

심근경색에 의해 유발된 심부전 백서에서 혈관작용물질의 변화에 관한 연구*

**

김철호 · 조주희 · 서정돈 · 이영우 · Brooks Edwards**

= Abstract =

Evolutional Change of Vasoactive Substances in Rat Model of Chronic Heart Failure

Cheol Ho Kim, M.D., Joo Hee Zo, M.D., Jung Don Seo, M.D.,
Young Woo Lee, M.D., Brooks Edwards, M.D.**

Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Korea
Mayo Clinic and Foundation, ** MN, USA

Background : Myocardial infarction(MI) in the rat is a model of ventricular dysfunction which is associated with activation of compensatory neurohumoral systems. This study was designed to determine the temporal evolution of the regulatory factors-atrial natriuretic peptide(ANP), endothelin(ET), plasma renin activity(PRA) in rats with more than moderate sized MI at 1, 4, 8 weeks in comparison to normal rats.

Methods and Results : MI was created in female Sprague Dawley rats weighing 250gms to 300gms by ligating the anterior descending artery. Before sacrifice, hemodynamics were measured and blood was drawn in control rats(n=8) and rats with MI 1(n=7), 4(n=10), and 8 weeks(n=9) after surgery. Heart weight index increased from 329.0 ± 7.3 mg/gm at baseline to 380.6 ± 18.4 mg/gm, 441.1 ± 23.2 mg/gm, 416.4 ± 29.2 mg/gm at the 1st, 4th, and 8th weeks after MI. Plasma ANP increased in the 1st week and remained elevated(16 ± 7 , 259 ± 65 , 404 ± 72 , 494 ± 73 pg/ml at baseline, 1st, 4th, 8th weeks after MI respectively). Plasma endothelin was suppressed at 4th week but elevated at 8th week(7.8 ± 0.2 , 5.3 ± 0.3 , 11.9 ± 1.3 pg/ml at baseline, 4th, 8th weeks respectively). PRA, indirect index of plasma angiotensin also decreased at 4th week but elevated at 8th week(14.9 ± 0.3 , 9.8 ± 1.0 , 20.3 ± 1.8 ng/ml/hr at baseline, 4th, 8th weeks respectively).

Conclusion : These results demonstrate a biphasic response of endothelin and PRA after MI despite the inhibitory effects of ANP. These data support the important differential regulation of humoral factors in the evolution of acute MI.

KEY WORDS : ANP · Endothelin · Plasma renin activity · Neurohumoral activation · Myocardial infarction.

서론

[illegible]

연구 대상 및 방법

1. 심근경색 백서의 준비

250gm 300gm 25mg/kg

Harvard rodent ventilator

가 4 6.0

가

가

가 1, 4, 8

가 24 25%

2. 혈액학적 인자의 측정

가 2,3,4,5) 1, 4, 8 가 Inactin U PE - 50

가 6,7) 9ml

가 5% paraformaldehyde Masson Trichrome

가 8) 25%

가 1

7, 4 10, 8
9 8

3. 호르몬의 측정

EDTA
2500rpm 4
-20
1ml
C-18 Bond Elute cartridge
1% trifluoroacetic acid/95% ethanol
ANP 99-126
C
Vycor glass
0.05mol 60%

4. 통계

ANOVA Student t-test
p 0.05

결 과

1. 백서의 심장 및 혈액학적 변화

124.2 ± 4.4 mmHg
1 101.8 ± 3.3 mmHg
4 112.2 ± 6.8 mmHg,
8 103.3 ± 8.0 mmHg
(/
) 가 329.0
± 7.3 mg/gm 1 380.6 ± 18.4
mg/gm, 4 441.1 ± 23.2 mg/gm, 8
416.4 ± 29.2 mg/gm
가 (p < 0.05).

2. 혈중 호르몬의 변화

ANP 가

16.4 ± 7.1 pg/ml, 1 259.0 ± 65.1 pg/ml,
4 404.7 ± 71.5 pg/ml, 8 493.7 ±
72.9 pg/ml
(p < 0.05, Fig. 1). CNP
5.6 ± 0.3 pg/ml, 1 9.6 ± 2.7 pg
/ml, 4 7.0 ± 0.4 pg/ml, 8 6.4 ±
0.4 pg/ml 1 가
(p < 0.05).

7.8 ± 0.2 pg/ml,
1 8.6 ± 0.8 pg/ml, 4 5.3 ± 0.3 pg/ml,
8 11.9 ± 1.3 pg/ml 4
8
가 (p < 0.05,

Fig. 2).

14.9 ± 0.3 ng/ml/hr, 1
12.8 ± 2.0 ng/ml/hr, 4 9.8 ± 1.0 ng/ml/

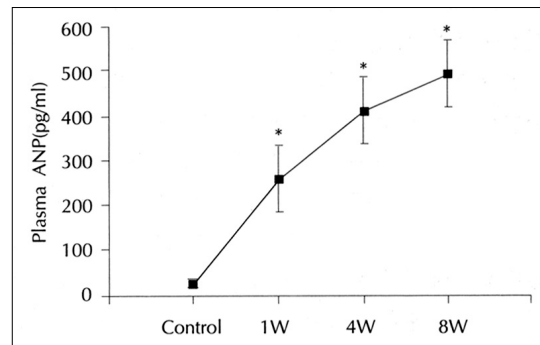


Fig. 1. Change of the plasma level of atrial natriuretic peptide (ANP) after myocardial infarction showing persistent elevation.
*p < 0.05

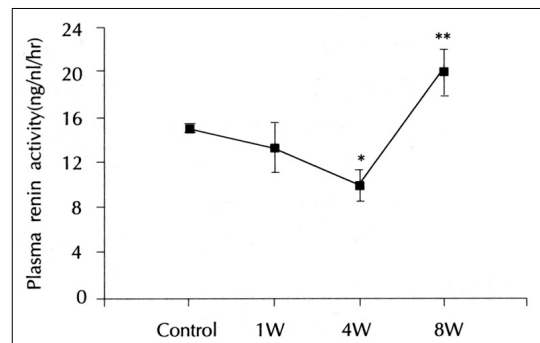


Fig. 2. Change of the plasma level of endothelin-1 after myocardial infarction showing decrease at 4th week (*p < 0.05) and increase at 8th week (**p < 0.05).

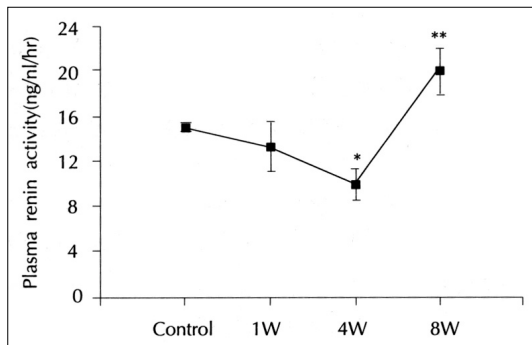


Fig. 3. Change of plasma renin activity after myocardial infarction showing significant decrease at 4th week (* $p < 0.05$) and increase at 8th week (** $p < 0.05$).

hr, 8 $20.3 \pm 1.8 \text{ ng/ml/hr}$ 4
8
가 ($p < 0.05$, Fig. 3).

고 안

가
9,10,11)

stress 가

가

12).

가 가

1

가

ozel

가

가 1

가

가

sham op

sham op

C

C

13)

14)

가

Wei

15)

가

가 가

1, 4, 16

Cl-

가

가

22).

가

가

가 가

,

,

-

-

-

References

- 1) Katz AM : Cardiomyopathy of overload ; A major determinant of prognosis in congestive heart failure. *N Engl J Med* 322 : 100-110, 1990
- 2) The SOLVD Investigators : Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 327 : 685-691, 1992
- 3) The SOLVD Investigators : Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325 : 293-302, 1991
- 4) Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldamn S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Jawkins M : Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 327 : 669-677, 1992
- 5) Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H : Effect of the early administration of enalapril on mortality in patients with acute myocardial infarction ; Results of the Cooperative New Scandinavian Enalapril Survival Study II (CON-SENSUS II) *N Engl J Med* 327 : 678-684, 1992
- 6) Cohn JN, Archibald D, Johnson G, et al : Effects of vasodilator therapy on peak oxygen consumption in heart failure : V-HeFT [abstract]. *Circulation* 76(suppl IV) : IV-443, 1987
- 7) Cohn JN, Johnson G, Ziesche S, et al : A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Eng J Med* 325 : 303-310, 1991
- 8) Packer M : The neurohumoral hypothesis : A theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 20 : 248-254, 1992
- 9) Burnett JC, Kao PC, Hu DC, Hesser DW, Heublein D, Granger JP, Opgenorth TJ, Reeder GS : Atrial natriuretic peptide elevation in congestive heart failure in the human. *Science* 231 : 1145-1147, 1986
- 10) Raine AEG, Erne P, Burgisser E, Muller FB, Bolli P, Burkart F, bulher FR : Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. *N Engl J Med* 315 : 533-537, 1986
- 11) Michel JP, Mercadier JJ, Galen FX, Urbaine R, Dussaule JC, Philippe M, Corvol P : Urinary cyclic guanosine monophosphate as an indicator of experimental congestive heart failure in rats. *Cardiovasc Res* 24 : 946-952, 1990
- 12) Drexler H, Jirth C, Stasch HP, Lu W, Neuser D, Just H : Vasodilatory action of endogenous atrial natriuretic factor in rat model of chronic heart failure as determined by monoclonal ANF antibody. *Circ Res* 66 : 1371-1380, 1990
- 13) Suga S, Nakao K, Itoh H, Komatsu Y, Ogawa Y, Hama N, Imura H : Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor-B : Possible existence of vascular natriuretic peptide system. *J Clin Invest* 90 : 1145-1149, 1992
- 14) Stingo AJ, Clavell AL, Aarhus LL, Burnett JC Jr : Cardiovascular and renal actions of C-type natriuretic peptide. *Am J Physiol* 262 : H308-H312, 1992
- 15) Wei CM, Heublein DM, Perrella MA, Lerman A, Rodheffer RJ, McGregor CGA, Edwards WD, Schaff HV, Brunett JC Jr : Natriuretic peptide system in human heart failure. *Circulation* 88 : 1004-1009, 1993
- 16) Wei CM, Kim CH, Miller V, Burnett JC Jr : Atrial natriuretic peptide and C-type natriuretic peptide in spontaneously hypertensive rats and their vasorelaxing action in vitro. *Hypertension* 23 : 903-907, 1994
- 17) Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitusi Y, Yasaki Y, Goto M, Masaki T : A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332 : 411-415, 1988
- 18) Cody RJ : The potential role of endothelin as a vasoconstrictor substance in congestive heart failure. *Europ Heart J* 13 : 1573-1578, 1992
- 19) Lerman A, Hildebrand FL Jr, Aarhus LL, Burnett JC, Jr : Endothelin has biologic actions at pathophysiological concentrations. *Circulation* 93 : 1808-1814, 1991
- 20) Kohno MK, Murakawa T, Horio N, Kurihara K, Yokokawa K, Yasunari T, Fukui, Takeda T : Endothelin stimulates release of atrial natriuretic factor in anesthetized rats. *Metabolism* 39 : 557-559, 1990
- 21) Saijonmaa O, Ristimaki A, Fyhrquist F : Atrial natriuretic peptide, nitroglycerin, and nitroprusside reduce basal and stimulated endothelin production from cultured endothelial cells. *Biochem Biophys Res Commun* 173 : 514-520, 1990
- 22) Teerlink JR, Loffler BM, Hess P, Maire JP, Clozel M, Clozel JP : Role of endothelin in the maintenance of blood pressure in conscious rats with chronic heart failure ; Acute effects of the endothelin receptor antagonist R047-0203 (Bosentan). *Circulation* 90 : 2510-2518, 1994
- 23) Emori T, Hirata Y, Ohta K, Kanno K, Eguchi S, Imai T, Shichiri M, Marumo F : Cellular mechanism of endothelin-1 release by angiotensin and vasopressin. *Hypertension* 18 : 165-170, 1991
- 24) Tsutamoto T, Kanamori T, Wada A, Kinoshita M : Uncoupling of atrial natriuretic peptide extraction and cyclic guanosine monophosphate production in the pulmonary circulation in patients with severe heart failure. *J Am*

- Coll Cardiol* 20 : 541-546, 1992
- 25) Riegger GAJ, Elsner D, Kromer EP, Daffner C, Forssmann WG, Muders F, Pascher EW, Kochsiek K : *Atrial natriuretic peptide in congestive heart failure in the dog : Plasma levels, cyclic guanosine monophosphate, ultrastructure of atrial myoendocrine cells and hemodynamic, hormonal and renal effects. Circulation* 77 : 398-406, 1988
- 26) Smit JB, Lincoln TM : *Angiotensin decreases cyclic GMP accumulation produced by atrial natriuretic factor. Am J Physiol* 253 : C147-C150, 1987