

본태성 고혈압 환자에서 안지오텐신 II 수용체 차단제의 단기치료 : 로사탄이 좌심실 확장기 기능 및 좌심실 질량, 대동맥의 경직도에 미치는 영향

이무용¹ · 한성식¹ · 류 센¹ · 이명용¹ · 김영권¹ · 유선미²

Short-Term Treatment with Angiotensin II Antagonist in Essential Hypertension : Effects of Losartan on Left Ventricular Diastolic Function, Left Ventricular Mass, and Aortic Stiffness

Moo-Yong Rhee, MD¹, Sung-Sik Han, MD¹, Sen Lyu, MD¹,
Myoung-Yong Lee, MD¹, Young-Kwon Kim, MD¹ and Sun-Mi Yu, MD²

¹Department of Internal Medicine, ²Familial Medicine, College of Medicine, Dankook University, Cheonan, Korea

ABSTRACT

Background and Objectives : Even short-term treatment with angiotensin converting enzyme inhibitor in essential hypertension has been known to improve left ventricular (LV) diastolic function, LV hypertrophy (LVH), and aortic stiffness. The purpose of this study was to examine the effects of angiotensin II receptor antagonist (Losartan) on LV diastolic function, LVH, and aortic stiffness in essential hypertension. **Materials and Methods** : Twenty-three hypertensive patients who were aged over 50 years, previously untreated, and without cardiac, renal, neurologic disease, or diabetes, were studied. Before and 12 weeks after monotherapy with Losartan 50 mg q.d., (1) supine arterial blood pressure by sphygmomanometry, (2) interventricular septum and LV posterior wall thickness, and LV end-diastolic dimension by M-mode echocardiography, (3) mitral peak E and A wave velocity by doppler echocardiography, (4) pulse wave velocity (PWV) in the descending aorta from aortic arch to the bifurcation by doppler echocardiography, were done. **Results** : Twelve weeks after treatment, systolic blood pressure was lowered from 168.2 ± 3.5 mmHg to 142.9 ± 2.9 mmHg ($p < 0.05$), diastolic blood pressure from 98.5 ± 2.4 mmHg to 87.5 ± 1.3 mmHg ($p < 0.05$). Peak E/A ratio was increased from 0.75 ± 0.04 to 0.82 ± 0.04 ($p < 0.05$). LV mass was decreased from 267.5 ± 15.8 g to 235.6 ± 12.6 g ($p < 0.05$), and LV mass index from 166.8 ± 8.0 g/m² to 146.9 ± 6.0 g/m² ($p < 0.05$). However, there were no significant change in PWV (from 7.18 ± 0.10 m/sec to 7.23 ± 0.30 m/sec, $p > 0.05$), compliance (from 1.31 ± 0.04 to 1.34 ± 0.12 , $p > 0.05$), and compliance index (from 0.16 ± 0.01 to 0.15 ± 0.01 , $p > 0.05$). **Conclusion** : Short-term treatment with Losartan decreases blood pressure, improves LV diastolic function and LVH, but not aortic stiffness. (Korean Circulation J 2000;30(11):1341-1349)

KEY WORDS : Essential hypertension · Angiotensin II antagonist · Left ventricular diastolic function · Left ventricular mass · Aortic stiffness.

: 2000 10 23
: 2000 12 19
: , 330 - 714 29
: (041) 550 - 3920 · : (041) 556 - 3256 E - mail : rheemy@anseo.dankook.ac.kr

서 론

1 4 .

II

가 , 1)2) , , ,

가 , 3) , .

가 , 4 - 6) , 7)8) 1 2

가 , 9)10) , 11) ,

가 , 12) 2

가 , 13 - 15) 16) , Acuson 128 XP (pulse

wave velocity : PWV) .

12

가 , 17) 1 50 mg

12 50 mg . 12

3 6

II , 18) .

가 , 19 - 22) , , , , , ,

AT1 23) II 가 ,

24)25) ,

Valsartan .

가 , 26)27) 10

3 , PWV

28)29) , 30) 가

가 4 (apical four chamber view) pulsed do- ppler sample volume

50 peak E velocity(m/sec),

II peak A velocity(m/sec) , peak E velocity

peak A velocity (peak E/A ratio) .

5 10

재료 및 방법

(parasternal short axis view) 2.5 MHz M

50 (left ventricular end - diastolic dimension : LVEDD),

(interventricular septal thickness : IVST)
 (posterior wall thickness : PWT)
³¹⁾
 (left ventricular mass index ; g/m²)

Left ventricular mass(g) =
 $1.04[(LVEDD + IVST + PWT)^3 - LVEDD^3] - 13.6$

(aortic bifurcation)
 volume
 curve
 T1 T2
 aortic velocity
 R
 ao -
 pulse
 wave delay(PWD = T2 - T1)
 (D)

2.5 MHz
 (pulsed doppler)
 foot - to - foot method¹²⁾³²⁾
 (Fig. 1).
 sample vol -

(PWV, m/sec) = D/PWD
 (compliance : C)
³³⁾
 $C = 66.7/PWV^2$

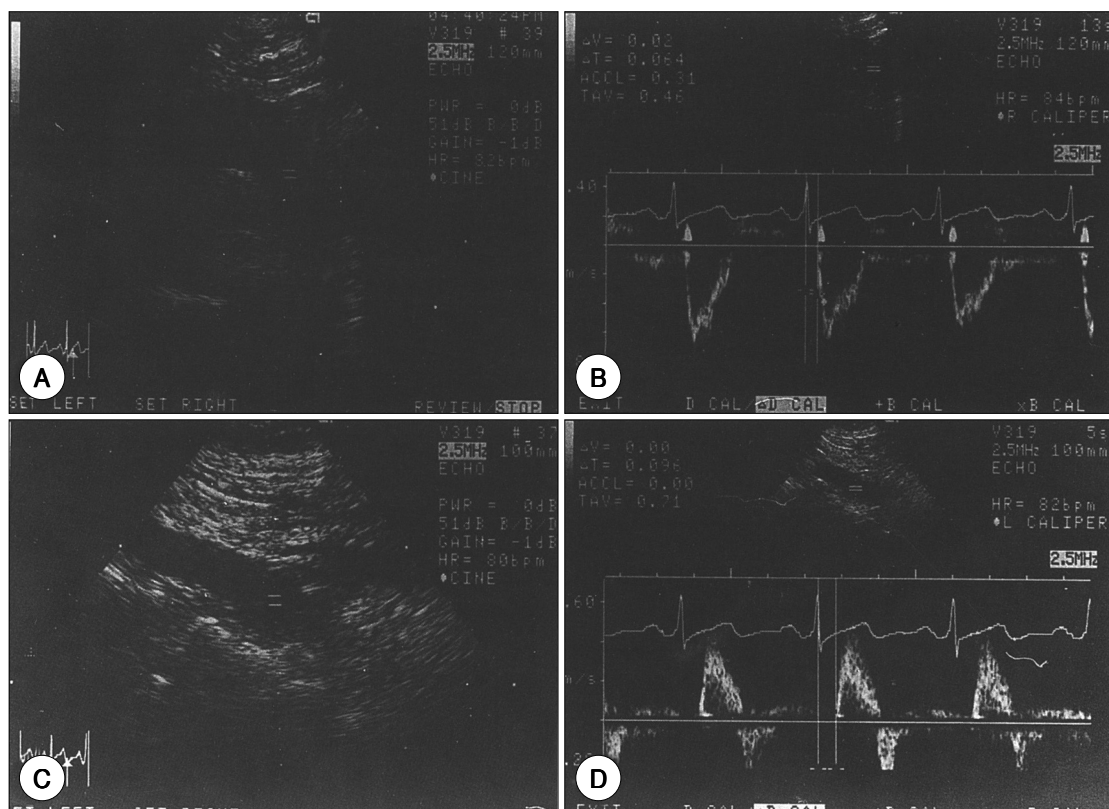


Fig. 1. Pulse wave velocity measurement by pulsed-wave Doppler. Aortic velocity tracings are recorded in the thoracic aorta after bifurcation of left subclavian artery (A and B) and before aortic bifurcation (C and D). To calculate pulse wave delay (PWD), time delay between ECG R wave and the foot of aortic velocity curve recorded respectively are measured. T1 is time delay of thoracic aorta and T2 is of abdominal aorta. PWD is calculated as $PWD = T2 - T1$.

compliance index(Ci)
(Pd), (Ps), (Pd)
33)
 $Ci = C \times (Pd \times 10^3) / \ln(Ps/Pd)$
 \pm
paired t - test
p 0.05
결 과
43 23 12
가 9 , 가 14
59 ± 6 23
10
3 1 1
7 5
20 15
1 4
23
168.2 ± 3.5 mmHg 142.
9 ± 2.9 mmHg , 98.5 ± 2.4 mmHg
87.5 ± 1.3 mmHg (p<0.05)
12 1 50 mg Losartan 가
가 (Table 1, Fig

Table 1. Effects of Losartan treatment (50 mg PO qd for 12 weeks) on supine systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR)

	Baseline	Follow-up	p
SBP (mmHg)	168.2 ± 3.5	142.9 ± 2.9	<0.05
DBP (mmHg)	98.5 ± 2.4	87.5 ± 1.3	<0.05
MAP (mmHg)	121.7 ± 11.2	106.0 ± 8.2	<0.05
HR (bpm)	67.5 ± 1.9	67.6 ± 1.8	NS

Values are given as mean ± SEM

2). 23 가
1 가
(Table 1).
가 peak E
velocity peak A velocity (peak E/A ratio)
0.75 ± 0.04 0.82 ± 0.04
가 (p<0.05)
(Table 2, Fig. 3).
267.5 ± 15.8 g 235.6 ± 12.6
(Fig. 4), 166.8 ± 8.0 g/
m² 146.9 ± 6.0 g/m² (Fig. 4)
(Table 2, p<0.05).
15
가 7.18 ± 0.10 m/sec 7.23 ± 0.30 m/sec

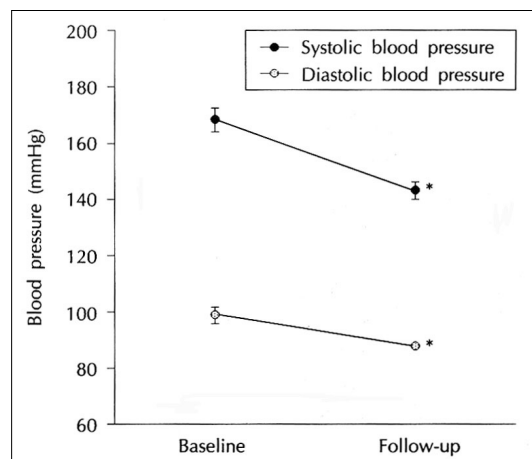


Fig. 2. Systolic and diastolic blood pressure at baseline and at follow-up, after treatment with Losartan 50 mg PO qd for 12 weeks, *: p<0.05.

Table 2. Effects of Losartan treatment (50 mg PO qd for 12 weeks) on left ventricular diastolic function, left ventricular mass, and aortic stiffness

	Baseline	Follow-up	p
Peak E/A ratio	0.75 ± 0.04	0.82 ± 0.04	<0.05
LV mass (g)	267.5 ± 15.8	235.6 ± 12.6	<0.05
LV mass index (g/m ²)	166.8 ± 8.0	146.9 ± 6.0	<0.05
PWV (m/sec)	7.18 ± 0.10	7.32 ± 0.30	NS
C (%/10 mmHg ⁻¹)	1.31 ± 0.04	1.34 ± 0.12	NS
Ci (dimensionless)	0.16 ± 0.01	0.15 ± 0.01	NS

Values are given as mean ± SEM

LV indicates left ventricle ; PWV, pulse wave velocity ; C, compliance ; Ci, compliance index

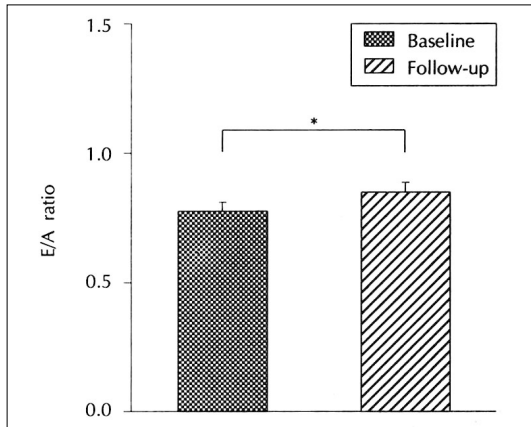


Fig. 3. Mitral E and A velocity ratio measured by pulsed doppler at baseline and at follow-up, after treatment with Losartan 50 mg PO qd for 12 weeks. *: $p < 0.05$

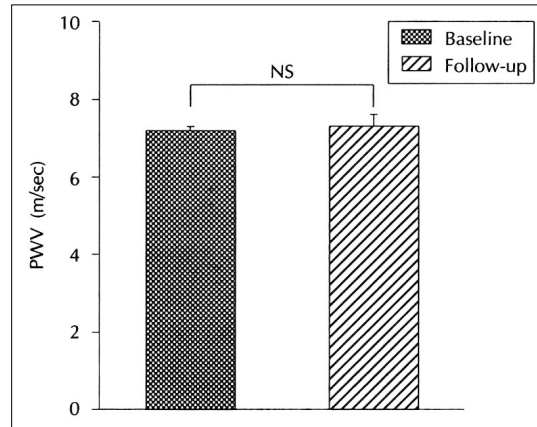


Fig. 5. Aortic pulse wave velocity at baseline and at follow-up, after treatment with Losartan 50 mg PO qd for 12 weeks. PWV indicates pulse wave velocity.

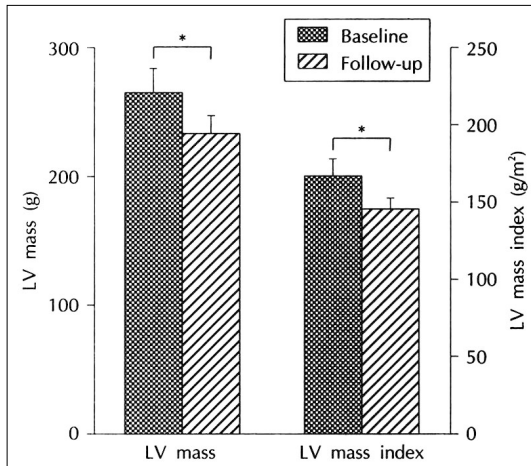


Fig. 4. Left ventricular (LV) mass and mass index at baseline and at follow-up, after treatment with Losartan 50 mg PO qd for 12 weeks. *: $p < 0.05$

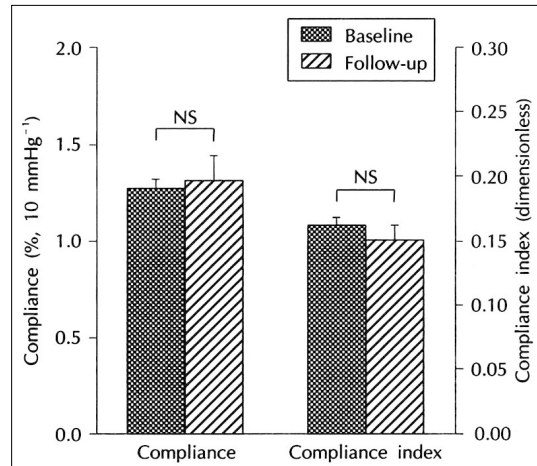


Fig. 6. Aortic compliance and compliance index at baseline and at follow-up, after treatment with Losartan 50 mg PO qd for 12 weeks.

(Fig. 5, $p > 0.05$), compliance가 1.31 ± 0.04 1. 34 ± 0.12 , compli -
ance index가 0.16 ± 0.01 0.15 ± 0.01 (Fig. 6, $p > 0.05$) 가 (Table 2).

고 찰

1 50 mg

12

mg

12

12

. Gradman

II

peak

Losartan

가

26 mmHg,

11

mmHg ,

³⁴⁾³⁵⁾ Thrmann Valsartan 8

²⁶⁾ Cot -

tone 50 mg 6

가

E/A ratio가 12

⁴⁶⁾ Himmelmann 29

가

³⁶⁾ Himmelmann

⁴⁷⁾ 97 g/

^{37 - 39)} m²

⁸⁾ 가 가

가 Himmelmann

^{19 - 22)} II Cuocolo 1 4

Valsartan 4

²⁷⁾ Cuocolo 가 (- 20 g/m²) II

12 12

E/A ratio가 1 가

가 가 가 ⁷⁾⁸⁾

가 가

(aortic stiffness)가 가 ⁵⁾⁴⁸⁾⁴⁹⁾

⁴⁰⁾⁴¹⁾ ³⁾⁵⁰⁾

12 가 ¹²⁾

가

aplanation tonometry ,

echotracking signal - ,

12 가 가

echo tracking signal ⁵¹⁾

¹⁾²⁾

⁴²⁾⁴³⁾ II 가

AT1 II 가

⁴⁴⁾ , nitrate ,

AT2 가

⁴⁵⁾ ^{29)52 - 54)} II 가

30)

55) Schiffrin 1 (small re - 2

sistant artery) II

가 II

가 12

55) 12

가 (conductance artery)

가

요 약

compliance index 연구배경 :

가

가

56)

가 II 가

가

방 법 :

1 4

가 II 50 12

가 II 1 50 mg

12

II

peak E A velocity, (pulse wave

velocity)

II 가 결 과 :

23

가

168.2±3.5 mmHg 142.9±2.9 mmHg

(p<0.05), 98.5±2.4 mmHg 87.5±

1.3 mmHg (p<0.05), peak

가 E/A 0.75±0.04 0.82±0.04

가 (p<0.05), 267.5±15.8 g

32) 235.6±12.6 g (p<0.05),

가 7 166.8±8.0 g/m² 146.9±6.0 g/m² (p<0.05)

7.18±0.10 m/

sec 7.23±0.30 m/sec , compliance 1.31±

0.04 1.34 ± 0.12 ,
compliance index 0.16 ± 0.01 0.15 ± 0.01

결 론 :

II 12

중심 단어 : II

REFERENCES

- Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham study. *N Engl J Med* 1990;332:1561-56.
- Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, et al. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol* 1996;78:197-202.
- Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L, et al. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines subcommittee. *Clin Exp Hypertens* 1999;21:1009-60.
- Safar ME, Levy BI, Laurent S, London GM. Hypertension and the arterial system: clinical and therapeutic aspects. *J Hypertens Suppl* 1990;8:S113-9.
- Safar ME, London GM, Asmar RG, Hugues CJ, Laurent SA. An indirect approach for the study of the elastic modulus of the brachial artery in patients with essential hypertension. *Cardiovasc Res* 1986;20:563-7.
- London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, et al. Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 1990;37:137-42.
- O'Rourke MF. Arterial Function in Health and Disease. Edinburgh: Churchill Livingstone;1982.
- Nichols WW, O'Rourke MF. Contours of pressure and flow waves in arteries. Wave reflections. In: McDonald's blood flow in arteries: Therapeutic, Experimental and Clinical Principles. 4th ed. London: Edward Arnold; 1998, p.170-201.
- Oxlund H, Rasmussen LM, Andreassen TT, Heickendorff L. Increased aortic stiffness in patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1989;32:748-52.
- Westerbacka J, Uosukainen A, Makimattila S, Schlenzka A, Yki-Jarvinen H. Insulin-induced decrease in large artery stiffness is impaired in uncomplicated type 1 diabetes mellitus. *Hypertension* 2000;35:1043-8.
- London GM, Guerin AP, Pannier B, Marchais SJ, Benetos A, Safar ME. Increased systolic pressure in chronic uremia. Role of arterial wave reflections. *Hypertension* 1992;20:10-9.
- Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;99:2434-9.
- Shimojo M, Tsuda N, Iwasaka T, Inada M. Age-related changes in aortic elasticity determined by gate radionuclide angiography in patients with systemic hypertension or healed myocardial infarcts and in normal subjects. *Am J Cardiol* 1991;68:950-3.
- Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. *Am J Cardiol* 1987;59:1300-4.
- Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation* 1989;80:78-86.
- Lehmann ED, Hopkins KD, Jones RL, Rudd AG, Gosling RG. Aortic distensibility in patients with cerebrovascular disease. *Clin Sci (Colch)* 1995;89:247-53.
- Inouye I, Massie B, Loge D, Topic N, Silverstein D, Simpson P, et al. Abnormal left ventricular filling: an early finding in mild to moderate systemic hypertension. *Am J Cardiol* 1984;53:120-6.
- Sadoshima J, Izumo S. Molecular characterization of angiotensin II-induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. *Circ Res* 1993;73:413-23.
- Covi G, Sheiban I, Gelmini G, Arcaro G, Tonni S, Bolner A, et al. Left ventricular diastolic function during adrenergic stress in essential hypertension: acute and chronic effects of ACE inhibition. *Cardiovasc Drugs Ther* 1996;10:321-9.
- Petersen JR, Draback H, Gleeup G, Mehlsen J, Petersen LJ, Winther K. ACE inhibition with spirapril improves diastolic function at rest independent of vasodilation during treatment with spirapril in mild to moderate hypertension. *Angiology* 1996;47:233-40.
- Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized doubleblind studies. *JAMA* 1996;275:1507-13.
- Dahlf B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A metaanalysis of 109 treatment studies. *Am J Hypertens* 1992;5:95-110.
- Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;334:1649-54.
- Zierhut W, Studer R, Laurent D, Kastner S, Allegrini P, Whitebread S, et al. Left ventricular wall stress and sarcoplasmic reticulum Ca²⁺-ATPase gene expression in renal hypertensive rats: dosedependent effects of ACE inhibition and AT1-receptor blockade. *Cardiovasc Res* 1996;31:758-68.
- Nicoletti A, Heudes D, Hinglais N, Appay MD, Philippe M, Sassy-Prigent C, et al. Left ventricular fibrosis in renovascular hypertensive rats. Effect of losartan and spirinolactone. *Hypertension* 1995;26:101-11.
- Thrmann PA, Kenedi P, Schmidt A, Harder S, Rietbrock N. Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. *Circulation* 1998;98:2037-42.
- Cuocolo A, Storto G, Izzo R, Iovino GL, Damiano M, Bertocchi F, et al. Effects of valsartan on left ventricular diastolic function in patients with mild or moderate essential hypertension: comparison with enalapril. *J Hypertens* 1999;17:1759-66.

- 28) Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. *Circulation* 1988;78:941-50.
- 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;90:2786-96.
- 30) Maeso R, Rodrigo E, Munoz-Garcia R, Navarro-Cid J, Ruilope LM, Cachofeiro V, et al. Chronic treatment with losartan ameliorates vascular dysfunction induced by aging in spontaneously hypertensive rats. *J Hypertens* 1998;16:665-72.
- 31) Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613-8.
- 32) Dahan M, Paillole C, Ferreira B, Gourgon R. Doppler echocardiographic study of the consequences of aging and hypertension on the left ventricle and aorta. *Eur Heart J* 1990;11 (Suppl G):39-45.
- 33) Lehmann ED, Gosling RG, Fatemi-Langroudi B, Taylor MG. Non-invasive Doppler ultrasound technique for the in vivo assessment of aortic compliance. *J Biomed Eng* 1992;14:250-6.
- 34) Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snively DB, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995;25:1345-50.
- 35) Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. *Am J Hypertens* 1999;12:414-7.
- 36) Tarazi RC. The heart in hypertension. *N Engl J Med* 1985;312:308-9.
- 37) Inouye I, Massie B, Loge D, Topic N, Silverstein D, Simpson P, et al. Abnormal left ventricular filling: an early finding in mild to moderate systemic hypertension. *Am J Cardiol* 1984;53:120-6.
- 38) Stauffer JC, Gaasch WH. Recognition and treatment of left ventricular diastolic dysfunction. *Prog Cardiovasc Dis* 1990;32:319-32.
- 39) Lorell BH, Grossman W. Cardiac hypertrophy: the consequences for diastole. *J Am Coll Cardiol* 1987;9:1189-93.
- 40) Zabalgoitia M, Rahman SNU, Haley WE, Abochamh DA, Oneschuk L, Amerena J, et al. Role of left ventricular hypertrophy in diastolic dysfunction in aged hypertensive patients. *J Hypertens* 1997;15:1175-9.
- 41) Miller TR, Grossman SJ, Schectman KB, Biello DR, Ludbrook PA, Ehsani AA. Left ventricular diastolic filling and its association with age. *Am J Cardiol* 1986;58:531-5.
- 42) Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994;90:1786-93.
- 43) Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E. Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 1995;13:1091-5.
- 44) Dahlf B. Effect of angiotensin II blockade on cardiac hypertrophy and remodelling: a review. *J Hum Hypertens* 1995;9 (suppl 5):37-44.
- 45) Liu YH, Yang XP, Sharov VG, Nass O, Sabbah HN, Peterson E, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists in rats with heart failure. Role of kinins and angiotensin II type 2 receptors. *J Clin Invest* 1997;99:1926-35.
- 46) Cottone S, Vadala A, Vella MC, Nardi E, Mule G, Contorno A, et al. Changes of plasma endothelin and growth factor levels, and of left ventricular mass, after chronic ATI-receptor blockade in human hypertension. *Am J Hypertens* 1998;11:548-53.
- 47) Himmelmann A, Svensson A, Bergbrant A, Hansson L. Long-term effects of losartan on blood pressure and left ventricular structure in essential hypertension. *J Hum Hypertens* 1996;11:729-34.
- 48) Safar ME, London GM, Laurent S. Hypertension and the arterial wall. *High Blood Pressure* 1993;2 (suppl 2):32-9.
- 49) Safar ME, Toto-Moukoko JJ, Bouthier JA, Asmar RE, Levenson JA, Simon AC, et al. Arterial dynamics, cardiac hypertrophy, and antihypertensive treatment. *Circulation* 1987;75:1156-61.
- 50) Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999;33:1111-7.
- 51) Asmar RG, Topouchian JA, Benetos A, Sayegh FA, Mourad JJ, Safar ME. Non-invasive evaluation of arterial abnormalities in hypertensive patients. *J Hypertens Suppl* 1997;15:S99-107.
- 52) Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. *Circulation* 1988;78:941-50.
- 53) Kelly R, Daley J, Avolio A, O'Rourke M. Arterial dilation and reduced wave reflection. Benefit of diltiazem in hypertension. *Hypertension* 1989;14:14-21.
- 54) London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, et al. Salt and water retention and calcium blockade in uremia. *Circulation* 1990;82:105-13.
- 55) Schiffrin EL, Park JB, Intengan HD, Touyz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. *Circulation* 2000;101:1653-9.
- 56) Strawn WB, Chappell MC, Dean RH, Kivlighn S, Ferrario CM. Inhibition of early atherogenesis by losartan in monkeys with diet-induced hypercholesterolemia. *Circulation* 2000;101:1586-93.