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Quantitative ^{1}H MR Spectroscopy of the Brain in Patients with Congestive Heart Failure before and after Cardiac Transplantation[1]

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Purpose : To evaluate the effects of cardiac transplantation on the brain in patients with congestive heart failure (CHF), using quantitative ^{1}H MR spectroscopy (^{1}H-MRS).

Materials and Methods : Ten patients with CHF underwent MRI and quantitative ^{1}H-MRS before and 1-2 and 4-9 months after cardiac transplantation. MR spectra were obtained from parietal white matter (PWM) and occipital gray matter (OGM) using PROBE (PROton Brain Exam). Changes in MR signal intensity were evaluated, and the cerebral metabolic concentrations in PWM and OGM were compared. For comparative purposes, 20 normal volunteers were included.

Results : No abnormal MR signal intensity was seen in the brain before or after cardiac transplantation.

Changes in cerebral metabolic concentrations were observed on ^{1}H-MRS; concentrations of creatine (Cr) in PWM, and of N-acetylacepartate (NAA), Cr and myo-Inositol (mI) in OGM were significantly lower before transplantation. After successful transplantation, Cr levels returned to their normal range in PWM and OGM, while a slightly increase choline (Cho) level was observed in PWM.

Conclusion : Cerebral hypoperfusion in CHF can be evaluated using ^{1}H-MRS. MRS may play a substantial role in monitoring the effect of cardiac transplantation.

Index words : Magnetic resonance (MR), spectroscopy
Brain, MRI
Brain, metabolism
Heart, failure

Cardiac transplantation has proven to be an effective and standardized method of treatment in patients with end-stage congestive heart failure (CHF), and access to a reliable and effective method for monitoring the success or failure of the procedure is clearly important.

When a patient with chronic congestive heart failure demonstrates abnormal cognitive function, abnormal brain metabolism due to chronic cerebral hypoperfusion may be suspected (1).

We evaluated MR images of the brain in patients with CHF that might be affected by hypoperfusion and employed quantitative localized ^{1}H MR spectroscopy to measure the brain metabolites before and after cardiac transplantation. We hypothesized that quantitative ^{1}H-MRS could be useful for the evaluation of metabolic changes occurring in the brain after cardiac transplantation in CHF patients.

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Materials and Methods

Subjects

Ten patients (age, 30-50; mean age; 32) with CHF who had undergone cardiac transplantation and 20 age-matched normal volunteers were examined. For the diagnosis of CHF, all patients underwent a standardized protocol which included cardiac muscle biopsy, echocardiography, and an excercise test. Degree of cognitive function was graded II - IV according to the New York Heart Association(NYHA) functional classification. Nine patients had dilated cardiomyopathy and one patient had ischemic cardiomyopathy. Patients with cerebrovascular disease, chronic liver disease or chronic renal failure that might affect the results of ^{1}H-MRS were excluded from the study, as were those whose condition was poor due to clinical or pathological failure of cardiac transplantation.

All subjects underwent two-dimensional Doppler echocardiography, and the left ventricular ejection fraction was measured using multigated blood pool scanning. In all subjects, good cardiac movement was observed, as well as an elevated ejection fraction level (mean 29 %). In all subjects ^{1}H-MRS of the brain was performed before and 2-6 months and 4-9 months after transplantation; seven underwent two follow-up examinations and three underwent three such examinations. All patients and control subjects gave their informed consent.

MRI and MRS

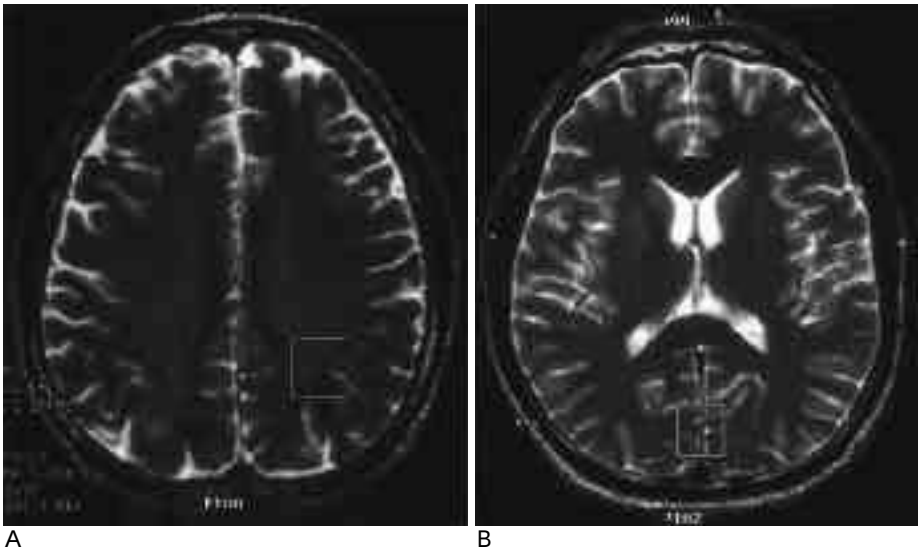
T1-weighted (TR/TE = 500/11 msec) and T2-weighted (TR/TE = 3500/102 msec) axial MR images were obtained with a section thickness of 5 mm. All were examined by two neuroradiologists who determined whether or not signal intensity was normal.

All MRI and ^{1}H-MRS examinations involved the use of a 1.5T Signa system equipped with shielded gradients(General Electric Medical System, Milwaukee, U.S.A.). T1- and T2-weighted imaging was followed by 1H-MRS. Using PROBE, image-guided STEAM (STimulated Echo Acquisition Method) spectra were obtained from parietal white matter(PWM) and occipital gray matter(OGM), with TE of 30msec, TR of 3.0 sec, 36 AVG, and a voxel volume of 7-9ml. The procedure was technically simple and successful. A three-pulse CHESS(CHEmical Shift Selective) sequence was used for suppression of the H_2O signal.

All raw PROBE data were transferred to a SUN-SPARC 10 workstation and processed according to the procedure described by Kreis et al (2). Peaks were assigned according to known chemical shifts: N-acetylacepartate (NAA) at 2.02 ppm, creatine and phosphocreatine (Cr) at 3.03 ppm, choline and choline containing compounds (Cho) at 3.22 ppm, and myo-Inositol (mI) at 3.56 ppm(2). To calculate peak areas, singlets of NAA, Cr, Cho and mI were individually fitted with the lorenzian line shape. For PWM and OGM spectra, absolute concentration was measured using the brain water signal as an internal reference from the PROBE data (3). The results were expressed as mmols/kg of wet weight.

Statistical Analysis

Data for continuous variables were expressed as mean ±standard deviation (SD). Continuous variables of the



A B

Fig. 1. T2-weighted axial images show no abnormal signal intensity in the gray and white matter A) before and B) after cardiac transplantation in the patient #8. Voxels for PROBE spectra are placed in A) parietal white and B) occipital gray matter respectively.

metabolites before and after cardiac transplantation were compared using a paired Student t test. For comparison between metabolites prior to cardiac transplantation and normal controls, an unpaired sampled t test was applied. Hierarchial multiple regression analysis was performed to identify the variables that predicted brain metabolite concentration. A p value of < 0.05 was considered statistically significant.

Results

MR imaging

Table 1 summarizes the results of MRI and ^{1}H-MRS, and includes the related clinical data. In only one patient signal abnormality was seen on T1- or T2-weighted images of the brain before or after transplantation (Fig. 1); in that patient, several lacunar infarctions were observed in both basal ganglia. Which did not change after transplantation.

MR Spectroscopy

In figure 2, the brain spectra of patients with CHF are compared with those of control subjects. In patients with CHF, the concentration of Cr in PWM was much lower than in normal controls($p < 0.05$ by unpaired t test). After successful cardiac transplantation, PWM Cr levels returned to normal. PWM Cho levels which were within the normal range before transplantation, increased significantly after transplantation, but were within normal limits (e.g., overshoot) (Fig. 2). The overshoot Cho level decreased again in one patient on the second follow-up, 9 months after transplantation (Fig. 2). In two patients, who underwent their second follow-up examination 4 and 5 months after transplantation, Cho levels remained high. In the OGM of the patients with CHF, NAA, Cr, and mI levels were lower than those of the normal controls. After successful cardiac

Table 2. Concentrations of Cerebral Metabolites (mmols/kg of wet weights) before and after Transplantation

		Before Transplantation	After Transplantation	Control
PWM	NAA	9.16 ± 1.08	9.87 ± 0.81	9.45±1.18
	Cr	6.11 ± 0.73*	7.02 ± 0.58†	7.47±0.69
	Cho	1.57 ± 0.25	1.93 ± 0.36§	1.71±0.23
	mI	4.82 ± 1.04	5.43 ± 0.78	5.46±0.90
OGM	NAA	9.58 ± 1.15*	10.23 ± 1.43‡	10.57±1.23
	Cr	7.08 ± 1.03*	7.90 ± 0.96†	8.86±0.52
	Cho	1.43 ± 0.27	1.59 ± 0.21	1.62±0.16
	mI	5.19 ± 1.78*	5.72 ± 1.09‡	6.87±1.14

Note: *: lower than the normal value ($p < 0.05$ by unpaired t test)
†: increased after transplantation ($p < 0.05$ by paired t test)
‡: increased after transplantation ($p = 0.07$ in both metabolites by paired t test)
§: increased after transplantation, above normal value (e.g., overshoot) ($p < 0.05$ by paired t test)

Table 1. Findings of MRI and ^{1}H MRS in 10 Cardiac Transplanted Patients

No.	age	Sx	1st MR/MRS(mmols/kg) (preop)					2nd MR/MRS(mmols/kg) 1st(2-6m) postop					3rd MR/MRS(mmols/kg) 2nd(4-9m) postop				
of pt.	/sex	duration		NAA	Cr	Cho	mI	MR	NAA	Cr	Cho	mI	MR	NAA	Cr	Cho	mI	MR
1.	33/M	3ys 6m	PWM	8.17	5.28	1.72	5.56	N	9.77	7.09	2.02	5.74	N	9.57	6.59	2.38	7.71	N
			OGM	7.9	6.14	1.12	4.27	N	9.32	7.17	1.87	5.09	N	8.58	6.14	1.22	6.78	N
2.	35/M	5ys	PWM	10.3	6.8	1.84	5.83	N	10.4	7.05	1.6	4.96	N					
			OGM	11.5	9.41	1.74	7.58	N	12.8	8.85	1.66	6.92	N					
3.	59/M	6ys	PWM	8.11	6.8	2.02	6.03	N	8.98	7.79	2.49	5.15	N					
			OGM	9.4	7.14	1.73	7.29	N	9.53	8.94	1.85	6.51	N					
4.	18/M	6m	PWM	7.92	5.42	1.64	4.32	N	9.36	7.62	2.45	6.83	N	9.14	6.81	1.69	6.46	N
			OGM	9.59	6.42	1.45	3.82	N	10.5	7.57	1.2	7.61	N	10.5	9.06	1.45	6.46	N
5.	23/M	3m	PWM	9.95	6.62	1.49	4.96	N	10.8	7.1	2.06	5.09	N	10.3	5.56	2.10	5.04	N
			OGM	10.8	7	1.42	5.13	N	11.7	8.92	1.59	5.62	N	8.61	7.46	1.78	4.77	N
6.	28/M	1yr 6m	PWM	10.9	5.82	1.18	5.48	N	11	6.63	1.43	4.1	N					
			OGM	10.0	8.02	1.59	6.73	N	10.7	7.76	1.36	4.19	N					
7.	16/M	9ys	PWM	9.61	6.87	1.42	4.09	N	10.3	5.64	1.46	6.22	N					
			OGM	9.55	7.05	1.72	4.99	N	11.3	8.19	1.67	6.27	N					
8.	47/M	1yr	PWM	7.86	4.86	1.51	5.38	N	8.38	7.2	2.01	5.5	N					
			OGM	8.74	6.91	1.17	5.79	N	8.51	7.92	1.65	5.44	N					
9.	29/M	8m	PWM	9.33	6.59	1.63	3.55	N	10.1	7.02	1.93	4.87	N					
			OGM	8.01	5.7	1	4.68	N	9.32	5.78	1.48	5.12	N					
10.	29/M	4m	PWM	9.5	6.02	1.28	2.95	N	9.66	7.03	1.89	5.95	N					
			OGM	10.2	7.04	1.35	1.65	N	8.53	7.93	1.56	4.47	N					

PWM: parietal white matter, OGM: occipital gray matter, N: Normal images

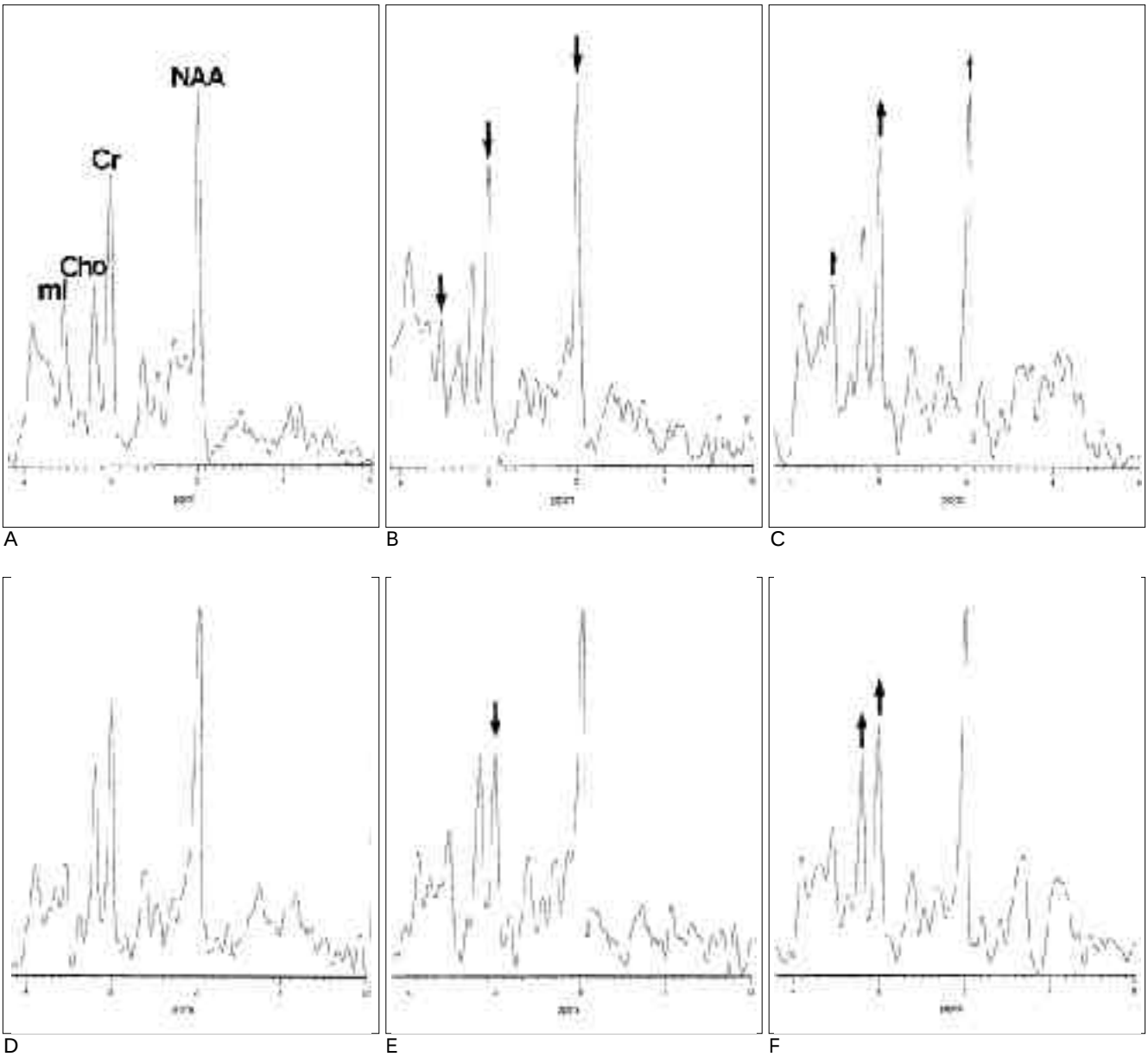


Fig. 2. Representative ^{1}H MR spectra in the patient #8 and subject control. A) Spectrum of normal, B) before and C) after cardiac transplantation in the OGM, D) spectrum of normal, E) before and F) after cardiac transplantation in the PWM.

transplantation, Cr levels increased significantly ($p < 0.05$ by paired t test), and NAA and mI levels increased slightly ($p = 0.07$ in both metabolites by paired t test). Table 2 summarizes cerebral metabolite concentrations measured before and after cardiac transplantation.

Discussion

The important finding of this study is that in patients with CHF, metabolic status was deranged. Cr concentration was low in PWM, and all metabolite concentrations except Cho were low in OGM. After cardiac transplantation, Cr levels appeared to normalize in PWM and OGM, while Cho levels in PWM overshot slightly though were within the normal range, which may decrease gradually over a period of time. NAA and mI also increased slightly after transplantation.

In patients with chronic CHF, cognitive function is known to be abnormal (1). The pathophysiology of which brain dysfunction in CHF depends on cerebral arterial blood flow, which might adversely affect the supply of neuronal oxygen as well as neuronal glucose utilization. Cerebral blood flow is usually maintained despite a reduction in blood perfusion pressure. In patients with chronic heart failure, however auto-regulation of the neuronal and humoral factors for nutrient

and oxygen supply to the brain is disrupted, and cerebral blood perfusion eventually becomes insufficient. During heart failure, hypoperfusion to the brain can therefore cause metabolic abnormalities. Increased or normalized metabolite concentrations after successful cardiac transplantation indicates that the procedure has led to improved hemodynamics (4, 5).

The Cr peak in ^{1}H-MRS is equal to the sum of creatine and phosphocreatine, which represents cerebral energy metabolism and reserve. Reduced Cr levels in the PWM region, as seen in this study, suggest a cerebral energy deficit. Reduced Cr levels might also be explained by the hypo-osmolar status of patients with CHF (6). mI, an idiogenic cerebral osmolyte marker, showed no change in PWM. We assume that reduced Cr levels seen in PWM reflect a cerebral energy deficit, an asumption supported by the fact that in OGM, Cr, NAA and mI levels were significantly lower. These metabolites increased significantly ($p < 0.05$) after successful cardiac transplantation with Cr increasing more significantly than the other two ($p = 0.07$). It may be assumed that the metabolic changes occuring in OGM might be affected in part by the osmotic changes seen in CHF, though the decreased Cr level observed in OGM may be characteristic of this condition.

The role of mI in the brain is not clearly understood. It has been speculated that inositol-containing compounds may function as idiogenic osmolyte in the brain (6) and are related to inositol polyphosphate second-messenger metabolism (7, 8). The reduced mI levels found in OGM in this study might be related to relatively low serum osmolarity.

Cho concentration after transplantation was slightly above the normal limit in PWM, though appeared to return to its normal level over a period of time. In this study, one of three patients who underwent more than two follow-up examinations showed normalized Cho levels on the second follow-up, 9 months after transplantation. In the remaining two patients, the second follow-up examination was performed only 4 or 5 months after transplantation. The fact that Cho levels fell over time after overshoot suggests that immunosuppressant cyclosporine-A has a possible tapering effect. Cho levels also overshot in liver transplantation (9). Cyclosporine related encephalopathy or neurotoxicity commonly affects the cingulate gyrus and the occipital lobe, with fine linear cortical hyperintensity visible on T2-weighted MR images (10). Except in patient #3, the MR images seen in our study showed no abnormal finding. Neurotoxicity is known to appear within a few hours, or days, or several months of cyclosporine-A therapy. Some reported cases of cyclosporine neurotoxicity have been correlated with elevated levels of cyclosporine-A and/or metabolites in the face of apparently normal blood levels (11-14). In this study slight overshoot in the concentration of Cho in PWM after transplantation may be related to neurotoxicity of cyclosporine-A or subclinical neurotoxicity.

Conventional T2-weighted spin-echo MRI demonstrates that when the blood-brain barrier breaks down, facilitating the extravasation of protein and accumulation of extravascular water, ischemic brain tissue is delineated as a high-intensity area (15). Without blood brain barrier breakdown, regions of early ischemic injury are not visualized on T2-weighted images (15). In our study, MRI showed no abnormal high signal intensity on T1- and T2-weighted images, a fact which may reflect chronic hypoperfusion injury without breakdown of the blood brain barrier.

A limitation of our study is that no objective method of the kind that Pujol et als. (16) employed for detecting changes in the signal intensity of the basal ganglia using the signal of amygdala as an internal reference to detect MRI signal changes in PWM, OGM and basal ganglia.

There are currently several diagnostic tools for determining the failure or success of cardiac transplantation: these include echocardiography, angiography of the coronary artery, and endomyocardial biopsy. Some procedures, however, are invasive or inconclusive. The outcome of cardiac transplantation has been determined by measuring the metabolic responses of skeletal muscle to exercise. In patients with advanced heart disease, the abnormalities seen in skeletal muscle usually persist for an indefinite period of time, and are also related to noncardiogenic factors. This may contribute to the reduced exercise capacity in spite of successful cardiac transplantation, though partial improvement can occur later.

In conclusion, ^{1}H-MRS can directly measure metabolic changes in the brain of patients with CHF and can be used to monitor the effects of cardiac transplantation.

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울혈성 심부전 환자에서 심장 이식 전후의 정량적 수소 자기공명분광법[1]

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임수미 · 이호규 · 최충곤 · 이정희[2] · 임태환

목적 : 울혈성 심부전 환자에서 심장 이식의 효과를 모니터하는데 있어 뇌의 정량적 수소 자기공명분광법(^{1}H-MRS)의 유용성에 대해 알아보았다.

대상 및 방법 : 울혈성 심부전 환자 10명을 대상으로 하여 심장 이식 전과 이식 후 1-2개월, 4-9개월에 MRI와 ^{1}H-MRS를 시행하였다. MR 스펙트럼은 두정부 백질과 후두부 회질에서 PROBE법을 이용하여 얻었다. MRI에서 신호강도의 변화 및 두정부 백질과 후두부 회질의 대사물 변화를 알아보았으며 비교 분석을 위해 20명의 정상군에서도 같은 검사를 시행하였다.

결과 : 울혈성 심부전 환자의 이식 전 후 MRI에서 신호강도의 변화는 없었으며 ^{1}H-MRS에서는 두정부 백질의 Cr 감소, 후두부 회질의 NAA, Cr, mI감소가 있었다. 또한 심장 이식술 후에 감소되었던 Cr이 두정부 백질 및 후두부 회질에서 정상화하였고, 두정부 백질에서 Cho의 증가가 있었다.

결론 : 울혈성 심부전 환자에서 ^{1}H-MRS는 뇌 혈류 감소를 진단할 수 있을 뿐만 아니라 심장 이식 수술후에 이식의 효과를 모니터 하는데 유용하리라 생각된다.