Phosphorus magnetic resonance spectroscopy of the human heart: current status and clinical implications

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Introduction

Magnetic resonance spectroscopy is a non-invasive technique which, by means of a spectrum, can be used to reveal the presence of certain molecules in a specific area. Magnetic resonance spectroscopy uses a strong external magnetic field and radiofrequency pulses to detect the magnetic resonance signal of nuclei which possess magnetic spin. Several biologically interesting atomic nuclei are suitable for magnetic resonance spectroscopy, such as hydrogen (1H), carbon (13C), sodium (23Na), and phosphorus (31P). For non-invasive studies of the heart in vivo, 31P magnetic resonance spectroscopy has been used extensively because it provides information about the high-energy phosphate metabolism of the heart. The first cardiac 31P magnetic resonance spectroscopy experiments were conducted by Gadian et al.1 in 1976, using isolated Langendorff-perfused animal hearts. In 1985 Bottomley2 reported the first localized human cardiac 31P spectra obtained in healthy volunteers. Since then, the development of 31P magnetic resonance spectroscopy for studies in men has grown steadily, but has been hampered by several technical difficulties. An important limitation of in vivo 31P magnetic resonance spectroscopy is the relatively low sensitivity of the technique resulting in long acquisition times and a low spatial resolution. Consequently, 31P magnetic resonance spectroscopy currently has no well-defined application in clinical cardiology. Future developments, such as the application of stronger magnetic field strengths, are expected to provide higher spatial resolution. The promise of non-invasive insight into the metabolic status of the heart seems so powerful, especially when combined with magnetic resonance imaging, that the question: 'when will this diagnostic tool be available in clinical cardiology?', is more prominent than 'whether 31P magnetic resonance spectroscopy will become available in clinical cardiology'.

The present report provides an overview of the status, prospects and possible clinical implications of cardiac 31P magnetic resonance spectroscopy. Results of major human studies conducted to evaluate myocardial ischaemia, heart transplantation, cardiomyopathy and left ventricular hypertrophy will be discussed.

Heart muscle metabolism

Adenosine triphosphate (ATP) serves as a high-energy intermediate for maintaining cellular homeostasis and contractile function of the heart. The ATP concentration in ventricular myocardium is remarkably constant and quite independent of work load. Under normal conditions, the main part (40-70%) of ATP is formed intramitochondrially, fuelled by β-oxidation of fatty acids. At the inner mitochondrial membrane, the high-energy phosphate bond of ATP is transferred to creatine to yield phosphocreatine and adenosine diphosphate (ADP), a reaction catalysed by mitochondrial creatine kinase. Through the phosphocreatine shuttle, phosphocreatine is then transported to the cytosol and the contractile elements where it is split by cytoplasmic creatine kinase (isoenzymes CK-MM and CK-MB) in order to form ATP and creatine. At the sarcomere level, ATP is split by myosine-ATPase, resulting in the formation of ADP, inorganic phosphate (Pi) and free energy — elements essential for contraction.

During myocardial ischaemia, glucose becomes the predominant fuel whereby lactate is formed by anaerobic glycolysis. Accumulation of NADH, H+ and lactate inhibits several regulatory sites of metabolism.
including glycolysis. During the early stages of ischaemia, the myocardial ATP concentration is preserved at the expense of phosphocreatine, which decreases rapidly during ischaemia.

Heart failure can lead to metabolic changes similar to those observed in ischaemia. The concentrations of creatine and phosphocreatine are diminished, and this is accompanied by reduced total activity of creatine kinase and altered isoenzyme distribution of creatine kinase. The mechanisms behind these adaptations are discussed later in the section entitled ‘magnetization transfer’.

**31P magnetic resonance spectroscopy**

Magnetic resonance spectroscopy is performed with a homogeneous magnetic field at a field strength of at least 1.5 Tesla. Only nuclei which possess a “magnetic spin moment” due to an odd number of protons and/or neutrons are suitable for the technique. When nuclei with a “magnetic spin moment” are situated in a strong external magnetic field, and are subjected to a radiofrequency pulse at the ‘resonance frequency’ of the nucleus, their spin state is altered. Following the radiofrequency pulse, the spins will precess around the direction of the external magnetic field and produce a radiofrequency signal which is detected by an antenna ('surface coil'), positioned as close as possible to the tissue of interest. The signal received by the surface coil is a time-dependent voltage. After mathematical processing by application of Fourier transformation, the frequency information is obtained as a spectrum. The separation of the peaks in a spectrum is caused by a phenomenon called ‘chemical shift’. Identical nuclei within one molecule or in different molecules experience a slightly different local magnetic field caused by differences in chemical environment. This local magnetic field of a nucleus gives rise to a specific resonance frequency. Differences in resonance frequency or ‘chemical shifts’ are expressed in Hertz, or as dimensionless parts per million (p.p.m.), making it independent of the applied magnetic field strength. The area under each peak is proportional to the number of nuclei resonating at that frequency and reflects the relative concentration of specific metabolites within the volume of interest (‘sample volume’).

Compared to hydrogen (1H), phosphorus (31P) is less magnetic resonance sensitive, but has a wider chemical shift range. The in vivo human 31P spectrum allows the identification of signals from several important high-energy phosphate metabolites (Fig. 1), such as phosphocreatine, the three separate signals (α, β and γ) from ATP, the overlapping signals from phosphomonoesters, 2,3-diphosphoglycerate and inorganic phosphate (P), and finally a combined signal from phosphodiesters and phosphatidylcholine (mainly serum phospholipids). Because technical difficulties preclude the measurement of accurate absolute metabolite concentrations relative concentrations are most frequently used[6-8]. In a recent study by Yabe et al[9], ‘absolute’ phosphocreatine and ATP concentrations were reported. However, these measurements were based on a number of estimations and assumptions resulting in high standard deviations[8]. Nevertheless, the use of ‘absolute’ instead of ‘relative’ concentrations has advantages especially for disease states which are associated with reduced or increased concentrations of both phosphocreatine and ATP. The ratios of phosphocreatine/ATP and phosphocreatine/P are considered to represent the phosphate potential (energy charge) of the myocardium within the volume of interest[7-10]. In studies of the human heart, the phosphocreatine/ATP ratio is most often used as an indication of energy charge since signal from P cannot usually be observed as a separate peak in the spectrum. This is due to the overlapping 2,3-diphosphoglycerate signal which arises from blood within the volume of interest. The chemical shift of P, and of 2,3-diphosphoglycerate are almost identical but in some cases the resonances can be resolved using a technique called proton-decoupling[11]. When the P peak is resolved, it can be used to estimate the pH within the volume of interest because the chemical shift of P, is pH-dependent at the physiological pH range whereas the chemical shift of phosphocreatine is practically pH-independent. The difference in chemical shift between the P, and phosphocreatine peaks in a spectrum therefore provides a non-invasive measure of intracellular pH[11]. The phosphocreatine/ATP or phosphocreatine/P ratios are usually determined after ‘curve fitting’ of the spectrum to estimate peak areas and chemical shifts. In most cases the area under the curve rather than the height of a peak is used to calculate ratios[12]. The β-ATP signal is preferably used to determine the phosphocreatine/ATP ratio since it is not contaminated with signal from ADP, NAD+ or NADH[12], as is the case for the α and γ ATP peaks.

To locate the volume of interest, several localization techniques have been developed, such as Depth REsolved Surface coil Spectroscopy (DRESS), Image Selected In vivo Spectroscopy (ISIS), and Chemical Shift Imaging (CSI), each with its own advantages and disadvantages. Depending on the technique used, localization is possible in one, two or three dimensions. Figure 2 shows an example of volume selection with two-dimensional ISIS combined with one-dimensional CSI. It is important to realize that, due to the sensitivity profile of the surface coil, spectra can be obtained from the anterior part of the left ventricular wall only. In obese patients, and in females with a more than average breast size, the distance between the heart and the surface coil can even be too large to obtain signal from the anterior myocardial wall. For a detailed description of the magnetic resonance spectroscopy technique we refer to more specific literature[7-9].

Localization techniques are necessary to minimize contamination of the spectra with signal from outside the volume of interest. Signal contamination is of serious concern in 31P magnetic resonance
To date, the smallest volume of interest reported is 8 cm$^3$, which requires an external magnetic field of 4 Tesla$^{15,16}$. Cardiac $^{31}$P magnetic resonance spectra may often contain signal from blood, skeletal muscle from the chest wall as well as from the diaphragm and signal from the liver$^{5,11-13}$. Such contamination will considerably influence the phosphocreatine/ATP ratio. For example, the phosphocreatine/ATP ratio of skeletal muscle is much higher than the myocardial phosphocreatine/ATP ratio. Correction for this type of contamination afterwards is not always possible$^{12,13}$. The contribution of signal arising from ATP in blood to the total signal of ATP in a cardiac $^{31}$P spectrum can be corrected for by determining the amount of 2,3-diphosphoglycerate in the $^{31}$P spectrum. The ratio ATP/2,3-diphosphoglycerate in blood is relatively constant, and blood contains 2,3-diphosphoglycerate in the absence of phosphocreatine$^{5,11,12,17}$.

The severity of signal contamination by extracardiac tissues may differ between measurements even within the same subject$^{18}$. Many factors are important in this respect, including positioning of the surface coil, the site of the sample volume, motion of the subject, and the used localization technique$^{10,18}$. Consequently, the results from different research centres vary widely. The reported limits of 'normal' for the phosphocreatine/ATP ratio in human myocardium range from 0·9 to 2·1$^{15,12}$, but are still a matter of debate. Small changes in acquisition technique and data processing may considerably alter the results, which makes it difficult to compare data from different centres$^{12}$. Interpretation and comparison of $^{31}$P magnetic resonance spectroscopy data would benefit from a consensus about the appropriate acquisition technique and data processing$^{5,12,18}$.

**Magnetization transfer**

Magnetic resonance spectroscopy can also be applied to determine the rate of enzymatic reactions using a technique called 'magnetization transfer'$.^{15,19-24}$ With this technique the kinetics of creatine kinase have been investigated in the myocardium of animals and men$^{22-24}$. The creatine kinase activity in patients with dilated cardiomyopathy or left ventricular hypertrophy (LVH) was 40% lower than in healthy controls$^{19}$. The relative contribution of the creatine kinase isoenzymes CK-MB and CK-BB was higher, and that of the isoenzyme CK-MM lower in the myocardium of the dilated cardiomyopathy patients. The altered expression of the creatine kinase isoenzyme genes appears to be stimulated by increased wall stress$^{19}$. Similar changes were observed in patients with ischaemic heart disease$^{19}$. Some investigators have suggested that, under stressful conditions, the relative increase in the creatine kinase isoenzymes CK-MB and CK-BB partly compensates for decreased energy reserve caused by depletion of phosphocreatine and the decreased total creatine kinase activity$^{19,22-24}$. Because of a higher affinity to ADP, the B-containing isoenzymes are considered to be more

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/17/8/1158/403647/1160H.P.Beyerbachtet-al)

**Figure 1** Myocardial $^{31}$P magnetic resonance spectrum obtained from a healthy volunteer. (a) Spectrum before curve-fitting. (b) Spectrum after curve fitting. p.p.m. = parts per million; PCR = phosphocreatine; ATP = adenosine triphosphate; PME = phosphomonoesters; a = 2,3-diphosphoglycerate (2,3-DPG, with $^{31}$P at position 3); b = inorganic phosphate (P) + 2,3-DPG (with $^{31}$P at position 2); PDE = phosphodiesters, mainly serum phospholipids (SPL).

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/17/8/1158/403647/1160H.P.Beyerbachtet-al)

**Figure 2** Sample volume selection with a combination of two localization techniques called 'Image Selected In vivo Spectroscopy' (ISIS) and 'Chemical Shift Imaging' (CSI). A transverse spin-echo image through the chest is used to determine the appropriate size and orientation of the sample volume in two dimensions. The $^{31}$P spectra are collected with a 10-cm diameter surface coil positioned directly above the left ventricular wall. The column projected over the heart consists of sections, 1 cm thick, from which separate spectra are collected.

spectroscopy$^{11,13}$. Currently, most scanners, used for clinical magnetic resonance spectroscopy operate at a field strength of 1.5 Tesla and require volumes of interest which exceed 25 cm$^3$ to acquire a spectrum with sufficient signal-to-noise ratio in a reasonable total examination time$^{14}$. The use of stronger magnetic field strengths improves spatial resolution but is expensive.
efficient than the MM isoenzyme in the formation of ATP from phosphocreatine[5,19,22-24].

**Initial results with magnetic resonance spectroscopy**

Using magnetic resonance spectroscopy, the high-energy phosphate metabolism has been evaluated most extensively in animal studies, allowing repeat experiments under controlled conditions. Examination of a heart in vitro using a Langendorff preparation prevents contamination of the spectrum by signal arising from blood and extracardiac tissue, and high spatial resolution can be obtained by the application of a very strong external magnetic field. Contamination of the spectrum by signal arising from extracardiac tissue can be markedly reduced in vivo with the surface coil directly at the myocardium during an open chest experiment in animals[25-27]. The absence of physiological circumstances, and the observed differences between different species in myocardial high-energy phosphate metabolism when subjected to stress[28], raise the question of how results from animal studies can be extrapolated to findings in man.

Despite all differences of opinion about the limits of 'normal' for the in vivo human myocardial phosphocreatine/ATP ratio, and about the optimal protocol for measuring the phosphocreatine/ATP ratio, much useful information about the cardiac high-energy phosphate metabolism of both animals and men has been gathered under a variety of physiological and pathophysiological states, such as myocardial ischaemia, transplanted hearts, cardiomyopathies and left ventricular hypertrophy. The following sections will deal with these clinical disease states.

**Myocardial ischaemia**

The effect of an ischaemic period on the myocardial high-energy phosphate metabolism depends upon the length and the severity of the ischaemic insult[28-34]. Both factors also influence the capability of recovery of the heart following reperfusion[27,29,30,32]. In a study of Zhang et al[25] the left anterior descending coronary artery of a canine heart was partially occluded for several hours. After onset of occlusion, the myocardial phosphocreatine concentration and phosphocreatine/ATP ratio initially decreased considerably, accompanied by a loss of contractile function. Several hours of hypoperfusion led to a normalization of the myocardial phosphocreatine concentration and phosphocreatine/ATP ratio, although ischaemic myocardial segments remained hypokinetic. Apparently, an adaptation process takes place which resembles the adaptation described for 'hibernating' myocardium. Consequently, a normal phosphocreatine/ATP ratio does not exclude the presence of ischaemia. Abnormal contractile function, as can be evaluated using magnetic resonance imaging, provides additional diagnostic information.

Weiss et al[35] examined 11 healthy volunteers and 16 patients with left main or left anterior descending coronary artery disease. Both groups were studied at rest and during isometric handgrip testing. At rest the myocardial phosphocreatine/ATP ratio was 1.72 ± 0.15 for controls and 1.45 ± 0.31 for patients. During exercise, the myocardial phosphocreatine/ATP ratio for healthy volunteers remained unchanged, but in patients with left main or left anterior descending coronary artery disease, the phosphocreatine/ATP ratio decreased significantly to 0.91 ± 0.24. In these patients the myocardial phosphocreatine/ATP ratio recovered to 1.27 ± 0.38 within 2 min of discontinuing exercise. Following revascularization, the myocardial phosphocreatine/ATP ratio normalized to 1.60 ± 0.70 at rest and to 1.62 ± 0.18 during exercise.

In 27 patients with severe left anterior descending coronary artery disease, Yabe et al[36] compared the results obtained with magnetic resonance spectroscopy to the findings with thallium-201 scintigraphy. Patients with a persistent scintigraphic defect did not show a significant decrease in myocardial phosphocreatine/ATP ratio during exercise (1.24 ± 0.30 at rest versus 1.19 ± 0.28 during exercise), whereas patients with a reversible scintigraphic defect had a significant decrease in phosphocreatine/ATP ratio from 1.60 ± 0.19 at rest to 0.96 ± 0.28 during exercise. The healthy controls studied by Yabe et al[36] had a myocardial phosphocreatine/ATP ratio of 1.85 ± 0.28 at rest versus 1.90 ± 0.23 during exercise. These studies indicate that 31P magnetic resonance spectroscopy is a technique that can clinically detect ischaemia of the anterior left ventricular wall.

Stress testing by means of physical exercise or administration of pharmacological agents, such as dobutamine, will play an important role in future 31P magnetic resonance spectroscopy studies[18,28,35,36]. Hearts that are hardly capable of maintaining their energy reserves at rest will show a decrease in myocardial phosphocreatine/ATP ratio when subjected to physically or pharmacologically induced stress[28,35,36]. The effects of a successful therapeutic intervention can be deduced from a smaller decrease of the myocardial phosphocreatine/ATP ratio during stress compared to the baseline situation.

Yabe et al[36] studied 41 subjects with significant left anterior descending coronary artery disease, and divided them into a group with fixed perfusion defects and a group with reversible defects as assessed by thallium-201 scintigraphy. The myocardial phosphocreatine concentration (expressed in µmol. g⁻¹ wet heart tissue) was significantly lower in the group with fixed perfusion defects compared with the group with reversible defects (3.94 ± 2.21 versus 7.64 ± 3.00, respectively). Also, the myocardial ATP concentration (expressed in µmol. g⁻¹ wet heart tissue) was significantly lower in the patients with fixed defects compared with the patients with reversible defects (6.35 ± 3.17 versus 4.35 ± 1.52, respectively). The authors concluded
that measurement of the ATP concentration in the human heart with $^{31}$P magnetic resonance spectroscopy can be used clinically for the evaluation of myocardial ischaemia and viability. Clinical use, however, is hampered by the fairly large standard deviations of the reported values.

The effects of a myocardial infarction on the high-energy phosphate metabolism of the human heart have been studied as well. In 20 patients with a previous myocardial infarction, Mitsunami et al. measured a decrease in myocardial concentrations of phosphocreatine and ATP. The phosphocreatine concentration in post-myocardial infarction patients was 7.4 ± 2.6 versus 11.3 ± 3.7 $\mu$mol.g$^{-1}$ myocardium in healthy volunteers and the ATP concentration was 4.9 ± 2.0 versus 7.4 ± 2.9 $\mu$mol.g$^{-1}$ myocardium, respectively. To determine whether myocardium is infarcted requires the measurement of absolute rather than relative concentrations of phosphocreatine and ATP.

In summary, $^{31}$P magnetic resonance spectroscopy in the assessment of myocardial ischaemia and viability can be applied clinically, but technical restraints limit its volume of interest to the anterior part of the left ventricular wall and the interventricular septum. This restriction is due to the loss of signal strength at greater distance from the surface coil. It is difficult to improve spatial resolution and to increase the depth at which spectra can be obtained, but if these limitations could be overcome the clinical value of $^{31}$P magnetic resonance spectroscopy in the assessment myocardial ischaemia and viability would increase considerably.

Transplanted hearts

Animal studies in rats have shown a significant correlation between the myocardial phosphocreatine/ATP ratio and histological evidence of rejection whereby a decrease of the phosphocreatine/ATP ratio even preceded the histological evidence of rejection. One explanation for the differences between human and animal studies might be the absence of immunosuppressive medication in the animal studies, leading to more severe acute rejection in rats.

In summary, both experimental and clinical results make it unlikely that, in the near future, $^{31}$P magnetic resonance spectroscopy will become available as a diagnostic modality for the management of patients receiving a heart transplant. Future developments however, such as the use of stronger magnetic fields, yielding higher sensitivity and resolution, and the measurement of absolute instead of relative concentrations, may help to overcome the present limitations.

Hypertrophic cardiomyopathy

Weiss et al. were the first to study patients with hypertrophic cardiomyopathy, and they observed no significant decrease in the myocardial phosphocreatine/ATP ratio. However, only five patients were studied. Conversely, subsequent $^{31}$P magnetic resonance spectroscopy studies by De Roos et al., Masuda et al., and Sakuma et al. showed a significantly lower phosphocreatine/ATP ratio in hearts of patients with hypertrophic cardiomyopathy compared with healthy controls. De Roos et al. found a lower myocardial phosphocreatine/ATP ratio in eight hypertrophic cardiomyopathy patients compared with nine healthy controls (1.32 ± 0.29 vs 1.65 ± 0.26). In the study of Masuda et al., 12 patients with hypertrophic cardiomyopathy had a myocardial phosphocreatine/ATP ratio of 1.43 ± 0.36 vs 2.09 ± 0.44 in 15 controls. Lastly, Sakuma et al. found in 19 hypertrophic cardiomyopathy patients a significant decrease in the phosphocreatine/ATP ratio when compared to controls, with values of 1.07 ± 0.10 and 1.71 ± 0.13, respectively. They observed no relationship between perfusion abnormalities assessed by thallium-201 scintigraphy and the decreased myocardial phosphocreatine/ATP ratio, indicating an uncoupling of perfusion and metabolism. As most studies show a decreased myocardial phosphocreatine/ATP ratio in hypertrophic cardiomyopathy patients, $^{31}$P magnetic resonance spectroscopy may find a clinical application in the diagnostic process when hypertrophic cardiomyopathy is suspected. The pathophysiological mechanism responsible for the lowered myocardial.

Eur Heart J, Vol. 17, August 1996
phosphocreatine/ATP ratio in hypertrophic cardiomyopathy patients has not been elucidated yet, but a lower vasodilator reserve, as demonstrated by Camici et al.\(^4\)\(^4\), could be a contributing factor.

**Dilated cardiomyopathy**

In patients with dilated cardiomyopathy a relationship has been established between the severity of heart failure and the decrease of the myocardial phosphocreatine/ATP ratio\(^5\). Neubauer et al.\(^4\)\(^5\) studied 19 dilated cardiomyopathy patients and found a myocardial phosphocreatine/ATP ratio of \(1.94 \pm 0.43\) in patients with only mild symptoms of heart failure whereas patients with severe signs of heart failure had a ratio of \(1.44 \pm 0.52\). The correlation between New York Heart Association (NYHA) class and phosphocreatine/ATP ratio was highly significant \((r = 0.60, P<0.005)\). Treatment of six patients with severe heart failure during 3 months, led to an average improvement in NYHA class by \(0.8 \pm 0.3\) points, which was accompanied by a rise in myocardial phosphocreatine/ATP ratio from \(1.51 \pm 0.32\) to \(2.15 \pm 0.27\). The authors\(^4\)\(^5\) also reported that such a relation could not be established for the left ventricular ejection fraction and the myocardial phosphocreatine/ATP ratio.

De Roos et al.\(^1\)\(^1\) compared nine healthy controls (phosphocreatine/ATP \(1.65 \pm 0.26\)) with nine patients with dilated cardiomyopathy. The dilated cardiomyopathy patients showed, on average, a normal myocardial phosphocreatine/ATP ratio \((1.52 \pm 0.58)\), although some individual dilated cardiomyopathy patients did show a lowered phosphocreatine/ATP ratio compared to healthy controls (Fig. 3). Differences in myocardial phosphocreatine/ATP ratio between dilated cardiomyopathy patients may be due to differences in severity of the disease between the patients. Measurement of accurate myocardial phosphocreatine/ATP ratios in dilated cardiomyopathy patients is hampered by a relatively thin anterior left ventricular wall. The sample volume may contain insufficient myocardium to generate a spectrum with an acceptable signal-to-noise ratio\(^1\)\(^1\). Follow-up studies in dilated cardiomyopathy patients with progressive heart failure and assessment of efficacy of therapy may become a clinical application of \(^3\)P magnetic resonance spectroscopy.

**Left ventricular hypertrophy**

Left ventricular hypertrophy is known to be associated with a decreased density of capillaries and a reduced vasodilator reserve\(^4\)\(^6\),\(^4\)\(^7\). In rats left ventricular hypertrophy has been shown to be associated with a decreased myocardial ATP concentration and increased sensitivity to ischaemia, when analysed in a Langendorff perfusion model\(^4\)\(^8\),\(^4\)\(^9\),\(^5\)\(^0\).

Patients with left ventricular hypertrophy represent a heterogenous group which may be divided into those with pressure overload (hypertension, aortic valve stenosis), volume overload (aortic valve insufficiency or mitral valve regurgitation), or physical training (athlete’s heart) as causal factor\(^\text{[51]}\).

Conway et al.\(^5\)\(^2\) studied 14 patients with left ventricular hypertrophy, six of whom were treated for heart failure (NYHA classes II–III). Only these six patients could be distinguished from healthy controls on the basis of the myocardial phosphocreatine/ATP ratio \((1.11 \pm 0.3\) vs \(1.5 \pm 0.2\)), whereas the patients without clinical signs of heart failure had an average myocardial phosphocreatine/ATP ratio in the normal range \((1.6 \pm 0.2)\).

In 15 patients with left ventricular hypertrophy due to aortic valve disease, Neubauer et al.\(^5\)\(^3\) showed that the myocardial phosphocreatine/ATP ratio was correlated to NYHA class, fractional shortening, pulmonary capillary wedge pressure and right atrial pressure. No correlation was found between the myocardial phosphocreatine/ATP ratio and the left ventricular ejection fraction or cardiac output\(^5\)\(^3\). Dell’Italia et al.\(^5\)\(^4\) studied 12 patients with left ventricular hypertrophy due to aortic stenosis both before and 3 months after aortic valve replacement. Before surgery they measured a myocardial phosphocreatine/ATP ratio which was significantly lower than in controls \((1.05 \pm 0.22\) vs \(1.30 \pm 0.15\)). Aortic valve replacement surgery led to a significant functional improvement of NYHA class, but not to an increase in myocardial

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*Figure 3 Myocardial \(^3\)P magnetic resonance spectrum from a patient with dilated cardiomyopathy and from a healthy control. Clearly visible is the larger 2,3-diphosphoglycerate signal in the spectrum of the dilated cardiomyopathy patient due to the larger amount of blood in the sample volume; in this particular dilated cardiomyopathy patient the phosphocreatine/ATP ratio was significantly lower than in the average healthy control. This was not the case for the dilated cardiomyopathy patients as a group. (With permission from de Roos et al.\(^1\)\(^1\).)*
phosphocreatine/ATP ratio. In concordance with these findings are the results of a study by Ito et al.\textsuperscript{15}, who observed that, after regression of left ventricular hypertrophy in rats, the heart remained more sensitive to ischemia. They showed that the vascular resistance, which was higher in hypertrophic hearts, did not normalize parallel with regression of left ventricular hypertrophy. They considered an increased vascular resistance as an independent risk factor for cardiac morbidity. Longer follow-up periods than those used in the previously mentioned studies\textsuperscript{34,35} may be warranted to observe whether or not a normalization of the myocardial phosphocreatine/ATP ratio follows left ventricular hypertrophy regression.

\[^{31}\text{P}\] magnetic resonance spectroscopy of the heart might become of clinical value in patients with left ventricular hypertrophy. Possible applications are improved detection of the optimal moment for surgery in patients with aortic or mitral valve disease, an assessment of efficacy of therapy in patients with valve disease or hypertension.

**Conclusions**

\[^{31}\text{P}\] magnetic resonance spectroscopy is a valuable diagnostic tool but is currently restricted mainly to research applications. Most likely in the future \[^{31}\text{P}\] magnetic resonance spectroscopy of the heart will become available as a clinically useful diagnostic modality. The combined information of structure, function and metabolism which can be obtained in a single study offers a unique method for investigating these modalities in a 'one-stop-shop' fashion.

The use of slightly differing data-acquisition protocols and localization techniques by several research groups warrants the development of a consensus about a normal value for the 'true' myocardial phosphocreatine/ATP ratio. Standardization of hardware, software and study protocols would improve the reproducibility of \[^{31}\text{P}\] magnetic resonance spectroscopy studies performed by different research groups\textsuperscript{12,13}. To date, reproducibility may even present a problem within one research group\textsuperscript{12,13}. This may be due, at least partly, to a different extent of signal contamination with different measurements, as the quantity of extracardiac tissue within the sample volume varies among different measurements. Small variations in sample volume selection may strongly affect the measured myocardial phosphocreatine/ATP ratio\textsuperscript{11,12,13,13,14}.

Another limitation to the clinical use of \[^{31}\text{P}\] magnetic resonance spectroscopy is the ability of the heart to maintain its high-energy phosphate metabolism within normal ranges. Changes in the high-energy phosphate metabolism may therefore reflect relatively late\textsuperscript{9}. Studies in patients with left ventricular hypertrophy or dilated cardiomyopathy\textsuperscript{13,33,33,35,51,52} showed myocardial phosphocreatine/ATP ratios which were decreased only if symptoms of heart failure were already present. Stress testing during magnetic resonance spectroscopy offers a means of showing latent shortages in high-energy phosphates and may improve sensitivity for detecting the early stages of heart disease\textsuperscript{13,18,26,35,36}.

Evaluation of therapy in patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular hypertrophy or myocardial ischemia located in the anterior wall of the left ventricular, may become a realistic clinical application for \[^{31}\text{P}\] magnetic resonance spectroscopy. The range of clinical applications may increase when absolute instead of relative metabolite concentration are measured. Then \[^{31}\text{P}\] magnetic resonance spectroscopy will allow evaluation of disease states in which myocardial phosphocreatine and ATP concentrations decrease or increase by equal amounts. Until now, the low spatial resolution of \textgreater\textgreater8\,cm\(^2\), due to a low intrinsic sensitivity and low abundance of phosphorus containing molecules, the relatively long exposure times, and the relatively high costs of magnetic resonance machines and dedicated software packages still limit major clinical applications. Ongoing technical progress will facilitate the implementation of \[^{31}\text{P}\] magnetic resonance spectroscopy in clinical cardiology.

**References**


