Cardiac FDG-PET: a straight forward tool with high potential

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Brunner and colleagues have recently introduced the concept of ‘dual stem cell therapy’ for the treatment of acute myocardial infarction (AMI),¹,² which is based on a pharmacological regimen consisting of two components:

1. Cells are mobilized from the bone marrow into peripheral blood by application of granulocyte colony-stimulating factor (G-CSF).
2. Homing of these mobilized cells into the myocardium is enhanced by administration of sitagliptin.

The latter component is based on the fact that homing into ischaemic tissue is mediated by stromal cell-derived factor (SDF)-1 expression in the myocardium which binds to its corresponding receptor CXCR-4 on circulating stem cells.² SDF-1 is usually inactivated by enzymatic cleavage via dipeptidyl peptidase IV (DPP-IV).³ Hence, pharmacological inhibition of DPP-IV stabilizes SDF-1 and enhances stem cell homing into ischaemic myocardium.

Brunner’s group has shown that combined treatment of AMI in mice with G-CSF and sitagliptin (GS) leads to a significant increase in both survival and cardiac function. These beneficial effects were attributed to increased cardiac homing of bone marrow-derived stem cells which induced neovascularization and reduced cardiac remodelling as well as apoptosis.²

The study of Gross et al.⁴ was now performed to substantiate the possible effects of this therapeutic concept on cardiac remodelling after AMI by use of 18F-FDG-based micro-PET.

Therefore, 13 mice were treated for 5 days with G-CSF and sitagliptin (GS) after surgical AMI induction according to a previously established protocol.² Ten mice receiving saline (placebo) after AMI induction served as control. On Day 6 and Day 30 after AMI induction, the animals were anaesthetized with isoflurane, and FDG-PET scans were acquired in a dedicated small animal PET scanner.

Analysis of these images revealed the following:

- Infarct size was significantly reduced on Day 30 after AMI in GS-treated animals. This finding is in line with the precedent study by Theiss et al.² and was verified in the current study by histological data.
- On Day 6 after AMI, cardiac %ID/g values were significantly lower for GS-treated animals compared with placebo. Furthermore, cardiac FDG uptake in the GS-treated group at Day 6 was as high as the FDG uptake that placebo animals showed in the late PET scan on Day 30 after AMI. The authors convincingly demonstrate that this observation is not mediated by direct effects of sitagliptin on glucose metabolism. By excluding this, they conclude that this difference in glucose uptake was caused by a shift of infiltrating macrophages from M1 towards the ‘anti-inflammatory’ M2 macrophage population. The authors aim to support this hypothesis by providing data from flow cytometric measurements of digested hearts. They show that GS treatment correlates with both decreased cardiac FDG uptake on Day 6 and a shift towards the M2 macrophage subpopulation which has lower rates of glucose metabolism than the M1 macrophages.⁵
- The authors introduce a novel method based on glucose metabolism to assess and quantify left ventricular myocardial hypertrophy. Details and validations of this method measuring the ‘left ventricular metabolic volume (LVMV)’ are to be published soon in a separate study. Based on comparing LVMV in treatment and placebo groups, Gross et al. show that unfavourable myocardial hypertrophy is significantly reduced in GS-treated animals. From this, they conclude that GS-treatment significantly attenuates adverse cardiac remodelling after AMI.

To summarize the results from a cardiovascular imaging point of view, Gross et al.⁴ used fluorine-18-labeled fluorodeoxyglucose positron emission tomography to gather information on possible effects of ‘dual stem cell therapy’ on cardiac glucose metabolism. The primary end point of the study is basically the percentage of the injected dose (FDG) per gram (%ID/g) in the heart. Based on different algorithms for image analysis, they extract solid information on scar size, inflammatory reaction, and left ventricular hypertrophy.
What is the key message of this study?

The relevance of nuclear cardiology imaging procedures in both small animals and patients is constantly increasing. The unique opportunity for non-invasive serial in vivo measurements makes this approach particularly attractive for translational research. Furthermore, once the techniques are well established, the number of animals used in preclinical studies could be tremendously reduced.

Deliberate choice of the end point, in this case cardiac glucose metabolism, can provide a lot of valuable information given that elaborate techniques for image analysis are available to the respective researcher.

Limitation

The study by Gross et al. clearly aimed at measuring glucose metabolism in the heart by the use of a non-invasive molecular imaging technology. 18F-FDG-PET is an established method in clinical use for quantitative assessment of vital myocardium and infarct size. This approach is based on the fact that viable myocytes show high rates of glucose metabolism.

In contrast, the preclinical protocol cited by the authors is based on the suppression of myocardial glucose uptake—and hence FDG uptake in viable myocardium—by application of ketamine/xylazine. This protocol for efficient suppression of glucose uptake in remote myocardium has recently been confirmed by Thackeray et al. Against the background that cardiomyocytes exceed inflammatory cells by far in post-AMI whole hearts, it is likely that optimal valid information on inflammatory processes from FDG-PET scans will require suppression of glucose uptake.

Therefore, given that imaging glucose metabolism was the aim of the study, an alternative explanation for the observed decrease of myocardial FDG uptake in GS-treated animals might be a metabolic switch from fatty acid to glucose metabolism in myocardium as an early marker of the onset of remodelling and LV hypertrophy. This would be in line with the work of Kundu et al. who show that increased glucose metabolism precedes LV hypertrophy in mice.

What can be learned for future studies?

Gross et al. demonstrated impressively that a single FDG-PET acquisition, a method widely applied in both preclinical and clinical studies, can provide a tremendous amount of information by the use of elaborate techniques for image analysis. Most preclinical studies use histological methods for determination of infarction size and hypertrophic remote myocardium. Left ventricular ejection fraction (LVEF) assessment is still mainly based on conductance catheter measurements and echocardiography.

Dedicated small animal MRT and PET scanners provide the option of both simultaneous acquisition of various physiological parameters and serial intra-individual in vivo monitoring. In contrast to MRT, PET offers the option for visualization and quantitation of metabolic processes such as the myocardial glucose uptake.

The elaboration of algorithms for the assessment of LV hypertrophy, LVEF, and scar size by the group provides the tools for obtaining multiple important parameters from a single PET acquisition in addition to the assessment of glucose metabolism. Yet, the approach may further benefit from separate PET scans for assessment of inflammatory processes using the glucose suppression protocols established by Lee et al. and Thackeray et al.

Taken together, Gross et al. show an excellent example of state-of-the-art live molecular imaging in the field of cardiology. Translation of this imaging concept, namely to obtain several precious parameters from one end point, might be part of an ongoing paradigm shift. Ultimately, this will lead to both less exposition to radioactive tracers in patients and smaller numbers of animals necessary for preclinical experimentation—in short both patient and animal protection.

References