Relationship Between Doppler Transmitral Flow Velocity Pattern and Plasma Atrial and Brain Natriuretic Peptide Concentrations in Anuric Patients on Maintenance Hemodialysis

Shigenori ITO,1 MD, Sumiko MURAI,2 MD, Norio TAKADA,1 MD, Atsushi OZASA,1 MD, Mayumi HANADA,1 MD, Masaya SUGIYAMA,1 MD, Kaoru SUZUKI,1 MD, Yuji NAGAE,1 MD, Toshiaki INAGAKI,1 MD, Yutaka TAKEDA,3 MD, Tatsuya FUKUTOMI,3 MD, and Takashi JOH,3 MD

SUMMARY

Plasma atrial (ANP) and brain (BNP) natriuretic peptide levels were compared to determine if transmitral flow velocity pattern is an instantaneous marker of body fluid balance in anuric patients on hemodialysis (HD).

We measured plasma ANP and BNP levels and performed Doppler echocardiography in 38 anuric patients before and after HD. Patients with valvular disease, left ventricular systolic dysfunction having a fractional shortening < 0.3, arrhythmia, or left ventricular hypertrophy were excluded. The relationships between plasma ANP or BNP levels and the transmitral flow velocity pattern were evaluated. We also determined if the magnitude of the decrease in plasma ANP level was related to that in the early peak of transmitral flow velocity (peak E). The mean age of the subjects was 61.1 ± 9.7 years.

The ANP level of 213.6 ± 146.1 pg/mL was related to peak E of 61 ± 15 cm/s before HD (R = 0.504, P < 0.001), but not after HD. Plasma ANP level was not related to peak late transmitral flow velocity (peak A) or peak E/peak A before or after HD. BNP level was not related to the transmitral flow velocity pattern. The magnitude of decrease in hANP level during HD was significantly related to that in peak E (R = 0.342, P < 0.05).

Before HD, peak E was related to the plasma ANP level, reflecting volume overload. Change in peak E showed a weak relationship with that of plasma ANP level in the same HD patient. The measurement of peak E during a HD session may potentially enable the assessment of hydration status during HD. (Int Heart J 2006; 47: 401-408)

Key words: Doppler echocardiography, Transmitral flow velocity pattern, Atrial natriuretic peptide, Brain natriuretic peptide, Hemodialysis, Preload

From the 1 Division of Internal Medicine, Nagoya City Moriyama Municipal Hospital, 2 Hemodialysis Center, Jinseikai Nishio Clinic, 3 Department of Internal Medicine and Bioregulation, Nagoya City University Graduate School of Medical Sciences, Aichi, Japan.

Address for correspondence: Shigenori Ito, MD, Division of Internal Medicine, Nagoya City Moriyama Municipal Hospital, 2-18-22, Moriyama, Moriyama-ku, Nagoya-shi, Aichi 463-8567, Japan.

Received for publication December 16, 2005.

Revised and accepted March 2, 2006.
Assessment of the hydration status in hemodialysis (HD) patients is crucial for reducing the risk of cardiovascular disease, which is more common in these patients than in the general population. The levels of plasma atrial (ANP) and brain (BNP) natriuretic peptides have been used as markers of hydration status. Transmitral flow velocity pattern obtained by Doppler echocardiography, as an instantaneous modality, also reflects preload status. However, the possibility of a direct relationship between the natriuretic peptides and transmitral flow velocity pattern in patients on maintenance HD has not been extensively investigated.

Methods

A total of 38 patients with chronic renal failure on maintenance HD therapy at the Jinseikai Nishio Clinic in Nishio, Japan were studied. Patients with a valvular disease, left ventricular systolic dysfunction having a fractional shortening less than 0.3 obtained by echocardiography, left ventricular hypertrophy, atrial fibrillation, or atrial flutter were excluded. Detection of left ventricular hypertrophy was based on the criteria of the Framingham Heart Study by M-mode measurements. All patients underwent a 4 hour HD session 3 times a week on Tuesday, Thursday, and Saturday. On Tuesday, 2-dimensional and Doppler echocardiography, chest x-rays, and blood sampling from the arterial side of the HD circuit were performed both immediately before and after HD. The levels of plasma ANP and BNP were determined. An immunoradiometric assay was used for ANP and a chemiluminescent enzyme immunoassay was used for BNP (Bio Medical Laboratories, Tokyo). Two-dimensional echocardiography and Doppler echocardiography were performed with a Toshiba ultrasound system (model 130A equipped with 2.5 and 3.75 MHz phased array transducers, Tokyo). Patients were examined in the left lateral recumbent position, and the standard transducer position was used. Two-dimensional echocardiographic parameters included left atrial diameter (LA), left ventricular end-diastolic (LVDd) and end-systolic diameter (LVDs), fractional shortening (FS), and maximal diameter of the inferior vena cava (IVC) during expiration. FS was calculated as (LVDd-LVDs)/LVDd. The peak early diastolic velocity (peak E), the peak late diastolic velocity (peak A), and deceleration time (DcT) of the early wave were measured in the apical 4-chamber view by pulsed-wave Doppler echocardiography. The beam direction was aligned with the transmitral inflow as best as possible and sample volumes were obtained at the level of the mitral annulus. The position was not changed between the measurements before and after HD. Patients who showed summation between the peaks of the early and late filling waves in the transmitral flow velocity pattern were excluded. Cardiothoracic ratio was mea-
sured from chest x-rays. Brachial artery systolic and diastolic blood pressures were measured with a mercury-column sphygmomanometer. Heart rate was monitored electrocardiographically. The following analyses were performed using the data obtained as described above; 1) the correlation between plasma ANP or BNP level and each of the indices of 2-dimensional echocardiography, transmitral flow velocity pattern, and cardiothoracic ratio before and after HD, and 2) the correlation of changes in plasma ANP or BNP level and the changes in each of the echocardiographic indices and cardiothoracic ratio. The study protocol was approved by the Ethics Committee of our institute and written informed consent was obtained from each patient before the study.

Statistics: Continuous variables are expressed as the mean ± SD. The changes in continuous variables between before and after HD were evaluated by the paired t-test. Univariate linear regression analysis was used to evaluate the correlation between the plasma ANP or BNP level and each of the other indices and between the magnitude of change in plasma ANP or BNP level and that in each of the other indices.

RESULTS

The mean age of the patients was 61.1 ± 9.7 years. Nine patients (23%) were male. Thirty-nine percent (15/38) had diabetes mellitus and 34% (13/38) had hypertension. Changes in clinical, laboratory, and radiographic parameters during HD are shown in Table I. Blood pressure, ANP and BNP levels, and cardiothoracic ratio decreased significantly during HD. In contrast, heart rate increased significantly.

The changes in 2-dimensional and Doppler echocardiographic indices during HD are shown in Table II. All indices except FS and DcT decreased significantly. FS was significantly correlated with ANP before HD (r = −0.328, CI = −0.586 to −0.009, P = 0.044). LA was significantly correlated with BNP after HD (r = 0.344, CI=0.027 to 0.596, P = 0.034). The changes in IVC were correlated

| Table 1. Changes in Clinical, Laboratory, and Radiographic Parameters During Hemodialysis |
|-----------------------------------------------|-----------------|-----------------|-------|
|                                               | Before hemodialysis | After hemodialysis | P     |
| Body weight (kg)                              | 49.8 ± 7.0       | 47.2 ± 6.9       | < 0.0001 |
| Total amount of ultrafiltration (L)           | Not applicable   | 2.9 ± 0.6        | < 0.0001 |
| Systolic blood pressure (mmHg)                | 156 ± 28         | 133 ± 28         | < 0.0001 |
| Heart rate (beats/minute)                     | 71 ± 9           | 80 ± 12          | < 0.0001 |
| ANP (pg/mL)                                   | 213.6 ± 146.1    | 53.4 ± 33.6      | < 0.0001 |
| BNP (pg/mL)                                   | 366.0 ± 292.3    | 233.9 ± 187.9    | < 0.0001 |
| Cardiothoracic ratio (%)                      | 50.0 ± 4.6       | 47.8 ± 4.3       | < 0.0001 |

ANP indicates atrial natriuretic peptide and BNP, brain natriuretic peptide.
with that of BNP during HD ($r = 0.465$, CI = 0.171 to 0.683, $P = 0.003$). No other correlations were found between plasma ANP or BNP levels and 2-dimensional
echocardiographic parameters. The relationships between plasma ANP or BNP levels and Doppler echocardiographic parameters are shown in Table III. Only peak E was significantly ($r = 0.504, P < 0.001$) correlated with plasma ANP levels before HD. This correlation did not exist after HD. Both before and after HD, plasma BNP level did not correlate with any Doppler echocardiographic parameter. Changes in the plasma ANP level correlated with that of peak E significantly ($r = 0.342, P = 0.035$). The cardiothoracic ratio was not correlated with ANP or BNP before or after HD. Changes in cardiothoracic ratio were correlated with BNP during HD ($r = 0.542, CI = 0.269$ to $0.734, P < 0.001$).

**DISCUSSION**

**Correlation between preload and transmitral flow velocity pattern:** Ultrafiltration during HD results in a marked reduction in circulating blood volume with a concomitant reduction in left atrial pressure. Lowering of left atrial pressure during HD has been documented by Kinet, et al$^{10}$ who observed a reduction in pulmonary capillary wedge pressure from an average of 12.5 mmHg to 3.1 mmHg. There have been several studies showing a relationship between this reduction of preload and transmitral flow pattern. In normal subjects, by reducing preload with inflation of blood pressure cuffs placed at the level of the root of the 4 limbs, peak E decreased, while no changes were found in peak A. This resulted in a significant decrease in the ratio of these 2 velocities.$^5$ In 18 patients with an old myocardial infarction, after lower body negative pressures (0, 10 mmHg, 20 mmHg), peak E decreased from 68.3 ± 13.9 to 59.8 ± 15.2 cm/s at 10 mmHg and further to 55.2 ± 11.0 cm/s at 20 mmHg.$^6$ In another protocol in 8 patients with an old myocardial infarction, peak E was significantly decreased and peak A remained unchanged.$^7$ In a different study using 12 HD patients without overt heart disease, peak E was significantly decreased from 95.3 ± 8.2 cm/s to 63.0 ± 5.7 cm/s. There was no significant change in peak A, although there was a slight decrease from 79.7 ± 6.3 cm/s to 74.1 ± 4.7 cm/s during HD. This resulted in the ratio of peak E/peak A decreasing from 1.19 ± 0.06 to 0.85 ± 0.04.$^8$ Our study also showed that HD resulted in a substantial modification of the transmitral flow pattern in patients on maintenance HD.$^8,11$ That is, the peak E, peak A, and the ratio of peak E/peak A decreased significantly. The decrease after HD appeared to reflect a reduction in left atrial pressure. However, an increase in heart rate and a decrease in afterload might have partially affected the transmitral flow velocity pattern.$^{12}$ In this study, the cases with tachycardia showing summation of peak E and peak A were excluded.

**Correlation between plasma ANP level and transmitral flow velocity pattern as a potential marker of preload during a session of HD:** Plasma ANP levels reflect
atrial distension and extracellular fluid volume alterations. A significant linear correlation has been found between the plasma ANP level and pulmonary capillary wedge pressure in 92 patients with various cardiac diseases. Furthermore, in 32 patients with chronic atrial fibrillation, correlations were observed between the transmitral peak flow velocity and mean pulmonary capillary wedge pressure ($r = 0.51$) as well as deceleration time ($r = 0.65$) and ANP ($r = 0.36$).

A direct relationship between transmitral flow velocity pattern and plasma ANP level in HD patients has not been previously reported. In the present study, preload reduction caused a decrease in peak E, peak A, and the ratio of peak E/peak A during HD. There was a significant correlation between plasma ANP level and peak E before HD and between the magnitude of decrease in plasma ANP level and that in peak E. These results suggest that peak E might be a potential reflection of the preload status before HD. These peak E changes can be evaluated without a time lag in contrast to changes in plasma ANP level. We believe that the explanation for the relatively low peak E/peak A ratio and the lack of a relationship between peak A or peak E/peak A and ANP level before HD, found in this study, was the transmitral flow velocity pattern showing a diastolic dysfunction pattern, which is often seen in patients with maintenance HD.

Lack of relationship between plasma BNP level and transmitral flow velocity pattern in HD patients: In this study, no significant relationship was found between the plasma BNP level and transmitral flow velocity pattern either before or after HD. BNP release is less affected by atrial filling pressures, providing a better reflection of myocardial disease. It has been reported that plasma BNP levels reflect left ventricular function in HD patients with coronary artery disease and left ventricular mass and blood pressure in HD patients without coronary artery disease. Plasma BNP levels in these patients seemed to be higher than those in HD patients who had no coronary artery disease. According to Shao, et al the plasma BNP level of HD patients with normal cardiac function was 62.8 pg/mL before HD and 20.7 pg/mL after HD. Thus, although we excluded patients with left ventricular systolic dysfunction and left ventricular hypertrophy based on echocardiographic evaluation, patients with hypertension and diabetes mellitus were included. These risk factors might have caused plasma BNP level elevation that was not proportional to peak E.

Secretion and plasma half-life of the natriuretic peptides: ANP is rapidly secreted from storage granules in atrial cardiocytes, mainly via a regulated pathway, in response to hemodynamic changes. The plasma half-life of ANP is only several minutes (fast, $1.7 \pm 0.07$ minutes and slow, $13.3 \pm 1.69$ minutes). BNP, which is secreted in a constitutive manner, also has a short plasma half-life (fast, $3.9 \pm 0.23$ minutes and slow, $20.7 \pm 1.87$ minutes) that is a little longer than ANP. Thus, we assumed ANP and BNP work as spontaneous markers that can
respond to rapid changes in left atrial pressure or intravascular volume during HD, and we believe this assumption makes our analyses reasonable. In this study, changes in cardiothoracic ratio and IVC were significantly correlated with changes in BNP, but not with changes in ANP. These 2 markers as well as BNP have been recognized as good markers of dry weight in HD patients. Although our results were consistent with previous reports, the reason why ANP was not correlated with these markers remains unknown.

**Limitations:** Patients on maintenance HD often have cardiomyopathy with left ventricular hypertrophy. The cardiomyopathy is due to some degree to uremia, hypertension, and diabetes mellitus, and may have caused the diastolic dysfunction. We speculated that after HD, left ventricular diastolic function affected the transmitral flow velocity pattern more than preload in this study. The natriuretic peptides and transmitral flow velocity pattern intrinsically do not appear to be independent markers of body fluid balance. Thus, they can be useful only when the change in body fluid balance is estimated in the same patient during a session of HD. Prior to the clinical use of these markers, a comparison with other isolated measurements such as bioimpedance measurements would be required.

**Conclusions:** Before HD, peak E was related to plasma ANP level, reflecting volume overload. The change in peak E showed a weak correlation with that of plasma ANP level in the same HD patient. Thus, the measurement of peak E during a HD session may potentially enable the assessment of hydration status during HD.

**REFERENCES**


