

# The Relationship between Plasma BNP Level and the Myocardial Phosphocreatine/Adenosine Triphosphate Ratio Determined by Phosphorus-31 Magnetic Resonance Spectroscopy in Patients with Dilated Cardiomyopathy

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## Key Words

B-type natriuretic peptide · Phosphorus-31 magnetic resonance spectroscopy · Dilated cardiomyopathy · High-energy phosphate · Heart

## Abstract

The purpose of this study was to evaluate the correlation between the plasma B-type natriuretic peptide (BNP) level and the myocardial phosphocreatine/adenosine triphosphate ratio determined using rapid phosphorus-31 magnetic resonance spectroscopy (<sup>31</sup>P-MRS) in patients with dilated cardiomyopathy (DCM). Thirteen DCM patients, who had slight or moderate heart failure, were examined. The plasma BNP was measured on a day close to the rapid <sup>31</sup>P-MRS study. <sup>31</sup>P-MRS measurements were conducted with a 1.5-T MR instrument. The plasma BNP levels tended to be correlated negatively with the myocardial phosphocreatine/adenosine triphosphate, although the correlation did not reach statistical significance ( $r = -0.54$ ,  $p = 0.06$ ). By contrast, the log of the plasma BNP levels was correlated negatively with the myocardial phosphocreatine/adenosine triphos-

phate ( $r = -0.73$ ,  $p < 0.01$ ). Our results indicate that the myocardial energy metabolism evaluated using <sup>31</sup>P-MRS tends to be correlated with the severity of heart failure and left ventricular dysfunction estimated using the plasma BNP levels in DCM patients. This paper provides additional information regarding the relationship between the BNP and myocardial energy metabolism in DCM patients.

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## Introduction

Dilated cardiomyopathy (DCM) is characterized by progressive dilatation of the heart with loss of contractile function [1]. Currently, its etiology is unclear in many cases.

B-type natriuretic peptide (BNP) is released from the cardiac ventricles in response to volume expansion and pressure overload. The plasma BNP levels are elevated in patients with left ventricular dysfunction. Furthermore, the plasma BNP level is felt by some to be the most single accurate predictor of the presence or absence of conges-

**Table 1.** The characteristics of the DCM patients (n = 13)

Age, years	51.0 ± 18.0
Male/female	10/3
NYHA class I	4
NYHA class II	7
NYHA class III	2
IVS thickness, mm	12.2 ± 2.15
LVEF, %	35.4 ± 9.7
PCr/ATP	1.82 ± 0.33
BNP, pg/ml	191.5 ± 240.1

tive heart failure. Therefore, the BNP may be a more sensitive and specific indicator of ventricular disorders [2–5].

Phosphorus-31 magnetic resonance spectroscopy ( $^{31}\text{P}$ -MRS) of the heart is unique in its ability to noninvasively quantify myocardial levels of high-energy phosphate compounds such as adenosine triphosphate (ATP) and phosphocreatine (PCr), which fuel contractile function and are critical to viability. Hence, the myocardial PCr/ATP ratio determined using  $^{31}\text{P}$ -MRS is used to evaluate patients with cardiac disease [6–10].

Nevertheless, the relationship between the BNP and the myocardial PCr/ATP ratio is not clear. Therefore, this study examined the correlation between the plasma BNP level and the myocardial PCr/ATP ratio determined using rapid  $^{31}\text{P}$ -MRS in patients with DCM.

## Patients and Methods

### Patients

Thirteen DCM patients were examined. Inpatients with DCM in the Department of Cardiovascular Medicine of Tohoku University Hospital were selected at random. All subjects gave their informed consent. Table 1 summarizes the information for the 13 DCM patients (10 men, 3 women; average age 51.0 ± 18.0 years, age range: 27–77 years), who had slight or moderate heart failure in NYHA functional classes, I, II or III. The left ventricular ejection fraction (LVEF) was assessed using angiocardiology. Four of the 13 DCM patients could not undergo cardiac catheterization. The DCM diagnoses were made from the clinical histories, ECG, and plasma creatine kinase levels, and all patients underwent echocardiography and either cardiac catheterization (including angiocardiology) or radionuclide scanning. Coronary artery disease was ruled out in all patients. DCM patients who had a pacemaker, severe arrhythmia, implants, vascular clips, unstable angina pectoris, or claustrophobia were excluded. Of the 13 patients with DCM, all patients were treated with diuretics, 8 with digitalis, 8 with angiotensin-converting enzyme inhibitors, and none with beta-blocker.

### Rapid $^{31}\text{P}$ -MRS Study

$^{31}\text{P}$ -MRS measurements were conducted with a 1.5-T MR instrument (Magnetom Vision Siemens, Erlangen, Germany), using a double-resonant ( $^{31}\text{P}/^1\text{H}$ ) single-turn surface coil. The experimental protocol for rapid cardiac  $^{31}\text{P}$ -MRS was described in detail in our previous study [11, 12]. Briefly, an automatic phase-sensitive shim map was generated, and the scan parameters were set to a 320 × 320-mm field of view, a 90° flip angle in the coil center, and an echo time of 3 ms. Using a two-dimensional phosphorus chemical-shift imaging sequence (2D-CSI) in combination with 30-mm axial slice-selective excitation, complete three-dimensional localization was performed. The rapid-sequence  $^{31}\text{P}$ -MRS procedure was phase encoded in arrays of 8 × 8 steps with an average of four acquisitions. K-space zero-filling (similar to matrix interpolation) was used, yielding 2 × 2 × 3-cm volume elements. The effect of partial saturation was considered using the mean repetition time (TR) of each experiment and saturation correction factors. The correction factors were calculated from the mean value determined from an analysis of  $^{31}\text{P}$ -MRS measurements of two healthy volunteers, and the PCr/ATP was measured as a function of TR at 0.5–5 s. A set of ECG-triggered proton images was obtained in the transverse, coronal and sagittal orientations using a modified gradient-echo technique. TR was set to one R–R interval for the phosphorus 2D-CSI measurements. The acquisition time was 3–5 min, and the total examination time, including proton imaging and shimming, for the rapid  $^{31}\text{P}$ -MRS procedure was 10–15 min, depending on the heart rate. The volume element for each 2D-CSI sequence was positioned on the interventricular septum of the anterior wall of the LV. The areas under each peak of the PCr and beta-ATP signal curves from the chosen volume element were evaluated using a built-in curve-fitting program.

### BNP Measurements

In the 13 patients with DCM, the plasma BNP levels were measured using a commercial specific immunoradiometric assay kit for human BNP (Shionoria BNP kit, Shionogi, Osaka, Japan). The plasma BNP was measured on a day close to the MRS study. The plasma BNP measurements were evaluated using both linear and logarithmic scales.

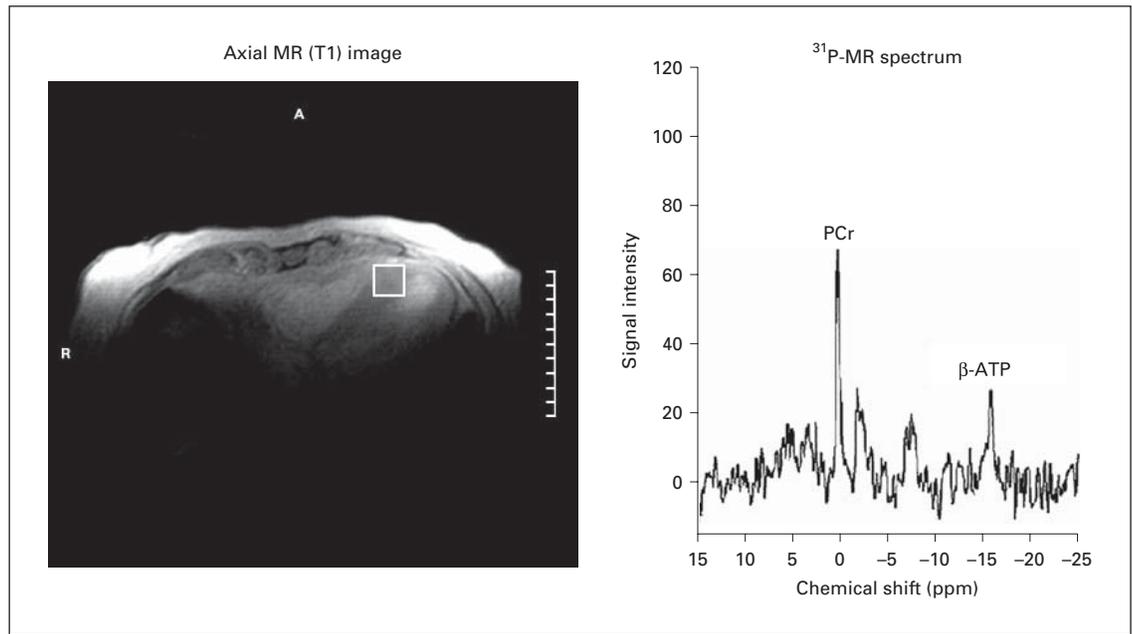
### Statistics

The correlations (BNP vs. PCr/ATP, log of BNP vs. PCr/ATP, LVEF vs. PCr/ATP) were analyzed using a linear regression. The p value was obtained from an analysis of variance.

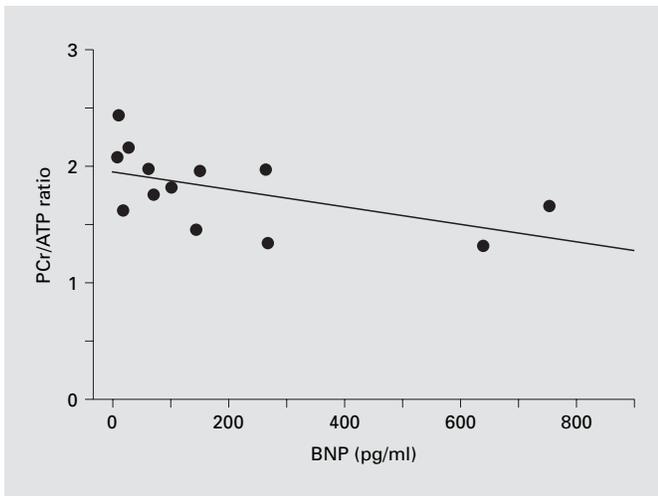
## Results

The results of our study are summarized in table 1. The mean plasma BNP level and mean PCr/ATP determined by rapid  $^{31}\text{P}$ -MRS of the 13 patients were 191.5 ± 240.1 pg/ml and 1.82 ± 0.33, respectively. A typical  $^{31}\text{P}$ -MR spectrum and MR imaging of a patient with DCM is shown in figure 1.

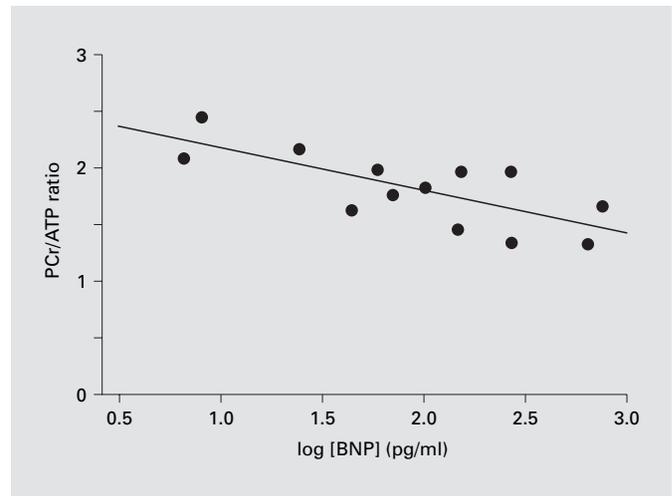
Figures 2 and 3 present the correlations between the myocardial PCr/ATP and the plasma BNP and the log of the plasma BNP of the 13 DCM patients, respectively.



**Fig. 1.** Typical rapid  $^{31}\text{P}$ -MR spectrum of a patient with DCM (a 69-year-old male). PCr/ATP = 1.83.



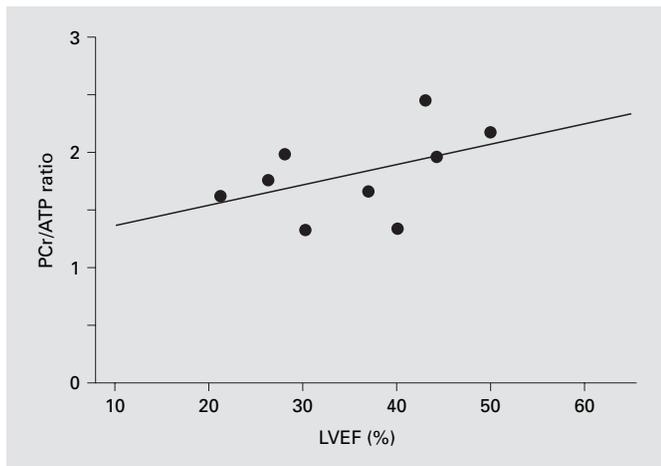
**Fig. 2.** The correlation between the myocardial PCr/ATP ratio and the plasma BNP of the 13 DCM patients ( $r = -0.54$ ,  $p = 0.06$ ).



**Fig. 3.** The correlation between the myocardial PCr/ATP ratio and the log of the plasma BNP of the 13 DCM patients ( $r = -0.73$ ,  $p < 0.01$ ).

The plasma BNP levels tended to be correlated negatively with the myocardial PCr/ATP, although the correlation did not reach statistical significance ( $r = -0.54$ ,  $p = 0.06$ ). In contrast, the log of the plasma BNP levels was correlated negatively with the myocardial PCr/ATP ( $r = -0.73$ ,  $p < 0.01$ ).

Figure 4 shows the correlations between the myocardial PCr/ATP and the LVEF of the nine DCM patients who underwent angiocardiology. The LVEF tended to be correlated with the myocardial PCr/ATP, but the correlation was not statistically significant ( $r = 0.47$ ,  $p = 0.20$ ).



**Fig. 4.** The correlation between the myocardial PCr/ATP ratio and the LVEF of the DCM patients ( $r = 0.47$ ,  $p = 0.20$ ).

## Discussion

Human myocardial high-energy phosphates in biopsy specimens have been evaluated relative to other heart failure parameters since the 1970s [13, 14]. Recently,  $^{31}\text{P}$ -MRS has enabled the unique possibility of studying cardiac energy metabolism noninvasively, without a biopsy.

To our knowledge, no study has examined on the correlation between plasma BNP levels and the myocardial PCr/ATP ratio determined using  $^{31}\text{P}$ -MRS in cardiac patients, largely because cardiac  $^{31}\text{P}$ -MRS requires long examination times, which many cardiac patients cannot tolerate, to compensate for its poor sensitivity [15, 16]. Hence, our laboratory has investigated the feasibility of faster-sequence cardiac  $^{31}\text{P}$ -MRS using a clinical MR system [11, 12]. Consequently, we are now able to examine the correlation between plasma BNP levels and the myocardial PCr/ATP ratio determined using rapid  $^{31}\text{P}$ -MRS in DCM patients. We found that the plasma BNP level (linear scale) tended to be correlated negatively with the myocardial PCr/ATP (the correlation did not reach statistical significance), while there was a significant correlation between the log of the plasma BNP level and myocardial PCr/ATP in DCM patients. Our results indicate that the myocardial energy metabolism evaluated using  $^{31}\text{P}$ -MRS tends to be correlated with the severity of heart failure and left ventricular dysfunction estimated using the plasma BNP levels in DCM patients.

Nakae et al. [17] reported that the plasma BNP levels were significantly negatively correlated with the myocardial total creatine (CR) determined using proton-MRS

( $^1\text{H}$ -MRS) in 18 patients with either DCM or hypertrophic cardiomyopathy (HCM) (11 DCM and 8 HCM,  $r = -0.54$ ,  $p = 0.022$ ), while the plasma BNP levels were not significantly correlated with the myocardial total CR in 11 DCM patients ( $p = 0.11$ ). This result (statistically non-significant in DCM patients) was similar to ours, but their study did not consider the correlation between the log of the plasma BNP levels and the total CR.

In DCM patients, the LVEF tended to be correlated with the myocardial PCr/ATP determined using rapid  $^{31}\text{P}$ -MRS, but the correlation was not statistically significant. Some previous studies found that the LVEF was not significantly correlated with the myocardial PCr/ATP or total CR in DCM patients: Hardy et al. [18] reported values of  $r = 0.34$  and  $p > 0.05$ , and Nakae et al. [17] reported  $p = 0.20$  but did not determine a value for  $r$ . These results were similar to ours.

Neubauer et al. [19] reported that abnormalities in PCr/ATP were an independent predictor of mortality in patients with DCM and heart failure. Hence, our finding that the plasma BNP level tended to be correlated negatively with the myocardial PCr/ATP is interesting for the evaluation of morbidity and mortality in DCM patients.

This study found that the log of the plasma BNP level was correlated negatively with the myocardial PCr/ATP in DCM patients. However, the correlation does not indicate a cause-effect relationship. There are innumerable parameters affecting the degree of heart failure, outcomes, mortality, and so forth, and most are linked to ventricular dysfunction and the severity of heart failure to varying degrees. However, we believe that our findings will provide additional insight into aspects of DCM.

In conclusion, in patients with DCM, the plasma BNP level tended to be correlated negatively with the myocardial PCr/ATP ratio determined using rapid  $^{31}\text{P}$ -MRS (although the correlation was not statistically significant). Moreover, the log of the plasma BNP level was significantly negatively correlated with the myocardial PCr/ATP. Our results provide additional new information regarding the relationship between the BNP and myocardial energy metabolism in DCM patients.

## Acknowledgments

We acknowledge Dr. Kunio Shirato of the Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Dr. Yoshifumi Saijoh of the Department of Medical Engineering and Cardiology, Institute of Development, Aging and Cancer, Tohoku University, and Mr. Tatsuo Nagasaka of the Department of Radiology, Tohoku University Hospital for their invaluable assistance.

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