Noninvasive assessment myocardial viability: Current status and future directions

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Observations of reversibility of cardiac contractile dysfunction in patients with coronary artery disease and ischemia were first made more than 40 years ago. Since that time a wealth of basic science and clinical data has been gathered exploring the mechanisms of this phenomenon of myocardial viability and relevance to clinical care of patients. Advances in cardiac imaging techniques have contributed greatly to knowledge in the area, first with thallium-201 imaging, then later with Tc-99m-based tracers for SPECT imaging and metabolic tracers used in conjunction with positron emission tomography (PET), most commonly F-18 FDG in conjunction with blood flow imaging with N-13 ammonia or Rb-82 Cl. In parallel, stress echocardiography has made great progress also. Over time observational studies in patients using these techniques accumulated and were later summarized in several meta-analyses. More recently, cardiac magnetic resonance imaging (CMR) has contributed further information in combination with either late gadolinium enhancement imaging or dobutamine stress. This review discusses the tracer and CMR imaging techniques, the pooled observational data, the results of clinical trials, and ongoing investigation in the field. It also examines some of the current challenges and issues for researchers and explores the emerging potential of combined PET/CMR imaging for myocardial viability.

Key Words: Myocardial viability • SPECT • PET • CMR • STICH • PARR-2 • meta-analysis

BACKGROUND

Left ventricular (LV) function is a powerful determinant of survival in patients with coronary artery disease (CAD).[1,2] The once previously held notion that LV dysfunction in patients with CAD is always due to irreversible myocardial fibrosis resulting from prior infarction has now been discounted for over 4 decades.

For the purposes of the current discussion the term myocardial viability is defined to identify myocardium with potentially reversible contractile dysfunction in patients with chronic CAD. Such reversibility may be seen with revascularization or other forms of therapy and lead to improvement in patient outcomes. This review will summarize some of the existing knowledge in the area of myocardial viability and will mainly discuss aspects of radionuclide (PET and SPECT) and cardiac magnetic resonance (CMR) imaging.

Echocardiography has also been clearly shown to have widespread utility for viability assessment, most commonly in combination with dobutamine stress for assessment of regional wall motion changes. There are many other echo parameters which can reflect viability also, including wall thickness, mitral deceleration time, and strain rate. Cardiovascular computed tomography (CCT) can show late contrast enhancement of the myocardium similar to that seen on CMR and may have an expanded role in the future to assess viability but has not yet reached such widespread use as that of the other modalities. Echo and CCT techniques lie beyond the scope of the current review and will not be discussed in detail below except where echo studies are included in the pooled study analyses presented.

Early Clinical Observations of Changes in LV Function Post Revascularization

In 1970, Saltiel et al[3] reported on ''reversibility of left ventricular dysfunction after aortocoronary bypass grafts.'' In 1972, Chatterjee et al reported on ''depression

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Funding: None.
Received for publication May 20, 2013; final revision accepted May 22, 2013.
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J Nucl Cardiol 2013;20:618–37.
1071-3581/$34.00

doi:10.1007/s12350-013-9737-8

of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous vein bypass''[4] and the following year on the effects of revascularization on LV function in patients *with* vs *without* prior infarction.[5] Forty years later, we are still studying potentially reversible LV dysfunction in patients with CAD and seeking to improve our understanding: of the best diagnostic approaches, of which patients may benefit most from diagnostic tests, and of which treatments may be most useful. Although much progress has been made there is still much more to be learnt.

Pathophysiologic Studies

Based on experimental and clinical studies, the concepts of myocardial stunning[6-10] and hibernation[11-13] were developed and studied. Stunning refers to temporary depression of cardiac contraction following a bout of ischemia. When repetitive, or chronic, this leads to myocardial hibernation. This term suggests an adaptive down regulation of muscle contraction in response to chronic reduction in tissue blood flow. Both of these concepts have had usefulness and also limitations when applied to the practice of clinical cardiology to date. However, these groundbreaking observations have stimulated a huge body of work in basic and clinical research.

Histopathologic Studies

Myocardium compromised by ischemic insult has been well characterized pathologically. Such examination of ischemic, dysfunctional myocardium reveals a number of distinct features, including progressive loss of myocyte bundles, increasing collagen and disorganized muscle fascicular structure, also fibrosis, increased glycogen storage, mitochondrial changes, reduction in connexin 43, vacuolization, and a reversion to fetal myoglobin.[14]

Swine Model of Myocardial Hibernation: Imaging Correlates

In recent years, a swine modal of hibernating myocardium has been successfully developed and studied using PET imaging of blood flow, metabolism, and sympathetic neuronal function. Elegant physiologic and pathologic correlative studies have confirmed many of the features previously observed in patients including flow/metabolism mismatch and abnormal sympathetic innervation. Such neuronal dysfunction has also been shown in humans.[15] This represents one potential mechanism for adverse events in patients with viable myocardium. These swine have also been shown to experience sudden cardiac death preceded by a rise in LVEDP. This model continues to add to our understanding of myocardial viability in humans.[16-20] It has also led to an ongoing human study for prediction of events (PAREPET).[21] A preliminary report from this study shows that extent of denervated myocardium on C-11 hydroxyephedrine PET in patients with heart failure predicts subsequent ventricular tachycardia/fibrillation.[22]

USE OF THE TERM: MYOCARDIAL VIABILITY

Beyond pathophysiologic and histopathologic definitions, clinicians over time have adopted the simpler term ''myocardial viability.'' This relies more on clinical phenomenology and as such refers to living but ischemically compromised dysfunctional myocardium in patients with chronic CAD. This is potentially salvageable with appropriate treatment and functional improvement can occur using revascularization, drugs, devices, or a combination thereof. Measures of benefit can include patient survival, improved symptoms, or test parameters, which include cardiac function measurements.

IMAGING TECHNIQUES EMPLOYED FOR VIABILITY ASSESSMENT

A myriad of diagnostic techniques have been used for identification and assessment of viable myocardium. Most of the methods currently used involve cardiac imaging, including SPECT and PET radionuclide imaging, CMR, echocardiography, and (emerging) cardiac computed tomography. There are also some non-imaging methods such as catheter-based electroanatomic mapping, an invasive technique which has been used in conjunction with intramyocardial delivery of treatments such as stem cells.

The use of myocardial viability imaging tests in an appropriate clinical setting has previously been given a class IIa recommendation in the American College of Cardiology/American Heart Association practice guidelines.[23,24] Viability testing was also recommended in 2010 for patients with CAD and severe LV dysfunction in the European guidelines based on the existing evidence at the time of publication.[25] How results of recent trials may affect future guidelines remains to be seen. Nonetheless, a recent conjoint appropriate use document (2013 ACCF/ACR/ASE/ASNC/SCCT/SCMR) has recommended the use of CMR and PET for investigation of viability in patients with severe LV dysfunction, while at the same time indicating possibility for the use of stress imaging with SPECT or echocardiography.[26]

SPECT

SPECT tracers include thallium-201 and the Tc-99m-based tracers, with Tc-99m sestamibi being the most

widely used of these. Thallium retention in myocardium reflects the intracellular potassium pool and is dependent on the integrity of the Na/K pump in the cell membrane. Tc-99m sestamibi binds to the mitochondrion and reflects its integrity as a marker of viability. There exist a proliferation of protocols and diagnostic criteria for these tracers in regards to viability assessment. This complexity means there is no single standardization of criteria, which can be a source of confusion to clinicians and frustration to investigators including those wishing to perform collaborative studies or pooled analyses. These diagnostic criteria may be based on relative resting tracer uptake, uptake after nitrate administration, late redistribution or improvement after rest reinjection (for thallium), or defect reversibility between stress and rest. SPECT has low spatial resolution and cannot assess transmurality of tracer distribution. On the other hand it is widely available. There are a multitude of published SPECT viability studies.

PET

Whilst there are a number of tracers which can be used with PET for viability assessment, F-18 FDG has become the one almost universally employed for clinical purposes. The seminal report on the diagnostic utility of FDG PET for viability assessment in humans was published by the UCLA group in 1986.[27] PET has higher spatial resolution than SPECT though still insufficient for adequate assessment of tracer distribution across the myocardial wall. The most commonly employed technique is to perform resting blood flow imaging with either N-13 ammonia or Rb-82 Cl and compare this with metabolic imaging of myocardial glucose uptake with F-18 FDG. Less commonly, the FDG study may be performed in isolation without a blood flow study, with >50% relative uptake taken to indicate viability. This technique optimally requires use of a metabolic clamping procedure to standardize regional glucose utilization.

This technique is based on the observation that viable myocardium preferentially switches from the usual free fatty acids to glucose as the preferred energy substrate. FDG uptake into the myocardium is dependent on the insulin-sensitive glucose transporters. These can be activated by either oral glucose loading or administration of insulin (together with some glucose to avoid hypoglycemia) prior to tracer administration.

FDG is effectively fixed in the myocardium through phosphorylation by hexokinase, with minimal reverse transport. It clears from the blood such that images of the myocardium can be acquired from 45-minute post injection onward.

Myocardial segments are assessed with PET as showing: (1) normal flow/metabolism (viable), (2) mild matched reduction in flow/metabolism (subendocardial scar), (3) severe matched defect, (transmural scar), or (4) mismatch (apparent reduction in resting flow but preserved glucose utilization) (Figure 1). All except pattern 3 indicate a degree of retained viability in the myocardium. The presence of mismatch can predict functional recovery after revascularization even when contractile reserve appears exhausted on functional testing.[28]

In regards to ability of FDG PET to predict improvement in LV function, positive predictive value in one study was 86%, negative predictive value was 100% and accuracy was 90%.[29]

Earlier vs later revascularization following identification of viable myocardium by FDG imaging has been shown to be more beneficial for patient outcome.[30,31]

The extent of viability in the LV needed to predict improvement in mortality after revascularization on FDG imaging varies in different studies between 7% of the LV,[32] 10%[33], and 20%.[34] However, this extent should be seen rather as a continuum, where increasing extent implies both increased risk and increased potential for recovery.[34,35]

Some issues with PET imaging are: it is less widely available than SPECT. Second, myocardial extraction of FDG can be reduced in diabetic patients, as glucose entry into the myocardium is dependent on the insulin-sensitive glucose transporters. This is apparent particularly in some type I diabetics, where additional late imaging after insulin administration may be necessary to obtain diagnostic images.

FDG imaging has also been performed using SPECT acquisition but this has not been widely adopted due to the increasing availability of PET tomographs with their higher resolution.

The expanding potential for both SPECT and PET imaging not only in identification of myocardial viability but also in increasing our understanding of its nature in both basic science and clinical correlates has been recently reviewed.[36]

Prognostic Risk of Radiation Exposure from Tracer Studies in Patients Undergoing Viability Testing

The potential theoretical hazard of exposure to ionizing radiation from tracer studies vs other test modalities in medical diagnosis is a frequently raised issue. It is worth considering that existing data suggest long lead times for the development of such possible radiation-related events in the order of decades.[37] In the cohort of patients with depressed LV function undergoing viability testing the 2-year cardiac survival rate can be very low, i.e., only a few years.[38] Even with optimal

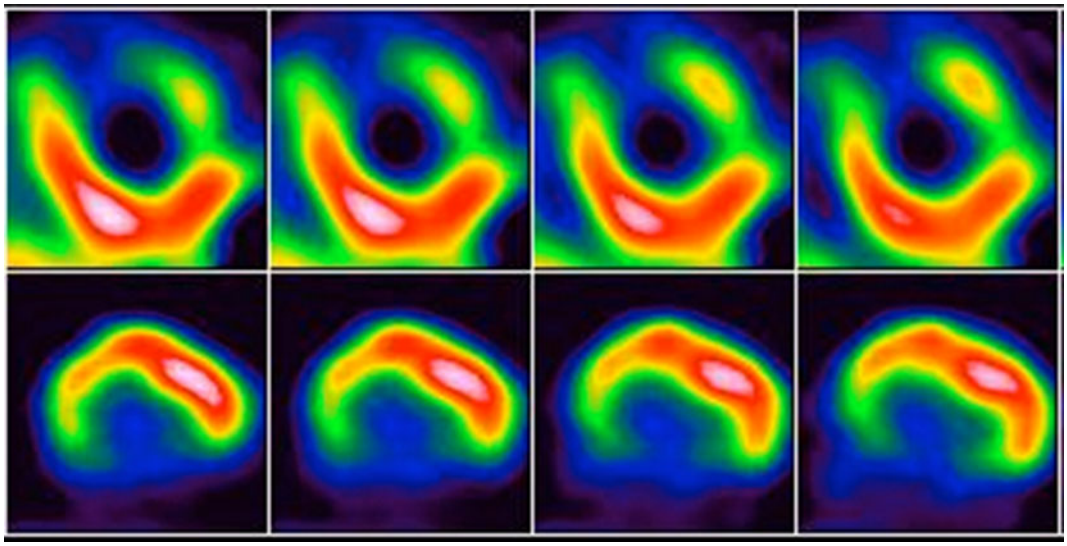

Figure 1. Midventricular short axis images of resting blood flow (*upper panel*) and FDG uptake on PET (*lower panel*) in a patient with recent LAD occlusion and LV dysfunction treated initially in a remote center with thrombolysis. Note extensive reduction in resting blood flow in the anterior wall with enhanced FDG uptake (flow/metabolism mismatch pattern). Patient had improvement in LV function following midCAB procedure *(images provided by the author)*.

cardiac therapy such patients are highly unlikely to live long enough to experience such adverse events linked to diagnostic medical radiation. Thus, the issue of ionizing radiation exposure for them is different than it is for young, healthy people with normal cardiac function undergoing ischemia testing, who would be expecting normal longevity and are likely to have normal imaging results anyway.

CMR Imaging

CMR imaging entered the diagnostic mainstream for viability imaging over a decade ago but remains the newest of the established contenders in the field. Thus, it does not yet enjoy quite the same accrual of published studies of diagnostic performance as for the older modalities. Nonetheless, given its high spatial resolution, ability to define extent of transmurality of scar, assess regional wall motion, ejection fraction, and LV volumes, these data are very rapidly accumulating. Potential drawbacks with CMR can include administration of gadolinium-based contrast agents to patients with renal impairment, and second, suitability for patients with implanted devices given issues such as potential rhythm disturbance, device motion, or lead ''heating.''

Methods for assessing viability using CMR. There are a number of well-established ways to use CMR for viability assessment including late gadolinium enhancement (LGE) to define transmurality and extent of scar, dobutamine stress CMR for stress-induced changes in regional wall motion, and LV wall thickness assessment from resting studies. These have been recently summarized.[39]

LGE CMR. The utility of CMR with LGE in humans was first reported by Kim et al[40] and has since become a standard viability imaging technique, now widely adopted. The phenomenon was initially termed delayed contrast enhancement (DCE) and this term is still current. The finding had first been validated in animal models.[41,42] After injection, gadolinium leaks into the interstitial space of non-viable, previously infarcted muscle and remains there for a time. Accumulation of gadolinium defines scar thickness. All tissue which does not enhance with gadolinium is then considered ''viable.'' Whether this tissue is capable of subsequent functional improvement is, however, a different matter (see below). Transmurality of greater than 50% enhancement is generally taken as indicative of nonviability, although a range of likelihoods of function recovery can be predicted based on the actual partial thickness of the myocardial wall which enhances (between 25% and 75%). Others have also reported on the clinical utility of CMR with LGE for viability testing.[43-46] This includes not only in regards to subsequent revascularization but also response to beta adrenergic receptor blockade in patients treated medically.[47]

The importance of late enhancement (LGE) as an indicator of viability vs that of early enhancement (EGE) as an indicator of myocardial salvage after acute infarction has also been recently shown.[48]

Dobutamine stress CMR. Dobutamine CMR is in one way analogous to a high resolution stress echo, where changes in regional wall motion/thickening with increasing doses of dobutamine can be correlated with viability status. This technique was established for viability assessment prior to the identification of LGE.[49]

Other CMR findings. CMR can also detect microvascular obstruction after acute myocardial infarction and this finding has prognostic significance.[50] The presence of small myocardial infarctions without clinical manifestation but demonstrable by CMR has also been shown to be important.[51,52]

Resting end-diastolic wall thickness is another CMR index of myocardial viability.[53] As wall thickness decreases, so too does likelihood of functional recovery.

LGE vs FDG PET imaging. CMR LGE does not differentiate the subepicardial non-enhancing region as normal vs hibernating myocardium as does FDG imaging.[54] The former would not be expected to change in contraction after intervention, whereas the latter should indeed thus manifest improvement. Flow/FDG PET in the latter situation would be expected to show the typical mismatch pattern. Patterson et al[55] has commented on the study of Kim et al[40] stating that there is a 36% rate of indeterminacy due to exactly this issue with LGE CMR alone, viz: the characterization of the non-enhancing myocardium in patients with transmurality between 25% and 75%. Roes et al[54] commented that only 53% of segments with subendocardial scar with 1%-50% transmurality in the study of Kim et al[40] showed functional recovery. The addition of dobutamine stress CMR has been advocated in patients with 25%-75% transmurality to improve diagnostic performance[56] and is mentioned further below.

OBSERVATIONAL STUDIES EMPLOYING VIABILITY IMAGING IN PATIENTS

The rationale for viability testing and many of the existing studies have been previously summarized.[38] As noted, viability testing has a strong foundation in both basic science and observational clinical studies which has been progressively developed over 4 decades. Existing observational studies of patients with imaging have pointed toward the identification of viable myocardium as a target for prognostic revascularization and other therapies in patients with ischemic LV dysfunction. Admittedly, such studies were frequently small, from single centers, without clear documentation of medical therapy, or comorbidities such as diabetes or renal disease. Many of them also predated the availability of PET and CMR, the advent of current medical and device therapies for heart failure and were performed in the days before current lower risk interventional options arose.

Furthermore, definitions of viability varied widely from study to study and duration of patient follow-up and definitions of positive patient outcome were at times far from standardized. Statistical methods employed for data analysis also varied. The severity of LV dysfunction ranged substantially and in some reports the patients had ejection fractions sometimes close to normal.

Nonetheless, from these studies data emerged concerning improvements following revascularization in regards to: regional tracer uptake, wall motion, LV ejection fraction and volumes, as well as the clinical indicators of symptoms, functional status, frequency of readmission to hospital with heart failure or reinfarction, and most importantly, patient mortality.

While the consensus appears to be that improvement in ejection fraction is necessary for improved survival this has not necessarily always been shown to be so. In a study by Samady et al in 1999[57], it was reported that survival benefit with revascularization did not necessarily depend on a change in EF. Hence, some of the other already mentioned contributing factors may have been operating. Unfortunately, this study did not include viability imaging, which would have contributed further knowledge.

Meta-analyses of Observational Studies Employing Tracer and Echocardiographic Imaging Tests

Over time sufficient data had amassed for several groups to perform meta-analysis of pooled data of such studies. Meta-analyses may pool either observational studies (retrospective or prospective) or trials data. Meta-analyses are generally considered as hypothesis generating when they summarize observational studies rather than trials.

In 1997, Bax et al[58] summarized, in an important study, the relative sensitivities and specificities of the then existing techniques for viability assessment (Figure 2). They pooled 37 studies published between 1980 and 1997, which utilized imaging for prediction of improvement in regional contractile function after revascularization.[27,59-94] The initial report included thallium-201 and Tc-99m sestamibi imaging, FDG imaging, and low dose dobutamine echo. All methods had high sensitivity but specificity was highest for LDDE and lowest for thallium-201 with the remaining techniques having intermediate specificity. Other literature also reports higher specificity for echo usually

concomitant with lower sensitivity than for tracer techniques. This may suggest the tracer and echo techniques operate at different points on a receiver operating characteristic curve but some observers have noted the potential issue may be that echo uses LV function as the diagnostic test endpoint as well as the study outcome endpoint in many clinical studies.[38]

This report was later updated first in 2001 with the addition of further studies and again in 2007 including CMR data supporting the original findings and extending them.[95,96]

In 2002, Allman et al[97] published a meta-analysis of 24 viability studies in 3,088 patients using SPECT with either thallium-201 or Tc-99m-based tracers, FDG imaging, and stress echocardiography.[98-121] This analysis showed a 79% reduction in mortality for patients with evidence of myocardial viability on SPECT, FDG PET, or echo, who received revascularization vs those who did not. It also suggested a small increase in mortality for patients without viability subjected to CABG but this was non-significant (Figure 3). Although significant differences in diagnostic performance of the three tests were not demonstrated, the confidence limits in the data were very large, reflecting at least in part the heterogeneity in the studies included and differences in viability definition criteria. This does not mean there is no difference between the tests but simply that none could be demonstrated for the reasons given. These data do not show that newer technology tests (PET, CMR) will perform no better than older tests (SPECT and echo). There were no CMR data in this meta-analysis in any case.

In an editorial accompanying publication of this meta-analysis, Bonow[122] pointed out that one in three meta-analyses have findings which are not subsequently

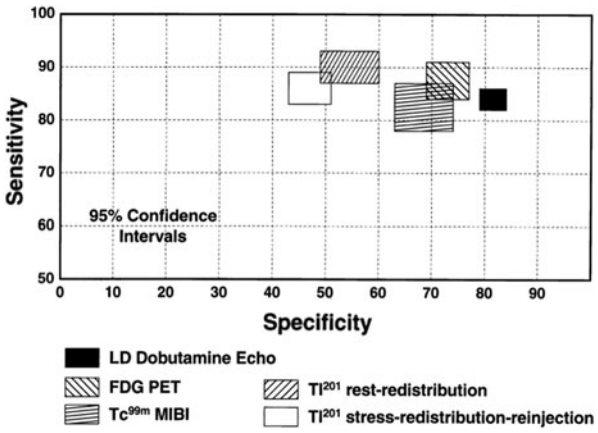

Figure 2. Receiver operating characteristic plot showing 95% confidence intervals for each test showing higher sensitivity for tracer studies but higher specificity for dobutamine echo *(reproduced from[58] with permission).*

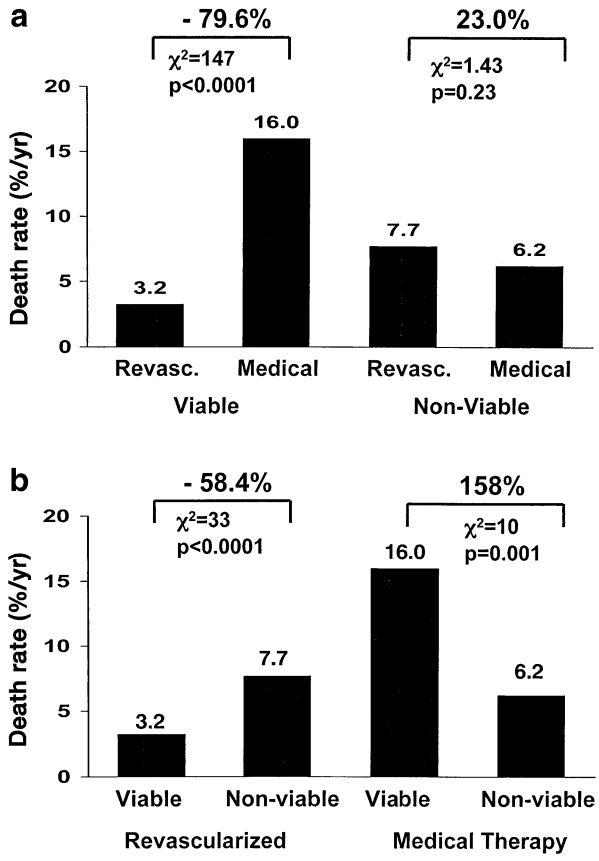

Figure 3. Mortality for patients treated by revascularization vs medical therapy with and without viability. (**A**) Grouped by viability status, (**B**) by treatment. There is a 79% reduction in mortality for patients with viability, who were revascularized vs received medicine. Patients without viability showed intermediate rate of death, slightly higher with revascularization (*reproduced from* [97] *with permission).*

confirmed by later prospective trials. This may be due to weaknesses in either the meta-analysis or the trials. He also correctly observed that medical therapy received was not reported in the study patients. This was something which would be firmly applied and documented in later studies including STICH (see below). Furthermore, it was noted that viability was assessed in a binary or dichotomous distribution, a deficiency which affects much of the literature in the area up to the present day including all the reported trials. It is likely that shades of gray will yield better insights than black and white.[123]

After this series of meta-analyses, several other groups subsequently published further pooled analyses of these and other studies [124,125] also suggesting benefit of revascularization of viable myocardium.

After publication of the 1997 and 2002 meta-analyses some physicians may have been sufficiently convinced by their conclusions that the issue of utility of

diagnostic imaging in guiding therapeutic options in patients with/without viability on testing was settled in favor of incorporating such testing into routine clinical practice. Conversely, there may have been equanimity amongst other clinicians, with many treating patients with aggressive medical and device therapies for heart failure and not using viability imaging for a variety of reasons including: non-availability, lack of prospective trials, or other reasons of personal clinical preference.

Outcomes Studies in Patients with CMR and LGE

There are a number of studies reporting that LGE CMR predicts outcomes in patients.[51,126-129]

Gerber et al[46] recently reported on 144 patients with mean EF 24% and ischemic cardiomyopathy, who underwent DCE CMR followed for three years. Seventy nine patients underwent CABG, 7 had PCI, and 58 patients received medical therapy alone. There were 49 deaths (34%). Patients with viability treated medically had 52% mortality, while those who were revascularized had 12% mortality. Patients without viability had intermediate rates of death: 23% for those treated medically increasing to 29% for those with revascularization. Using propensity score-matched patients (43 pairs) hazard for death (ratio 2.5, $P = .02$) remained significantly higher for patients with viability treated medically vs by revascularization. This is also one of very few studies to report on the completeness of revascularization. This pattern of findings is similar to those of a previous meta-analysis, where patients *with* myocardial viability treated medically had the worst prognosis but if treated by revascularization, the best prognosis, with those *without* viability having intermediate rates of mortality regardless of treatment option.[97]

Meta-analysis of Prospective Studies Using CMR

In a recent report in 2012, Romero et al[130] examined the pooled reported diagnostic accuracy of CMR for viability assessment from 24 studies including 698 patients using criteria of end-diastolic wall thickness (4 studies), response to low dose dobutamine stress (9 studies), or DCE (11 studies). The analysis used a bivariate random effects model. These authors report LGE CMR to have highest sensitivity (95%) and NPV (90%) for predicting improved regional wall motion post revascularization, followed by end-diastolic wall thickness. Dobutamine CMR had highest specificity (91%) and PPV (93%). The overall weighted diagnostic accuracy was 70%. Only changes in regional wall motion were reported, with no information on patient status, symptoms, ejection fraction improvement, or clinical events. There were only a few studies of EDWT and there was a borderline publication bias for the dobutamine studies. The authors conclude that the best diagnostic result from CMR testing may be a combination of LGE and dobutamine studies. Such an approach has been advocated by others also.[53,131,132]

CLINICAL TRIALS

Given the growing observational literature in the 1990s there was a need for prospective trials designed to determine whether the conclusions being drawn from the existing literature could be confirmed or refuted when subjected to a more rigorous approach. There were a number of related issues outstanding. Why did revascularization appear to improve outcome? Did it relate to improved LV function, less reinfarction, reduction or reversal in LV remodeling, and/or mitral regurgitation? Was the myocardium more electrically stable and less prone to lethal disturbance of cardiac rhythm? Would revascularization by either CABG or PCI have an additive benefit after optimal medical therapy (OMT) was first used in all patients? Any one study was never going to be able to answer all these questions but the overriding concern was whether or not revascularization of viable myocardium as an additive treatment led to improved patient survival.

These more recent prospective clinical studies have struggled to confirm the earlier findings, at the same time illustrating potential confounding factors in an ever changing diagnostic, clinical, and therapeutic environment. However, they have not succeeded in definitively refuting the utility of viability testing either. Recent trial findings have also spurred substantial reflection on the potential limitations in the existing observational data.

These recent trials also illustrate some of the difficulties in performing and analyzing trials of diagnostic tests when the tests themselves are the target of study (rather than the *treatment* being the target, as in most clinical trials in cardiology).

The Christmas Trial

The acronymously named The Carvedilol Hibernation Reversible Ischemia Trial: Marker of Success (Christmas Trial)[133] is noteworthy because it demonstrated in a randomized clinical trial using cardiac imaging that viable myocardium could be effectively treated medically, in this case with carvedilol, a beta adrenergic receptor blocker with vasodilatory action. This double blind trial randomized 387 patients with chronic CAD and depressed LV function (EF 29%) to either placebo or carvedilol treatment with patients split

into either ''hibernators'' or ''non-hibernators'' based on results of nitrate-enhanced Tc-99m sestamibi scan uptake using pre-specified criteria. Only 19% of patients had angina, 58% showed hibernation, and 54% ischemia on SPECT. The endpoint was LV ejection fraction at 6 months. 305 (79%) patients completed the study which was analyzed by intention to treat. Patients receiving carvedilol all had an improvement in EF, while those on placebo did not ($P<.0001$). The treatment effect was greater in patients showing more extensive vs less extensive hibernation ($P = .0002$).

Historically, from this point onward it was no longer possible to dichotomize patients enrolled in viability outcome studies as receiving simply revascularization vs medical management. A paradigm of optimal medical management (OMT) vs OMT plus revascularization had emerged. In retrospect, it may have at least been possible that some of the apparent benefits of revascularization in earlier observational studies were at least in part contributed to deficits in the quality of medical therapy compared with current best practice.

The Canadian Positron Emission Tomography and Recovery Following Revascularization (PARR) Studies

Two studies utilizing FDG PET have been performed in Canada, PARR-1[30] and PARR-2.[32,35] A post hoc OTTAWA-FIVE analysis of PARR-2 has also been published.[134]

PARR-1 was set up to develop a model for prediction of recovery of LV function post revascularization for use in a subsequent randomized trial. It employed FDG PET in 82 patients with EF $< 35\%$. The investigators found that scar extent score on the FDG study, time spent awaiting revascularization and the presence of diabetes to be independent predictors of an improvement in EF. Multivariate analysis showed extent of scar to be a significant independent predictor of improved EF at 3 months.

PARR-2 demonstrates the difficulty for both trialists and clinicians encountered when a trial protocol requires management based on viability testing results. PARR-2 was a randomized study performed to examine the utility of FDG PET in guiding management in patients with severe LV dysfunction in regards to revascularization benefit. After stratification by recent coronary angiography vs no recent angiography 218 patients were allocated to FDG PET assisted management and 212 to standard care, which could include another viability test but not PET. It does not appear that the PET studies were read at a central core laboratory. A composite end point at 1 year was measured, involving cardiac death, MI, or hospital readmission for heart disease. 30% patients in the PET arm had an event vs 36% in the standard care arm. The difference was not statistically significant. However, a number of important points were demonstrated:

A significant number of patients (25%) were not managed according to the trial protocol. That is, they did not undergo the revascularization directed by PET results. These patients had less extensive viability than those where protocol adherence occurred. This suggests clinicians were sensitive to extent of demonstrated viability and when it was less extensive they were less inclined to revascularize, perhaps because other patient factors were considered more important (the previous PARR-1 study had also shown the importance of extent of non-viable vs non-viable tissue in terms of LV function outcome at 3 months). The authors also noted that the finding of viability on PET led to angiography being performed in a substantial number of patients where this had not occurred close to the time of trial entry.

By post hoc analysis a significant reduction in adverse outcomes was observed in patients where there was adherence to the PET recommendations for revascularization (Figure 4). This analysis illustrates the difficulties of trying to study sick patients when the clinician's treatment is directed by the results of an imaging study.

In a first sub-study of the PARR-2 data[35], the investigators observed a relationship between extent of hibernating myocardium defined on PET and benefit with revascularization. In this analysis, if more than 7% of the LV showed hibernation there was benefit from revascularization in terms of subsequent events and this increased with increasing extent of hibernating myocardium (Figure 5). In addition, renal impairment emerged as a significant independent prognostic indicator and this is demonstrated in other studies also.[135,136]

The PARR-2 authors performed a further post hoc analysis entitled the Ottawa-Five sub-study of PARR-2.[134] Here, the authors studied outcomes of 111 patients in PARR-2, who were treated at a large integrated facility with ready access to PET and experienced readers and cardiologists, surgeons, and others who worked in a close knit team compared with the remaining patients treated in other centers. Some of these centers mostly performed PET for non-cardiac studies (oncology) and did not have the same level of expertise and integration in evaluating and treating patients with myocardial viability and LV dysfunction as the larger facility.

The analysis showed significantly better outcomes in patients managed at the more experienced center: 19% composite event occurrence with PET-directed management vs 41% for those with standard care

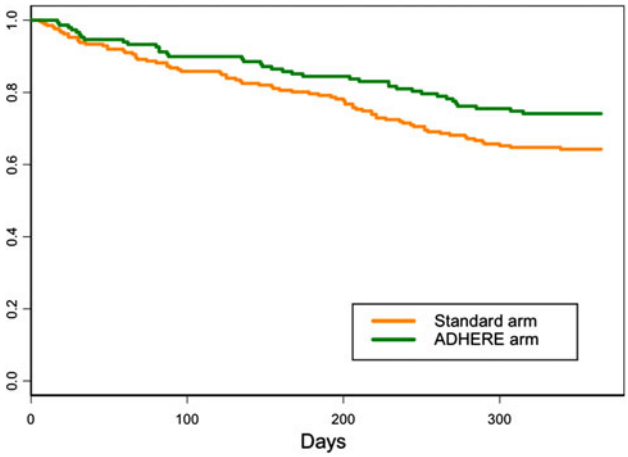

Figure 4. Patients treated by adherence to the PET protocol (ADHERE arm) showed better survival in the PARR-2 trial than those in the standard arm ($P = .019$) *(reproduced from* [32] *with permission.*

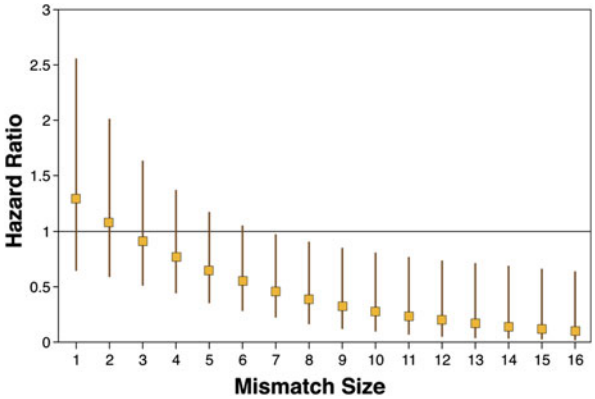

Figure 5. As extent of FDG PET mismatch increases above 7% of the LV there is increasing survival benefit from revascularization in the PARR-2 study patients by post hoc analysis *(reproduced from* [35] *with permission).*

($P = .005$), despite these patients being older and with lower EF than those at the other centers. In patients at the other centers, there was no difference in event rate between PET-directed and standard management (Figure 6). This finding suggests the importance of experience and integration across the spectrum of investigation, test interpretation, and treatment implementation in these sick patients. It is quite important to note, however, that most of the patient events here were readmissions (22 patients) with only 6 deaths and 4 myocardial infarctions, i.e., a small number of hard events.

The Canadian group has documented, by the high non-adherence rate to PET-directed management, that whilst such a trial protocol appeals to imaging specialists in terms of seeking the answers they desire in terms of diagnostic utility of their tests, that this may not be an approach which can be successfully executed: it involves very sick patients where other clinical factors come into decision making. These can include physician clinical judgment, patient willingness, comorbidities, and competition from other heart failure trials involving new drugs and devices recruiting from the same population of patients.

The Heart Failure Revascularization Trial (HEART)

The UK HEART trial[137,138] illustrates the problem of lower than anticipated patient enrollment. This investigator-initiated study was funded by the Medical Research Council of the United Kingdom. Conducted at 13 centers, this was an unblinded trial planned for 800 patients with EF $< 35\%$ and evidence of substantial viability on any standard imaging test. They would be randomized to conservative management or angiography with a view to revascularization. The trial funding was withdrawn due to low recruitment with only 79 patients enrolled in the first year (The STICH trial was also under way by then). Enrollment continued without funding until 138 patients were randomized before final study termination in 2004. Follow-up of these patients showed no difference in outcomes for the two groups but this was inconclusive as the requirements for statistical significance were not met. Subsequent to closure physicians were asked to direct candidates to the STICH trial.

The STICH Trial

The Surgical Treatment of IsChemic Heart Failure trial was an investigator-initiated NHLBI-funded trial

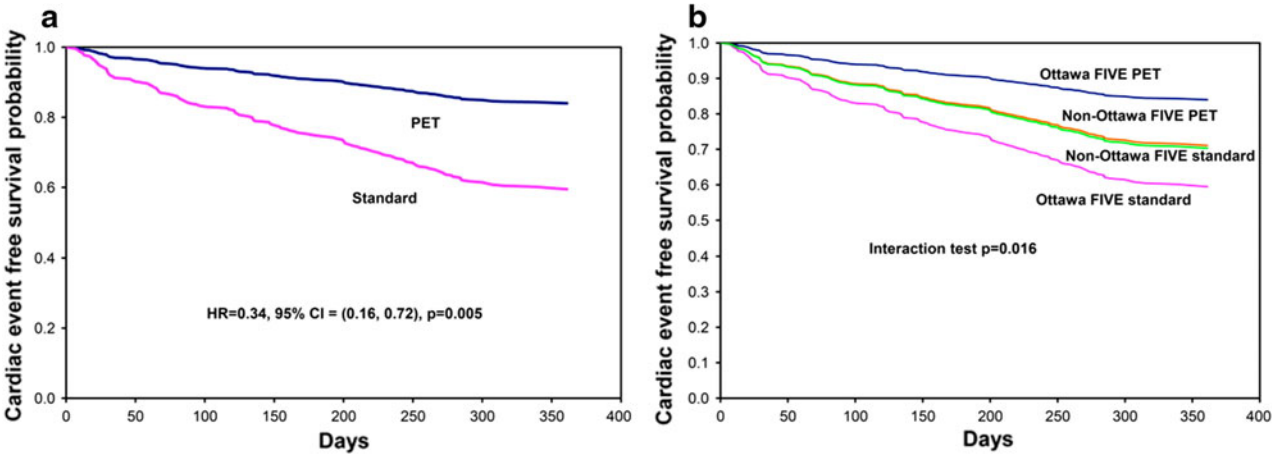

Figure 6. **A** In the Ottawa-5 sub-study of PARR-2 patients in the PET arm fared better than those in the standard care arm ($P = .005$, **B**). Patients treated in an experienced center fared better in the PET vs standard arm but this difference was not seen in less experienced centers (*right panel*) *(reproduced from* [134] *with permission).*

(NCT00023595, https://www.stichtrial.org).[139] To date, there have been 12 publications from this study group.[140-151]

The main STICH (hypothesis 1) investigators examined outcomes in 1,212 CAD patients amenable to CABG with EF $\leq$ 35% (by CMR, SPECT, or ventriculography) randomized to either OMT or OMT plus CABG.[146] With 50 recruiting centers initially planned, this increased to 127, spread across 26 countries to enable completed enrollment between July 2002 and May 2007. Sites averaged 2 recruitments per annum and details of screened but not randomized patients are unknown.

There were also multiple sub studies related to surgical ventricular reconstruction (SVR), mitral regurgitation, myocardial viability imaging, and stress-induced ischemia.

The STICH (hypothesis 1) investigators found no significant difference in all cause death between the two treatment groups at 56 months median follow-up using intention to treat analysis. 11% of the OMT group went on the CABG during follow-up. However, with a ''treatment received'' analysis a difference in favor of CABG was seen. In a subgroup of 490 patients allocated to SVR in addition to CABG there was no benefit for the patients who had postoperative ESVI greater than 70 mL/m^2.[141] These and other findings have generated much controversy and discussion.

Viability sub-study. Within STICH there is a sub-study concerning myocardial viability testing.[145] Originally, it was foreseen that *all* 1,212 patients enrolled in STICH would have viability testing and statistical power calculations were projected accordingly. This aspiration did not eventuate and many patients were not imaged for viability. STICH has been described by the authors as ''the first prospective randomized trial testing the hypothesis that CABG improves survival in patients with ischemic LV dysfunction compared to the outcome with aggressive medical therapy.'' This is true for the greater STICH trial (hypothesis 1) but scrutiny shows that in regards to the viability sub-study there was *no* randomization in regards to viability testing and results of such testing did not mandate/direct subsequent treatment. Viability testing was *optional* and just under half the patients underwent either SPECT or stress echo assessment for this purpose: Of the 1,212 STICH trial patients only 601 underwent viability imaging.

The results of the viability sub-study show 37% of patients with viable myocardium died vs 51% of those without viability ($P = .003$) (Figure 7A). However, after baseline variables adjustment this was no longer significant. Furthermore, there was no demonstrable relationship among viability information, treatment allocation, and patient outcome ($P = .53$) (Figure 7B).

In short, this sub-study failed to show an association between myocardial viability on imaging and additional benefit from revascularization. Again, the study was underpowered for this analysis.

There has been a substantial body of commentary on the STICH viability sub-study findings and on the authors' interpretations.[152-162] A range of issues have been identified: there were significant differences in regards to symptoms, medications, LV function and volumes, race, prior MI and PCI, and pattern of CAD in enrolled patients with vs without viability. There was more CABG performed on those who had viability testing performed at the time of enrollment vs

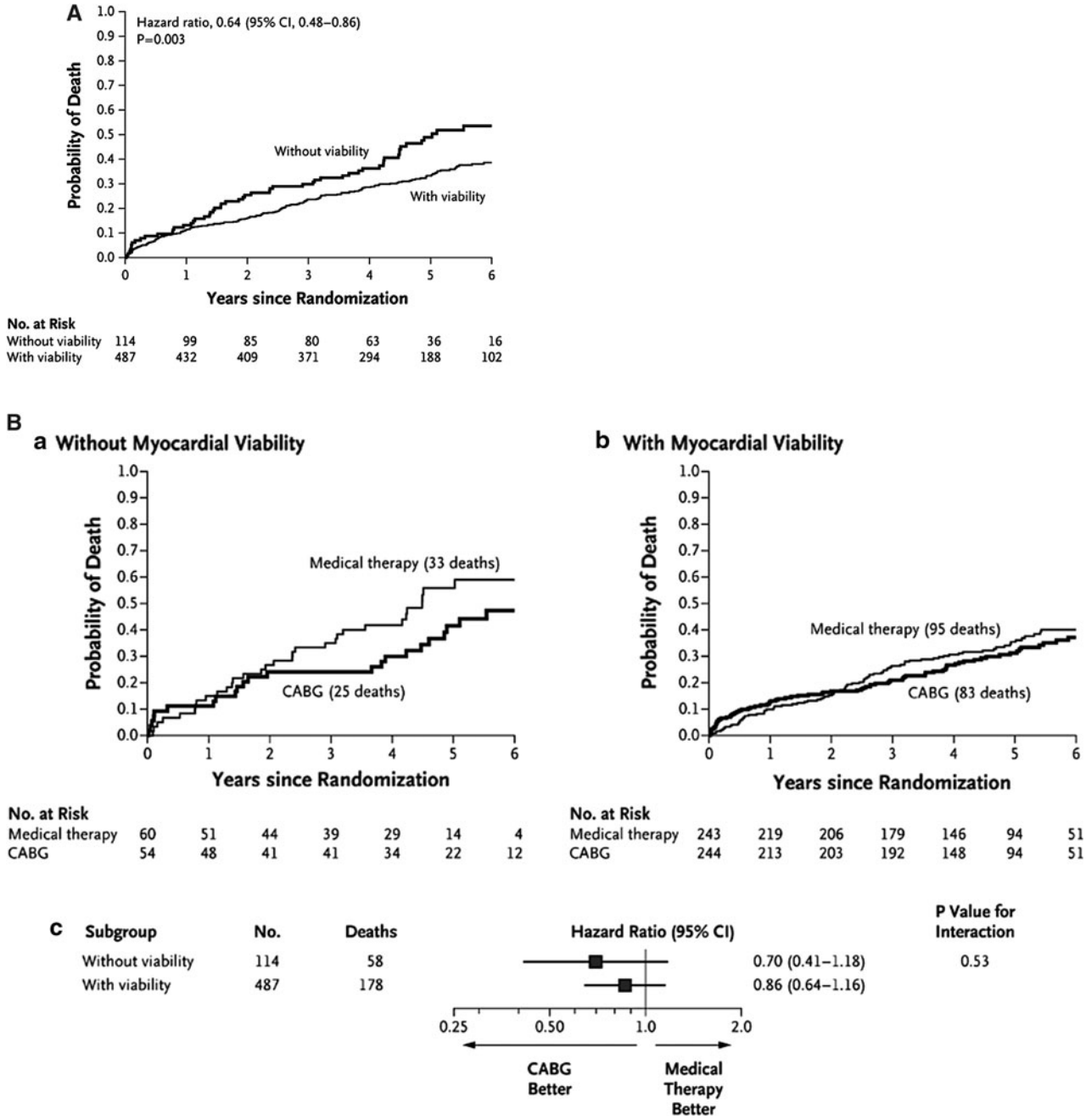

Figure 7. A In the STICH trial viability sub-study, the unadjusted probability of death was greater for patients without myocardial viability ($P = .003$). Kaplan-Meier plot shown *(reproduced from* [145] *with permission).* **B** In the STICH trial viability sub-study at 5 years by intention to treat analysis there was no demonstrable difference in mortality in regards to viability presence/absence or treatment choice of revascularization with OMT vs OMT alone. *a* Results for patients *without* myocardial viability, *b* for those *with* viability, and *c* interaction between viability status and treatment assignment (n.s.). Not all the STICH patients underwent viability testing (*reproduced from* [145] *with permission).*

beforehand (non-significant). Viability was analyzed as a dichotomous variable in STICH although some of the authors previously and correctly identified this as an important limitation in the literature.[122] Most of the imaging studies were performed with SPECT. There were multiple SPECT protocols used at the 217 sites. Some would call this ''real world'' testing but such an approach may be less rigorous than might be hoped for

in an optimally designed prospective clinical trial. The extent of LV viability for SPECT and echo tests considered significant were quite different and the justification for this was based at least partly on existing retrospective data even though the authors note that the resulting criteria were applied prospectively in the trial. Furthermore, the relationship between SPECT tracer uptake and regional wall motion in individual segments was not reported. Information on changes in EF and LV volumes may have also proven useful in interpreting the trial results but were not reported. In regards to those patients undergoing stress echo: the presence of a ''biphasic response'' with increasing dobutamine dose was not used as a criterion indicating viability, which would be usual clinical practice.

Perhaps most importantly of all, the number of patients *without* demonstrated viability in STICH is very small (19% without vs 81% with viability) so there appears to be a basic imbalance in the patient recruitment. This reflects one problem with testing being optional and not mandated at randomization. Other studies have also had unbalanced recruitment favoring patients with viability present. Furthermore, in STICH relatively ''old'' imaging tests were used, with no information collected in regards to PET or CMR imaging.

Finally, it is unclear in the patients receiving revascularization whether only viable tissue or also scar was grafted. Revascularization of scar tissue may not lead to any benefit.

Reversible ischemia sub-study. More recently, the STICH investigators have published on the presence of reversible ischemia demonstrated on stress imaging and patient outcomes.[151] Reversible ischemia is one indicator of viable myocardium. Again, contrary to existing notions, the authors reported that the presence of ischemia identified: (1) neither patients with worse subsequent outcome nor (2) patients who were more likely to benefit from CABG. Gibbons et al[163] have recently reviewed the existing literature in this area and criticized this STICH sub-study report citing: lack of statistical power, high rate of ICDs in the study population (22%), differences in baseline variables, and the apparent anomalies in differing criteria for ischemia between SPECT and echo, similar to those for viability cited above.

A further follow-up of the STICH Patients (STICH ES, Extended Study) is currently being performed. It will be of interest to learn whether longer follow-up can confirm or refute the non-significant trend to diverging outcomes in the patients initially reported in 2011.

The final conclusion from the STICH viability and ischemia sub studies must be that they are both inconclusive. The viability study does not show benefit for CABG but there is the distinct possibility of a type II error in the analysis.

MORE RECENT CLINICAL STUDIES

BARI 2D: Myocardial Perfusion SPECT Findings at 1- and 5-Year Mortality

In a recent report on the BARI 2D study, the investigators examined scintigraphically determined findings in 1,505 patients at 12-month post randomization viz. extent of scar and ischemia on SPECT together with level of LV function in diabetic patients with CAD randomized to revascularization or medical therapy. Patients were followed for 5 years for endpoint of death. They found that the reduction of ischemia by revascularization and extent of scar as defined on SPECT at 1 year to be powerful predictors of patient outcome.[164]

PET: Hibernating (Viable) Myocardium vs Inducible Ischemia and Scar

A recent prospective observational study reported on 648 patients (65 years mean age, 77% male), with CAD and LV dysfunction (mean EF 31%), who underwent stress/rest Rb-82 and F-18 FDG PET imaging with automated analysis and were followed up for 2.8 years.[33] (patients undergoing early revascularization within 92 days of PET were excluded from analysis to avoid ''waiting-time'' bias).

Using a Cox proportional hazards model which included a propensity score to take into account the non-randomized nature of treatment, they observed 165 (27.5%) patient deaths. Hibernating (viable) myocardium (flow/metabolism mismatch), ischemia (reversible Rb-82 defect), and scar (fixed Rb-82 defect) were all associated with all cause mortality: ($P = .0015$, $P = .0038$, and $P = .0010$). There was an interaction between significant hibernating myocardium >10% LV extent and revascularization which conferred survival benefit. The authors concluded that hibernating myocardium identifies patients with LV dysfunction, who derive survival benefit from revascularization.

SOME FACTORS IN PERFORMING CLINICAL TRIALS WITH MYOCARDIAL VIABILITY TESTING

Recruitment

Recruiting high risk patients with LV dysfunction into clinical studies is challenging. Patients may not which to take part and clinicians can be reluctant to follow study pathways especially when they feel patients are deteriorating or not improving on a particular treatment path. This was evident in the PARR 2 study as outlined above in the subsequent OTTAWA 5 report.[134] It is also possible that some clinicians, based

on their past practice, clinical observations and results of observational studies and the existing meta-analyses may still not be keen to enter patients into trials.

Changing Treatment Options and Compliance with Medical Treatment

In earlier studies, medical treatments for LV dysfunction were not aggressive and used older medicines. Drugs such as ACE inhibitors, ARB blockers, statins, and beta adrenergic receptor blockers with vasodilatory actions were not in routine use in all patients. In many of the older studies, manuscripts contained little information about details of therapy and adherence to same. Hence, the current approach of best medical therapy vs best medical therapy plus revascularization was not employed.

Second, implantable defibrillators and resynchronization devices were not available as treatment options at the time of earlier observational studies.

Kidney Function

The presence of renal impairment has already been mentioned as an adverse prognostic factor in patients undergoing revascularization for viable myocardium with LV dysfunction.[35,135,136] It is unclear how the combination of renal disease and viable myocardium should be weighed when making management decisions. It remains to be determined how much remaining renal function and what extent of myocardial viability are required for a beneficial outcome in a given patient.

Mitral Regurgitation

The presence of mitral regurgitation is another factor to take into account in decision making. In patients with ischemic mitral regurgitation undergoing CABG, the presence of viability is a good predictor of beneficial outcome.[165,166]

LV Volume

Progression of LV remodeling adversely affects outcome in patients with LV dysfunction. Once the left ventricle is too dilated the ability for functional improvement is lost and there may be no value in revascularization on prognostic grounds.[167]

Severity of LV Dysfunction

The severity of LV dysfunction was identified in itself as a powerful marker of patient prognosis at the beginning of this review.[1] However, published viability studies do not usually stratify patients according to severity of LV dysfunction at entry. Even the PARR-2 and STICH trials report on the mean ejection fraction of the patients. One of the previously published meta-analyses suggests increasing survival benefit of revascularization with decreasing LV ejection fraction.[168] Given this observation together with the natural history data[1] it may prove fruitful to ask whether viability testing is potentially more beneficial in those patients with lower vs higher ejection fractions. It is possible that there may be a range of ejection fractions over which testing is most useful. This could mean that not all patients across the spectrum of LV dysfunction would need viability testing as part of their diagnostic work up but this is currently somewhat unclear.

Changing Disease Patterns

Clinicians are today seeing older and sicker patients than in the 1980s when observational studies were starting to accrue. This is largely due to advances in medical therapies for chronic diseases reflected in improved longevity. The patients have more of the mentioned comorbidities, in particular diabetes and renal disease, both of which contribute substantially to mortality within the follow-up period after myocardial viability assessment.

Adequacy of Revascularization in Relation to Viable Tissue Segments

The completeness of revascularization is also not usually reported in terms of perfusion study improvement for example. A call for a ''personalized'' approach to viability assessment has recently been made by Iskandrian and Hage.[169] These authors advocate an individual patient approach to correlating imaging test findings with coronary angiography to (a) determine if there is sufficiently extensive viable myocardium which is supplied by vessels in which stenosis can be adequately relieved by revascularization and (b) to determine a preoperative ''road map'' of which viable myocardial segments to target for prognostic revascularization. This appears to be a sound suggestion based on the findings and conclusions from the OTTAWA-5 study.[134]

Cardiac Sympathetic Neuronal Dysfunction in Patients with CAD

Myocardial sympathetic innervation has been shown to be abnormal in viable myocardium.[15,170] This represents one potential cause for cardiac death in such subjects. The PAREPET trial[21] has shown (in a

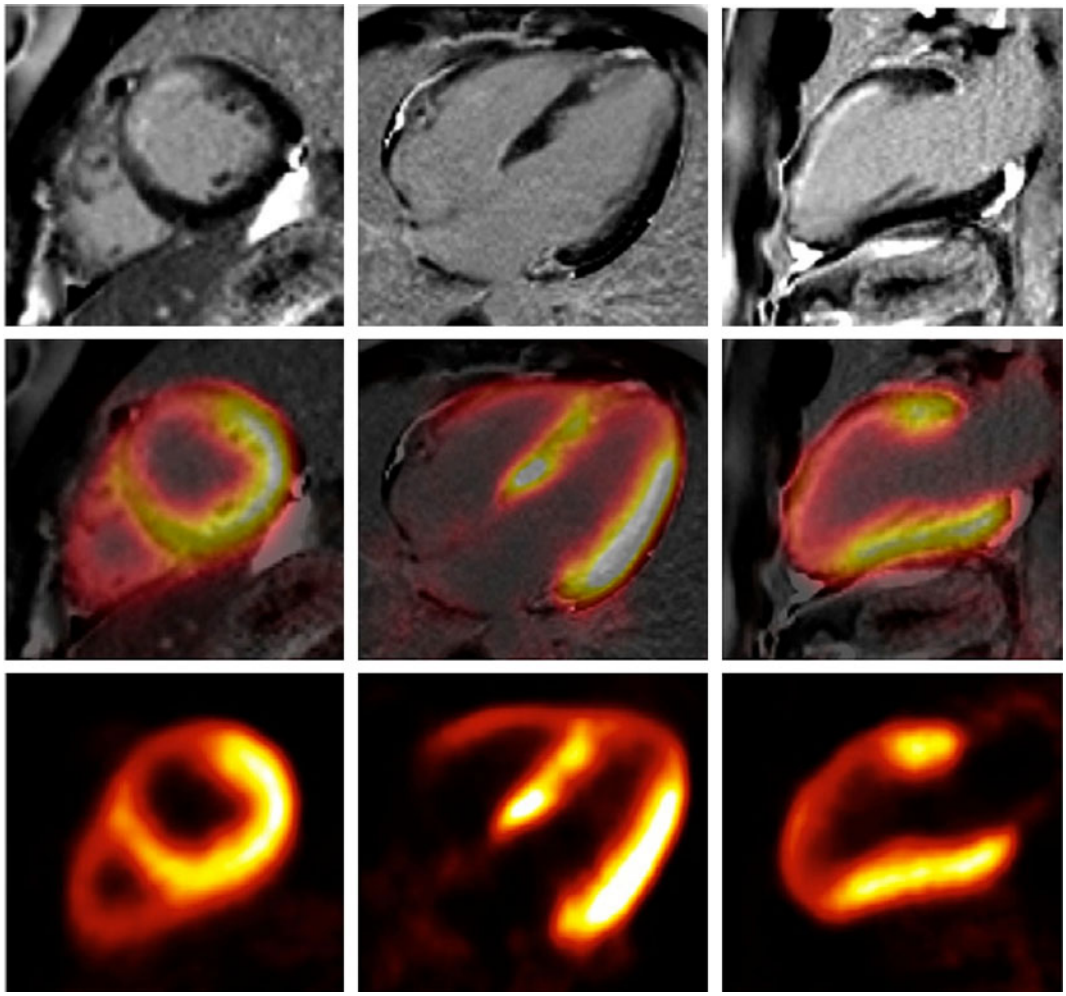

Figure 8. Cardiac PET/CMR: patient with prior myocardial infarction. LGE CMR images (*top panel*), FDG PET images (*bottom panel*), and co-registered images (*center*). CMR shows subendocardial anterior wall and apical enhancement. This corresponds with reduced metabolic uptake at these sites on FDG PET *(reproduced from* [175] *with permission)*.

preliminary report) that extent of denervation determined by C-11 hydroxyephedrine PET is an independent predictor of cardiac arrest in patients with CAD and heart failure.[22] Further studies in this area are required.

ARE TRIAL DESIGNS ORIGINALLY UTILIZED FOR EVALUATING TREATMENTS USEFUL FOR EVALUATING PERFORMANCE OF DIAGNOSTIC TESTS?

As mentioned above, randomized controlled trials are mostly used to assess the effects of treatments including medications, interventions, devices, and surgery. The use of the treatment may be compared against placebo, a differing dose of the same medication, or an alternate treatment. Primary and secondary endpoints are predefined and some may be specified post hoc. Patients may complete the trial protocol, reach a specified endpoint, voluntarily withdraw, die, or be withdrawn due to an adverse event or new medical problem.

On the other hand, the situation with diagnostic testing is different. The test results may mandate a treatment strategy (PARR-2) or not (STICH) but are not in themselves a treatment. One alternative approach is the use of prospective data registries, of which at least one is currently recruiting: Ontario Cardiac PET Registry (CADRE) (MOHLTC Grant # 06374).[171]

WHAT NEXT?

PET vs CMR or PET Plus CMR?

Previous reviews have at times debated the pros and cons of PET vs CMR imaging.[55,172] Others have called

for a combined approach.[123,173] There may be a role for combined PET/CMR studies in patients with intermediate values of transmurality, whilst CMR defines the transmurality of scar, the PET study can characterize the state of the non-scarred subepicardium and help refine the likelihood of functional recovery in cases without too much thickness of scar.[43,174] It is possible that by combining the high sensitivity of PET with the high specificity of LGE CMR that a superior diagnosis may result in intermediate cases.

The emergence of hybrid PET/MR tomographs recently has enhanced the capability to perform such combined imaging studies (Figure 8). This subject has been recently reviewed by Rischpler et al.[175] These authors note the potential strengths as well as technical challenges inherent in the design and application of this dual approach to cardiac imaging. CMR offers greater soft tissue contrast than that obtainable with PET/CT but does not readily provide the attenuation correction map obtainable from CT or radionuclide sources and this is a real challenge. Issues for cardiac patients related to contrast and magnetic field have already been mentioned above.

IMAGE HF Study

This is a collaborative Canadian/Finnish funded study (NCT01288560)[176] which is currently recruiting. It aims to study patients with ischemic heart disease and heart failure studied by PET/CT, CMR, and CCT imaging compared with conventional SPECT imaging in regards to a composite endpoint as used in the PARR-2 trial.

CONCLUSION

A vast amount of basic science, diagnostic testing expertise, and clinical information in relation to myocardial viability has been accumulated over more than 40 years now. Much has been learned and some controversies, apparent contradictions and challenges have been raised. It appears likely that improvements in basic sciences knowledge, imaging techniques, new therapies, and results from further well-designed, well-executed, and well-analyzed clinical studies will increase our understanding of how to investigate and appropriately treat individual patients with chronic CAD and potentially reversible contractile dysfunction.

Conflict of interest

The author has indicated that he has no financial conflict of interest.

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