Myocardial Tissue Imaging Using Simultaneous Cardiac Molecular MRI

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Molecular MRI in London Ontario

The Lawson Health Research Institute (the "Lawson") is located within St. Joseph's Healthcare in London Ontario, and is affiliated with Western University. This group received the first Biograph mMR in Canada in March 2012. With strong existing research groups in MRI and nuclear medicine this group is ideally positioned to drive research and innovation using this platform. In advance of the installation of the hybrid molecular MR, researchers at the Lawson had been developing novel MR-based attenuation correction methods, and novel tracer developments. In addition to the molecular MR this site has a PET-CT, a SPECT-CT, and an Inveon small animal PET as well as two 1.5T MAGNETOM Aera systems, a 16.5MeV medical cyclotron and radiochemistry facilities.

Myocardial tissue imaging

Hybrid imaging platforms incorporating PET have become available for cardiovascular imaging applications over the past decade. These platforms have been primarily aimed at providing superior tissue attenuation correction of the emitted photon signal and to provide spatial anatomic registration for the localization of abnormal tracer signal. While this has resulted in substantial improvements in the clinical performance of cardiac PET, the exploitation of complementary imaging data has yet to be fully realized.

The recent availability of hybrid platforms allows for an expansive range of PET applications to be explored.

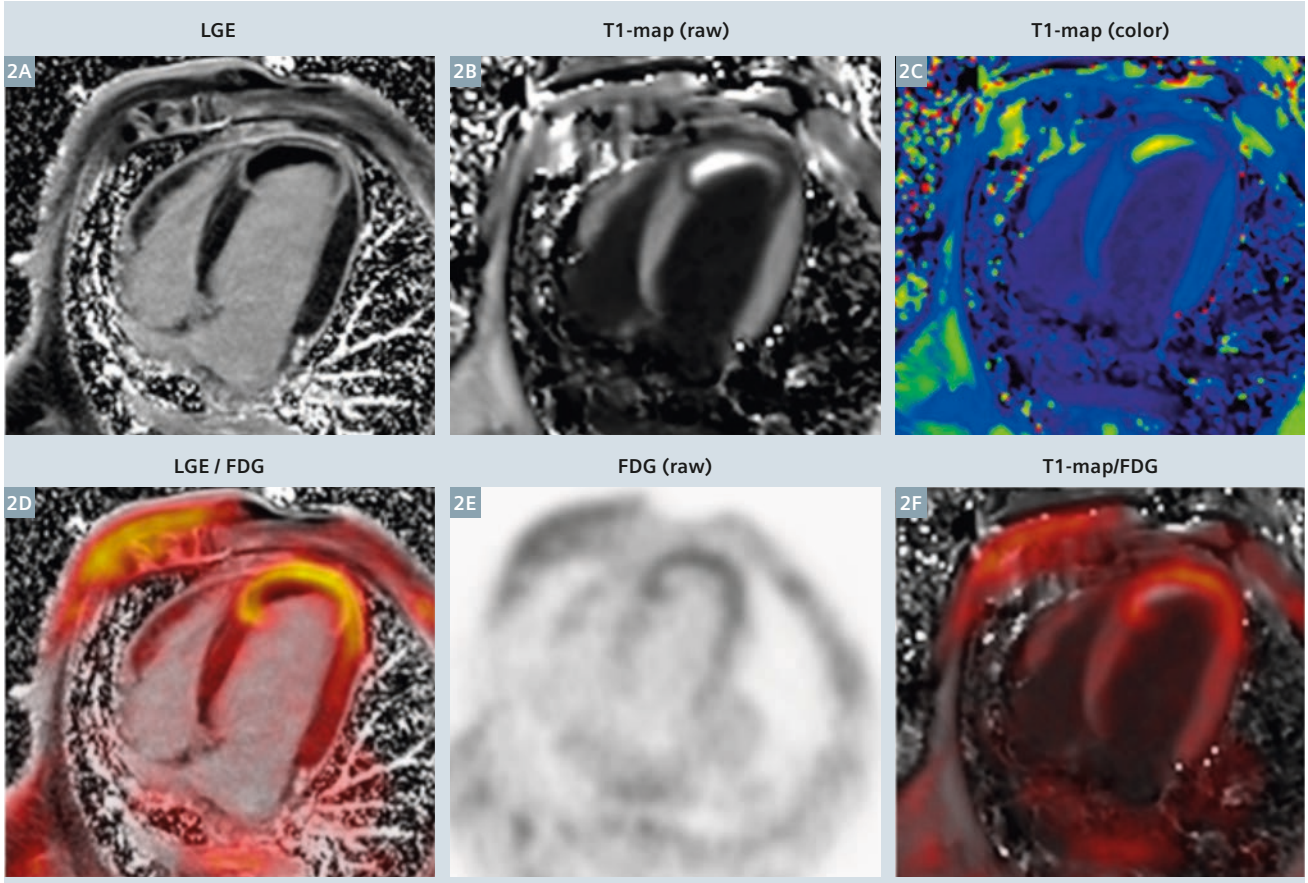
1 The Lawson Health Research Institute.

For example the capacity of cardiovascular MRI to provide complementary 2D and 3D morphological data with excellent soft tissue contrast and high temporal resolution is of benefit for anatomic registration and novel motion correction algorithms. However, its incremental capacity to provide exquisite tissue characterization through intrinsic tissue contrast and altered kinetics of exogenous paramagnetic contrast is of particular interest in the context of the PET imaging environment.

Clinical adoption of myocardial tissue imaging is expanding in response to mounting evidence that the 'health' of myocardium strongly modulates benefit from heart failure therapies (pharmacologic, surgical and device-based) and is predictive of future arrhythmic events among patients with ischemic and non-ischemic cardiomyopathy [1-5]. To date, this literature has focused on isolated and disparate markers of tissue health using both PET and MRI. However, within this brief report we discuss several synergies of these platforms that hold promise towards a new era of hybrid imaging for the optimal performance of myocardial tissue imaging.

Molecular MRI in the setting of acute ischemic injury

Among those surviving acute myocardial infarction (AMI), appropriate myocardial healing is believed to be reliant upon a highly choreographed process of early inflammatory cell invasion, collagen degredation, debris removal by activated macrophages, and myofibroblast proliferation with reconstitution of a new collagen matrix. While



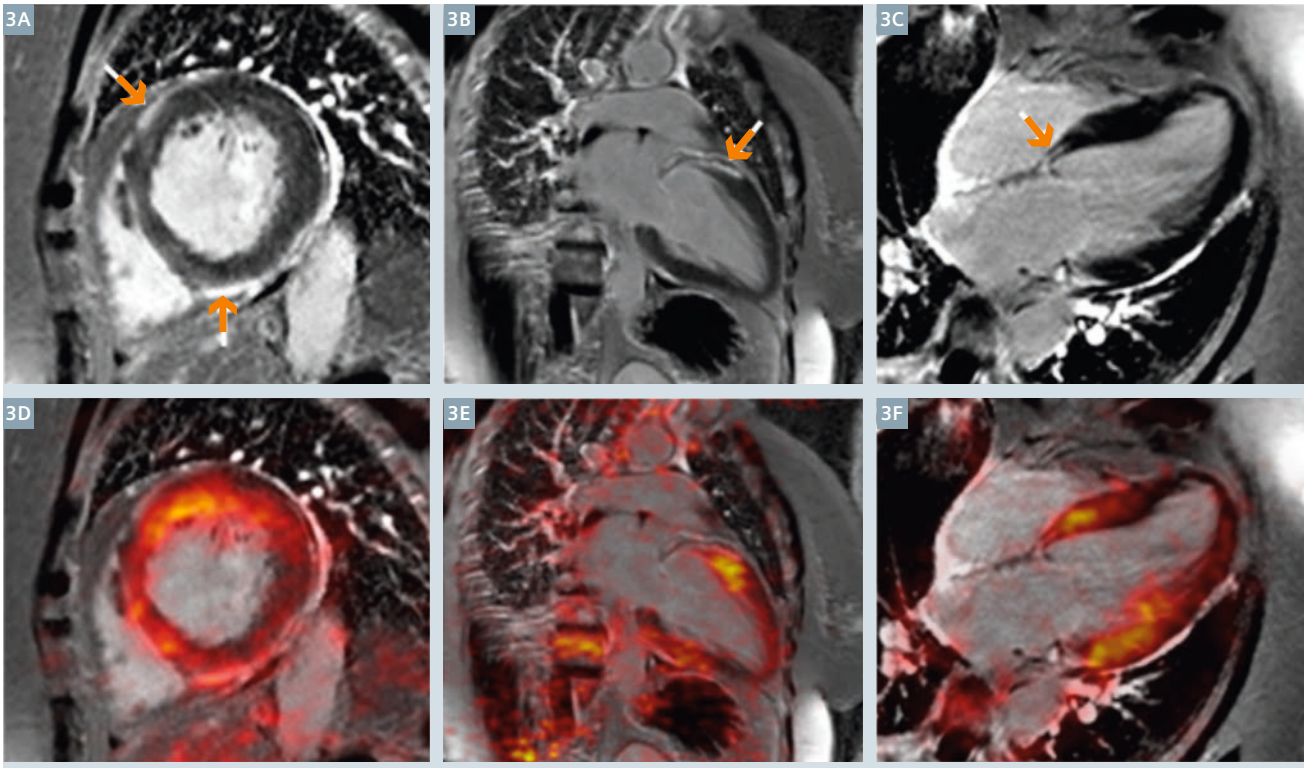
2 Example of a non-reperfused myocardial infarction from LAD ligation in a canine model, imaged one week post ligation. A large area of microvascular obstruction (MO) is seen by LGE imaging with a corresponding marked prolongation of T1 shown using MOLLI-based T1 mapping. Simultaneously acquired FDG imaging (binned to cardiac phase) has been fused to both LGE imaging and raw T1 map and illustrates a marked reduction in inflammation within the region of MO. There is intense inflammatory activity evident within the perfused infarct rim.

such findings can be characterized histologically, our capacity to quantify markers of the inflammatory process *in vivo*, and evaluate influences of its modulation on the remodeling process has been limited.

We have started examining this process in a canine infarct model using the Biograph mMR 3T-PET platform using simultaneous 3D LGE / ^{18}F-FDG imaging, the latter imaged following normal myocardial glucose metabolism using intravenous heparin and lipid infusion. In these experiments we have focused on evaluating the influence of microvascular obstruction (MO) on mitigating appropriate inflammatory cell recruitment to the infarct core – a postulated mechanism of how MO may adversely impact on left ventricular remodeling post infarct. Figure 2 illustrates how the region of MO can be elegantly visualized using both LGE imaging and T1 mapping CMR techniques. ^{18}F-FDG imaging shows intense inflammatory activity within the perfused infarct rim, however a marked reduction in activity is seen in regions of MO. This imaging may therefore provide novel insights towards mechanisms by which MO contributes to adverse outcomes following AMI, and offers a new tool to evaluate therapies aimed at modulation of this pathway.

Molecular MRI in the setting of acute non-ischemic (inflammatory) injury

Both PET and CMR have been investigated for their diagnostic accuracy in the setting of suspected inflammatory cardiomyopathy – particularly among patients with known pulmonary Sarcoid. While their respective diagnostic performance has been compared in the past, this remains inappropriate, as the information gathered and interpreted from each technique could not be more unique. PET imaging (typically performed using ^{18}F-FDG following prolonged fasting, fatty meal consumption and intravenous heparin to suppress normal myocardial glucose utilization) exploits the hypermetabolic signal of activated inflammatory cells (i.e. macrophages) and therefore indicates disease 'activity' among patients with active cardiac Sarcoid. In contrast, LGE imaging indicates regions of mature granulomatous fibrosis among patients with prior or current cardiac Sarcoid. Therefore, these two commonly employed diagnostic techniques provide complementary but unique information.



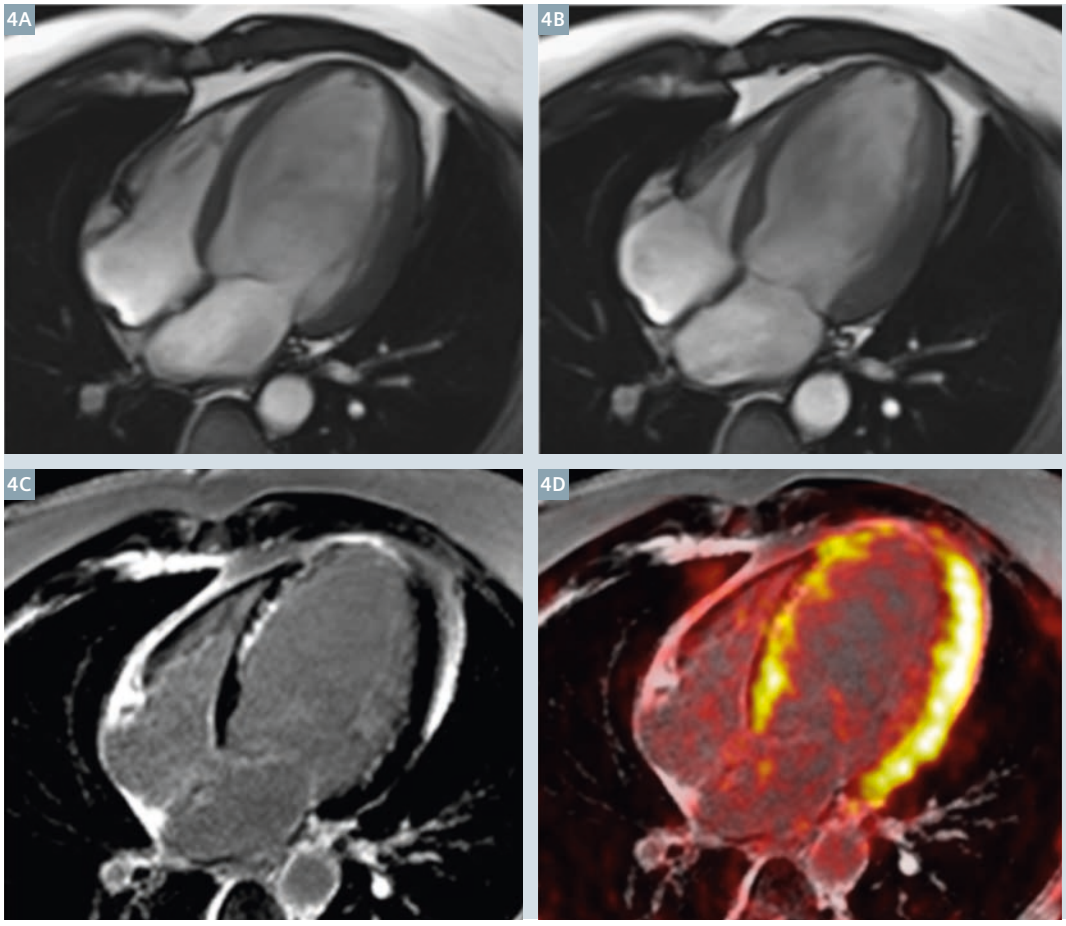
3 72-year-old female with suspected new-onset heart failure and non-sustained ventricular tachycardia and prior history of biopsy-proven systemic Sarcoid. Top rows show late gadolinium enhancement (LGE) imaging with characteristic sub-epicaridal based scar (arrows), consistent with prior inflammatory injury. Lower row shows fused FDG-PET images with evidence of focal signal enhancement, consistent with active inflammation surrounding regions of established scar.

Figure 3 illustrates the capacity of hybrid MR and PET to spatially register these techniques using simultaneously acquired data, and potentially improve diagnostic accuracy while expanding our understanding of disease pathophysiology. In this case of a 72-year-old female presenting with heart failure and non-sustained ventricular tachycardia we can identify a leading edge of inflammation (intense FDG uptake) with a trailing edge of irreversible injury or 'scar' (indicated by hyperenhancement on LGE imaging) at the sub-epicardial zone. This approach ushers in a new era of imaging for inflammatory-mediated disease where a more complete spectrum of disease activity can be visualized in a single, spatially registered examination.

Molecular MRI in the setting of non-acute myocardial disease

Another clinical setting where MR and PET have established their respective roles for therapeutic decision-making is for the assessment of tissue viability in chronic ischemic cardiomyopathy. Evidence supports that both the regional reduction of FDG signal [6, 7] and regional scar transmurality by LGE are strongly predictive of absence of functional recovery following coronary revascularization. The performance of these studies are therefore commonly considered to be mutually exclusive, with absence of FDG signal being the *sine qua non* of myocardial scar, and the lack of scar by LGE imaging being equivalent to tissue health. However, it is recognized that the spatial resolution and signal-to-noise of LGE imaging is superior to FDG for the detection of subendocardial scar, and also for the characterization of tissue viability among those with marked thinning of the ventricular wall [8]. Conversely, FDG-PET based metabolic abnormalities can be documented within tissue that fails to demonstrate myocardial scar on LGE MRI, lack of FDG uptake being predictive of absence of functional recovery. Accordingly, the marriage of PET-based metabolic imaging and LGE-based scar imaging may provide a more robust platform for the prediction of improved outcomes following coronary revascularization.

In figure 4 we see a 42-year-old male referred for viability imaging prior to coronary artery bypass surgery late following myocardial infarction. Cine imaging shows a large region of thinned and akinetic myocardium in the distribution of the left anterior descending artery, this territory demonstrating varying degrees of transmural scar following gadolinium administration. Simultaneous MR and PET with ^{18}F FDG imaging shows metabolic activity within non-scarred regions surrounding the infarct zone and normal metabolic tracer activity within remote myocardium.



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42-year-old male with large anterior wall myocardial infarction being considered for surgical revascularization in the setting of triple vessel disease. Cine MRI shows akinesia of the septum and apex with a reduced ejection fraction of 32%. Late gadolinium enhancement (LGE) imaging shows a large infarct of the LAD territory with variable scar transmurality ranging from 25% to 100% throughout the infarct region. FDG-PET imaging, shown fused with LGE imaging, shows matched reductions in metabolic tracer uptake.

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