In this issue of Circulation: Cardiovascular Imaging, Bulluck et al. introduce simultaneous positron emission tomography and magnetic resonance (PET-MR) imaging as a sophisticated research tool to correlate cardiac function, area of risk, metabolism, and infarct size in patients with acute myocardial infarction. Imaging is increasingly applied for the noninvasive characterization of acute and chronic ischemic injury. Improved perfusion and wall motion are considered to be diagnostic hallmarks of ischemic injury. Therefore, myocardial perfusion imaging and echocardiography are commonly used to identify location, extent, and severity of ischemic injury. With the advent of cross-sectional imaging, such as single photon emission tomography (SPECT), PET, and MR, more sophisticated means have become available for tomographic visualization of myocardial ischemia and its consequences. At the same time, new tracer techniques have been introduced to provide molecular signals beyond myocardial perfusion. Thallium-201 imaging was the first technology to be applied for the differentiation between reversible perfusion abnormalities as a marker of viable myocardium and persistent defects associated with scar formation, but this imaging approach is only rarely used anymore because of high radiation exposure. With the introduction of PET in the 1980s, metabolic characterization of regional ischemic injury became possible. Using tracers such as C-11 palmitate, C-11 acetate, and FDG, acute metabolic effects of ischemia have been documented.

See Article by Bulluck et al

On the basis of these first metabolic imaging studies, the clinical application of 18F-fluorodeoxyglucose (FDG) emerged as a sensitive marker of tissue viability. Multiple studies in patients with chronic coronary artery disease and impaired ventricular function established the role of PET/FDG as a prognostic marker for functional recovery after revascularization. The observation of reversible dysfunction after revascularization provoked several experimental and clinical studies to elucidate the mechanism of hibernating or stunned myocardium as the pathophysiological explanation for reduced left ventricular function in the presence of viable myocardium. With the clinical acceptance of reversible dysfunction as a therapeutic target in patients with heart failure, several imaging methods competed for clinical application, from which FDG-PET and cardiac MR imaging with late gadolinium enhancement (LGE) emerged as “gold standards” for tissue viability and scar formation, respectively. However, the lower risk of revascularization either by percutaneous techniques or by surgery has reduced the clinical imperative for viability studies in recent years. In addition, a large prospective trial (Surgical Treatment to Ischemic Heart Failure [STICH] trial) suggested that the delineation of myocardial viability did not significantly affect clinical outcome of patients considered for revascularization. However, limitations in study design of this trial remain, questioning the validity of the conclusions, and further studies are needed to refine the clinical role of viability testing in chronic ischemic heart failure.

In contrast to studies in patients with chronic ischemic ventricular dysfunction, the application of imaging studies in patients with acute myocardial infarction are reserved primarily to research questions. With cross-sectional imaging modalities, it is now possible to assess many parameters in vivo, which were in the past only obtainable in experimental settings. Today, parameters such as area of risk can be assessed by SPECT and MR imaging during and after acute myocardial injury. In addition, the extent of acute myocardial necrosis can be accurately quantified by the gadolinium kinetics. Evaluation of LGE by MR imaging has been found to correlate closely with extent of acute necrosis, as shown by triphenyltetrazolium staining. With the recent introduction of PET/MR, simultaneous and coregistered acquisition of established PET and MR signals can be performed in patients with acute myocardial infarction. In the article by Bulluck et al., interesting first results of the application of this new and unique multimodal technology in patients with acute myocardial infarction are presented. PET/MR after glucose insulin load was performed in 21 patients early after acute myocardial infarction. PET and MR parameters were compared and correlated with a follow-up PET/MR study 12 months later. The main finding of this study is that there is good agreement of FDG/PET as well as cardiac MR late in the follow-up study, confirming the validity of both methods to estimate infarct size several months after infarction. During the acute phase, however, the relative FDG defect in the infarct territory seemed to be larger when compared with LGE as a marker of necrosis. In addition, the area of reduced FDG uptake correlated closely with T2 mapping as a marker of area of risk. These results suggest that in reversibly injured myocardium...
FDG uptake is reduced and recovers over time, as shown in a subset of patients with follow-up PET/MR study. To interpret this unexpected finding of reduced FDG uptake in viable but injured myocardium, one has to consider various methodological aspects of PET. As stated above, the FDG uptake reflects cardiac metabolism depending on the overall metabolic state. During glucose and insulin loading, FDG uptake in normal myocardium is maximized. Therefore, the relative uptake of FDG within an ischemic injury highly depends on thresholds applied to define abnormal FDG. As shown in figure 6 of the article by Bulluck et al., the correlation of FDG uptake with extent of LGE strongly depends on threshold values, and as indicated in the article, the best agreement with T2 MR signal as a marker of area of risk was observed with a threshold of 50%. However, a threshold of 45% best predicted functional recovery of ventricular segments in a subgroup of 12 patients. The data indicate that there is not a sharp drop of FDG uptake but a gradual decrease of metabolic activity in the area of ischemic injury, reflecting the heterogeneity of infarcted tissue.

It is not surprising that areas with necrosis exhibit close correlation between LGE and low metabolic activity. However, the finding of reduced FDG uptake in the area of risk is not expected and little supported by currently available experimental data. Animal data suggest that glucose metabolism is actually enhanced and fatty acid oxidation impaired in the border zone of myocardial infarction. However, there are numerous data indicating that reversibly injured myocardium is associated with transient dysfunction, which exhibits slow recovery and most likely also reduced metabolic demand when compared with remote myocardium. In addition, there are methodological issues reflecting the poor spatial resolution of PET in comparison with the dimensions of left ventricular wall. Nonthickening myocardium shows, relative to contracting myocardium, a significantly lower apparent tracer uptake induced by partial volume effects. This mechanism may at least partially play an important role in the observed findings because FDG uptake in same segments recovered to normal levels at follow-up. As discussed in the article, only studies with simultaneous gating of FDG and PET and partial volume correction may provide accurate representation of tissue FDG concentration. In addition, absolute quantification of tracer uptake by PET will overcome limitations of relative measurements of regional tracer accumulation. Most recently, FDG-PET studies have been performed under fasting condition early after myocardial infarction. Markedly enhanced relative FDG uptake has been observed in the infarcted area. Under such conditions, FDG uptake is relatively enhanced in the areas of ischemic injury. In the presence of high serum fatty acids and low insulin, little FDG is taken up in normal myocardium. However, PET measurements of standard uptake value in these areas are much lower than values in remote myocardium under glucose-loaded conditions. Although experimental studies indicate that myocardial cells injured by ischemia exhibit upregulation of glucose transporters independently of the action of insulin, the infiltration of inflammatory cells has recently been recognized as an important pathophysiological component of acute myocardial injury. Activated macrophages as well as other inflammatory cells exhibit increased FDG uptake reflecting glucose use.

Recent studies have shown that quantitative measurements of FDG uptake are associated with functional outcome, suggesting that exaggerated inflammatory responses are detrimental for healing process. Therefore, even in the presence of acute inflammation, PET studies after glucose load or insulin exposure show relatively reduced FDG uptake in the ischemically injured area. For this reason, interpretation of relative FDG uptake in ischemically injured myocardium has to be evaluated in the context of the overall metabolic milieu and absolute quantification of FDG uptake may support an improved interpretation of the results.

The PET/MR study by Bulluck et al indicates that multimodality imaging provides many important parameters, which can be related to extent, severity and outcome of an ischemic injury. PET/MR performed 5 days after myocardial infarction can accurately predict outcome of an ischemic injury. This may be most appropriate in intervention studies evaluating new drug regimens to modify myocardial salvage or remodeling. In addition, combination of MR with other PET tracers addressing specific molecular targets may be helpful in the setting of acute myocardial infarction. With the advent of multimodality imaging, various physiological and molecular parameters can be simultaneously studied and represent a major step in translating experimental knowledge into clinical imaging protocols. Myocardial performance can be modified by therapeutic interventions and evaluated how these interventions relate to clinical outcome of patients with acute myocardial infarction.

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Combined Positron Emission Tomography and Magnetic Resonance as Translational Tool in Cardiology
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