

## 치료받지 않은 고혈압환자에서 혈중 단핵구 $\beta$ ARK1의 농도와 좌심실질량의 비교연구

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### Association between $\beta$ ARK1 Level of Circulating Mononuclear Leukocytes and Left Ventricular Mass in Non-treated Hypertensive Patients

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#### ABSTRACT

**Background** : Beta-adrenergic receptor Kinase 1 ( $\beta$ ARK1) is a serine/threonine kinase attached, which inhibits the coupling of  $\beta$ -adrenergic receptor with G-protein. Myocardial  $\beta$ ARK1 level is usually elevated in heart failure and hypertrophy, but it is not known whether the circulating  $\beta$ ARK1 level is related with the degree of cardiac hypertrophy. This study was performed to evaluate the association of the  $\beta$ ARK1 level in circulating mononuclear leukocytes (MNL) in untreated hypertension with left ventricular mass in hypertensive patients.

**Method** : Nineteen non-treated hypertensive patients were included for this study. High blood pressure was confirmed when systolic BP is over 150 mmHg or diastolic BP is over 95 mmHg. Echocardiography was performed to evaluate the degree of hypertrophy by measuring the left ventricular mass index (LVMI) and relative wall thickness (RWT), and test the LV function by measuring the ejection fraction (EF) according to ASE guideline. At the same time, blood was collected from each patient and MNL were isolated by gradient centrifuge with Ficoll-400. Total RNA was purified from MNL and semi-quantitative RT-PCR was performed. After reverse transcription, PCR was done with primers for human  $\beta$ ARK1 and GAPDH as external control.

$\beta$ ARK1 levels were expressed by ratio to GAPDH level and estimated the relations with clinical and Echocardiographic parameters. **Result** : We studied confirmed 19 hypertensive patients (10 men and 9 women, mean age of 50.6 years). Echocardiographically measured indices (mean  $\pm$ SD) were as follows ; LVMI ( $137.3 \pm 30.6$  g/m<sup>2</sup>), PWT ( $0.53 \pm 0.09$ ) and EF ( $54.6 \pm 8.5\%$ ). Ratio of  $\beta$ ARK1 levels to GAPDH was from 0.10 to 0.96 ( $0.62 \pm 0.25$ ).  $\beta$ ARK1 levels were correlated with LVMI (correlation coefficient :  $r = 0.502$ ,  $p = 0.029$ ) and RWT ( $r = 0.627$ ,  $p = 0.004$ ). But Systolic BP ( $r = -0.009$ ,  $p = 0.93$ ), diastolic BP ( $r = 0.07$ ,  $p = 0.85$ ) or EF ( $r = 0.045$ ,  $p = 0.84$ ) were not related to level of  $\beta$ ARK1. **Conclusions** : The  $\beta$ ARK1 level of circulating MNL was correlated well with the degree of the cardiac hypertrophy estimated by LVMI and RWT. This data

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suggests that activation of sympatho-adrenal system would exert a major role in developing cardiac hypertrophy and we can expect the decreased responsiveness to catecholamine in the heart of hypertensive patients.

ARK1 in circulating MNL might be used as a predictor or marker for LV hypertrophy in hypertensive patients. **(Korean Circulation J 2000;30(12):1530-1539)**

**KEY WORDS :** ARK1 (beta-adrenergic receptor Kinase 1) · Hypertrophy · LVMI (Left Ventricular Mass Index).

17)

서 론 가 (blunting) ,

가 (homologous desen-

sitization) 가

G - protein G - protein -

coupled receptor kinase(GRK) 18)

GRK serine/threonine kinase family ,

12% 30% 6 GRK

가 5-7)

GRK2( ARK1),

GRK3( ARK2) GRK5가

17)19)20) ARK1

G - protein - su -

bunit

C - terminal

G - protein uncoupling

renin - angio -

tensin neurohumoral system 가 Takashi 21)

8 - 15)

down regulation

(inotropic), norepine -

(lucitropic) (chronotropic) phrine 가

16)

7 transmembrane 가 Choi

G - protein adenylyl cyclase ARK1 가

cyclic AMP 가 22)

ARK1  
 , ARK1

adenylyl cyclase

Gross R <sup>23)</sup>

ARK1

가 , ARK1

가

가 , ARK1

가

ARK1

ARK1

ARK1

ARK1

대상 및 방법

대 상

3

140 mmHg , 90 mmHg

5

2 cm

cuff

3

방 법

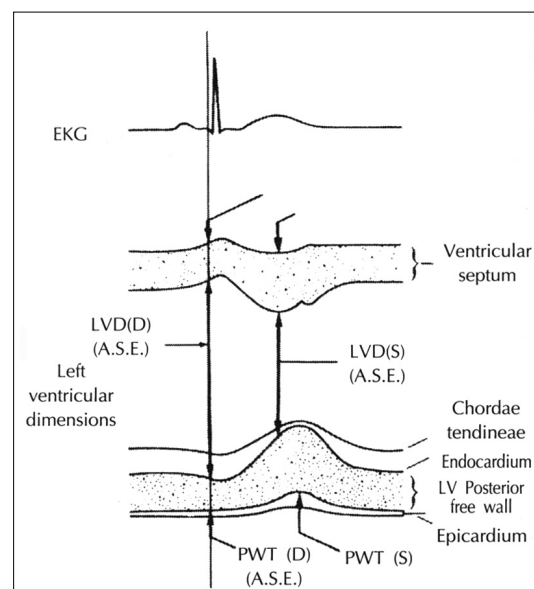
Hewlett Packard SONOS 2500, 2.5  
 MHz ultrasonic probe ,  
 15 30 °  
 3 - 5 M <sup>24)</sup>

3

(Fig. 1).

Devereux <sup>25)</sup>

Dubois<sup>26)</sup>



**Fig. 1.** Schematic diagram of M-mode of the left ventricle. The left ventricular interval dimension at end-diastole was measured at onset of the QRS complex and systolic (S) measurement was done at the maximal excursion of the ventricular septum. Interventricular septum and left ventricular posterior wall thickness were measured at the onset of the QRS complex. Abbreviations : ST (D) ; Ventricular septal thickness at end-diastole. LVD (D) ; Left ventricular internal dimension at end-diastole. LVD (S) ; Left ventricular internal dimension at end-systole. PWT (D) ; Left ventricular posterobasal free wall thickness at end-diastole.

LVM(g) =  
 $0.8[1.04(\text{IVSTd} + \text{LVIDd} + \text{PWTd})^3 - \text{LVIDd}^3]$   
+ 0.6  
BSA(m<sup>2</sup>) =  
 $0.007184[\text{height(cm)}]^{0.725}[\text{weight(kg)}]^{0.425}$   
Ejection Fraction(%) =  
 $[(\text{LVIDd}^2 - \text{LVIDs}^2) - \text{LVIDd}^2] \times 100$   
Relative Posterior Wall Thickness = 2PWTd/LVIDd  
Left Ventricular Mass Index(g/m<sup>2</sup>) = LVM/BSA  
(LVM : Left Ventricular Mass, LVIDd :  
, LVIDs : , IVSTd :  
, PWTd : , BSA :  
)

total RNA  
20

cc  
ACD(acid citrate Dextrose solution)  
Byum<sup>27)</sup>  
PBS 1 : 2 Ficoll - 400  
× 400 g 30 Buffi  
coat  
Trireagent(BM<sup>®</sup>) total RNA  
total RNA  
RNA

Reverse transcription  
2 µg total RNA reverse transcription  
Buffer(50 mM Tris - HCl, pH 8.3, 75 mM KCl, 3  
mM MgCl<sub>2</sub>, 5 mM DTT, 0.5 mM dNTP) random  
hexamer(Gibco BRL<sup>®</sup>), reverse transcriptase(Per -  
kin Elmer<sup>®</sup>) 70  
5 25 10 annealing 37  
60 extension 95 5 denature  
DNA

PCR protocol  
Reverse transcription DNA tem -  
plate polymerase chain reaction(PCR)  
Template DNA PCR Buffer(20 mM Tris -  
HCl, pH 8.4, 50 mM KCl, 1.5 mM MgCl<sub>2</sub>, 0.1%

Triton X - 100, 0.01% Gelatin) 1 mM dNTP, 1  
pmol primers, 3 unit Taq polymerase  
94 1 denature , 55 1 an -  
nealing, 72 1.5 extension cycle

primer sequence  
ARK1 : 1,050 bp(1,549 - 1,532)  
sense primer :  
5' - GCAACATGTACGCCATGAAGTGC  
antisense primer :  
5' - TCATCGAAGGAGCCAATGTCTG  
GAPDH : 580 bp(603 - 581)  
sense primer :  
5' - GCTTTTAACTCTGGTAAAGTGG  
antisense primer :  
5' - TACCGCCACAGTTTCCCGGAGG

PCR cycle  
ARK1 GAPDH 27 cycle 35  
cycle 3cycle , PCR product  
gel running PCR  
cycle cycle glyceraldehyde -  
3 - phosphate dehydrogenase(GAPDH) ARK1  
DNA cycle  
가 가 plateau cycle

ARK1  
cycle total RNA  
GAPDH ARK1 PCR PCR pro -  
duct gel loading gel running  
UV illumination , SigmaGel<sup>®</sup>  
ARK1 reverse transcripta - se -  
polymerase chain reaction(RT - PCR) DNA  
GAPDH ARK1  
가

통계적 방법  
±  
, M - mode  
ARK1 SPSS

p 0.05 심초음파상의 지표

## 결 과

### 임상양상

19  
10 , 9 . 24 70 ( :  
10.4 ± 12.3 ), 150 cm 178.1 cm(  
: 160.3 ± 10.5 cm, 43 kg 93.7 kg  
( : 62.4 ± 14.5 kg), 1.45 m<sup>2</sup>  
2.14 m<sup>2</sup>( : 1.66 ± 0.23 m<sup>2</sup>),  
168.68 ± 17.94  
mmHg, 103.68 ± 6.42 mmHg  
70.3 ± 8.3 (Table 1).

**Table 1.** Clinical characteristics (n = 19)

Gender	Men 10, Female 9
Age (yr)	50.4 ± 12.3
Height (cm)	160.3 ± 10.5
Body weight (kg)	62.4 ± 14.5
Body surface area (m <sup>2</sup> )	1.66 ± 0.23
SBP (mmHg)	
Systolic	168.7 ± 17.9
Diastolic	103.6 ± 6.4
Heart rate (/min)	70.3 ± 8.3

Values are mean ± SD.

**Table 2.** Echocardiographic data (n = 19)

LVD (S) (mm)	31.4 ± 3.5
LVD (D) (mm)	46.8 ± 2.8
ST (D) (mm)	12.4 ± 2.0
PWT (D) (mm)	12.4 ± 1.8
RWT	0.53 ± 0.1
LVEF (%)	54.6 ± 8.5
LVM (g)	243.3 ± 61.7
LVMI (g/m <sup>2</sup> )	137.3 ± 30.6

Values are mean ± SD.

LVD (D) : Left ventricular internal dimension at end-diastole

LVD (S) : Left ventricular internal dimension at end-systole

ST (D) : Ventricular septal thickness at end-diastole

PWT (D) : Left ventricular posterobasal free wall thickness at end-diastole

RWT : Relative posterior wall thickness

LVEF : Left ventricular ejection fraction

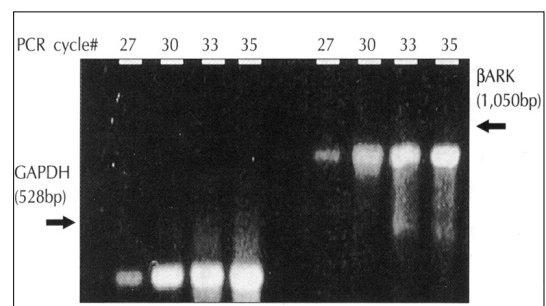
LVM : Left ventricular mass

LVMI : Left Ventricular mass index

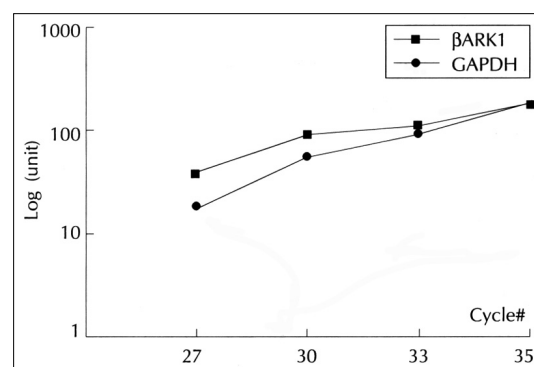
31.4 ± 3.5 mm, 46.8 ±  
2.8 mm, 12.4 ± 2.0 mm  
12.4 ± 1.8 mm  
0.35 0.70 0.53 ± 0.09  
(Ejection Fraction) 42.24% 68.85%  
54.6 ± 8.5% (LVM) 140.12  
g 348.72 g 243.3 ± 61.7 g  
(LVMI) 91.87 g/m<sup>2</sup> 206.26 g/m<sup>2</sup>  
137.3 ± 30.6 g/m<sup>2</sup> (Table 2).

### PCR cycle의 결정

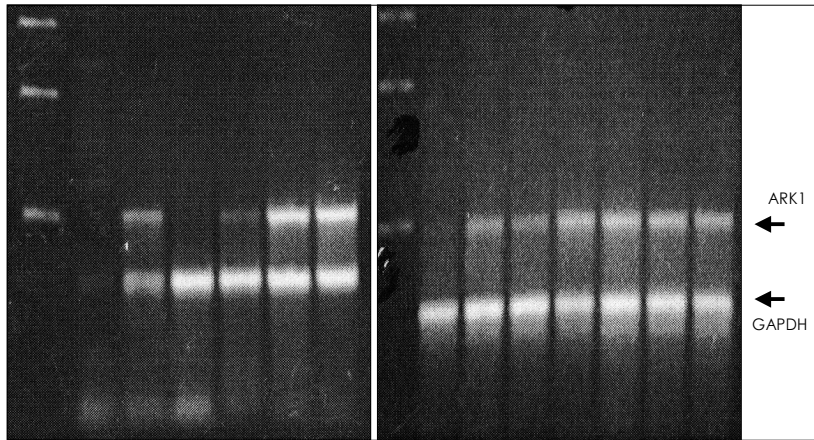
PCR cycle GAPDH  
ARK1 cycle PCR (Fig. 2)



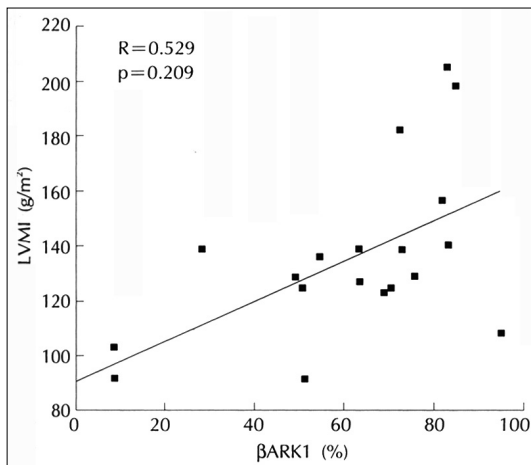
**Fig. 2.** Semiquantitative RT-PCR. Semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to determine the adequate cycles for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and beta-adrenergic receptor kinase 1 (ARK1).



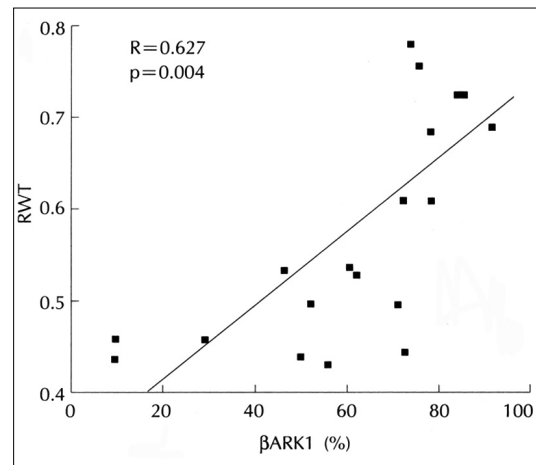
**Fig. 3.** Quantitation of PCR product. Proper polymerase chain reaction (PCR) cycle is determined as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) 30 cycle and beta-adrenergic receptor kinase 1 (ARK1) 33 cycle.



**Fig. 4.** RT-PCR sample of patients. After completion of PCR, each sample was run on the agarose gel and quantitated relative density of ARK1 compared with glyceraldehy-de-3-phosphate dehydrogenase (GAPDH) by SigmaGel<sup>®</sup> with UV exposed photography. Ratio of ARK1 levels to GAPDH was from 0.10 to 0.96 ( $0.62 \pm 0.25$ ).



**Fig. 5.** Correlation between ARK1 and LVMI. ARK1 : beta-adrenergic receptor kinase 1. LVMI : left ventricular mass index.



**Fig. 6.** Correlation between ARK1 and RWT. ARK1 : beta-adrenergic receptor kinase 1. RWT : relative posterior wall thickenss.

(Fig. 3). GAPDH ARK1  
27 cycle 35 cycle  
cycle GAPDH 30 cycle,  
ARK1 33 cycle PCR

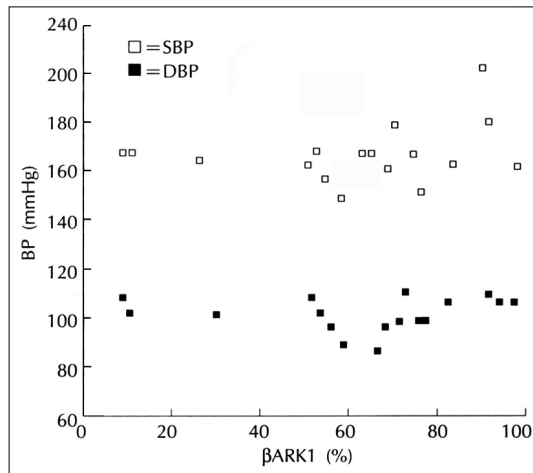
ARK1 (r =  
0.502, p=0.029) (r=0.627, p=  
0.004) (Figs. 5 - 8).

## 고 찰

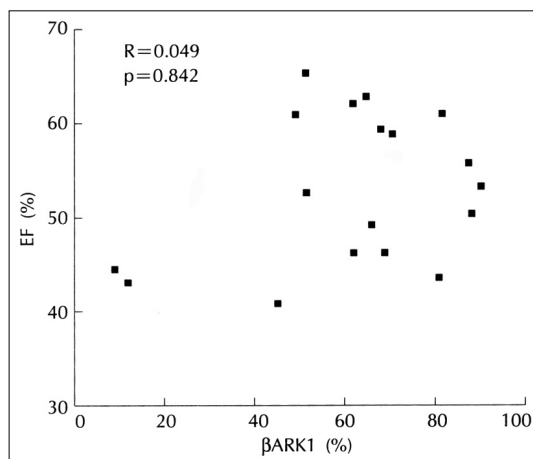
### βARK1 발현의 반정량분석

GAPDH ARK1 (Fig. 4) 0.10  
0.96( $0.62 \pm 0.25$ ) 가  
ARK1  
(r = - 0.009, p=0.97),  
(r=0.07, p=0.85) (r=0.045, p=  
0.84)

가 (sarcomere)  
가 가



**Fig. 7.** Correlation between  $\beta$ ARK1 and BP.  $\beta$ ARK1 : beta-adrenergic receptor kinase 1. SBP : systolic pressure. DBP : diastolic pressure.



**Fig. 8.** Correlation between  $\beta$ ARK1 and EF.  $\beta$ ARK1 : beta-adrenergic receptor kinase 1. EF : ejection fraction.

uncoupling . GRK in vitro in vivo - G - protein

adenylyl cyclase 가 , ARK1(GRK - 2) 가 cytosolic A - kinase GRK - 5/6

ARK1 ARK1 가 ARK1

adenylyl cyclase GRK 가 가

가 ARK1

가

Choi

가 , GRK 가

22) ARK1 ARK1

가

GRK 가

34)35) 가 가

가

36) adenylyl cyclase 가

adenylyl cy -

clase

G - protein 28 - 30) 가

G - protein

GRK가

kinase forskolin adenylyl cyclase A - ARK1

37)





receptor G - protein

ARK1

가

ARK1

ARK1

대상 및 방법 :

3

가

150 mmHg

95 mmHg

19

(LVMI),

(RWT),

(EF)

ARK1

RNA

GAPDH

RT - PCR

ARK1

결 과 :

19

가

10

가

50.42 ± 12.36

168.68 ± 17.94 mmHg,

103.68 ± 6.42 mmHg

LVMI

137.3 ± 30.6 g/m<sup>2</sup>, RWT

0.53 ± 0.09

EF 54.6 ± 8.5%

GAPDH

ARK1

0.10 0.96(0.62 ± 0.25)

ARK1

LVMI

(correlation coefficient : r=0.502, p=0.029)

, RWT

(r=0.627,

p=0.004)

ARK1

(r= -0.009, p=0.93),

(r=0.07, p=

0.85)

EF(r=0.045, p=0.84)

결 론 :

ARK1

ARK1

ARK1

중심 단어 : ARK1(beta -adrenergic receptor Ki - nase 1)

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