients. Several factors, however, may reconcile, at least in part, this controversy in viability assessment, treatment and clinical outcome of ischaemic CMP patients, such as (1.) the timing of coronary revascularisation, (2.) absence or presence of ischaemically compromised but viable myocardium, (3.) stage of the myocardial remodelling process and (4.) use of suboptimal imaging protocols and techniques to determine the presence or absence of ischaemically jeopardised but viable myocardium. These aspects and the role of other imaging modalities will be discussed.

Key words: cardiomyopathy; coronary artery disease; hibernating myocardium; PET; SPECT; STICH trial; viability

Funding / potential competing interests:
No financial support and no other potential conflict of interest relevant to this article was reported.

Introduction

Ischaemic heart disease predominantly accounts for the majority of patients with heart failure, followed by idiopathic cardiomyopathy (CMP), valvular disease, and hypertensive heart disease [1]. Although there is continuous progress in the treatment of heart failure with beta-blockers, angiotensin-converting enzyme (ACE) inhibition, angiotensin II type 1 receptor (AT-1) blockers and aldosterone beneficially influencing morbidity and mortality, the 5-year mortality rate for heart failure still remains as high as 50%. In the United States more than four million people suffer from heart failure [2]. In view of the increasingly elderly population and improved survival of acute coronary syndrome (ACS) patients [3], an increasing prevalence of heart failure is likely to emerge as a considerable public health concern.

Mechanisms of left ventricular dysfunction in ischaemic CMP may be related to an activation of the myocardial renin-angiotensin system (RAS), development of interstitial myocardial fibrosis, toxic catecholamine actions, stimulation of matrix metalloproteinases [4], and maladaptive cellular and molecular alterations that accompany the left ventricular remodelling process [5]. In the past two decades, it has been widely appreciated that ischaemic left ventricular dysfunction may be sustained by repeated ischaemia during times of increased metabolic demand or exercise. This myocardial "stunning" may proceed to myocardial ischaemia at rest and is referred to as myocardial "hibernation" [6–8]. Such stunned and/or hibernating myocardium can potentially completely or partially recover in a substantial number of patients who undergo coro-

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nary revascularisation, as numerous investigations have shown [6, 7, 9, 10]. In this scenario, "myocardial viability" is commonly referred to as an impairment of regional myocardial contractile function that is potentially reversible if the region is revascularised [11–13].

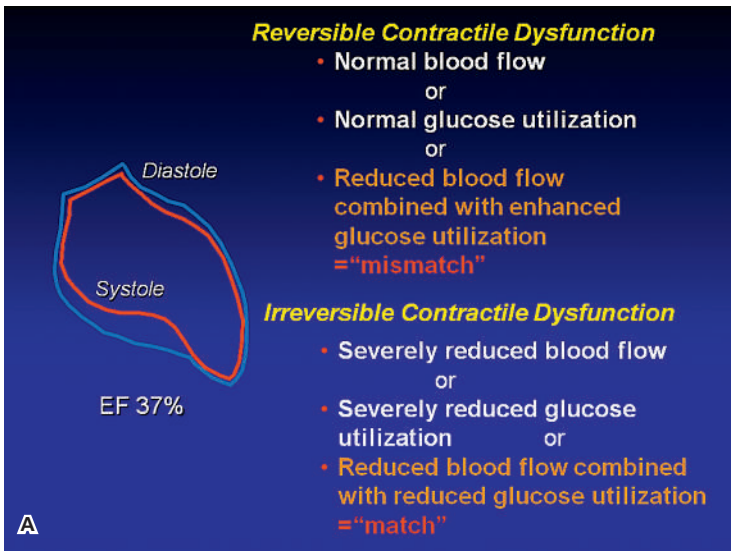
Fluorine-18-labelled fluorodeoxyglucose positron emission tomography (FDG-PET) is widely accepted as the reference standard for the identification of viable myocardium in patients with ischaemic CMP [8, 10, 13]. In clinical studies using FDG-PET for the detection of viable myocardium in these patients, mean sensitivity and specificity are reported to be 92% and 63%, respectively [13, 14]. Viable and ischaemic jeopardised myocardium, however, is preferentially identified with PET alone or in concert with single-photon emission computed tomography (SPECT) perfusion imaging [10, 13]. When applying the concept of perfusion-metabolism "match" (nonviable myocardium; reduced blood flow with concurrent reduction in glucose utilisation) and "mismatch" (viable myocardium; reduced blood flow combined with enhanced glucose utilisation) patterns (fig. 1), a pooled analysis of 17 studies (including SPECT perfusion imaging and FDG-PET) demonstrated increased diagnostic performance with a positive predictive value of 76% (range 52%–100%) and a negative predictive value of 82% (range 67%–100%) [14, 15].

Several clinical investigations have shown a close relation between viability assessment with FDG-PET and various clinical outcome parameters [8, 10]. As regards functional recovery of viable myocardium in ischaemic CMP patients, numerous investigations have shown an improvement of regional and global left ventricular ejection fraction (LVEF) after successful restoration of coronary flow to viable myocardial segments identified with FDG-PET [7, 10, 14, 16, 17]. Notably, Di Carli et al. [17] demonstrated that the preoperative extent of a flow-metabolism mismatch was closely related to the magnitude of improvement in postrevascularisation heart failure symptoms ($r = 0.65$, $p < 0.001$). A viability extent of ≥18% had a sensitivity of 76% and a specificity of 78% for the greatest clinical benefit in improvement of functional status [17].

The minimum amount of viable myocardium required for a functional recovery after coronary revascularisation is still a matter of ongoing debate [8]. On the other hand, it has been widely accepted that if more than 20% of the left ventricle is identified as ischaemic, jeopardised but viable myocardium, it is "functionally" significant, with the potential to recover contractile function after restoration of coronary blood flow [18]. With the use of this criterion, functionally significant viability can be expected in 25% of patients with ischaemic CMP, who might benefit from coronary revascularisation (fig. 2) [19]. Conversely, dysfunctional but viable myocardium may be considered as only "prognostically significant" when less than 20% of the left ventricle is involved [18]. More recent investigations have refined this threshold to a "mismatch" extent of 7%–8% of the left ventricle [20]. Notably, restoration of coronary flow to viable but ischaemic, compromised myocardium may not only beneficially affect regional left ventricular function but also the left ventricular remodelling process [8, 13, 21]. However, most of these

Figure 1

(A) Reversible and irreversible contractile dysfunction in akinetic myocardial segments as defined by SPECT and/or PET assessment of myocardial perfusion and metabolism. (B) Examples of normal perfusion and FDG uptake (left panel), "match" finding with concordant reduction in perfusion and metabolism in the anteroapical and inferior wall, indicative of nontransmural and transmural scar without ischaemia (middle panel), and "mismatch" finding with reduced resting perfusion anteroapical, apical and inferoapical, and preserved metabolism, suggestive of classical hibernating myocardium (right panel). (Figure displayed by courtesy of HR Schelbert).
FDG = fluorine-18-labelled fluorodeoxyglucose; PET = positron emission tomography



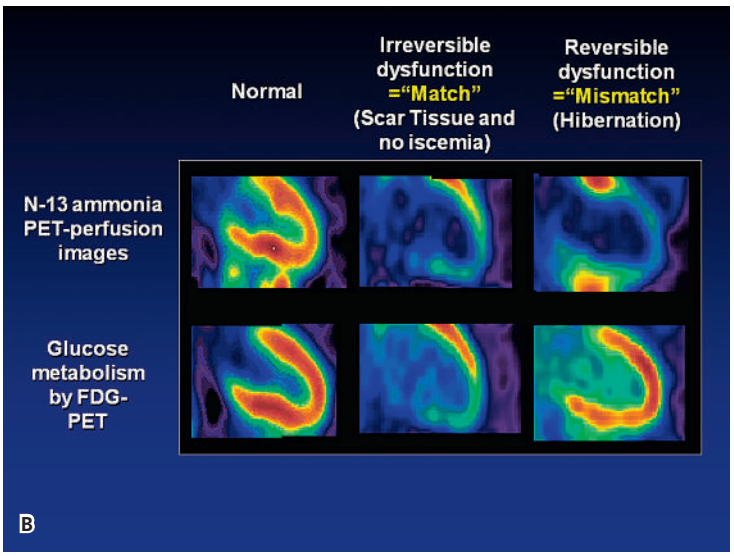
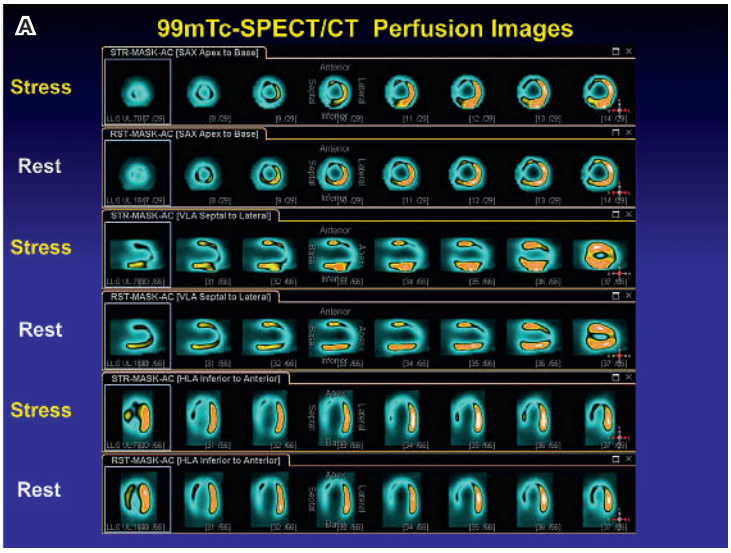
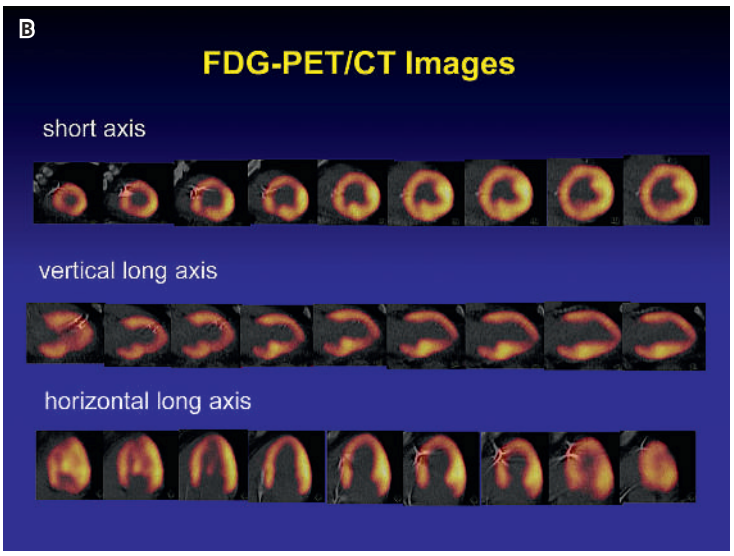


Figure 2

^{99m}Tc-SPECT/CT perfusion images in a 56-year-old man presenting with recent non-ST-elevation myocardial infarction and stable coronary artery disease. Short axis, vertical and horizontal long axis demonstrate a widely fixed and extended perfusion defect in the anterior, septal, apical and infero-septal wall (A) with a "mismatch" (widely preserved although diminished FDG-uptake on PET/CT images) (B), consistent with hibernating myocardium in the LAD and RCA territory. Invasive coronary angiography demonstrated two proximal LAD lesions with ≈90%, LCx with ≈40%–50%, and RCA with ≈90% stenosis diameter. The patient underwent a percutaneous coronary intervention with dilation of stenosis and stent implantation in LAD and RCA lesions. Echocardiographic follow-up examination after 3 months demonstrated a marked improvement of global left ventricular ejection fraction from 25% to 40%.

^{99m}Tc = technetium-99; CT = computed tomography; FDG = fluorine-18-labelled fluorodeoxyglucose; LCx = left circumflex coronary artery; LAD = left anterior descending coronary artery; PET = positron emission tomography; RCA = right coronary artery; SPECT = single-photon emission computed tomography





clinical investigations assessing the association between coronary revascularisation of viable myocardium and improvement in left ventricular function, symptoms and prognosis were retrospective, which may have introduced a certain evaluation bias. For this reason, it still remains uncertain whether the decision to perform coronary-artery bypass grafting (CABG) and/or a percutaneous coronary intervention (PCI) was driven by the results of imaging tests to identify viable myocardium, whether adjustment for pivotal baseline variables was appropriate, and whether patients who were not referred for CABG received adequate medical therapy for heart failure.

As a consequence, the STICH (Surgical Treatment for Ischemic Heart Failure) trial [22] was designed and performed, in which 1,212 ischaemic heart failure patients were randomly assigned to receive medical therapy alone or medical therapy plus CABG. In 601 of these patients myocardial viability was determined with SPECT, dobutamine echocardiography, or both [22]. The presence of viable myocardium was observed to be associated with a greater likelihood of survival in patients with coronary artery disease (CAD) and left ventricular dysfunction. However, this relationship was not significant after adjustment for other baseline clinical variables. In addition, and somewhat surprisingly, the assessment of myocardial viability with SPECT or dobutamine echocardiography did not prove to be superior in identifying those patients who are likely to benefit with respect to survival from CABG as compared with those who received optimal medical therapy alone [22].

At first glance, these observations may be surprising and contradictory to previous investigations in the assessment of myocardial viability in ischaemic heart failure patients [6–8, 10]. Several factors, however, may reconcile this controversy in viability assessment, treatment, and clinical outcome of ischaemic CMP patients, such as (1.) the timing of coronary revascularisation, (2.) absence or presence of ischaemic, compromised but viable myocardium, (3.) stage of the myocardial remodelling process, and (4.) use of suboptimal imaging protocols and techniques to determine the presence or absence of ischaemic, jeopardised but viable myocardium (table 1).

Table 1

Factors potentially affecting the effect of flow restoration on viable but dysfunctional myocardium.

Timing of coronary revascularisation
Extent and severity of myocardial ischaemia in dysfunctional but viable myocardium
Myocardial remodelling
Left ventricular dilation

Timing of coronary revascularisation

As regards the timing of coronary revascularizsation in patients with ischaemic CMP, the improvement in left ventricular function and prognosis may be less favourable if coronary revascularisation is not performed in a timely manner. For this reason, Bax et al. [9] investigated whether delayed coronary revascularisation may result in a less favourable outcome. Eighty-five patients with ischaemic CMP and substantial viability (≥25% of the left ventricle) on low-dose dobutamine stress echocardiography were referred for surgical revascularisation. Patients were divided into two groups: early (≤1 month waiting time) and late (>1 month waiting time) revascularisation. LVEF was assessed before and 9 to 12 months after revascularisation, and follow-up data were acquired up to 2 years after revascularisation. It was observed that early revascularisation (20 ± 12 days) of viable myocardium in these patients conferred a high likelihood of an improvement in LVEF (from 28% ± 9% to 40% ± 12%). Conversely, when coronary revascularisation was relatively delayed (85 ± 47 days) in these patients, no significant alteration in LVEF (27% ± 10% to 25% ± 7%) was noted. Similarly, early rather than delayed coronary revascularisation in these patients manifested in an improved clinical outcome or prognosis (mortality: 5% vs 20%) [9]. Also, the rehospitalisation rate for heart failure was less in the early than the delayed revascularisation group (10% vs 24%), although this difference did did not achieve statistical significance.

Similarly, Beanlands et al. [23] investigated the use of FDG-PET in the assessment of myocardial viability for preoperative risk evaluation. Forty-six patients with ischaemic CMP and an LVEF of ≤35% were considered candidates for revascularisation based on FDG-PET viability imaging. Finally, 35 of the 46 patients were subsequently accepted for coronary revascularisation. The aim was to investigate the impact of prolonged waiting time on cardiac outcomes in these ischemic CMP patients referred for revascularisation on the basis of FDG-PET imaging. Based on the median waiting time, patients were divided into two groups : an early group (<35 days; n = 18) and a late group (≥35 days; n = 17). Preoperative mortality rates were significantly increased in the late group (4 of 17 [24%] vs 0 of 18 in the early group; p <0.05). Furthermore, in postoperative follow-up (17 ± 7 months), cardiac events occurred in 2 of 18 (11%) and 1 of 13 (7.8%) patients in the early and late groups, respectively. LVEF increased after early revascularisation (from 24% ± 7% to 29% ± 8%, p <0.001, baseline vs 3 months) but not in the late group (27% ± 5% to 28% ± 6%, p = not significant). At least from these clinical observations in ischaemic CMP, it appears advisable to strive for early (within 35 days) coronary revascularisation of stunned and/or hibernating myocardium for functional recovery of the left ventricle, and improved clinical outcome and prognosis.

It is worth noting that in the two randomised viability and revascularisation trials (PARR-2 [24] and STICH [22]), patients with acute coronary syndrome (ACS) within 4 weeks or 3 months, respectively, were excluded from the study analysis. In fact, the targeted study populations were patients with stable and mostly known ischaemic CMP. For example, in both the PARR-2 and STICH trials 80% of the heart failure patients had had previous myocardial infarction, and patients presented with differing stages of angina symptoms or dyspnoea according to the Canadian Cardiovascular Society Angina and New York Heart Association classifications, respectively. Accordingly, most of these study patients most likely had already relatively longstanding ischaemic CMP with advanced cardiac remodelling and interstitial fibrosis [21, 25, 26], which may have hampered recovery of left ventricular function and improved cardiovascular prognosis after delayed rather than early CABG. Furthermore, in both the PARR-2 and STICH-trials no detailed information on the time interval between viability assessment and coronary revascularisation was provided. For example, in the STICH trial [22], ischaemic CMP patients were enrolled if a viability study had been done within 90 days. This would suggest that patients were included in whom viability assessment was done 2 to 3 months prior to revascularisation and, therefore, the coronary revascularisation was delayed, lowering the likelihood of functional recovery of viable myocardium in these CMP patients.

Taking these considerations into account, it may not be necessarily a surprise that both the PARR-2 and STICH trials [22, 24] did not report a significant reduction in cardiac events in patients with ischaemic left ventricular dysfunction who had imaging-assisted viability assessment, as compared with those receiving standard medical care for heart failure, because coronary revascularisation was relatively delayed. However, in the PARR-2 trial a *post-hoc* analysis demonstrated that in patients in whom PET assessment for viability was performed and recommendations were followed, a significant survival benefit ensued [24]. Overall, the failure of viability assessment to identify those patients with a survival benefit from CABG as compared with medical treatment of heart failure in the randomised PARR-2 and STICH trials [22, 24] is likely to be related, at least in part, to relatively delayed coronary revascularisation in ischaemic CMP patients, as several investigations suggest [9, 27, 28].

Extent and severity of myocardial ischaemia

Apart from the timing of coronary revascularisation in patients with ischemic CMP, the extent and severity of myocardial ischaemia compromising dysfunctional but

viable myocardium remains unknown in the STICH trial [22]. Thus, it is quite possible that a non-negligible portion of patients with proof of ≥11 viable myocardial segments did not have myocardial ischaemia or had only mildly ischaemic compromised myocardium. It has been widely appreciated that in patients with chronic ischemic CMP, stress-induced or resting myocardial ischaemia is prevented by the induction of collaterals by the myocardial hypoxic stimulus, which strives to balance reduced flows during times of increased metabolic demand in myocardial regions subtended by high-grade epicardial narrowing or even occluded vessels [29–31]. In addition, medical therapy which aims and improves the coronary vasodilatory capacity, such as HMG-CoA reductase or ACE inhibitors, may prevent or even reduce clinically manifest myocardial ischemia in CAD patients [32, 33].

Such a constellation with the absence of myocardial ischaemia may also occur in patients who have suffered myocardial infarction related to an occluded artery but who are otherwise clinically stable. The absence of a significant amount of stress-induced myocardial ischaemia in the infarcted territory with residual viability subtended by an occluded artery might explain, in part, why the interventional reopening of the occluded infarct-related artery did not lead to a significant reduction in the occurrence of death, reinfarction, or hospitalisation for class IV heart failure over a 3-year and also a 6-year mean follow-up when compared with optimal medical therapy alone [34, 35]. This consideration is supported by a previous investigation of Beanlands et al. [36] using ^{201}thallium (^{201}Tl) myocardial scintigraphy for the assessment of perfusion and viability in 23 patients with occluded arteries after myocardial infarction. The assessment of the extent of perfusion defects in dysfunctional and viable myocardium with ^{201}Tl myocardial scintigraphy proved to be useful for identifying those patients who will most benefit from reopening of the occluded vessel [36].

Because in the STICH trial only those patients without an ACS within the last 3 months were considered for coronary revascularisation, it is equally possible that a certain number of patients with demonstrated myocardial viability on SPECT images or low-dose dobutamine echocardiography did not have extensive and/or severe myocardial ischaemia, owing to the development of collateral flow and medically improved MFR. Coronary revascularisation in these patients without, or with only mild, ischaemic jeopardised myocardium, therefore, may not have conferred the expected benefit in improvement of left ventricular function and prognosis as reported previously [7–10, 18, 20, 37].

Stage of the myocardial remodelling process

Another critical point is the stage of the myocardial remodelling process in patients with ischaemic CMP. Left-ventricular remodelling, defined clinically as alterations in volume, shape, and/or function of the heart chambers in response to chronically elevated loading conditions, plays a pivotal role in the clinical course and survival of patients with systolic heart failure. Catecholamine actions [2], the development of interstitial fibrosis [25], energy-depleted hibernating myocardium triggering and maintaining contractile dysfunction [21], continuous tissue degeneration and cardiomyocyte loss due to autophagic cell death and apoptosis [26], and the activation of the myocardial RAS system [5] may predominantly account for the central maladaptive cellular and molecular response which commonly accompanies the left ventricular remodelling process. Extensive left ventricular remodelling in patients with ischaemic CMP may, in fact, prevent functional recovery of hibernating myocardium after revascularisation [38, 39].

In an extended clinical investigation, which included 79 patients with ischaemic CMP who were referred for surgical revascularisation, Bax et al. [28] could demonstrate that the change in LVEF after revascularisation was linearly related to the baseline left ventricular end-systolic volume. Higher left ventricular end-systolic volume was associated with a low likelihood of improvement in LVEF after revascularisation. Thus, even in the presence of a sufficient amount of hibernating myocardium, as detected with FDG-PET and perfusion SPECT, coronary revascularisation failed to improve LVEF when baseline left ventricular end-systolic volume was high [28]. In the group without improvement in LVEF after revascularisation, left ventricular end-systolic volume was observed to be 141 ± 31 ml, which greatly exceeded that of those with an improvement in LVEF, at 109 ± 46 ml. From these observations it may be concluded that assessment of hibernating myocardium should always be placed in proper context with left ventricular end-systolic volume in ischaemic CMP patients who are being considered for surgical revascularisation.

Suboptimal imaging protocols for viability assessment and evaluation

Finally, the failure of the STICH trial to demonstrate a survival benefit of ischaemic CMP patients with proven myocardial viability after revascularisation may also be related in part to suboptimal imaging protocols and techniques used to determine the presence or absence of hibernating myocardium. In the STICH trial [22], apart from low-dose dobutamine echocardiography, myocardial viability was assessed predominantly with ^{99m}technetium- (^{99m}Tc-) labelled radiotracers or ^{201}Tl-SPECT. Four different SPECT protocols for determining myocardial viability were applied. These included ^{201}Tl imaging using rest-redistribution or stress-rest-reinjection protocols [40], rest-redistribution ^{201}Tl im-

aging as part of a dual isotope protocol with a ^{99m}Tc perfusion tracer [41], or imaging with a ^{99m}Tc tracer at rest after the administration of nitroglycerin [42]. On the basis of regional radiotracer uptake of ^{99m}Tc or ^{201}Tl on SPECT images, viability was signified in those patients demonstrating at least 11 (of 17) viable myocardial segments. A 50% threshold of radiotracer uptake was used to differentiate viable from nonviable myocardial segments. In addition, the extent of viable myocardium was prespecified with ≥11 viable myocardial segments in order to classify patients in a "binary" fashion as either having or not having a substantial amount of myocardial viability [22]. Such a criterion to define patients with a sufficient amount of myocardial viability, however, has not been fully explored in clinical investigations. In addition, the power of SPECT using thresholds of relative radiotracer uptake or viable myocardium in the prediction of recovery of dysfunctional myocardial segments may not be high [43, 44], in particular when the extent and severity of myocardial ischaemia is unknown [10, 18]. Overall, for the STICH trial [22], it is not reported how many patients were evaluated with echocardiography and how many with SPECT imaging. It is also unclear which specific SPECT methodology was used in how many patients. This then complicates an analysis of the limitations in the assessment of myocardial viability. Further, assessing only resting myocardial perfusion with SPECT is not evaluating the presence of ischaemic, compromised but viable myocardium, but rather provides information on the extent of scar tissue, as there is an inverse relationship between resting myocardial blood flow and the percent scar tissue [43, 44]. As such, the approach is similar to that with late gadolinium-enhanced cardiac magnetic resonance imaging [45]. Accordingly, in the STICH trial [22] we do not know in how many of the 11 segments perfusion was entirely normal and in how many it was reduced. As it was not specified whether the 11 or more myocardial segments required for defining viability were counted only among those segments demonstrating contractile dysfunction in the sense of akinesia and/or dyskinesia, or segments with evidence of normal or contractile dysfunction of any degree (hypokinesia, akinesia and dyskinesia), it remains unknown in how many segments a wall motion abnormality was present.

Nuclear cardiac imaging with ^{99m}Tc or ^{201}Tl and SPECT are routinely used for the detection and characterisation of stress-induced myocardial ischaemia and necrosis. This may result in several scenarios such as (a) normal stress-rest perfusion, (b) stress-induced ischaemia without scarring, (c) nontransmural scarring with stress-induced peri-infarction ischaemia, and (d) a "fixed" stress-rest perfusion defect, which may suggest transmural scarring, nontransmural scarring with viable but ischaemic, compromised myocardium, or, in rare instances, no scar but resting ischaemia that does not aggravate during stress testing. The latter scenario may be observed in 20%–40% of ischaemic CMP patients with LVEF <30% [14]. Here the conventional ^{99m}Tc or ^{201}Tl and SPECT approach is limited and FDG-PET is necessary in order to differentiate clearly between the three different conditions in ischaemic CMP [7, 15–19]. Use of ^{99m}Tc or ^{201}Tl and SPECT to identify myocardial viability in dysfunctional myocardial segments is, therefore, suboptimal in ischaemic CMP. For example, same-day rest/stress ^{99m}Tc-sestamibi SPECT imaging will incorrectly identify 36% of myocardial regions as being irreversibly impaired and nonviable when compared with both ^{201}Tl redistribution/reinjection and FDG-PET as the reference standard [46]. A ^{201}Tl stress-rest and reinjection protocol with SPECT was also compared with FDG-PET imaging for the identification of viable myocardium [47]. In 16 patients with angiographically proven chronic multivessel CAD and left ventricular dysfunction (LVEF: 27% ± 9%; range 16%–47%), a ^{201}Tl stress-rest and reinjection protocol with SPECT was compared with FDG-PET [47]. Most irreversible defects with only mild or moderate reduction in ^{201}Tl activity reflected viable myocardium as confirmed by FDG uptake. In myocardial regions with severe irreversible ^{201}Tl defects on standard exercise-redistribution ^{201}Tl imaging, ^{201}Tl reinjection identified segments as viable or nonviable quite similarly to FDG-PET.

Conversely, FDG-PET seems to outperform ^{201}Tl-SPECT in the detection of viable myocardium when ^{201}Tl stress image acquisition is followed by redistribution imaging after 4 and 24 hours without a reinjection protocol [48]. For example, Brunken et al. [48] found, in twenty-six CAD patients with impaired left ventricular function (LVEF: 32% ± 13%) and perfusion defects on 24-hour ^{201}Tl-SPECT images, a potential diagnostic value of FDG-PET in viability detection. In 100 fixed, 17 partially reversible and 12 completely reversible defects on ^{201}TI- SPECT images, PET identified tissue metabolic activity in 51 (51%) segments with fixed defects (21 PET ischaemia, 30 PET normal) and 9 (53%) segments with partially reversible defects (5 PET ischaemia, 4 PET normal). When the relative number of segments with fixed ^{201}Tl defects and metabolic viability on FDG-PET were displayed as a function of the 24-hour ^{201}Tl score, the relative number of segments with metabolic viability declined with increasing severity of ^{201}Tl defect or increase in defect score. Conversely, even for defects with severe reductions in 24-hour ^{201}Tl score (2.61–3.00), there was an approximately one in seven chance that FDG-PET imaging would still identify some viable myocardium. In these ischaemic CMP patients, however, FDG-PET detected viable myocardium in the majority of fixed 24-hour ^{201}Tl defects, although very severe 24-hour ^{201}Tl defects were associated with a relatively low likelihood of demonstrating viable myocardium on FDG-PET images. Similar observations

were reported by Akinboboye et al. [49], in which significant metabolic activity by PET was found in 51% of fixed and severe defects on ^{201}Tl-SPECT with various protocols. Thus, ^{201}Tl-SPECT may underestimate myocardial viability relative to FDG-PET in patients with severely reduced left ventricular dysfunction, when only 4 and 24 hours redistribution ^{201}Tl images without ^{201}Tl reinjection protocol are evaluated [48–51].

The exact cause of this underestimation of myocardial viability with ^{201}Tl-SPECT on 4- or 24-hour redistribution images in ischaemic CMP patients remains unknown. Potential explanations include impaired sarcolemma function, attenuation of low-energy photons of ^{201}Tl in dilated ventricles, and severe hypoperfusion limiting ^{201}Tl delivery. From these investigations, it appears advisable to include FDG-PET [47–50] or a ^{201}Tl-SPECT with reinjection protocol [37, 46, 52, 53] in the clinical evaluation of ischaemic CMP patients with persistent ^{201}Tl defects on redistribution images in whom coronary revascularisation is a viable option.

Application in clinical practice

In clinical practice, cardiac FDG-PET, or nowadays PET/CT, should be applied in CMP patients with a LVEF ≤30%, who present a stress-rest fixed perfusion defect of ≥4 and akinetic segments of the left ventricle as determined with SPECT or PET / computed tomography (CT) perfusion imaging. In this scenario, adding FDG-PET/CT may unmask following four conditions that can be divided into two groups (see fig. 1):

"Match" findings between perfusion and viability assessment, indicative of

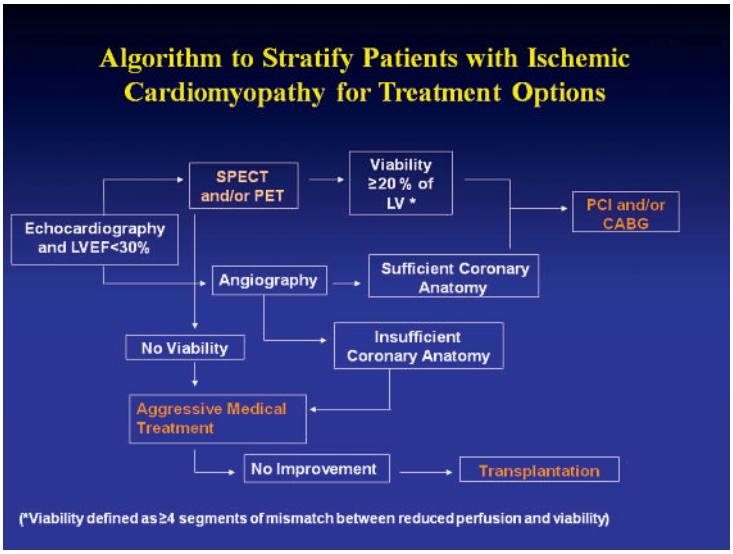
a) transmural necrosis,
b) nontransmural necrosis and no ischaemic component.

"Mismatch" findings, denoting

c) nontransmural necrosis with viable but ischaemic, compromised myocardium,
d) completely viable and ischaemic, compromised myocardium.

In about 20%–40% of these patients [14, 19], FDG-PET/CT is likely to detect a sufficient amount of viable myocardium, unmasking viable but ischemic-compromised myocardium (c and d). This so-called stunned-hibernating myocardium, if large enough (≥4 segments), principally may benefit, in terms of recovery of left-ventricular function and clinical outcome, from restoration of myocardial flow or perfusion [14]. If such patients present also suitable coronary anatomy and clinical condition, they are commonly referred for coronary revascularisation (fig. 3). Conversely, in the absence of stunned-hibernating myocardium, the patient will undergo optimal medical heart failure treatment. If over time, however, a further worsening of left-ventricular function despite optimal medical heart failure treatment ensues, heart transplantation may be considered.

Figure 3
Diagnostic and decision-making process in patients with ischaemic cardiomyopathy. CABG = coronary artery by-pass grafting; LV = left ventricle; LVEF = left ventricular ejection fraction; PCI = percutaneous coronay intervention; PET = positron emission tomography; SPECT = single-photon emission computed tomography



Role of echocardiograpy and magnetic resonance imaging in viability assessment

Echocardiography and magnetic resonancce imaging (MRI) identify hibernating myocardium by stimulating the contractile reserve (mono- or bi-phasic) in response to low-dose inotropic agents. Both imaging modalities with stimulation of inotropic response are well established in clinical routine with sensitivities and specifities for predicting improvement in segmental left-ventricular function of 80% and 74% and of 78% and 82%, respectively [14] (table 2). For more in depth-information on multimodality imaging in the assessment of myocardial viability in heart failure patients we refer to a recently published excellent review article [14].

Most centres using cardiac MRI for viability assessment, however, apply late gadolinium enhancement imaging with MRI (LGE-MRI) in order to visualise in the infarcted area, and the extent of myocardial viability is estimated by denoting the non-LGE myocardial area. The high spatial resolution of cardiac magnetic resonance (CMR) imaging (often as good as 1.5 mm in-plane resolution) provides the reader with the ability to determine the transmural thickness of the scar. The extent of myocardial scarring in the left ventricular wall is commonly expressed as 1%–25%, 26%–50%, 51%–75% and 76%–100%. In a pioneer investigation, Kim et al. [45] assessed the ability of transmural scarring to predict recovery following coronary revascularisation. It was observed that, of akinetic and dyskinetic segments with no evidence of scar, 100% had recovery of function. Similar segments with 1%–25% transmural scar showed 82% recovery of func-

Table 2
Pooled analysis of different modalities of viability assessment for predicting improvement in segmental left-ventricular function.

Imaging modality	Mean sensitivity (%)	Mean specificity (%)	NPV (%)	PPV (%)
Dobutamine echocardiography	80	78	83	75
^{201}Tl-SPECT	87	54	79	67
^{99m}Tc-SPECT	83	65	76	74
FDG-PET	92	63	87	74
MRI diastolic wall <6 mm	95	41	92	56
Dobutamine MRI	74	82	78	78
LGE-MRI	84	63	78	72

^{201}Tl = thallium-201; ^{99m}Tc = technetium-99m; FDG = fluorine-18-labeled fluorodeoxyglucose; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single-photon emission computed tomography. Reproduced with permission from Schinkel et al. [13]

tion, segments with 26%–50% transmural scar had a 45% recovery, segments with 51%–75% transmural scar had 7% recovery, and similar segments with 76%–100% scar had 0% recovery.

The diagnostic accuracy of LGE-MRI in myocardial regions with 1%–75% transmural scar may, however, be partly limited [54]. In 29 ischaemic CMP patients and with a dual protocol of low-dose dobutamine testing and LGE-MRI, the evaluation of the contractile reserve response with MRI was superior to LGE-MRI in the prediction of functional recovery after coronary revascularization for a range of transmural scar of 1%–74% on LGE-MRI. Adding dobutamine MRI to LGE-MRI enhances the specificity of MRI in the prediction of myocardial viability in akinetic or dyskinetic segments from 62% to 82% [14]. The lower sensitivity of LGE-MRI may be related to gadolinium accumulation not only in the necrotic area but also in surrounding myocardial oedema in particular in patients with acute myocardial infarction. Such oedema may last between 4 weeks and 6 months, as recent investigations suggest [55]. Conversely, T2-weighted MRI images may clearly identify peri-infarctional oedema, affording an optimal characterisation of the extent of the myocardial necrosis by subtraction of T2 (oedema) from T1 (necrosis) weighted LGE-MRI images [55]. Although this diagnostic approach of LGE-MRI combining T1- and T2-weighted images may emerge as most accurate in delineation of the extent of myocardial necrosis, it needs further validation studies.

When conventional cardiac LGE-MRI is compared with FDG-PET/CT, both techniques are highly concordant and reliable for diagnosis and prediction of functional recovery of viable but dysfunctional myocardial segments in ischemic CMP patients. There are only a few head-to-head investigations between these two imaging modalities [56–58]. Overall, it appears that FDG-PET/CT is more sensitive, in particular in the intermediate range, for the detection of myocardial viability, whereas LGE-MRI can be regarded as more specific in the prediction of recovery of segmental left ventricular function following coronary revascularisation. More recently, delayed contrast CT has also been suggested for myocardial viability assessment. This diagnostic approach may be useful for identifying myocardial scar tissue, but currently it does not appear to be accurate enough for clinical application when compared with FDG-PET imaging [59].

Conclusions

The results of the PARR-2 [24] and STICH [22] trials raise the awareness that in the clinical decision-making process for the revascularisation of ischaemic CMP patients, not only the presence of viable myocardium but also several clinical determinants, such as a timely revascularisation of ischaemic, jeopardised but viable myocardium, effects of advanced stages of myocardial remodelling, and the extent of left ventricular dilation need to be taken into account. It is expected that future studies in this field will search for more refined diagnostic and clinical criteria in order to identify those ischaemic CMP patients who are likely to benefit most, both symptomatically and prognostically, from coronary revascularisation.

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