Dialysis Therapies

Effects of the Creation of Arteriovenous Fistula for Hemodialysis on Cardiac Function and Natriuretic Peptide Levels in CRF

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● *Background:* Cardiac failure occasionally is caused by the creation of vascular access for hemodialysis. However, the influence of an arteriovenous (AV) fistula on cardiac function has not been fully elucidated. The present study investigated serial changes in cardiac function and hormonal levels after the AV fistula operation. *Methods:* Sixteen patients with chronic renal failure underwent echocardiographic studies before and 3, 7, and 14 days after the AV fistula operation. Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations were measured before and 1, 3, 6, 10, and 14 days after the operation. *Results:* Creation of an AV fistula produced significant elevations in left ventricular (LV) end-diastolic diameter (+4%), fractional shortening (+8%), and cardiac output (CO; +15%). In LV inflow velocities measured by Doppler echocardiography, deceleration time of the early diastolic filling wave shortened (−12%) and the ratio of the peak velocity of early diastolic to atrial filling (E-A ratio) increased (+18%). The difference in duration of LV inflow and pulmonary venous flow at atrial contraction, a marker of LV end-diastolic pressure, significantly shortened day 14 after the operation (−37%). That is, creation of an AV fistula induced LV diastolic dysfunction toward a restrictive filling pattern. Both ANP and BNP levels increased after the operation, and maximal percentages of increase were observed after 10 days (ANP, +48%; BNP, +68%). In the relationship between cardiac function and hormonal response, the increase in CO was associated with elevation of ANP levels ($r = 0.61$; $P = 0.01$), but not BNP levels. Conversely, the increase in E-A ratio correlated only with BNP level elevation ($r = 0.60$; $P = 0.01$). *Conclusion:* Our observations indicate that creation of an AV fistula has significant effects on cardiac systolic and diastolic performance, and ANP release is induced by volume loading, but BNP release is stimulated by LV diastolic dysfunction. *Am J Kidney Dis* 40:974-982.
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CREATION OF AN arteriovenous (AV) fistula for hemodialysis therapy is a technique that provides convenient access to the circulation in patients with end-stage renal disease.[1] A number of studies showed that cardiac failure could be induced by creation of an AV fistula for dialysis.[2-7] The contribution of an AV fistula to cardiac performance has been studied using different methods.[8-17] In many of these studies, patients were already on dialysis therapy, and at some stage, cardiac function was studied while a short manual compression over the fistula attempted to eliminate the effect of the fistula itself.[8-13] Only a few prospective evaluations comparing cardiac performance before and after creation of an AV fistula have been performed in humans.[14-17] However, in most of those studies, considerable time (≥2 weeks) had passed after the creation of the fistula.[15-17] Therefore, the short-term effect of AV fistula creation on cardiac function remains to be elucidated. Chronic volume overload by the AV fistula surely is involved in cardiac structural and functional changes, including left ventricular (LV) remodeling in patients with end-stage renal disease on hemodialysis therapy.[18,19] However, it also is important to examine serial changes in cardiac function during the early phase in time after fistula creation, apart from its long-term effects, because most of the increase in fistula blood flow occurs within the first 2 weeks of surgery.[20]

LV systolic function frequently is preserved in patients with congestive heart failure. Previous studies reported that diastolic dysfunction should be considered in patients presenting with heart failure symptoms, but normal systolic func-

tion.[21-23] Diastolic dysfunction precedes LV systolic impairment and, alone, accounts for approximately 30% to 40% of patients with heart failure.[21,22] Thus, it is essential to evaluate LV diastolic dysfunction as a primary cause of cardiac failure in patients with chronic renal failure.[18,24] Nevertheless, no study has examined the effect of AV fistula creation on LV diastolic function.

Therefore, we conducted the present study to investigate serial changes in cardiac performance, including hormonal responses, before and after creation of an AV fistula in patients with chronic renal failure and determine whether alterations in LV systolic and diastolic function were linked to activation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) release.

METHODS

Patients

This prospective study involved 20 patients with chronic renal failure admitted to our hospital to create an AV fistula between 1999 and 2000. All had end-stage renal failure and were candidates for chronic hemodialysis treatment. Patients with ischemic heart disease, including myocardial infarction, congestive heart failure, valvular heart disease, or atrial fibrillation, were excluded from this study. All patients had normal cardiac sinus rhythm, and no patient had regional wall-motion abnormalities on echocardiography. All AV fistulas were created by the same surgeon using an end-to-side model (radiocephalic fistulae) under local anesthesia. Because our patients had severely decreased renal function before surgery, 4 patients required initiation of dialysis therapy or needed to change medication during the study period, and these patients were excluded from analysis.

In the other 16 patients (11 men, 5 women), the present study was completed and analyses were performed. Mean age was 68 ± 11 (SD) years (range, 41 to 80 years). Fifteen patients (94%) were treated with calcium channel blockers; 13 patients (81%), diuretics; 4 patients (25%), β-blockers; and 4 patients (25%), other classes of antihypertensive agents. These treatments were not changed during the study period. No patient was administered exogenous erythropoietin before or during the study period. Causes of renal failure were diabetic nephropathy in 5 patients, nephrosclerosis in 5 patients, chronic glomerulonephritis in 4 patients, chronic interstitial nephritis in 1 patient, and unknown in 1 patient. All subjects gave informed consent to participate in the present study.

Blood Sampling and Assay for ANP and BNP

Blood sampling for measurement of plasma ANP and BNP levels was performed before and 1, 3, 6, 10, and 14 days after the operation. Blood samples were obtained from the brachial vein opposite the side of the operation after a resting period of at least 30 minutes in the supine position. Blood was immediately transferred into chilled glass tubes containing EDTA (1 mg/mL) and aprotinin (500 U/mL).[25] After centrifugation for 10 minutes at 4°C, plasma was immediately frozen and stored at −80°C until assayed. Plasma ANP and BNP concentrations were measured using specific immunoradiometric assay kits (Shiono RIA ANP assay kit and Shiono RIA BNP assay kit; Shionogi Co Ltd, Osaka, Japan), as previously reported.[26]

Echocardiographic Measurement

Echocardiographic studies were performed before and 3, 7, and 14 days after the operation. Echocardiographic measurements, body weight, blood pressure, and heart rate before surgery were measured in the morning after patients had fasted overnight. Comprehensive two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500; Hewlett Packard, Andover, MA), as previously described.[26] Measurements included left atrial end-systolic dimension (LAD), interventricular septal thickness, posterior wall thickness, LV diameter at end-diastole (LVDd), LV diameter at end-systole (LVDs), and inferior vena cava. Fractional shortening (FS) was calculated as (LVDd − LVDs)/LVDd. Cardiac output (CO) was calculated using the Teichholz correction of the cube formula.[27]

To assess LV diastolic function, LV diastolic filling (LV inflow) was examined using Doppler echocardiography. LV diastolic filling pattern was obtained with the sample volume at the tips of the mitral valve in the apical four-chamber view and recorded at end-expiratory phase during quiet breathing.[28] Peak velocity of early diastolic filling (E) and peak velocity of atrial filling (A) were recorded, and E-A ratio was calculated. Duration of the A wave also was measured. Deceleration time (DcT) was measured as the time between the top of the E wave and the point at which the descending part of the E wave or its asymptote crossed the zero line.

After LV inflow velocities were examined, pulmonary venous flow velocities were obtained from the apical four-chamber view and recorded at end-expiration.[28] Left atrial filling from the pulmonary vein is characterized by red signals along the interatrial septum in the upper part of the left atrium in the color Doppler mode. The orifice of the right pulmonary vein is imaged at the bottom of the flame-like red signals, and pulsed Doppler sample volume was set at 0.5 to 1.0 cm into the upper right pulmonary vein. Peak forward-flow velocities during ventricular systole (S) and diastole (D) and peak reverse-flow velocity at atrial contraction (PVa) were measured, and the S-D ratio was calculated. Duration of the PVa wave (PVad) also was measured, and the difference between duration of the mitral A wave and pulmonary reversal wave (Ad-PVad) was calculated.

Statistical Analysis

Values are expressed as mean ± SE. Unpaired t-test was used for comparison between the two points. Time-dependent changes in variables were evaluated by repeated-measure analysis of variance with subsequent Fisher's multiple comparison test. Relations between variables were assessed using linear regression analysis and Pearson's cor-

Table 1. Laboratory Data Before and After the AV Fistula Operation

	Before	Day 14
Blood hemoglobin (g/dL)	8.8 ± 0.2	8.5 ± 0.2
Hematocrit (%)	27 ± 1	26 ± 1
Serum sodium (mEq/L)	139 ± 1	138 ± 1
Serum potassium (mEq/L)	4.3 ± 0.1	4.3 ± 0.2
Serum urea nitrogen (mg/dL)	73 ± 5	71 ± 5
Serum creatinine (mg/dL)	7.9 ± 0.4	7.8 ± 0.4
Creatinine clearance (mL/min)	5.3 ± 0.6	—

NOTE. Values expressed as mean ± SE. Differences between the two study points are not statistically significant. For SI conversions, multiply by 0.357 for urea nitrogen (mmol/L) and by 88.4 for creatinine (μmol/L).

relation coefficient. *P* less than 0.05 is considered statistically significant.

RESULTS

Changes in Clinical and Echocardiographic Findings After the AV Fistula Operation

Table 1 lists laboratory parameters for the 16 patients. Severe renal dysfunction and moderate anemia were observed, but these parameters did not differ between the two study points, ie, before and 14 days after AV fistula creation.

Changes in body weight, hemodynamic variables, and echocardiographic parameters in response to the AV fistula operation are listed in Table 2. Diastolic and systolic blood pressure decreased significantly days 7 and 14 after AV fistula creation, respectively. Heart rate and body weight did not change during this study. LAD increased significantly days 7 and 14. The inferior vena cava dilated days 3 and 7, and then its dimension slightly decreased day 14. A significant increase in LVDd was observed days 3 to 14 after the operation, but LVDs was not altered. As a result, creation of the AV fistula produced a significant increase in FS and CO after 3 to 14 days. Maximal increases in these parameters concerning LV systolic function were obtained day 7 (FS, +8%; CO, +15%).

In evaluation of LV diastolic function with LV inflow profiles, the peak velocity of the E wave

Table 2. Clinical and Echocardiographic Findings Before and After the AV Fistula Operation

	Before	Day 3	Day 7	Day 14
Body weight (kg)	55.6 ± 1.6	55.8 ± 1.6	55.9 ± 1.6	55.9 ± 1.6
Systolic blood pressure (mm Hg)	159 ± 4	153 ± 5	151 ± 4	147 ± 4†
Diastolic blood pressure (mm Hg)	83 ± 3	79 ± 2	77 ± 3*	78 ± 3
Heart rate (beats/min)	66 ± 2	65 ± 2	66 ± 3	66 ± 2
LAD (mm)	39.4 ± 1.5	40.1 ± 1.4	40.5 ± 1.5*	40.9 ± 1.4†
Inferior vena cava (mm)	16.4 ± 0.9	17.6 ± 1.0*	17.8 ± 1.0*	17.3 ± 0.9
Interventricular septal thickness (mm)	12.0 ± 0.5	11.7 ± 0.4	11.9 ± 0.5	11.9 ± 0.5
Posterior wall thickness (mm)	11.9 ± 0.4	11.4 ± 0.4	11.8 ± 0.4	11.8 ± 0.4
LVDd (mm)	48.3 ± 1.0	49.8 ± 0.8†	50.3 ± 0.6†	50.3 ± 0.6†
LVDs (mm)	30.3 ± 1.0	30.3 ± 1.0	30.0 ± 1.0	30.3 ± 1.1
FS (%)	37.4 ± 1.5	39.3 ± 1.5*	40.4 ± 1.7†	40.0 ± 1.7†
CO (L/min)	4.74 ± 0.22	5.22 ± 0.20*	5.46 ± 0.26†	5.41 ± 0.17†
E (cm/s)	74.6 ± 4.6	84.1 ± 4.8†	88.6 ± 4.8†	88.9 ± 6.1†
A (cm/s)	95.1 ± 4.6	99.1 ± 4.0	100.4 ± 4.3*	97.3 ± 5.0
Duration of A wave (ms)	152 ± 4	153 ± 6	151 ± 5	149 ± 5
DcT (ms)	249 ± 8	240 ± 10	225 ± 8†	220 ± 8†
E-A ratio	0.79 ± 0.04	0.86 ± 0.05*	0.89 ± 0.05†	0.93 ± 0.06†
S (cm/s)‡	70.4 ± 4.0	72.3 ± 3.8	72.5 ± 4.3	70.8 ± 3.6
D (cm/s)‡	42.4 ± 4.2	45.3 ± 3.5	47.4 ± 3.3	44.4 ± 2.3
PVa (cm/s)‡	34.8 ± 3.4	31.0 ± 1.5	32.1 ± 2.0	32.5 ± 1.9
PVad (ms)‡	117 ± 6	120 ± 5	124 ± 5	126 ± 6
S-D ratio‡	1.76 ± 0.12	1.66 ± 0.09	1.58 ± 0.10*	1.62 ± 0.09
Ad-PVad (ms)‡	35.9 ± 6.9	33.0 ± 8.4	26.2 ± 7.3	22.7 ± 8.2*

NOTE. Values expressed as mean ± SE.

*$P < 0.05$ compared with baseline (before) for each parameter.

†$P < 0.01$ compared with baseline (before) for each parameter.

‡N = 13.

Table 3. Plasma ANP and BNP Concentrations Before and After the AV Fistula Operation

	Before	Day				
		1	3	6	10	14
ANP (pg/mL)	75 ± 13	77 ± 13	86 ± 16	90 ± 14*	101 ± 14zzzz	89 ± 12
BNP (pg/mL)	182 ± 48	213 ± 61	222 ± 57	238 ± 56*	256 ± 65zzzz	248 ± 66zzzz

NOTE. Values expressed as mean ± SE.
*$P < 0.05$ compared with baseline (before) for each concentration.
zzzz$P < 0.01$ compared with baseline (before) for each concentration.

increased days 3 to 14 after creation of the AV fistula, and that of the A wave increased significantly only day 7 (Table 2). A time-related increase in E-A ratio was observed (+18% day 14), and DcT shortened time dependently (−12% day 14). Adequate pulmonary venous flow Doppler recordings were obtained in 13 of 16 subjects (81%). Although peak velocity of the S, D, or PVa wave did not change during the study, pulmonary venous S-D ratio decreased significantly day 7 after fistula creation. Ad-PVad decreased day 14.

Changes in Plasma ANP and BNP Concentrations After the AV Fistula Operation

Changes in plasma concentrations of ANP and BNP in response to the AV fistula operation are listed in Table 3. ANP concentrations increased significantly days 6 and 10, and BNP concentrations increased days 6, 10, and 14. Thus, creation of the AV fistula produced a significant elevation in mean plasma levels of both ANP and BNP, and their maximal elevations were observed day 10 after the operation. Because preoperative plasma ANP and BNP concentrations varied widely,

elevations in these peptide levels also were expressed as percentages of change from control values to evaluate the rate of increase in the two natriuretic peptide levels. As a result, maximal percentages of increase in plasma ANP and BNP levels obtained day 10 were +48% and +68%, respectively (Fig 1). In general, the time course of changes in levels of the two peptides was similar. However, no direct association was detected between the elevation from control value in plasma ANP and BNP concentrations days 6, 10, or 14 (data not shown). Therefore, it was suggested that stimulation of ANP and BNP release might be regulated differently by other hemodynamic factors.

Association Between Changes in Cardiac Function and Hormonal Response

To assess whether release of these two natriuretic peptides was related to change in cardiac function, we examined the relationship between changes in LV systolic and diastolic function and ANP and BNP response after the AV fistula operation. Increases in plasma ANP concentrations days 10 and 14 correlated with increased
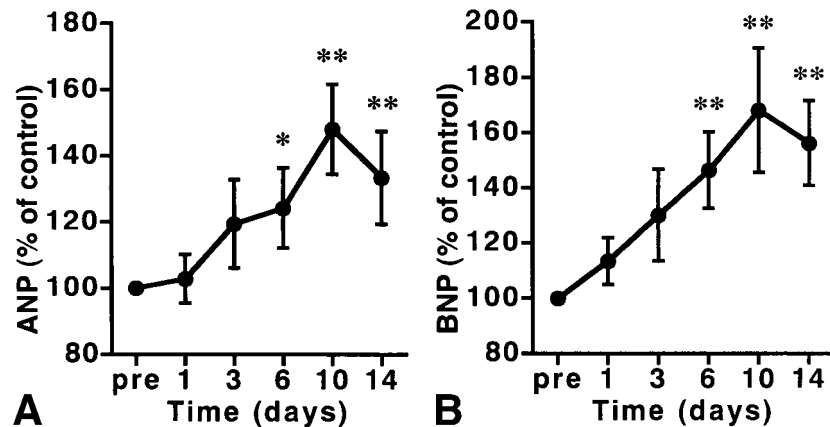

Fig 1. Percentage of increase in plasma concentrations of (A) ANP and (B) BNP after the AV fistula operation. Values given as mean ± SE. *$P < 0.05$. **$P < 0.01$ compared with control (pre) for each peptide.

Table 4. Correlation Between Changes in Cardiac Systolic (CO), Diastolic Function (E-A Ratio), and Natriuretic Peptide Response After the AV Fistula Operation

	CO Increase		E-A Ratio Increase	
	Day 7	Day 14	Day 7	Day 14
ANP increase				
Day 10	0.61*	0.50	0.40	0.24
Day 14	0.44	0.53*	0.31	0.34
BNP increase				
Day 10	−0.06	−0.11	0.63zzzz	0.41
Day 14	0.03	0.18	0.56*	0.60*

*$P < 0.05$.
zzzz$P < 0.01$.

CO days 7 and 14, respectively (Table 4; Fig 2), although the increase in ANP level was not associated with the change in E-A ratio. The elevation in plasma ANP level day 14 also correlated with the increase in LAD day 14 ($r = 0.54$; $P = 0.03$). Conversely, increases in plasma BNP concentrations days 10 and 14 correlated with increased E-A ratios days 7 and 14, respectively (Table 4; Fig 3), although the increase in BNP level was not associated with the CO increase. The elevation in plasma BNP level day 14 also correlated with the decrease in Ad-PVad day 14 ($r = 0.61$; $P = 0.02$; n = 13).

DISCUSSION

Cardiac failure occasionally is caused by the creation of vascular access for hemodialysis.[2-7] However, the short-term effect of an AV fistula on cardiac function has not been sufficiently studied. In the present study, we used a prospec-

tive design and noninvasive methods to investigate changes in cardiac function and hormonal levels after the AV fistula operation. Here, we show serial changes in cardiac performance and hormonal response after creation of an AV fistula for hemodialysis in patients with chronic renal failure. We show that creation of an AV fistula induced increases in CO and produced a significant increase in E-A ratio and decrease in DcT, suggesting that AV fistula creation induced cardiac volume loading and decreased LV compliance. We also show that both plasma ANP and BNP concentrations increased after the operation, with peak levels after 10 days, and the elevated ANP level was associated with the increase in CO, whereas the elevation in BNP level was associated with the increase in E-A ratio.

Creation of an AV fistula produced significant increases in LAD, LVDd, FS, and CO after 3 to 14 days. The present findings are consistent with previous observations that the physiological response to AV fistula creation was an increase in CO.[16,17] It has been shown that most increases in fistula diameter and blood flow occur within the first 2 weeks.[20] Mahmutyazicioglu et al[29] reported that radial artery flow of the AV fistula day 1 after the operation was 23-fold greater than preoperative flow, and an increase of 800 mL/min was observed postoperative day 7. Because our study clearly shows that CO increased maximally corresponding to this period, it is probable that the increase in CO after creation of an AV fistula was induced directly by the increased volume flow of the fistula.

It is important to evaluate impairment in LV
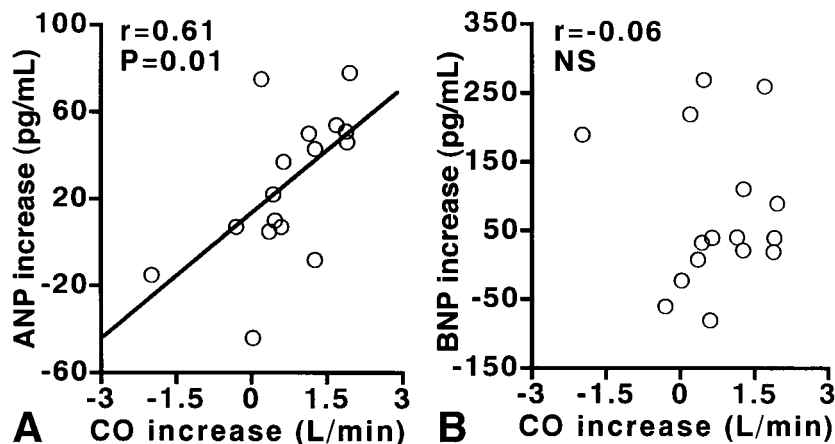
Fig 2. Correlation between change in CO day 7 after AV fistula creation and change in plasma concentrations of (A) ANP and (B) BNP day 10. The increase in CO day 7 correlated significantly only with increase in ANP level ($r = 0.61$; $P = 0.01$).

Fig 3. Correlation between change in E-A ratio day 14 after the AV fistula operation and change in plasma concentrations of (A) ANP and (B) BNP day 14. The increase in E-A ratio day 14 correlated significantly only with increase in BNP level ($r = 0.60$; $P = 0.01$).
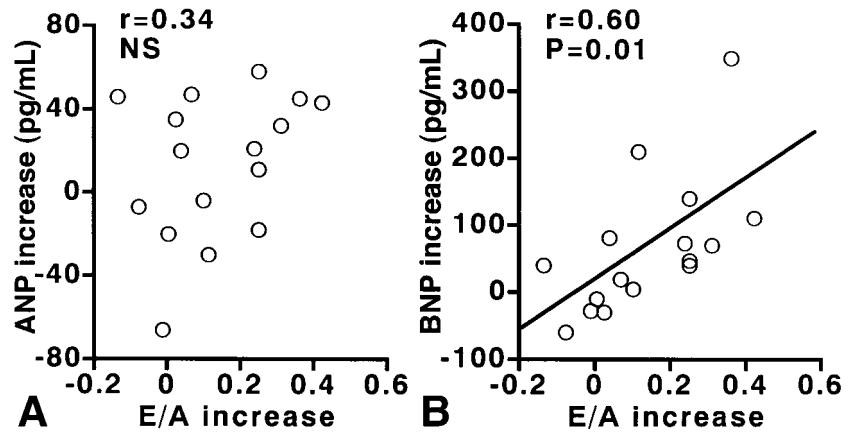
diastolic function in patients with hypertension and chronic renal failure because diastolic failure is a primary cause of cardiac failure in subjects with increased LV stiffness and without LV systolic dysfunction. However, no study has examined the effect of creation of an AV fistula on LV diastolic function. The present study investigated serial changes in LV systolic and diastolic function after AV fistula formation, and we show for the first time that creation of an AV fistula in patients with chronic renal failure significantly influences not only LV systolic function, but also diastolic function. Our findings suggest that evaluation of LV diastolic filling patterns is essential for early detection of cardiac failure after an AV fistula operation.

Doppler echocardiography is the most widely used technique to assess LV diastolic performance. Two-directional abnormal patterns of LV inflow (impaired relaxation and restrictive pattern) are well characterized.[30-32] In the present study, creation of an AV fistula induced an increase in E-A ratio and decrease in DcT, suggesting the fistula operation caused LV diastolic dysfunction toward a restrictive filling (or pseudonormalized) pattern.

Although it is not simple to determine whether an LV inflow-velocity profile indicates normal diastolic filling (a true normal pattern) or reflects a pseudonormalization pattern, evaluation of pulmonary venous flow velocities helps differentiate these two patterns. The combination of velocities at atrial contraction in LV inflow and pulmonary venous flow provides powerful information regarding LV end-diastolic pressure. Especially, shortening of the difference between

duration of both waves (Ad-PVad) is a reliable index to detect the elevation in LV end-diastolic pressure.[33-35] The present study shows that AV fistula creation induced a significant decrease in Ad-PVad mainly because of prolongation of PVad. Because pseudonormal and restrictive Doppler flow patterns are associated with high filling pressure and increased LV end-diastolic and left atrial pressures,[30-32] it therefore was reasonable that after creation of an AV fistula, the LV diastolic filling pattern did not tend to normalize, but changed toward a pseudonormalized pattern.

It may be uncommon in the normal heart that an increase in preload directly induces an elevation in LV end-diastolic pressure. However, because LV stiffness commonly is increased (compliance of the left ventricle is mildly decreased) by cardiac hypertrophy and fibrosis in patients with chronic renal failure,[36,37] volume overload by AV shunt flow appears to be easily connected with the elevation in LV diastolic filling pressure. Therefore, it is probable that changes in the LV diastolic filling pattern obtained in our patients did not just observe the effect of preload increase by the AV fistula, but implied the deterioration of diastolic function linked to the increase in LV diastolic filling.

Significant elevations in plasma ANP and BNP levels in patients with chronic renal failure are well known.[38-40] Greater plasma concentrations of ANP and BNP probably are caused by volume overload, intrinsic heart disease, and reduced clearance of the two peptides from circulation.[41] In the present study, creation of an AV fistula induced further elevations in plasma ANP and

BNP levels. Naruse et al[39] suggested that elevated plasma ANP level was induced by volume expansion in patients with chronic renal failure. Because ANP is released mainly by atrial myocytes in response to atrial stretching, the significant increase in plasma ANP level might be a result of atrial volume expansion and atrial stretching by the creation of an AV fistula. The elevation in ANP level after the operation was well associated with the increase in LAD and CO in the present study.

Conversely, the elevated plasma BNP level correlated with the increase in E-A ratio, an index of LV diastolic dysfunction. Yamamoto et al[42] showed that an elevated BNP level was a powerful marker of LV diastolic dysfunction. Lubien et al[43] recently reported that greater plasma BNP levels in patients with normal systolic function were linked to more severe diastolic dysfunction (pseudonormal and restrictive-like filling patterns). Furthermore, it has been shown that plasma BNP is superior to ANP level as a predictor of high LV end-diastolic pressure.[42,44] Because BNP is produced by ventricular myocytes in response to increases in ventricular pressure and/or stretch,[45,46] the significant increase in plasma BNP level might be attributable to increases in LV filling and end-diastolic pressures. Therefore, our present findings clearly indicate that stimulation of ANP and BNP release was regulated differently by other hemodynamic factors; ie, BNP secretion predominantly reflected the degree of LV pressure overload, and that of ANP reflected the degree of volume overload. Measurement of plasma BNP levels and their increase may be useful to detect LV diastolic dysfunction and predict the occurrence of diastolic failure after an AV fistula operation.

We cannot completely exclude the possibility that antihypertensive treatments may have affected cardiac function and ANP and BNP releases because the majority of patients on this study were administered antihypertensive drugs, including diuretics. Anemia observed in our patients also may have affected cardiac systolic and diastolic performance, mediated by increased preload, decreased afterload, and positive inotropic and chronotropic effects.[18,47] In particular, LV inflow patterns detected by Doppler echocardiography depend on loading conditions and heart rate. However, no medication was changed throughout this study. In addition, blood hemoglobin and hematocrit levels did not change significantly during the study. Therefore, it is unlikely that different loading conditions other than AV fistula creation influenced their cardiac performance.

In conclusion, the present study shows that creation of an AV fistula had significant effects on cardiac performance and hormonal response within 1 or 2 weeks after the operation and suggests that ANP release is induced by volume loading, but BNP release is stimulated by diastolic dysfunction. However, further investigations are necessary with respect to the prediction or prevention of cardiac failure caused occasionally after fistula creation.

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