CHAPTER III

RESULTS

According to the previous experimental protocol, this chapter of results are composed of four major different parts. First is the results of whole body model. Second is the effects of AM on dorsal skinfold chamber model, and third is the isolated heart model. Fourth, by using isolated heart model the effect of AM on the amount of ventricular cAMP production was studied. Besides, the effects of AM with different inhibitors including indomethacin, L-NNA, and glibenclamide were also reported.

I. The whole body model: the effect of AM on arterial pressure

Bolus i.v. administration of AM, 1 nmol/kg BW, into anesthetized rats produced a transient decrease in systemic arterial pressure. This reduction was rapid in onset, reached its peak effect in thirty seconds and returned to its basal level within half an hour. The example of tracing was shown in the appendix on page 138.

The mean arterial pressure (MAP) at minute control (0) 30 sec., 1, 5, 10, 30 and 60 were 98.43±3.90, 68.57±0.84, 73.14±1.74, 89.00±5.42, 91.86 ±4.97, 95.43±4.12 and 96.14±4.03 mmHg, respectively, (Table 3.1 and Figure 3.1). Mean arterial pressure difference between minute 0 and 30 sec was 29.86±3.31 mmHg. There was no reflex increase in heart rate (Table 3.2).

II. The dorsal skinfold chamber model: the effect of AM on rat skin microcirculation

The diameter of the second (A_2) and the third order (A_3) arterioles was assessed from the fluorescence videoimages obtaind before and after the topical application of AM (10^{-7} M). The changes in arteriolar diameter were summarized in Table 3.3. The percent changes from baseline diameter were shown in Table 3.4 and Figure 3.2. The significant arteriolar dilatation was observed in both A_2 and A_3 arterioles at 3 min after the application (A_2 arterioles : from 56.80±2.08 μm to 59.60±2.80 μm ; A_3 arterioles : from 35.00±3.83 μm to 40.40±5.49 μm). The arteriolar dilatation appear to be more sensitive in A_3 arterioles than in A_2 arterioles (Percent changes are 4.78±1.34% and 14.15±3.55% in A_2 and A_3 arterioles, respectively). Figure 3.3 revealed the example of intravital fluorescent videoscopic images of A_2 and A_3 arterioles recorded from one experiment.

Table 3.1 The effect of intravenous injection of adrenomedullin (1 nmol/kg BW) on mean arterial blood pressure.

	MAP after AM injection (mmHg)					
0 min	30 sec	1 min	5 min	10 min	30 min	60 min
98.43 ±3.90	68.57[a] ±0.84	73.14[a] ±1.74	89.00[b] ±5.42	91.86[c] ±4.97	95.43 ±4.12	96.14 ±4.03

Values are mean ± SEM, n = 7.

MAP, mean arterial pressure; AM, adrenomedullin

[a] $p < 0.001$, [b] $p<0.01$, [c] $p<0.05$ compared to the basal values.

Table 3.2 The effect of intravenous injection of adrenomedullin (1 nmol/kg BW) on heart rate.

	HR after AM injection (beats/min)					
0 min	30 sec	1 min	5 min	10 min	30 min	60 min
407 ±13	404 ±13	406 ±12	406 ±14	404 ±11	406 ±12	409 ±12

Values are mean ± SEM, n = 7.

HR, heart rate; AM, adrenomedullin

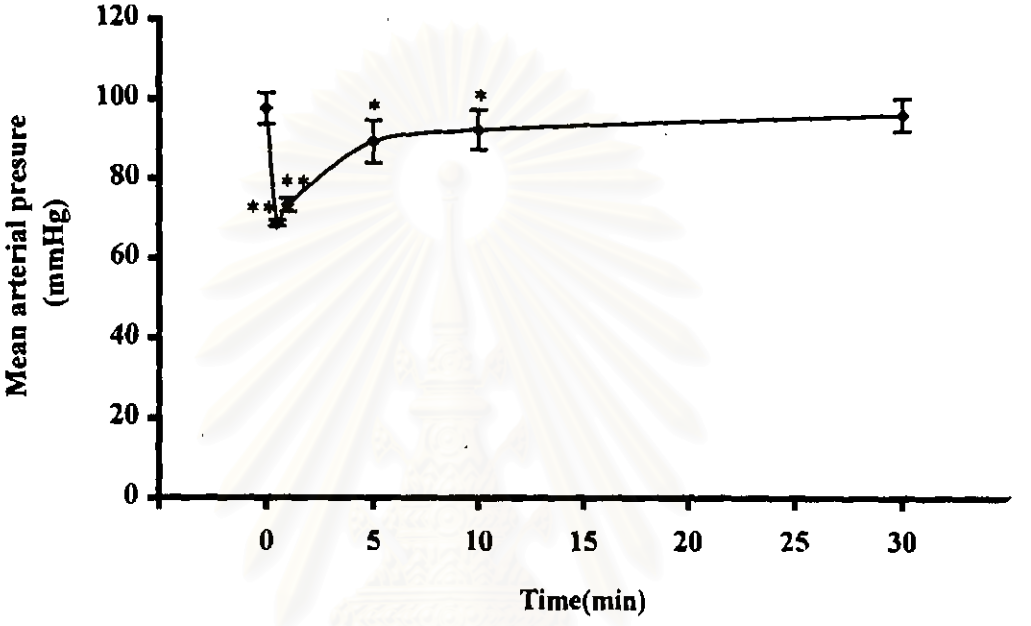

Figure 3.1 Time course of mean arterial pressure (MAP) following intravenous administration of adrenomedullin(1 nmol/kg BW).Values are mean ± SEM.n=7. **p<0.001, *p<0.05 vs basal values.

Table 3.3 The effect of topical application of AM (10^{-7} M) on arteriolar diameter of rat skin microcirculation.

	Arteriolar diameter after topical application of AM (μm)					
	0 min	1 min	3 min	5 min	10 min	20 min
A_2	56.80 ±2.08	58.80 ±2.59	59.60* ±2.80	59.40 ±2.83	58.60 ±2.67	58.20 ±2.69
A_3	35.00 ±3.83	38.60 ±5.10	40.40* ±5.49	38.60 ±5.17	38.20 ±5.03	37.40 ±4.80

Values are mean ± SEM, n = 5. AM, adrenomedullin

A_2 : 2nd order arteriole (diameter = 50-70μm)

A_3 : 3rd order arteriole (diameter = 25-50μm)

* $p < 0.05$ vs basal values

Table 3.4 The percent change from baseline diameter of rat skin microcirculation after topical application of AM (10^{-7} M)

	% Changes after topical application of AM				
	1 min	3 min	5 min	10 min	20 min
A_2	3.42 ±1.17	4.78* ±1.34	4.45 ±1.80	3.07 ±1.51	2.35 ±1.51
A_3	9.44 ±3.33	14.15* ±3.55	9.14 ±2.96	8.15 ±2.64	5.93 ±2.21

Values are mean ± SEM, n = 5. AM, adrenomedullin

A_2 : 2nd order arteriole (diameter = 50-70μm)

A_3 : 3rd order arteriole (diameter = 25-50μm)

* $p<0.05$ vs basal values

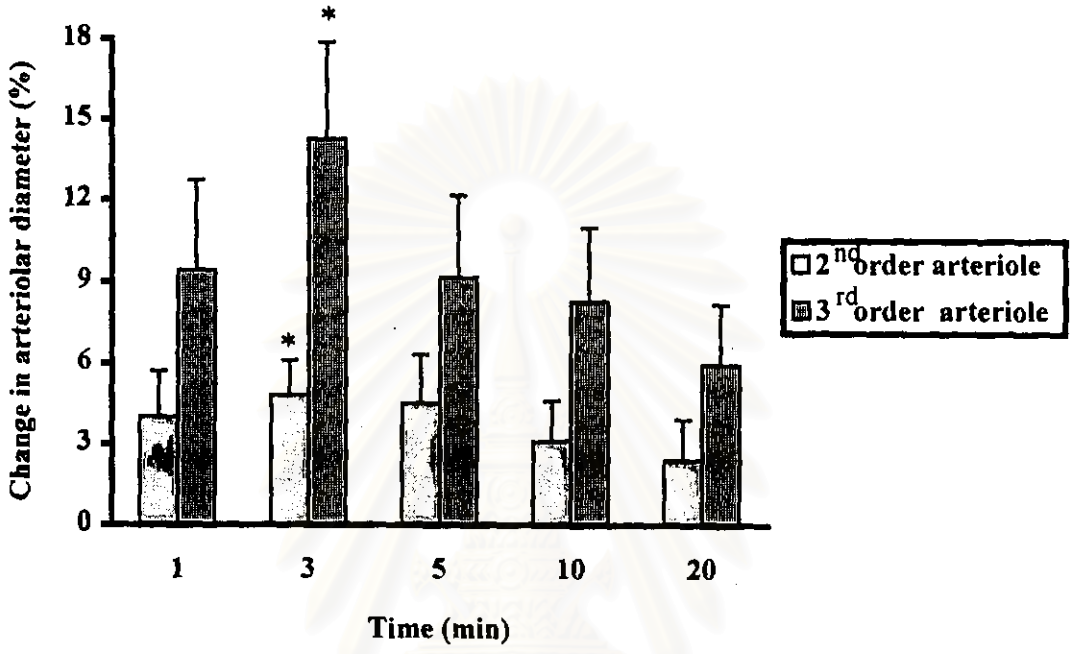

Figure 3.2 Percent change of arteriolar diameter with time after the topical application of adrenomedullin at 10^{-7} M on rat skin microcirculation. Values are mean ± SEM.n=5.*$p<0.05$ vs basal values.

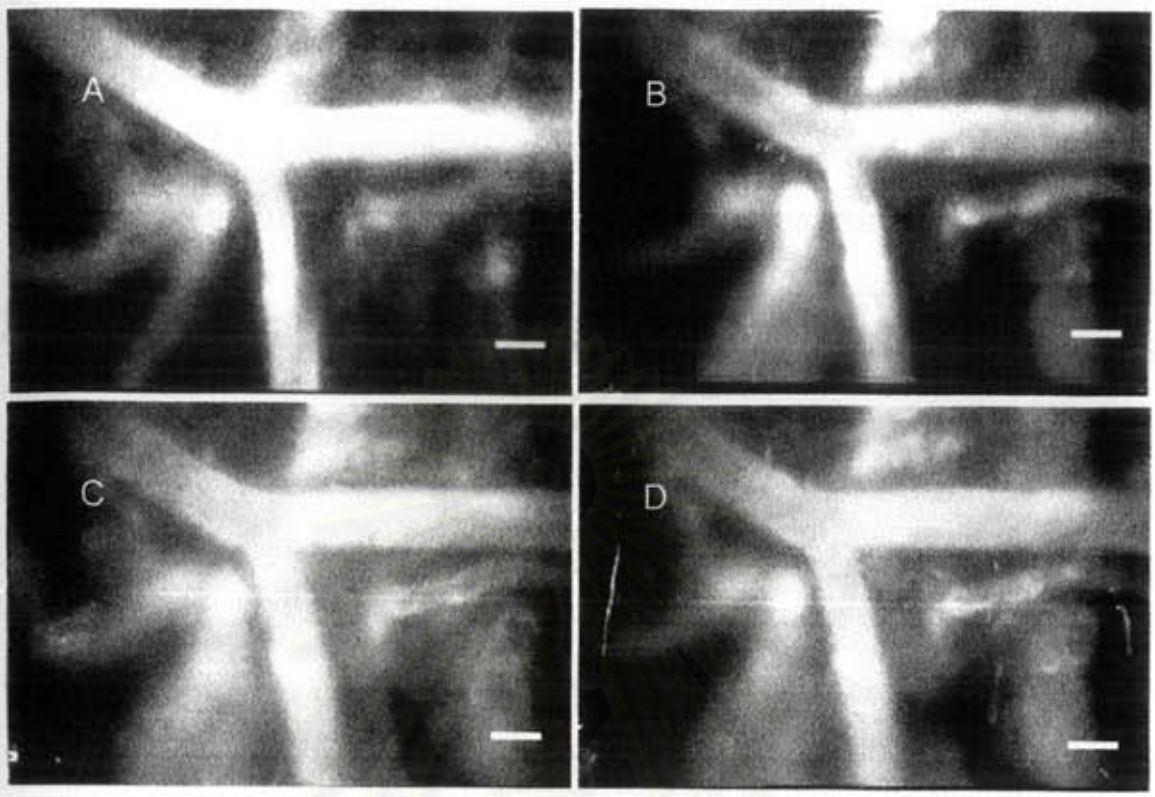

Figure 3.3 The example of intravital fluorescent videoscopic images of the second - and the third - order arterioles recorded from one experiment.

A) Before the topical application of AM (10^{-7} M).
B) 1 min after the application.
C) 3 min after the application.
D) 5 min after the application.
Significant dilatation of the skin microvessels is demonstrated.
Bar = 50 μm.

III. The isolated heart model: the effect of AM on cardiac performance and coronary circulation

The data of all parameters were continuously recorded by the isolated heart apparatus used in our study. The evaluated data not only can be displayed on the overview screen during the experiment but also can be stored in a data file on the harddisk for further analysis. The results of the experiments carried out on spontaneously beating isolated perfused rat hearts preparation were presented in Table 3.5. The percent changes from baseline values of each parameter were shown in Table 3.6.

When AM (20 μg) was injected into the heart via an aortic cannulation, cardiac contraction ($+dP/dT_{max}$) and cardiac relaxation ($-dP/dT_{max}$) decreased whereas coronary blood flow (CBF) and heart rate (HR) increased. AM slightly but significantly decreased both cardiac contraction and cardiac relaxation. The percentage decrease in $+dP/dT_{max}$ and $-dP/dT_{max}$ at 5 minute after the administration of AM is 3.72±1.14% and 4.91±1.54%, respectively (Table 3.6, Figure 3.4, Figure 3.5). The reduction in $+dP/dT_{max}$ was in proportional with the reduction in $-dP/dT_{max}$ as seen from the ratio of $-dP/dT_{max}/+dP/dT_{max}$ (or Q ratio) which the significant change was not observed throughout the experiment (Table 3.5).

AM at the dose of 20 μg also caused the increase in HR. An increase in HR occurred at 1 minute after the injection and reached its peak at 5 minute. The magnitude of increase in HR at 5 minute is 9.48±1.35% (Table 3.6 and Figure 3.6). After 5 min, the degree of tachycardia induced by AM injection began to reduce.

CBF started to rise immediately after the injection, reaching peak values at 3 minute. This effect persisted for at least 20 minute (Figure 3.7). The maximum increase in CBF was evidenced at 3 minute post-injection, the magnitude of increase is 18.93±0.63% (Table 3.6 and Figure 3.7). After 5 minute, the degree of coronary vasodilation as shown by the increase in CBF began to decline.

Electrocardiogram (EKG) of the isolated perfused rat hearts was also investigated and the results showed that EKG was not affected by the bolus injection of AM except that the rate of heartbeat increased (Figure 3.8). The continued presence of P wave and 1:1 correspondence of P and R wave in EKG tracing was observed throughout the experiment. The sinus tachycardia was determined from the time intervals between QRS complexes and was computed by the computer software as shown by the result of HR.

An injection of normal saline solution (vehicle for AM) equal to the volume of AM to the heart had no effect on the measured parameters (Table 3.7).

Table 3.5 The effect of bolus injection of adrenomedullin (20 μg) on cardiac performance in isolated perfused rat heart

	Cardiac parameters after bolus injection of AM					
	0 min	30 sec	1 min	3 min	5 min	10 min	20 min
CBF (ml/min)	7.00 ±0.27	8.18[a] ±0.28	8.24[a] ±0.28	8.32[a] ±0.29	8.28[a] ±0.33	8.06[b] ±0.41	7.68[b] ±0.34
HR (beats/min)	278 ±6	283 ±4	296[b] ±7	301[b] ±7	305[b] ±9	296[b] ±7	289[c] ±7
$+dP/dT_{max}$ (mmHg/sec)	1740 ±78	1717 ±77	1728 ±79	1702[c] ±81	1678[c] ±89	1686 ±88	1690 ±87
$-dP/dT_{max}$ (mmHg/sec)	941 ±55	907 ±48	919 ±54	914 ±61	897[c] ±62	921 ±61	914 ±56
Q	0.54 ±0.02	0.53 ±0.02	0.53 ±0.02	0.54 ±0.02	0.53 ±0.02	0.55 ±0.02	0.54 ±0.02

Values are mean ± SEM, n = 5. CBF, coronary blood flow; HR, heart rate; $+dP/dT_{max}$, left ventricular contraction; $-dP/dT_{max}$, left ventricular relaxation; Q, ratio of $-dP/dT_{max}$ / $+dP/dT_{max}$.

[a] $p < 0.001$, [b] $p<0.01$, [c] $p<0.05$ vs baseline values.

Table 3.6 The percent change from baseline values of cardiac parameters after the bolus injection of adrenomedullin (20 μg) in isolated perfused rat heart

	% changes after bolus injection of AM					
	30 sec	1 min	3 min	5 min	10 min	20 min
CBF	+16.93[a] ± 1.06	+17.80[a] ± 0.91	+18.93[a] ± 0.63	+18.26[a] ± 0.73	+14.92[b] ± 1.82	+ 9.65[b] ± 1.87
HR	+ 2.17 ± 1.25	+ 6.41[b] ± 0.93	+ 8.21[b] ± 1.40	+ 9.48[b] ± 1.35	+ 6.48[b] ± 1.39	+ 3.84[c] ± 1.28
$+dP/dT_{max}$	− 1.36 ± 0.82	− 0.72 ± 0.96	− 2.26[c] ± 0.63	− 3.72[c] ± 1.14	− 3.23 ± 1.29	− 2.92 ± 1.07
$-dP/dT_{max}$	− 3.40 ± 1.76	− 2.36 ± 1.04	− 3.08 ± 1.36	− 4.91[c] ± 1.54	− 2.10 ± 3.76	− 2.83 ± 2.54
Q	− 1.91 ± 1.99	− 1.93 ± 1.61	− 1.59 ± 1.10	− 1.59 ± 1.10	+ 0.60 ± 1.19	− 0.37 ± 0.37

Values are mean ± SEM, n = 5. CBF, coronary blood flow; HR, heart rate; $+dP/dT_{max}$, left ventricular contraction; $-dP/dT_{max}$, left ventricular relaxation; Q, ratio of $-dP/dT_{max}$ / $+dP/dT_{max}$.

[a] $p < 0.001$, [b] $p<0.01$, [c] $p<0.05$ vs baseline values.

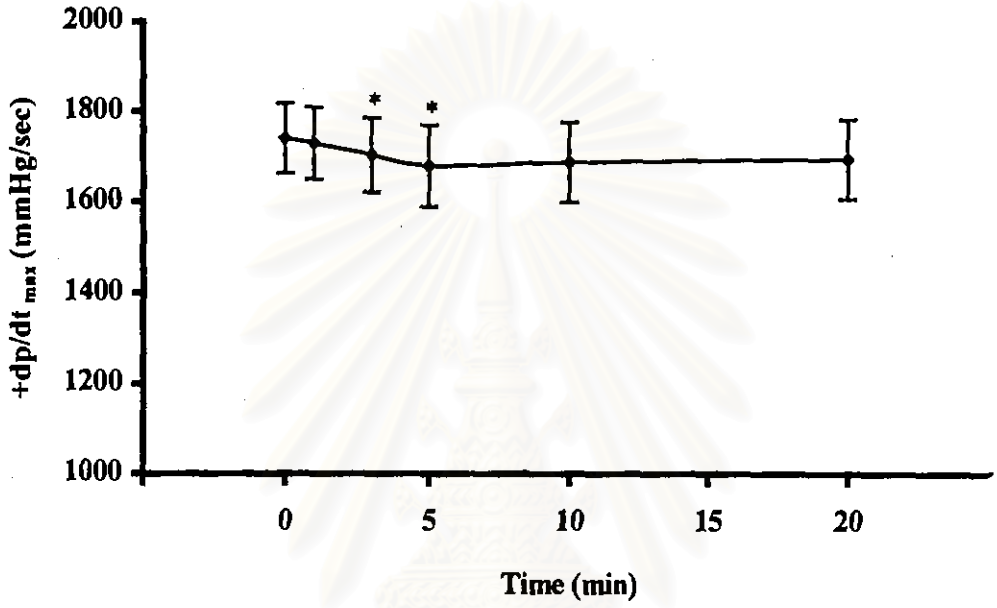

Figure 3.4 Time course of miximum rate of cardiac contraction ($+dp/dt_{max}$) following bolus injection of adrenomedullin, 20 μg, in isolated perfused rat hearts. Values are mean ± SEM. n=5. *$p<0.05$ vs basal values.

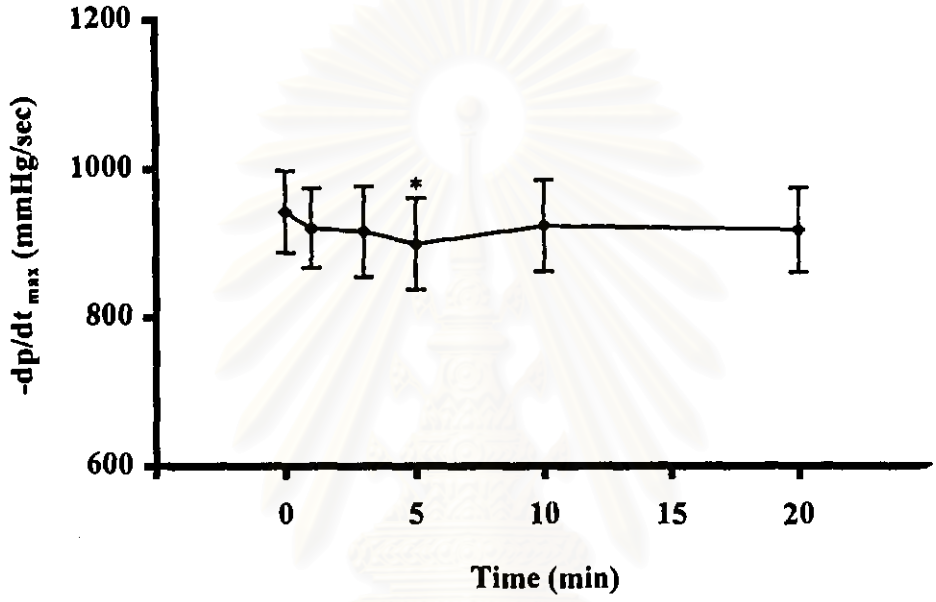

Figure 3.5 Time course of miximum rate of cardiac relaxation ($-dp/dt_{max}$) following bolus injection of adrenomedullin, 20 μg, in isolated perfused rat hearts. Values are mean ± SEM. n=5. *$p<0.05$ vs basal values.

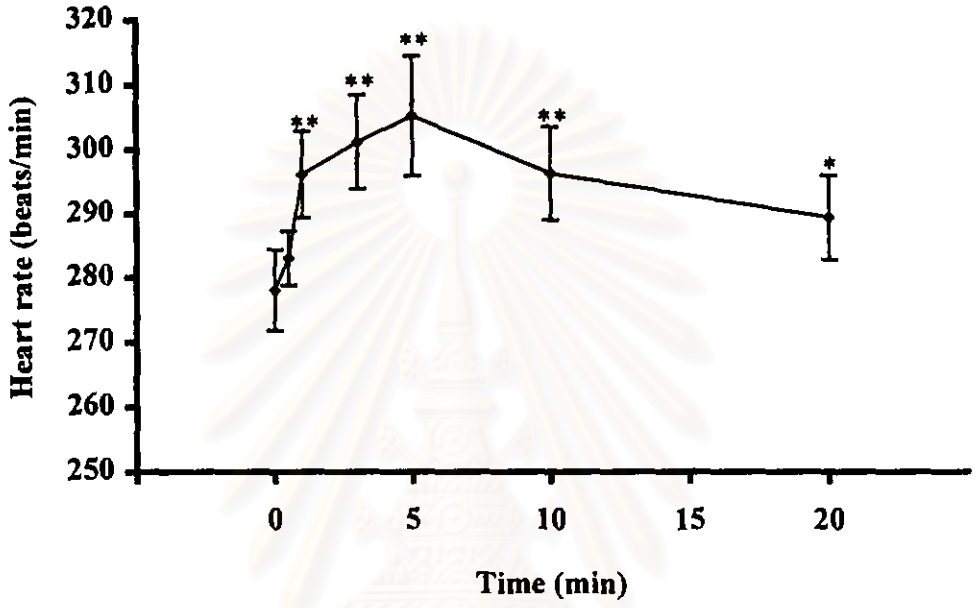

Figure 3.6 Time course of heart rate following bolus injection of adrenomedullin, 20 μg, in isolated perfused rat hearts. Values are mean ± SEM. n=5. **p<0.01, * p<0.05 vs basal values.

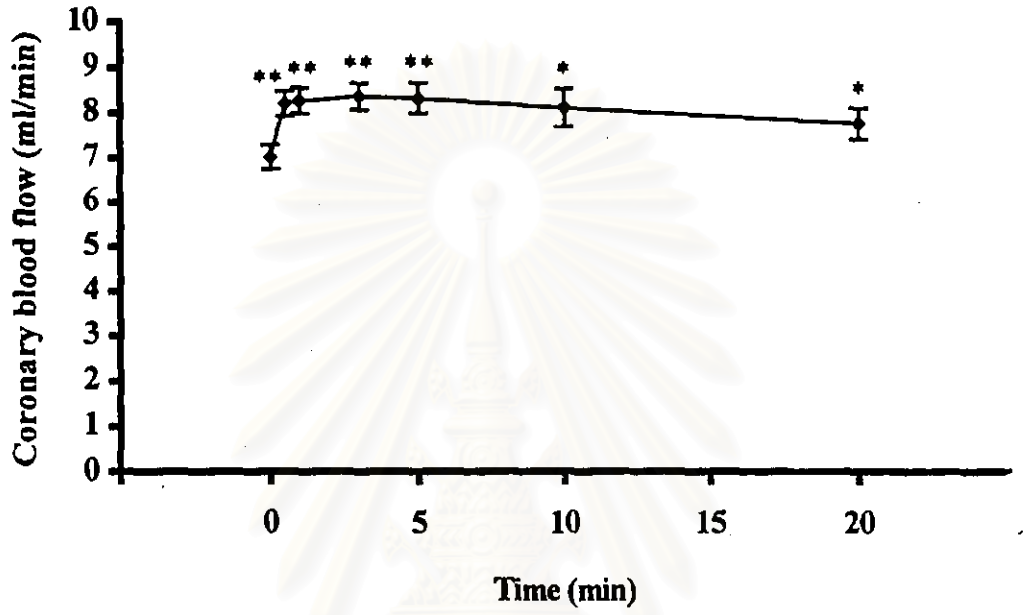

Figure 3.7 Time course of coronary blood flow following bolus injection of adrenomedullin, 20 μg, in isolated perfused rat hearts. Values are mean ± SEM.n=5.** $p<0.001$, * $p<0.01$ vs basal values.

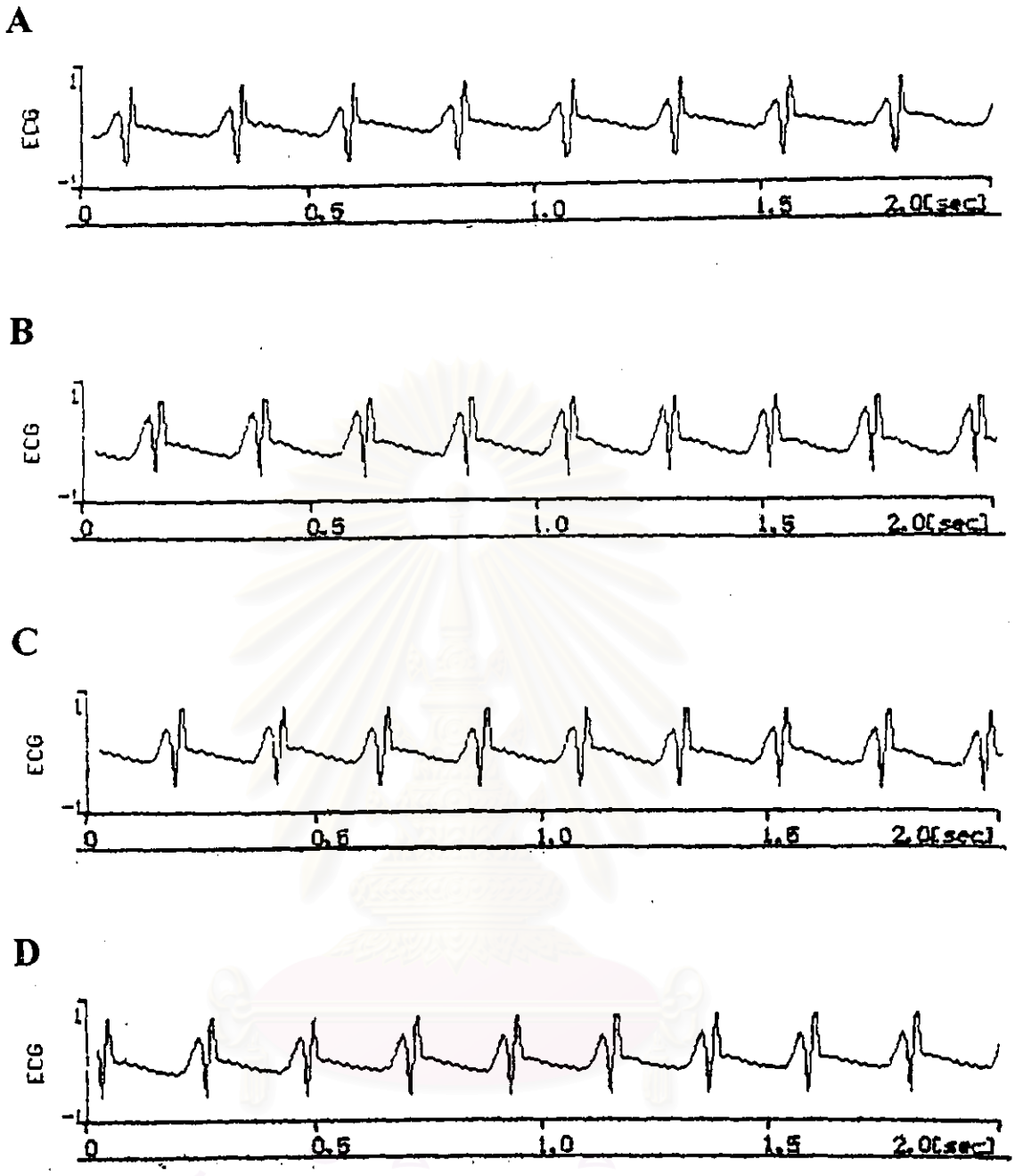

Figure 3.8 The example of electrocardiogram recorded from one experiment.

A) Before injection of AM (20μg)
B) 1 min after the injection
C) 3 min after the injection
D) 5 min after the injection

Electrocardiogram is normal after the injection of AM except that the rate of heartbeat increases (sinus tachycardia). Heart rate is about 300 beats per minute instead of 275 beats per minute as seen before the injection.

Table 3.7 The Effect of bolus injection of normal saline solution on cardiac performance in isolated perfused rat heart

	Cardiac parameters after bolus injection of NSS					
	0 min	1 min	3 min	5 min	10 min	20 min
CBF (ml/min)	7.24 ±0.22	7.30 ±0.21	7.22 ±0.23	7.22 ±0.23	7.16 ±0.25	7.14 ±0.27
HR (beats/min)	284 ±8	277 ±6	283 ±10	284 ±9	281 ±9	275 ±10
$+dP/dT_{max}$ (mmHg/sec)	1754 ±94	1742 ±102	1766 ±115	1758 ±112	1774 ±113	1785 ±129
$-dP/dT_{max}$ (mmHg/sec)	1037 ±76	1000 ±87	1049 ±88	1040 ±92	1059 ±105	1053 ±107
Q	0.59 ±0.02	0.57 ±0.03	0.59 ±0.02	0.59 ±0.03	0.59 ±0.03	0.59 ±0.02

Values are mean ± SEM, n = 5. NSS, normal saline solution; CBF, coronary blood flow; HR, heart rate; $+dP/dT_{max}$, left ventricular contraction; $-dP/dT_{max}$, left ventricular relaxation; Q, ratio of $-dP/dT_{max}$ / $+dP/dT_{max}$.

The effect of AM on ventricular cAMP accumulation

To examine whether cAMP is a second messenger for the cardiac and coronary action of AM, we measured cAMP accumulation in the ventricles of the isolated perfused rat hearts that were perfused and freeze - clamped at 3 min after the injection of saline or AM. The assay for cAMP content were performed as deseribed in "Methods". The result showed that in the isolated perfused rat hearts, AM at a concentration of 20 μg did not alter ventricular cAMP production. (saline : 434 ± 20 pmol/g tissue; AM : 417 ± 26 pmol/g tissue) (Table 3.8).

Table 3.8 The effect of bolus injection of adrenomedullin (20μg) on ventricular cAMP accumulation in isolated perfused rat heart.

Group	Ventricular cAMP accumulation (pmol/g tissue)
Saline (n = 5)	434±20
AM (n = 6)	417±26

Values are mean ± SEM

AM: adrenomedullin

IV. The isolated heart model: the mechanism of action of AM on coronary vasodilation

Role of the endothelium in the coronary response to AM

The coronary vasodilator effect of AM, 20 μg, was investigated without and with endothelial degradation by intracoronary infusion with 0.2 ml of 0.5% Triton X-100. In our preliminary experiments with beating heart, the infusion of Triton X-100 was followed by a marked decrease in myocardial performance. To avoid the variations in coronary tone associated with these metabolic changes, the series of experiments were carried out after cardiac arrested by high K^+ perfusate.

In order to re-check the effect of Triton X-100 on endothelium, the bolus injection of bradykinin (0.1μg), the endothelium-dependent vasodilator, was used. And also to check that the coronary smooth muscle was able to vasodilate in response to an endothelium-independent dilator, a bolus of sodium nitroprusside (15 μg) was injected at the end of each Triton X-100 treated experiment. Table 3.9 and Table 3.10 revealed the effect of treatment with Triton X-100 on coronary response to bradykinin and sodium nitroprusside. In the arrested heart without Triton X-100 administration, bradykinin significantly increased coronary blood flow from 6.64±0.23 ml/min to 7.55±0.22 ml/min (13.84±0.54%), thus reflecting coronary vasodilatation. This vasodilatation was not observed in the Triton X-100 treated group. However, coronary vasodilatation by sodium nitroprusside, reflected by an increase in CBF from 2.57±0.20 ml/min to 2.94±0.23 ml/min (14.13±2.50%) was still observed after Triton X-100 treatment. The

comparison of percent changes in coronary blood flow following bolus injection of bradykinin and sodium nitroprusside was shown in Figure 3.9.

Table 3.11 and Table 3.12 summarized the results of coronary response to AM with and without Triton X-100 administration. In the arrested heart without Triton X-100 treatment, AM significantly increased coronary blood flow from 6.62±0.40 ml/min to 7.66±0.52 ml/min (15.70± 0.91%). The physical damage of endothelium by Triton X-100 was shown to attenuate the effect of AM-induced coronary vasodilation, coronary blood flow increased only 4.64±1.50% (from 2.10±0.09 ml/min to 2.20±0.09 ml/min).

Table 3.9 The effect of treatment with Triton X-100 on coronary response to bradykinin (0.1μg) and sodium nitroprusside (15 μg) in isolated perfused arrested rat hearts.

Group	CBF (ml/min)
Without Triton X-100	
Control	6.64±0.23
BK (0.1 μg)	7.55±0.22**
With Triton X-100	
Control	2.55±0.14
BK (0.1 μg)	2.54±0.19
Control	2.57±0.20
SNP (15 μg)	2.94±0.23*

Values are mean ± SEM, n = 4

CBF, coronary blood flow; BK, bradykinin;

SNP, sodium nitroprusside

* $p < 0.05$, * * $p < 0.001$ vs control values

Table 3.10 The percent change from baseline value of coronary blood flow following bolus injection of bradykinin (0.1 μg) in endothelium-intact and endothelium-damaged coronary arteries and following bolus injection of sodium nitroprusside (15μg) in endothelium-damaged coronary arteries of isolated perfused arrested rat heart.

Group	Δ% (CBF)
Endothelium-intact	
BK	13.84±0.54**
Endothelium-damage	
BK	-0.61±1.84
SNP	+14.13±2.50*

Values are mean ± SEM., n = 4. Δ% (CBF), change in coronary blood flow as percentage of baseline values; BK, bradykinin; SNP, sodium nitroprusside.

* $p < 0.05$, ** $p < 0.001$ vs its baseline values.

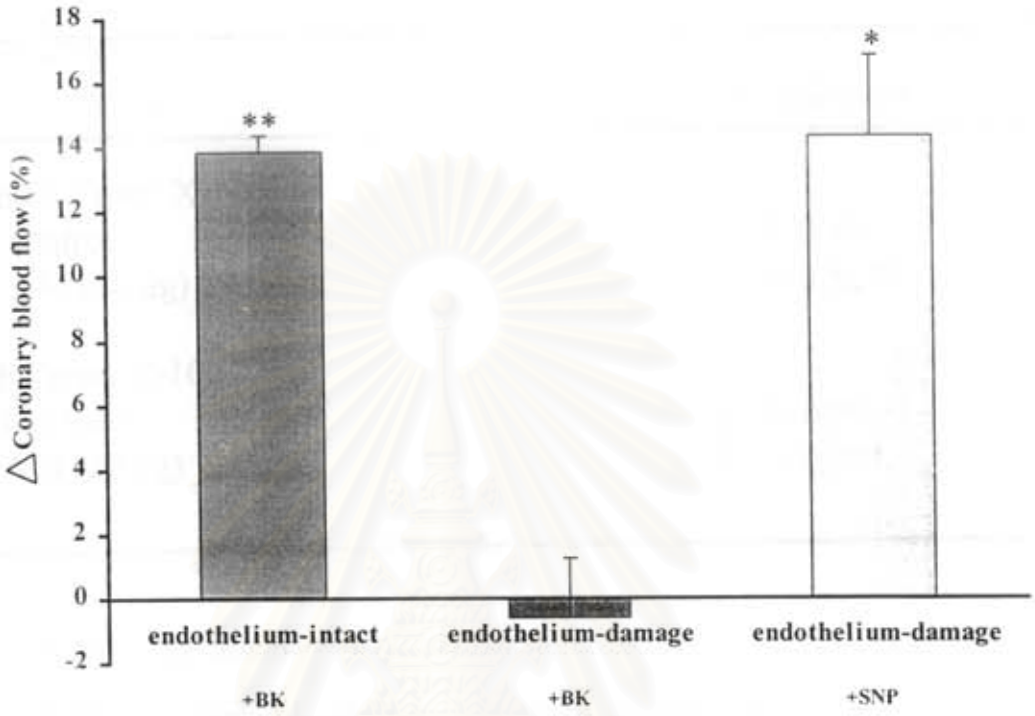

Figure 3.9 Comparison of precente change in coronary blood flow following bolus injection of bradykinin (BK), 0.1 μg, in endothelium-intact and endothelium damaged coronary arteries and following bolus inject of sodium nitroprusside (SNP), 15 μg, in endothelium-damaged coronary anterior of isolated perfused arrested rat heart.Values are mean ± SEM.n=4.*p<0.05,**p<0.001 vs baseline values.

Table 3.11 The effect of treatment with Triton X-100 on coronary response to adrenomedullin (20 μg) in isolated perfused arrested rat hearts.

Group	CBF (ml/min)
Without Triton X-100	
control	6.62±0.40
AM (20 μg)	7.66±0.52**
With Triton X-100	
Control	2.10±0.09
AM (20 μg)	2.20±0.09*

Values are mean ± SEM., n = 5

CBF, coronary blood flow; AM, adrenomedullin

* $p < 0.05$, * * $p < 0.001$ vs control values

Table 3.12 The percent changes from baseline value of coronary blood flow following bolus injection of adrenomedullin (20 μg) in endothelium-intact and endothelium damaged coronary arteries of isolated arrested rat hearts.

Group	Δ% (CBF)
Endothelium-intact	+15.70±0.91
Endothelium-damage	+4.64±1.50*

Values are mean ± SEM., n = 5. Δ% (CBF), changes in coronary blood flow as percentage of baseline values.
* $p < 0.001$ vs endothelium-intact.

Role of the cyclooxygenase pathway in coronary response to AM

Infusion of indomethacin, an inhibitor of cyclooxygenase pathway, decreased coronary blood flow from 7.32±0.41 ml/min to 5.72±0.37 ml/min (Table 3.13). Subsequent injection of AM produced the increase in coronary blood flow from 5.72±0.37 ml/min to 6.66±0.46, 6.72±0.43 and 6.84±0.45 ml/min at 1, 3, and 5 minute after the injection, respectively (Table 3.14, and Figure 3.10). Change in coronary blood flow was +19.62±2.46% at 3 minute post injection. Whereas in control group (AM alone), the change in coronary blood flow was +18.93±1.42% (Table 3.15 and Figure 3.13).

Role of the NO pathway in coronary response to AM

Continuous infusion of L-NNA, an inhibitor of NO synthesis, induced a signifieant decrease in coronary blood flow from 7.60±0.40 ml/min to 5.78±0.35 ml/min (Table 3.13). After 40 minute of L-NNA infusion, AM injection promoted an increase in coronary blood flow from 5.78±0.35 ml/min to 6.64±0.41, 6.64±0.39, and 6.66±0.41 ml/min at 1, 3, and 5 minute after the injection, respectively (Table 3.14, and Figure 3.11). However, the increase in coronary blood flow (+14.90±1.22%) was smaller when compare to control group (+18.93±1.42%) (Table 3.15 and Figure 3.13)

Role of the K_{ATP} channels in coronary response to AM

Infusion of glibenclamide, an inhibitor of K_{ATP} channels, significantly reduced coronary blood flow from 7.34±0.38 ml/min to 5.08±0.46 ml/min (Table 3.13). Injection of AM after the continuous infusion of glibenclamide still caused the increase in coronary blood flow from 5.08±0.46 ml/min to 5.32±0.50, 5.36±0.50, and 5.34±0.52 ml/min at 1, 3, and 5 minute post injection, respectively (Table 3.14, and Figure 3.12). However, coronary vasodilatory response to AM was markedly decreased. The response to AM was +5.46±0.67% with and +18.93±1.42% without glibenclamide (Table 3.15 and Figure 3.13).

Table 3.13 Changes of coronary blood flow produced by continuous infusion of indomethacin, N^G - nitro - L - arginine, glibenclamide in isolated perfused rat heart

Group	CBF (ml/min)
Control	7.32±0.41
Indo	5.72±0.37*
Control	7.60±0.40
L-NNA	5.78±0.35*
Control	7.34±0.38
Glib	5.08±0.46*

Values are mean ± SEM after 40 min infusion, n = 5

CBF, coronary blood flow; Indo, indomethacin;

L-NNA, N^G-nitro-L-arginine; Glib, glibenclamide

* $p < 0.05$ vs pre-infusion (control values)

Table 3.14 Changes in coronary blood flow following bolus injection of adrenomedullin (20 μg) alone and during the pharmacological blockade

Group	CBF (ml/min)						
	0 min	30 sec	1 min	3 min	5 min	10 min	20 min
AM	7.00 ±0.27	8.18[a] ±0.28	8.24[a] ±0.28	8.32[a] ±0.29	8.28[a] ±0.33	8.06[b] ±0.41	7.68[b] ±0.34
AM+Indo	5.72 ±0.37	6.66[b] ±0.46	6.72[b] ±0.43	6.84[b] ±0.45	6.88[b] ±0.44	6.64[b] ±0.43	6.46[b] ±0.43
AM+L-NNA	5.78 ±0.35	6.60[a] ±0.38	6.64[a] ±0.41	6.64[a] ±0.39	6.66[a] ±0.41	6.52[b] ±0.43	6.37[b] ±0.42
AM+Glib	5.08 ±0.46	5.32[b] ±0.47	5.32[b] ±0.50	5.36[b] ±0.50	5.34[c] ±0.52	5.22 ±0.52	5.16 ±0.50

Values are mean ± SEM., n = 5

CBF, coronary blood flow; AM, adrenomedullin;

Indo, indomethacin; L-NNA, N^G-Nitro-L-arginine;

Glib, glibenclamide.

[a] $p < 0.001$, [b] $p<0.01$, [c] $p<0.05$ vs its baseline value (0 min)

Table 3.15 Changes in coronary blood flow at 3 minute following injection of adrenomedullin (20μg) alone and during the pharmacological blockade in isolated perfused rat heart

Group	CBF (ml/min)		
	Baseline	3 min	Δ%
AM	7.00±0.27	8.32±0.29	+18.93±1.42
AM + Indo	5.72±0.37	6.84±0.45	+19.62±2.46
AM + L-NNA	5.78±0.35	6.64±0.39	+14.90±1.22*
AM + Glib	5.08±0.46	5.36±0.50	+ 5.46±0.67**

Values are mean ± SEM, n = 5

Δ%, changes in coronary blood flow as percentage of baseline values.

CBF, coronary blood flow; AM, adrenomedullin; Indo, indomethacin; L-NNA, N^G-Nitro-L-arginine; Glib, glibenclamide.

* $p < 0.05$, ** $p<0.001$ vs AM alone.

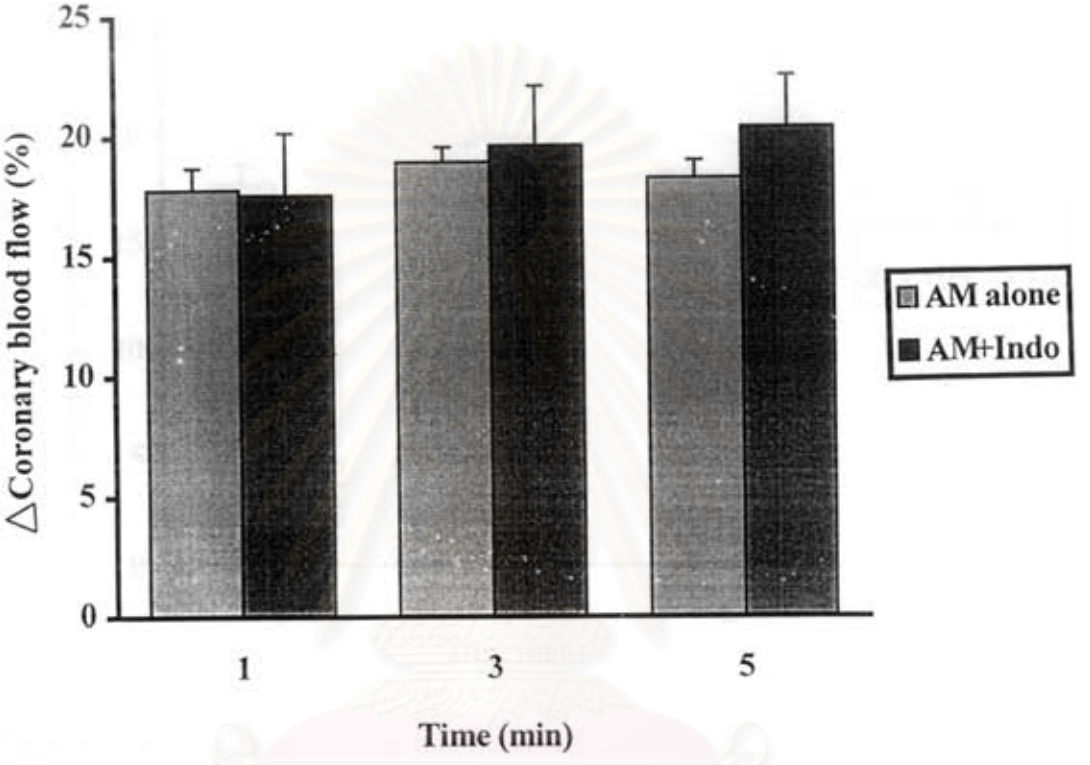

Figure 3.10 Percent change in coronary blood flow following bolus injection of adrenomedullin (AM) alone and during continuous infusion of indomethacin (Indo). Values are mean ± SEM. n=5.

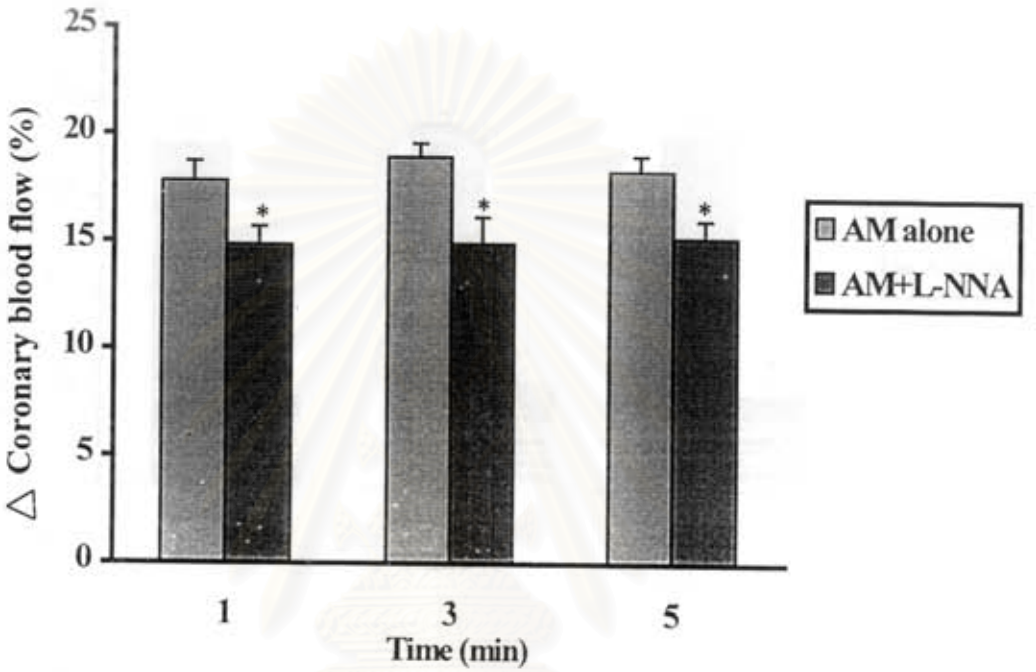

Figure 3.11 Percent change in coronary blood flow following bolus injection of adrenomedullin (AM) alone and during continuous infusion of N^G-Nitro-L-arginine (L-NNA).Values are mean ± SEM. n=5. *p<0.05 vs AM alone.

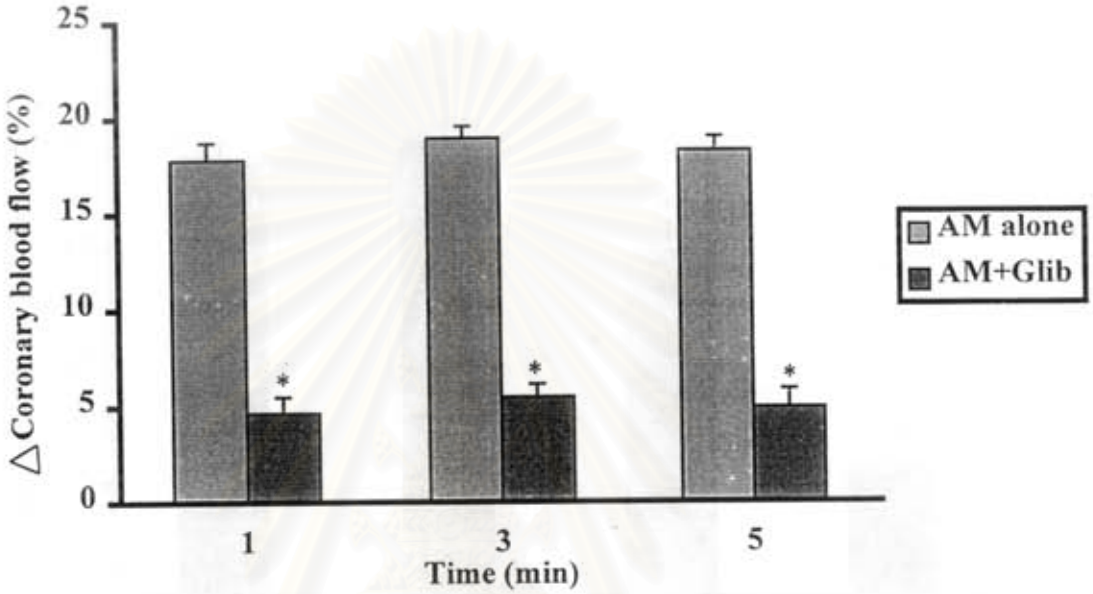

Figure 3.12 Percent change in coronary blood flow following bolus injection of adrenomedullin (AM) alone and during continuous infusion of glibenclamide (Glib). Values are mean ± SEM.n=5.*p<0.001 vs AM alone.

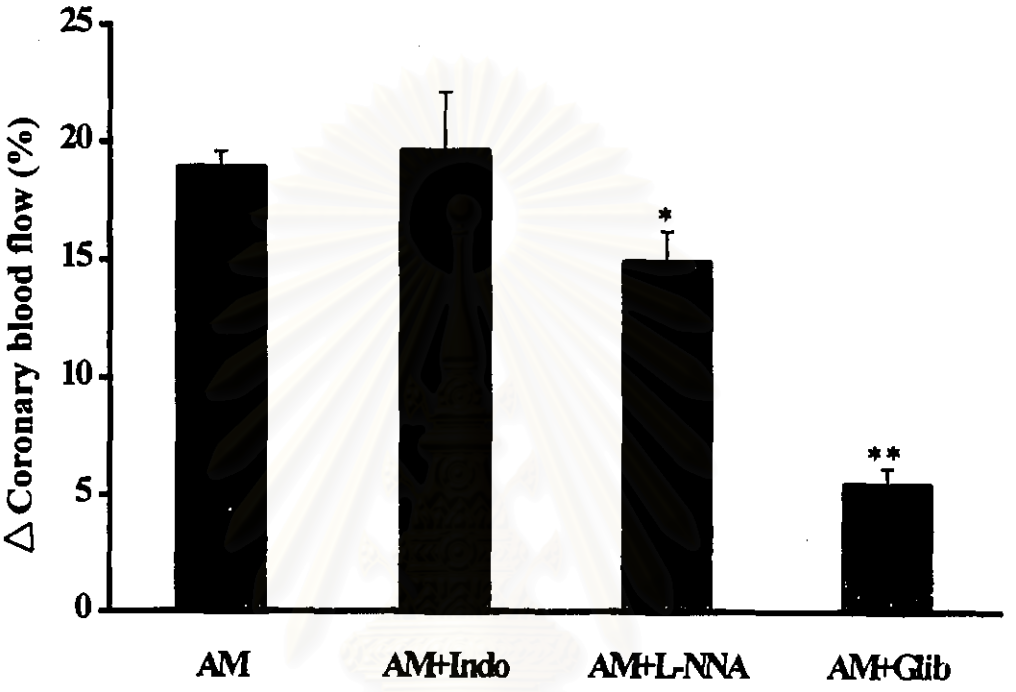

Figure 3.13 Comparison of percent change in coronary blood flow following bolus injection of adrenomedullin (AM) alone, or during continuous infusion of indomethacin (Indo), N^G-Nitro-L-arginine (L-NNA), Glibenclamide (Glib). Values are Mean + SEM after 3 min of AM injection.n=5.*$p<0.05$, **$p<0.001$ vs AM alone.