Complex cellular physiology underlies the use of FDG-PET imaging in investigating post-infarction remodeling

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The regulation of metabolism and inflammation are crucial to normal cardiac function, as well as to adaptations to pathophysiologic states such as myocardial stress/injury. Both alterations in metabolism at the cardiomyocyte level as well as migration and activation of inflammatory macrophages are part of the myocardial ischemic stress/injury response. Some of the changes in these pathways are adaptive, while others are pathophysiologic.

Cardiac metabolism is constantly changing and adapting to energetic needs and stresses of the heart. Cardiomyocytes can utilize many substrates such as fatty acids, glucose, lactate, amino acids, and ketones for energy generation, depending upon substrate availability and the regulatory status of cellular metabolic pathways. While fatty acids constitute the primary fuel source for the heart during the fasted state, ischemia leads to a shift in myocardial metabolism towards glucose.¹ This shift to glucose metabolism can quickly occur through a highly regulated set of coordinated process to increase uptake, phosphorylation, and metabolism of glucose that is stimulated in the response to ischemic stress through activation of energetic stress sensing pathways, including changes in the sarcolemma concentration of one of two glucose transporters, GLUT1 and GLUT4.

The cardiac inflammatory response to injury is also integrally linked to metabolic changes in the heart. First,

inflammatory macrophages are primarily glycolytic in their metabolism. This provides a significant challenge to investigators when trying to use markers of glucose utilization as a specific read-out of inflammation in settings of myocardial infarction, where the cardiomyocytes surrounding the inflammatory macrophages have concomitant upregulation of glucose utilization. Secondly, many of the pro-inflammatory pathways involved in the macrophage response to myocardial injury are both upregulated in the macrophage as well as have direct autocrine/paracrine signaling effects on cardiomyocyte metabolism. For example, our group has shown the complex interplay of the pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF), with the cardio-protective pathway governed by AMP-activated protein kinase (AMPK) whose activation increases glucose uptake through GLUT4 translocation.² This MIF-AMPK pathway directly links the myocardial cardiometabolic response to ischemia with inflammatory macrophage activation. Thirdly, post-infarct remodeling involves a multifaceted interplay of local and remote-zone cytokine signaling events, matrix changes, and mechanical stress alterations that can alone, or in combination, change both inflammatory cell activation and/or cardiomyocyte metabolic pathways.

With that background in this issue of the Journal, Xi et al. (REF) report their findings of the relationship between a large animal (swine) model of experimentally induced myocardial infarction with reperfusion (catheter-based 90 minute balloon LAD occlusion) followed by a series of FDG-PET exams to evaluate for cardiac metabolic changes. The FDG-PET findings were compared to left ventricular function measured by echocardiography as well as immunohistochemical staining of post-mortem heart samples for various glucose transporters (GLUT1, GLUT3, GLUT4) and a macrophage marker (CD68).

The FDG-PET data show a striking increase in FDG signal in the infarct zone as measured by SUVmax. This

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increase in FDG signal was present both early (day 1) as well as late (day 14) after the experimental myocardial infarction. This was associated with an increase in CD68 staining, as well as an increase in glucose transporter staining, with GLUT1, GLUT3, and GLUT4 all increased in the infarct zone at all time points relative to the remote zone. Not surprisingly given the experimental myocardial infarction, there was echocardiographic evidence of deleterious cardiac remodeling over the 28-day course of follow-up, including a reduction in left ventricular ejection fraction and an increase in end-diastolic and end-systolic volumes.

These data suggest that a swine model of ischemia-reperfusion injury and infarction leads to metabolic changes in the infarct zone that persist and can be measured with FDG-PET. The long duration of the increase in FDG uptake (at least 14 days based on this data) is interesting and deserves further explanation. The authors speculate that the increase in FDG signal is due to macrophage infiltration, measured by CD68-positive cells and an increase in the immunohistochemical staining for GLUT3, which is more likely to be related to macrophages than cardiomyocytes. However, based on the current data, it is difficult to ascribe causality to the inflammatory cascade as being responsible for the FDG signal. Immunohistochemistry is notoriously non-quantitative and does not differentiate between cell surface and intracellular glucose transporters, which is important particularly in the case of GLUT4 that dynamically transits from intracellular storage pools to the cell surface in response to stress such as myocardial ischemia. A more quantitative approach to understanding the dynamic changes in GLUT isoform expression over the 28-day experimental period, sub-cellular location, and/or activity would be important to understand. Similarly, ascribing the presence of pathophysiological inflammation in the infarct zone simply by the persistence of CD68 positive cells does not allow for a deeper understanding of the complex immune-regulatory pathways that likely are vigorously changing during the post-infarction period used in this study. Future studies with experimental designs that allow for pharmacological and/or genomic manipulation of inflammatory pathways could help better understand this issue.

Another challenge to interpretation of this data is its reliance on FDG as a marker for inflammation. FDG uptake is not specific for myocardial inflammation, and it is commonly known that dietary preparations are critical to using FDG as a tracer to differentiate normal myocardium from inflammatory cardiomyopathies.³ However, even with meticulous control of metabolic preparations, FDG-PET imaging has a measurable percentage of ‘failure,’ where accentuated FDG uptake

appears where it should not or does not appear where it should be.⁴ The authors acknowledge that this abject failure of FDG-PET imaging to perform as expected occurred in 10% (2 out of 20) of their experimental preparations. In addition, the interpretation of FDG uptake in the heart can be accomplished many different ways, including looking at both the intensity of uptake as well as the volume of abnormal FDG signal. In their report, the authors only describe the peak intensity of FDG uptake (SUVmax). It would be very interesting to know whether and how the volume of abnormal FDG signal changes over the course of the experimental period, as one would speculate that the volume would decrease over a 14-day post-infarction period. It would be very interesting to see if either the total volume of the abnormal metabolic signature or its change correlated with the degree of left ventricular remodeling.

In summary, this paper nicely describes the time course of myocardial FDG-PET imaging abnormalities in the acute/sub-acute recovery after myocardial infarction in a swine model. The challenge for future investigators is to build on this foundation, using and/or developing more specific radiotracers for cardiac inflammation, experimentally manipulating the inflammatory signaling cascades, and relating quantitative changes in radiotracer intensity and distribution to functional outcomes of post-infarction remodeling. Key to this work is a comprehensive understanding of the complex metabolic/inflammatory signaling network that controls these responses.

Disclosure

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