Cardiovascular Magnetic Resonance in Myocarditis

Myocarditis is a broad diagnosis based on the presence of tissue inflammation. Making a pathologic diagnosis is difficult with the nonspecific methods available. Daniel M. Couri, MD, Southern Illinois University School of Medicine, Springfield, Illinois, USA, discussed the benefits of cardiac MRI (cMRI) for diagnosing myocarditis.

Cardiac troponin T (cTnT) can be elevated in more than 30 conditions. Assomull et al. [*Eur Heart J* 2007] recruited 60 consecutive patients within 3 months of presentation with ST elevation, normal coronary arteries, and cTnT elevation. After cMRI, an identifiable basis for troponin elevation was established in 65% of patients. The most common underlying cause was myocarditis (50%). Cardiac MRI has broad performance advantages with regard to morphology, function, and the unique ability to directly visualize tissue characteristics [Freidrich MG et al. *J Am Coll Cardiol Img* 2008].

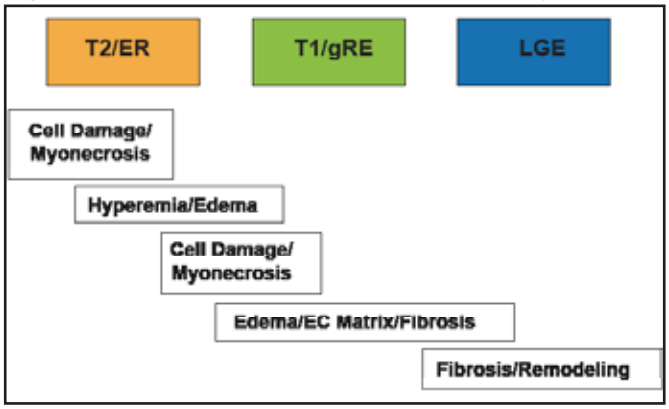
In the acute phase of myocarditis (Days 1 to 7), the virus spreads to the heart with minimal myocyte damage and necrosis. The subacute phase (up to 30 days) is characterized by viral shedding, cellular damage, and the secondary immune response with antibody generation, cell destruction, inflammation, and hyperemia. Advanced fibrosis predominates in chronic myocarditis, with interstitial replacement, myocardial dilation, and heart failure.

Tissue characterization with cMRI is primarily based on T2- and T1-weighted imaging. T2 imaging focuses on hyperemia and edema in the acute and subacute phases. A diffuse pattern or patchy hyperenhancement scattered throughout the myocardium is consistent with myocarditis. T2 imaging can be quantitated by indexing it to the skeletal muscle; an increase in the edema ratio (ER) ≥2 times that in skeletal muscle is significant.

T1-weighted cardiac imaging is based on gadolinium (Gd) enhancement, which shortens the T1 time and accentuates T1 tissue characteristics. Gd is an extracellular agent with low infiltration into normal myocardium, where myocytes are densely packed and there is little extracellular space. Gd has a high myocyte infiltration rate in damaged myocardium and significantly prolonged infiltration in fibrotic areas. T1 imaging shows early enhancement in the acute and subacute phases, revealing cell damage, hyperemia, and extracellular matrix changes. Late enhancement is focused on focal fibrosis and remodeling.

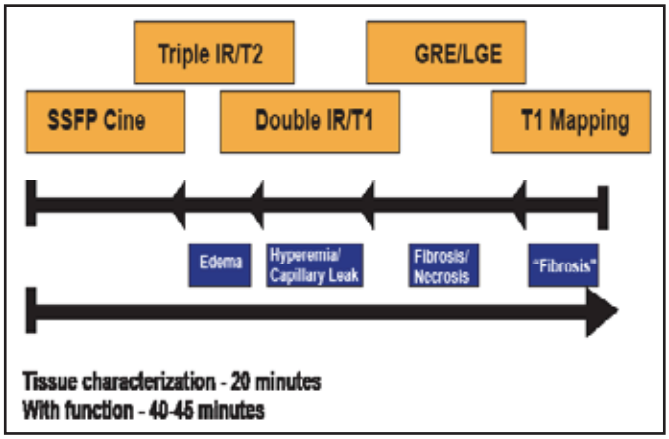
A comprehensive cMRI protocol for diagnosing and assessing myocarditis involves T2 imaging with ER in the acute and subacute phases, T1 imaging with early Gd enhancement ratio (gRE) in the subacute phase, and late Gd enhancement (LGE) in the chronic phase (Figure 1). Figure 2 shows the sequence of cMRI techniques, with steady-state free-precession (SSFP) cine, triple inversion recovery (IR)/T2 (edema), double IR/T1 (hyperemia/capillary leak), GRE/LGE (fibrosis/necrosis), and T1 mapping (fibrosis).

Figure 1. Comprehensive cMRI Protocol for Myocarditis.



EC=endothelial cell; ER=edema ratio; gRE=Gd; enhancement ratio; LGE=late Gd enhancement.

Figure 2. Comprehensive cMRI Protocol Sequence.



IR=inversion recovery; SSFP=steadystate free-precession.

The Lake Louise Consensus Criteria require at least 2 of the following: relative enhancement index (T2) ≥2.0, increased global myocardial gRE ≥4.0, at least 1 focal LGE lesion with nonischemic regional distribution [Friedrich MG et al. *J Am Coll Cardiol* 2009]. These criteria were developed from pooled data from <300 patients, with no multicenter data. Sensitivity is 69%, specificity is 91%, and accuracy is 78%. Table 1 shows the diagnostic performance of global myocardial edema, global relative myocardial enhancement, LGE, and Lake Louise Criteria.

Table 1. Diagnostic Performance of Global Myocardial Edema, Global Relative Myocardial Enhancement, Late Gd Enhancement, and Lake Louise Criteria.

	Edema	RE	LGE	LLC
Sensitivity	91.7%	58.3%	58.3%	75.0%
Specificity	81.8%	63.6%	45.4%	72.7%
Accuracy	87.0%	60.9%	52.2%	73.9%

RE=myocardial enhancement; LGE=Late Gd Enhancement; LLC=Lake Louise Criteria.

Dr. Couri concluded that noninvasive imaging offers an efficient and safe means for acute management of patients. Cardiac MRI is the most versatile and powerful imaging modality for the comprehensive assessment of cardiac pathology. Despite its current success, however, cMRI in myocarditis remains a work in progress.

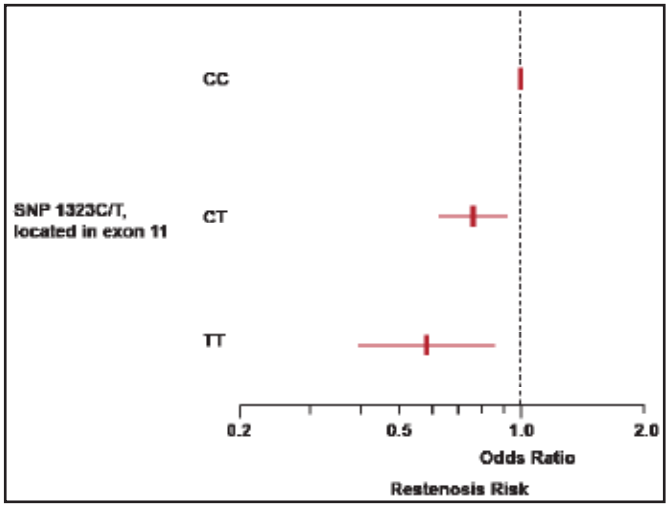
Inflammation and Vascular Injury

The focus of Dr. Daniel I. Simon's research at University Hospitals Harrington Heart & Vascular Institute, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, is on a class of leukocyte adhesion molecules, leukocyte β_2-integrins, among which Mac-1 ($\alpha_M b_2$, CD11b/CD18) is the most common integrin on neutrophils. The leukocyte Mac-1 receptor interacts with the glyocoprotein Ibα (GPIbα) receptor on platelets, thereby regulating pro-inflammatory and pro-thrombotic bidirectional signals in both inflammatory cells and platelets. Dr. Simon has centered his research on the structure, function, and signaling of Mac-1, identifying the Mac-1 binding site for GPIbα and developing tools to disrupt leukocyte-platelet complexes that promote vascular inflammation.

The repair response following vascular injury is an inflammatory process in which neutrophils and monocytes are rapidly recruited to sites of arterial injury, including stented human blood vessels. Neutrophils appear within hours; monocytes/macrophages predominate at 7 days. Inflammatory cells are the most abundant cells in the stented human intima for months following injury. The inflammatory cells enter the blood vessel through a 2-step process, involving selectin-mediated rolling and then firm adhesion and diapedesis through the integrin Mac-1.

Inoue et al. [*J Am Coll Cardiol* 1996] observed that upregulation of the Mac-1 receptor on neutrophils predicts restenosis risk. Dr. Simon used Mac-1 knockout mice to prove the importance of the receptor in the vascular injury response [Simon DI et al. *J Clin Invest* 2000]. Following arterial injury, the wild-type mouse (Mac-1+/+) develops thick neointima while the Mac-1-/- mouse is protected from neointima growth. In stented rabbit arteries, brisk recruitment of inflammatory cells was disrupted by antibody targeting of the Mac-1 receptor, resulting in dramatically reduced restenosis [Rogers C et al. *Proc Natl Acad Sci U S A* 1998]. In humans, a single nucleotide polymorphism (SNP) in the CD18 locus of the β2 integrin is highly predictive of restenosis following stenting [Koch W et al. *Am J Cardiol* 2001] (Figure 1).

Figure 1. CD 18 Genetic Polymorphism Linked to Restenosis Risk.



Reproduced with permission from Elsevier. Koch W et al. Association of a CD18 gene polymorphism with a reduced risk of restenosis after coronary stenting. *Am J Cardiol* 2001;88(10):1120.

Mac-1 signaling via ligand engagement and clustering is important in amplifying the inflammatory response. Clustering of Mac-1 activates the master inflammatory transcription factor NFkB via a Toll/IL-1 receptor family-like signaling pathway [Shi et al. *Circulation Research* 2001]. Mac-1 signaling also regulates the expression of the transcription factor Foxp1 [Shi C et al. *J Clin Invest* 2004], which serves as a repressor of the gene encoding the M-CSF receptor. Mac-1 signaling downregulates the expression of Foxp1, thereby promoting monocyte differentiation and pro-inflammatory macrophage functions. Overexpression of Foxp1 specifically in monocytes/macrophages prevents monocyte maturation, resulting in reduced vascular inflammation and atherosclerosis.

The interaction between Mac-1 and platelet GPIbα broadly regulates inflammation in diverse animal models, including restenosis, vasculitis, glomerulonephritis, and demyelinating diseases. Dr. Simon is using these model systems to develop anti-inflammatory drugs for this diverse disease subset. Using chimeric integrins, his laboratory identified the 16-amino acid sequence within the I-domain of Mac-1 that is necessary and sufficient for Mac-1 binding to GPIbα. A peptide (M2) corresponding to this sequence or an antibody targeting