

Featured research

Abstracts and commentaries

The circadian clock within the cardiomyocyte is essential for responsiveness of the heart to fatty acids

Durgan DJ, Trexler NA, Egbejimi O, et al. *J Biol Chem.* 2006; In press.

It has long been appreciated that both experimental animals and humans exhibit diurnal variations in several cardiovascular parameters, including blood pressure, heart rate, electrical properties of the heart, and cardiac output. These rhythms have been ascribed primarily to fluctuations in neurohumoral influence during the day, which in turn are due to both environmental factors and the central circadian clock within the suprachiasmatic nucleus. Diurnal variations in physiological cardiovascular parameters have been attributed to the same factors (eg, sympathetic activity) responsible for diurnal variations in fatal cardiovascular events, which have an increased incidence in the early hours of the morning. However, few studies have investigated whether the intrinsic properties of the heart fluctuate during the day, or whether a loss of synchronization between the presence of a stimulus (eg, increased sympathetic activity in the early hours in the morning) and responsiveness of the heart plays a part in the instigation of contractile dysfunction.

One extracellular influence to which the heart must adapt rapidly is a change in circulating fatty acid concentrations. Fatty acids are the primary fuel source for the normal myocardium. However, fatty acids are more than just a fuel for cardiomyocytes, as they act as both structural and signaling precursors [1]. Consequently, a balance between fatty acid availability and rates of fatty acid β -oxidation must be maintained. If the latter fails, detrimental fatty acid derivatives accumulate within the myocardium, which has been linked to the pathogenesis of various cardiomyopathies. A major way in which the heart prevents accumulation of intracellular fatty acids during periods of increased availability is through induction of

fatty-acid-responsive genes that promote β -oxidation. Increasing evidence exists in support of the hypothesis that the circadian clock *intrinsic* to the cardiomyocyte has a critical role in synchronizing cardiac metabolism with the environment. Circadian clocks are intracellular transcriptional mechanisms composed of positive and negative feedback loops, with a free running period of approximately 24 h. This molecular mechanism confers the selective advantage of anticipation, permitting the cell to respond rapidly to a given stimulus at the appropriate time of the day. The purpose of this study was to test the hypothesis that the circadian clock within the cardiomyocyte mediates diurnal variations in the responsiveness of the heart to fatty acids.

Commentary

Two strategies were used in this research: investigation of the responsiveness of cardiomyocytes to fatty acid *ex vivo*, and disruption of the circadian clock within the heart *in vivo*, through disruptions of either the light/dark cycle or metabolic genetics. Oscillations in metabolic genes were observed *in vitro* only under conditions in which the circadian clock was operational; furthermore, they exhibited the same temporal pattern as observed in the intact heart *in vivo*, when compared with circadian clock genes. Using oscillations of circadian clock genes as a marker of the subjective time perceived by the cardiomyocytes, experiments showed that diurnal variations in the responsiveness of cardiomyocytes to fatty acids persisted *ex vivo*. Furthermore, disruption of the circadian clock within the heart, either through manipulation of the light/dark cycle or through use of genetically modified mice, severely impaired the responsiveness of the myocardium to fatty acids. A mismatch between fatty acid availability and fatty acid oxidation rates results in accumulation of detrimental intracellular fatty acid derivatives. In

addition to β -oxidation, one way in which a cell prevents the accumulation of such derivatives is through their storage as triglyceride.

The authors report here that impairment of the circadian clock within the cardiomyocyte not only attenuated the induction of enzymes promoting β -oxidation, but also markedly attenuated triglyceride synthesis during fasting. Accumulation of detrimental fatty acid derivatives is not only a possible source of arrhythmia and contractile dysfunction, but is also associated with hallmarks of type 2 diabetes mellitus and the metabolic syndrome. This study is the first to ascribe a functional role for the circadian clock within the cardiomyocytes of the heart in vivo. Whether alterations in the circadian clock contribute to the progression of cardiovascular disease will require further investigation.

REFERENCE

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Danielle Feuvray

Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

Fox K, Garcia AA, Ardissini D, et al. *Eur Heart J*. 2006;27:1341–1381.

The new European guidelines are a welcome and comprehensive overview of the management of stable angina pectoris. They review the definition and pathophysiology, epidemiology, natural history and prognosis, diagnosis, and treatment, with clear algorithms covering the initial evaluation and medical management. Metabolic agents are reviewed and their anti-anginal efficacy confirmed. They are recommended as add-on treatment to hemodynamic agents or as a substitution when conventional drugs are not tolerated. The recent Cochrane Collaboration report [1] has also confirmed the effectiveness of the metabolic approach with trimetazidine in stable angina as monotherapy or in combination.

The lack of adverse effects with trimetazidine emphasizes its role when hemodynamic agents are limited by adverse effects, especially in the elderly. The important improvement in impaired left ventricular function may have prognostic implications, but these need to be confirmed in a large-scale trial

comparing trimetazidine with placebo, in addition to currently established evidence-based therapy.

REFERENCE

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Graham Jackson

Tissue distribution of ^{18}F -FDG-labeled peripheral haematopoietic stem cells after intracoronary administration in patients with myocardial infarction

Kang WJ, Kang HJ, Kim HS, Chung JK, Lee MC, Lee DS. *J Nucl Med*. 2006;47:1295–1301.

Adult stem cell therapy is expected to improve left ventricular function in patients with myocardial infarction. Because of the low risk of arrhythmia and the maximal concentration at the target tissue, intracoronary infusion of stem cells is preferred. The aim of this study was to investigate the homing and tissue distribution of intracoronarily injected peripheral hematopoietic stem cells labeled with [^{18}F]2-fluoro-2-deoxyglucose (FDG). Seventeen patients with myocardial infarction were included as the intracoronary injection group (14 men, three women; ages 58 ± 12 years). Three patients underwent intravenous stem cell injection as the intravenous injection group (three men, no women; ages 50 ± 20 years). After mobilization with granulocyte colony-stimulating factor, peripheral stem cells were collected by means of apheresis. [^{18}F]-FDG labeling of stem cells was performed for 40 min with gentle intermittent mixing at 37°C . The mean labeling efficiency was 72% (range 46–95%), and 44.4–175 MBq (1.2–5 mCi) of [^{18}F]-FDG-labeled stem cells were injected via an intracoronary catheter after stenting in infarct-related arteries. Images obtained by positron emission tomography (PET)/computed tomography were obtained with a 3-dimensional acquisition mode, 2 h after intracoronary infusion. Two hours after intracoronary infusion, 1.5% (range 0.2–3.3%) of injected stem cells accumulated at the infarcted myocardium. Outside the myocardium, spleen, liver, bladder, and bone marrow showed a high accumulation of stem cells. The delayed image of a patient up to 20 h showed a prolonged residence of stem cells at the myocardium. Intravenous injection of stem cells showed a high initial uptake by the lungs, with no myocardial activity. We have shown that [^{18}F]-FDG-labeled stem cell

PET could be used to assess the tissue distribution of stem cells and to measure their amount at a target tissue. [¹⁸F]-FDG-labeled stem cell PET can be used to measure and optimize the amount of stem cells injected.

Comments

Stem cell therapy for acute myocardial infarction has entered the stage of large-scale clinical trials. Earlier, small studies have shown that stem cell therapy may lead to decreased infarct size, improved regional and global function, decreased cardiac volumes, and improved perfusion in the infarct area. These early promising results have now provided the justification for larger randomized and blinded trials to address the efficacy of cellular therapy.

To evaluate the effects of stem cell therapy, assessment of the homing, distribution, and differentiation of cells are important. These factors may largely influence the ultimate clinical outcome in patients. In the present study, the authors successfully labelled the stem cells with FDG before their administration to patients who had suffered an infarct; using PET, they were able to visualize the presence of the labelled stem cells clearly. Moreover, they were able to measure the distribution and to quantify the percent injected dose of stem cells in the myocardium.

One of the interesting results of the study was that intravenous administration of stem cells, in contrast to the intracoronary route, did not result in any measurable uptake of labeled stem cells. As an example, *Figure 1* shows one of the figures from the paper, showing the uptake of FDG-labelled cells in the myocardium.

Thus, this technique of labeling stem cells with FDG gives quantitative information on cell homing and distribution, and may be used to optimize methods of administration and calculation of the dose of

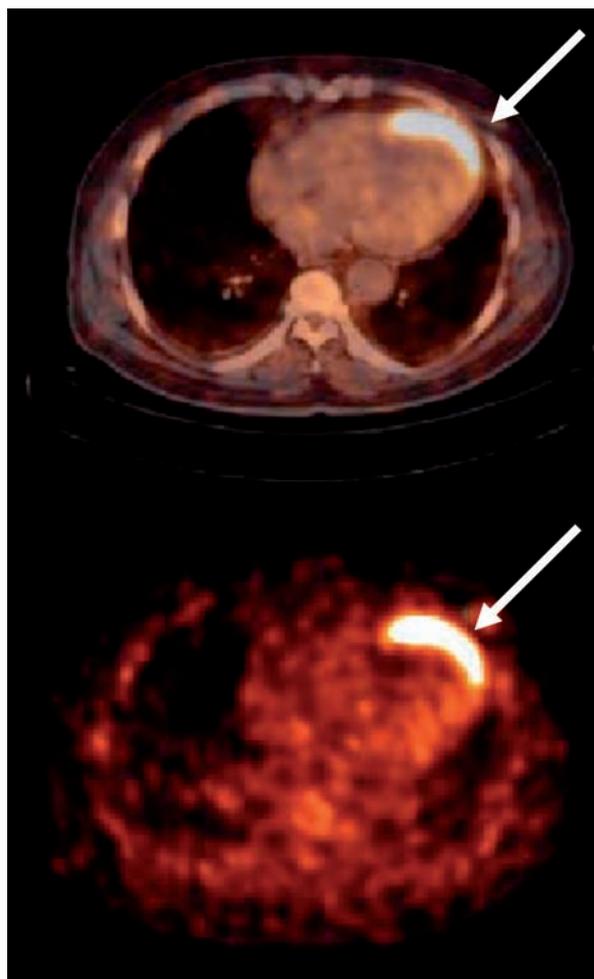


Figure 1. Positron emission tomography/computed tomography image of a patient after myocardial infarction. The arrow shows the distribution of FDG-labeled stem cells in the myocardium after intracoronary injection.

stem cells, and to predict the clinical outcome of treatment

Frans Visser