

측뇌실에 Losartan 투여후 출혈시 혈압 및 심박수 변이도의 스펙트럼 분석*

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= Abstract =

Spectral Analysis of Blood Pressure and Heart Rate Variability during Hemorrhage After Losartan Administration into the Lateral Ventricle

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This study was aimed to elucidate the effect of intracerebroventricular losartan administration on arterial pressure regulation during hemorrhage in rats by power spectral analysis of blood pressure and heart rate variability.

Nineteen male Sprague-Dawley rats weighing 240-300g were divided into losartan-administered (n=10) and control (n=9) groups. Hemorrhage was induced with a withdrawal pump from the femoral artery at 3ml/kg/min for 5min. Arterial pressure was measured with a pressure transducer connected to the contralateral femoral artery for 5 min before, during and after hemorrhage. The blood pressure signal digitized at 500 Hz through a data acquisition system was analyzed with fast Fourier transform algorithm to yield power spectra of systolic (SP) and diastolic (DP) blood pressure and instantaneous heart rate (HR). Powers of very low frequency (VLF, 0.02 -0.26Hz), low frequency (LF, 0.26 -0.75Hz) and high frequency (HF, 0.75 -5.00Hz) band were obtained.

Basal systolic and diastolic blood pressure was 149 ± 9 and 99 ± 2 mmHg, respectively, and was not changed by hemorrhage in control rats. Basal blood pressure in losartan group was 143 ± 9 and 97 ± 6 mmHg and was significantly lowered to 116 ± 13 and 77 ± 9 mmHg, respectively. HR was significantly increased during and after hemorrhage in both groups. Total power of SP variability in losartan group was 13.9 ± 3.2 mmHg² before hemorrhage and was significantly increased to 66.6 ± 25.3 mmHg² during hemorrhage. VLF, LF and HF powers of SP variability were 7.3 ± 2.0 , 3.8 ± 1.1 and 2.8 ± 0.7 mmHg², respectively, in losartan group and 5.5 ± 1.4 , 3.7 ± 1.5 and 2.8 ± 0.8 mmHg² in control rats. VLF and HF powers of SP were increased to 33.0 ± 15.2 and 20.3 ± 6.4 mmHg² in losartan group, and VLF power was increased to 7.9 ± 1.5 mmHg² in control group. VLF power of DP variability increased from 3.3 ± 0.9 before hemorrhage to 5.9 ± 1.0 mmHg² during hemorrhage in control group. Powers of

DP variability in losartan group and those of HR variability in both groups were not changed by hemorrhage.

The above results suggested that losartan aggravated the arterial pressure fall during hemorrhage by impairing the sympathetic nerve activation by central angiotensin II.

KEY WORDS : Angiotensin II · Fast Fourier transform · Intracerebroventricular.

서 론

가²³⁻²⁶⁾ 0.4 Hz
가^{20,23,27)},
1-3) Korner²⁾, Courneya Korner³⁾,^{18,20,22,28)}
Oliver⁴⁾ 0.02 0.2Hz,
angiotensin II renin-angiotensin system,
(Ang II), vasopressin,
^{5,6)},^{19,23,29,30)}
^{7,8)} Ang II
renin-angiotensin system
^{9,10)} Ang II
Ang II AT₁
^{11,12)} Ang II losartan
AT₁ AT₂ 가, AT₁
circumventricular org- Ang II가
ans, ¹³⁾ AT₂
inferior olivary nucleus
¹⁴⁾ Ang
II AT₁
vasopressin
¹⁵⁾
,
,
, 가
(spectral analysis)
¹⁶⁻¹⁸⁾ (high frequency, HF), (low
frequency, LF) (very low frequency,
VLF)^{19,20)}
1.5 Hz
²¹⁾
^{18,22,23)} sodium
1. 실험동물 및 수술
240 300g Sprague-Dawley
19, losartan 10
9 pentobarbital
sodium(40mg/kg, i.p.)
(stereotaxic instrument, Model 1404, David Ko -
pf) . Paxinos Watson³¹⁾
(bregma AP= - 0.8mm, L= 1.
5mm, H=4mm) 22gauge
cement resin,
5
pentobarbital
heparin

(PE - 50, Clay Adams) 5 5 (P50,
 (22 × 32 × 17cm) Gould) polygraph(Model 79E, Grass Inst -
 (ampicillin 25mg/ rument)
 kg, i.m.) (Model 1401 Plus, CED) 500 Hz
 2. Losartan 투여 및 출혈 on - line
 Losartan off - line CED
 Losartan Ang II Spike2
 AT₁ losartan(5 μg/μl) 4 μl Ahn¹²⁾ 1) 0.1
 20
 withdrawal pump (time series) 32) (sam -
 (Model 22, Harvard Apparatus) 3ml/kg/min pling time)
 5 losartan
 (peak)
 3. 혈압 기록 및 분석 (tro -
 , losartan , ugh)

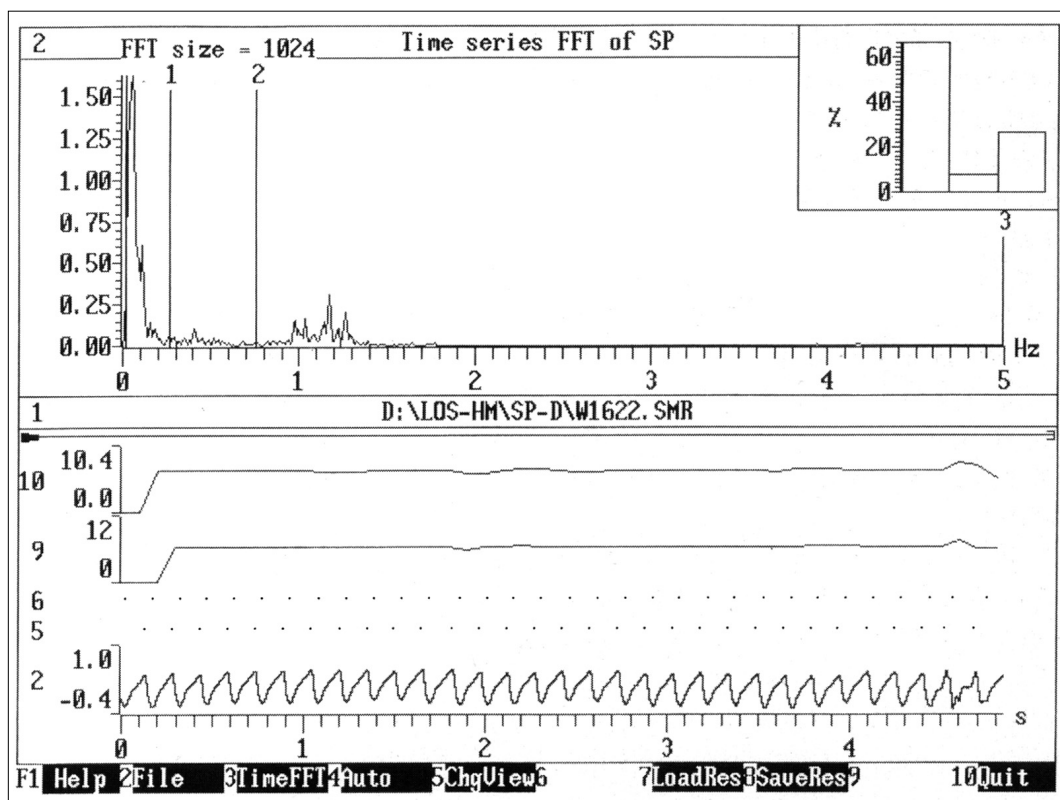


Fig. 1. A copy of computer screen showing blood pressure and heart rate signals(lower panel) and the power spectrum of systolic pressure(upper panel). Vertical bars dissect the spectrum into 3 bands, i.e. very low frequency (VLF), low frequency(LF), and high frequency(HF), whose powers are plotted as percent of total power in the inset.

(upstroke)
(U)
2 U (U' U) , U
(US)
2)
3³³⁾
3) Fast Fourier transform(FFT)
FFT size 1,024
(epoch=1,024 × 0.1=102.4)
epoch epoch 50%
4)
(0.02 0.26Hz), (0.26 0.75Hz)
(0.75 5.00Hz)
(total power)
(Fig. 1).

4. 통계처리

paired t - test $p < 0.05$

결 과

losartan
143 ± 9 97 ± 6 mmHg 149 ± 9
99 ± 2 mmHg 가 (Fig. 2). Losar -
tan losartan
가 ,
losartan 116 ± 13 77 ± 9 mmHg
losartan
losartan 371 ± 7
beats/min 369 ± 21 beats/min
가 . Losartan losartan
가 , lo -
sartan 442 ± 9 421
± 22 beats/min losartan
가

losartan
13.9 ± 3.2 17.2 ± 6.5 mmHg²
12.0 ± 3.1 7.4 ± 2.2 mmHg²
가 (Fig. 3). losartan
189 ± 37 (beats/min)² 98
± 48 (beats/min)² 가 . Losar -
tan losartan
가 losartan
66.6 ± 25.3 mmHg²
가
19.6 ± 3.
0 mmHg² 가
losartan
losartan
가 7.3 ± 2.0, 3.8 ± 1.1
2.8 ± 0.7 mmHg² (= 50 : 29 : 21)
5.5 ± 1.4, 3.7 ± 1.5 2.8 ± 0.8 mmHg² (
= 45 : 28 : 27) 가 (Table 1).

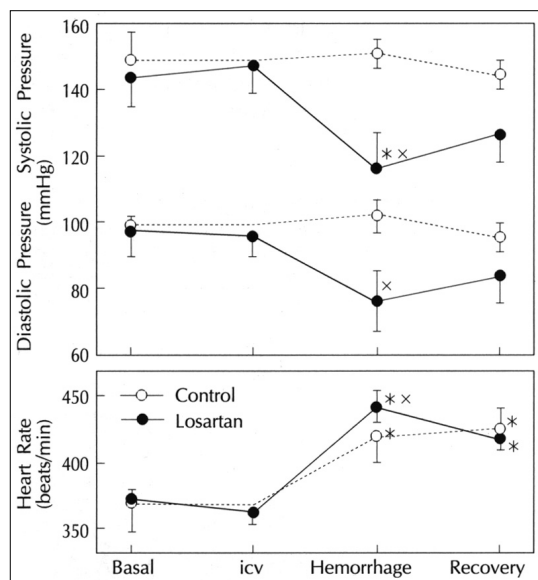


Fig. 2. Blood pressure and heart rate at basal state, immediately after losartan injection(icv), during hemorrhage(3ml/kg/min for 5min), and during 5-10min after hemorrhage(Recovery) in losartan and control groups. Vertical bars indicate standard errors. * $p < 0.05$ vs. basal, $p < 0.05$ vs. icv, # $p < 0.05$ vs. control.

가 , losartan

가

 $7.9 \pm 1.5 \text{ mmHg}^2$ $3 \pm 6.4 \text{ mmHg}^2$

가

가

 33.0 ± 15

가	33.0 ± 15.2	20.
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20.

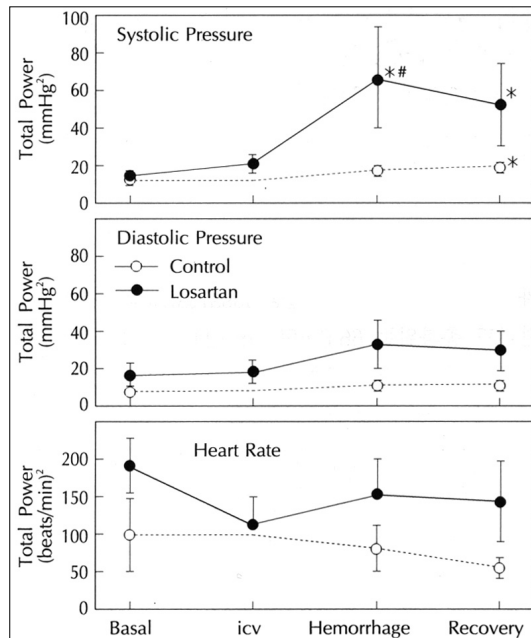


Fig. 3. Total powers of blood pressure and heart rate variability at basal state, immediately after losartan injection (icv), during hemorrhage (3ml/kg/min for 5min), and during 5-10 min after hemorrhage (Recovery) in losartan and control groups. Vertical bars indicate standard errors. * $p<0.05$ vs. basal, # $p<0.05$ vs. control.

losartan

가

 $8.4 \pm 3.4, 4.9$
$$\pm 2.4 \quad 3.9 \pm 2.2 \text{ mmHg}^2 (\quad = 53 : 28 : 19)$$
 $3.3 \pm 0.9, 2.4 \pm 0.9$ $1.7 \pm 0.8 \text{ mmHg}^2$

(=48 : 33 : 20)

가 (Table

2).

가 $5.9 \pm 1.0 \text{ mmHg}^2$

가 . Losartan

losartan

losartan

가

 $86 \pm 21, 18 \pm 6$
$$85 \pm 27 (\text{beats/min})^2 \quad (=47 : 8 : 45)$$
 $38 \pm 16, 13 \pm 9$ $46 \pm 27 (\text{beats/min})^2$ (
$$= 41 : 9 : 50)$$

가 (Table 3).

losartan

losartan

61

± 6% losartan

가

Table 1. Powers of systolic pressure variability at basal state, immediately after losartan injection (icv), during hemorrhage (3ml/kg/min for 5min), and during 5 - 10min after hemorrhage (Recovery) in losartan and control groups

		Basal	icv	Hemorrhage	Recovery
Losartan	VLF (mmHg ²)	7.3 ± 2.0	7.6 ± 2.0	33.0 ± 15.2* ^x #	25.3 ± 8.7
	LF (mmHg ²)	3.8 ± 1.1	7.1 ± 1.9	13.3 ± 6.3	14.0 ± 6.7
	HF (mmHg ²)	2.8 ± 0.7	1.6 ± 1.6	20.3 ± 6.4* ^x #	17.2 ± 7.0* ^x #
	%VLF (%)	50 ± 6	44 ± 8	44 ± 8	45 ± 9
	%LF (%)	29 ± 5	36 ± 5	21 ± 4 ^x	24 ± 6
	%HF (%)	21 ± 4	20 ± 5	36 ± 5	30 ± 4
Control	VLF (mmHg ²)	5.5 ± 1.4		7.9 ± 1.5 [*]	9.8 ± 2.5
	LF (mmHg ²)	3.7 ± 1.5		4.4 ± 2.0	3.9 ± 1.2
	HF (mmHg ²)	2.8 ± 0.8		4.5 ± 0.5	5.8 ± 1.0
	%VLF (%)	45 ± 7		47 ± 6	48 ± 6
	%LF (%)	28 ± 4		21 ± 5	18 ± 3
	%HF (%)	27 ± 6		32 ± 7	34 ± 7

Values are means standard errors

*p<0.05 vs. basal, p<0.05 vs. icv, #p<0.05 vs. control

VLF : very low frequency, LF : low frequency, HF : high frequency

%VLF etc. : (VLF etc.)/(total power)100

Table 2. Powers of diastolic pressure variability at basal state, immediately after losartan injection(icv), during hemorrhage (3ml/kg/min for 5min), and during 5 - 10min after hemorrhage(Recovery) in losartan and control groups

		Basal	icv	Hemorrhage	Recovery
Losartan	VLF (mmHg ²)	8.4±3.4	7.4±3.1	22.4±10.3	16.8±4.9
	LF (mmHg ²)	4.9±2.4	6.2±2.1	7.1±3.5	8.1±3.9
	HF (mmHg ²)	3.9±2.2	4.3±2.1	5.1±2.1	5.3±2.6
	%VLF (%)	53±7	43±8	58±9	56±10
	%LF (%)	28±4	37±5	24±6	28±8
	%HF (%)	19±4	20±4	17±3	16±3
Control	VLF (mmHg ²)	3.3±0.9		5.9±1.0*	7.2±2.0
	LF (mmHg ²)	2.4±0.9		3.3±1.4	2.8±0.7
	HF (mmHg ²)	1.7±0.8		2.2±0.9	1.5±0.3
	%VLF (%)	48±8		58±6	62±5
	%LF (%)	33±4		25±4	24±3
	%HF (%)	20±5		17±2	14±3

Values are means standard errors

*p<0.05 vs. basal

For abbreviations, see Table 1

Table 3. Powers of heart rate variability at basal state, immediately after losartan injection(icv), during hemorrhage (3ml/kg/min for 5min), and during 5 - 10min after hemorrhage(Recovery) in losartan and control groups

		Basal	icv	Hemorrhage	Recovery
Losartan	VLF (beats/min) ²	86±21	46±13	106±35	98±46
	LF (beats/min) ²	18±6	12±5	9±2	9±2
	HF (beats/min) ²	85±27	54±17	39±7	34±5
	%VLF (%)	47±7	40±7	61±6 ^x	60±8
	%LF (%)	8±1	8±2	7±1	8±2
	%HF (%)	45±7	51±7	32±6	32±7
Control	VLF (beats/min) ²	38±16		44±17	24±9
	LF (beats/min) ²	13±9		12±9	6±2
	HF (beats/min) ²	46±27		28±9	25±9
	%VLF (%)	41±9		45±10	42±8
	%LF (%)	9±2		9±3	9±2
	%HF (%)	50±9		46±11	48±9

Values are means standard errors *p<0.05 vs. icv. For abbreviations, see Table 1

고 안 가 가 1-3).

Ang II가

Ang II AT₁

losartan 가 가 .

renin - angiotensin

system, , 19,23,29,30).

가 , losartan

가 가 . Ang

가 II, vasopressin

가 .

18,20,22,28) Losartan
가 가가
가 가
. .
. .
0.07Hz 4.2 cyc - 23 - 26) losartan
les/min 가 가 , losartan
4 가 가
. 가
가
. .
Losartan 39)
losartan Ang II losartan
34) 가 가
Ang II , losartan
35,36) vasopressin 가^{12,37)}
. vasopressin V₁ losartan Ang II
. .
Ang II losartan
38) V₁
prazosin³⁸⁾ pentolinium¹²⁾ Ang II
Ang II
. losartan
Ang II 요 약
vasopressin
. losartan
Losartan
가 가 가
가 . 가
. 240 300g Sprague - Dawley los -
artan 10 9
가 3ml/kg/min 5
. , losartan ,
losartan vasopressin 5 500 Hz
losartan fast Fourier transform
Ang II
. Lee¹⁵⁾ (0.02 0.
losartan 26Hz), (0.26 0.75Hz), (0.75 5.00Hz)
vasopressin 가가 renin
가 가 . losartan
renin 가 Ang II가 가 149 ± 9
가 가 . 99 ± 2mmHg

losartan 143 ± 9 97 ± 6mmHg
 116 ± 13 77 ± 9mmHg
 가 . Losartan
 13.9 ± 3.2mmHg² 6
 6.6 ± 25.3mmHg² 가 .
 . losar -
 tan ,
 가 7.3 ± 2.0, 3.8 ± 1.1 2.8 ±
 0.7mmHg² 5.5 ± 1.4, 3.7 ± 1.5 2.8
 ± 0.8mmHg² 가 .
 가 7.9 ± 1.5mm
 Hg² 가 , losartan
 가 33.0 ± 15.2 20.3 ± 6.4
 mmHg² 가 .
 3.3 ± 0.9mmHg²
 5.9 ± 1.0mmHg² 가
 , losartan losartan
 losartan
 losartan an -
 giotensin II .

References

- 1) Kato N, Sheriff DD, Siu CO and Sagawa K : *Relative importance of four pressoregulatory mechanisms after 10% bleeding in rabbits. Am J Physiol* 256 : 291-296, 1989
- 2) Korner PI, Oliver JR, Zhu JL, Gipps J and Hanneman F : *Autonomic, hormonal, and local circulatory effects of hemorrhage in conscious rabbits. Am J Physiol* 258 : 229-239, 1989
- 3) Courneya CA and Korner PI : *Neurohumoral mechanisms and the role of arterial baroreceptors in the renovascular response to haemorrhage in rabbits. J Physiol (London)* 437 : 393-407, 1991
- 4) Oliver JR, Korner PI, Woods RL and Zhu JL : *Reflex release of vasopressin and renin in hemorrhage is enhanced by autonomic blockade. Am J Physiol* 258 : 221-228, 1990
- 5) Zerbe RL, Feuerstein G, Meyer DK and Kopin IJ : *Cardiovascular, sympathetic and renin-angiotensin system responses to haemorrhage in vasopressin-deficient rats. Endocrinology* 111 : 608-613, 1982
- 6) Pang CCY : *Effect of vasopressin antagonist and saralasin on regional blood flow following hemorrhage. Am J Physiol* 245 : 749-755, 1983
- 7) Schadt JC and Ludbrook J : *Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. Am J Physiol* 260 : 305-318, 1991
- 8) Park YY, Park JS and Lee WJ : *Effects of ethanol on neurohumoral mechanisms for blood pressure regulation in hemorrhaged conscious rats. Korean J Physiol* 29 : 91-102, 1995
- 9) Ferguson AV and Wall KM : *Central actions of angiotensin in cardiovascular control : Multiple roles for a single peptide. Can J Physiol Pharmacol* 70 : 779-785, 1992
- 10) Phillips MI : *Functions of angiotensin in the central nervous system. Ann Rev Physiol* 49 : 413-435, 1987
- 11) Ferrario CM : *Neurogenic actions of angiotensin II. Hypertension* 5 (suppl. V) : V73-V79, 1983
- 12) Ahn DK, Oh ST, Yang EK, Park JS and Lee WJ : *Effects of intracerebro-ventricular angiotensin II on the cardiovascular and endocrine systems in conscious normotensive and hypertensive rats. J Korean Soc Endocrinol* 7 : 364-372, 1992
- 13) Steckelings UM, Lebrun C, Qadri F, Veltmar A and Unger Th : *Role of brain angiotensin in cardio-vascular regulation. J Cardiovasc Pharmacol* 19 (suppl 6) : S72-S79, 1992
- 14) Rowe PB, Grove KL, Saylor DL and Speth RC : *Discrimination of angiotensin II receptor subtype distribution in the rat brain using non-peptidic receptor antagonists. Regul Pept* 33 : 45-53, 1991
- 15) Lee WJ, Yang EK, Ahn DK, Park YY, Park JS and Kim HJ : *Central ANG II-receptor antagonists impair cardiovascular and vasopressin response to hemorrhage in rats. Am J Physiol* 268 : R1500-R1506, 1984
- 16) Kotrly KJ, Ebert TJ, Vucins EJ, Igler FO, Barney JA and Kampine JP : *Baroreceptor reflex control of heart rate during morphine sulfate, diazepam, NO₂-O₂ anesthesia in human. Anesthesiology* 61 : 558-563, 1984
- 17) Takeshima R and Dohi S : *Comparison of arterial baroreflex function in humans anesthetized with enflurane or isoflurane. Anesth Analg* 69 : 284-290, 1989
- 18) Cerutti C, Gustin MP, Paultre CZ, Lo M, Julien C, Vincent M and Sassard J : *Autonomic nervous system and cardiovascular variability in rats : A spectral analysis approach. Am J Physiol* 261 : 1292-1299, 1991
- 19) Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC and Cohen RJ : *Hemodynamic regulation : Investigation by spectral analysis. Am J Physiol* 249 : 867-875, 1985
- 20) Japundzic NM, Grichois ML, Zitoun P, Laude D and Elghozi JL : *Spectral analysis of blood pressure and heart rate in conscious rats : Effects of autonomic blockers. J*

- Auton Nerv Syst* 30 : 91-100, 1990
- 21) Persson PB, Stauss H, Chung O, Wittmann U and Unger T : *Spectrum analysis of sympathetic nerve activity and blood pressure in conscious rats. Am J Physiol* 263 : 1348-1355, 1992
 - 22) Malliani A, Pagani M, Lombardi F and Cerutti S : *Cardiovascular neural regulation explored in the frequency domain. Circulation* 84 : 1482-92, 1991
 - 23) Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH and Cohen RJ : *Transfer function analysis of the circulation : Unique insights into cardiovascular regulation. Am J Physiol* 261 : 1231-1245, 1991
 - 24) Peters J, Kindred MK and Robotham JL : *Transient analysis of cardiopulmonary interactions, I : diastolic events. J Appl Physiol* 64 : 1506-1517, 1988
 - 25) Peters J, Kindred MK and Robotham JL : *Transient analysis of cardiopulmonary interactions, II : systolic events. J Appl Physiol* 64 : 1518-1526, 1988
 - 26) Peters J, Fraser C, Stuart RS, Baumgartner W and Robotham JL : *Negative intrathoracic pressure decreases independently left ventricular filling and emptying. Am J Physiol* 257 : 120-131, 1989
 - 27) Appel ML, Berger RD, Saul JP, Smith JM and Cohen RJ : *Beat to beat variability in cardiovascular variables : Noise or music? J Am Coll Cardiol* 14 : 1139-1148, 1989
 - 28) Parati G, Castiglioni P, Di Rienzo M, Omboni S, Pedotti A and Mancia G : *Sequential spectral analysis of 24-hour blood pressure and pulse interval in humans. Hypertension* 16 : 414-421, 1990
 - 29) Ponchon P, Grichois ML and Elghozi JL : *Effect of losartan on short term variability of blood pressure of renovascular hypertensive rats : A spectral study. J Hypertens* 11 (suppl 5) : 246-247, 1993
 - 30) Persson PB, Baumann JE, Ehmke H, Nafz B, Wittmann U and Kirchheim HR : *Phasic and 24-h blood pressure control by endothelium-derived relaxing factor in conscious dogs. Am J Physiol* 262 : 1395-1400, 1992
 - 31) Paxinos G and Watson C : *The rat brain in stereotaxic coordinates. New York, Acad Press, 1982*
 - 32) Gaudet E, Blanc J and Elghozi JL : *Effects of losartan on short-term variability of blood pressure in SHR and WKY rats. Fundam Clin Pharmacol* 9 : 30-46, 1995
 - 33) Bernardi L, Leuzzi S, Radaelli A, Passino C, Johnston JA and Sleight P : *Low-frequency spontaneous fluctuations of R-R interval and blood pressure in conscious humans : a baroreceptor or central phenomenon? Clin Sci* 87 : 649-654, 1994
 - 34) 황경원 · 양은경 · 김형진 · 박재식 · 이원정 : 정상혈압쥐에서 측뇌실에 주입한 angiotensin II 수용체 길항제가 출혈반응에 미치는 영향. *경북의대지* 34 : 349-356, 1993
 - 35) Severs WB and Daniels-Severs A : *Effects of angiotensin on the central nervous system. Pharmacol Rev* 25 : 415-434, 1973
 - 36) Sumners C and Phillips MI : *Central injection of angiotensin II alters catecholamine activity in rat brain. Am J Physiol* 244 : R257-R263, 1983
 - 37) Steckelings UM, Obermuller N, Bottari SP, Qadri F, Velthuis A and Unger Th : *Brain angiotensin : Receptors, actions and possible role in hypertension. Pharmacol Toxicol* 70 : S23-S27, 1992
 - 38) Unger T, Rascher W, Shuster C, Pavlovitch R, Schomig A, Dietz R and Gantem D : *Central blood pressure effects of substance P and angiotensin II : Role of the sympathetic nervous system and vasopressin. Eur J Pharmacol* 71 : 33-42, 1981
 - 39) Howell SJ, Wanigasekera V, Young JD, Gavaghan D, Sear JW and Garrard CS : *Effects of propofol and thiopentone, and benzodiazepine premedication on heart rate variability measured by spectral analysis. Br J Anaesth* 74 : 1168-73, 1995