

## Diltiazem이 심근기절 및 미세혈관기절에 미치는 영향에 대한 실험적 연구

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박창규 · 김영훈 · 서홍석 · 심완주 · 오동주 · 노영무

### Effect of Diltiazem on Myocardial and Microvascular Stunning in Open Chest Dog

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#### ABSTRACT

**Background :** Post-ischemic myocardial dysfunction (myocardial stunning) is known to be associated with low reflow phenomenon or the reduction of coronary vasodilatory reserve. However, it remains controversial whether a relationship between myocardial stunning and post-ischemic impairment of coronary flow reserve exists. With increased influx of calcium into myocardial cells precipitated by ischemia and reperfusion known to be involved not only in the progression of myocardial tissue damage but also in the pathogenesis of post-ischemic myocardial dysfunction and impaired coronary vasodilatory reserve, it has been hypothesized that calcium channel blockers exert protective effects on post-ischemic myocardial dysfunction and microvascular dysfunction. **Purpose :** To investigate the effects of diltiazem, a calcium channel blocker, on post-ischemic myocardial dysfunction and coronary vasodilatory reserve, vehicle or diltiazem was administered before brief coronary artery occlusion in open chest dogs. Peak coronary flow and myocardial contractile function were measured after intracoronary infusion of endothelium-dependent vasodilator acetylcholine and endothelium-independent vasodilator adenosine. The parameters measured before and after reperfusion in control dogs and diltiazem-treated dogs were compared. **Method :** Open chest dogs (n = 17) underwent 20 minutes occlusion of left circumflex artery followed by reperfusion for 60 minutes ; the subjects were divided into two groups (n = 10 in control group and n = 7 in diltiazem group). Diltiazem dogs received diltiazem (0.2 mg/kg) intravenously 15 minutes before coronary occlusion. Control dogs received vehicle-a saline solution. Coronary blood flow was measured with electromagnetic flow probe. Coronary flow reserve was determined by peak coronary flow after intracoronary infusion of acetylcholine (ACH, 0.01 ug/kg) and adenosine (ADE, 1.5 mg/kg) ; it was also determined by reactive hyperemia (RH) measured after coronary occlusion for 20 seconds at baseline and 30 and 60 minutes after reperfusion. Segmental left ventricular function was assessed by 2-D echocardiography at the level of mid-papillary muscle, and changes of left ventricular function was

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**KEY WORDS :**  $\text{Ca}^{++}$  blocker microvascular stunning · Ischemia-reperfusion.

서론

593

acetylcholine  
adenosine 20  
2)  
zem  
diltiazem 20

cc 0.2 cc  
acetylcholine  
가 3  
adenosine(1.5 µg/kg)  
20

## 방법 및 재료

실험동물의 준비  
(15 25 kg) sodium pentobarbital  
(30 mg/kg) Ha -  
Harvard Respirator

반동성 충혈(Reactive hyperemia)의 측정  
30 60  
20  
1) 2)  
(peak/baseline flow ratio) 3)

(electromagnetic flow probe,  
Coriolina Medical Electronics, Cliniflow Model FM  
701D)  
30 gauge  
0.5 cc heparin

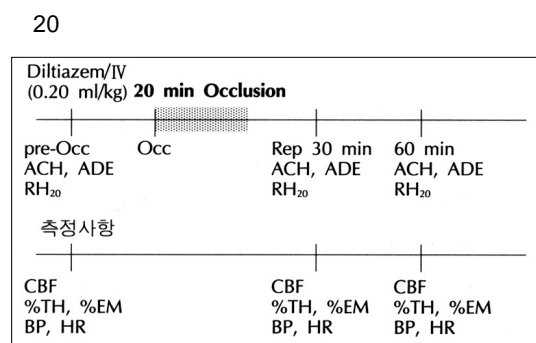
국소적 심근기능의 측정  
Hewlett - Packard  
(SONOS 1000A, 5MHZ)  
30 60  
NOVA MICROSONICS cent -  
online  
%

## 실험 계획(Protocol)(Fig. 1)

### 실험군의 구분

(n = 10)  
20  
Diltiazem (n = 7)  
diltiazem 0.20 mg/kg 1  
15 20

### 심근 손상의 확인



**Fig. 1.** Experimental protocol.  
ACH : acetylcholine, ADE : adenosine  
Occ : occlusion, Rep : Reperfusion  
RH 20 : reactive hyperemia for 20 seconds occlusion  
CBF : coronary blood flow  
%TM : % myocardial thickening  
%EM : % endocardial wall motion  
BP : blood pressure, HR : heart rate

### 약물의 투여

30 60  
acetylcholine(0.01 µg/kg) 1

(triphenyl tetrazolium chloride) TTC 32.6 ± 15.4 ml/min 26.9 ± 7.9 ml/min 가 (p=0.98) diltiazem 42.8 ± 18.5 ml/min 37.7 ± 15.8 ml/min 가 (p=0.84) 60 (co - ntinuous variables) Student's t - test, (p=0.13, p=0.81, Table 2). Chi - square test, Pearson P 0.05 P 0.06 0.09

관동맥 혈류와 관동맥 최저 저항의 변화

## 결 과

Diltiazem 투여군에서의 혈액학적 변화

Diltiazem 60 (Table 1). 60

**Table 1.** Hemodynamic data at baseline and reperfusion 60 minutes

1) Baseline			
	Control	Diltiazem	p value
Systolic	135.8 ± 14.2	134.3 ± 8.3	0.728
Diastolic	84.1 ± 11.8	78.7 ± 7.4	0.206
HR	165.1 ± 44	147.8 ± 37.1	0.379
2) Reperfusion 60 minutes			
	Control	Diltiazem	p value
Systolic	135.8 ± 14.2	128.0 ± 16.1	0.34
Diastolic	84.1 ± 11.8	75.7 ± 13.4	0.07
HR	165.1 ± 44	165.3 ± 37.0	0.98

p : control group vs. diltiazem group  
HR : Heart rate

30 , 60  
30 , 60 acetylcholine  
58.1 ± 12.4, 59.2 ± 12.0  
ml/min 82.1 ± 14.6 ml/min  
(p=0.006, p=0.037, Table 3,  
Fig. 2) diltiazem 30 , 60 ac -  
etylcholine 113.0 ± 58.1,  
114.6 ± 14.4 ml/min 125.4 ±  
17.5 ml/min 가 (p =  
0.781, p=0.578, Table 3, Fig. 3) diltiazem  
acetylcholine 30 , 60

**Table 2.** Baseline and reperfusion 60 minutes coronary flow and coronary vascular resistance

Flow	Baseline	Rep.60	p value
Control	32.6 ± 15.4	26.9 ± 7.9	0.98
Diltiazem	42.8 ± 18.5	37.7 ± 15.8	0.84
CVR	Baseline	Rep.60	p value
Control	1.41 ± 0.05	1.79 ± 0.59	0.13
Diltiazem	0.87 ± 0.31	0.85 ± 0.29	0.81

p : baseline vs. reperfusion 60  
Rep : reperfusion

**Table 3.** Baseline, reperfusion 30 minutes and 60 minutes peak flow on acetylcholine, adenosine and reactive hyperemia

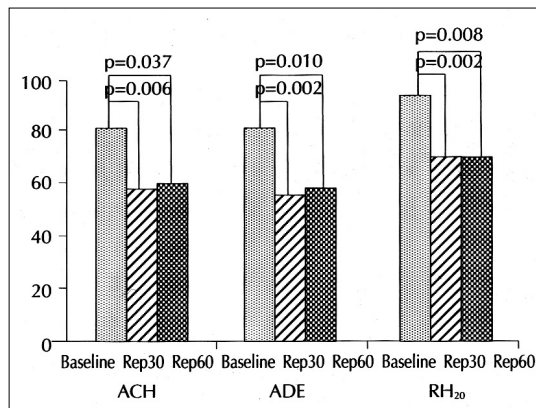
	Baseline	Rep 30	p	Rep 60	p value
ACH					
Control	82.1 ± 14.6	38.1 ± 12.4	0.006	59.2 ± 12.0	0.037*
Diltiazem	125.4 ± 17.5	113.0 ± 58.1	0.781	114.6 ± 14.4	0.578
ADE					
Control	83.2 ± 0.084	53.1 ± 5.11	0.002	57.4 ± 4.8	0.010*
Diltiazem	113.2 ± 9.7	109.6 ± 7.28	0.158	115.6 ± 6.8	0.469
RH <sub>20</sub>					
Control	94.9 ± 6.1	67.6 ± 10.4	0.002	67.9 ± 9.0	0.008*
Diltiazem	117.5 ± 9.6	146.8 ± 13.3	0.375	135.0 ± 11.6	0.156

ACH : Acetylcholine

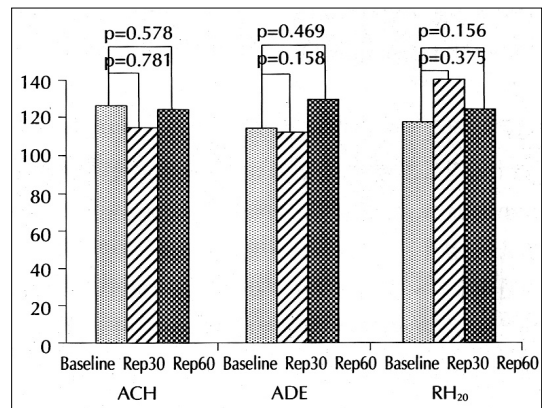
RH<sub>20</sub> : Reactive hyperemia after 20 seconds occlusion

ADE : Adenosine

p : baseline vs. rep.30, rep 60



**Fig. 2.** Peak flow at baseline, reperfusion 30 minutes and 60 minutes in control group.



**Fig. 3.** Peak flow at baseline, reperfusion Rep 30 minutes and 60 minutes in diltiazem group.

ACH : Acetylcholine ADE : Adenosine  
RH<sub>20</sub> : Reactive hyperemia

(Peak/Base ratio)  
2.71 ± 0.29 30 , 60  
2.09 ± 0.21, 2.1 ± 0.21  
(p = 0.014, p = 0.064, Table 4) diltiazem  
2.97 ± 0.35, 2.85 ± 0.25, 3.0 ± 0.26 (p = 0.469, 0.469)  
(Table 4).  
Adenosine  
83.2 ± 8.4 ml/min 30 , 60  
53.1 ± 5.11 (p = 0.002), 57.4 ± 4.8 (p = 0.01)  
(Table 3, Fig. 2). Diltiazem 30 , 60  
109.6 ± 7.2 ml, 115.6 ± 6.8 ml  
113.2 ± 9.7 ml 가  
(p = 0.158, p = 0.469, Table 3, Fig. 3).  
adenosine

2.79 ± 0.22 30 , 60  
1.85 ± 0.20 (p = 0.004), 1.94 ± 0.18 (p = 0.006)  
가 (Table 4), diltiazem  
30 , 60 3.55 ± 0.3, 3.37 ± 0.24  
3.26 ± 0.26  
(p = 0.688, p = 0.468, Table 4).  
20  
94.9 ± 6.1 ml/min  
30 , 60 67.6 ± 10.4 ml/min (p = 0.002), 67.9 ± 9.0 ml/min (p = 0.008)  
(Table 3, Fig. 2). Diltiazem  
117.5 ± 9.6 ml/min 30 , 60  
146.0 ± 13.3 (p = 0.325), 135.0 ± 11.6 (p = 0.156)  
가 (Table 3, Fig. 3).

**Table 4.** Peak/baseline flow ratio at baseline and reperfusion 30 minutes and 60 minutes

	Baseline	Rep 30	p	Rep 60	p
ACH					
Control	2.71 ± 0.29	2.09 ± 0.21	0.014	2.1 ± 0.21	0.064
Diltiazem	2.97 ± 0.35	2.85 ± 0.25	0.469	3.0 ± 0.26	0.469
ADE					
Control	2.79 ± 0.22	1.85 ± 0.20	0.004	1.94 ± 0.18	0.006
Diltiazem	3.26 ± 0.26	3.55 ± 0.31	0.688	3.37 ± 0.24	0.468
RH 20					
Control	3.28 ± 0.25	2.5 ± 0.21	0.002	2.33 ± 0.24	0.008
Diltiazem	3.8 ± 0.32	3.83 ± 0.25	0.812	3.69 ± 0.29	0.297

\*p : P value

P : vs. Baseline

P/B Flow : Peak/Baseline Flow

3.28 ± 0.25 30 , 60 2.5 ± 0.21 (p = 0.002), 2.33 ± 0.24 (p = 0.008) (Table 4), diltiazem 3.8 ± 0.32 30 , 60 3.83 ± 0.25 (p = 0.812), 3.69 ± 0.29 (p = 0.297) 가 (Table 4).

, 30 , 60

acetylcholine 1.41 ± 0.17 mmHg/ml/min 30 , 60 1.73 ± 0.13 mmHg/ml/min, 1.79 ± 0.15 mmHg/ml/min (p = 0.039) 가 (Table 5). dil - tiazem acetylcholine 30 , 60 0.88 ± 0.16 mmHg/ml/min, 0.84 ± 0.19 mmHg/ml/min 0.87 ± 0.14 mmHg/ml/min 가 (p = 0.81, Table 5). Adenosine 1.28 ± 0.10 mmHg/ml/min 30 , 60 1.93 ± 0.14 mmHg/ml/min (p = 0.002), 1.87 ± 0.18 mmHg/ml/min (p = 0.004) 가 (Table 5), diltiazem 30 , 60 0.68 ± 0.15 mmHg/ml/min, 0.66 ± 0.22 mmHg/ml/min 0.72 ± 0.13 mmHg/ml/min 가 (p = 0.385, p = 0.50, Table 5). 20

1.05 ± 0.07 mmHg/ml/min 30 60 1.94 ± 0.12 mmHg/ml/min (p = 0.02), 1.51 ± 0.10 mmHg/ml/min (p = 0.004) 가 (Ta -

ble 5), diltiazem 30 , 60 0.62 ± 0.15 mmHg/ml/min, 0.66 ± 0.12 mmHg/ml/min 0.63 ± 0.08 가 (p = 0.66, p = 0.34, Table 5). Diltiazem diltiazem acetylcholine 0.87 ± 0.14 mmHg/ml/min 0.900. 37mmHg/ml/min (p = 0.89), adenosine 0.72 ± 0.13 mmHg/ml/min 0.770.36mmHg/ml/min (p = 0.37) 가 20 0.63 ± 0.08 mmHg/ml/min 0.68 ± 0.35 mmHg/ml/min (p = 0.016) 가 (Table 5).

60 ,

Acetylcholine 60 18.8 ± 35.0% [( 60 - )/ 60 ], diltiazem 6.9 ± 22.4% (p = 0.44), adenosine 29.1 ± 20.3% diltiazem 5.1 ± 20.0% (p = 0.029) adenosine . 20 26.3 ± 23.5% diltiazem 9.1 ± 15.4% (p = 0.285, Table 6).

60 (Peak/Baseline ratio) acetyl - choline, 20

**Table 5.** Coronary vascular resistance (CVR) at baseline, reperfusion 30 minutes and 60 minutes

CVR		Baseline	Pre-occlusion (Diltiazem)	Rep 30	Rep 60
Control group	ACH	1.41 ± 0.17		1.73 ± 0.13*	1.79 ± 0.15*
	ADE	1.28 ± 0.10		1.93 ± 0.14*	1.87 ± 0.18*
	RH <sub>20</sub>	1.05 ± 0.07		1.94 ± 0.12*	1.51 ± 0.10*
Diltiazem group	ACH	0.87 ± 0.14	0.90 ± 0.37	0.88 ± 0.16	0.84 ± 0.19
	ADE	0.72 ± 0.13	0.77 ± 0.36	0.68 ± 0.15	0.66 ± 0.22
	RH <sub>20</sub>	0.63 ± 0.08	0.68 ± 0.35*	0.62 ± 0.15	0.66 ± 0.12

\* : p < 0.05 vs. baseline ACH : Acetylcholine ADE : Adenosine RH<sub>20</sub> : Reactive hyperemia

(p=0.084, p=0.0625),  
adenosine 27.7 ± 22.8%  
, diltiazem 6.1 ± 15.5%  
가 (p=0.039)  
diltiazem

diltiazem  
가

(Table 6).

acetylcholine 40.8  
± 60.6% 가 diltiazem 1.2 ± 20.4%  
(p =  
0.10), adenosine  
44.1 ± 32.5% 가 diltiazem  
6.3 ± 18.7% (p=0.002) adenosine  
(Table 6).

심근수축기능의 변화

Diltiazem

diltiazem  
가

% di -

**Table 6.** % Change of peak flow between baseline and reperfusion 60 minutes in both groups

1. % Change of peak flow			
	Control	Diltiazem	p value
ACH	-18.8 ± 35.0	-6.9 ± 22.4	0.44
ADE	-29.1 ± 20.3	-5.1 ± 20.0	0.029
RH <sub>20</sub>	-26.3 ± 23.5	-9.1 ± 15.4	0.285
2. % Change of % flow			
	Control	Diltiazem	p value
ACH	-18.3 ± 26.8	4.5 ± 6.22	0.084
ADE	-27.7 ± 22.8	6.1 ± 15.5	0.0039
RH <sub>20</sub>	-27.6 ± 22.9	-6.9 ± 18.2	0.0625
3. % Change of CVR			
	Control	Diltiazem	p value
ACH	40.8 ± 60.6	-1.2 ± 20.4	0.10
ADE	44.1 ± 32.5	-6.3 ± 18.7	0.002
RH <sub>20</sub>	44.9 ± 34.4	10.3 ± 19.3	0.0298

p : control group vs. diltiazem group

ltiazem 53.6 ± 10.7% diltiazem  
42.1 ± 3.5%  
(p=0.031), 68.6 ±  
17.3% 55.6 ± 10.0%  
(p=0.062, Table 7).

, 30 , 60

62.5 ± 7.1% , -19.0 ±  
22.3% 30 , 60 24.4 ± 12.4%, 23.3  
± 5.0 % diltiazem 53.6 ±  
10.7%, -10.0 ± 12.2%, 30  
27.9 ± 10.4%, 60 26.4 ± 12.1%  
(p=0.10,  
0.34, 0.98, 0.82),  
diltiazem  
(Table 8).

60  
( 60 -  
) 40.0 ± 7.5% , dilt -  
iazem 34.3 ± 5.3% diltiazem  
(p=0.0072, Table 8).

관동맥 혈류의 변화와 심근수축기능의 변화와의 관계  
60 ac -

etylcholine, adenosine

[( - )/ ]  
(acetylcholine :  
r = 0.33, p = 0.47, adenosine : r = 0.51, p = 0.24),  
가 (ac -  
etylcholine : r = 0.21, p = 0.65, adenosine : r = 0.14,  
p = 0.76, Fig. 4) .

Diltiazem 60  
acetylcholine

**Table 7.** Endocardial wall motion and total myocardial thickening at baseline and preocclusion in diltiazem group

	Baseline	Pre-occlusion	p value*
EM(%)	53.6 ± 10.7	42.1 ± 3.5	0.031
TM(%)	68.6 ± 17.5	55.0 ± 10.0	0.062

EM : Endocardial wall motion  
TM : Total myocardial thickening  
\* : baseline vs. pre-occlusion

( $r = 0.802$ ,  $p = 0.0299$ ) adenosine  
 ( $r = 0.7999$ ,  $p = 0.0308$ , Fig. 5).

20  
 acetylcholine

**Table 8.** Endocardial wall motion and total myocardial thickening

	Control	Diltiazem	p value*
EM			
Baseline	62.5 ± 7.1	53.6 ± 10.7	0.10
Occl	-19.0 ± 22.3**	-10.0 ± 12.2**	0.34
Rep30	24.4 ± 12.48**	27.9 ± 10.4**	0.98
Rep60	23.3 ± 5.0**	26.4 ± 12.1**	0.82
Rep60-Base line	40.0 ± 7.5	34.3 ± 5.3	0.0072
TM			
Baseline	82.8 ± 16.0	68.6 ± 17.5	0.08
Occl	-25.0 ± 16.3***	-15.8 ± 8.0***	0.15
Rep30	33.5 ± 16.2***	39.3 ± 10.2***	0.34
Rep60	31.6 ± 13.0***	34.3 ± 14.8***	0.61
Rep60-Base line	48.8 ± 19.2	34.3 ± 5.3	0.085

EM : Endocardial wall motion

TM : Total myocardial thickening

\* : control group vs. diltiazem group

\*\* : vs. baseline of EM,  $p < 0.05$

\*\*\* : vs. baseline of TM,  $p < 0.05$

TTC(Triphenyl Tetrazolium Chloride)염색의 결과  
 20

diltiazem 2

TTC

고 안

가

(myocardial stunning)

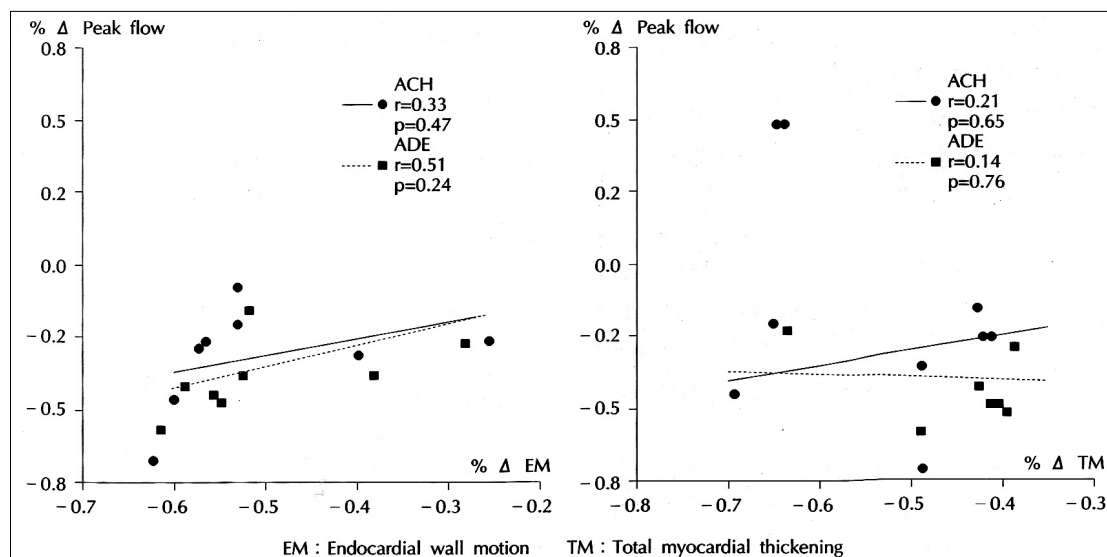
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가

27)28)

29-32)

가



**Fig. 4.** Relation between % change in segmental % endocardial thickening and peak flow after acetylcholine and adenosine in control group.



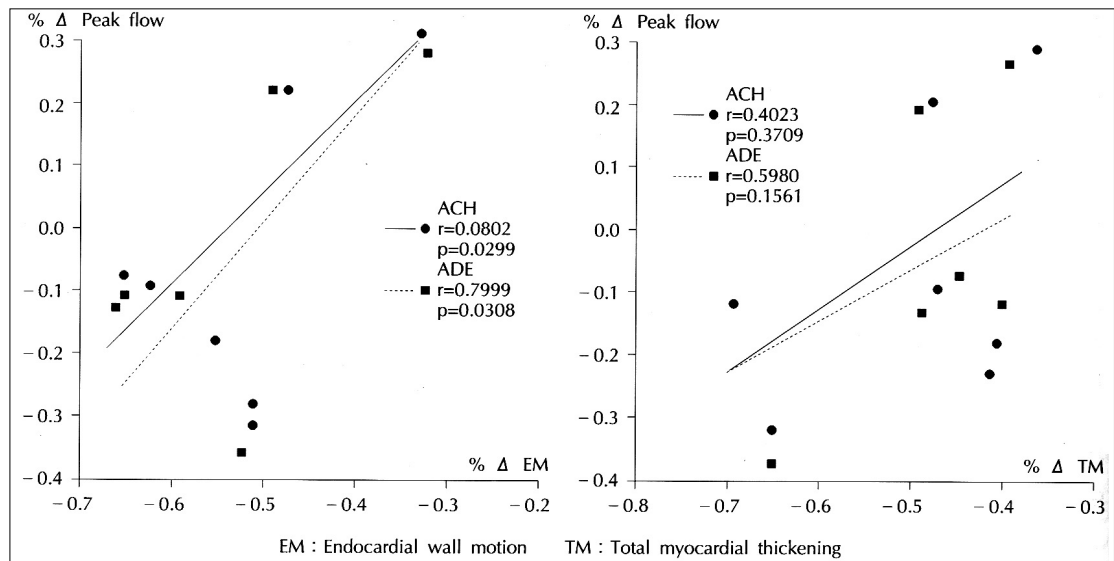


Fig. 5. Relation between % change in segmental % endocardial thickening and peak flow after acetylcholine and adenosine in diltiazem group.

심근기절현상과 미세혈관기절현상과의 관계

36)

Ca<sup>++</sup>

37)38)

가

가

17)

,

(vascular stunning)

가 7) Bolli 7) 15

4

adenosine

가

39)

가

30, 60  
acetylcholine, adenosine

60

가

Kim<sup>33)</sup> 20 /60  
60

가

Bolli

심근기절에서 Ca<sup>++</sup>의 역할

ATP(Adenosine Triphosphate)가

ATP

가가

가

가

34)35) ATP

가

가

601

59)  $Ca^{++}$  60) 가  
가  
.  
diltiazem 가  
.  
20)49) Heusch 31) 가  
 $Ca^{++}$   $Ca^{++}$   
 $Ca^{++}$  가  
가  
가  
가  
61 - 63) 가  
가  
가  
64) 가  
가  
diltiazem  
60 ( )가  
가 가  
60  $Ca^{++}$   
가 diltiazem 가  
가 diltiazem  
60  $Ca^{++}$   
diltiazem  
가  $Ca^{++}$   
 $Ca^{++}$  가  
Ca<sup>++</sup> 약  
연구배경 :  
본 연구의 제한점  
가  
가 20  
가  
Ca<sup>++</sup>  
(stunning)  
가  
Ca<sup>++</sup>

가 (Table 5).  
4) 60

방 법 : (15 25 kg) (Peak/Base ratio) acetylcholine  
(Table 6) adenosine  
diltiazem  
가 (Table 6) dilti -  
zem (n = 7) diltiazem  
(n = 10) diltiazem 0.20 ml/kg 1  
15 20  
30 60  
acetylcholine(0.01  $\mu$ g/kg), adenosine(1.5  $\mu$   
g/kg) acetylcholine  
20  
30 60  
%  
(p = 0.03,  
p = 0.06),  
30 , 60  
% 가 (Table 8).  
6) Acetylcholine adenosine  
60  
(acetylcholine : r = 0.33, p = 0.47,  
adenosine : r = 0.52, p = 0.24, acetylcholine : r =  
0.21, p = 0.65, adenosine r = 0.14, p = 0.76, Fig. 4)  
가  
(acetylcholine : r = 0.40, p =  
0.37, adenosine : r = 0.59, p = 0.16)  
(acetylcholine : r  
= 0.80, p = 0.30, adenosine : r = 0.79, p = 0.03, Fig. 5).  
결 론 :  
1) Diltiazem diltiazem  
60 (Ta - ble . Diltiazem  
1) 60 (acetylcholine : r = 0.40, p =  
0.37, adenosine : r = 0.59, p = 0.16)  
(Table 2). (acetylcholine : r  
2) 30 , 60 acetylch - = 0.80, p = 0.30, adenosine : r = 0.79, p = 0.03, Fig. 5).  
oline, adenosine 20  
(Table 3, Fig. 2) diltiazem  
가 (Table 3, Fig.  
3). Ca<sup>++</sup>  
30 , 60 가  
(Table 4) diltiazem Ca<sup>++</sup>  
30 , 60 가  
(Table 4).  
3) Acetylcholine, adenosine  
30 , 60  
가 (Table 5), diltiazem

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