RESULTS

PART I

CARDIOPROTECTIVE EFFECT OF TIMOLOL AND PRENYLAMINE IN ACUTE MYOCARDIAL ISCHEMIA IN ANAESTHETIZED CATS:

I- Electrophysiological Parameter:

a) S-T Segment elevation:

1- Control group:

In this group of animals (n=5), which were given saline (Nacl. 0.9%) only 15 min. before ligation of left anterior desending coronary artery (LAD), the S-T segment was nearly isoelectric (0.05 MV), at 0 time (immediately before ligation of LAD). Then the S-T segment tended to be elevated immediately after ligation of LAD, and reached maximum elevation at 30 min. after ligation ranging from 0.5 MV to 1 MV with a mean of 0.7 ± 0.09 MV. When the mean value of S-T segment elevation at 30 min. after ligation of LAD was compared to that at 0 time, there was a highly significant increase ($t=6.9$ and $P<0.01$). S-T segment remained elevated to the end of the experiment at 300 min. and ranged between 0.45 MV and 1 MV with a mean of 0.67 ± 0.07 MV. when the mean value of S-T segment at end of experiment was compared to mean S-T segment level at 0 time, it was found to be elevated significantly ($t=6.2$ and $P < 0.01$). On the other hand, when the S-T segment

level at 30 min. was compared to that level at 300 min., there was a statistically insignificant decrease (t= 0.2 and P > 0.05) Fig. (1) and Tables (1,4).

2- Timolol-treated group :

In this group of cats (n=5), timolol maleate (25 ug/kg i.v) was given 15 min. prior to ligation of LAD. S-T segment was nearly isoelectric before ligation of LAD (at 0 time), it ranged between 0 and 0.05 MV with a mean of 0.03 $\pm$ 0.01 MV. At 30 min. after ligation of LAD, it was raised to reach a level between 0.05 and 0.8 MV with a mean of 0.35$\pm$0.13 MV. When the mean level of S-T segment was compared to that at 0 time there was a significant increase (t=3.25, P<0.05). On the other hand, when when the mean S-T segment value at 30 min.of this group was compared to that value of control group, there was a statistically significant decrease (t=2.33 and P<0.05). At 300 min. after ligation of LAD, S-T segment ranged between 0.05 and 0.3 MV with a mean of 0.13$\pm$0.04 MV. When this mean value of S-T segment elevation at 300 min was compared to that value at 0 time, there was an insignificant elevation (t=2 and P>0.05), also, when the mean level of S-T segment at 300 min was compared to that at 30 min., it was insignificantly changed (t=1.7 and P>0.05). On the

other hand, when the mean value of S-T segment elevation at 300 min. of this group was compared to that value at 300 min of control group, a highly significant reduction of elevation of S-T segment in the timolol-treated group was found ($t=6$ and $P<0.01$), Fig. (2) and Tables (2,4).

3- Prenylamine-treated group :

In this group of animals (n=5), prenylamine lactate (3mg/kg i.v.) was given 15 min. prior to ligation of LAD. S-T segment was isoelectric before ligation of LAD (at 0 time) and it ranged between 0 and 0.05 MV with a mean of 0.01 ± 0.01 MV. At 30 min. after ligation of LAD, it was found to range between 0.2 and 0.6 MV with a mean of 0.46 ± 0.07 MV. when the mean value of S-T segment was compared to that at 0 time, there was a highly significant increase ($t=5.6$ and $P<0.01$). But, when this level of S-T segment at 30 min. of this group was compared to that of control group at 30 min., it was insignificantly changed ($t=2$ and $P>0.05$). At 300 min after ligation of LAD, S-T segment ranged between 0.05 and 0.25 MV with a mean of 0.15 ± 0.04 MV. when the mean elevation of the S-T segment at 300 min. was compared to that at 0 time, it was found to be statistically significant ($t=3.35$ and $P<0.05$). Also, when the mean value of S-T segment at

300 min, was compared to that at 30 min., there was a significant decrease ($t=3.26$ and $P<0.05$). Moreover, when the mean level of S-T segment elevation at 300 min. of this group was compared with mean S-T segment elevation at 300 min. of control group, there was highly significant reduction of S-T segment elevation of the prenylamine-treated group ($t=5.7$ and $P<0.01$). Fig. (3) and Tables (3, 4).

The mean ($\pm$S.E.) S-T segment elevation in the groups of cats investigated is illustrated in form of a bar chart in Fig. (4).

Fig. (1): E.C.G. tracing (Lead V_3) of control group of cats with coronary ligation:

A- Control tracing ,normal sinus rhythm at 0 time (before occlusion of left anterior descending coronary artery; LAD):

1- Heart rate: 188 beats/minute.

2- S-T segment elevatin: isoelectric.

B- E.C.G. tracing at 30 minute from occlusion of LAD:

1- Heart rate: 188 beats/min.

2- S-T segment elevation: 1MV.

C- E.C.G. tracing at 60 min. from occlusion of LAD:

1- Heart rate: 177 beats/min.

2- S-T segment elevation: 1MV.

D- E.C.G. tracing at 120 min. after occlusion of LAD:

1- Heart rate: 177 beats/min.

2- S-T segment elevation: 1MV.

E- E.C.G. tracing at 240 min. after occlusion of LAD:

1- Heart rate: 166 beats/min.

2- S-T segment elevation: 0.9 MV.

F- E.C.G. tracing at 300 min. after occlusion of LAD:

1- Heart rate: 166 beats/min.

2- S-T segment elevation: 0.85 MV.

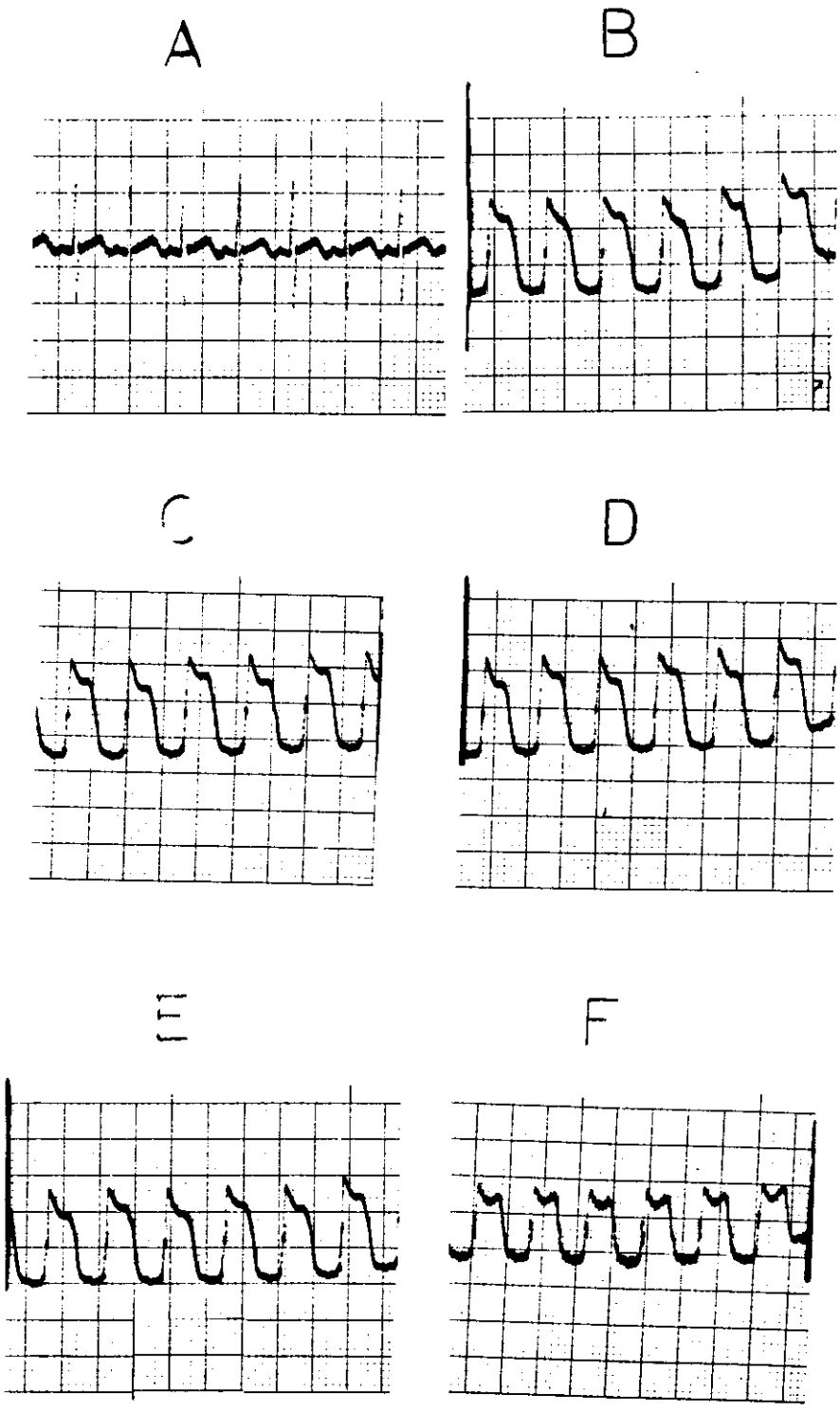

A
B
C
D
E
F

Fig. (2): E.C.G. tracing (Lead V_3) of timolol-treated cats with coronary ligation:

A- Control tracing, normal sinus rhythm. at 0 time (before occlusion of LAD):

1- Heart rate: 157 beats/min.

2- S-T segment elevation: isoelectric.

B- Timolol maleate 25 ug/kg was injected i.v. 15 min. prior to ligation of LAD:

1- Heart rate: 157 beats/min.

2- S-T segment elevation: isoelectric.

C- E.C.G. tracing at 30 min. after occlusion of LAD.

1. Heart rate: 136 beats/min.

2- S-T segment elevation: 0.35 MV.

D- E.C.G. tracing at 60 min. after occlusion of LAD:

1- Heart rate: 79 beats/min.

2- S-T segment elevation: 0.35 MV.

E- E.C.G. tracing at 120 min. after occlusion of LAD:

1- Heart rate: 77 beats/min.

2- S-T segment elevation: 0.3 MV.

F- E.C.G. tracing at 240 min. after occlusion of LAD:

1- Heart rate: 75 beats/min.

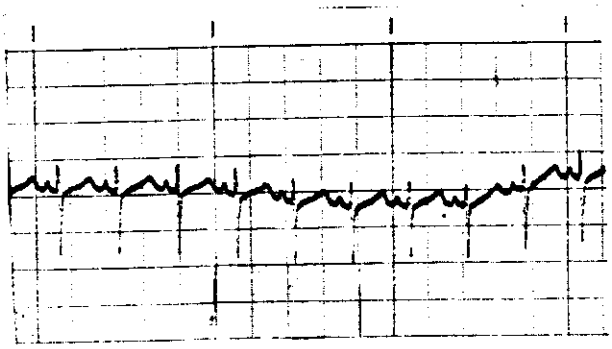
2- S-T segment elevation: 0.3 MV.

G- E.C.G. tracing at 300 min. after occlusion of LAD:

1- Heart rate: 75 beats/min.

2- S-T segment elevation: 0.15 MV.

A



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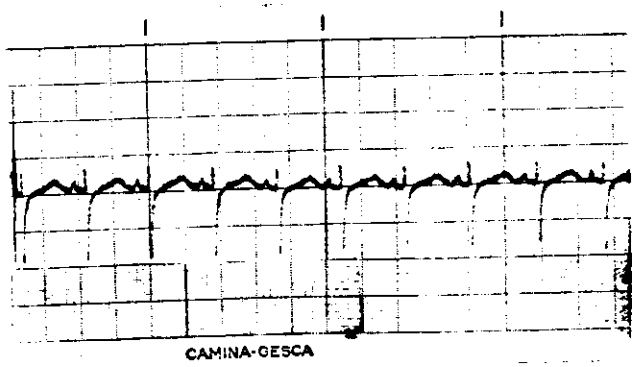

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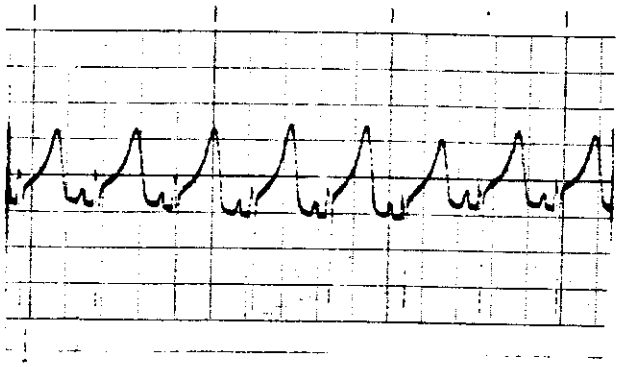

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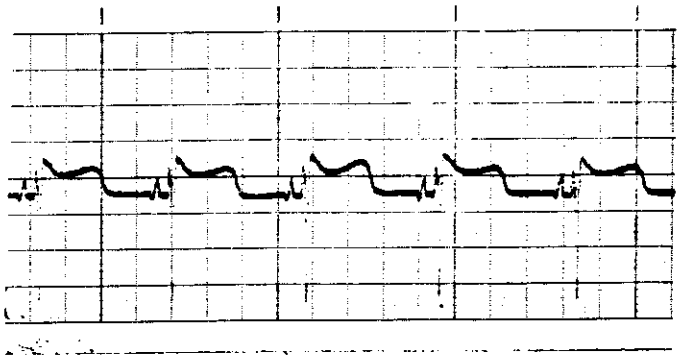
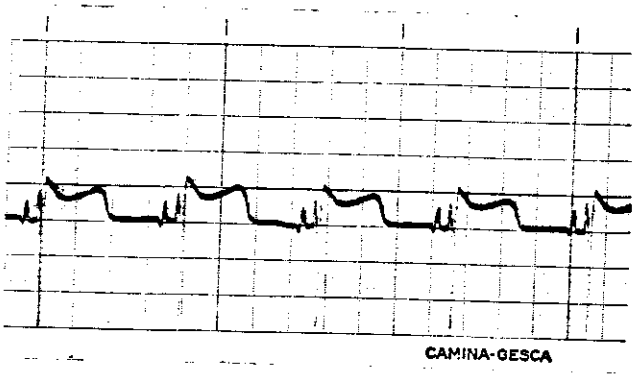


E



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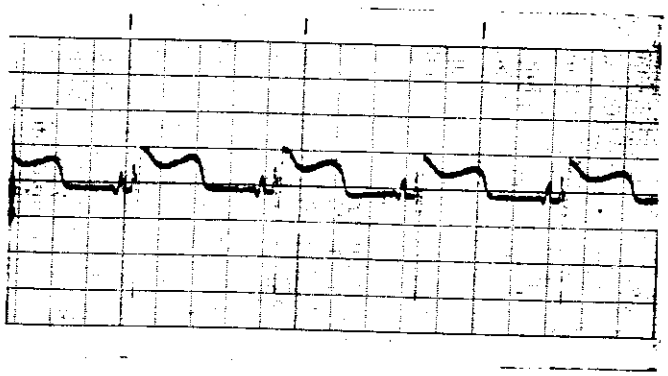

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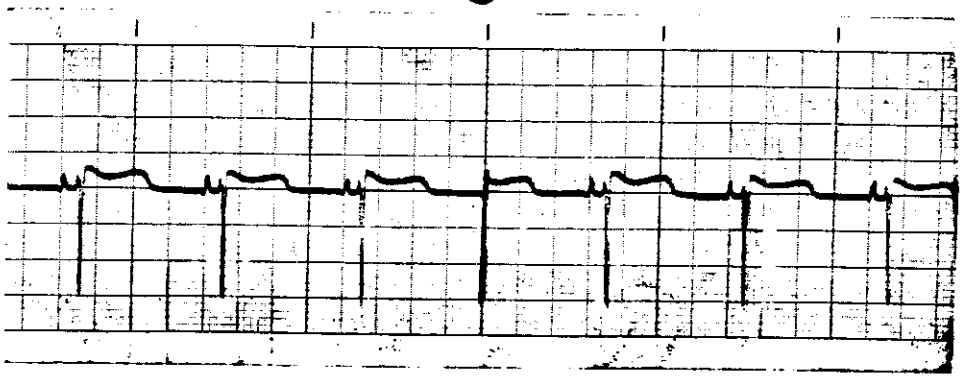


Fig. (3): E.C.G. tracing (Lead V_3) of prenylamine-treated cats with coronary ligation:

A- Control tracing, normal sinus rhythm at 0 time (before ligation of LAD):

1- Heart rate: 150 beats/min.

2- S-T segment elevation: isoelectric.

B- Prenylamine 3 mg/kg was injected i.v., 15 min prior to ligation of LAD:

1- Heart rate: 115 beats/min.

2- S-T segment elevation: isoelectric.

C- E.C.G. tracing at 30 min. after occlusion of LAD:

1- Heart rate: 100 beats/min.

2- S-T segment elevation: 0.6 MV.

D- E.C.G. tracing at 60 min. after ligation of LAD:

1- Heart rate: 88 beats/min.

2- S-T segment elevation: 0.5 MV.

E- E.C.G. tracing at 120 min. after ligation of LAD:

1- Heart rate: 83 beats/min.

2- S-T segment elevation: 0.4 MV.

F- E.C.G. tracing at 240 min. after ligation of LAD:

1- Heart rate: 83 beats/min.

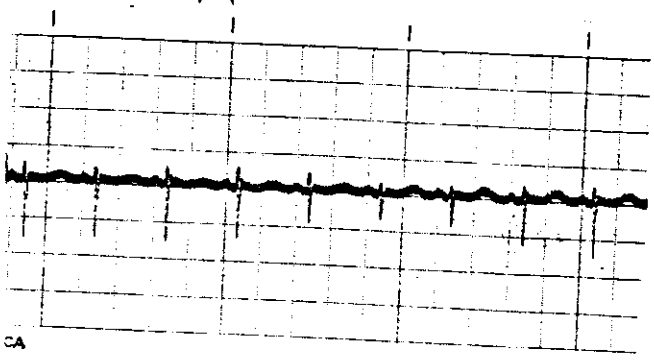
2- S-T segment elevation: 0.35 MV.

G- E.C.G. tracing at 300 min. after ligation of LAD:

1- Heart rate: 56 beats/min.

2- S-T segment elevation: 0.15 MV.

A



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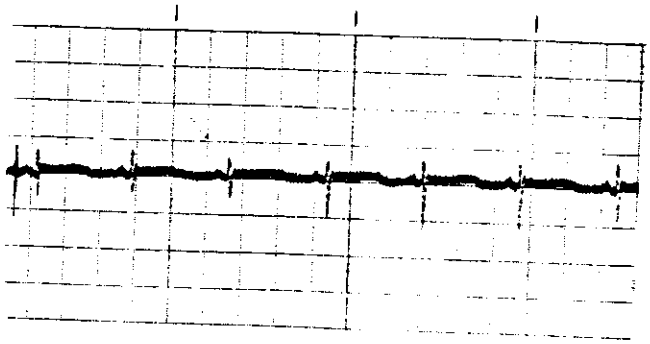

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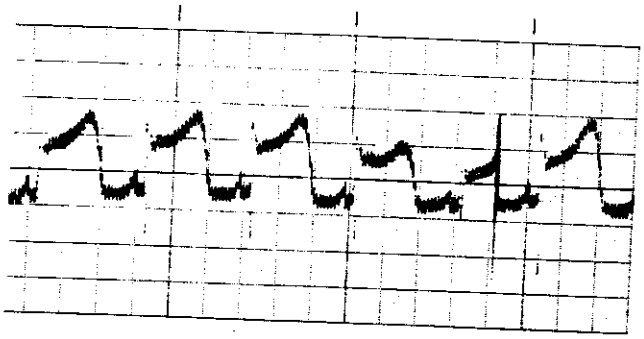

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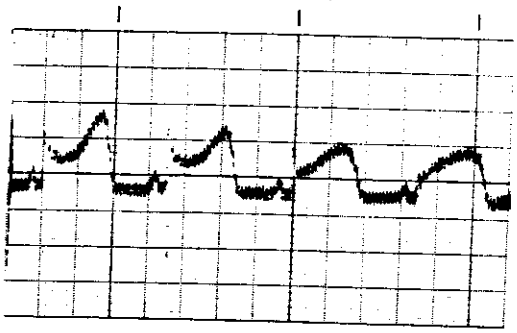

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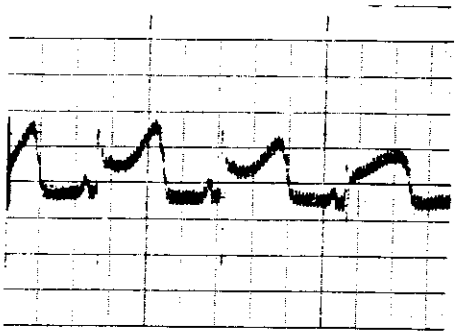
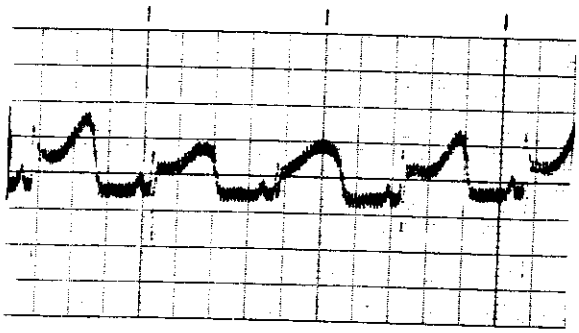


F



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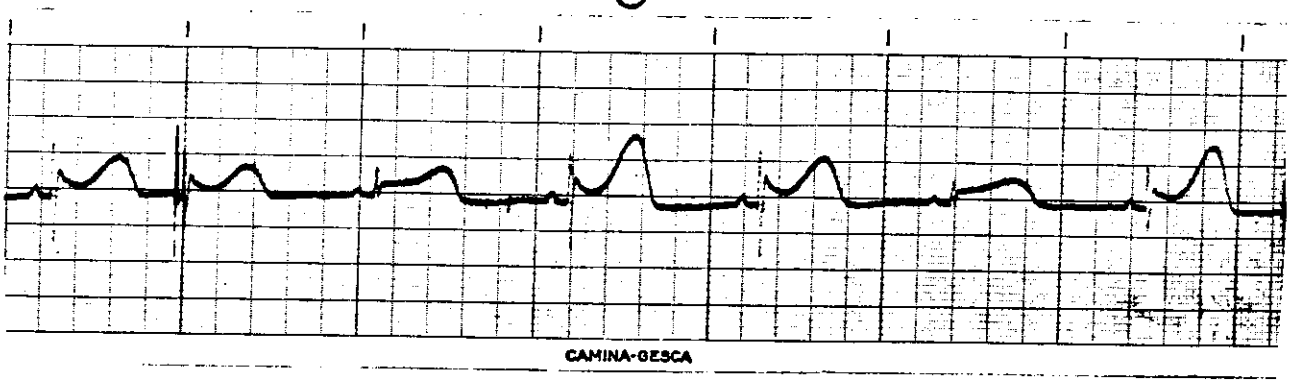


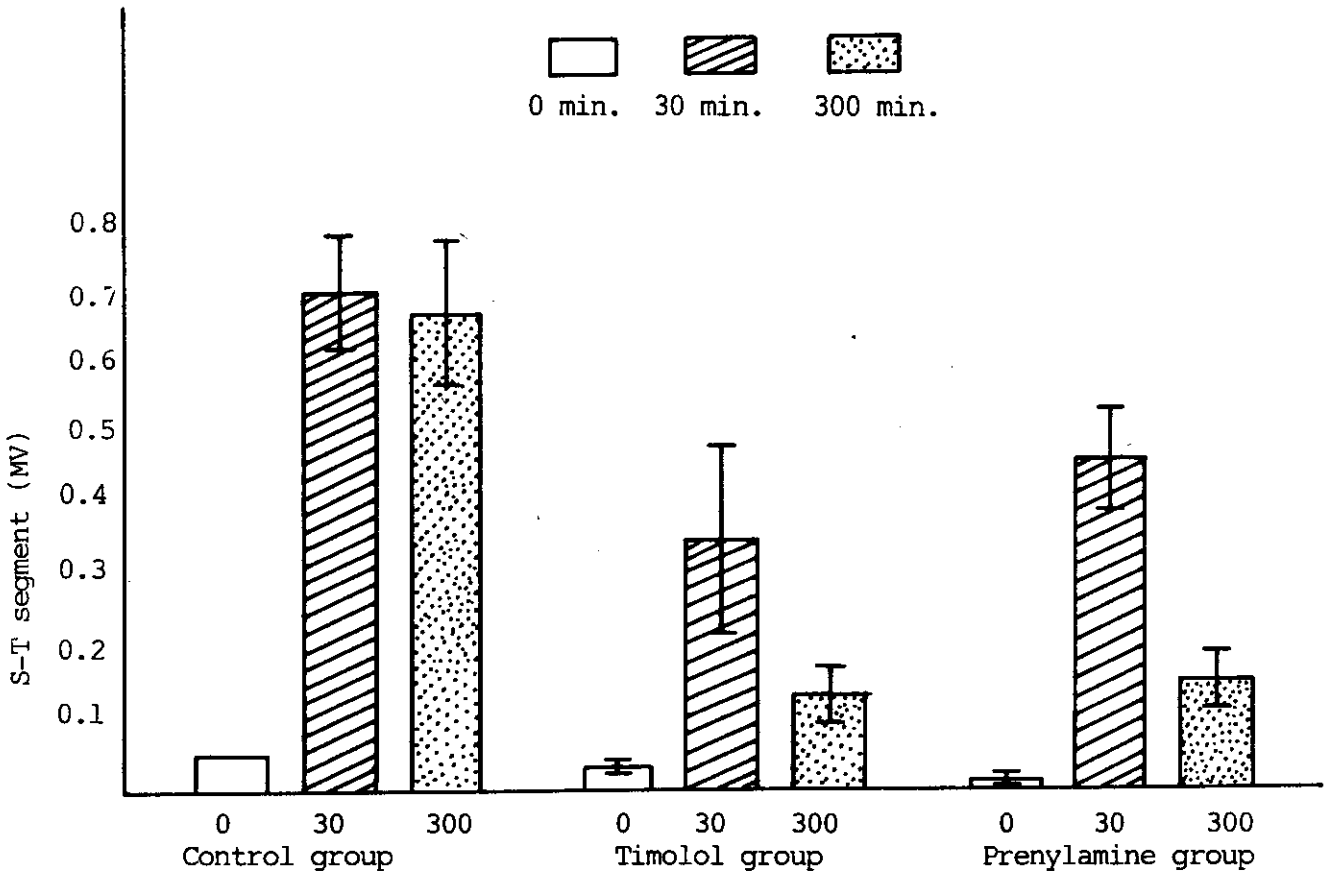


Fig. (4): S-T segment elevation after ligation of LAD in control, timolol, and prenylamine treated cats.

0 min. = immediately before ligation of LAD.

30 min. = at 30 min. after ligation of LAD.

300 min. = at 300 min. after ligation of LAD

n = 5

Table (1)

S-T segment elevation in control group.

Exp. No.	S-T segment elevation (MV)*		
	at 0 time	at 30 min. after ligation of LAD	at 300 min. after ligation of LAD
1	0.05	0.5	0.5
2	0.05	0.7	0.7
3	0.05	0.8	0.8
4	0.05	1	0.85
5	0.05	0.5	0.5
Mean	0.05	0.7	0.67
S.E.M.	0.0	±0.09	±0.07

at 0 time = immediately before ligation of LAD.

* S-T segment elevation above isoelectric line.

Table (2)

S-T segment elevation in timolol-treated group.

Exp. No.	S-T segment elevation (MV)*		
	at 0 time	at 30 min. after ligation of LAD	at 300 min. after ligation of LAD
1	0.05	0.05	0.05
2	0.0	0.15	0.05
3	0.05	0.35	0.15
4	0.0	0.4	0.1
5	0.05	0.8	0.3
Mean	0.03	0.35	0.13
S.E.M.	±0.01	±0.13	±0.04

at 0 time = immediately before ligation of LAD.

* S-T segment elevation above isoelectric line.

Table (3)

S-T segment elevation in prenylamine group.

Exp. No.	S-T segment elevation (MV)*		
	at 0 time	at 30 min. after ligation of LAD	at 300 min. after ligation of LAD
1	0.0	0.2	0.05
2	0.0	0.6	0.15
3	0.05	0.4	0.05
4	0.0	0.6	0.25
5	0.0	0.5	0.25
Mean	0.01	0.46	0.15
S.E.M.	±0.01	±0.07	±0.04

at 0 time = immediately before ligation of LAD.

* S-T segment elevation above isoelectric line.

Table (4)

Statistical significance of ST segment changes in timolol and prenylamine treated cats compared to control group.

Mean S-T segment elevation ± S.E. (MV)								
Control group			Timolol group			Prenylamine group		
At 0 time	at 30 min.	at 300 min.	At 0 time	at 30 min.	at 300 min.	At 0 time	at 30 min.	at 300min.
0.05 ± 0	0.7 ± 0.09	0.67 ± 0.07	0.03 ± 0.01	0.35 ± 0.13	0.13 ± 0.04	0.01 ± 0.01	0.46 ± 0.07	0.15 ± 0.04

P<0.01 — P>0.05

P<0.01

P<0.05 — P>0.05

P>0.05

P<0.01 — P<0.05

P<0.05

P<0.01

P>0.05

P<0.01

at 0 time = immediately before LAD ligation. at 30 Min.= at 30 min after ligation of LAD. at 300 Min. = at 300 min. after ligation of LAD.

P < 0.05 = significant, n = 5.

b) Heart rate:

1- Control group:

In this group, heart rate ranged between 125 and 190 beats/min. with a mean of 167±11 before occlusion of LAD. It was decreased 30 min. after ligation of LAD to range between 120 and 180 beats/min. with a mean of 159±11 beats/min. The difference between heart rate at 0 time and 30 min after occlusion of LAD was statistically insignificant (t= 0.5 and P>0.05). At 300 min. after ligation of LAD, heart rate ranged between 95 and 170 beats/min. with a mean of 144±13 beats/min. Also, there was no significant difference between heart rate at 0 time and 300 min. (t=1.3 and P>0.05), or between heart rate at 30 and 300 min. (t=0.9 and P>0.05) table (13).

2- Timolol-treated group:

In this group, heart rate at 0 time ranged between 150 and 250 beats/min. with a mean of 195±17. 30 min. after ligation of LAD, heart rate ranged between 100 and 150 beats/min. with a mean of 133±9 beats/min. When this value of heart rate at 30 was compared to that at 0 time there was a significant decrease [t=3.2 and P<0.05). At 300 min, the heart rate was found to range between 68 and 130 with a mean of 102±12. When this value of heart rate was compared to that at 0 time, there was highly signi-

ficant decrease (t= 4.4 and P<0.01). But there is no significant difference between heart rate at 30 and 300 min. (t=2.1 and P> 0.05), Table (13).

3- Prenylamine-treated group:

In this group, heart rate was found to range between 115 and 240 beats/min. with a mean of 172±16 beats/min before ligation of LAD. At 30 min. after occlusion of LAD, heart rate ranged between 88 and 182 beats/min. with a mean of 122±11 beats/min. there was a significant decrease of heart rate at 30 min. (t=2.9 and P<0.05). At 300 min. after ligation of LAD, heart rate was decreased and ranged between 60 and 150 beats/min. with a mean of 92±7 beats/min. Also there was a highly significant decrease of heart rate at 300 min. compared to that at 0 time (t=3.8 and P<0.01), but there was no significant difference between heart rate at 30 and 300 min. (t=1.9 and P>0.05), Table (13).

C- Mean arterial blood pressure :

1- Control group :

In this group, the mean arterial blood pressure was 155±13 mm/Hg before ligation of LAD, 145±11 mm/Hg at 30 min. after ligation of LAD and decreased to 140±9 mm/Hg at 300 min. after ligation of LAD. There was neither significant difference between the mean arterial blood pressure at 0 time and 30 min. ($t=0.56$ and $P>0.05$), nor between the mean arterial blood pressure at 0 time and 300 min. ($t=0.83$ and $P>0.05$). Also there was no significant difference between the mean arterial blood pressure at 30 min. and 300 min. ($t=0.37$ and $P>0.05$), Table (13).

2- Timolol treated group :

In this group, the mean arterial blood pressure was 202±18 mm/Hg at 0 time, decreased to 187±13 mm/Hg at 30 min. after ligation of LAD and decreased more to 172±15 at 300 min. after ligation of LAD. There was no significant decrease between the mean arterial blood pressure at 30 min. and at 0 time ($t= 0.83$ and $P>0.05$). But, there was a significant decrease of the mean arterial blood pressure at 300 min. Compared to that at 0 time ($t=2.27$ and $P<0.05$). Although there was no significant decrease of the mean arterial blood pressure between values at 30 and 300 min. ($t=0.88$ and $P>0.05$), Table (13).

3- Prenylamine group :

In this group, the mean arterial blood pressure was 205±14 mm/Hg at 0 time, 185±16 mm/Hg at 30 min. and decreased to 165±11 mm/Hg at 300 min. after ligation of LAD. There was neither significant decrease between the mean arterial blood pressure at 0 time and 30 min. ($t=1.86$ and $P > 0.05$) nor between the mean arterial blood pressure at 30 min. and 300 min. ($t = 1.9$ and $P > 0.05$), but, there was highly significant decrease of the mean arterial blood pressure at 300 min. compared to that at 0 time ($t=3.6$ and $P<0.01$), Table (13).

II- Biochemical Parameter :

1- Control group :

In this group, the serum creatine-phosphokinase (CPK) levels before ligation of LAD ranged between 76 and 102 u/L with a mean of 94+5 u/L. At 300 min. after ligation of LAD, serum CPK level ranged between 617 u/L and 957 u/L with a mean of 724+60 u/L. The mean level of CPK was about 8 times the initial value at 0 time and this increase found to be highly significant statistically when compared to mean CPK level before ligation of LAD ($t=10.4$ and $P<0.01$), Table (5, 8).

2- Timolol-treated group :

In this group of cats, serum CPK level at 0 time ranged between 73 and 115 u/L, with a mean of 91+8u/L. At 300 min. after ligation of LAD, serum CPK level ranged between 140 and 240 u/L with a mean of 195+17. This mean value of CPK at 300 min. was about two times the mean value at 0 time. Although there was a significant rise when compared to mean CPK at 0 time ($t=5.6$ and $P<0.01$), highly significant decrease was noticed when this mean value of CPK was compared to mean value of CPK at 300 min. in the control group. ($t=8.45$ and $P<0.01$), Table (6, 8).

3- Prenylamine-treated group :

In this group of cats, serum CPK level at 0 time before occlusion of LAD, ranged between 43 and 131 u/L with a mean of 72±15 u/L. At 300 min. after ligation of LAD, serum CPK level ranged between 124 and 281 u/L with a mean of 193±25 u/L. When the mean value of serum CPK level at 300 min was compared with that at 0 time, it was about 2.5 times the initial value and it was significantly raised ($t=4.17$ and $P<0.01$). But, when the mean value of CPK at 300 min. after ligation of LAD in this group was compared with mean CPK value at 300 min. in control group, there was a highly significant reduction of CPK level in prenylamine group ($t=7.17$ and $P<0.01$), Table (7, 8).

Fig. (5) is a bar chart illustrating mean (±S.E.) serum CPK activity before and after ligation of LAD in control group and in groups of cats pretreated with timolol (25 ug/kg) and prenylamine (3 mg/Kg).

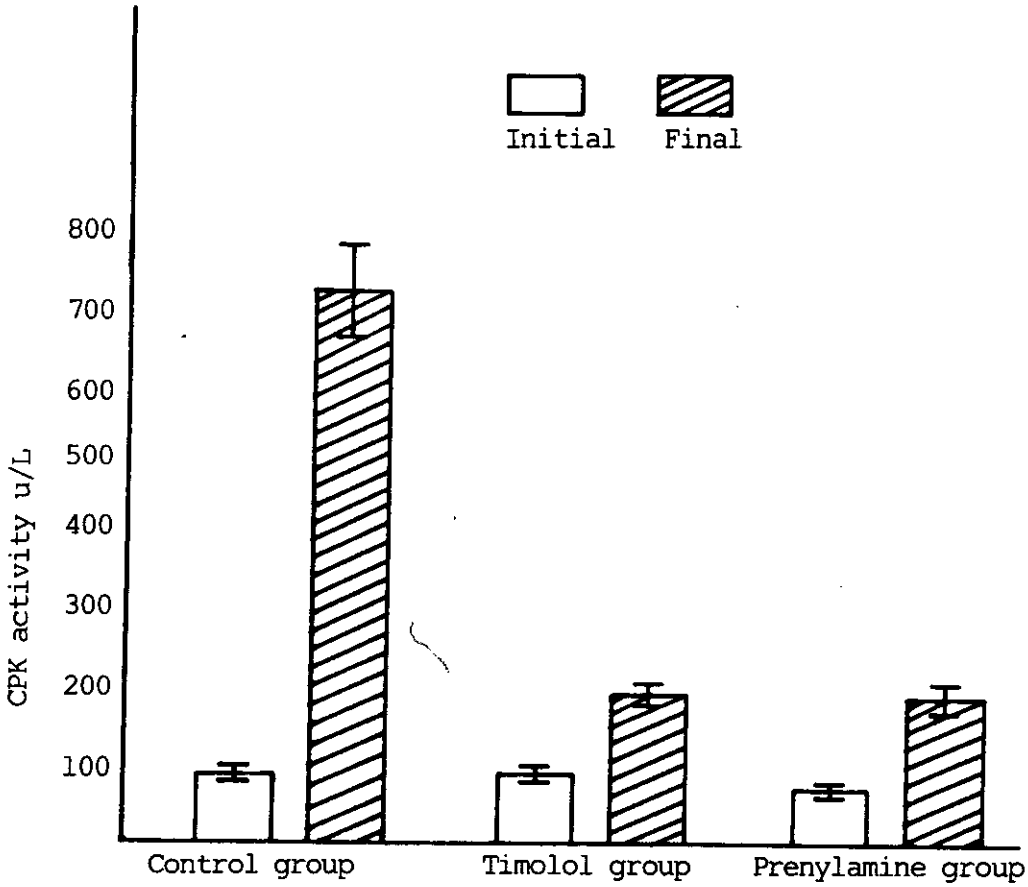


Fig. (5): Serum CPK activity in control, timolol and prenylamine treated cats with coronary ligation.

Initial = before occlusion of LAD.

Final = 5 hours after LAD ligation

n = 5

Table (5)

The serum CPK level (IU) in control group.

Exp. No.	Enzyme level at 0 time before ligation of LAD	Enzyme level at 300 min after ligation of LAD
1	95	617
2	101	711
3	76	657
4	102	957
5	97	676
mean ± S.E.	94±5 U/L	724±60 U/L

Table (6)

The serum CPK level (I.U) in timolol-treated group.

Exp. No.	Enzyme level at 0 time (before ligation of LAD)	Enzyme level at 300 min. after ligation of LAD
1	100	140
2	115	200
3	92	180
4	73	215
5	76	240
mean ± S.E.	91±8 U/L	195±17 U/L

Table (7)

The serum CPK level (I.U) in

prenylamine-treated group.

Exp. No.	Enzyme level at 0 time (before ligation of LAD)	Enzyme level at 300 min, after ligation of LAD
1	131	186
2	65	183
3	72	191
4	43	281
5	47	124
mean ± S.E.	72±15 u/L	193±25 u/L

When CPK level of prenylamine group at 0 time (72±15) was compared to CPK level of control group at 0 time (94±5), the difference was insignificant statistically (6=1.17 and P>0.05).

Table (8)

Statistical significance of serum CPK changes in timolol and prenylamine treated cats compared to control group.

Mean CPK level ± S.E. (U/L)					
Control group		Timolol group		Prenylamine group	
At 0 time	At 300 min.	At 0 time	At 300 min.	At 0 time	at 300 min.
94 ± 5	724 ± 60	91 ± 8	195 ± 17	72 ± 15	193 ± 25

P < 0.01 (Control group: At 0 time — At 300 min.)

P < 0.01 (Timolol group: At 0 time — At 300 min.)

P < 0.01 (Prenylamine group: At 0 time — at 300 min.)

P < 0.01 (Control group: At 300 min. — Timolol group: At 300 min.)

P < 0.01 (Control group: At 300 min. — Prenylamine group: at 300 min.)

At 0 time = immediately before LAD ligation.

At 300 min. = at 300 min. after LAD ligation.

P < 0.05 = significant. n = 5

III- Histochemical Parameter:

1- Control group:

In this group, the total surface area of the heart segments ranged between 920 mm^2 and 1040 mm^2 with a mean of 995.8±22 mm^2. While the infarct surface area ranged between 218 mm^2 and 426 mm^2 with a mean of 315.4±34 mm^2. The mean value of the infarct was 31.67% of mean value of the total surface area of all cardiac segments Fig. (6) and Table (9).

2- Timolol-treated group:

In this group, the total surface area of the heart segments ranged between 704 mm^2 and 1027 mm^2 with a mean of 908.2±58 mm^2. While, the surface area of the infarct ranged between 48 mm^2 and 165 mm^2 with a mean of 83.4±22 mm^2. The mean value of the infarct was 9.18% of mean value of the total surface area of all cardiac segments. When the mean value of the infarct was compared to that in control group, a highly significant reduction of the mean surface area of heart infarct occurred in timolol-treated group ($t=5.7$ and $P<0.01$) Fig. (7), and tables (10, 12).

3- Prenylamine-treated group:

In this group, the total surface area of the heart segments ranged between 759 mm^2 and 1065 mm^2 with a mean

of 922.2±56 mm^2. While the surface area of the infarct ranged between 73 mm^2 and 212 mm^2 with a mean of 119.2±25 mm^2. The mean value of the infarct represented 12.93% of mean value of the total surface area of heart segments. When the mean value of the heart infarct in this group was compared to that in control group, there was a highly significant reduction of the mean surface area of heart infarct in the prenylamine-treated group. ($t=4.6$ and $P<0.01$) Fig. (8), and Tables (11, 12).

The infarct surface area represented as percentage of the total surface area of all cardiac segments, in the control group, and in groups pre-treated with timolol and prenylamine is represented in form of a bar chart in Fig. (9).

Table (13) is a cumulative table showing S-T segment elevation, heart rate, M.A.B.P., CPK level and infarction surface area in the control group, and in animals pre-treated with timolol and prenylamine.

Fig. (6): Heart sections of control group stained by triphenyl tetrazolium stain, healthy tissue is stained chrimosen red, infarct tissue is pale.

Fig. (7): Heart sections of timolol treated group stained by triphenyl tetrazolium stain, healthy tissue is stained chrimosen red, infarct tissue is pale.

Fig. (8): Heart sections of prenylamine group, stained by triphenyle tetrazolium stain , healthy tissue is stained chrimosen red, infarct tissue is pale.

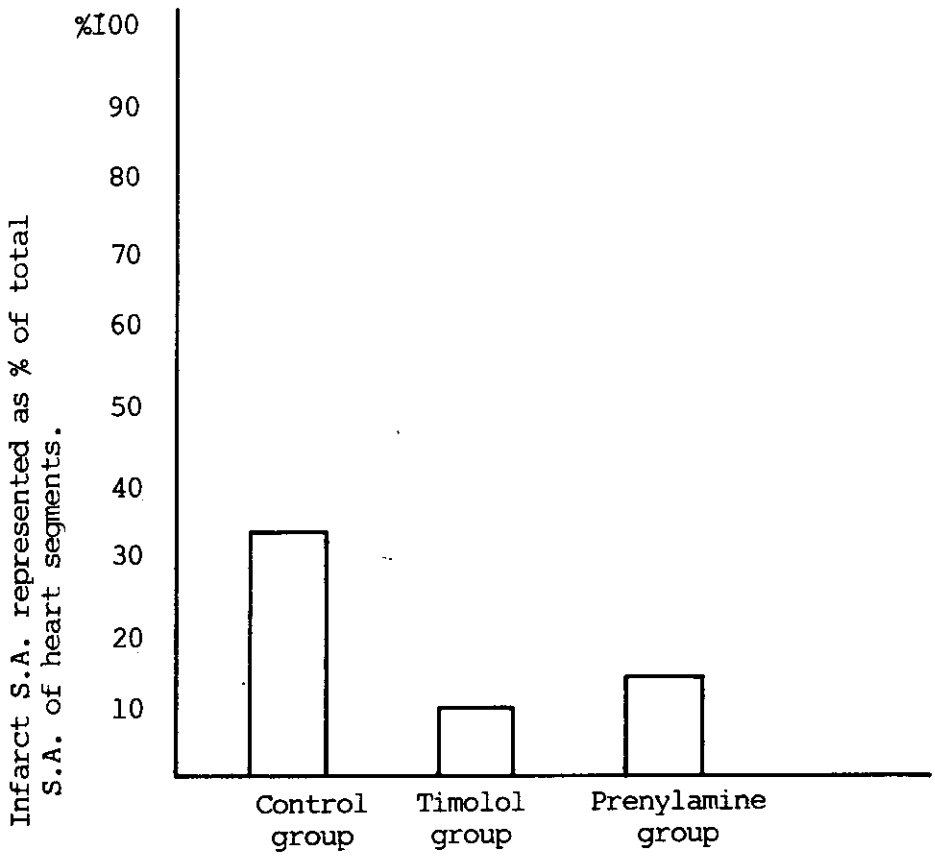


Fig. (9): Infarct surface area represented as % of total surface area of heart segments in cats, 300 min. after LAD ligation.
n = 5.

Table (9)

Total surface area of heart segments and infacted cardiac tissue in control group at 300 min. after ligation LAD in cats (MM^2).

Exp. No.	S. A. of total heart segments	S. A. of infact heart
1	1018	289
2	920	303
3	1040	341
4	1028	426
5	973	218
Mean	995.8	315.4
S.E.M.	±22	±34

Table (10)

Total surface area (S.A.) of heart segments and infarcted cardiac tissue in timolol-treated cats at 300 min. after ligation of LAD (MM^2)

Exp. No.	S. A. of total heart segments	S. A. of infact heart
1	890	48
2	1010	60
3	704	47
4	1027	165
5	910	97
Mean	908.2	83.4
S.E.M.	±58	±22

Table (11)

Total surface area (S.A.) of heart segments and infacted cardiac tissue in prenylamine-treated cats at 300 min. after ligation of LAD (MM^2).

Exp. No.	S. A. of total heart segments	S. A. of infact heart
1	838	73
2	938	92
3	759	83
4	1065	212
5	1011	136
Mean	992.2	119.2
S.E.M.	±56	±25

Table (12)

Statistical significance of surface area (S.A.) of infarcted cardiac tissue in timolol and prenylamine treated cats compared to control group at 300 min. after ligation of LAD.

Group n = 5	Mean S.A. of infarcted cardiac tissue (MM^2) $\pm$ S.E.	Significance of change from control (P)
Control group	315.4±34	-
Timolol-treated group.	83.4±22	$P < 0.01$
Prenylamine treated group.	119.2±25	$P < 0.01$

$P < 0.05$ = significant.

Table (13)

Effect of timolol and prenylamine on heart rate, (H.R.), mean arterial blood pressure (MABP), S-T segment elevation, creatine phosphokinase (CPK) and infarct size in cats during acute myocardial ischemia.

Group	S-T segment (MV)			HR (beats/min.)			MABP (mm/Hg)			CPK (u/L)		Infarct size	
	0 min.	30 min.	300 min.	0 min.	30 min.	300 min.	0 min.	30 min.	300 min.	0 min.	300 min.	Surface area (mm^2)	% to total heart segments
I- Control group	0.05 ± 0	0.7 ± 0.09	0.67 ± 0.07	167 ± 11	159 ± 11	144 ± 13	155 ± 13	145 ± 11	140 ± 9	94 ± 5	724 ± 60	315.4 ± 34	31.7
II- Timolol group	0.03 ± 0.01	0.35 ± 0.13	0.13 ± 0.04	195 ± 17	133 ± 9	102 ± 12	202 ± 18	187 ± 13	172 ± 15	91 ± 8	195 ± 17	83.4 ± 22	9.2
III- Prenylamine group	0.01 ± 0.01	0.46 ± 0.07	0.15 ± 0.04	172 ± 16	122 ± 11	92 ± 7	205 ± 14	185 ± 16	165 ± 11	72 ± 15	193 ± 25	119.2 ± 25	12.9

ALL values are mean ± S.E.M. for 5 cats.

Dose of timolol = 25 ug/Kg i.v. 15 min. prior to ligation of LAD.
Dose of prenylamine = 3 mg/Kg i.v. 15 min. prior to ligation of LAD.
0 min. = immediately before ligation of LAD.
30 min. = 30 min. after ligation of LAD.
300 min. = 300 min. after ligation of LAD.

Cardioprotective Effect of Timolol Versus Prenynlamine in Experimental Acute Myocardial Ischemia in Cats:

Comparison cardio-protective effects of timolol and prenylamine as evaluated by infarct surface area, degree of S-T segment elevation and level of serum CPK 5 hours after ligation of LAD in cats revealed that:

a) There was no significant difference between both timolol and prenylamine in decreasing myocardial infarct size ($t=1.05$ and $P>0.05$) Table (14).

b) There was no significant difference between timolol and prenylamine in decreasing S-T segment elevation at 300 min. after ligation of LAD ($t=0.33$ and $P>0.05$) Table (14).

c) There was no significant difference between timolol and prenylamine in decreasing serum CPK at 300 min. after ligation of LAD ($t=0.06$ and $P>0.05$) Table (14).

Table (14)

Cardio protective effect of timolol versus prenylamine in acute myocardial ischemia in cats at 300 min. after ligation of LAD.

Parameter M ± S.E.	Group of animals (n=5) Timolol group	Prenylamine group	Statistical difference between timolol and prenylamine groups
Surface area of infact cardiac tissue (MM^2)	83.4 ± 22	119.2 ± 25	P > 0.05
S-T segment elevation (MV)	0.13 ± 0.04	0.15 ± 0.04	P > 0.05
CPK (U/L)	195 ± 17	193 ± 25	P > 0.05

P > 0.05 = Non significant.

PART II

EFFECT OF TIMOLOL AND PRENYLAMINE ON OUABAIN, ADRENALINE-INDUCED AND POST-INFARCTION ARRHYTHMIAS IN ANAESTHETIZED CATS:

1- Effect of Timolol and Prenylamine on Ouabain Induced Arrhythmia in Cats:

a) Ouabain-induced arrhythmia was in the form of a change in the P-R interval, loss of the P wave and multifocal ventricular ectopic beats which were followed by sustained ventricular tachycardia.

In cats receiving ouabain only (20 ug/Kg every 15 min. until death) (n=5), the mean time to arrhythmia and to death were 19±5 min. and 31±5 min. respectively. All of these animals died in ventricular fibrillation (V.F.). Fig. (10) and Table (15).

b) In cats pretreated with timolol (3 mg/kg i.v., 15 min. prior to ouabain injection, n=5), the mean time to arrhythmia and to death were increased to 71±7 min. and 93±5 min. respectively. Fig. (11), (15) and Table (16, 18). When the mean time to arrhythmia in timolol-treated group was compared to that in ouabain group, there was highly significant increase. ($t = 5.9$ and $P < 0.01$). Also, when the mean time to death in timolol-treated group was compared to that of ouabain group, there was highly significant increase ($t=9.1$ and $P<0.01$).

On the other hand, acute treatment with timolol (5 mg/kg i.v.) on top of ouabain-induced ventricular arrhythmia (tachycardia) failed completely to reverse the rhythm, Fig. (12).

c) In cats pretreated with prenylamine (3 mg/kg i.v., 15 min. prior to ouabain injection, n=5), the mean time to arrhythmia and to death had increased to 60±4 min. and 92±4 min. respectively, Fig. (13 & 15) and Table (17, 18). When the mean time to arrhythmia in prenylamine-treated group was compared to that of ouabain group, there was highly significant increase ($t=6.5$ and $P<0.01$). Also, when the mean time to death in prenylamine-treated group was compared to that of ouabain group, there was highly significant increase ($t=7.8$ and $P<0.01$).

On the other hand, acute treatment with prenylamine (5 mg/kg i.v.) on top of ouabain-induced ventricular tachycardia had failed completely to reverse the rhythm, Fig. (14).

The mean (±S.E.) time to occurrence of arrhythmia and to death in the groups of cats investigated is illustrated in form of a bar chart in Fig. (15).

Fig. (10): E.C.G. tracing (Lead II) of ouabain-induced arrhythmias in cats; (control group):

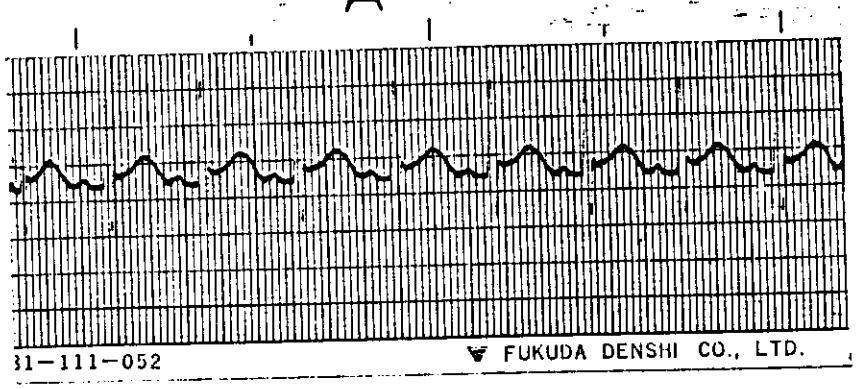
A- Control tracing, normal sinus rhythm:
Heart rate: 115 beats/min. rhythm: sinus rhythm, regular.
P wave: amplitude: 1 mm. duration 0.08 sec.
PR interval: 0.16 sec.
QRS complex: amplitude: 18 mm. duration: 0.08 sec.
S-T segment: isoelectric. T wave: amplitude: 4 mm., duration: 0.2 sec.

B- Nineteen minutes after ouabain injection, multiple, multifocal ventricular extrasystoles.

C- Twenty five minutes after ouabain injection, multiple, successive ventricular extrasystoles.

D- Thirty minutes after ouabain injection, ventricular tachycardia at a rate of 188 beats/min. followed by ventricular fibrillation and death at 32 min. from start of ouabain injection.

A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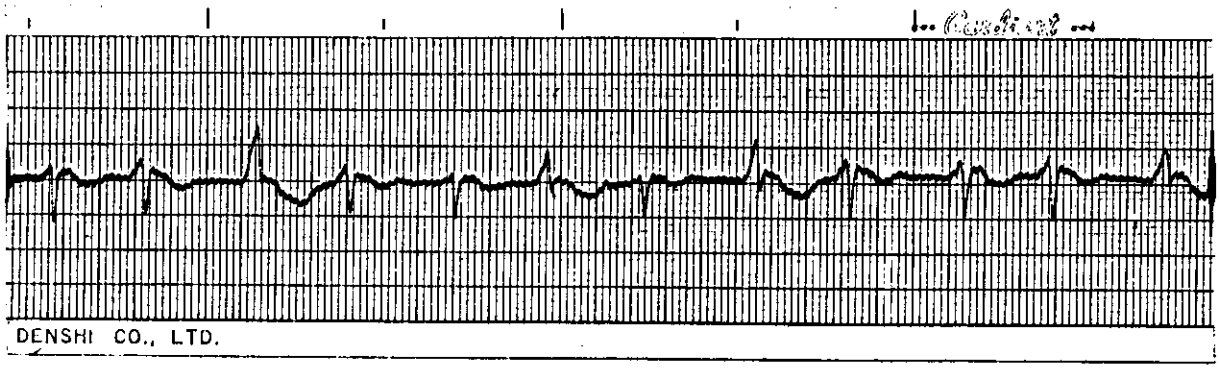
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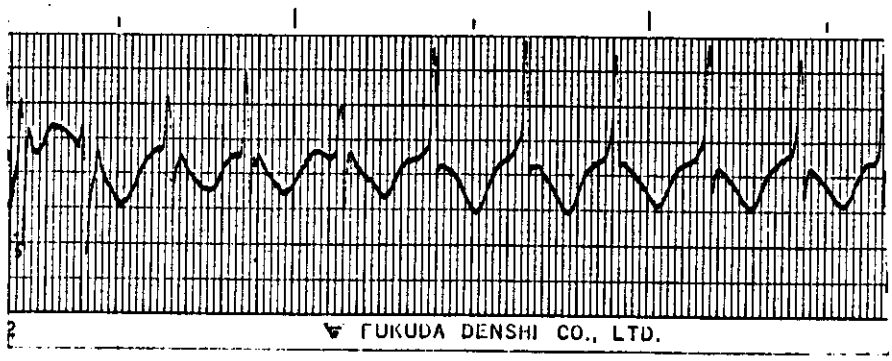
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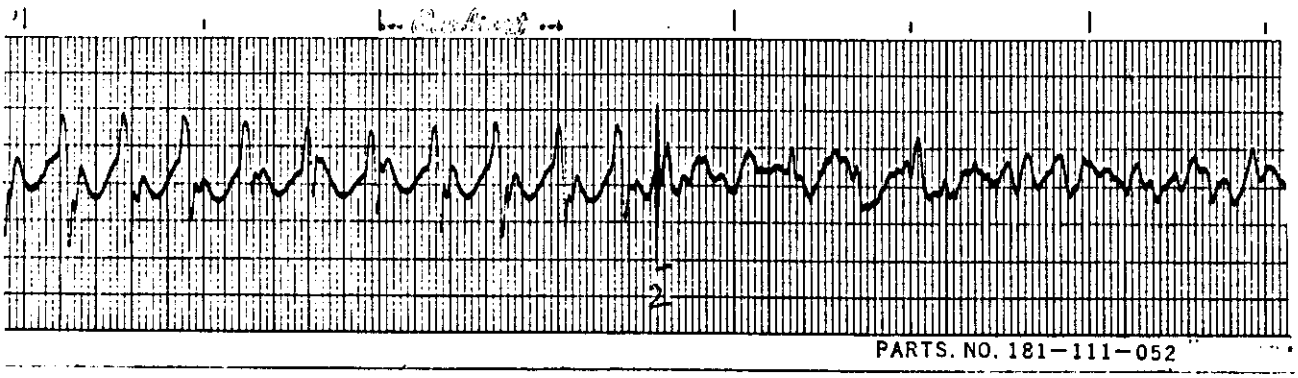
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Fig. (11): E.C.G. tracing (Lead II) of timolol-treated cats (ouabain arrhythmia) :

A- Control tracing, sinus rhythm (before timolol and ouabain injection):
Heart rate: 84 betas/min. rhythm: regular sinus rhythm.
P wave: amplitude: 1 mm, duration: 0.08 sec.
P-R interval: 0.16 sec.
QRS complex: amplitude: 8 mm, duration: 0.08 sec.
S-T segment: isoelectric, T-wave: amplitude: 3 mm, duration: 0.12 sec.

B- Timolol 3 mg/kg was injected 15 min. prior to ouabain injection.
Heart rate: 75 beats/min., rhythm: regular sinus rhythm.

C- Multifocal, multiple ventricular extrasystoles occurred at 93 min. from begining of ouabain injection.

D- Successive ventricular extrasystoles followed by ventricular fibrillation and death occurred at 107 min from start of ouabain injection.

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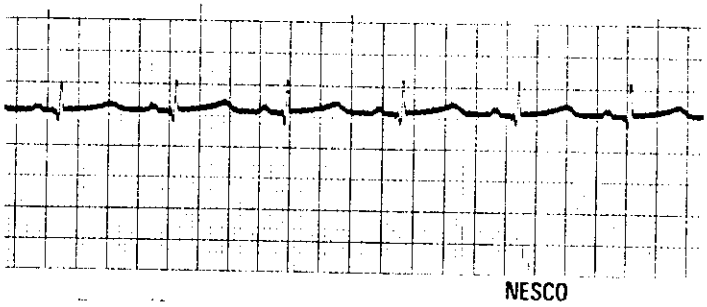

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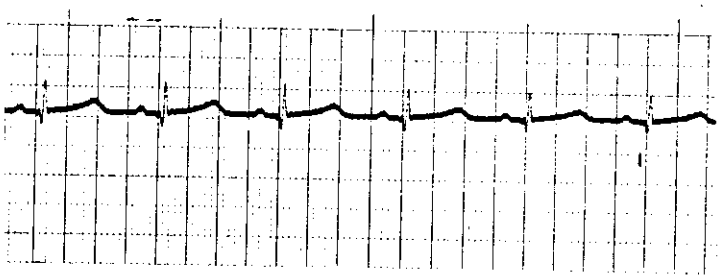

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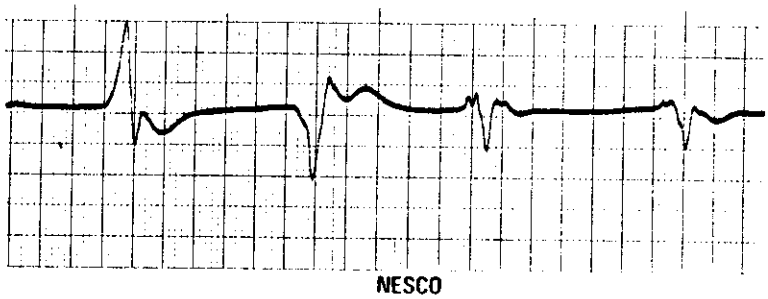

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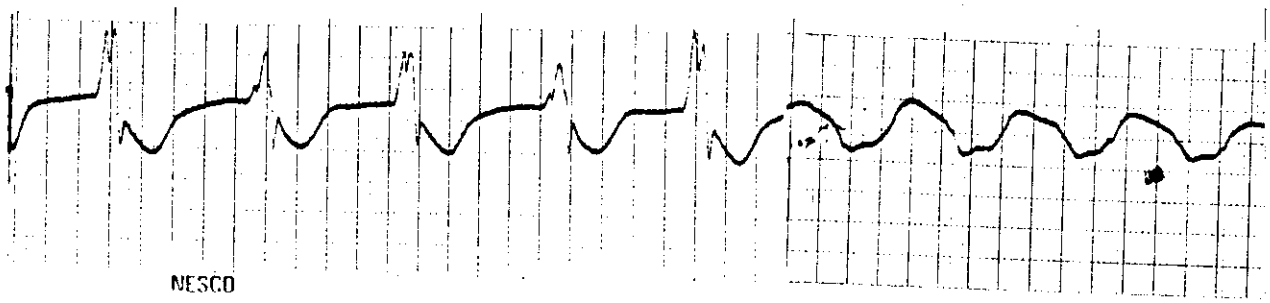

Fig. (12): Effect of timolol on ouabain induced arrhythmia in cats (E.C.G. tracing, lead II):

A- Control tracing, normal sinus rhythm:
Heart rate: 120 beats/min. rhythm: regular, sinus rhythm.
P-wave: amplitude: 1 mm, duration: 0.08 sec., PR: 0.2 sec.
QRS: amplitude: 6 mm, duration: 0.08 sec.
S-T: isoelectric. T-wave: amplitude: 0.5 mm, duration: 0.08 sec.

B- Ventricular tachycardia induced by ouabain injection .
Heart rate: 115 beats/min.

C- Timolol 5 mg/kg on top of ventricular tachycardia induced by ouabain failed to reverse the rhythm, and this ventricular tachycardia degenerated into ventricular fibrillation.

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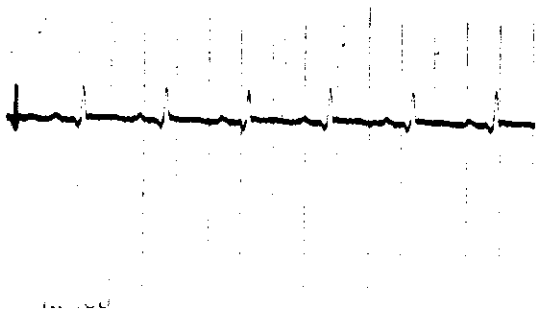

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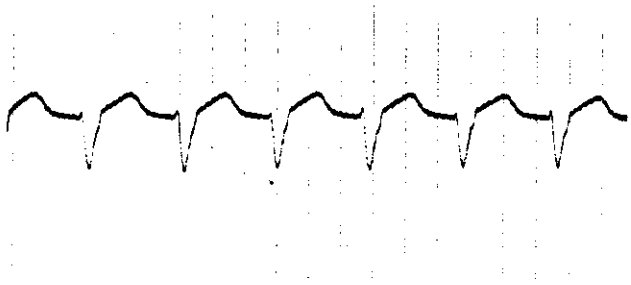

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Fig. (13): E.C.G. tracing (Lead II) of prenylamine-treated cats (ouabain arrhythmia):

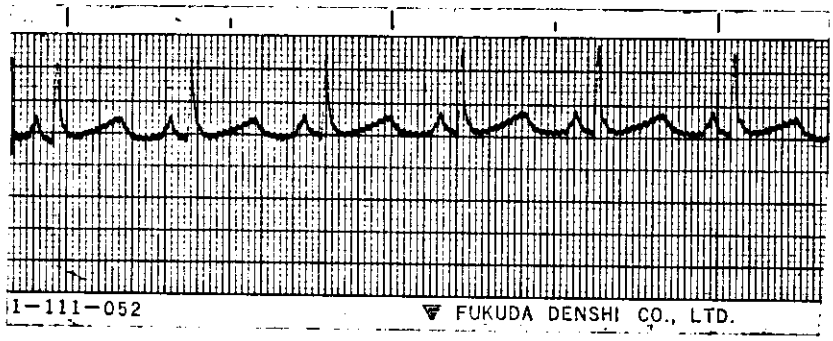
A- Control tracing, normal sinus rhythm (before ouabain and prenylamine injection):
Heart rate: 72 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 2 mm. duration: 0.08 sec.
P-R interval: 0.16 sec.
QRS complex: amplitude: 13 mm, duration: 0.06 sec.
S-T segment: isoelectric T-wave: amplitude: 4 mm, duration: 0.2 sec.

B- Prenylamine 3 mg/kg was injected i.v., 15 min., prior to ouabain injection.
Heart rate: 52 beats/min. rhythm: regular sinus rhythm.

C- Multiple, multifocal ventricular extrasystoles occurred at 65 min. after begining of ouabain injection.

D- Successive ventricular extrasystoles followed by ventricular fibrillation and death occurred at 95 min. from start of ouabain injection.

A



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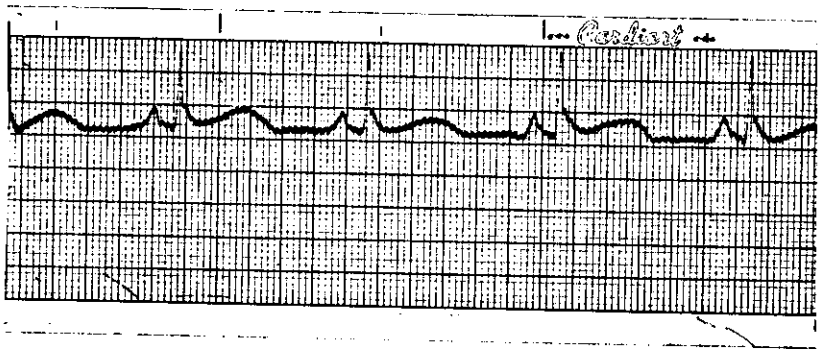

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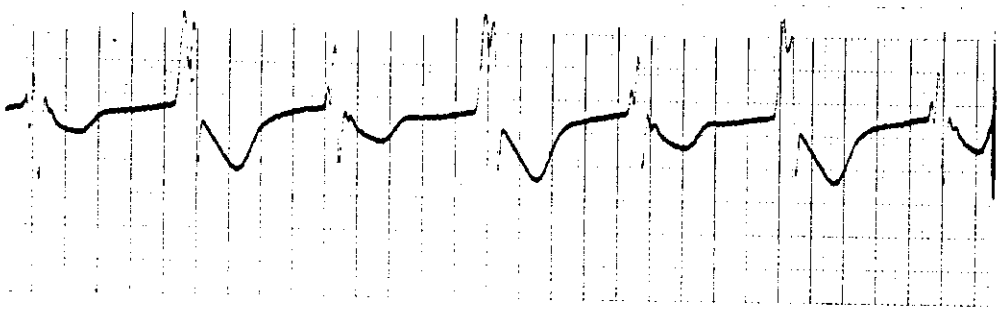

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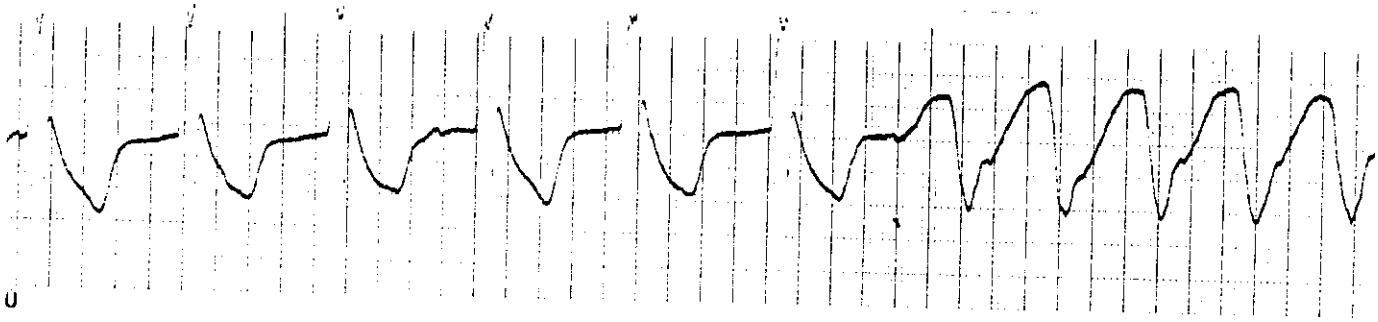

Fig. (14): Effect of prenylamine on ouabain induced arrhythmia in cats ,E.C.G. tracing (Lead II):

A- Control tracing, normal sinus rhythm:
Heart rate: 108 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 2 mm, duration: 0.08 sec.
P-R interval: 0.15 sec.
QRS complex: amplitude: 7 mm, duration: 0.04 sec.
S-T- segment: isoelectric, T-wave: Flat.

B- Ventricular tachycardia induced by ouabain injection.
Heart rate: 140 beats/min.

C- Prenylamine 5 mg/kg was injected on top of ouabain-induced ventricular tachycardia failed to correct this arrhythmia which was degenerated into ventricular fibrillation.

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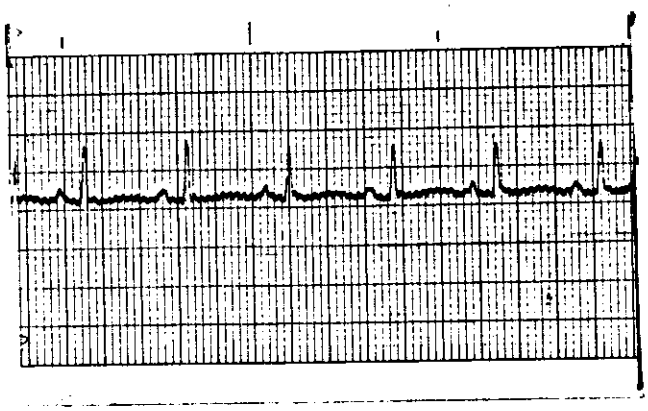

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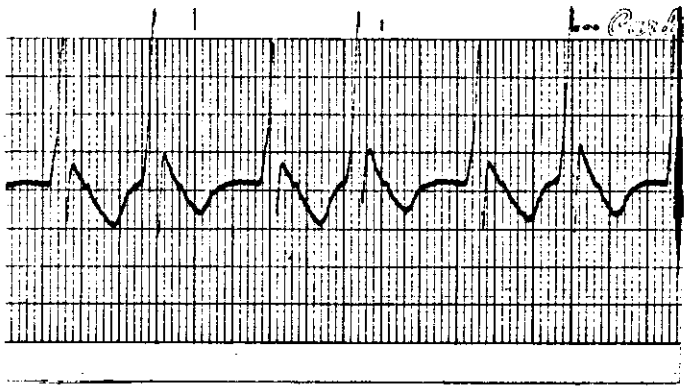

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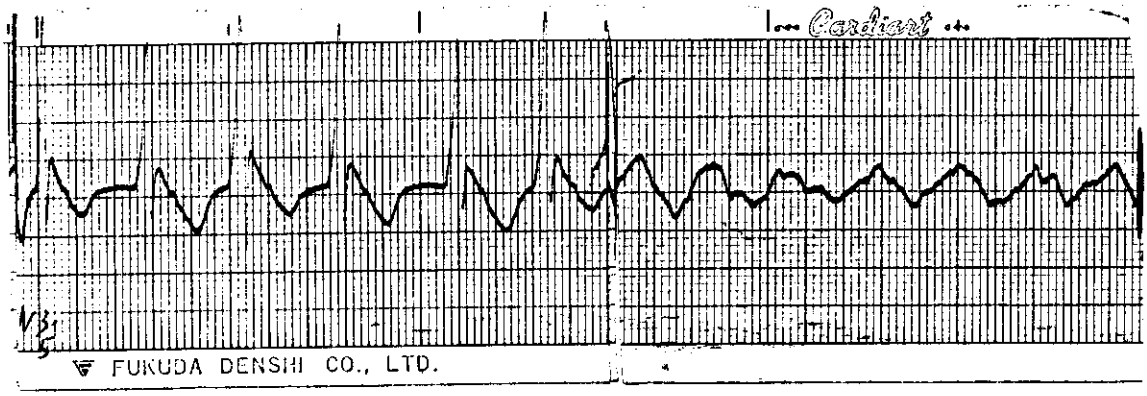

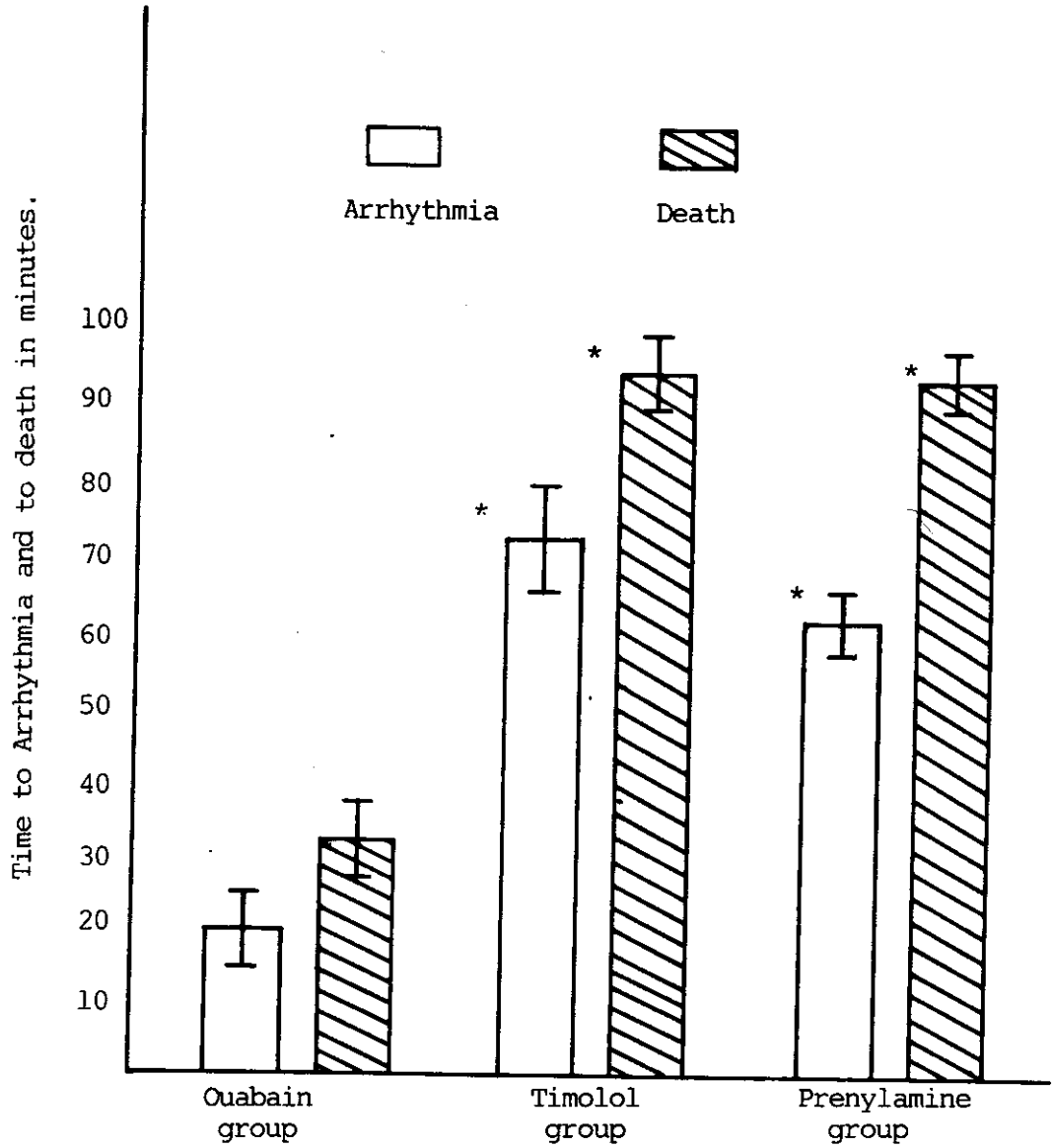

Fig, (15): Time to arrhythmia and time to death in ouabain (control group), timolol-ouabain group and prenylamine-ouabain group in cats. n = 5.

* Significant change from control group ($P < 0.01$).

Table (15)

Ouabain induced arrhythmia in anaesthetized cats

(Control group)

Exp. No.	Time to arrhythmia (Min.)	Time to death (Min.)
1	19	32
2	2	15
3	35	46
4	17	30
5	20	32
Mean	19	31
S.E.M.	±5	±5

Table (16)

Effect of timolol on ouabain induced arrhythmia in anaesthetized cats.

Exp. No.	Time to arrhythmia (Min.)	Time to death (Min.)
1	50	80
2	93	107
3	70	100
4	65	87
5	77	93
Mean	71	93
S.E.M.	±7	±5

Table (17)

Effect of prenylamine or ouabain induced arrhythmia in anaesthetized cats.

Exp. No.	Time to arrhythmia (Min.)	Time to death (Min.)
1	65	95
2	55	90
3	50	80
4	60	97
5	70	100
Mean	60	92
S.E.M.	±4	±4

Table (18)

Statistical significance of timolol and prenylamine on ouabain induced arrhythmia in cats compared to control group.

Group	Mean time to Arrhythmia ± S.E.	Significance of change from control (P)	Mean time to death ± S.E.	Significance of change from control (P)
Ouabain group (control group)	19±5	-	31±5	-
Ouabain-Timolol group	71±7	P<0.01	93±5	P<0.01
Ouabain-prenylamine group	60±4	P<0.01	92±4	P<0.01

P < 0.05 = Significant, n = 5

2- Effect of Timolol and Prenylamine on Adrenaline-induced Arrhythmia in Cats:

a) In cats receiving adrenaline (n=5), before injection of timolol, the mean minimal arrhythmogenic dose of adrenaline was 26 $\pm$ 2 ug/kg.

After restoration of normal rhythm and injection of timolol 25 ug/kg i.v. for 15 min., the mean dose of adrenaline that could produce arrhythmia after timolol was 800 ug/kg in two cats, Fig. (16 , 18) and Table (19), while in other 3 cats, doses of adrenaline up to 2000 ug/kg failed to produce arrhythmia after timolol. When the dose of adrenaline that could produce arrhythmia after timolol was compared to that dose of adrenaline that could produce arrhythmia before timolol injection, there was highly significant increase ($t= 12.6$ and $P<0.01$).

b) In cats receiving adrenaline before injection of prenylamine (n=5), the mean minimal arrhythmogenic dose of adrenaline that could produce arrhythmia was 12 ± 3 ug/kg.

After restoration of normal rhythm and injection of prenylamine 5 mg/kg i.v. for 15 min., the mean dose of adrenaline that could produce arrhythmia after prenylamine was 19 ± 8 ug/kg. When the dose of adrenaline that could produce arrhythmia after prenylamine was compared to that dose of adrenaline that could produce arrhythmia before prenylamine injection, it was insignificant. ($t=0.8$ and $P>0.5$) Fig. (17, 18) and Table (20).

The mean ($\pm$S.E.) arrhythmogenic dose of adrenaline before and after injection of timolol and prenylamine is illustrated in form of a bar chart in Fig. (18).

Fig. (16): Effect of Timolol on adrenaline-induced arrhythmia in cats, E.C.G. tracing (Lead II):

A- Control tracing, normal sinus rhythm:
Heart rate: 100 beats/min. - rhythm: regular sinus rhythm.
P-wave: amplitude: 1 mm, duration: 0.06 sec.
P-R interval: 0.16 sec.
QRS complex: amplitude: 5 mm, duration: 0.06sec.
S-T segment: isoelectric, T-wave: inverted.

B- Adrenaline 20 ug/kg was injected i.v. produced successive ventricular extrasystoles which persisted for 2 minutes.

C- Timolol, 25 ug/kg was injected i.v.
Heart rate: 73 beats/min - rhythm: regular sinus rhythm.

D- Adrenaline 20 ug/kg was injected i.v., 15 min. after timolol injection failed to produce ventricular arrhythmia.

E- Adrenaline 800 ug/kg was injected i.v. after timolol injection produced one ventricular extrasystole only.

F- Adrenaline 1000 ug/kg was injected after timolol injection produced successive ventricular extrasystoles.

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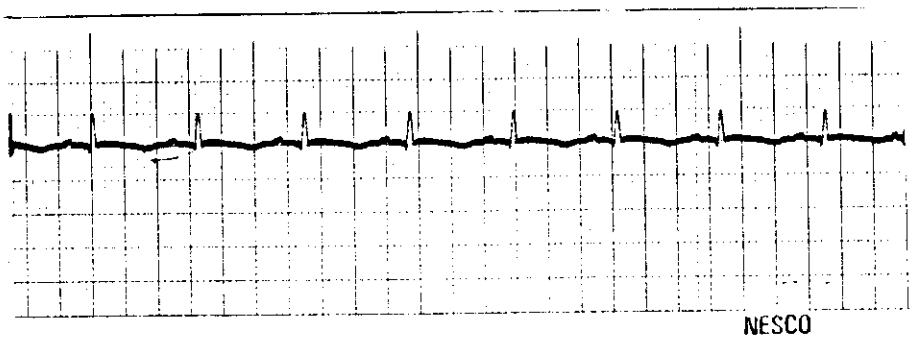

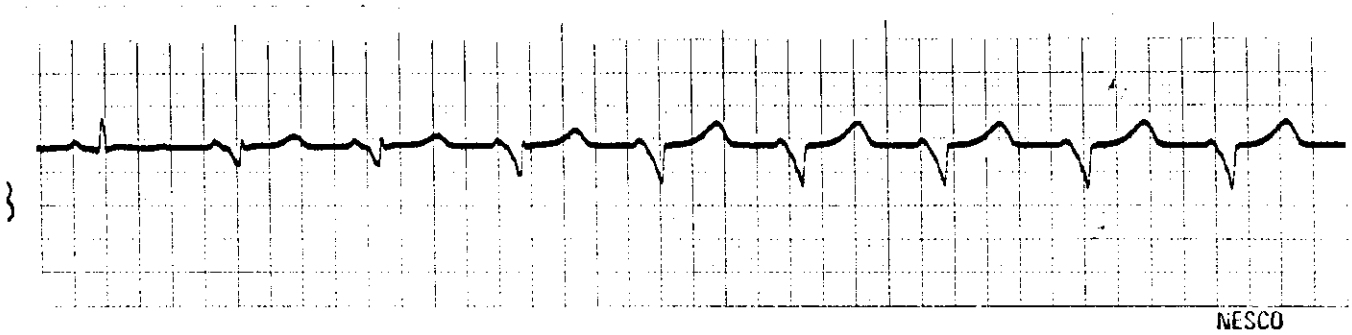

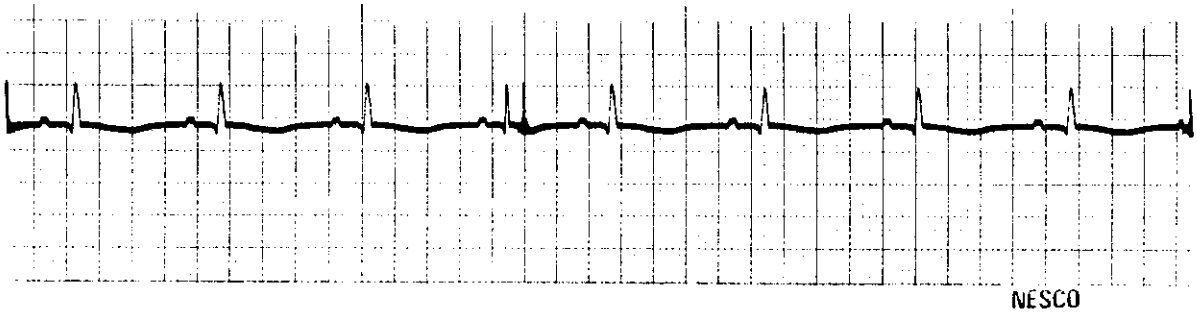

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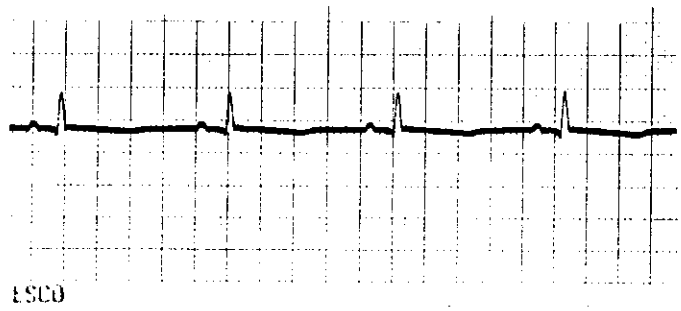

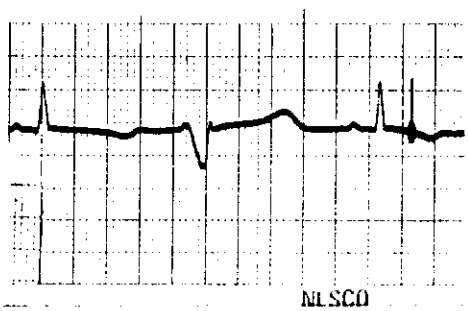

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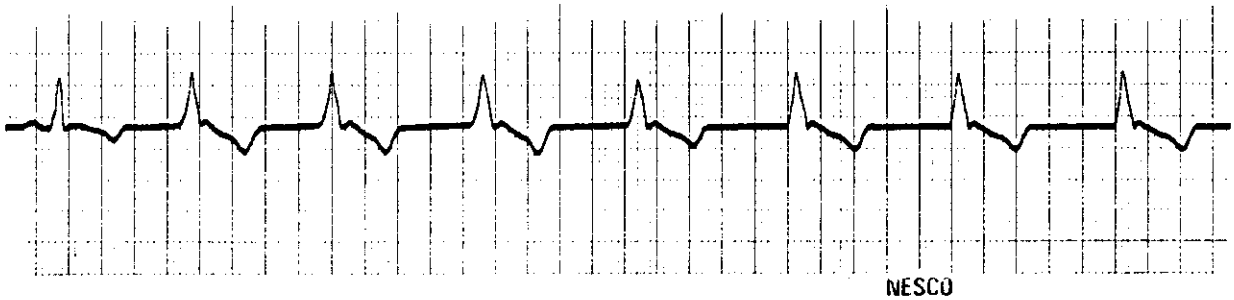


Fig. (17): Effect of prenylamine on adrenaline induced arrhythmia in cats, E.C.G. tracing (Lead II):

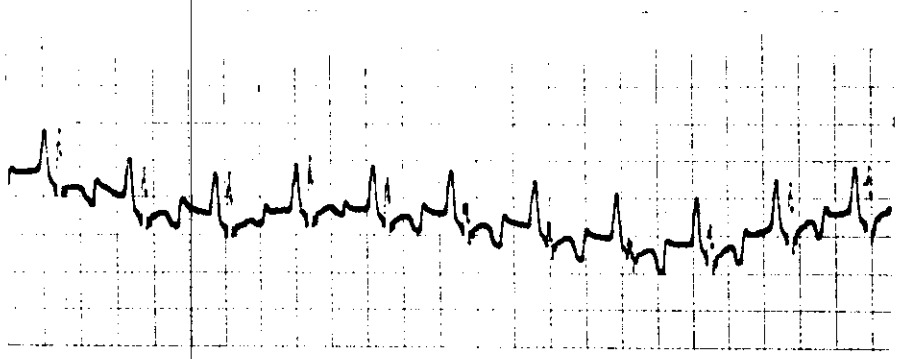
A- Control tracing, normal sinus rhythm:
Heart rate: 150 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 7 mm, duration: 0.08 sec.
P-R interval: 0.12 sec.
QRS complex: amplitude: 10 mm, duration: 0.06 sec.
S-T segment: isoelectric. T-wave: biphasic.

B- Adrenaline 10 ug/kg was injected i.v. produced successive ventricular extrasystoles which persisted for 2 minutes.

C- Prenylamine 5 mg/kg was injected i.v.
Heart rate: 115 beats/min. rhythm: regular sinus rhythm.

D- Adrenaline 10 ug/kg was injected i.v., 15 min. after prenylamine injection produced successive ventricular extrasystoles again.

A



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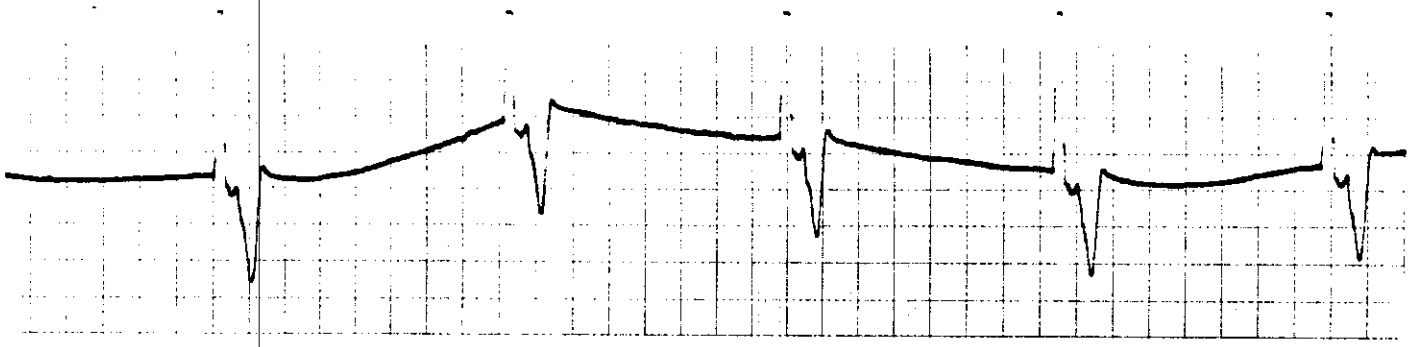

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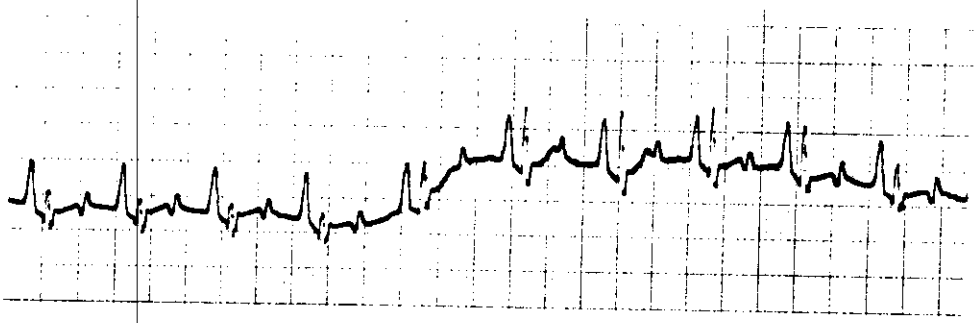

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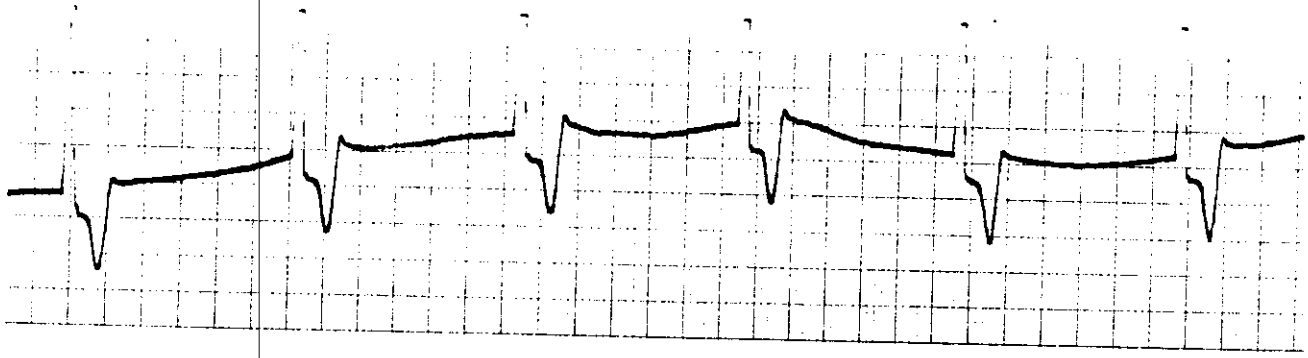


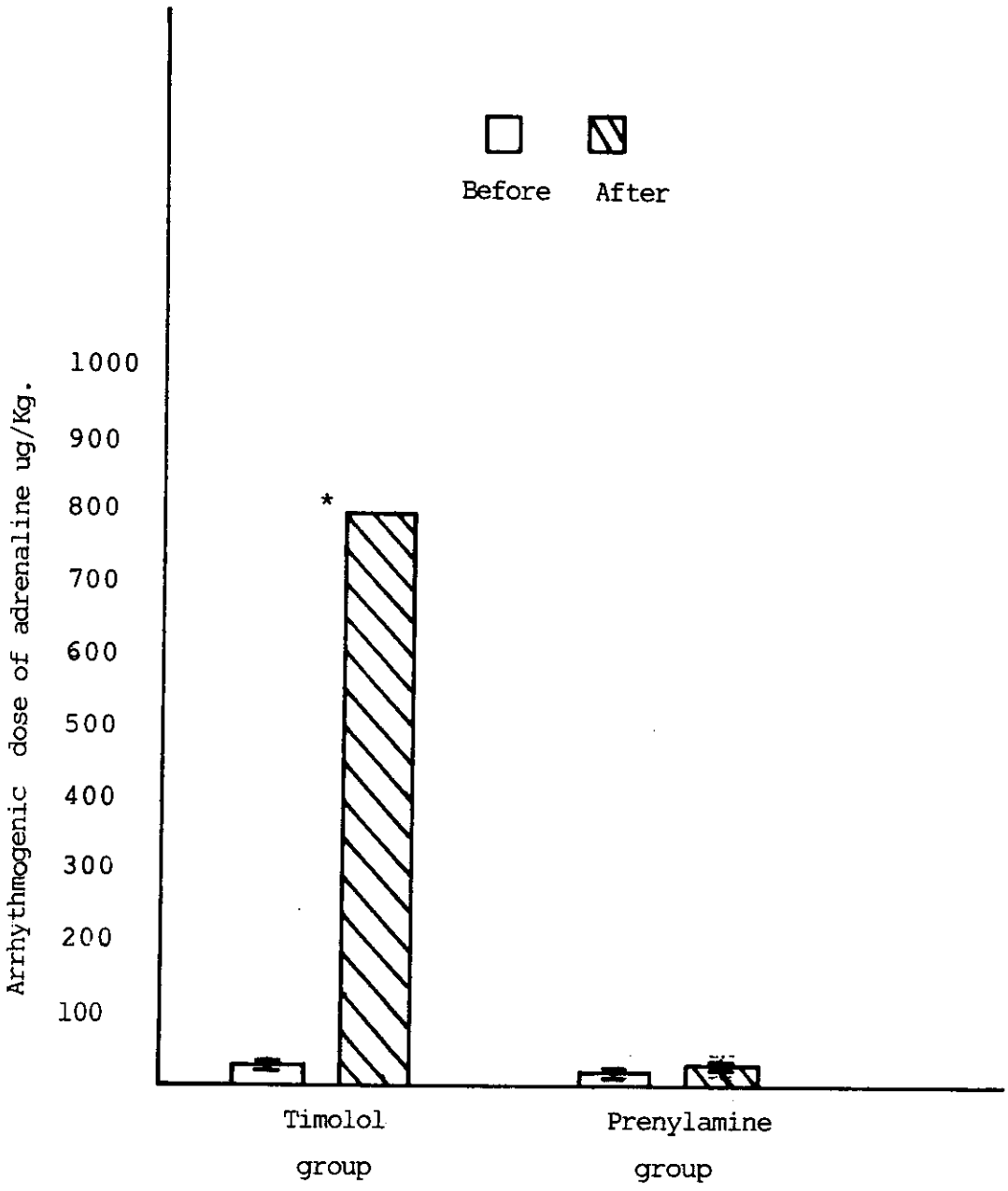


Fig. (18): Effect of timolol and prenylamine on arrhythmogenic dose of adrenaline in cats.
n = 5.
Before= before injection of timolol or prenylamine.
After = After injection of timolol or prenylamine.
* = significant at ($P<0.01$), mean of 2 experiments.

Table (19)

Effect of timolol on arrhythmogenic dose of adrenaline in anaesthetized cats.

Exp. No.	Arrhythmogenic dose of adrenaline (ug/kg)	
	Before	After
1	30	600
2	30	>1000
3	20	>2000
4	20	1000
5	30	>1600
Mean	26	800*
S.E.M.	±2	-

* Mean of two experiments.
Before = before timolol injection.
After = after timolol injection.

Table (20)

Effect of prenylamine on arrhythmogenic dose of adrenaline in anaesthetized cats.

Exp. No.	Arrhythmogenic dose of adrenaline (ug/kg)	
	Before	After
1	5	5
2	10	10
3	10	10
4	20	50
5	15	20
Mean	12	19
S.E.M.	±3	±8

Before = before prenylamine injection.
After = after prenylamine injection.

3- **Effect of Timolol and Prenylamine on Post-Infarction Arrhythmia in Cats:**

a) In the control group (cats subjected to LAD ligation), some of cats had shown multiple ventricular extrasystoles every now and then. One cat showed multiple ventricular extrasystoles followed by ventricular tachycardia, ventricular fibrillation and death 30 min. after LAD ligation, Fig. (19).

b) In timolol treated group (cats subjected to LAD ligation, 15 min. after timolol injection). All the animals survived the period of the experiment (5 hours) without showing any of the ventricular arrhythmias.

c) In prenylamine-treated group (cats subjected to LAD ligation 15 min. after prenylamine injection). There were no ventricular extrasystoles through the period of the experiment. Only one cat suffered a sudden ventricular tachycardia immediately after ligation of LAD, which persisted for about 2 min., and then this ventricular tachycardia was reversed to normal sinus rhythm spontanously, Fig. (20). All the animals in this group had survived the period of the experiment (5 hours).

Fig. (19): Post-ischemic arrhythmia in cats, E.C.G. tracing of control group (Lead V_3):

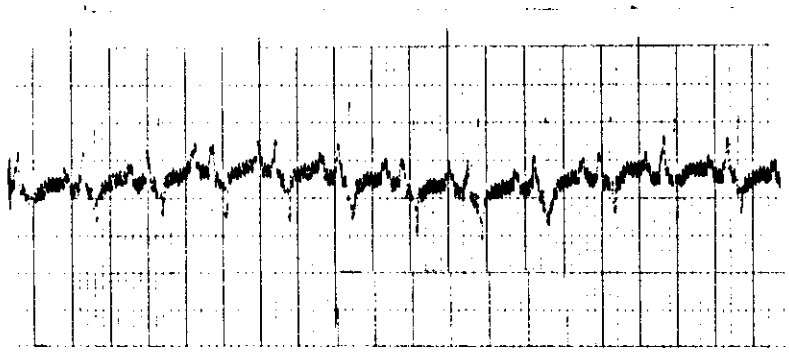
A- Control tracing, normal sinus rhythm (before occlusion of LAD):
Heart rate: 166 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 4mm, duration: 0.08 sec.
P-R interval: 0.12 sec.
QRS complex: amplitude: 15 mm, duration: 0.8 sec.
S-T segment: isoelectric. T-wave: amplitude: 2 mm, duration: 0.08 sec.

B- E.C.G. tracing immediately after occlusion of LAD:
Heart rate: 214 beats/min-rhythm: regular sinus rhythm.
-Deep Q wave, inverted T-wave.

C- Multiple ventricular extrasystoles occurred at 10 min. after ligation of LAD.

D- Ventricular tachycardia at a rate 250 beats/min. followed by ventricular fibrillation and death at 30 min. after ligation of LAD.

A



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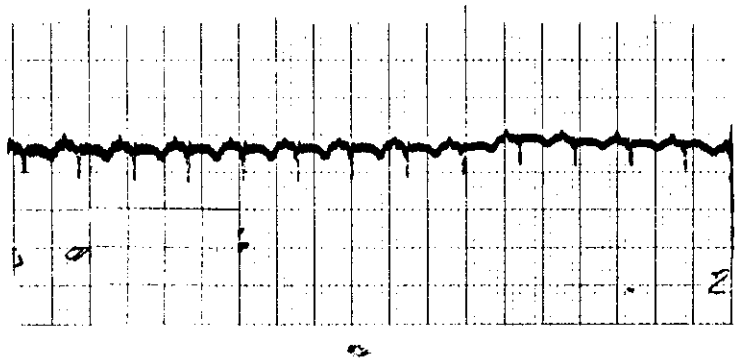

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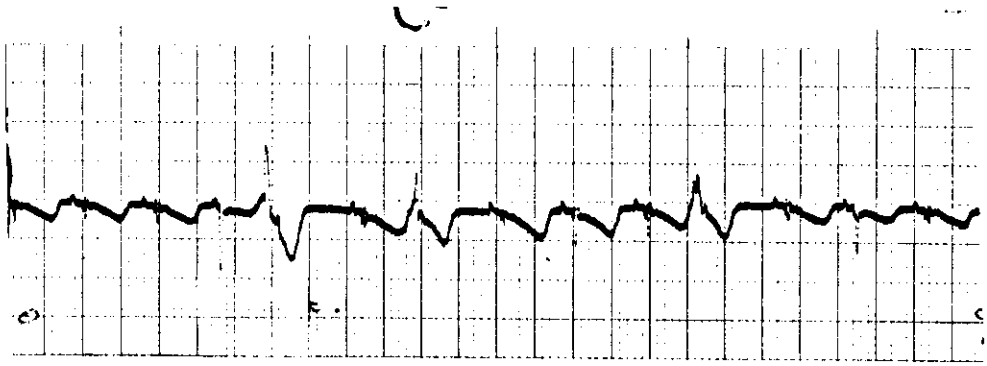

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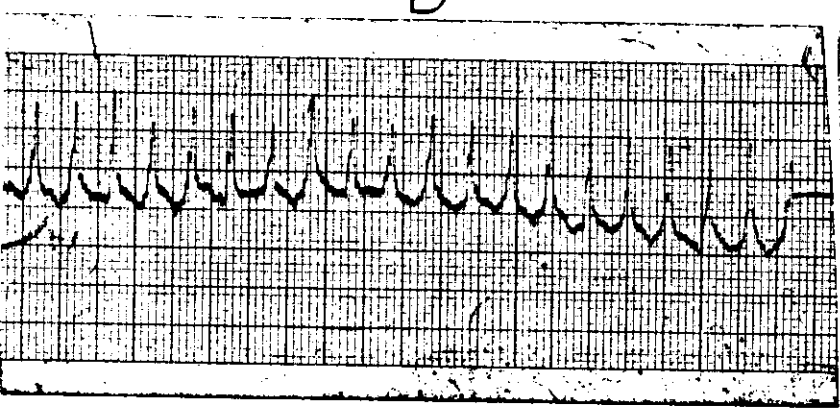

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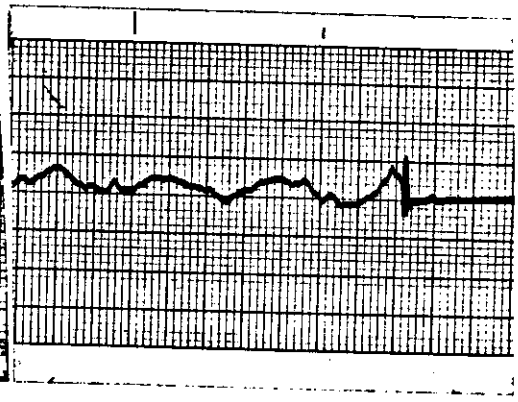


Fig. (20): Effect of prenylamine on post-ischemic arrhythmia in cats, E.C.G. tracing (Lead V_3):

A- Control tracing, normal sinus rhythm (before ligation of LAD):
Heart rate: 188 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 3 mm, duration: 0.04 sec., P-R interval: 0.12 sec.
QRS complex: amplitude: 14 mm, duration: 0.06 sec.
S-T segment: isoelectric. T-wave: inverted.

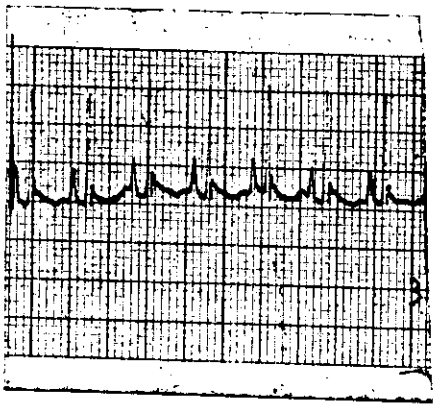
B- Prenylamine 3 mg/kg was injected i.v., 15 min. prior to ligation of LAD.
Heart rate: 166 beats/min.

C- Multiple ventricular extrasystoles occurred immediately after ligation of LAD.

D- Ventricular tachycardia at a rate of 250 beats/min. occurred 10 min. after ligation of LAD.

E- This ventricular tachycardia had been reversed spontanously to normal sinus rhythm.

A



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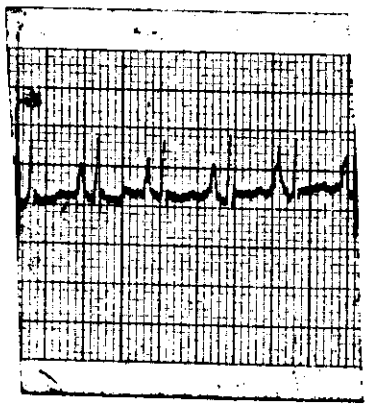

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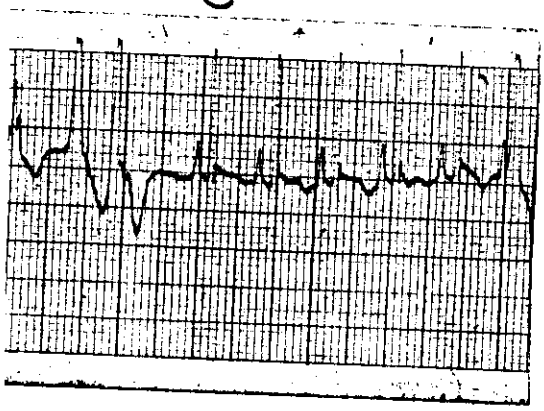

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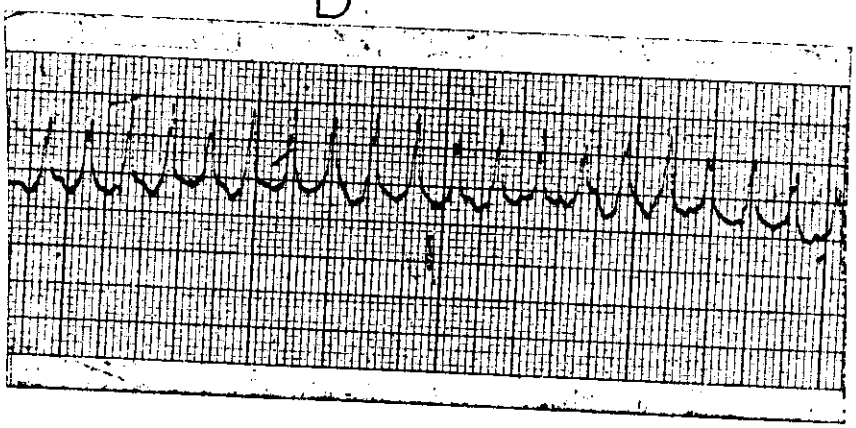

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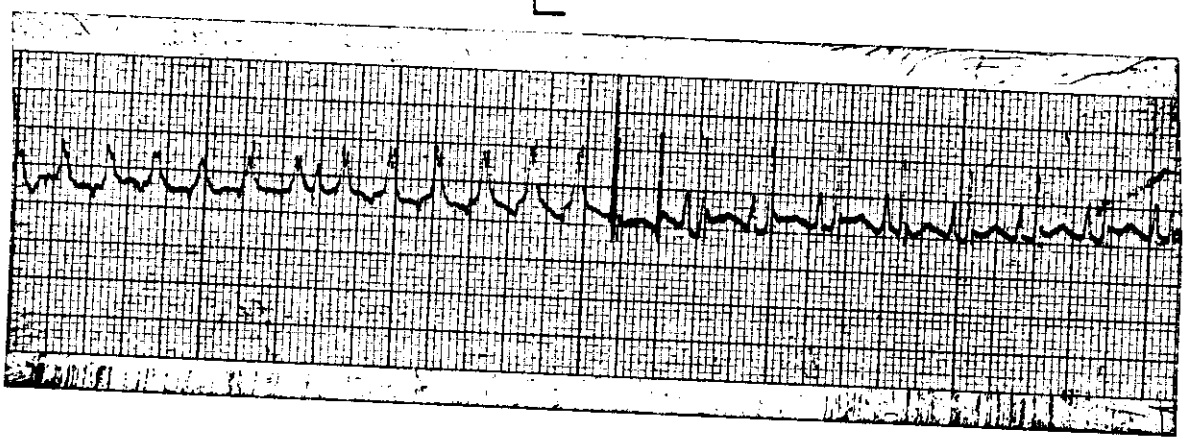


PART III

EFFECT OF TIMOLOL AND PRENYLAMINE ON ERGOTAMINE-INDUCED CORONARY VASOSPASM AND HYPERTENSION IN ANAESTHETIZED CATS:

1- Effect of Timolol and Prenylamine on Ergotamine-induced Coronary Vasospasm in Cats:

a) Ergotamine tartarate 400 ug/kg given i.v. in cats produced coronary vasospasm manifested in the E.C.G. by elevated S-T segment and highly peaked T-wave. (Fig. (21, 22, 24).

b) Effect of Timolol on Ergotamine-induced Coronary Vasospasm in Cats:

i) Timolol 25 ug/kg i.v. was given 15 min., prior to ergotamine injection (400 ug/kg) could not prevent the coronary spasm induced by ergotamine, as timolol had failed to prevent neither the raised S-T segment nor the peaked T-wave (Fig. 21).

ii) Timolol 25 ug/kg i.v. was given on top of ischemic changes induced by ergotamine injection, also failed to correct these ischemic changes Fig. (22).

c) **Effect of Prenylamine on Ergotamine-induced Coronary Vasospasm in Cats:**

i) When prenylamine was injected in a dose of 3 mg/kg i.v., 15 min., prior to ergotamine injection (400 ug/kg i.v.). It could prevent the coronary spasm induced by ergotamine, as it prevented the appearance of ischemic changes in the E.C.G. Fig. (23).

ii) Moreover, when prenylamine (3 mg/kg i.v.) was given on top of ergotamine-induced coronary vasospasm, it could correct the ischemic changes induced by ergotamine, as it decreased the elevation of S-T segment and normalized the highly peaked T wave. Fig. (24).

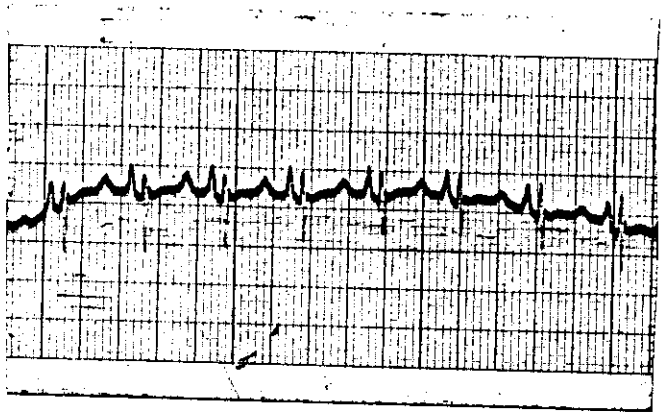
Fig. (21): Effect of timolol on ergotamine-induced coronary vasospasm in cats, E.C.G. tracing (Lead V_3):

A- Control tracing,normal sinus rhythm (before injection of timolol and ergotamine):
Heart rate: 150 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 2 mm, duration: 0.08 sec-
P-R interval: 0.12 sec.
QRS complex: amplitude: 8 mm, duration: 0.06 sec.
S-T segment: isoelectric. T-wave: amplitude 2mm, duration: 0.08 sec.

B- Timolol 25 ug/kg was injected i.v.
Heart rate: 115 beats/min.
S-T segment: isoelectric. T-wave: as before.

C- Ergotamine 400 ug/kg was injected 15 min. after timolol injection produced coronary vasospasm as the S-T segment was elevated and the T-wave was high and peaked.

A



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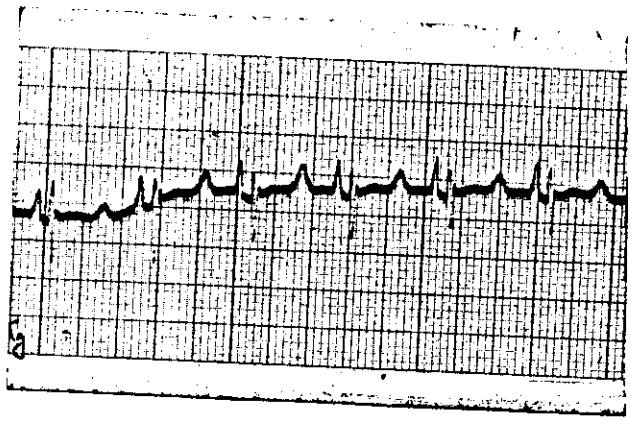

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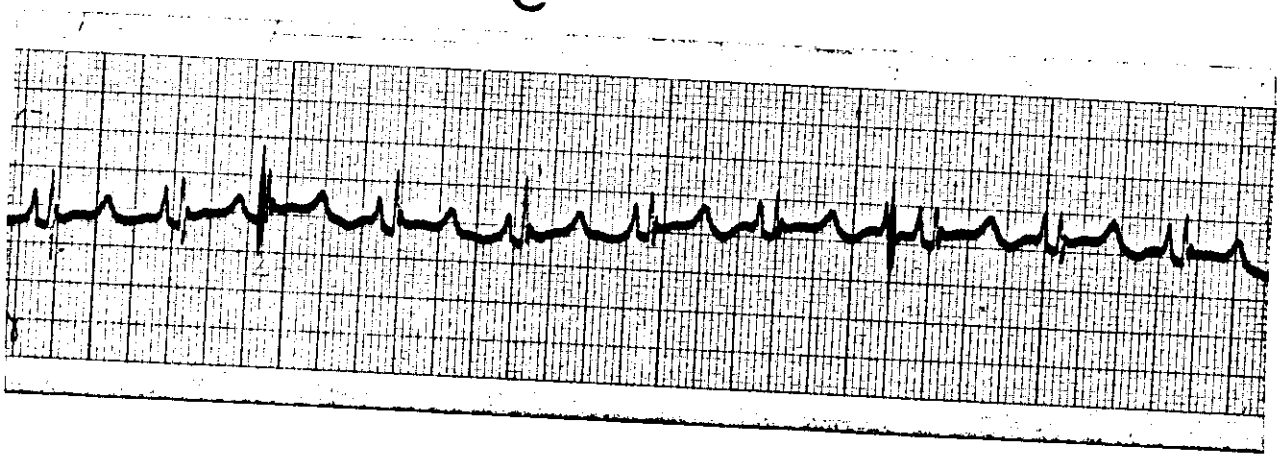

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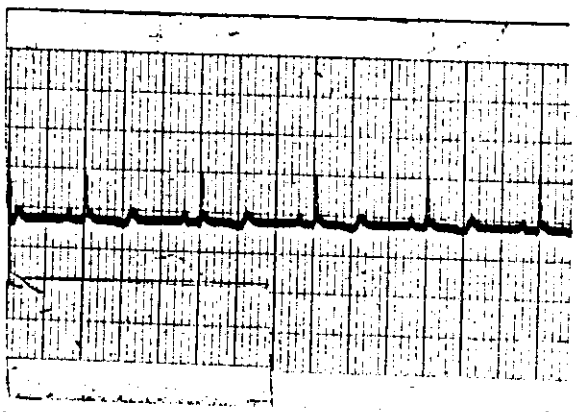

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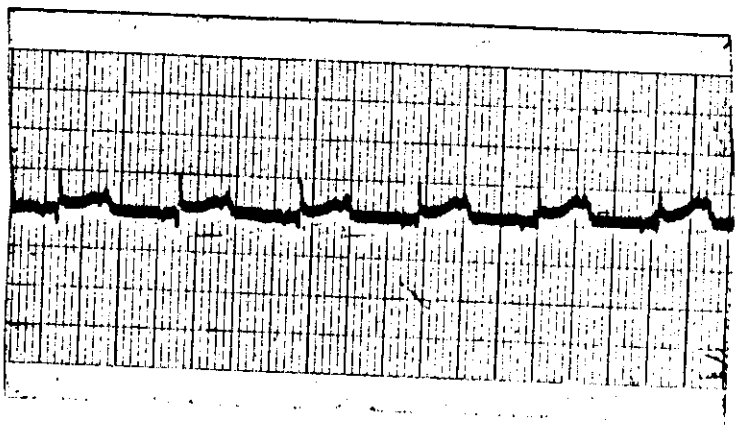

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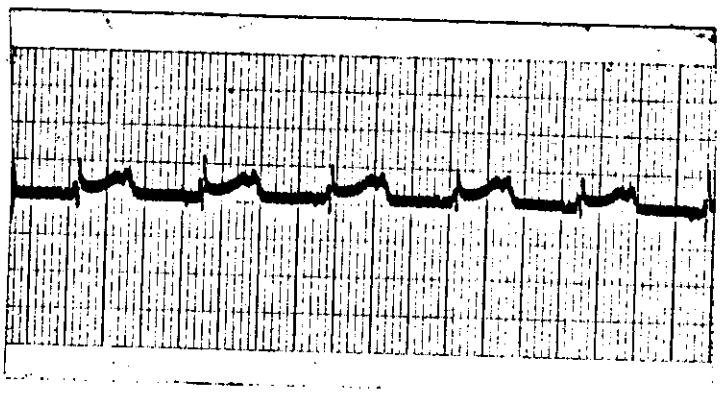

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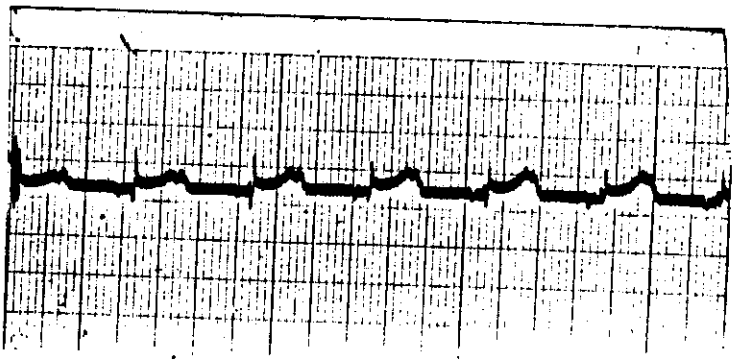


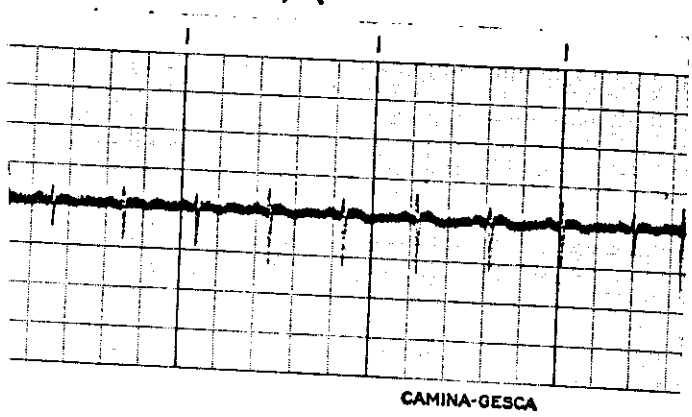
Fig. (23): Effect of prenylamine on ergotamine-induced coronary vasospasm in cats, E.C.G. tracing (Lead V_3):

A- Control tracing, normal sinus rhythm (before injection of prenylamine and ergotamine).
Heart rate: 160 beats/min. rhythm: regular sinus rhythm.
P-wave: 1mm in amplitude, 0.04 sec. in duration.
P-R-interval: 0-12 sec.
QRS complex: 8 mm in amplitude, 0.04 sec. in duration.
S-T segment: isoelectric. T-wave: inverted.

B- Prenylamine 3 mg/kg was injected i.v.
Heart rate: 125 beats/min.
S-T segment: isoelectric. T-wave: flat.

C- Ergotamine 400 ug/kg was injected i.v., 15 min. after prenylamine injection, failed to produce coronary vasospasm as the S-T segment remained isoelectric and the T-wave remained Flat.

A



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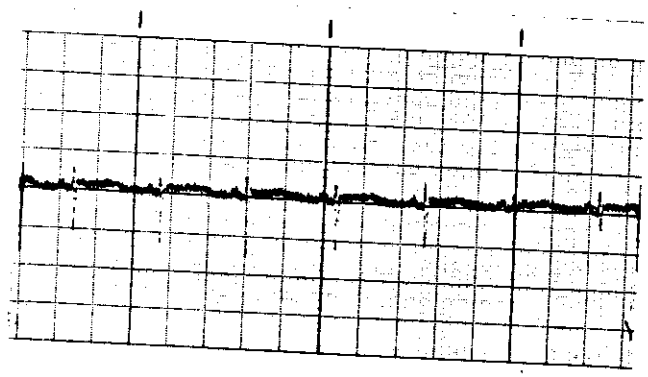

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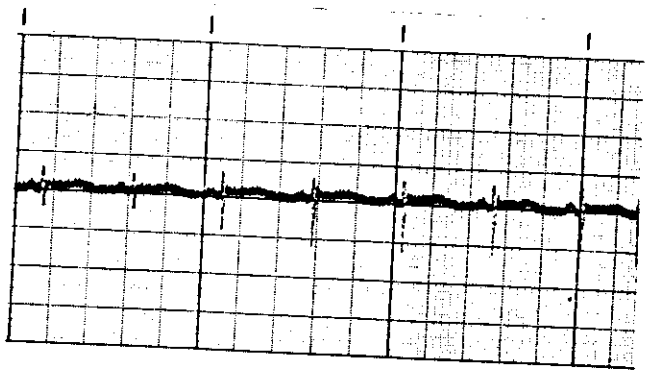


Fig. (24): Effect of prenylamine on ergotamine-induced coronary vasospasm in cats & E.C.G. tracing (Lead V_3):

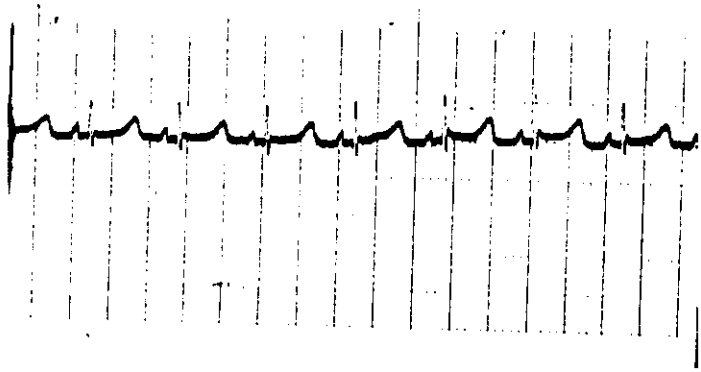
A- Control tracing, normal sinus rhythm (before injection of ergotamine and prenylamine).
Heart rate: 136 beats/min. rhythm: regular sinus rhythm.
P-wave: amplitude: 2 mm, duration, 0.04 sec.
P-R interval: 0.12 sec.
QRS complex: 6 mm in amplitude, 0.04 sec in duration.
S-T segment: isoelectric. T-wave: 3 mm in amplitude 0.12 sec in duration.

B- Ergotamine 400 ug/kg was injected i.v. produced coronary vasospasm as the S-T segment was highly elevated and the T-wave was highly peaked and high.

C- Prenylamine 3 mg/kg was injected i.v. on top of ergotamine-induced coronary vasospasm, could releive that coronary vasospasm as prenylamine had returned the S-T segment to the isoelectric line and normalized the T-wave.

D- Ergotamine 400 ug/kg was injected again 15 min. after prenylamine failed to produce coronary vasospasm as the S-T segment remained isoelectric and the T-wave remained normal.

A



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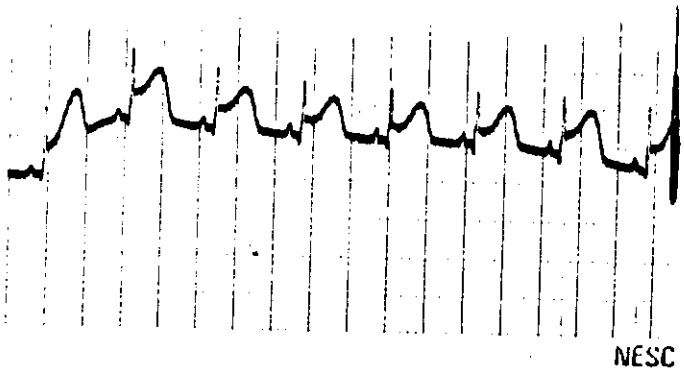

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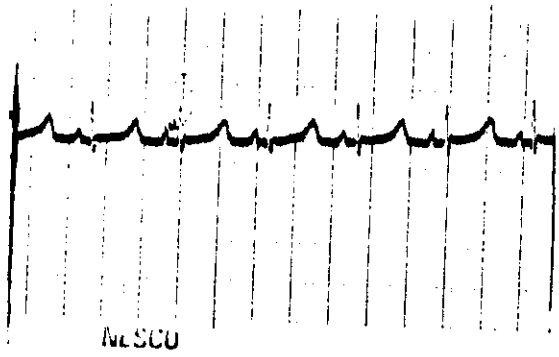

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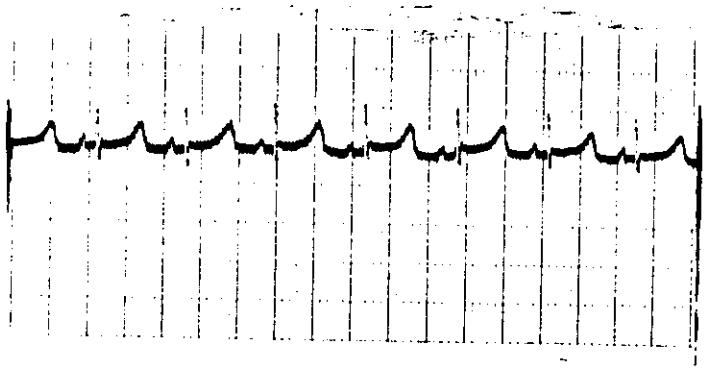


2- **Effect of Timolol and Prenylamine on Ergotamine-Induced Hypertension in Cats:**

a) Ergotamine 400 ug/kg i.v. in cats produced sustained acute rise of blood pressure for about 30 min. Figs. (25, 26).

b) Effect of timolol on ergotamine-induced hypertension in cats:

Timolol in a dose of 25 ug/kg i.v., 15 min. prior to ergotamine injection could not prevent the rise of blood pressure induced by ergotamine (400 ug/kg). In the same time when timolol (25 ug/kg i.v.) was given on top of hypertensive response induced by ergotamine in cats, it failed to reduce the pressor response to ergotamine, Fig. (25).

c) Effect of prenylamine on ergotamine-induced hypertension in cats:

Prenylamine in a dose of 3 mg/kg i.v. on top of ergotamine-induced hypertension could reverse the pressor response immediately after injection and induce a hypotensive effect which was sustained for about 45 min. Meanwhile, prenylamine injection could prevent the rise in blood pressure induced by another dose of ergotamine (400 ug/kg), Fig. (26).

Fig. (25): Effect of timolol on ergotamine induced hypertension in anaesthetized cats:

- Ergotamine in a dose of 400 ug/kg i.v. produced a rise of blood pressure for about 30 min.
- Timolol (25 ug/kg i.v.) was given produced no effect on the blood pressure.
- Then, injection of ergotamine (400 ug/kg i.v.) 15 min. after timolol injection produced again a rise of blood pressure.
- Timolol (25 ug/kg i.v.) was given on top of ergotamine-induced hypertension failed to antagonise this rise of blood pressure.

E = Ergotamine.
T = Timolol.
T.M.= Time marker.

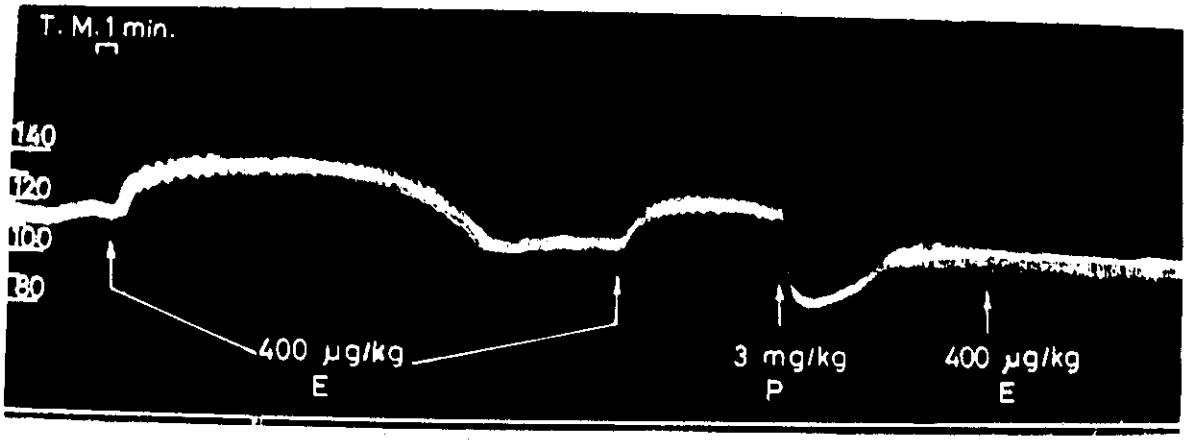


Fig. (26): Effect of prenylamine on ergotamine-induced hypertension in anaesthetized cats:

- Ergotamine in a dose of 400 ug/kg i.v. produces a rise of blood pressure for about 30 min.
- Prenylamine (3 mg/kg i.v.) was given on top of ergotamine-induced hypertension could antagonize and reverse this rise of blood pressure.
- Ergotamine (400 ug/kg i.v.) was given after prenylamine failed to induce pressor response:

E = Ergotamine.
P = Prenylamine.
T.M. = Time Marker.

Effect of Timolol and Prenylamine on Isoprenaline Induced Tachycardia and Depressor Responses in Anaesthetized Cats:

Timolol in a dose of 25 ug/kg i.v. antagonised the tachycardia and hypotension induced by isoprenaline in a dose of 1 ug/kg i.v. in anaesthetized cats Fig. (27, 28).

Prenylamine in a dose of 3 mg/kg i.v. failed to antagonise the +ve chronotropic and the hypotensive responses to isoprenaline (1 ug/kg). in anaesthetized cats, Fig. (29, 30).

Fig. (27): Effect of Timolol on isoprenaline +ve chronotropic effect in cats (E.C.G. tracing, Lead II):

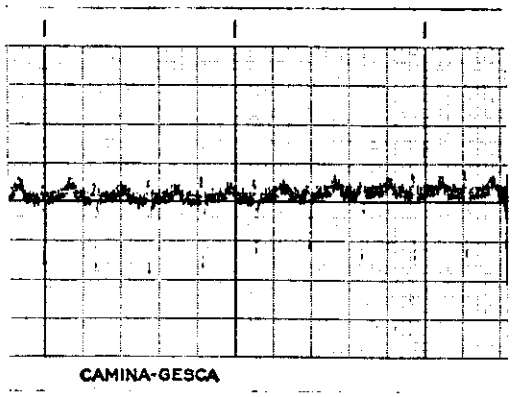
A- Control tracing, normal sinus rhythm (before injection of isoprenaline and timolol).
Heart rate: 210 beats/min. rhythm; regular sinus rhythm. P wave: 1 mm in amplitude and 0.04 sec in duration.
P.R. interval: 0.08 sec.
QRS complex: 10 mm in amplitude, 0.04 sec in duration.
S-T: isoelectric, T wave: 2 mm in amplitude 0.12 sec induration.

B- Isoprenaline 1 ug/kg was injected i.v. produced increase in heart rate to 230 beats/min. which persisted for 2 min.

C- Timolol 25 ug/kg was injected i.v. decrease the heart rate to 150 beats/min.

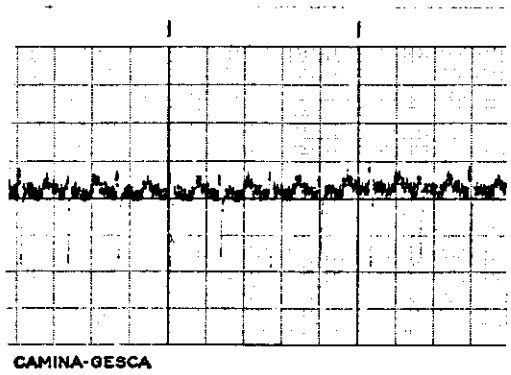
D- Isoprenaline 1 ug/kg was injected again, 15 min. after timolol injection failed to increase the heart rate.

A



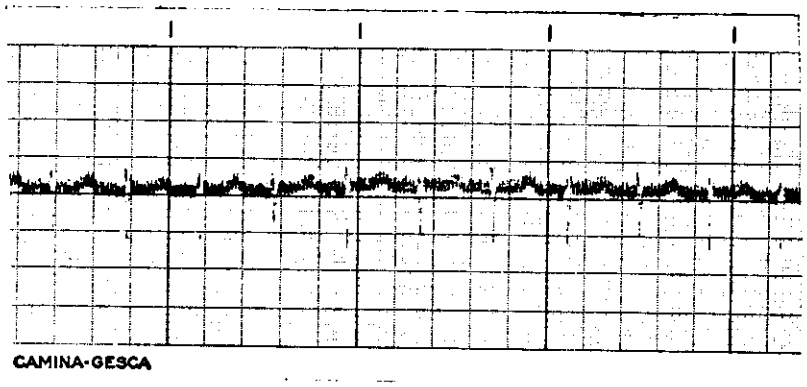
CAMINA-GESCA

B



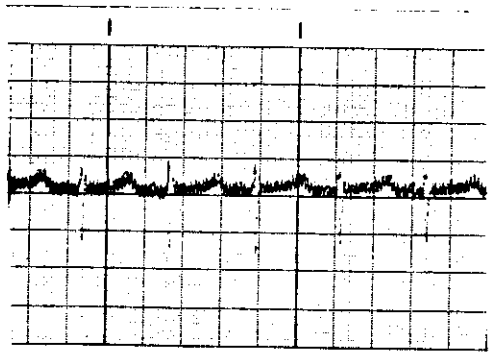
CAMINA-GESCA

C



CAMINA-GESCA

D



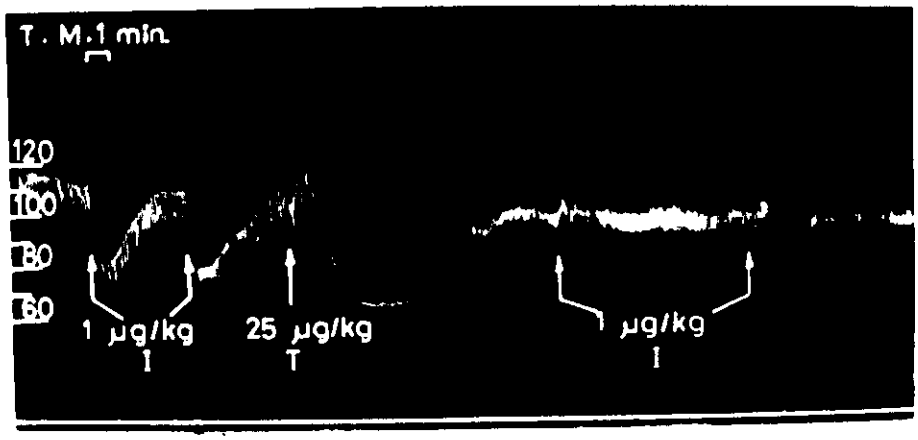


Fig. (28): Effect of timolol on isoprenaline hypotensive effect in anaesthetized cats:

- Isoprenaline in a dose of 1 ug/kg i.v. produced a marked fall of blood pressure.
- Timolol (25 ug/kg i.v.) produced a decrease in blood pressure.
- Then, injection of isoprenaline (1 ug/kg i.v.) 15 min. after timolol injection failed completely to produce hypotensive effect (vasodilator effect).

I = Isoprenaline.

T = Timolol.

T.M.= Time marker.

Fig. (29): Effect of prenylamine on isoprenaline +ve chronotropic effect in cats (E.C.G. tracing, Lead II):

A- Control tracing, normal sinus rhythm (before injection of isoprenaline and prenylamine).
Heart rate: 125 beats/min. rhythm: regular sinus rhythm. P wave: 1 mm in amplitude, 0.04 sec in duration. P-R interval: 0.08 sec.
QRS complex: 7mm in amplitude, 0.04 sec in duration.
S-T segment: isoelectric . T-wave: Flat.

B- Isoprenaline 1 ug/kg was injected i.v. produced increase in heart rate to 150 beats/min. and produced inversion of T wave which persisted for 2 min.

C- Prenylamine 3 mg/kg was injected i.v. had decreased the heart rate to 100 beats/min. and it normalized the T-wave.

D- Isoprenaline 1 ug/kg was injected again, 15 min. after prenylamine injection increase the heart rate to 150 beats/min. and inverted the T-wave.