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박사학위논문

N-terminal pro B-type Natriuretic Peptide (NT-proBNP) and the evaluation of Cardiac Dysfunction and Severity of Disease in Cirrhotic Patients

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*N-Terminal pro B-type Natriuretic Peptide (NT-proBNP)*를 이용한 간경화증 환자의 중증도와 심장 이상의 평가

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배경 및 목적 : 간경화증 환자에서는 과역동적인 체순환과 심장 이상이 관찰되는 경우가 흔하다. 증가된 심장부하에 반응하여 심실로부터 분비되는 심장 신경호르몬인 BNP (brain natriuretic peptide)와 아미노기 말단 proBNP (NT-proBNP)는 조기 심실 이상을 나타내는 지표이다. 따라서 본 연구는 간경화증 환자에서 NT-proBNP의 혈중 농도, 간경화증의 중증도, 그리고 심장 이상과의 사이에 어떤 연관 관계가 있는 지 알아보고자 시행되었다.

대상 및 방법 : 63명의 간경화증 환자와 (남/녀=40/23, 평균연령 55.8세) 15명의 비슷한 연령대의 건강한 대조군을 (남/녀=9/6, 평균연령 52.9세) 대상으로 하였다. Child-Turcotte-Pugh 분류법에 따라 class A (n=16), class B (n=29), class C (n=18)로 분류되거나, 복수를 동반한 3군 (group 3, n=35)과 동반하지 않은 2군 (group 2, n=28)으로 각각 분류된 간경화증 환자와 1군 (group 1)으로 분류된 건강대조군에서 심초음파를 시행하고 NT-proBNP의 혈중 농도를 측정하였다.

결과 : NT-proBNP의 혈중 농도는, 간경화증 환자인 2군 (155.88 ± 69.75

pg/ml)과 3군 (198.26 ± 146.69 pg/ml)에서 각각 건강대조군 (40.27 ± 13.58 pg/ml) 에 비해 유의하게 증가되어 있었으나 ($p < 0.05$), 복수를 동반하지 않은 2군과 동반한 3군간에 NT-proBNP의 혈중 농도는 통계적으로 유의한 차이가 없었다. 또한 NT-proBNP의 혈중 농도가 Child 분류 C군 (250.00 ± 176.60 pg/ml)에서 건강대조군은 물론이고, Child 분류 B군 (168.63 ± 71.34 pg/ml)이나 A군 (119.60 ± 67.29 pg/ml)과 비교하여 각각 유의하게 증가되어 있었으나 ($P < 0.05$), Child 분류 B군과 A군의 NT-proBNP의 혈중 농도는 통계적으로 유의한 차이가 없었다. 심초음파검사상, 간경화증 환자 (2군; 39.71 ± 4.75 mm, 3군; 40.51 ± 4.60 mm)에서 건강대조군 (35.07 ± 7.39 mm)에 비해 유의하게 좌심방직경이 증가되어 있었다. 또한 간경화증 환자에서 심실중격의 두께 (IVSd, 2군; 10.07 ± 2.02 mm, 3군; 10.14 ± 1.70 mm)와 좌심실 후벽의 두께 (LVPWd, 2군; 9.21 ± 1.77 mm, 3군; 9.63 ± 1.22 mm)가 건강대조군 (IVSd; 8.67 ± 1.54 mm, LVPWd; 8.20 ± 1.66 mm)에 비해 각각 유의하게 증가된 소견을 보였다 ($P < 0.05$). 좌심실 구혈률(EF)도 간경화증 환자 (2군; 70.50 ± 7.81 % , 3군; 71.17 ± 7.02 %)에서 건강대조군 (59.33 ± 6.17 %)에 비해 각각 유의하게 증가된 소견을 보였다 ($P < 0.05$). 한편 도플러 심초음파검사상, 간경화증 환자에서 이완기초 경승모판 혈류 속도와 승모판륜 속도의 비 (E/E′, 2군; 10.51 ± 1.93, 3군; 11.78 ± 2.25)와 E파의 감속시간 (EDT, 2군; 254.29 ± 60.75 msec, 3군; 271.13 ± 53.74 msec)이 건강대조군 (E/E; 8.81 ± 1.08, EDT; 206.00 ± 35.32 msec)에 비해 각각 유의하게 증가되어 있는 소견이었다 ($P < 0.05$). 좌심실질량지수는 복수를 동반하지 않은 2군 (110.18 ± 23.06 g/㎡)이나 건강대조군 (102.80 ± 23.54 g/㎡)에 비해 복수를 동반한 3군 (123.54 ± 22.50 g/㎡)에서 증가되고, 경승모판 혈류 속도의 E파와 A파의 비 (E/A ratio)는 2군 (1.01 ± 0.37)이나 건강대조군 (1.15 ± 0.37)에 비해 3군 (0.90 ± 0.32)에서 감소되는 양상이었다 ($P < 0.05$). 간경화증 환자에서 NT-proBNP의 혈중 농도와 심초음파검사 측정상 좌심실이완기말직경 ($r = 0.277$, $P = 0.028$)과 E/E′ ($r = 0.450$, $P = 0.01$)이 유의한 상관관

계를 보였다.

결론 : 간경화증 환자에서 NT-proBNP의 혈중 농도는 상승되어 있었으며, 이것은 간경화증의 중증도가 증가함에 따라 보다 더 밀접한 연관이 있었다. 결론적으로 진행된 간경화증에서 심장의 구조적, 기능적 이상이 더욱 진행된 상태였으며, 따라서 NT-proBNP의 혈중 농도는 간경화증의 진행과 이와 동반된 심장 이상을 평가하는데 유용한 예측 인자로 생각된다.

Ⅰ. *INTRODUCTION*

Relations between cardiovascular pathophysiology and the complications of liver disease have been increasingly recognized for half a century (Kowalski et al., 1953; Abelmann et al., 1955). The systemic circulation in patients with cirrhosis is hyperdynamic and is characterized by an increased heart rate and cardiac output and reduced systemic vascular resistance with normal or decreased arterial blood pressure (Kowalski et al., 1953; Abelmann et al., 1955; Schrier et al., 1988; Llach et al., 1988; Møller et al., 1995; Møller et al., 1997; Naschitz et al., 2000). Additionally, cirrhosis is associated with other cardiovascular abnormalities, including portal hypertension, hepatopulmonary syndrome and changes in several different vascular territories, such as, in the renal and cerebral vasculatures (Baik et al., 2004). In cirrhotic patients, cardiac output is increased at rest, and it has been assumed that systolic function is normal or even supranormal (Hu et al., 2004; Baik et al., 2004). However, many cirrhotic patients present with dyspnea, fluid retention, and a limited exercise capacity (Møller et al., 1997; Epstein et al., 1998; Fallon et al., 2000). The new clinical entity of impaired cardiac contractility and performance in cirrhotic patients, cirrhotic cardiomyopathy, was introduced in the middle 1990s. This term implies a condition with defective myocardial contractility, under physical and pharmacological strain, although this disease entity has not yet been finally classified and the mechanisms behind the cardiac abnormalities are not fully understood (Ma et al., 1996; Møller et al., 2002; Baik et al., 2004). Several previous studies have shown increased plasma concentrations of brain natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) in

some patients with cirrhosis, and these findings may suggest cardiac dysfunction (La Villa et al, 1992; Bendtsen et al., 1993; La Villa et al., 1995; Bernardi et al., 1998; Iwau et al., 2000; Wong et al., 2001; Møller et al., 2002; Henriksen et al., 2003; Baik et al., 2004). BNP is a neurohormone synthesized in cardiac ventricles, and is released as preproBNP and then enzymatically cleaved to NT-proBNP and BNP upon ventricular myocyte stretching. Moreover, blood measurements of BNP and NT-proBNP have been used to identify patients with congestive heart failure (McCullough et al., 2003). BNP measurements are the diagnostic test of choice because NT-proBNP is influenced by age and renal function. Nevertheless, NT-proBNP was suggested recently to be a even better indicator of early cardiac dysfunction due to its stability and longer biological half life (Hunt et al., 1997; Hughes et al., 1997; Campell et al., 2000; Goetze et al 2001; McCullough et al., 2003). However, until now few study have assessed levels of circulating NT-proBNP in patients with cirrhosis. Therefore, the present study was undertaken to search for relations between circulating levels of NT-proBNP and the severities of liver disease and cardiac dysfunction, and further, to investigate cardiac structures and functions by echocardiography, and assess their correlations with disease severity and cardiac dysfunction in cirrhotic patients.

Ⅱ. *MATERIALS AND METHODS*

Study population

Sixty-three cirrhotic patients were included in the present study. They consisted of 40 men and 23 women, with a mean age of 55.8 ± 10.1 years (range 40-71 years). Diagnoses were based on established clinical, biochemical, and ultrasonography criteria. The cause of cirrhosis was post-hepatic cirrhosis due to hepatitis B virus infection in 32 patients, hepatitis C virus infection in six patients, alcoholic in 19 patients, autoimmune in 2 patients, and cryptogenic in 4 patients. According to the Child-Turcotte-Pugh classification 16 patients were in class A, 29 in class B and 18 in class C. The control group (group 1) comprised fifteen healthy adults with a mean age of 52.9 ± 10.5 years (range 41-67 years). We divided the cirrhotic patients into a compensated group without ascites (group 2, n=28) and a decompensated group with ascites (group 3, n=35). The patients in group 3 had received diuretic therapy along with a less strict dietary salt restriction (440 mmol sodium per day), but additional cardiovascular medication, including beta blockers, was not prescribed for any of these patients. Seventeen patients had a hepatic encephalopathy history. Exclusion criteria for study subjects were presence of cardiac, pulmonary, and renal diseases, hypertension, and other major organic diseases. All patients and controls received a normal cardiac physical examination, chest X-ray, and electrocardiography (ECG). The baseline clinical and biochemical characteristics of the patients and controls are summarized in Table 1.

Study protocol

Blood was drawn from a forearm vein after at least ten minutes of resting supine, and was collected in standard sampling tubes for NT-proBNP analysis, and in appropriate tubes for other laboratory determinations. A complete blood count, prothrombin time (PT; as reflected by the international normalized ratio (INR)), liver and renal function tests were performed using standard laboratory automated techniques. Serum NT-proBNP levels were determined using a commercially available immunoassay based on the sandwich technique (Elecsys proBNP, Roche Diagnostics); its lower and upper limits of detection were 5pg or 35,000pg/ml, respectively. This is a rapid assay with a test time of approximately 18 min for a single sample; test results are calculated automatically. All patients and controls were studied by M-mode, two-dimensional, and Doppler echocardiography via a transthoracic approach. Cardiac dimensions and left ventricular hypertrophy were evaluated by measuring echocardiographic parameters including interventricular septum thickness in diastole (IVSd), left ventricular posterior wall thickness in diastole (LVPWd), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular mass index (LVMI), and left atrial diameter (LAD). Systolic pump function of the left ventricle (LV) was evaluated by ejection fraction (EF). Diastolic function of the left ventricle was evaluated by the peak filling velocity of E (E) and A waves (A) of Doppler mitral valve inflow velocities, E/A ratio, E wave deceleration time (EDT), mitral valve annular

velocities (E′) by Doppler tissue imaging, and E′/E. In addition, LV-Tei index was used as a parameter of combined systolic and diastolic myocardial performance of the LV.

Statistical analysis

All statistical evaluations were performed using the SPSS statistical package (Version 11, SPSS, Chicago, Illinois). Results are expressed as means ± SD for raw values. One way analysis of variance (ANOVA) with Tukey's B post hoc pairwise multiple comparison procedure was used for assessment of the between group (1, 2, and 3) differences in baseline characteristics, echocardiographic parameter, and circulating levels of NT-proBNP. Correlations were performed by Pearson regression analysis, and P values of < 0.05 were considered statistically significant.

Ⅲ. *RESULTS*

Echocardiographic parameters according to the decompensation component of cirrhosis are given in Table 2. Left atria were significantly enlarged in cirrhotic patients (groups 2, 3) than in the group (group 1) of normal controls (39.71 ± 4.75 mm in group 2 and 40.51 ± 4.60 mm in group 3 vs. 35.07 ± 7.39 mm in group 1) and wall thickness of left ventricles were increased in cirrhotic patients than in controls (10.07 ± 2.02 mm or 9.21 ± 1.77 mm in group 2 and 10.14 ± 1.70 mm or 9.63 ± 1.22 mm in group 3 vs. 8.67 ± 1.54 mm or 8.20 ± 1.66 mm in group 1, IVSd or LVPWd in each group, $P < 0.05$). EF or E/E′ were also increased and EDT was prolonged in patients with cirrhosis versus controls (70.50 ± 7.81 % or 10.51 ± 1.93 or 254.29 ± 60.75 msec in group 2 and 71.17 ± 7.02 % or 11.78 ± 2.25 or 271.13 ± 53.74 msec in group 3 vs. 59.33 ± 6.17 % or 8.81 ± 1.08 or 206.00 ± 35.32 msec in group 1, respectively, $P < 0.05$). On the other hand, no statistically significant differences were observed for LVEDD and LV-Tei index between groups 1, 2 and 3. Increased LVMI and a decreased E/A ratio were noted in the group of patients with ascites as compared with the other groups (123.54 ± 22.50 g/㎡ or 0.90 ± 0.32 in group 3 vs. 110.18 ± 23.06 g/㎡ or 1.01 ± 0.37 in group 2 and 102.80 ± 23.54 g/㎡ or 1.15 ± 0.37 in group 1, respectively, $P < 0.05$). Circulating levels of NT-proBNP were significantly higher in cirrhotic patients than in normal controls (155.88 ± 69.75 pg/ml in group 2 and 198.26 ± 146.69 pg/ml in group 3 vs. 40.27 ± 13.58 pg/ml in group 1, respectively, $P < 0.05$), but no significant mean NT-proBNP level difference was observed between groups 2 and 3 ($P > 0.05$; Figure 1). When patients were grouped according to the Child-Turcotte-Pugh

classification, circulating levels of NT-proBNP were significantly higher in Child class C than in classes B and A, and in controls (250.00 ± 176.60 pg/ml in Child class C vs. 168.63 ± 71.34 pg/ml in Child class B, 119.60 ± 67.29 pg/ml in Child class A, and 40.27 ± 13.58 pg/ml in controls, respectively, $P < 0.05$), and no significant NT-proBNP level difference was observed between Child classes B and A ($P > 0.05$). When circulating NT-proBNP concentrations in cirrhotic patients were correlated with echocardiographic parameters, significant positive correlations were found with LVEDD ($r = 0.277$, $P = 0.028$) and E/E′ ($r = 0.450$, $P = 0.01$) (Table 3, Figure3). However, no significant correlations were found between NT-proBNP levels and EF, LAD, IVSd, LVPWd, LVMI, E/A ratio, EDT, or LV-Tei index ($P > 0.05$), In addition, circulating NT-proBNP concentrations were not found to be related to biochemical parameters such as hemoglobin, albumin, INR of PT, or bilirubin ($P > 0.05$; Table 3).

Ⅳ. *DISCUSSION*

Cardiac dysfunction in cirrhosis lies at the intersection between two fields of study and is often ignored by hepatologists and cardiologists. However, cirrhosis is associated with many cardiovascular changes or abnormalities including hyperdynamic circulation, portal hypertension, hepatopulmonary syndrome, and hepatorenal syndrome. The main change of cardiovascular function in cirrhotic patients, i.e., a hyperdynamic circulation, as manifested by an increased cardiac output and a decreased arterial pressure, has been recognized for a long time (Kowalski et al., 1953; Abelmann et al., 1955; Schrier et al., 1988; Llach et al., 1988; Møller et al., 1995; Møller et al., 1997; Naschitz et al., 2000). Increased cardiac output in cirrhotic patients is associated with several factors including increased sympathetic nervous activity, increased blood volume, and the presence of arteriovenous communications (Levy et al., 1988; Fernandez-Rodriguez et al., 1993; Henriksen et al., 1998). Moreover, due to the presence of increased cardiac output at rest, it tends to be assumed that cardiac contractile function is normal or even supranormal in cirrhotic patients (Baik et al., 2004). However, many patients present with dyspnea, fluid retention, and limited exercise capacity that is suggestive of early cardiac dysfunction or overt heart failure (Møller et al., 1997; Epstein et al., 1998; Fallon et al., 2000). Thus, there is a need to consider cardiovascular function changes in cirrhotic patients from a different standpoint. From a functional point of view, the heart in cirrhosis is both hyperdynamic and dysfunctional. Experimental and clinical studies of cirrhotic patients strongly suggest the presence of latent heart failure with impaired reactions to standardized provocations (Møller et al., 2002). In the

1970s, latent or mild alcoholic cardiomyopathy was presented by some studies of cardiac function in patients with alcoholic cirrhosis, as showing depressed ventricular responsiveness to stimuli such as drugs or exercise (Gould et al., 1969; Limas et al.,1974). For instance, Gould and co-workers (Gould et al., 1969) showed that exercise induced a doubling of the left ventricular end-diastolic pressure associated with an insignificant change in cardiac output in alcoholic patients with chronic liver disease, indicating a markedly blunted cardiac response. Over the intervening period, blunted and depressed ventricular contractile responses to stimuli have been reported in animal models and in patients with nonalcoholic cirrhosis (Ahmed et al., 1984; Friedman et al., 1992; Wong et al., 1994; Møller et al., 1995; Ma et al., 1996; Epstein et al., 1998; Wong et al., 1999; Fallon et al., 2000; Perello et al., 2000). Therefore, in patients with all forms of cirrhosis, concomitant cardiac dysfunction is characterized by baseline hypercontractility. However, depressed contractile response to physiologic or pathophysiologic stimuli has recently been referred to as cirrhotic cardiomyopathy, a clinical entity which is clinically and pathophysiologically different from alcoholic heart muscle disease (Lee et al., 1989; Ma et al., 1996). Left ventricular performance is usually reduced in alcoholic heart muscle disease or alcoholic cardiomyopathy. On the other hand, cirrhotic cardiomyopathy comprises compound changes in increased cardiac output related to normal or increased systolic performance without stimuli at rest, but depressed contractile response to various strain, decreased beta-adrenergic receptor function, postreceptor dysfunction, defective excitation contraction coupling, and in some patients conductance abnormalities (Bernardi et al., 1998; Møller et al., 2002). Cirrhotic cardiomyopathy has been described as an asymptomatic condition

that may assume clinical importance during volume or pressure overload. That is, clinically significant cardiac dysfunction and latent heart failure associated with impaired cardiac contractility during preload and afterload, may be outcome (Ahmed et al. 1984; Pozzi et al., 1997). Thus, it appears that patients with a cirrhotic heart may present with sodium fluid retention and strain often unmasks the presence of latent heart failure. No specific treatment can be recommended, and evident ventricular failure in patients with cirrhotic cardiomyopathy should be treated as having a non-cirrhotic etiology by sodium restriction, diuretics, and afterload reduction, but special caution should be taken during and after stressful procedures, such as, surgery, shunt implantation, and liver transplantation (Møller et al., 2002; Baik et al., 2004). Since heart failure is characterized by complicated cardiorenal, hemodynamic, and neurohormonal alterations, information on numerous variables is required, e.g., clinical status, exercise capacity, hemodynamic variables, echocardiographic parameters, several markers of neurohumoral activation, and biochemical markers of end-organ dysfunction, to assess and monitor patients with heart failure (Mann et al., 1999; Mair et al., 2005). In general, structural or functional changes in the cirrhotic heart are easily evaluated by M-mode, two-dimensional, and Doppler echocardiographic studies via the transthoracic approach. Main structural changes in the cirrhotic heart are observed in the left heart, and include, left atrium dilatation, and hypertrophy or dilatation of the left ventricle. Histological changes including myocardial fibrosis, subendocardial edema, and nuclear and cytoplasmic vacuolation of cardiomyocytes have been reported by necropsy studies in a patient population limited to alcoholic cirrhosis (Ma et al., 1996; Liu et al., 1999; Møller et al., 2002; Baik et al., 2004). In the present study, left atrial enlargement, increased

wall thickness and EF of the left ventricle, and E/E′ of mitral annulus velocity were noted in cirrhotic patients as compared with controls. In addition, increased LVMI and a decreased E/A ratio were noted in the group of ascitic patients as compared with pre-ascitic patients or healthy controls. On the other hand, no statistically significant difference was observed between these three groups in terms of LVEDD or LV-Tei index. These findings are similar to the structural changes reported by previous studies, it is expected that E/E′ measurements, make up for the weak points of Doppler transmitral inflow measurement, and that E/E ′may be used as a reliable marker of diastolic dysfunction in cirrhotic patients. More prevalent left ventricular hypertrophy and relaxation abnormality in decompensated patients with more advanced cirrhosis suggests that advanced cirrhosis is associated with more advanced cardiac dysfunction. Additionally, it has been reported that functional and electrophysiological abnormalities also develop in the cirrhotic heart. In cirrhotic patients, systolic function was normal or even supranormal at rest without a stimulus, but cardiac contractile function in response to strains attenuated these functions compared with healthy controls. Diastolic dysfunction in the cirrhotic heart appears to be more prevalent than systolic dysfunction, thus echocardiography may reveal abnormal diastolic function under circumstances without strain or even at rest (Kelbaek et al., 1984; Wong et al.,1989; Grose et al., 1995; Finucci et al., 1996; Pozzi et al., 1997; Wong et al., 1999). Electrophysiological changes including prolonged repolarization and impaired cardiac excitation-contraction coupling have been demonstrated in cirrhotic patients (Kempler et al., 1993; Bernardi et al., 1998; Finucci et al., 1998; Trevisani et al., 2003; Bal et al., 2003). Moreover, the natriuretic peptides

have been recently highlighted as major markers for the diagnosis, severity, and prognosis of heart failure. In contrast other conventional cardiac function tests are time consuming and often do not correlate well with symptomatic changes in patients' conditions. B-type natriuretic peptide (BNP) is a neurohormone synthesized with atrial natriuretic peptide (ANP) in cardiac ventricles, and is released as preproBNP and then enzymatically cleaved to N-terminal-proBNP (NT-proBNP) and BNP depend upon ventricular myocyte stretching and volume overload (McCullough et al., 2003). In cases of heart failure, ventricular BNP production is markedly elevated, and circulating BNP concentrations are consistently elevated in untreated heart failure (Mair et al., 2001). Accordingly, blood measurements of BNP and NT-proBNP have been found to be of diagnostic value in congestive heart failure (CHF) related to CHF severity. Moreover, they could be used for adjusting treatment and have been shown to be powerful prognostic markers in both chronic and acute heart failure, independently of standard echocardiographic parameters (Yu et al., 1999; Packer et al., 2003; McCullough et al., 2003; Hartman et al., 2004). However, NT-proBNP is influenced by age and the age-related normal decline in glomerular filtration rate, and thus, two cutoff points must be used, i.e., NT-proBNP >125 pg/mL in patients younger than 75 years and > 450 pg/mL in patients older than 75 years (McCullough et al., 2003). Despite a tight relationship between age and renal function, NT-proBNP, the circulating propeptide of BNP, has been recently suggested to be an even better marker of early cardiac dysfunction or heart failure than BNP, because it is more stable and less sensitive to rapid fluctuations caused by short term secretion stimuli due to its appreciably longer biological half life (Hunt et al. 1997; Hughes et

al., 1999; Campell et al., 2000; Goetze et al., 2001; McCullough et al., 2003;4). A study by Henriksen et al., (Henriksen et al., 2003) showed that circulating proBNP concentrations are significantly increased in patients with advanced cirrhosis and that these are closely related to BNP concentrations, but no signs of reduced hepatic degradation of proBNP or of BNP are present in patients with cirrhosis, which suggests that elevated levels of proBNP and BNP are related to markers of cirrhotic severity and indicate the presence of cardiac dysfunction in advanced cirrhosis. In the present study, circulating NT-proBNP levels were found to be significantly higher in cirrhotic patients than in controls, and also higher in Child class C patients than in Child class B or A patients, or controls. In addition, we found that circulating NT-proBNP concentrations are significantly and positively correlated with the standard echocardiographic parameters LVEDD and E/E′ in cirrhotic patients. On the other hand, circulating NT-proBNP concentrations were not found to be related to biochemical parameters such as hemoglobin, albumin, INR of PT, or bilirubin. Importantly, a significant correlation was observed between NT-proBNP and Child class, which suggests that circulating NT-proBNP levels are likely to be related to the severity of cirrhosis. In addition, the findings that circulating NT-proBNP levels increased with the same incremental tendencies with respect to LVEDD and E/E′ suggest that NT-proBNP provides valuable information about abnormal cardiac function and structural abnormalities in patients with liver cirrhosis. Ascites is one of the parameters of the Child-Turcotte-Pugh classification that indicates liver disease severity. Thus, progressive increases in the ascites ratios in patients from Child Classes A, B and C is expected, however, no significant circulating NT-proBNP level differences were

observed between pre-ascitic and ascitic cirrhotic patients in the present study. This result represents a study pitfall, which may be attributable to diuretic therapy before blood sampling in cirrhotic patients with ascites. De Lemos and his colleagues (De Lemos et al., 2003) have advocated that the net effect of beta-blockers and diuretics is often to reduce BNP concentration. Therefore, further pathophysiological and clinical research is needed to assess the significance of therapy with diuretics andbeta-blockers. In conclusion, the present study shows that circulating NT-proBNP concentrations, LAD and LVEDD, E/A ratio, EDT, and E/E′ may be reliable indicators of the extent of cardiac abnormalities in cirrhotic patients. Additionally, increased levels of NT-proBNP were found to be related to disease severity in patients with all forms of cirrhosis. Thus, it may be suggested that cardiac dysfunction is related to an increased circulating proBNP concentration, which in turn is more prominent in severe disease, and that NT-proBNP has predictive value in cases of concomitant cardiac dysfunction and cirrhotic progression.

V. SUMMARY

Background and Objectives : Cardiac dysfunction and a hyperdynamic systemic circulation may be present in cirrhotic patients. B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) are cardiac neurohormones that reflect early ventricular dysfunction, and are released from cardiac ventricles in response to increased wall tension. The purpose of the present study was to identify relations between circulating levels of NT-proBNP and the severity of liver disease and cardiac dysfunction in patients with cirrhosis.

Materials and Methods : Sixty-three cirrhotic patients (M/F=40/23, mean age 55.8 ± 10.1 years) and fifteen healthy controls (M/F=9/6, mean age of 52.9 ± 10.5 years, group 1) were included in the present study. Circulating levels of NT-proBNP were determined in echocardiographically examined patients, which were allocated to one of three groups (16 patients in class A, 29 in class B and 18 in class C) according to the Child-Turcotte-Pugh classification or into two groups, i.e., a compensated group without ascites (group 2, pre-ascitics, n=28), and decompensated group with ascites (group 3, ascitics, n=35).

Results : Circulating NT-proBNP levels were significantly higher in cirrhotic patients (groups 2, 3) than in normal controls (155.88 ± 69.75 pg/ml in group 2 and 198.26 ± 146.69 pg/ml in group 3 vs. 40.27 ± 13.58 pg/ml in group 1, respectively, $P < 0.05$), but no significant mean NT-proBNP level difference was observed between groups 2 and 3 ($P > 0.05$). However, NT-proBNP levels were significantly higher in Child class C patients than in classes B and A patients or controls (250.00 ± 176.60 pg/ml in Child class C vs. 168.63 ± 71.34 pg/ml in Child class B, 119.60 ±

67.29 pg/ml in Child class A, and 40.27 ± 13.58 pg/ml in controls, respectively, $P < 0.05$), and no significant NT-proBNP level difference was observed between Child classes B and A ($P > 0.05$). Left atria were significantly enlarged in groups 2 and 3 than in group 1 (39.71 ± 4.75 mm in group 2 and 40.51 ± 4.60 mm in group 3 vs. 35.07 ± 7.39 mm in group 1) and wall thickness of left ventricles were increased in cirrhotic patients than in controls (10.07 ± 2.02 mm or 9.21 ± 1.77 mm in group 2 and 10.14 ± 1.70 mm or 9.63 ± 1.22 mm in group 3 vs. 8.67 ± 1.54 mm or 8.20 ± 1.66 mm in group 1, IVSd or LVPWd in each group, $P < 0.05$). EF or E/E′ were also increased and EDT was prolonged in patients with cirrhosis versus controls (70.50 ± 7.81 % or 10.51 ± 1.93 or 254.29 ± 60.75 msec in group 2 and 71.17 ± 7.02 % or 11.78 ± 2.25 or 271.13 ± 53.74 msec in group 3 vs. 59.33 ± 6.17 % or 8.81 ± 1.08 or 206.00 ± 35.32 msec in group 1, respectively, $P < 0.05$). Increased LVMI and a decreased E/A ratio were noted in the group of patients with ascites as compared with the other groups (123.54 ± 22.50 g/㎡ or 0.90 ± 0.32 in group 3 vs. 110.18 ± 23.06 g/㎡ or 1.01 ± 0.37 in group 2 and 102.80 ± 23.54 g/㎡ or 1.15 ± 0.37 in group 1, respectively, $P < 0.05$). Circulating NT-proBNP levels of cirrhotic patients significantly and positively correlated with LVEDD ($r = 0.277$, $P = 0.028$) and E/E′ ($r = 0.450$, $P = 0.01$).

Conclusion : Circulating NT-proBNP levels were high in patients with cirrhosis, and are likely to be related to the severity of disease in cirrhotic patients. Advanced cirrhosis is associated with an advanced cardiac dysfunction, and NT-proBNP has predictive value for concomitant cardiac dysfunction and cirrhosis progression.

Table 1. Baseline clinical and biochemical characteristics of the cirrhotic patients and controls

Parameter	Control	Cirrhotic group	
		Pre-Ascitic	Ascitic
	N = 15	N = 28	N = 35
Age	52.87±10.49	56.68±9.22	54.94±11.01
Sex (male/female)	6/9	18 / 10	22 / 13
Hb (g/L)	13.66±1.54	10.76±2.16 *	10.31±2.04 *
PT (INR)	0.96±0.11	1.34±0.24 *	1.62±0.34 +*
Album (g/L)	4.13±0.40	3.40±0.55 *	2.85±0.43 +*
Total bilirubin (mg/dl)	0.62±0.14	3.05±6.95	4.66±4.11 *
Na	143.67±2.35	138.39±4.57 *	136.49±5.73 *
K	4.31±0.91	3.98±0.71	4.32±0.59
Cr	1.00±0.18	1.04±0.28	1.07±0.30
Etiology			
HBV		14	18
HCV		3	3
Alcohol		9	10
Autoimmune		0	2
Cryptogenic		3	1

Hb ; Hemoglobin, PT ; Prothrombin time, Cr ; Creatinine

* P < 0.05, compared with control. + P < 0.05, compared with preascitic group.

Table 2. Echocardiographic parameters in cirrhotic patients and controls

Parameter	Control	Cirrhotic group	
		Pre-Ascitic	Ascitic
	N = 15	N = 28	N = 35
EF (%)	59.33±6.17	70.50±7.81 *	71.17±7.02 *
LAD (mm)	35.07±7.39	39.71±4.75 *	40.51±4.60 *
LVEDD (mm)	46.47±2.56	49.00±3.06	48.23±4.59
IVSd (mm)	8.67±1.54	10.07±2.02 *	10.14±1.70 *
LVPWd (mm)	8.20±1.66	9.21±1.77 *	9.63±1.22 *
LMI (g/m^2)	102.80±23.54	110.18±23.06	123.54±22.50 *
E/A ratio	1.15±0.37	1.01±0.37	0.90±0.32 *
E/E′	8.81±1.08	10.51±1.93 *	11.78±2.25 *
EDT(msec)	206.00±35.32	254.29±60.75 *	271.13±53.74 *
LV Tei index	0.33±0.07	0.34±0.12	0.33±0.13

Hb ; Hemoglobin, PT ; Prothrombin time, Cr ; Creatinine
EF ; Ejection fraction of left ventricle, LAD ; Left atrium diameter
LVEDD ; Left ventricular end-diastolic diameter
IVSd ; Interventricular septum thickness in diastole
LVPWd ; Left ventricular posterior wall thickness in diastole
LVMI ; Left ventricular mass index, E/A ratio ; Ratio of velocity of E wave to velocity of A wave of Doppler mitral valve inflow
EDT ; Deceleration time of E wave, E′; Mitral valve annular velocities

* $P < 0.05$, compared with control. + $P < 0.05$, compared with preascitic group.

Table 3. Correlation of circulating NT-proBNP concentrations with echocardiographic parameters in cirrhotic patients

Parameter	Correlation coefficients (r)	p value
Hb (g/L)	-0.076	0.556
Albumin (g/L)	-0.105	0.415
Total bilirubin (mg/dl)	0.195	0.127
PT (INR)	0.172	0.178
EF (%)	0.022	0.864
LAD (mm)	0.150	0.239
LVEDD (mm)	0.277	0.028
IVS (mm)	0.111	0.386
LVPWD (mm)	0.124	0.333
LV mass index (g/㎡)	0.080	0.532
E/A ratio	0.058	0.653
E/E′	0.450	0.01
DT (msec)	0.144	0.260
Tei index	0.099	0.442

EF ; Ejection fraction of left ventricle, LAD ; Left atrium diameter
LVEDD ; Left ventricular end-diastolic diameter
IVSd ; Interventricular septum thickness in diastole
LVPWd ; Left ventricular posterior wall thickness in diastole
LVMI ; Left ventricular mass index, E/A ratio ; Ratio of velocity of E wave to velocity of A wave of Doppler mitral valve inflow
EDT ; Deceleration time of E wave, E′; Mitral valve annular velocities

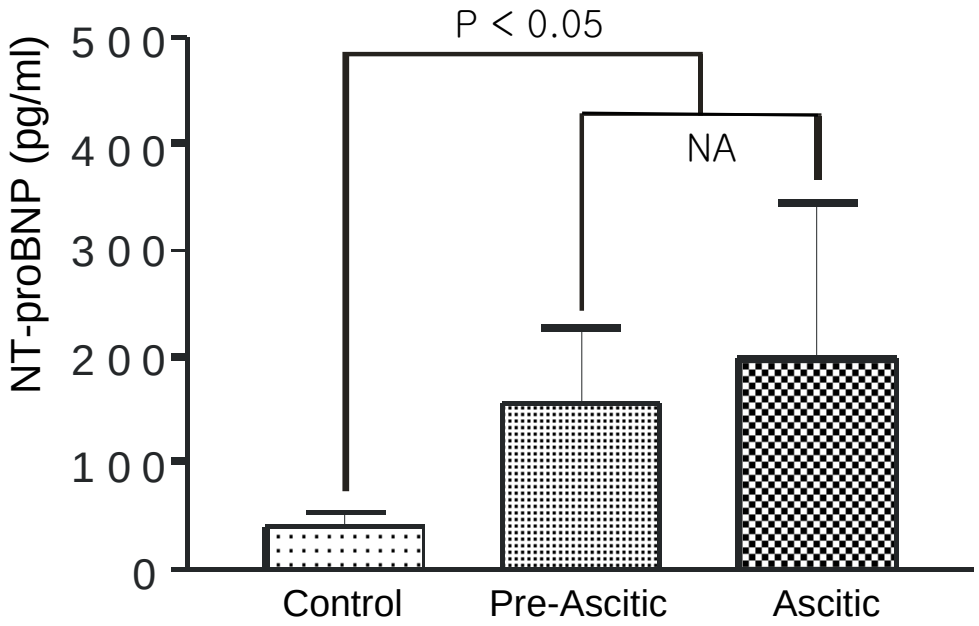

Figure 1. Circulating levels of NT-proBNP in controls and cirrhotic patients divided into a compensated group without ascites (pre-ascitic) and a decompensated group with ascites (ascitic).

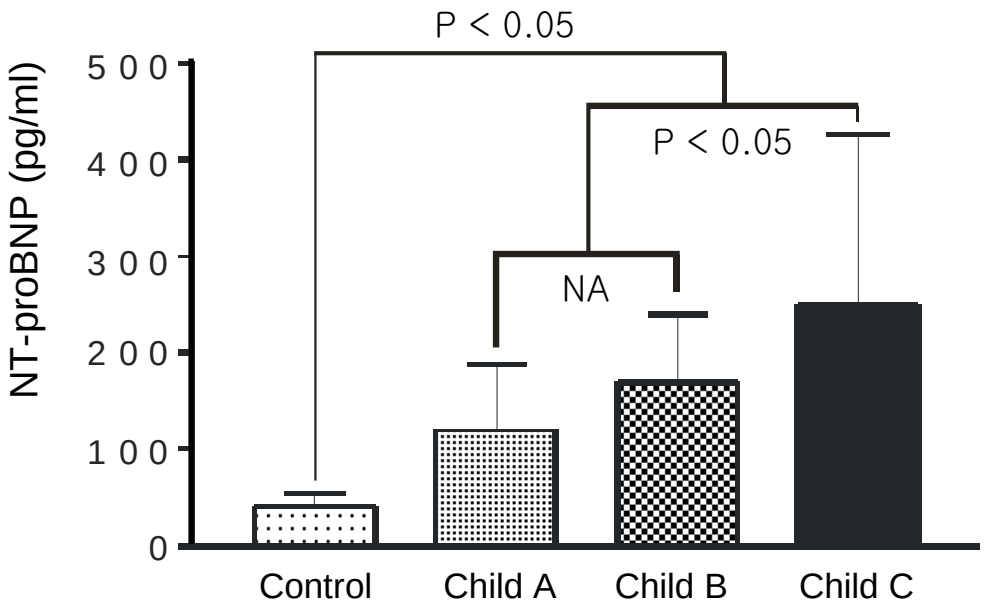

Figure 2. Circulating concentrations of NT-proBNP in controls and cirrhotic patients grouped as class A, B, C according to the Child-Turcotte-Pugh classification.

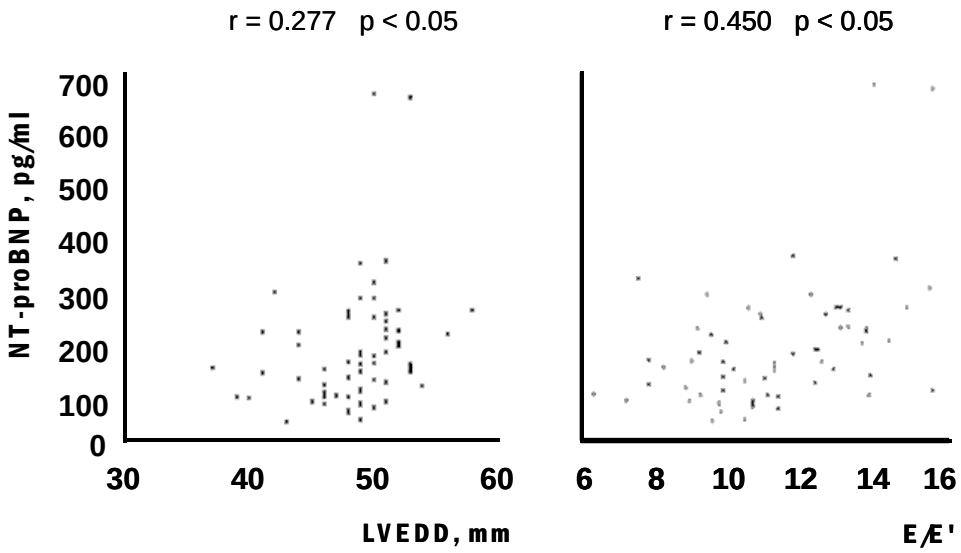

Figure 3. Circulating NT-proBNP levels in cirrhotic patients versus echocardiographic parameters. NT-proBNP levels were found to correlate significantly and positively with LVEDD and E/E′.

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