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Is it Still Important to Evaluate Patients with Ischemic Cardiomyopathy for Viable Dysfunctional Myocardium Prior to Myocardial Revascularization?

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In this issue of Trends in Cardiovascular Medicine, Kalra and colleagues¹ provide a state of the art summary of the contemporary approaches available to evaluate myocardial viability and address the increasingly controversial question as to whether it is still clinically relevant in the management of patients with ischemic cardiomyopathy. The historical view and answer to this question would be a resounding yes! The presence of viable dysfunctional myocardium in patients with severely depressed left ventricular function has been used to identify a subgroup of patients that had left ventricular dysfunction on the basis of chronic repetitive ischemia who were previously felt to have irreversible scar². A variety of imaging modalities were advanced to show that at least partial recovery of regional and global function could be predicted prior to coronary bypass surgery³. The presence of hibernating myocardium vs. scar was always reassuring to our surgical colleagues when asked to operate on these high-risk patients as it predicted at least partial recovery of left ventricular function. Furthermore, in nonrandomized studies, coronary revascularization based upon the presence of viable dysfunctional myocardium was associated with improved survival vs. medical therapy and, in some patients, improvement of heart failure symptoms⁴. Not unlike many things in medicine, our clinical description of this state preceded our understanding of the complexity of its underlying pathophysiological basis that could reflect non-transmural scar, remodeled remote myocardium, chronically stunned myocardium and hibernating myocardium. The latter was particularly important to distinguish from scar since in both circumstances resting flow was reduced.

While our clinical insight into viable dysfunctional myocardium preceded our ability to study it at a basic level, we subsequently developed preclinical animal models to reproduce chronic coronary stenoses with critically impaired coronary flow reserve that recapitulated this in the absence of dysfunction from healed infarction. A variety of studies demonstrated that viable dysfunctional myocardium could arise from chronic stunning where resting flow

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was normal⁵. When reductions in flow reserve were severe, this could progress to hibernating myocardium where regional myocardial flow, function and metabolism were reduced. The intrinsic adaptations allowed myocytes subjected to repetitive ischemia to survive at the expense of contractile dysfunction⁶. Even when myocardial scar was absent, the progression to hibernating myocardium was associated with regional myocyte loss and compensatory myocyte cellular hypertrophy⁷. These cellular changes limited the extent of functional recovery after coronary revascularization even in the absence of infarction⁸. In addition, when the heart was not revascularized or treated with contemporary medical therapy (including beta blockers, angiotensin inhibition and aldosterone antagonists), the preclinical studies identified a high mortality rate which arose from sudden cardiac death from ventricular fibrillation in the absence of heart failure or myocardial infarction⁹. This was like the high mortality rate of patients with viable dysfunctional myocardium that was not revascularized⁴.

Despite our clinical experience and expert opinion about the role of viability testing in practice guidelines, clinical studies completed over the last ten years have seriously challenged the importance of assessing myocardial viability prior to revascularization of patients with ischemic heart failure. As outlined by Kalra and colleagues, the results of the STICH trial (Surgical Treatment for Ischemic Heart Failure)¹⁰ and its recently reported ~10-year follow-up STICHES (STICH Extension Study)¹¹, have now led to considerable uncertainty as to the role of viability testing in the management of patients with ischemic cardiomyopathy. This trial randomized patients with an EF 35% on optimal medical therapy for ischemic cardiomyopathy to CABG plus medical therapy vs. medical therapy alone without consideration of the amount or presence of viable dysfunctional myocardium. Patients allocated to CABG demonstrated no significant reduction in all-cause mortality at completion of the original study (36% with CABG vs. 41% with medical therapy alone, $p=0.12$) but this became significant on long-term follow up after approximately 10-years (58.9% with CABG vs 66.1% with medical therapy alone, $p=0.02$). Secondary end-points of cardiovascular mortality and a post-hoc as treated analysis showed a favorable survival benefit of CABG that persisted on late follow-up (cardiovascular mortality 40.5% with CABG vs 49.3% with medical therapy alone, $p=.006$). Viability testing was not required at entry but performed in approximately half of the patients using multiple imaging modalities¹². The results were quantified in a less common fashion as the total amount of viable myocardium. They did not differentiate whether the viable segments were dysfunctional nor whether they were subtended by significant coronary stenoses. While these results were not utilized in the treatment allocation or clinical decision making, they were discordant with the prevailing clinical use of viability testing in practice. Not surprisingly, patients with more viability (less scar and/or hibernating myocardium) had a better survival than those with less viability. Nevertheless, viability assessed in this fashion had no impact on predicting the outcome of patients managed with CABG vs medical therapy alone.

The mechanism through which CABG might confer a survival advantage to patients with heart failure irrespective of viability remains speculative but posthoc analyses of STICH have shed some interesting insight. A sub analysis evaluating cause specific cardiac mortality demonstrated that sudden death was the most frequent mode of death and

outnumbered pump failure deaths by approximately two-fold¹³. Both were significantly reduced after CABG (as was death from myocardial infarction). Predictors of increased risk of SCD were increased LV end-systolic volume and an elevated BNP. Interestingly, these same variables along with regional myocardial sympathetic denervation, were found to be risk factors that predicted SCA in patients with ischemic cardiomyopathy in the Prediction of Arrhythmic Events with Positron Emission Tomography Study (PAREPET)^{14,15}. Thus, the survival benefit of CABG was largely due to the profound effect of coronary revascularization on reducing arrhythmic death with smaller contributions from reducing deaths from pump failure and fatal myocardial infarction. Of importance, these results were found in conjunction with an extremely low utilization of primary prevention ICDs (~20% of the STICH enrollees). While speculative, it is likely that broader implementation of primary prevention ICDs in this population could have improved survival in both groups and may have diminished the impact of revascularization on cardiac mortality.

With the data from STICHES demonstrating a significant benefit of “prophylactic” surgical revascularization on long-term survival, the role of preoperative viability testing (as well as preoperative evaluation for reversible ischemia) is now less clear. In contrast to our original tenet, the survival benefit of CABG seems to increase as the extent of nonviable myocardium increases and is to a large extent related to reducing SCD. This is the exact opposite of our established treatment paradigm. Patients with large amounts of scar and without viable dysfunctional myocardium are less likely to undergo revascularization since it would not be associated with reversal of contractile dysfunction and improvement in symptoms of heart failure. In fact, therapeutic bias arising from this approach could have amplified the perceived difference in survival benefit between those allocated to medicine (with less viability and higher risk) vs. surgery (increased viability and lower risk) in previous retrospective nonrandomized observational studies of CABG in hibernating myocardium.

Considering the survival advantage of CABG in the STICHES long-term follow-up, it seems that most patients with suitable targets for revascularization in the setting of an EF less than 35% with 2 or 3 vessel CAD should be considered for CABG regardless of the results of viability testing. Competing risks such as the severity of heart failure, age and increasing noncardiac mortality need to be carefully weighed in considering the recommendation¹⁶. While many patients can undergo CABG without preoperative viability assessment, in this author’s opinion, testing will continue to play a role in selected patients in relation to procedural planning for optimal revascularization. For example, it continues to be important to demonstrate significant viability when severe LV dysfunction is present with single vessel CAD where a percutaneous interventional approach targeted at a dysfunctional segment would usually be the preferred approach. Whether identification and quantification of viable dysfunctional myocardium in regions subtended by a coronary stenosis can better inform the decision to proceed to CABG in patients with multivessel CAD remains an open question. This will probably be best studied in patients with clinical heart failure and an EF >35% based on the favorable long-term outcome on survival following CABG in STICH when EF is depressed.

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