BBA - Molecular Basis of Disease xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Evaluation of cardiac energetics by non-invasive ^{31}P magnetic resonance spectroscopy☆,☆☆

Desiree Abdurrachim[a,b], Jeanine J. Prompers[a,c,*]

[a] Biomedical NMR, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
[b] Functional Metabolism Group, Singapore Bioimaging Consortium, Agency for Science, Technology and Research, Singapore
[c] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

ARTICLE INFO

Keywords:
^{31}P magnetic resonance spectroscopy
Heart
Cardiac energetics
Creatine kinase
Heart failure
Diabetes

ABSTRACT

Alterations in myocardial energy metabolism have been implicated in the pathophysiology of cardiac diseases such as heart failure and diabetic cardiomyopathy. ^{31}P magnetic resonance spectroscopy (MRS) is a powerful tool to investigate cardiac energetics non-invasively *in vivo*, by detecting phosphorus (^{31}P)-containing metabolites involved in energy supply and buffering. In this article, we review the historical development of cardiac ^{31}P MRS, the readouts used to assess cardiac energetics from ^{31}P MRS, and how ^{31}P MRS studies have contributed to the understanding of cardiac energy metabolism in heart failure and diabetes.

This article is part of a Special issue entitled Cardiac adaptations to obesity, diabetes and insulin resistance, edited by Professors Jan F.C. Glatz, Jason R.B. Dyck and Christine Des Rosiers.

1. Introduction

Alterations in myocardial energy metabolism have been thought to contribute to the development of heart failure [1]. In the healthy heart, about 60–70% of the energy production is provided by fatty acids, while the other major proportion is fulfilled by glucose substrates [2]. In the failing non-diabetic heart, it is generally accepted that the substrate balance shifts towards glucose utilization [3]. On the other hand, in type 2 diabetes, the cardiac substrate balance is shifted towards fatty acids and the diabetic heart almost exclusively relies on fatty acids for energy production [4]. Interestingly, cardiac energy status is reduced in both the failing non-diabetic heart [5,6] and the diabetic heart [7,8]. Patients with type 2 diabetes have a 2–3 times higher risk to develop heart failure compared to subjects without diabetes [9] and heart failure is one of the most common initial manifestations of cardiovascular diseases in type 2 diabetes [10], suggesting that the impaired cardiac energetics makes the diabetic heart more prone to heart failure development.

In the heart, the majority of adenosine triphosphate (ATP) is produced in the mitochondria by oxidative phosphorylation. However, the energetic status of the heart cannot be simply determined by the size of the ATP pool, as the amount of ATP being produced and consumed per unit of time, *i.e.* the ATP turnover, is many times greater than that [6]. To cope with variations in work load, the heart uses energy reserve systems, of which the most important one is the creatine kinase (CK) system (Fig. 1) [11–13]. In the mitochondria, the mitochondrial CK enzyme mediates the transfer of a phosphoryl group from ATP to phosphocreatine (PCr), which is the primary energy buffer in the heart. PCr then carries the phosphoryl group from the mitochondria to the cytosol, where the phosphoryl group is transferred back to ATP by the cytosolic CK, ready for utilization by the contractile proteins (myosin ATPase) and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) for maintaining calcium homeostasis, and for all other cellular processes which require energy [14]. Although the CK system is considered the most important energy reserve system in normal conditions, experiments in CK knockout mice and creatine-deficient mice suggest redundancy in the energy buffering mechanisms in the heart, as the cardiac phenotype of these mouse models was rather mild [15–18].

^{31}P magnetic resonance spectroscopy (MRS) is a non-invasive technique allowing detection of phosphorus (^{31}P)-containing metabolites involved in energy metabolism, such as PCr and the α-, β-, and γ-phosphate moieties of ATP, *in vivo*. Using ^{31}P MRS, various indices of the CK system, such as dynamic changes in high-energy phosphates upon ischemia and reperfusion, the PCr/ATP ratio, and the CK flux, have been measured to assess mitochondrial energetics. In addition, inorganic phosphate (Pi) can also be detected. The chemical shift of Pi

☆ In memory of Professor Klaas Nicolay, who deceased on January 10th 2017.
☆☆ This article is part of a Special issue entitled Cardiac adaptations to obesity, diabetes and insulin resistance, edited by Professors Jan F.C. Glatz, Jason R.B. Dyck and Christine Des Rosiers.

* Corresponding author at: Biomedical NMR, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands.
E-mail address: j.j.prompers@tue.nl (J.J. Prompers).

https://doi.org/10.1016/j.bbadis.2017.11.013
Received 7 July 2017; Received in revised form 17 November 2017; Accepted 18 November 2017

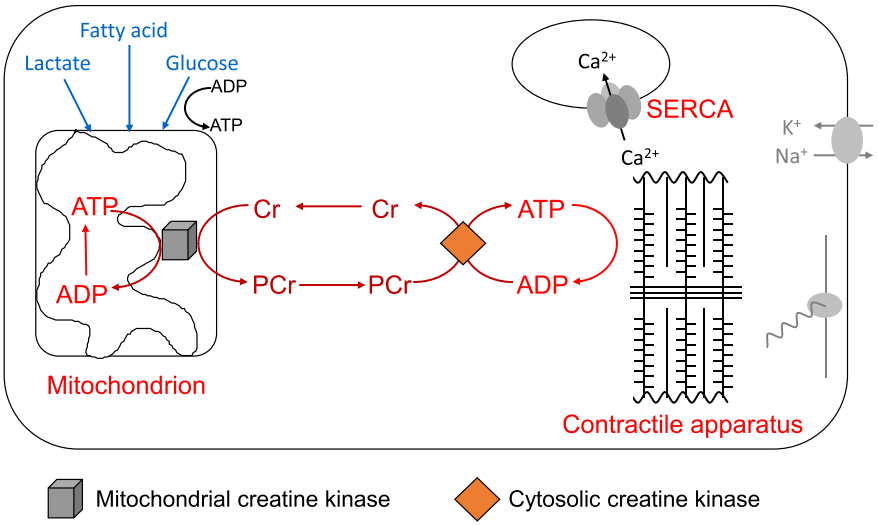

Fig. 1. Illustration of the creatine kinase (CK) system in the cardiomyocyte. The CK system is responsible for buffering and transferring energy between mitochondria, where the majority of ATP is being produced (left side of the figure), and sites of ATP consumption (right side of the figure), in the form of phosphocreatine (PCr). The primary ATP consuming reactions in the cardiomyocyte are the myosin ATPase in the contractile apparatus leading to contraction and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) maintaining calcium homeostasis. Also depicted are the Na^+/K^+-ATPase in the sarcolemma and the ATP-requiring process of protein synthesis.

is pH-dependent, and as such, intracellular pH can be calculated from the change in the position of the Pi peak in the ^{31}P MR spectra [19]. However, depending on the localization technique used, cardiac Pi detection can be problematic as it may be obscured by the 2,3-diphosphoglycerate (2,3-DPG) signals arising from the blood pool [19].

^{31}P MRS provides us with cardiac energetics readouts, which cannot be obtained using other, invasive techniques. For example, while the concentration of ^{31}P metabolites can be determined using traditional biochemical analysis, this does not provide information about metabolic fluxes [20]. Furthermore, traditional biochemical analysis involves invasive tissue biopsy, and, given their inherent instability, this may lead to breakdown of high-energy phosphates, in particular of PCr [21]. Importantly, the non-invasive nature of ^{31}P MRS offers the opportunity for longitudinal studies, allowing repeated measurements within the same animal or subject. This reduces variation due to inter-individual differences and is beneficial in the monitoring of disease progression or treatment efficacy.

In this review, we will first touch upon the historical development and current status of cardiac ^{31}P MRS. Then, we describe how ^{31}P MRS can be used to obtain indices of cardiac energetics, and how ^{31}P MRS has contributed to the understanding of cardiac energetics in heart failure and type 2 diabetes.

2. Historical development of cardiac ^{31}P MRS

The first studies on cardiac energetics using ^{31}P MRS – or then known as ^{31}P NMR (Nuclear Magnetic Resonance) – date from four decades ago. However, due to the lack of spatial localization techniques, these studies were performed in isolated perfused hearts of rats [22–24], rabbits [25], and guinea pigs [26], by inserting the hearts in an NMR tube, and mostly investigated the effect of global myocardial ischemia or global changes in the heart after regional ischemia. Later on, with the advent of surface coils [27], one could also study regional changes in energy metabolism upon local ischemia in perfused rabbit hearts [28].

Following these *ex vivo* studies, cardiac ^{31}P NMR was applied *in situ* in open chest rats [29–31], cats [32,33], dogs [34], and pigs [35]. In these studies, a surface coil placed on top of the heart or a solenoidal coil surrounding the heart was used. In another study, a catheter coil was inserted *via* a peripheral blood vessel in dogs [36], which is less invasive compared to the open chest approach.

Along the invasive *in situ* open chest studies, advancements in spatial localization techniques, such as 'topical magnetic resonance' [37] and depth-resolved spectroscopy [38,39], allowed non-invasive *in vivo* ^{31}P NMR measurements in animal hearts. Importantly, these non-invasive techniques also made ^{31}P NMR applications in the human heart possible, of which the earliest studies used depth-resolved ^{31}P NMR spectroscopy [40], rotating frame depth-selection ^{31}P NMR [41], or 3D image selected *in vivo* spectroscopy (ISIS) [42].

2.1. Current status of ^{31}P MRS

Nowadays, cardiac ^{31}P MRS in humans is typically performed using clinical magnetic resonance imaging (MRI) scanners with a magnetic field strength of 1.5 T–3 T. Very recent technical advancements allowed human cardiac ^{31}P MRS to be performed at a higher magnetic field strength of 7 T, resulting in an increase in signal-to-noise ratio (SNR) or shorter measurement time [43] (Fig. 2). The generation of genetically modified mouse models to study heart diseases and the availability of pre-clinical MRI scanners with high magnetic field strengths (4.7 T–11.7 T) has also stimulated the development of ^{31}P MRS for the study of cardiac energetics in mice [44,45]. However, in rodents, particularly in mice, the application of ^{31}P MRS in the heart *in vivo* is challenging because the mouse heart is 1000–2000 times smaller than the human heart, and the heart beats ~10 times faster than the human heart. In addition, the respiration rate of mice is also 10 times faster. These characteristics necessitate proper synchronization of the ^{31}P MRS experiment with the heart and breathing motion for accurate localization (reviewed in [46]).

For the application in the heart, ^{31}P MR spectra are usually acquired in a single three-dimensional (3D) voxel covering the left ventricle using ISIS [44,47,48], or from multiple slices, columns, or voxels at the same time using 1D [45,48], 2D [49,50], or 3D [43] Chemical Shift Imaging (CSI), respectively, which allows spectra from different locations within the myocardium to be resolved (Fig. 3). Also combinations of 1D or 2D CSI with 1D or 2D ISIS localization [48,51] have been applied, to ensure that the signal from the non-encoding directions of the CSI experiment is restricted to the heart. However, whatever localization technique is used, one should always be aware of potential contamination from liver (which does not contain PCr) and skeletal muscle (with a higher PCr/ATP ratio than heart) tissue [47,48]. Further technical aspects of the different localization schemes for cardiac ^{31}P MRS have recently been reviewed in [52].

3. Ischemia/reperfusion studies

The early applications of ^{31}P NMR in the study of cardiac energetics investigated the changes in high-energy phosphates during ischemia