

고혈압 환자에서 내피의존성 혈관반응에 대한 안지오텐신 전환효소 억제제와 비타민 C의 효과에 대한 연구

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Improvement in Endothelial Function by Angiotensin-Converting Enzyme Inhibition and Vitamin C in Essential Hypertension

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ABSTRACT

Background and Objectives : The endothelium plays an important role in maintaining vascular tone and function. This essential hypertension may be associated with alterations in endothelial function. The effects of antihypertensive agents on endothelial function have not been fully evaluated in human hypertension and data on the forearm circulation of humans is controversial. The aim of this study was 1) to evaluate endothelial function in hypertensive patients 2) to investigate whether vitamin C administration has a benefit on endothelial function and 3) to determine whether treatment with ACE inhibitor improve improves endothelial dysfunction in hypertensive patients. **Materials and Methods :** The endothelial function was estimated using venous occlusion plethysmography (VOP) in 8 hypertensive patients and 8 healthy volunteers. The patients in the hypertension group were treated with enalapril, then reexamined. The change of forearm blood flow (FBF) was measured under conditions of acetylcholine infusion through the brachial artery as well as with intra-arterial vitamin C. The measurement of forearm volume change was repeated 7 times for each stage. **Results :** The forearm blood flow response to acetylcholine was significantly enhanced with intra-arterial infusion of vitamin C in the hypertensive group before antihypertensive treatment ($302 \pm 58\%$ - $446 \pm 43\%$). Co-infusion of L-NMMA, an inhibitor of nitric oxide synthase, the blunted forearm blood flow response to acetylcholine (Vit C (+); $446 \pm 43\%$ - Vit C + L-NMMA; $229 \pm 23\%$). After Following antihypertensive treatment with enalapril for 2 months in the hypertensive group, endothelium-dependent vasorelaxation (vasodilatory response to acetylcholine) was significantly improved in the treated group as compared to measurements taken before enalapril treatment ($302 \pm 58\%$ - $643 \pm 78\%$). **Conclusions :** Although the mechanisms leading to depressed endothelial function in essential hypertension remains to be elucidated, our study shows

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that vitamin C and ACE inhibitor result in a demonstrable improvement by a mechanism that is probably related to antioxidant activity. (**Korean Circulation J 2001;31 (4):411-419**)

KEY WORDS : Plethysmography · Endothelium · Hypertension · Ascorbic acid · ACE inhibitor.

서 론

가

가

가

10-12)

(nitric oxide,

NO)

(superoxide)

가

13)

가

가

superoxide xathine oxidase, cyclooxygenase
NADP/NADPH oxidase

가

14)15)

(substance P)
ctive hyperemia)

, P
(rea -

16)

C

(brachial artery),¹⁻³⁾

,⁴⁾

5)6)

7)

17)

8)

가

C

가

8-10)

가

C

가

가

11)12)

대상 및 방법

대상환자
 가 140/90 mmHg 24
 1) , 2) , 3) , 4)
 가 240 mg/dL , 8
 , 4) 8
 VOP(venous occlusion plethysmography)
 C 10 20
 mg 8 VOP 7.5, 15, 30 μ g
 C VOP C 10 24 mg
 C 가 C VOP C 2
 C 7.5, 15, 30 μ g
 5 C 24 mg
 Venous occlusion plethysmography 20
 C 24 mg
 nitric oxide L - NMMA(N -

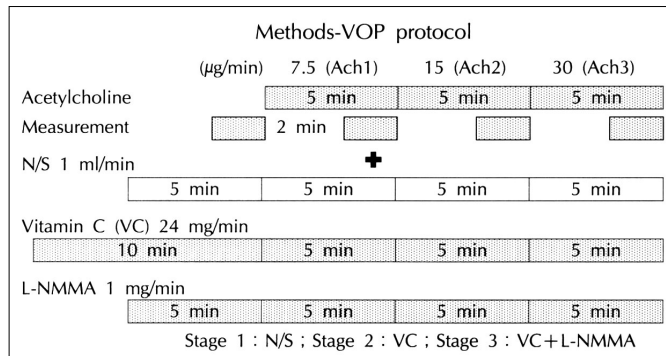


Fig. 1. Methods : venous occlusion plethysmography. Acetylcholine was infused intra-arterially at 7.5, 15 and 30 g/min for 5 minutes for each dose level, and forearm blood flow was measured during the last 2 minutes of each dose. Forearm blood flow response to acetylcholine was assessed during the infusion of dextrose solution (stage 1), intra-arterial infusion of vitamin C (stage 2), and intra-arterial coinfusion of vitamin C and L-NMMA (NG-monomethyl-L-arginine) (stage 3).

monomethyl-L-arginine, Sigma chemical)
 4 μmol (1 mL/min)
 2
 L-NMMA
 7.5, 15, 30 μg
 2
 L-NMMA
 0.22 μm filter

(Fig. 1).

통계방법

itney test

C

C

2 way ANOVA Wilcoxon signed ranks
 test SPSS ver 9.0
 ± (mean ±
 standard error of mean, SEM)
 p 0.05

결 과

(p<0.05, Table 1).

Table 1. Subject characteristics

	Clinical characteristics of the subjects		
	NC	HT	p
Number	8	8	
Age	50 ± 3	57 ± 4	0.13
Sex (M : F)	2 : 6	2 : 6	1.0
Cholesterol	182 ± 20	199 ± 12	0.43
SBP*	115 ± 4	166 ± 5	<0.001
DBP*	65 ± 3	94 ± 3	<0.001

values are mean ± SEM

2

(Table 2).

Table 3

정상대조군과 고혈압군에서의 전완혈류량

448 ± 63%,

302 ± 58%

(Fig. 2).

Table 2. Clinical characteristics of the subjects

	Clinical characteristics of the subjects		
	Pre-treatment	Post-treatment	p
Number	8	8	
SBP	163 ± 5	128 ± 4	<0.05
DBP	94 ± 3	71 ± 2	<0.05

values are mean ± SEM

Table 3. Absolute FBF responses before and after anti-hypertensive treatment

	NC	HT	Post-Tx	p
Basal	4.2 ± 0.6	5.7 ± 0.5	4.3 ± 0.7	0.09
Ach1	9.2 ± 1.8	7.2 ± 0.7	10.7 ± 2.9	0.31
Ach2	12.9 ± 1.9	12.1 ± 1.2	17.8 ± 3.5	0.18
Ach3	17.6 ± 1.9	15.9 ± 1.6	26.4 ± 4.2	0.03

Values are means ± SEM in ml/100 ml forearm/min

Ach1 : acetylcholine infusion with 7.5 μg/min

Ach2 : acetylcholine infusion with 15 μg/min

Ach3 : acetylcholine infusion with 30 μg/min

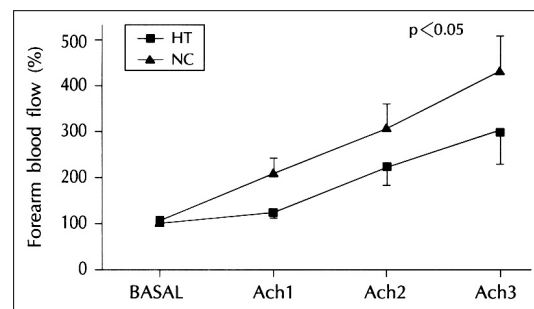


Fig. 2. FBF responses to three doses of acetylcholine in normal control and hypertensive patients. FBF is expressed as the percentage change in the ratio to the baseline period preceding the administration of acetylcholine. Values are mean ± SEM. Ach1, Ach2 and Ach3 represent 7.5, 15 and 30 μg/min, respectively. Vasodilatory response to acetylcholine was significantly greater in normal control group compared to hypertensive group.

정상대조군과 고혈압군에서의 비타민 C의 효과

C
302 ± 58%
가 (Fig. 3A).

C 383 ± 51%
(Fig. 3B). NO
L - NMMA C 가 가
C (Vit C (+) ; 446 ± 43%, Vit C +
L - NMMA ; 229 ± 23%, Fig. 4).

C 448 ± 63%

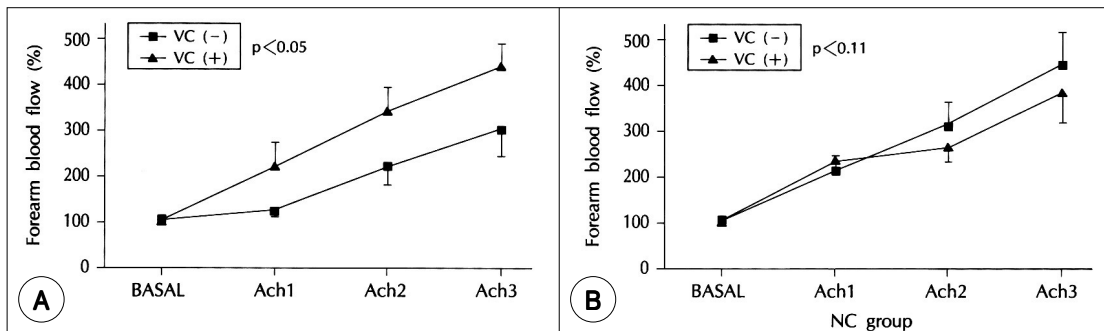


Fig. 3. FBF response to acetylcholine was significantly enhanced with intra-arterial infusion of vitamin C in hypertensive group (3A). Such an enhanced response was not observed in normal control group (3B). VC (-) : before intra-arterial infusion of vitamin C, VC (+) : after intra-arterial infusion of vitamin C.

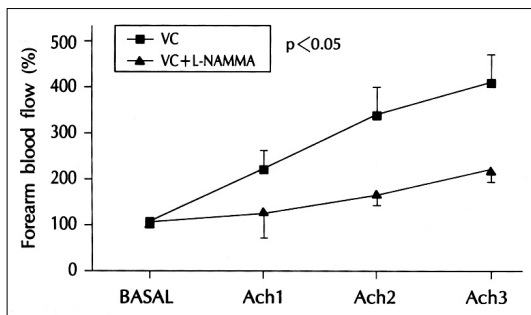


Fig. 4. FBF response to acetylcholine was blunted by co-infusion of vitamin C and L-NMMA, an inhibitor of nitric oxide synthase.

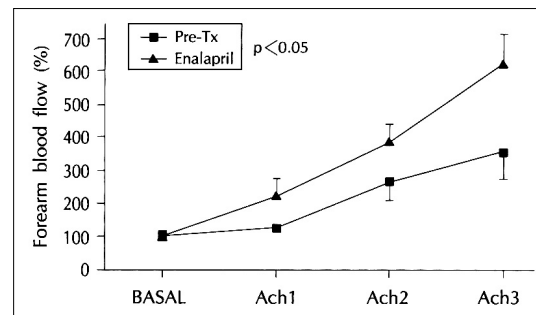


Fig. 5. Vasodilatory response to acetylcholine was significantly improved in enalapril treated group compared to before-treatment.

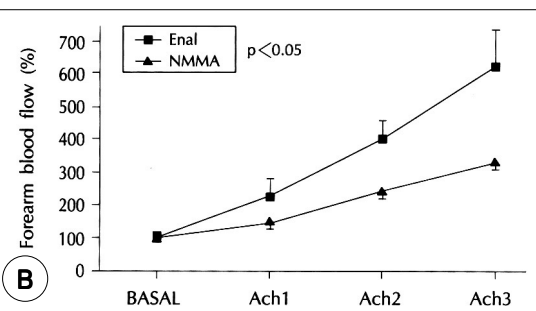
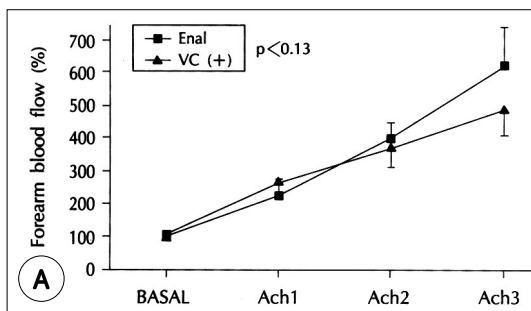


Fig. 6. Intra-arterial infusion of vitamin C in enalapril-treated hypertensive group did not change the forearm blood flow response to acetylcholine (6A). Co-infusion of L-NMMA, an inhibitor of nitric oxide synthase, blunted forearm blood flow response to acetylcholine in enalapril treated hypertensive group (6B). Enal : enalapril, L-NMMA : NG-monomethyl-L-arginine.

고혈압환자군에서의 에날라프릴 투여후의 전완혈류량의 변화

Solzbach

C

2

643 ± 78%
302 ± 58%
가 (Fig. 5).
C

¹⁹⁾

가

가

(Vit C (-) ; 643 ± 78%,
Vit C (+) ; 468 ± 52%, p=0.13, Fig. 6A).

C

²⁰⁾²¹⁾

NO

L - NMMA

2 g

C 1

500

mg

가 가

(

가

²²⁾²³⁾

L - NMMA (-) ; 643 ± 78%, L - NMMA (+) ;
332 ± 21%, p<0.05, Fig. 6B).

C
C가

고 찰

가

²⁴⁾ 가

C 가

가

C, E,

가

(beta carotene) 1

²⁵⁾

C

C 40

24 mg/min

C

가

Gilligan ²⁵⁾

C

NO

1000 mg

C, 800 IU

E, 30

mg

가

L - NMMA

C

(NO pathway)가

C

LDL

LDL

²⁶⁾

C

C

LDL

glutathione

³⁾¹⁸⁾

NO

가

2 C 500 mg
 glutathione 가 47% 가 II endothelin
 27) glutathione , 가,
 가 28) Creager 13)
 가 C , Creager
 가
 가 C
 E quinapril
 가
 C 가
 35-37)
 NADPH oxidase(nicotinamide adenine dinucle-
 tide phosphate oxidase)
 38)39) qui -
 pril
 12)29)30)
 가
 가
 II
 . Higashi 가 , 40)
 가 II
 가 41)
 10) captopril, 31) perin -
 opril, 32) cilazapril, 11) temocapril 9)
 captopril,
 enalapril, 13) cilazapril 33)
 . Taddei li -
 inopril , 1 , 1 , C
 가 34)
 8 C
 Higashi 10) C

(643 ± 78% 468 ±

C
(NO pathway)

52%, p=0.13).

L - NMMA

가

요 약

결 론 :

C

연구목적 :

가

C

가

가

C

중심 단어 :

C.

가

C

가

(HMP - 98 - M - 3 - 0043)

REFERENCES

방 법 :

가 140/90 mmHg

8

8

2

Plethysmography

가

C

(nitric oxide, NO)

L - NMMA

결 과 :

(448 ± 63% 302 ± 58%, p<0.05)

가

(302 ± 58%

643 ± 78%, p<0.05).

C

C

가

(302 ± 58% 446 ±

43%, p<0.05).

C

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