Original Article

Effects of Imidapril on Left Ventricular Mass in Chronic Hemodialysis Patients

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Left ventricular hypertrophy is considered to be a major cardiovascular risk factor in hemodialysis patients. Not only high blood pressure but also humoral factors such as angiotensin II and aldosterone are thought to contribute to the increase in left ventricular mass. We examined the effects of an angiotensin converting enzyme (ACE) inhibitor, imidapril, on left ventricular mass in patients with end-stage renal diseases on maintenance hemodialysis. Thirty patients on chronic hemodialysis were randomly divided into 2 groups of 15 patients each and given placebo or 2.5 mg imidapril once daily for 6 months. Before and after the 6-month period, left ventricular mass was evaluated by echocardiography, and circulating factors of the renin-angiotensin-aldosterone system were measured. Background characteristics such as age, gender ratio, causes of renal failure, duration of hemodialysis, body mass index and pre-dialysis blood pressure were comparable between the placebo and the imidapril groups. Systolic and diastolic blood pressures were not significantly changed in either group during the study period. In the imidapril group, serum ACE was reduced (12±1 to 5±2 U/l, $p<0.01$) and plasma renin activity was increased (3.3±0.8 to 8.1±3.2 ng/ml/h, $p<0.01$), but plasma angiotensin II and aldosterone were not significantly changed after 6 months (13±3 to 17±3 pg/ml and 365±125 to 312±132 pg/ml, respectively). On the other hand, left ventricular mass index was significantly decreased in the imidapril group (132±10 to 109±6 g/m^2, $p<0.05$) but was unchanged in the placebo group (129±6 to 126±5 g/m^2). These results suggest that an ACE inhibitor reduces left ventricular mass in hemodialysis patients by a mechanism that is independent of changes in blood pressure. (*Hypertens Res* 2006; 29: 253–260)

***Key Words*: imidapril, left ventricular hypertrophy, hemodialysis**

Introduction

Patients with end-stage renal disease undergoing dialysis therapy have increased morbidity and mortality as compared with the general population. In particular, the high incidence of cardiovascular diseases and infection limits the life expectancy of dialysis patients (*1*, *2*). With regard to the risk factors of cardiovascular diseases, the presence of left ventricular hypertrophy, as well as diabetes, hypertension and high age, greatly increases the risk of developing cardiovascular diseases not only in the general population but also in dialysis patients (*3*, *4*). Therefore, inhibition of the increase in left ventricular mass would seem to be one of the prerequisites for preventing cardiovascular diseases effectively and improving the prognosis of dialysis patients.

Development of left ventricular hypertrophy is promoted by hypertension and volume overload in hemodialysis patients (*5–9*). In addition, much attention is being paid to the involvement of the renin-angiotensin-aldosterone system (RAAS) in the process of development and progression of cardiovascular tissue and organ injuries (*10–12*). It would be expected that inhibitors of the RAAS, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II

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Table 1. Background Characteristics of the Study Subjects

	Placebo group	Imidapril group
Age (years)	54.2±3.7	54.6±3.3
Sex (men/women)	8/7	7/5
Cause of renal failure		
Chronic glomerulonephritis	11	8
Diabetic nephropathy	2	3
Others	2	1
Duration of hemodialysis (years)	9±2	7±2
Body mass index (kg/m^2)	21.2±0.7	21.3±0.7
Systolic blood pressure (mmHg)	148±4	152±5
Diastolic blood pressure (mmHg)	80±2	83±3
Pulse rate (bpm)	76±2	79±3
Antihypertensive medication		
Calcium channel blocker	6	4
α-Blocker	2	2
β-Blocker	2	2

Mean±SEM.

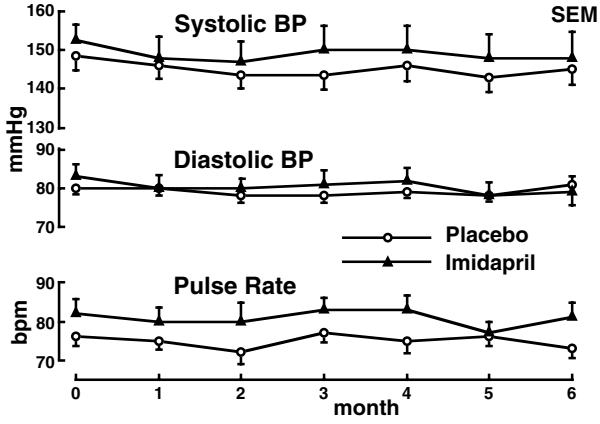

Fig. 1. *Time-course changes in pre-dialysis blood pressure (BP) and pulse rate in hemodialysis patients given placebo or imidapril.*

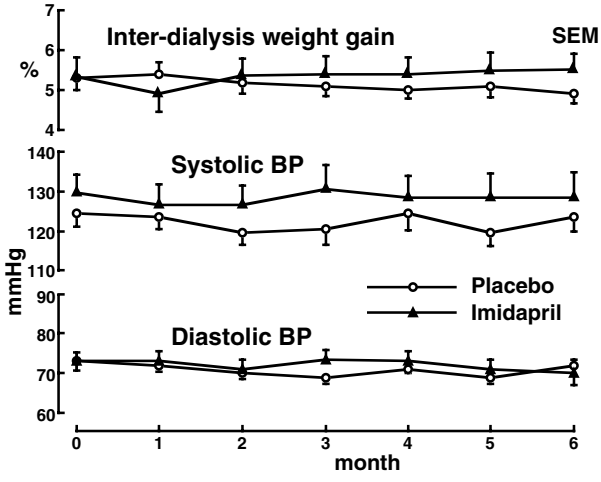

Fig. 2. *Time-course changes in inter-dialysis weight gain and post-dialysis blood pressure (BP) in hemodialysis patients given placebo or imidapril.*

receptor blockers (ARB), would show preventive effects against cardiovascular organ injuries beyond their antihypertensive effects. In the present study, we investigated the long-term effects of imidapril, an ACE inhibitor developed in Japan (*13*, *14*), on the left ventricular mass in chronic hemodialysis patients.

Methods

We enrolled a total of 30 patients with end-stage renal diseases undergoing maintenance hemodialysis. Patients with valvular or ischemic heart diseases were not included. The enrolled patients had not been given ACE inhibitors or ARB for at least 6 months. Fifteen patients were given 2.5 mg of imidapril and the other 15 patients were given placebo. Either placebo or imidapril was given once daily in the morning on non-dialysis days and after the dialysis session on dialysis days. The treatment was continued for 6 months. The assignment of placebo or imidapril was performed in a random manner.

Blood pressure was measured before and after each dialysis session with patients in a supine position after resting more than 10 min. These measurements were made at six dialysis sessions in 2 weeks, and the average of the six values was used for evaluation (*15*, *16*). Body weight gains between dialysis sessions were also averaged for 2 weeks. At the beginning and the end of each treatment period, echocardiography and blood samples were obtained. Standard M-mode and two-dimensional echocardiography were performed after the dialysis session when the patients were at their dry weight using a Toshiba SSH-380A unit with a 2.5 MHz transducer (Toshiba, Tokyo, Japan). Fractional shortening, as an index of left ventricular systolic function, was calculated as (LVIDd – LVIDs)/LVIDd × 100 (%), where LVIDd and LVIDs are left ventricular end-diastolic and end-systolic internal diameters, respectively. Left ventricular mass (LVM) was calculated according to Devereux's formula:

$$\text{LVM (g)} = 0.8 \times [1.04 \times \{(\text{IVST} + \text{LVIDd} + \text{PWT})^3 - (\text{LVIDd})^3\}] + 0.6,$$

where IVST and PWT are interventricular septal thickness and left ventricular posterior wall thickness, respectively (*17*). LVM was divided by body surface area in m^2 to obtain the left ventricular mass index (LVMI). Relative wall thickness (RWT) was measured as (IVST+PWT)/(IVST+PWT+LVIDd) × 100 (%). Pulsed Doppler recordings of transmitral flow were taken from the apical long axis

Table 2. Clinical and Laboratory Findings before and after the 6 Months of Study Period

Parameter	Placebo group		Imidapril group	
	0-month	6-month	0-month	6-month
Body weight (kg)	53.1±2.0	52.7±2.1	54.4±3.2	54.3±3.3
Inter-dialysis weight gain (%)	5.3±0.3	5.0±0.4	5.3±0.5	5.5±0.4
Cardiothoracic ratio (%)	49.3±1.1	49.7±1.4	48.7±1.5	49.5±1.2
White blood cells ($\times 10^3/\mu l$)	6.46±0.67	6.40±0.57	5.82±0.44	5.40±0.31
Red blood cells ($\times 10^6/\mu l$)	3.15±0.06	3.24±0.09	3.36±0.11	3.08±0.12*
Blood hemoglobin (g/dl)	10.2±0.2	10.3±0.2	10.7±0.3	9.7±0.3*
Hematocrit (%)	30.3±0.5	31.6±0.6	31.9±1.1	28.9±0.9*
Platelet count ($\times 10^3/\mu l$)	188±18	174±12	196±16	189±16
Blood chemistry				
Total protein (g/dl)	6.9±0.1	6.7±0.1	6.6±0.2	6.4±0.2
Albumin (g/dl)	4.2±0.1	4.1±0.1	4.1±0.1	4.0±0.1
AST (U/l)	14±2	14±2	12±2	11±1
ALT (U/l)	11±1	12±1	12±2	9±1
Urea nitrogen (mg/dl)	84±5	76±4	77±6	80±5
Creatinine (mg/dl)	12.5±0.7	12.7±0.8	12.7±1.0	13.7±1.1
Uric acid (mg/dl)	6.5±0.3	6.1±0.2	6.9±0.3	7.2±0.3
Na (mEq/l)	138±1	139±1	138±1	139±1
K (mEq/l)	5.0±0.3	5.1±0.2	4.8±0.2	5.2±0.3
Ca (mg/dl)	9.8±0.3	9.5±0.1	9.3±0.3	9.1±0.2
P (mg/dl)	6.0±0.4	5.8±0.5	6.0±0.4	5.6±0.4
Erythropoietin use (U/week)	4,100±764	3,500±699	3,688±721	4,063±859

Data are mean±SEM. AST, aspartate aminotransferase; ALT, alanine aminotransferase. *$p<0.05$ *vs*. 0-month.

Table 3. Echocardiographic Measurements before and after the 6 Months of Study Period

Parameter	Placebo group		Imidapril group	
	0-month	6-month	0-month	6-month
Interventricular septal thickness (mm)	10.9±0.3	10.6±0.3	11.5±0.5	10.9±0.4
Posterior wall thickness (mm)	10.5±0.3	10.2±0.2	11.4±0.4	10.9±0.3
Left ventricular diastolic diameter (mm)	48.1±1.9	48.0±1.9	48.3±2.2	45.4±2.3
Left ventricular systolic diameter (mm)	30.4±2.0	30.2±2.0	31.6±2.0	29.1±1.6
Fractional shortening (%)	37.3±1.9	37.7±1.8	34.7±2.0	35.8±1.8
Left ventricular mass (g)	188±11	180±9	211±24	175±13*
Relative wall thickness (%)	31.1±1.0	30.5±1.1	32.3±1.3	32.8±1.7
E/*A* of transmitral flow velocity	0.92±0.07	0.85±0.05	0.81±0.06	1.04±0.09*

E, peak early velocity; *A*, peak late velocity. Data are mean±SEM. *$p<0.05$ *vs*. 0-month.

view. The sample volume was placed at the tips of the mitral leaflets. The peak early velocity (*E*) and peak late velocity (*A*) of ventricular filling were measured, and their ratio (*E*/*A*) was used as an index of left ventricular diastolic function.

A peripheral blood sample was obtained before starting each dialysis session after more than 15 min of supine rest. In addition to routine hematological tests and blood chemistry, circulating components of the renin-angiotensin system were evaluated. Plasma renin activity and plasma concentrations of aldosterone were determined by respective radioimmunoassays. Plasma angiotensin II and B-type natriuretic peptide (BNP) were directly radioimmunoassayed using an Angiotensin II RIA kit (SRL Inc., Tokyo, Japan) and ShionoRIA BNP assay kit (Shionogi & Co., Ltd., Osaka, Japan), respectively. Serum ACE activity was determined by colorimetry according to the method described by Kasahara and Ashihara (*18*).

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Edinburgh version, 2000) and was approved by the institutional review board. Informed consent was obtained from all subjects.

Values are expressed as the means±SEM. Clinical data were compared between the two groups by unpaired Stu-

dent's *t*-test for parametric data, by Mann-Whitney's *U*-test for nonparametric data, and by χ^2 test for categoric data. The effects of drug treatments in the two groups were analyzed using two-way ANOVA followed by Tukey's method for post-hoc multiple comparisons. Correlations between two parametric variables were analyzed by linear regression analysis. A p value less than 0.05 was considered to indicate statistical significance.

Results

During the 6-month study period, 2 patients of the imidapril group experienced cough and stopped taking imidapril. In addition, 1 patient of the imidapril group withdrew from the study due to the development of hyperkalemia reaching 6.9 mEq/l. The remaining 12 patients of the imidapril group and all 15 patients of the placebo group completed the study period. Table 1 shows the background characteristics of these subjects. The placebo and imidapril groups were not significantly different in terms of age, sex ratio, causes of renal failure and average duration of hemodialysis. Physical findings such as body mass index, blood pressure and pulse rate were also comparable between the two groups. Seven out of 15 patients of the placebo group and 5 out of 12 patients of the imidapril group had been taking antihypertensive drugs before entering the study period. The 3 placebo group patients and the 2 imidapril group patients were taking more than two antihypertensive drugs. Calcium channel blockers were most frequently used and there was no significant difference between the two groups as to the classes of antihypertensive drugs having been used. These antihypertensive medications were not changed throughout the 6-month study period.

Figure 1 depicts the changes in pre-dialysis blood pressure and pulse rate during the study period in the placebo and the imidapril groups. Imidapril did not significantly lower either systolic or diastolic blood pressure, and the averaged blood pressure values were comparable between the two groups throughout the 6-month study period. The pulse rate was not significantly affected by the imidapril treatment and did not significantly differ between the two groups during the study period. Figure 2 shows the changes in inter-dialysis weight gain and post-dialysis blood pressure. The body fluid volume drawn in the dialysis session and blood pressure levels after the dialysis session did not significantly vary during the study period either in the placebo or the imidapril group.

Table 2 shows the clinical and laboratory data of the patients before and after the study period. The body weight, inter-dialysis weight gain and cardiothoracic ratio on chest roentgenogram were not significantly changed. There were no significant changes in any of the blood chemistry data, such as serum proteins, electrolytes or liver enzymes. With regard to the hematological data, the red blood cell count, blood hemoglobin and hematocrit were significantly reduced after the 6 months of imidapril treatment, while such changes were not observed in the placebo group. The dose of erythropoietin did not significantly differ between before and after the study period in either group. The changes in white blood cell and platelet counts were also not significant either in the placebo or the imidapril group.

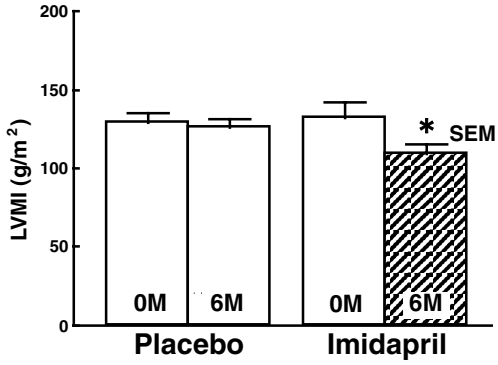

Fig. 3. *Changes in left ventricular mass index (LVMI) in hemodialysis patients given placebo or imidapril.* *p < *0.05* vs. *0-month. M, month.*

Table 3 lists the echocardiographic measurements of the study patients before and after the study period. None of the measurements of left ventricular dimensions were significantly changed in the placebo group. On the other hand, the 6-month imidapril treatment resulted in a slight, but not significant, reduction in IVST, PWT and left ventricular diameter, and these changes resulted in a significant, 17% reduction of LVM. Fractional shortening, an index of left ventricular systolic function, was not significantly changed in either group. The E/A ratio of transmitral flow velocity, an index of left ventricular diastolic function, was significantly increased in the imidapril group, while a significant change was not observed in the placebo group. Figure 3 depicts the changes in LVMI. The imidapril group showed a significant, 18% reduction in LVMI after the study period, while the change was not significant in the placebo group. Table 4 shows the correlations of changes in LVM with the values of blood pressure or the body weight changes. The change in LVM was positively correlated with systolic and diastolic blood pressure levels during the study period in the placebo group; however, such correlations were not observed in the imidapril group. The difference between the 0-month blood pressure and the average blood pressure during the 6-month study period or the increase in body weight between the dialysis session averaged during the study period did not significantly correlate with the LVM changes either in the placebo or the imidapril group.

The bar graphs in Fig. 4 show the changes in plasma renin activity, serum ACE activity and plasma concentrations of angiotensin II, aldosterone and BNP before and after the 6-month study period. These parameters of the RAAS were not significantly changed in the placebo group. In the imidapril group, serum ACE activity was suppressed and plasma renin activity was significantly increased, as expected, but the

Table 4. Correlations of Changes in Left Ventricular Mass with Levels and Changes in Blood Pressure and Body Weight during the 6 Months of Study Period

Blood pressure	Placebo group		Imidapril group	
	r	*p* value	*r*	*p* value
Average systolic presssure	0.546	0.035	0.232	0.467
Average diastolic pressure	0.741	0.001	0.063	0.845
Systolic pressure change	−0.112	0.690	0.337	0.284
Diastolic pressure change	−0.031	0.912	0.077	0.813
Inter-dialysis weight gain	−0.355	0.194	−0.220	0.492

Average blood pressure values are the averaged values during the 6 months given placebo or imidapril, and blood pressure changes are the differences of these averaged blood pressure values from the 0-month blood pressure values. *r*, correlation coefficient of regression analysis.

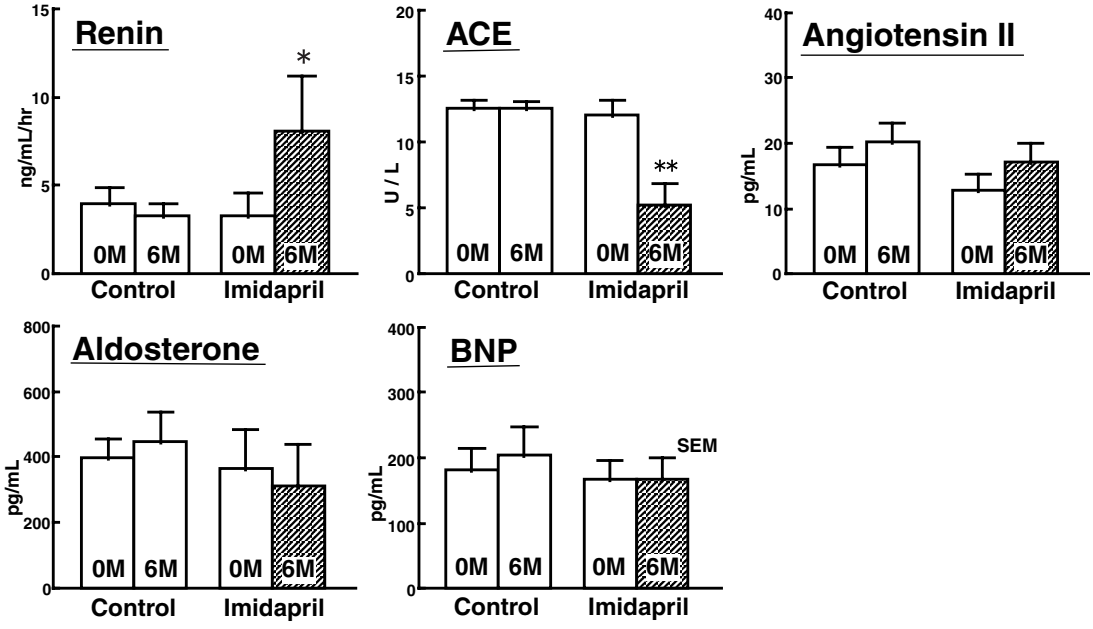

Fig. 4. *Changes in parameters of the renin-angiotensin-aldosterone system and plasma B-type natriuretic peptide (BNP) at the end of each treatment period.* *p < *0.05,* **p < *0.005* vs. *0-month. M, month.*

plasma concentrations of angiotensin II and aldosterone were not significantly different from the levels before the study period. There was also no significant change in plasma BNP either in the placebo or the imidapril group.

Discussion

Hemodialysis patients are at high risk for developing cardiovascular diseases. In our prospective study following 534 chronic hemodialysis patients for 3 years, 29% of patients experienced cardiovascular events, and cardiovascular diseases such as stroke and heart failure were responsible for 46% of the total mortalities (*19*). It is well recognized that left ventricular hypertrophy is a risk factor for ischemic heart disease, heart failure and ventricular arrhythmia. In addition, left ventricular hypertrophy is associated with arteriosclerosis and the risk of stroke (*20*, *21*). Our prospective study also showed that the risk of cardiovascular events is two times higher in chronic hemodialysis patients with electrocardiographic signs of left ventricular hypertrophy than in patients without cardiac hypertrophy (*19*).

Strict control of blood pressure and body fluid volume is important in order to prevent the development and progression of left ventricular hypertrophy in hemodialysis patients (*22–25*). In the present study, imidapril did not significantly lower the blood pressure in chronic hemodialysis patients. We used a low dose of imidapril, but ACE inhibitors are excreted mainly through the kidneys, and thus the blood concentration of imidapril and its active metabolite, imidaprilat, should have become higher and lasted longer in our patients

with renal failure than in those without (*26*). However, it has been suggested that the blood pressure of hemodialysis patients may be more dependent on the degree of blood volume increase than on the activity of the RAAS (*27*, *28*).

Recent basic research has revealed that the RAAS is involved in the process of remodeling and injuries of cardiovascular organs and tissues (*10–12*). Especially, angiotensin II and aldosterone promote hypertrophy of cardiovascular cells and fibrosis of the cardiovascular tissues (*10–12*). Therefore, antihypertensive drugs suppressing the RAAS, such as ACE inhibitors and ARB, are expected to have protective effects against hypertensive damage of cardiovascular organs beyond their hypotensive effects. Indeed, several studies have reported that the regression of left ventricular hypertrophy by ACE inhibitors or ARB reduced LVM in end-stage renal disease patients on chronic hemodialysis (*29–32*); however, the decreases in LVM were accompanied by blood pressure reduction in these studies. In the present study, long-term treatment with a low dose of imidapril, an ACE inhibitor, was ineffective in lowering blood pressure in chronic hemodialysis patients, but it did reduce their LVM. We speculate that local inhibition of the RAAS by a subpressor dose of imidapril contributed to the reduction in LVM, at least partly through a mechanism that was independent of blood pressure changes. In this context, Cannella *et al*. (*33*) have treated normotensive hemodialysis patients with an ACE inhibitor, lisinopril, for 2 years and observed a reduction in LVM without significant changes in blood pressure, although the reduction was not significant after 1 year. Information obtained from their study is limited because the assignment of lisinopril treatment was not randomized and hypertensive patients were excluded. Considering that a large portion of dialysis patients are hypertensive (*34–36*), the results of their study may not be directly applicable to the general practice of dialysis therapy.

With regard to the effects of imidapril on RAAS, serum ACE activity was suppressed and plasma renin activity was increased as might be expected; however, plasma angiotensin II and aldosterone were not significantly decreased after 6 months. It has been reported that ACE inhibitors and ARB reduce plasma levels of angiotensin II and aldosterone initially, but that an escape or rebound phenomenon may occur during long-term therapy (*11*, *37*, *38*). On the other hand, the cardiovascular tissues have been shown to express enzymes generating angiotensin II and aldosterone, and the tissue concentrations may become higher than the circulating levels (*10*, *11*, *39*, *40*). Furthermore, it has been reported that such RAAS factors in the cardiovascular tissues are enhanced by various stimuli in the process of organ injuries in cardiovascular diseases (*10*, *11*, *41*). Therefore, in order to prevent cardiovascular organ injuries effectively, it may be important to suppress the cardiovascular tissue RAAS rather than lowering plasma angiotensin II or aldosterone levels (*42*). In this respect, imidapril has been shown to inhibit ACE activity not only in circulating blood but also in cardiovascular tissues more potently than other ACE inhibitors such as captopril and enalapril (*43*). We speculate that tissue RAAS inhibition participated in the mechanism of LVM reduction by chronic imidapril treatment in the hemodialysis patients of this study.

With regard to the adverse effects of ACE inhibitors, cough is the most frequent side effect bothering patients; however, imidapril has been shown to cause a lower incidence of cough than other ACE inhibitors (*44*). In the present study, 2 out of 15 patients (13%) treated with imidapril experienced cough and stopped taking imidapril. Hyperkalemia can take place as a side effect of ACE inhibitors even in hemodialysis patients by inhibiting residual urinary excretion, colonic excretion and cellular uptake of potassium (*45*, *46*). One patient of the imidapril group of this study stopped taking imidapril because of this side effect, although the change in serum potassium was not significant in the 12 patients who completed the 6-month imidapril treatment. ACE inhibitors may exacerbate anemia in patients with chronic renal failure by decreasing endogenous erythropoietin production, blunting the response to erythropoietin and reducing angiotensin II, which has erythropoietic action (*46–49*). The 6-month imidapril treatment reduced red blood cell count, blood hemoglobin and hematocrit in this study. This side effect is likely to occur when patients are taking a high dose of ACE inhibitor (*50*, *51*). Care should be taken to avoid the progression of anemia in dialysis patients given ACE inhibitors, because the drug metabolism is prolonged in patients with renal failure, as mentioned earlier (*26*). Progression of anemia is thought to promote cardiac hypertrophy in hemodialysis patients (*52*), but the imidapril group in this study showed reduction in LVM although the blood hemoglobin was reduced by the administration of imidapril. This suggests that the antihypertrophic effect of imidapril on LVM overcame the decrease in blood hemoglobin.

Several studies have reported a correlation between plasma BNP and LVM in hemodialysis patients (*53*, *54*). In the present study, however, plasma BNP was not significantly decreased in the imidapril group, although the LVM was reduced. Plasma BNP levels in hemodialysis patients were markedly increased by the reduced clearance and increased body fluid volume. Considering these influences, plasma BNP may not sensitively reflect the changes in LVM of hemodialysis patients.

In summary, the present study showed that chronic treatment with low-dose imidapril reduces LVM in patients on maintenance hemodialysis without causing significant changes in blood pressure. Therefore, it is suggested that an ACE inhibitor can improve left ventricular hypertrophy by a mechanism independent of its antihypertensive effect. However, in hemodialysis patients, ACE inhibitors should be used with care to prevent the aggravation of anemia and development of hyperkalemia.

References

1. Collins AJ, Kasiske B, Herzog C, *et al*: Excerpts from the United States Renal Data System 2004 annual data report:

atlas of end-stage renal disease in the United States. Outcomes: hospitalization and mortality. *Am J Kidney Dis* 2005; **45** (1 Suppl 1): S117–S138.
2. Japanese Society for Dialysis Therapy: An overview of dialysis treatment in Japan (as of Dec. 31, 2003). *J Jpn Soc Dial Ther* 2005; **38**: 1–16.
3. Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 1989; **36**: 286–290.
4. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE: Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; **11**: 1277–1285.
5. Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS: Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. *J Am Soc Nephrol* 1994; **4**: 1486–1490.
6. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 1996; **49**: 1379–1385.
7. Washio M, Okuda S, Mizoue T, *et al*: Risk factors for left ventricular hypertrophy in chronic hemodialysis patients. *Clin Nephrol* 1997; **47**: 362–366.
8. Zoccali C, Mallamaci F, Tripepi G, *et al*: Prediction of left ventricular geometry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodialysis patients: CREED investigators. *J Hypertens* 1999; **17**: 1751–1758.
9. Assanelli D, Cannella G, Guerra UP, Cumintti S, Gaggiotti M: Effects of intravascular volume loading and unloading on atrial sizes and left ventricular function in dialyzed uremic man. *Am J Noninvas Cardiol* 1990; **4**: 53–59.
10. Brewster UC, Setaro JF, Perazella MA: The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states. *Am J Med Sci* 2003; **326**: 15–24.
11. Struthers AD, MacDonald TM: Review of aldosterone- and angiotensin II–induced target organ damage and prevention. *Cardiovasc Res* 2004; **61**: 663–670.
12. Diamond JA, Phillips RA: Hypertensive heart disease. *Hypertens Res* 2005; **28**: 191–202.
13. Hayashi K, Nunami K, Kato J, *et al*: Studies on angiotensin converting enzyme inhibitors. 4. Synthesis and angiotensin converting enzyme inhibitory activities of 3-acyl-1-alkyl-2-oxoimidazolidine-4-carboxylic acid derivatives. *J Med Chem* 1989; **32**: 289–297.
14. Hosoya K, Ishimitsu T: Protection of the cardiovascular system by imidapril, a versatile angiotensin-converting enzyme inhibitor. *Cardiovasc Drug Rev* 2002; **20**: 93–110.
15. Conion PJ, Walshe JJ, Heinle SK, Minda S, Krucoff M, Schwab SJ: Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients. *J Am Soc Nephrol* 1996; **7**: 2658–2663.
16. Zoccali C, Mallamaci F, Tripepi G, *et al*: Prediction of left ventricular geometry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodialysis patients: CREED investigators. *J Hypertens* 1999; **17**: 1751–1758.
17. Devereux RB, Alonso DR, Lutas EM, *et al*: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.
18. Kasahara Y, Ashihara Y: Colorimetry of angiotensin-I converting enzyme activity in serum. *Clin Chem* 1981; **27**: 1922–1925.
19. Ishimitsu T, Tsukada K, Ohta S, *et al*: Increased cardiovascular risk in long-term hemodialysis patients carrying deletion allele of ACE gene polymorphism. *Am J Kidney Dis* 2004; **44**: 466–475.
20. Nitta K, Akiba T, Uchida K, *et al*: Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. *Hypertens Res* 2004; **27**: 47–52.
21. Kawamura M, Fijimoto S, Hisanaga S, Yamamoto Y, Eto T: Incidence, outcome, and risk factors of cerebrovascular events in patients undergoing maintenance hemodialysis. *Am J Kidney Dis* 1998; **31**: 991–996.
22. Cannella G, Paoletti E, Delfino R, Peloso G, Molinari S, Traverso GB: Regression of left ventricular hypertrophy in hypertensive dialyzed uremic patients on long-term antihypertensive therapy. *Kidney Int* 1993; **44**: 881–886.
23. Lopez-Gomez JM, Verde E, Perez-Garcia R: Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. *Kidney Int Suppl* 1998; **68**: S92–S98.
24. Ozkahya M, Toz H, Qzerkan F, *et al*: Impact of volume control on left ventricular hypertrophy in dialysis patients. *J Nephrol* 2002; **15**: 655–660.
25. Gunal AI, Karaca I, Aygen B, Yavuzkir M, Dogukan A, Celiker H: Strict fluid volume control and left ventricular hypertrophy in hypertensive patients on chronic haemodialysis: a cross-sectional study. *J Int Med Res* 2004; **32**: 70–77.
26. Agarwal R, Lewis R, Davis JL, Becker B: Lisinopril therapy for hemodialysis hypertension: hemodynamic and endocrine responses. *Am J Kidney Dis* 2001; **38**: 1245–1250.
27. Lins RL, Elseviers M, Rogiers P, *et al*: Importance of volume factors in dialysis related hypertension. *Clin Nephrol* 1997; **48**: 29–33.
28. Ventura JE, Sposito M: Volume sensitivity of blood pressure in end-stage renal disease. *Nephrol Dial Transplant* 1997; **12**: 485–491.
29. London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JL: Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994; **90**: 2786–2796.
30. Paoletti E, Cassottana P, Bellino D, Specchia C, Messa P, Cannella G: Left ventricular geometry and adverse cardiovascular events in chronic hemodialysis patients on prolonged therapy with ACE inhibitors. *Am J Kidney Dis* 2002; **40**: 728–736.
31. Shibasaki Y, Masaki H, Nishiue T, Nishikawa M, Matsubara H, Iwasaka T: Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. *Nephron* 2002; **90**: 256–261.
32. Kanno Y, Kaneko K, Kaneko M, *et al*: Angiotensin receptor antagonist regresses left ventricular hypertrophy associated with diabetic nephropathy in dialysis patients. *J Cardiovasc Pharmacol* 2004; **43**: 380–386.
33. Cannella G, Paoletti E, Delfino R, Peloso G, Rolla D, Moli-

nari S: Prolonged therapy with ACE inhibitors induces a regression of left ventricular hypertrophy of dialyzed uremic patients independently from hypotensive effects. *Am J Kidney Dis* 1997; **30**: 659–664.
34. Salem MM: Hypertension in the hemodialysis population: a survey of 649 patients. *Am J Kidney Dis* 1995; **26**: 461–468.
35. Mittal SK, Kowalski E, Trenkle J, *et al*: Prevalence of hypertension in a hemodialysis population. *Clin Nephrol* 1999; **51**: 77–82.
36. Grekas D, Bamichas G, Bacharaki D, Goutzaridis N, Kasimatis E, Tourkantonis A: Hypertension in chronic hemodialysis patients: current view on pathophysiology and treatment. *Clin Nephrol* 2000; **53**: 164–168.
37. Lakkis J, Lu WX, Weir MR: RAAS escape: a real clinical entity that may be important in the progression of cardiovascular and renal disease. *Curr Hypertens Rep* 2003; **5**: 408–417.
38. Sato A, Saruta T: Aldosterone breakthrough during angiotensin-converting enzyme inhibitor therapy. *Am J Hypertens* 2003; **16**: 781–788.
39. Navar LG, Harrison-Bernard LM, Imig JD, Wang CT, Cervenka L, Mitchell KD: Intrarenal angiotensin II generation and renal effects of AT1 receptor blockade. *J Am Soc Nephrol* 1999; **10** (Suppl 12): S266–S272.
40. Delcayre C, Silvestre JS: Aldosterone and the heart: towards a physiological function? *Cardiovasc Res* 1999; **43**: 7–12.
41. Davies E, MacKenzie SM: Extra-adrenal production of corticosteroids. *Clin Exp Pharmacol Physiol* 2003; **30**: 437–445.
42. Takai S, Jin D, Sakaguchi M, Miyazaki M: Significant target organs for hypertension and cardiac hypertrophy by angiotensin-converting enzyme inhibitors. *Hypertens Res* 2004; **27**: 213–219.
43. Kubo M, Ochiai T, Kato J, Ishida R: Pharmacological studies on TA-6366, a new ACE inhibitor: II. Effect of long-term administration from the pre-hypertensive stage on blood pressure, relative heart weight and ACE activity of various tissues in spontaneously hypertensive rats (SHRs). *Jpn J Pharmacol* 1991; **57**: 517–526.
44. Saruta T, Arakawa K, Iimura O, *et al*: Difference in the incidence of cough induced by angiotensin converting enzyme inhibitors: a comparative study using imidapril hydrochloride and enalapril maleate. *Hypertens Res* 1999; **22**: 197–202.
45. Knoll GA, Sahgal A, Nair RC, Graham J, van Walraven C, Burns KD: Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. *Am J Med* 2002; **112**: 110–114.
46. Hörl MP, Hörl WH: Drug therapy for hypertension in hemodialysis patients. *Semin Dial* 2004; **17**: 288–294.
47. Akpolat T, Gumus T, Bedir A, Adam B: Acute effect of trandolapril on serum erythropoietin in uremic and hypertensive patients. *J Nephrol* 1998; **11**: 94–97.
48. Erturk S, Ates K, Duman N, Karatan O, Erbay B, Ertug E: Unresponsiveness to recombinant human erythropoietin in haemodialysis patients: possible implications of angiotensin-converting enzyme inhibitors. *Nephrol Dial Transplant* 1996; **11**: 396–397.
49. Nakao K, Shirakura T, Azuma M, Maekawa T: Studies on erythropoietic action of angiotensin II. *Blood* 1967; **29**: 754–760.
50. Albitar S, Genin R, Fen-Chong M, Serveaux MO, Bourgeon B: High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. *Nephrol Dial Transplant* 1998; **13**: 1206–1210.
51. Marathias KP, Agroyannis B, Mavromoustakos T, Matsoukas J, Vlahakos DV: Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Curr Top Med Chem* 2004; **4**: 483–486.
52. Sikole A, Polenakovic M, Spiroska V, Polenakovic B, Klinkmann H, Scigalla P: Recurrence of left ventricular hypertrophy following cessation of erythropoietin therapy. *Artif Organs* 2002; **26**: 98–102.
53. Nishikimi T, Futoo Y, Tamano K, *et al*: Plasma brain natriuretic peptide levels in chronic hemodialysis patients: influence of coronary artery disease. *Am J Kidney Dis* 2001; **37**: 1201–1208.
54. Mallamaci F, Zoccali C, Tripepi G, *et al*: Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 2001; **59**: 1559–1566.