¹⁸F-FDG PET imaging of myocardial inflammation and viability following experimental infarction and anti-inflammatory treatment with compound MCC950

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Received Mar 8, 2020; accepted Mar 9, 2020

doi:10.1007/s12350-020-02104-5

See related article, pp. 2346–2357

In this issue of the *Journal of Nuclear Cardiology*, Li and Yang et al. explore the role of ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging to assess myocardial inflammation and viability in the context of treatment with the anti-inflammatory molecule sulfonylurea MCC950 following acute myocardial infarction (AMI).¹ The effect of MCC950, a NOD [nucleotide-binding and oligomerization domain]-like receptor pyrin domain-containing protein-3 (NLRP-3) inflammasome inhibitor, was assessed using various FDG PET protocols to image the myocardium following experimental ligation of the left main coronary artery and ensuing AMI in C57BL/6 adult male mice.² MCC950 was administered immediately after surgery and daily for 7 days. Following surgery, FDG PET imaging was conducted to (i) quantify myocardial inflammation at days 3 and 5, and (ii) determine myocardial viability at days 7 and 28.

Funding Dr. Packard is supported by VA Merit I01 BX004558.

See related article, pp. 2346–2357

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J Nucl Cardiol 2021;28:2358–60.

1071-3581/\$34.00

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Histology, immunohistochemistry, and Western blotting were used as reference standards and cardiac mechanical parameters were obtained by echocardiography.

Following an AMI, myocardial necrosis releases damage-associated molecular patterns (DAMPs) and cytokines which promote pro-inflammatory signaling and activation of the innate immune system.^{3,4} While inflammation is known to recruit monocytes and other leukocytes that are necessary for tissue repair, amplified inflammation has also been associated with infarct expansion and adverse remodeling.^{5–7} Several key mediators of post-MI inflammation have been identified. For example, Toll-like receptors (TLRs) are upregulated in response to DAMPs and activate macrophages. Pharmacological inhibition of TLR-4 in mice significantly reduces the infarct size and inflammatory response following reperfusion.⁸ Similarly, TLR-2 deficiency has been associated with reduced myocardial fibrosis and ventricular remodeling following AMI.⁹

The NLRP-3 inflammasome is a protein complex induced by cellular debris, for example necrotic cardiomyocytes following an AMI, resulting in the activation of pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18.¹⁰ These and other inflammatory mediators provide a mechanistic link between dying cardiomyocytes and worsening inflammation, infarct expansion, and adverse remodeling.¹¹ This detrimental cascade of inflammatory activation provides the rationale for use of the anti-inflammatory compound MCC950 inhibiting NLRP-3 following AMI.^{12,13} Indeed, MCC950 which was initially developed as a compound to inhibit IL-1 β release,¹⁴ modifies the active conformation of NLRP-3, and blocks NLRP-3 oligomerization in response to external stimuli or in the

setting of NLRP-3 gain-of-function mutations, thereby inhibiting its action.¹⁵ Importantly, favorable effects of MCC950 were previously established in mouse¹⁶ and pig¹⁷ experimental AMI models.

The authors indicate that MCC950 decreases the recruitment of inflammatory M1 macrophages, also known as classical macrophages, but not reparative M2 macrophages, otherwise known as alternatively activated macrophages¹⁸—a binary classification that is likely an oversimplification of macrophage biology and function and is increasingly being questioned.¹⁹ An association between MCC950 treatment and decreased cardiomyocyte necrosis and apoptosis was also proposed by the investigators, although more rigorous experiments are needed to definitively imply causality. Favorable effects of MCC950 were further confirmed by echocardiographic analyses of systolic function and ventricular dimensions. Following glucose suppression, regions with < 60% of the maximal myocardial FDG uptake in healthy, non-infarcted regions were defined as having a viability ‘defect.’ Here as well, MCC950 had a favorable effect, increasing the amount of viable myocardium. Using a manual overlay approach prone to subjectivity, error, and with spatial limitations, the authors suggest an approximate correspondence between the extent of inflammation and subsequent viability PET signals.

Despite evidence that targeting inflammatory processes in experimental models may improve cardiac function and mitigate remodeling, these therapies are not clinically translatable without direct in vivo verification of the modulated target pathway. Given technical limitations in obtaining myocardial tissue by biopsy following an AMI due to feared complications such as hemorrhagic pericardial effusion, the authors propose FDG PET will permit translation of their observations into the clinical realm by allowing the non-invasive monitoring of the effects of MCC950 in humans. Indeed, while 3-D echocardiography and cardiac magnetic resonance imaging have been the standard for measuring post-MI cardiac sequelae, they do not provide sufficient mechanistic insight into the therapeutic efficacy of targeting inflammation in vivo.

Several key points however need to be considered. First, whereas a favorable effect of MCC950 was demonstrated, this amounted to a ~ 25% decrease in the FDG myocardial inflammation signal and a ~ 12% improvement in the myocardial viability ‘defect’—or non-viable myocardium—following MCC950 treatment. Whether such relatively modest changes in the FDG PET signal will be sufficient to follow the effect of compound MCC950 in humans needs to be scrutinized, particularly given a lack of consensus in ideal patient preparation protocols to suppress normal myocardial glucose utilization,²⁰ as well as concerns for reproducibility and

repeatability in FDG PET inflammation²¹ and viability²² protocols. Furthermore, caution is required when considering MCC950 in humans following an AMI. Indeed, such anti-inflammatory treatment may lead to residual ‘islets’ of live cardiomyocytes surrounded by heterogeneous and disorganized scar tissue, an ideal substrate for potentially fatal ventricular tachyarrhythmias.^{23,24} Moreover, MCC950 interference with cardiomyocyte death and fibroblast function may lead to inadequate deposition of extracellular matrix proteins such as collagen in the infarcted area, with potentially catastrophic consequences, e.g., ventricular wall rupture.²⁵ Thus, more research is needed to explore the role of MCC950 treatment when initiated in the subacute MI setting, and at additional time-points following an AMI, to scrutinize its effects on the extracellular matrix network crucial for the structural integrity of the heart,²⁶ and on post-MI fibrosis.²⁷

In summary, Li and Yang et al. present a carefully conducted study on the potential role of FDG PET cardiac imaging protocols in quantifying the favorable effect of compound MCC950 following AMI. Further work is required to determine whether the anti-inflammatory and anti-fibrotic effects of MCC950—if deemed clinically safe during the peri-infarct period—will be of sufficient magnitude to be captured by FDG PET protocols for myocardial inflammation quantification and viability determination in humans.

Disclosures

All authors declare that they have no conflict of interest.

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