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EDITORIAL COMMENT

Myocardial Viability

Dead or Alive Is Not the Question!*

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When talking about viability—or better: hibernating myocardium—the question is not: "dead or alive," the question is rather "what needs to be done to improve the patient's symptoms and prognosis." Little is known to answer this question.

The difficulties start with the definition of hibernating myocardium as "a state of myocardial hypocontractility during chronic hypoperfusion, in the presence of completely viable myocardium which recovers functionally upon revascularization." This

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definition is problematic in the clinical setting because it is not entirely clear how we exactly define myocardial hypocontractility, how we define hypoperfusion (especially given that there is perfusion contraction matching), how we define functional recovery, and most important for a clinical test, how can we predict functional recovery?

The next level of complexity is the question of what is most important for the prognosis of the patient: left ventricular volumes and function, presence and extent of myocardial infarction, presence and extent of hibernating myocardium, presence and extent of myocardial ischemia, or a combination of some or all of the parameters mentioned?

There are several things we know:

1. End-diastolic volume (EDV) and ejection fraction (EF) are strong parameters of outcome in a large variety of patient groups (1–3).
2. The presence and extent of myocardial infarction are strong parameters of outcome and seem to be superior to EDV and EF in a large variety of patient groups (4,5).
3. The presence of large amounts of myocardial ischemia is a strong predictor of negative outcome (6).

However, we do not know:

1. Whether the presence of viable myocardium is relevant to predict outcome.
2. Whether areas of peri-infarct ischemia are relevant.
3. Whether improvement of function after revascularization reduces the patient's risk for subsequent events.
4. Which test/parameter to use to define hibernating myocardium.

The recent imaging substudy of the prospective multicenter outcome STICH (Surgical Treatment for Ischemic Heart Failure) trial can be used as an example to highlight these difficulties (7). Hibernating myocardium was assessed in 601 patients with ischemic cardiomyopathy (EF <35%) with single-photon emission computed tomography (SPECT) or dobutamine stress echocardiography (DSE). Two hundred ninety-eight patients received medical therapy and coronary artery bypass grafting, and 303 were randomized to optimal medical therapy alone. There was no association of hibernating

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myocardium and outcome in all patients and, importantly, no differences in prognosis, irrespective of whether patients with significant amounts of hibernating myocardium were revascularized or received medical therapy only. Considering the unknown variables mentioned in the previous text, it is important to note that the amount of myocardium required to classify the patients as having significant amounts of hibernating myocardium were different for SPECT and DSE and more than usually used in clinical practice. With SPECT, 65% of the myocardium had to be hibernating (≥11 segments), and with DSE, 31% of the myocardium (≥5 segments). In addition, the study considered the presence of hibernating tissue, irrespective of whether it was subtended by a diseased coronary artery or not. Furthermore, we need to acknowledge that SPECT and DSE may not represent the optimal investigation for hibernating myocardium because they have inherent technical limitations, such as a lower resolution and lower sensitivity of SPECT to detect subendocardial scarring in comparison to cardiac magnetic resonance (CMR) (8), as well as limited endocardial border definition and acoustic windows for DSE. The fact that different noninvasive investigations provide information on different aspects of the pathophysiology (metabolism, scar, contractile reserve) consequently leads to results that may depend on the chosen imaging test (9). Indeed, previous meta-analyses have demonstrated the feasibility of noninvasive testing to guide revascularization when including positron emission tomography and CMR (10,11). Even though there is less evidence, the importance of an additional ischemic component to the presence of hibernating myocardium in patients with ischemic cardiomyopathy is increasingly recognized (12).

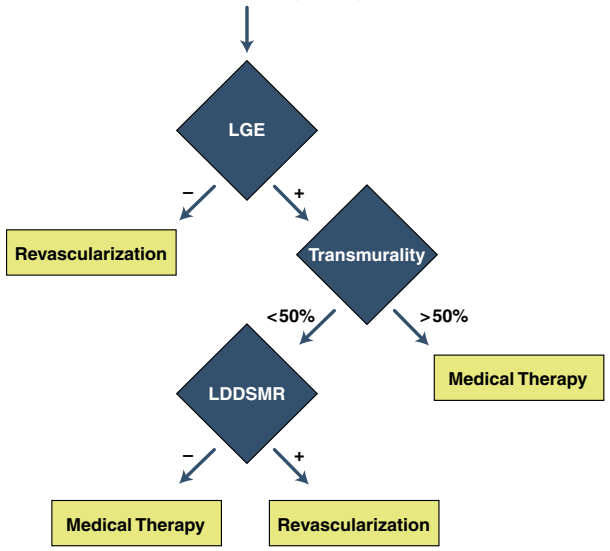

Figure 1. Algorithm to Assess Hibernating Myocardium With CMR

In the presence of wall motion abnormalities at rest in segments subtended by a diseased coronary artery, scar imaging serves as a first-line test. In the absence of scar (likelihood of functional recovery ~78% [19]) and in the presence of scar with a transmurality of >50% (likelihood of functional recovery ~8% [19]), late gadolinium enhancement (LGE) is sufficient to predict functional recovery. In the presence of scars with a transmurality of 1% to 50% (likelihood of functional recovery ~53% [19]), low-dose dobutamine stress magnetic resonance (LDDSMR) testing allows for the assessment of contractile reserve, which guides further management. CMR = cardiac magnetic resonance.

CMR has several options to characterize patients with suspected hibernating myocardium (13). It is the established reference standard to measure global left ventricular volumes and function (14), and it is optimally suited to assess regional wall thickness and motion (15). This is further advanced by using dobutamine stress testing and assessing quantitative parameters such as strain, for example, with tagging (16) or feature tracking (17). In addition, the amount of late gadolinium enhanced (LGE) tissue represents scar with unprecedented accuracy (18,19). Viable tissue is then defined as dysfunctional myocardium without scar.

In this issue of *iJACC*, Romero et al. (20) provide a meta-analysis of the value of 3 different diagnostic strategies with CMR to predict functional recovery after revascularization. Hibernating tissue is defined as a segment: 1) of end-diastolic wall thickness of <5.5 to 6 mm; 2) with a wall motion abnormality at rest, but <50% transmurality of scar; or 3) that demonstrates functional recruitment (contractile reserve) during low-dose dobutamine stress. They also tested other cutoffs for LGE as well as a combination of LGE with low-dose dobutamine stress. The major findings are:

1. LGE with a cutoff value of 50% transmurality yields the highest sensitivity and negative predictive value (NPV). Using a higher or a lower cutoff value for the definition of hibernation can increase either sensitivity (with reduced specificity) or specificity (with reduced sensitivity). However, the strongest differentiation between improvement and nonimprovement is reached with the standard cutoff used by most authors and recommended in the guidelines (21).
2. Low-dose dobutamine yields the highest overall accuracy and the best specificity and positive predictive value (PPV).

3. End-diastolic wall thickness shows a good sensitivity and NPV but only reasonable PPV and poor specificity.

These results are very interesting and bring us back to point 4 of the aforementioned unknown variables. Which parameter to assess when looking at hibernating myocardium? If we would like to look at "dead" tissue with scar imaging, we reach excellent sensitivity (95%) and NPV (90%). On the other hand, if we would like to look at "living" tissue with contractile reserve dobutamine testing, we reach excellent specificity (91%) and PPV (93%). It is therefore not surprising that a combination of different CMR parameters—most importantly, a nonviability test (LGE) and a viability test (inotropic stimulation with dobutamine)—seem to be the optimal combination to assess hibernating myocardium (22–24). However, as pointed out by the authors of the current paper (20), it is also important to note that in the absence of scar or in the presence of scar with >50% transmurality, LGE imaging alone, seems to be sufficient without exposing the patient to additional stress testing (Fig. 1).

Importantly, this meta-analysis is conducted on the basis of segments rather than patients and functional improvement rather than outcome. Thus, many of the questions in the previous text cannot be finally answered and require further research.

Given the number of variables that remain unknown at this stage, we can only speculate about the best diagnostic strategy. For the time being, our main target may remain to improve regional function by revascularization, in those patients who have a high likelihood of functional recovery, but sparing those with low likelihood of functional recovery from interventional procedures. As such, a combination of scar imaging providing information on irreversible damage, with a functional test providing information on the likelihood of functional recovery, seems to be the best strategy.

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Key Words: cardiac magnetic resonance ■ hibernating myocardium ■ late gadolinium enhancement imaging ■ low dose dobutamine stress testing ■ myocardial viability ■ revascularization.