Review article

MR compatible ergometers for dynamic ^{31}P MRS

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Abstract

Magnetic Resonance (MR) compatible ergometers are specialized ergometers used inside the MR scanners for the characterization of tissue metabolism changes during physical stress. They are most commonly used for dynamic phosphorous magnetic resonance spectroscopy (^{31}P MRS), but can also be used for lactate production measurements, perfusion studies using arterial spin labelling or muscle oxygenation measurements by blood oxygen dependent contrast sequences. We will primarily discuss the importance of ergometers in the context of dynamic ^{31}P MRS. Dynamic ^{31}P MRS can monitor muscle fatigue and energy reserve during muscle contractions as well as the dynamics of recuperation of skeletal muscle tissue during the following recovery through signal changes of phosphocreatine (PCr), inorganic phosphate and adenosine triphosphate (ATP). Based on the measured data it is possible to calculate intracellular pH, metabolic flux of ATP through creatine-kinase reaction, anaerobic glycolysis and oxidative phosphorylation and other metabolic parameters as mitochondrial capacity.

This review primarily focuses on describing various technical designs of MR compatible ergometers for dynamic ^{31}P MRS that must be constructed with respect to the presence of magnetic field. It is also expected that the construction of ergometers will be easy for the handling and well accepted by examined subjects.

Keywords: Dynamic ^{31}P magnetic resonance spectroscopy; Exercise; MR ergometer; Muscle examination

Highlights:

- Different types of MR compatible ergometers are shown in clear illustrations.
- Advantages and disadvantages of different types of MR compatible would be highlighted.
- Short overview of dynamic ^{31}P magnetic resonance spectroscopy is done.

Introduction

Magnetic resonance (MR) is a non-invasive, non-ionising and non-destructive examination technique routinely used in medicine and biology. Clinical MR imaging (MRI) and spectroscopy (MRS) examination is based on the observation of proton signals (^1H). However, other nuclei are also observable by MR, e.g. phosphorus (^{31}P), and these are of high interest for specific applications. Phosphorous atoms are key parts of metabolites responsible for energy turnover, e.g., adenosine triphosphate (ATP), and phosphocreatine (PCr). Although the concentrations of these metabolites in human muscles are relatively high, i.e. [ATP] ~ 8.2 mmol/l and [PCr] ~ 33 mmol/l in cell water (Kemp et al., 2007), the MR sensitivity of ^{31}P nuclei is much lower than proton sensitivity (only $\sim 6.6\%$ of signal intensity of ^1H atom). Thus, accumulation of signals and localization of relatively big volumes are often necessary. On the

other hand, due to the inherent safety of MR, ^{31}P MRS can be arbitrarily repeated and used for the long-term monitoring of patient treatment or disease progression (Table 1). This makes ^{31}P MRS extremely valuable, as the only alternative technique providing insight into cellular energy metabolism is highly invasive, i.e. tissue biopsy.

Higher magnetic fields ($\geq 3\text{T}$) together with optimized radiofrequency (RF) coils result in a significantly increased signal to noise ratio (SNR). As a result, well localized ^{31}P MR spectra can be measured and specific information from a small volume of interest (e.g. "single muscle") is obtainable (Meyerspeer et al., 2005; Moll et al., 2018; Valkovič et al., 2014). Typical ^{31}P MR spectrum from the calf is shown in Fig. 1. It should be mentioned that in comparison with proton MRS the evaluation of ^{31}P MRS is easier because signals are better separated and the baseline is not distorted by macromolecules and lipids. Moreover, none of the ^{31}P MRS signals are extremely dominant.

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Table 1. Short overview of ^{31}P MRS clinical applications

Clinical review (Argov et al., 2000; Mattei et al., 2004)
Classic use – glycogenosis (Chance et al., 1982; Wary et al., 2010)
• mitochondrial disorder (Argov et al., 2000; Jeppesen et al., 2007)
• muscular dystrophy (Kemp et al., 1993; Lodi et al., 1999)
• uremic syndrome (Nishida et al., 1991; Táborský et al., 1993)
• peripheral artery disease (Anderson et al., 2009; Kemp et al., 2001)
Hot topic – diabetes and obesity (Cree-Green et al., 2015; Valkovič et al., 2013)
• cardiac ^{31}P MRS (Dass et al., 2015; Levelt et al., 2016)

Fig. 1. Rest ^{31}P MRS spectrum from the calf muscle.

The spectrum was measured by non-localized sequence of FID with parameters: TR = 15 s, nominal FA = 90° , Acq = 16 on 3T MR system Trio Siemens equipped with dual $^1\text{H}/^{31}\text{P}$ flexi coil (diameter = 11 cm, Rapid company). Phosphomonoesters (PME), i.e. phosphoethanolamine 6.78 ppm and phosphocholine 5.88 ppm; inorganic phosphate 5.02 ppm (Pi); phosphodiester (PDE), i.e. glycerol-3-phosphocholine 2.76 ppm and glycerol-3-phosphoethanolamine 3.20 ppm; phosphocreatine 0 ppm (PCr, reference signal); adenosine triphosphate -2.48 ppm (γATP); -7.52 ppm (αATP); -16.26 ppm (βATP); nicotinamide adenine dinucleotide -8.3 ppm (NADH).

Dynamic ^{31}P MRS is an examination method which enables *in vivo* monitoring of metabolic changes during and/or after physical exercise. Muscle tissue utilizes ATP for its contraction, but at the same time this is compensated by the ATP production. In the initial phase of exercise, ATP is resynthesized primarily from PCr and adenosine diphosphate via creatine-kinase reaction. But once the anaerobic glycolysis in cytosol and oxidative phosphorylation in mitochondria of muscle cells are properly started, these reactions take over. The changes in ATP, PCr, and inorganic phosphate (Pi) concentrations during exercise can be dynamically measured by ^{31}P MRS. Their intensities and chemical shifts at each time point of the exercise are calculated and can be used for the calculation of pH, PCr recovery rate time (τ_{PCr}), initial recovery rate of PCr resynthesis (V_{PCr}), and mitochondrial capacity (Q_{max}). In Fig. 2 changes in signal intensities and pH during a 14 minute experiment are demonstrated.

More details about the biochemical reactions and their measurement by dynamic ^{31}P MRS can be found in other review articles (Kemp and Radda, 1994; Kemp et al., 2015; Valkovič et al., 2017a).

Fast biochemical reactions in muscles have to be observed immediately during and after exercise, and thus, MR compatible exercise devices, i.e. MR ergometers, operating inside the magnet are required. Construction of MR ergometers must re-

Fig. 2. PCr, Pi and pH dependency during dynamic ^{31}P MRS.

Integral values were evaluated by program jMRUI (jMRUI consortium). The subject was at rest for 2 minutes (60 spectra with TR = 2 s), 6 minutes of exercise (180 spectra with TR = 2 s) and 6 minutes at rest again (180 spectra with TR = 2 s).

spect static and dynamic magnetic and radiofrequency fields of the MR system and the narrow space of the bore of the MR system. Information on dedicated coils and sequences for dynamic ^{31}P MR spectroscopy is mentioned together with a description of different types of ergometers.

MR compatible ergometers

The dynamic ^{31}P MRS was introduced in the early 80's of the 20th century when subject's extremities were examined on experimental MR systems originally dedicated to small animals studies. The exercise was first applied outside of the MR system bore (Chance et al., 1980; Zatina et al., 1986), but when it became apparent that the observed reactions have very fast rates, it was decided that the exercise has to be performed whilst in the MR system. At that time the space limitation of the magnet bore of experimental MR systems (bore diameter of up to 30 cm) slightly favored construction of simple ergometers for the examination of forearm muscles. Today's MR ergometers are mostly designed for examining the lower limbs or the heart, and electronics controlling the exercise are available.

The construction of whole-body MR systems with sufficient space in the bore enabled the examination of all extremities; the first dynamic ^{31}P MR study on whole-body system was published in 1986 (Itoh et al., 1986). Many different home types of ergometers have been constructed since that time and used for the examination of volunteers and patients. There are also a variety of commercially sold ergometers available for the more common exercise types (Ergospect medical company, Austria; LODE, The Netherlands), that might be attractive for more clinically oriented sites, diminishing the need for a MR ergometer to be built in the lab.

When designing an ergometer, it is important to address the main physiological, mechanical and material requirements (e.g. most natural but also controlled realization of extremities motion within the scanner bore, matching the ergometer and joint axes, ergonomics, suppression of adjacent motion, MR compatibility of ergometer material, appropriate embedment of RF coils into ergometer frames, exercise monitoring). These requirements are discussed in more detail in the following paragraphs.

Generally, an MR compatible ergometer is connected to the MR console and consists of three main parts: 1) mechanical body of the ergometer for exercise inside the bore of the MR

tomograph; 2) resistance mechanisms and 3) monitoring system (Fig. 3).

Fig. 3. Simplified scheme of an MR compatible ergometer.

Orange: hardware and software of the MR system; green: mechanical part of the ergometer; red: system of monitoring exercise, triggering and self-controlling system. For details see the text. (For colour resolution see the on-line edition.)

Body of the MR compatible ergometer

The different constructions of ergometers enable examining almost all muscles in the human body – calf (Duteil et al., 2004; Francescato and Cettolo, 2001; Greiner et al., 2006; Gussew et al., 2012; Hosseini Ghomi et al., 2011; Mancini et al., 1992; Meyerspeer et al., 2005; Naimon et al., 2017; Quistorff et al., 1990; Raymer et al., 2006; Šedivý et al., 2015; Sinha et al., 2012; Tschiesche et al., 2014), thigh (González de Suso et al., 1993; Jeneson et al., 2009; Larson et al., 1994; Layec et al., 2008; Valkovič et al., 2013; Vanderthommen et al., 1999), back muscle (Hiepe et al., 2014), forearm muscle (Kimura et al., 2006; Minotti et al., 1989; Sairyo et al., 2003; Wilson et al., 1988) and the heart (Gusso et al., 2012; Le et al., 2017). On one side, the construction of an MR compatible ergometer can be very simple – e.g. rubber bulb of a sphygmomanometer (Arnold et al., 1984), flex band (Whipp et al., 1999) or weights attached to the moving extremity (Sleigh et al., 2016). However, ergometers can obviously be highly complex machines with patient management and electronic control of exercise load and performance (Gusso et al., 2012; Raymer et al., 2006; Tschiesche et al., 2014). Fig. 4 shows schemes of various MR compatible ergometer bodies used in different studies. In particular, ergometer with pedal resistance against extension of foot, i.e. plantar flexion, is used for examination of gastrocnemius muscle (Meyerspeer et al., 2005; Šedivý et al., 2015), or soleus muscle if knee is bent up to 60° (Niess et al., 2018; Valkovič et al., 2016). If the resistance of pedal foot ergometer is applied in the opposite way, i.e. against pulling towards the body, then the tibialis anterior muscle is loaded and its metabolism can be studied (Raymer et al., 2006). Quadriceps muscles are typically examined in a prone position using knee extension (Layec et al., 2008). In this case ^{31}P MR coil is in a standard horizontal position on the patient table and motion artefacts are minimized. On the other hand, the examination of loaded quadriceps is also possible in a supine position with a raised/bended knee (Larson et al., 1994), using bicycle (Jeneson et al., 2009) or push-pull (González de Suso et al., 1993)

ergometers with coil fixed on the top of the thigh. Ergometers for examination of back muscles were also designed, but are not that commonly used (Hiepe et al., 2014). Positioning of patient and ergometers loading forearm and arm inside the whole-body MR scanners (with bore diameters of 50–60 cm) is not very comfortable and feasible. Thus short-bore magnets (e.g. experimental/animal MR systems) or non-calibrated exercises are utilized.

To produce whole body systemic load for cardiac ^{31}P MRS, ergometers for a “whole-body” exercise are necessary. The schemes of three types of these ergometers are shown in Fig. 5 – classical bicycle (spinning movement), up/down and push/pull ergometers.

Significant attention in the body ergometer design must be focused to the ergonomics of patient motion. Exercise on the MR ergometer must be comfortable, complying with natural axes and angles. The exercise motion should not cause motion artefacts in the RF-coil region. On the other hand, exercise load has to be sufficient to produce metabolic changes in PCr, Pi etc. for a reliable calculation of metabolic parameters. Layec et al. (2009) and Šedivý et al. (2015) showed that higher workload increased the reproducibility of metabolic parameter calculation.

Ergometer body design should also take into account the potential range of shapes and sizes of the patients under investigation. There has to be sufficient space for the exercise and for the stable position of the remaining part of the body to prevent motion artefacts (Greiner et al., 2006; Naimon et al., 2017). In addition, the possibility to switch fixation of left and right extremities on one ergometer could prove very useful.

The following technical requirements of the ergometer construction have to be fulfilled: (i) the use of non-magnetic materials, (ii) not too heavy construction for easy handling, and (iii) the robustness and high mechanical stability. MR compatible ergometers are, therefore, typically made from stiff plastics, e.g. polyvinylchloride (PVC), nylon for highly mechanically stressed components, acrylonitrile butadiene

Fig. 4. Schemes of several types of ergometers for the MR examination.

(A) back muscles; (B, C) quadriceps muscles; (D) gastrocnemius muscle with a holder of leg; (E) tibialis anterior muscle; (F) forearm muscles; (G, H) arm muscle; (I) forearm muscle (experimental MR system); (J) push-pull bicycle with a coil position for quadriceps or heart muscle measurement. The position of RF coil is labeled in red. (For colour resolution see the on-line edition.)

Fig. 5. Three types of cardiac ergometers.

(A) standard bicycle; (B) up/down; (C) push/pull.

styrene (ABS) and polyethylene terephthalate (PET(G)) for 3D printing parts; but wood or other non-magnetic materials, i.e. aluminum, titanium, are also used. To avoid the formation of eddy currents and torque, a non-magnetic metal has to be used for parts that are designed to move in a magnetic field.

Resistance mechanisms

Resistance mechanism of an ergometer must enable easy and reliable setting of a workload with a large dynamic range to enable the examination of various subjects. Usually, the workload is set as a fraction of patient maximal voluntary force of contraction (MVC), so it is beneficial if the ergometer construction and dynamic range of workload setting also enables the measurement of the MVC. It is simpler when pneumatic ergometers are used.

In the other cases the resistance has to be set up manually based on the measurement of MVC outside of magnet room. Similar construction of the device should be used, fixation of studied extremities has to be the same as in the ergometer in the magnet room. Details how to measure MVC can be found in the paper of (Mayhew et al., 2008). Another possibility is to use an isometric measurement of MVC – for a review see (Schaefer and Bittmann, 2017).

Real time adjustments of the workload during exercise are useful especially in examination protocols with increasing/stepped load. Mechanical or pneumatic solution of ergometer resistance is the easiest way for workload adjustment, although more complex systems, where pneumatic and mechanical principles are combined together, have also been constructed (Gusso et al., 2012; Ryschon et al., 1995). Mechanical

resistance is usually realized by weights (Hiepe et al., 2014; Hosseini Ghomi et al., 2011; Layec et al., 2008; Raymer et al., 2006; Šedivý et al., 2015), elastic rubber bands (Francescato

and Cettolo, 2001; Mancini et al., 1992; Naimon et al., 2017) or brake mechanism (Gusso et al., 2012; Jeneson et al., 2009), see Fig. 6.

Fig. 6. Different types of workload mechanisms.

(A) weights (potentiometer is connected by the second cord and monitors the exercise); (B) elastic bands; (C) pneumatic with pressure bottle; (D) brake (frictional force) with three different possibilities of setting friction (by weights, air pressure or screw); (E) pneumatic with throttle valve.

The brake mechanism is primarily used in bicycle types of MR ergometers. Its advantage is the possibility of continuously increasing resistance during exercise (Gusso et al., 2012), which is difficult in the weights and elastic bands resistance mechanism.

The system for force transmission from weights/brakes to pedal ergometer is also very important. Systems with small friction can be realized by cords (Layec et al., 2008; Šedivý et al., 2015) or a solid rod mechanism (Hosseini Ghomi et al., 2011; Raymer et al., 2006), see Fig. 4. When using cords, these should be rather non-elastic to prevent loose motion of the weights or the cords. While solid rod ergometers are more robust, they often require the weights to be part of the apparatus, which can be rather inconvenient.

The pneumatic mechanism of ergometer resistance is based on the principle of pistons. One air piston mechanism (Gussew et al., 2012; Meyerspeer et al., 2005; Sinha et al., 2012; Quistorff et al., 1990) is used in single pedal ergometers (Fig. 6C). A mechanism using two pistons (oil or water and throttle valve) (González de Suso et al., 1993; Rodenburg et al., 1994) is more suitable for a push/pull system of two pedal ergometers (Fig. 6E). The resistance can be changed continuously and major part of the construction can be outside of magnet room. On the other side, the possibilities of fluid or air leakages are the general disadvantages of pneumatic ergometers.

Control and self-monitoring system and control system of an ergometer

The system for monitoring exercise (Francescato and Cettolo, 2001; Gusso et al., 2012; Layec et al., 2008; Meyerspeer et al., 2005; Naimon et al., 2017; Raymer et al., 2006; Sinha et al., 2012; Tschiesche et al., 2014) is very important, as the overall

exercise workload and the mean exercise energy output consists of the ergometer resistance and the path of the subject's motion. Workload monitoring systems enable measuring the length and frequency of exercises, force, workload etc. The construction of a monitoring system is based on a sensor, typically potentiometer, which detects and transforms the motion of the ergometer into an electric or optical signal (Gusso et al., 2012; Meyerspeer et al., 2005; Tschiesche et al., 2014). This signal is then transferred out of the magnet room and recorded on a personal computer. Optical signal is preferred because optical fibers do not interfere with electromagnetic signals.

In addition, the extent of motion of the subjects, especially patients, can diminish during the exercise challenge, and thus, the online monitoring provides a possibility of verbal motivations of patients to increase their exercise performance. This system of exercise monitoring has been also utilized as a feedback system for real-time self-adjustment (Boss et al., 2018; Gussew et al., 2012; Ryschon et al., 1995; Tschiesche et al., 2014), which automatically informs the subject about his/her exercise performance. For example, this can be achieved by a graphical demonstration of the pedal depression. Such a feedback system improves reproducibility of the measurement (Tschiesche et al., 2014). The reproducibility of exercise can also be increased by a mechanical limitation of the exercise, e.g., by allowing only a small range of angle rotation of the ergometer pedal.

Visual or sound signalization triggers motion of a subject on the ergometer. It helps to synchronize subject motion with signal acquisition in MR sequence and to reduce motion artefacts in MR signal. Visual signalization is very useful in complicated examination protocols with several exercise blocks (Slade et al., 2006).

³¹P coils and ³¹P MR sequences

An RF coil tuned to ³¹P resonance frequency, which is different from the ¹H frequency, is another indispensable part of equipment for dynamic ³¹P MR spectroscopy. Generally, the main features of ³¹P coils are: a) the size; b) number of channels, i.e. single loops or phased arrays; c) the type of the construction, i.e. solid or flexible surface and volume coils. Surface coils are often positioned close to the examined tissue which guarantees the best available SNR. In addition, surface ³¹P coils are popular because they can be applied universally, i.e. on leg muscles, forearms, back muscles or other organs, such as the heart, liver or brain. On the other hand, surface coils provide a restricted and inhomogeneous excitation RF field (Chmelík et al., 2014). Therefore, absolute quantification of metabolites from signal intensities or investigation of deeper lying skeletal muscles and the heart is extremely difficult. Signal sensitivity of phosphorous coils can be improved by combining multiple elements into phased arrays of several receiver channels. More receiver channels are also used in volume coils (Valkovič et al., 2017b), half-volume coils and surface coils (Boss et al., 2018; Goluch et al., 2015). Combination of ³¹P MR coil with other magnetic circuits of ¹H channel (dual transmit/receive ³¹P/¹H coil) improves SNR and sensitivity of ³¹P measurement due to the option of using ¹H decoupling and signal enhancement by nuclear Overhauser effect. In addition, ¹H channel of dual coils also offers the possibility of combining ³¹P MRS measurements with ¹H MRI and/or ¹H MRS (Meyerspeer et al., 2005; Schmid et al., 2014) during one exercise.

In ³¹P MRS several basic signal acquisition techniques are used. Measurement of ³¹P spectra by simple free induction decay (FID) relying only on the rough localization by the surface coil is still popular. However, localization of ³¹P spectra by DRESS (Moll et al., 2018; Valkovič et al., 2014), LASER (Niess et al., 2017), 2D CSI (Valkovič et al., 2016) sequences thus increases the specificity of the examination of the selected muscles. On the other hand, localized sequences, in particular the multivoxel ones, result in lower SNR and worse temporal resolution than the FID sequence.

Conclusions

This review describes the basic part of equipment for dynamic ³¹P MRS, i.e. the MR compatible ergometer. Characterization of muscle metabolism by dynamic ³¹P MRS has a great potential in clinics for treatment monitoring of metabolic syndrome and in sports medicine for streamlining the training and/or substrate intake of athletes. For those purposes, new self-controlling MR compatible ergometers with automated workload adjustment based on the monitoring of the exercise performance would be beneficial.

Conflict of interests

The authors have no conflict of interests to declare.

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