

CHAPTER IV

RESULTS

I. General observations of STZ-rats and Cilazapril-treated STZ-rats

The streptozotocin treated rat was used as an experimental model of diabetes mellitus in these studies. The objective of this part of the work was to investigate the effects of cilazapril on the diabetic model with respect to plasma glucose levels and body weights. The results showed in Table 4.1 indicated that all these groups (8, 12, 16-weeks) of five STZ-rats and five cilazapril-treated STZ-rats were severe hyperglycemia. There was no significantly difference of plasma glucose between STZ-rats and cilazapril-treated STZ-rats. The body weights of both STZ-rats and cilazapril-treated STZ-rats were significantly decreased as compare to the age-matched controls.

II Studies of cardiovascular functions in STZ-rats and Cilazapril-treated STZ-rats

Cardiovascular functions are CAP, HR, AFR, CFR and LVIC were determined for all three different age groups (8, 12, 16 weeks) of five age-matched controls, five STZ-rats and five cilazapril-treated STZ-rats as summarized in Table 4.2-4.7 by using the experimental protocol as described previously in chapter III. Means and standard deviations of all these assessed cardiovascular parameters were also demonstrated graphically as showed in Figure 4.1 - 4.5.

The overall results of this part of the work showed that :

1. In the five STZ-rats of each age groups (8, 12, 16 weeks), CAP were significantly higher than their age-matched controls. But in the five cilazapril-treated STZ-rats of all three age groups (8, 12, 16 weeks), CAP were significantly lower than the CAP values of the STZ-rats at the same age.

2. In the five STZ-rats of each different age groups (8,12,16 weeks), heart rates were significantly slower than the age-matched controls. But there was no significantly difference between heart rates of cilazapril-treated STZ-rats and the age-matched controls in all three age groups.

3. The same as the result of heart rate determination, aortic flow rates of all three different age groups of STZ-rats were significantly decreased as compared to the age-matched controls, but there was no significantly difference between cilazapril-treated STZ-rats and the age-matched controls.

4. Coronary flow rates (CFR) of all three different age groups (8, 12, 16 weeks) of five STZ-rats were significantly less than the age-matched controls. And this decreasing of CFR seemed to be worse with the duration of diabetes (Figure 4.4). However, cilazapril seemed to improve or prevent this situation eventhough the results were not as good as the control values.

5. The results showed in Table 4.8 demonstrated that after the values of LVIC (gm) were normalized by dividing by 100 gram of heart weight, the LVIC (gm/100 gm heart weight) of STZ-rats became significantly different than the controls

at 12 and 16 - weeks. Figure 4.5 showed that LVIC of the five cilazapril-treated STZ-rats were significantly higher than the LVIC values of STZ-rats in all three aged groups (8, 12, 16 weeks).

6. The R values, ratios of heart weights per 100 gram body weights (Table 4.8), indicated that hearts of STZ-rats have become hypertrophy as compared to the age matched controls. That are concomitant with the results of LVIC, and cilazapril seemed to attenuate this abnormality.

III Studies of morphological examinations of hearts of STZ-rats and Cilazapril-treated STZ-rats

As showed in Figures 4.10 - 4.18 the cross-section of hearts specimens were obtained from three controls, three STZ-rats and three Cilazapril-treated STZ-rats from each aged groups (8, 12, 16 weeks) by using the experimental procedure as described previously in chapter III. Thickness of left ventricular wall, right ventricular wall and interventricular septum wall were measured randomly by the micrometer of light microscope with 4X-objective. Means and standard deviation of these wall thickness values were calculated and summarized in Table 4.9 and Figures 4.10-4.18.

The results of these morphological examinations indicated that :

1. Left ventricular walls of the three hearts of STZ-rats were thicker than the controls for all three aged groups (8, 12, 16 weeks).

2. The right ventricular wall was thicker than control significantly at 12 and 16 weeks after the STZ injections.

3. Wall thickness of both left and right ventricle of cilazapril-treated STZ-rats was not significantly different from the age-matched control values for all three groups (8, 12, 16 weeks)

IV Study of coronary vascular wall thickness of STZ-rats and Cilazapril-treated STZ-rats.

The cross-sections of heart specimens were obtained from three controls, three STZ-rats and three cilazapril-treated STZ-rats from each aged group (8,12, 16 weeks). The intramural coronary arteries were located on the left ventricle of each heart. In this investigation, light microscopic examination did not provide sufficient spatial resolution of the coronary arterial wall compartment. Therefore, the results of this section will be described as general observation of selected coronary arteries, and comparison between control and STZ-rats, and between STZ-rats and cilazapril-treated STZ-rats. The results of morphological observations of intramural coronary arteries indicated that :

1. Intramural coronary artery wall of the three hearts of STZ-rats were notably thicker than the controls for all three different aged group (8, 12, 16 weeks).

2. Wall thickness of intramural coronary arteries of cilazapril-treated STZ-rats was no different from the age-matched controls for all three groups (8, 12, 16 weeks).

Table 4.1 Plasma glucose (mg/dl) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	106.28 \pm 8.67	109.37 \pm 9.27	109.20 \pm 14.32
STZ-rats (n=5)	430.00 \pm 43.79 [■]	476.00 \pm 25.09 [■]	451.00 \pm 41.67 [■]
Cilazapril- treated STZ-rats (n=5)	417.20 \pm 12.85 ^{NS}	412.60 \pm 14.95 ^{NS}	420.00 \pm 13.76 ^{NS}

■ Statistical difference as compared to controls (p < 0.05).

NS = non significant difference as compared to STZ-rats (p < 0.05).

Table 4.2 Body weight (Bw, gm) and Heart weight (Hw, gm) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8		12		16	
	Bw	Hw	Bw	Hw	Bw	Hw
Control (n=5)	349.71 + 22.60	1.23	413.60 + 18.36	1.40	456.25 + 9.65	1.57
STZ-rats (n=5)	280.00 + 17.26 [■]	1.14	280.60 + 22.82 [■]	1.17	281.40 + 12.83 [■]	1.24
Cilazapril- treated STZ-rats (n=5)	280.80 + 19.575 ^{NS}	1.06	275.20 + 9.65 ^{NS}	1.028	293.40 + 20.44	1.09

■ Statistical difference as compared to controls ($p < 0.05$).

* NS = non significant difference as compared to STZ-rats ($p < 0.05$).

Table 4.3 Ratio of heart weight per 100 gram body weight (%) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	0.35 \pm 0.01	0.34 \pm 0.01	0.34 \pm 0.06
STZ-rats (n=5)	0.41 \pm 0.04 [*]	0.42 \pm 0.05 [*]	0.44 \pm 0.02 [*]
Cilazapril -treated STZ-rats (n=5)	0.36 \pm 0.05 ^{NS}	0.37 \pm 0.43 ^{NS}	0.37 \pm 0.03 ^{**}

* Statistical difference as compared to controls (p< 0.05).

** Statistical difference as compared to STZ-rats (p< 0.05).

NS = non significant difference as compared to STZ-rats (p<0.05).

Table 4.4 Common carotid arterial pressure (mmHg) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	76.51 \pm 2.34	86.79 \pm 4.31	82.33 \pm 4.05
STZ-rats (n=5)	93.98 \pm 6.09 [*]	98.32 \pm 3.34 [*]	100.66 \pm 7.69 [*]
Cilazapril-treated STZ-rats (n=5)	77.99 \pm 10.16 ^{**}	83.33 \pm 7.07 ^{**}	85.33 \pm 6.91 ^{**}

* Statistical difference as compared to controls (p < 0.05).

** Statistical difference as compared to STZ-rats (p < 0.05).

Table 4.5 Heart rate (beats/min) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	185.70 \pm 10.60	179.20 \pm 21.00	182.50 \pm 28.70
STZ-rats (n=5)	147.20 \pm 9.20 [*]	128.80 \pm 18.40 [*]	136.00 \pm 18.10 [*]
Cilazapril-treated STZ-rats (n=5)	184.00 \pm 12.33 ^{**}	198.80 \pm 23.82 ^{**}	192.00 \pm 14.96 [*]

* Statistical difference as compared to controls (p < 0.05).

** Statistical difference as compared to STZ-rats (p < 0.05).

Table 4.6 Aortic flow rate (ml/min) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	72.80 \pm 2.70	78.00 \pm 7.60	80.60 \pm 7.30
STZ-rats (n=5)	52.00 \pm 7.50 [▪]	49.00 \pm 4.18 [▪]	38.80 \pm 2.20 [▪]
Cilazapril -treated STZ-rats.(n=5)	70.00 \pm 3.54 ^{▪▪}	70.00 \pm 3.54 ^{▪▪}	78.00 \pm 5.70 ^{▪▪}

▪ Statistical difference as compared to controls (p<0.05).

▪▪ Statistical difference as compared to STZ-rats (p<0.05).

Table 4.7 Coronary flow rate (ml/min) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8	12	16
Control (n=5)	5.00 \pm 0.50	5.62 \pm 0.41	5.69 \pm 0.37
STZ-rats (n=6)	3.40 \pm 0.42 [▪]	2.80 \pm 0.27 [▪]	1.90 \pm 0.74 [▪]
Cilazapril -treated STZ-rats (n=6)	3.10 \pm 0.42 ^{▪▪}	4.30 \pm 0.67 ^{▪▪}	4.90 \pm 0.74 ^{▪▪}

▪ Statistical difference as compared to controls (p< 0.05).

▪▪ Statistical difference as compared to STZ-rats (p< 0.05).

Table. 4.8 Left ventricular isotonic contraction (LVIC, gm) and LVIC (gm/100 gm of heart weight) of 8-16 weeks of controls, STZ-rats, and cilazapril-treated STZ-rats.

Weeks	8		12		16	
	gm	gm/100 gm heart weight	gm	gm/100 gm heart weight	gm	gm/100 gm heart weight
Control (n=5)	3.14 ₊	255.23 ₊	3.85 ₊	276.47 ₊	3.96 ₊	266.01 ₊
	0.37	16.41	0.22	33.29	0.38	55.33
STZ-rats (n=5)	2.50 ₊	221.45 ₊	1.90 ₊	163.28 ₊	1.25 ₊	101.98 ₊
	0.61 [*]	63.42 ^{NS}	0.65 [*]	59.94 [*]	0.70 [*]	60.49 [*]
Cilazapril	3.20 ₊	302.17 ₊	3.26 ₊	320.47 ₊	3.1 ₊	285.32 ₊
-treated	0.27 ^{**}	31.00 ^{**}	0.23 ^{**}	48.71 ^{**}	0.22 ^{**}	25.98 ^{**}
STZ-rats (n=5)						

* Statistical difference as compared to Controls (p< 0.05).

** Statistical difference as compared to STZ-rats (p< 0.05).

NS = non significant difference as compared to controls
(p<0.05)

Table 4.9 Sizes of left and right ventricular wall and interventricular septum wall of (μm) 8-16 weeks of controls, STZ-rats, and Cilazapril-treated STZ-rats.

	Left ventricular wall (LV)	Right ventricular wall (RV)	Interventricular septum wall (IVS)
8-Weeks			
Control (n=3)	2153.33 \pm 94.52	723.16 \pm 28.15	1771.66 \pm 38.83
STZ-rats (n=3)	2406.66 \pm 48.04 [*]	766.66 \pm 65.25 ^{**}	2000.00 \pm 117.57 [*]
Cilazapril-treated STZ-rats.(n=3)	2071.66 \pm 120.86 ^{**}	756.66 \pm 59.23 ^{**}	1730.00 \pm 257.34 ^{**}
12-Weeks			
Control (n=3)	2278.33 \pm 38.19	645.00 \pm 55.67	1800.00 \pm 157.87
STZ-rats (n=3)	2513.33 \pm 128.67 [*]	881.66 \pm 115.79 [*]	2113.33 \pm 363.05 ^{**}
Cilazapril-treated STZ-rats (n=3)	2236.66 \pm 177.78 ^{**}	673.35 \pm 49.32 ^{**}	1613.33 \pm 125.53 ^{**}
16-Weeks			
Control (n=3)	2376.66 \pm 80.20	790.00 \pm 75.49	1710.00 \pm 72.62
STZ-rats (n=3)	2613.33 \pm 63.70 [*]	1078.33 \pm 205.93 [*]	1838.33 \pm 607.99 ^{**}
Cilazapril-treated STZ-rats (n=3)	2220.00 \pm 171.09 ^{**}	713.33 \pm 72.85 ^{**}	1430.00 \pm 242.53 ^{**}

* Statistical difference as compared to controls ($p < 0.05$).

** Statistical difference as compared to STZ-rats ($p < 0.05$).

NS = non significant different as compared to controls, and STZ-rats ($p < 0.05$).

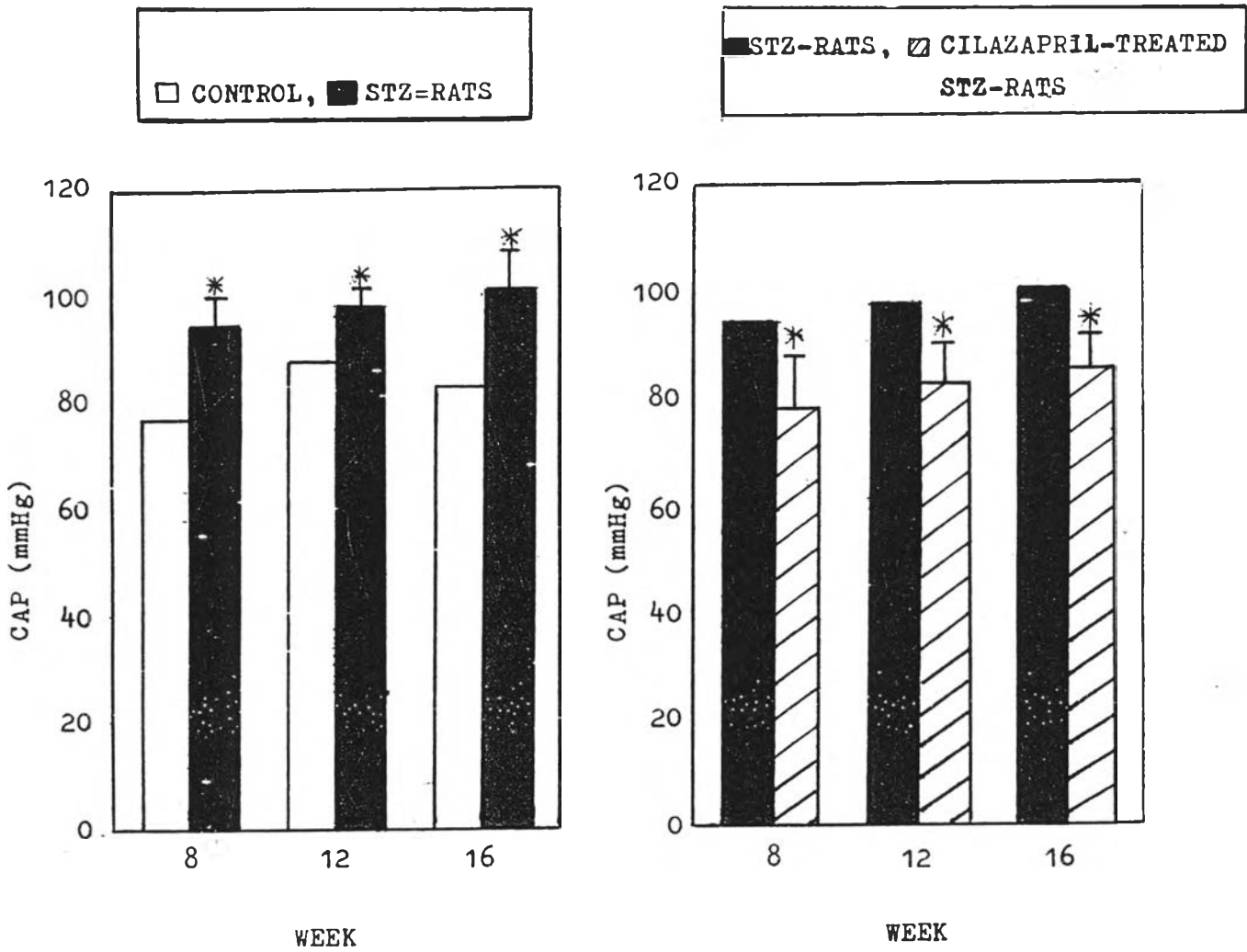


Figure 4.1 Means and SD of common carotid arterial pressure (CAP, mmHg) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ-rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

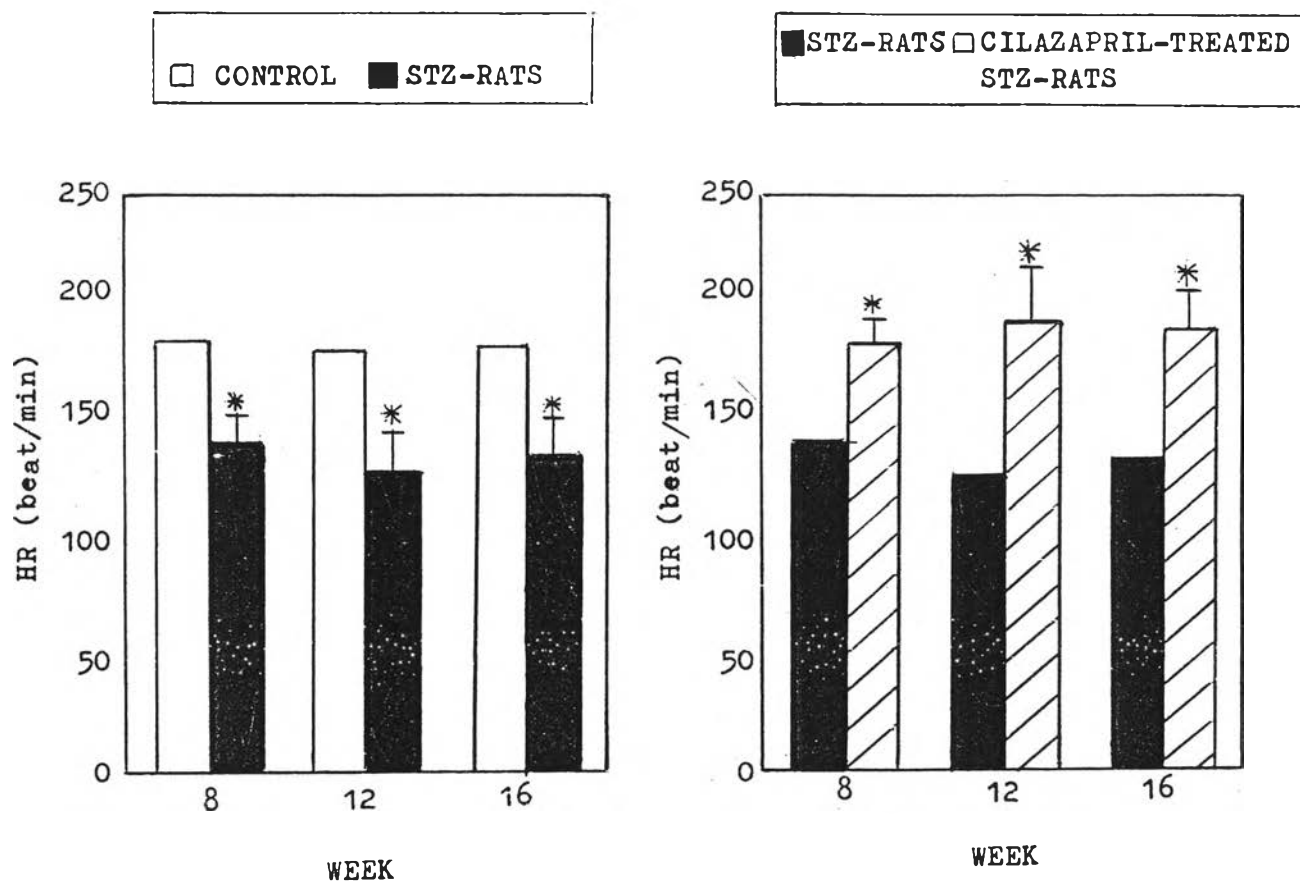


Figure 4.2 Means and SD of heart rate (HR, beat/min) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ-rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

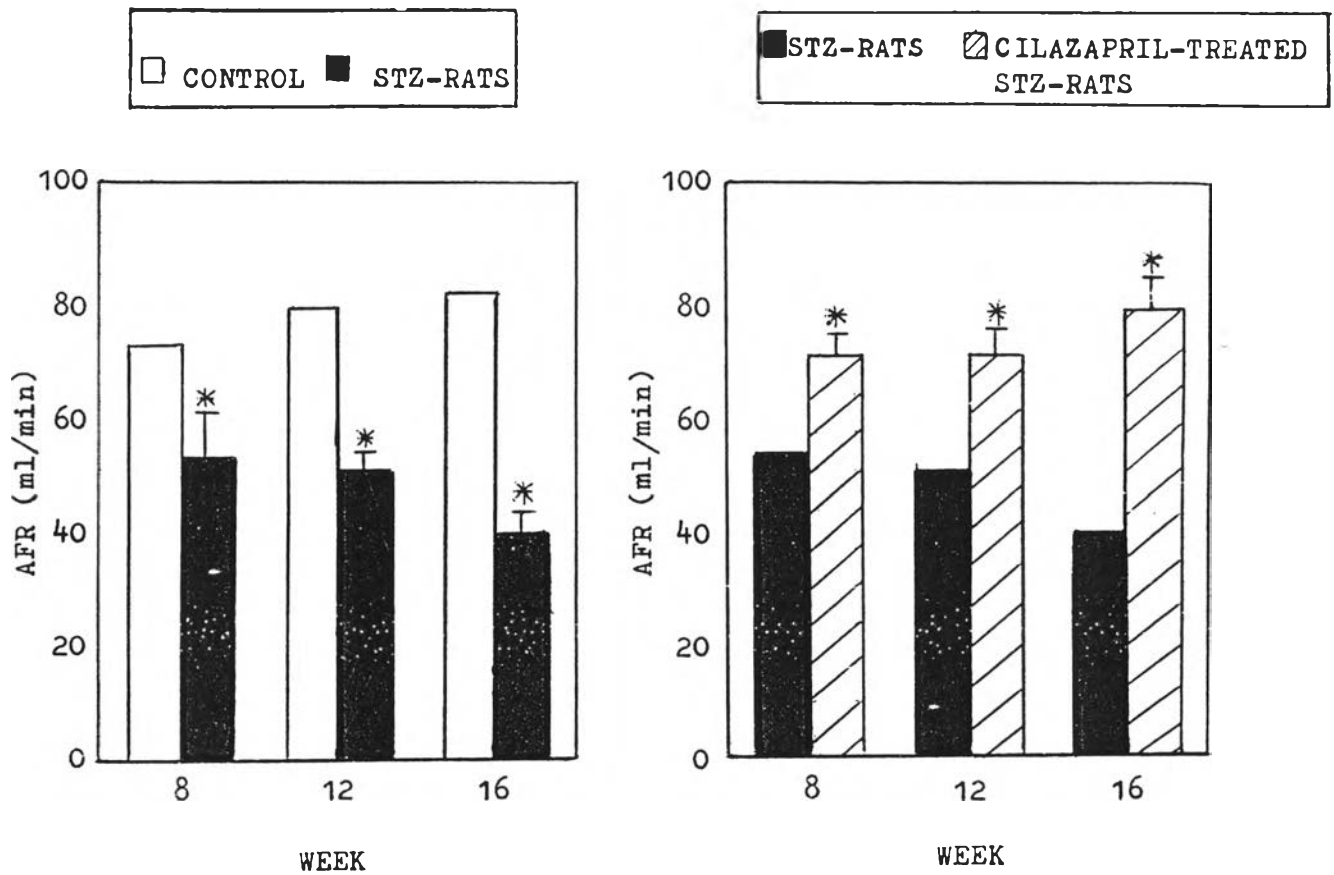


Figure 4.3 Means and SD of aortic flow rate (AFR, ml/min) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ-rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference (p < 0.05).

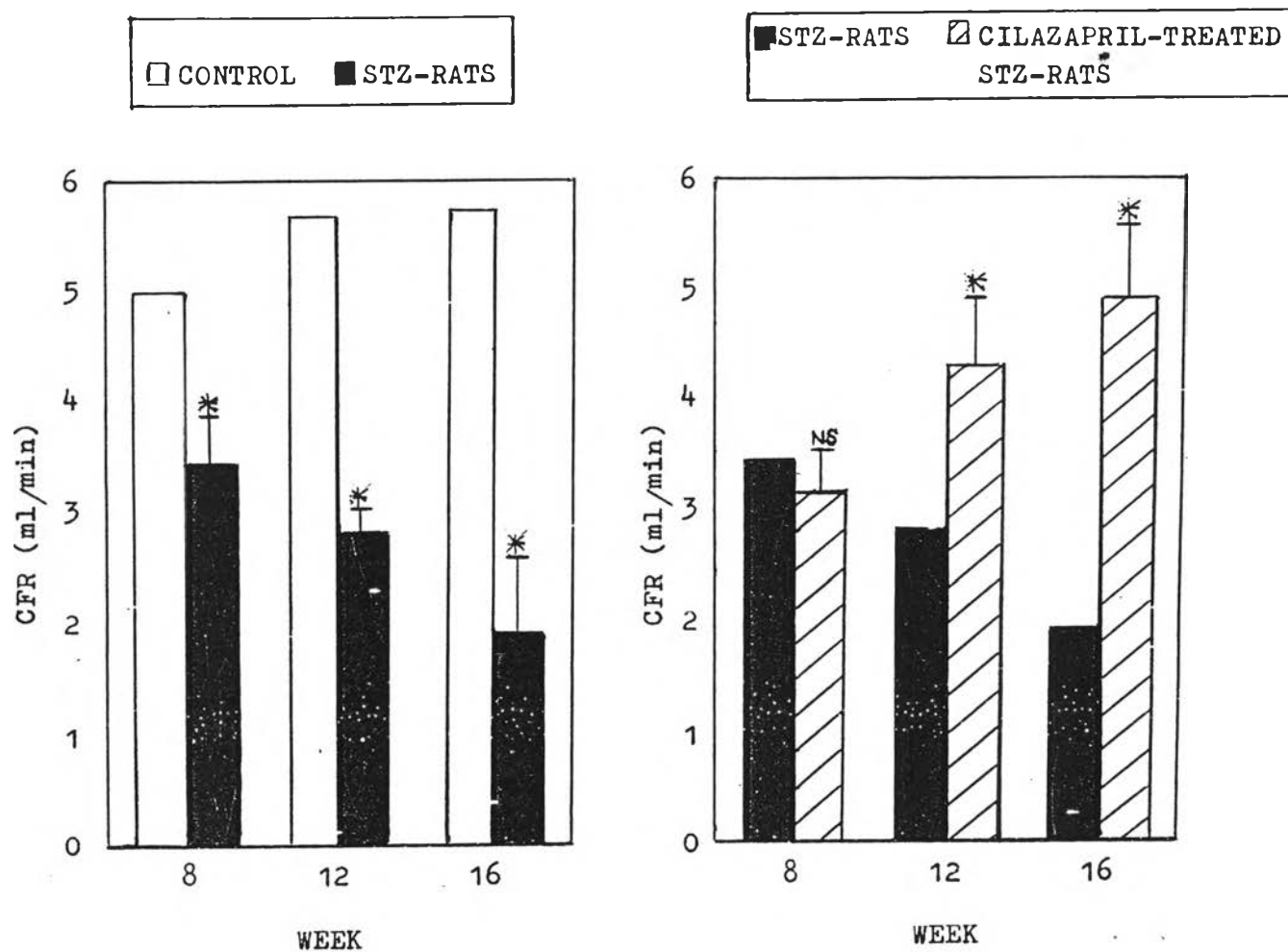


Figure 4.4 Means and SD of coronary flow rate (CFR, ml/min) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

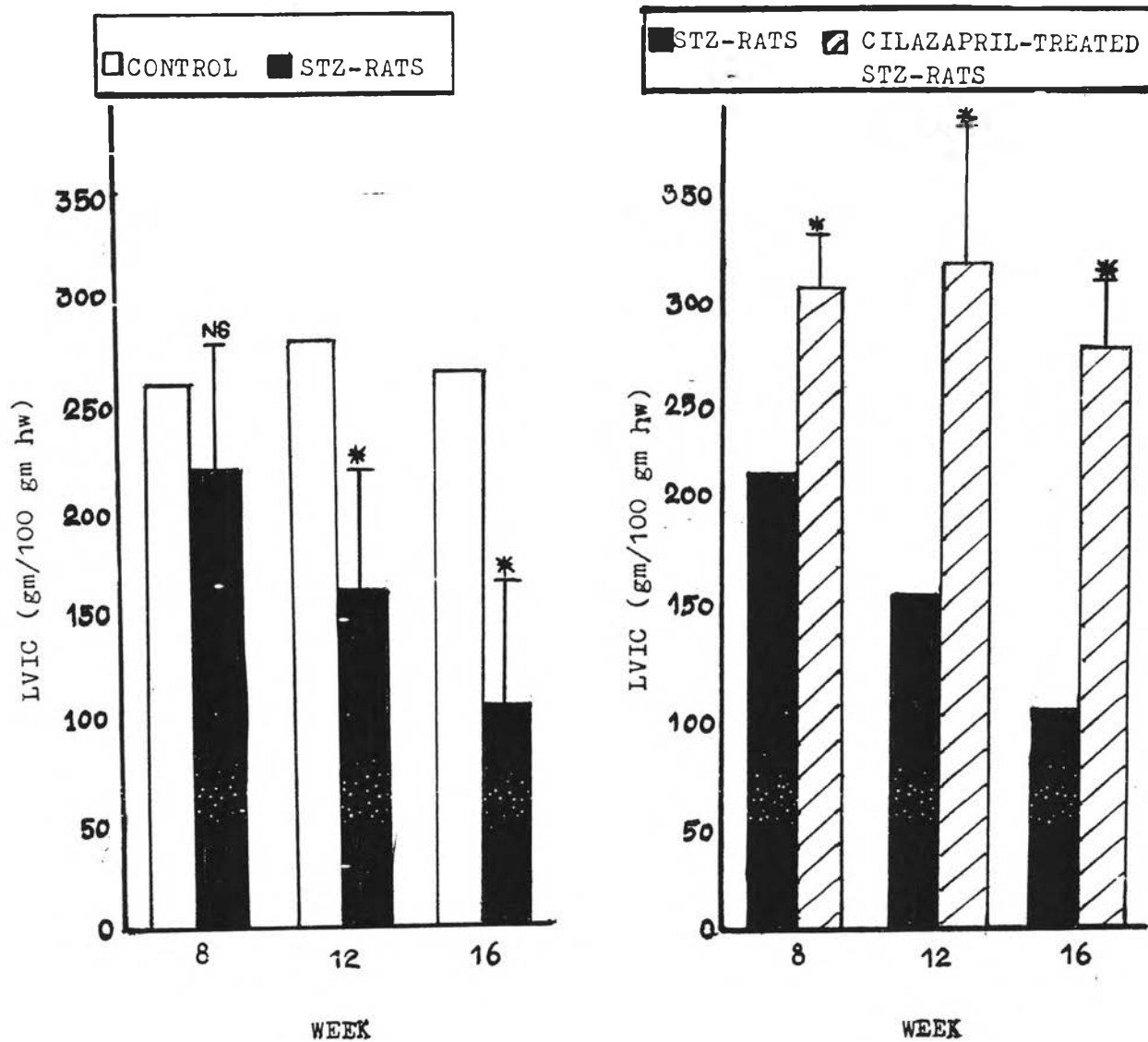


Figure 4.5 Means and SD of left ventricular isotonic contraction (LVIC, gm/100 gm hw) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

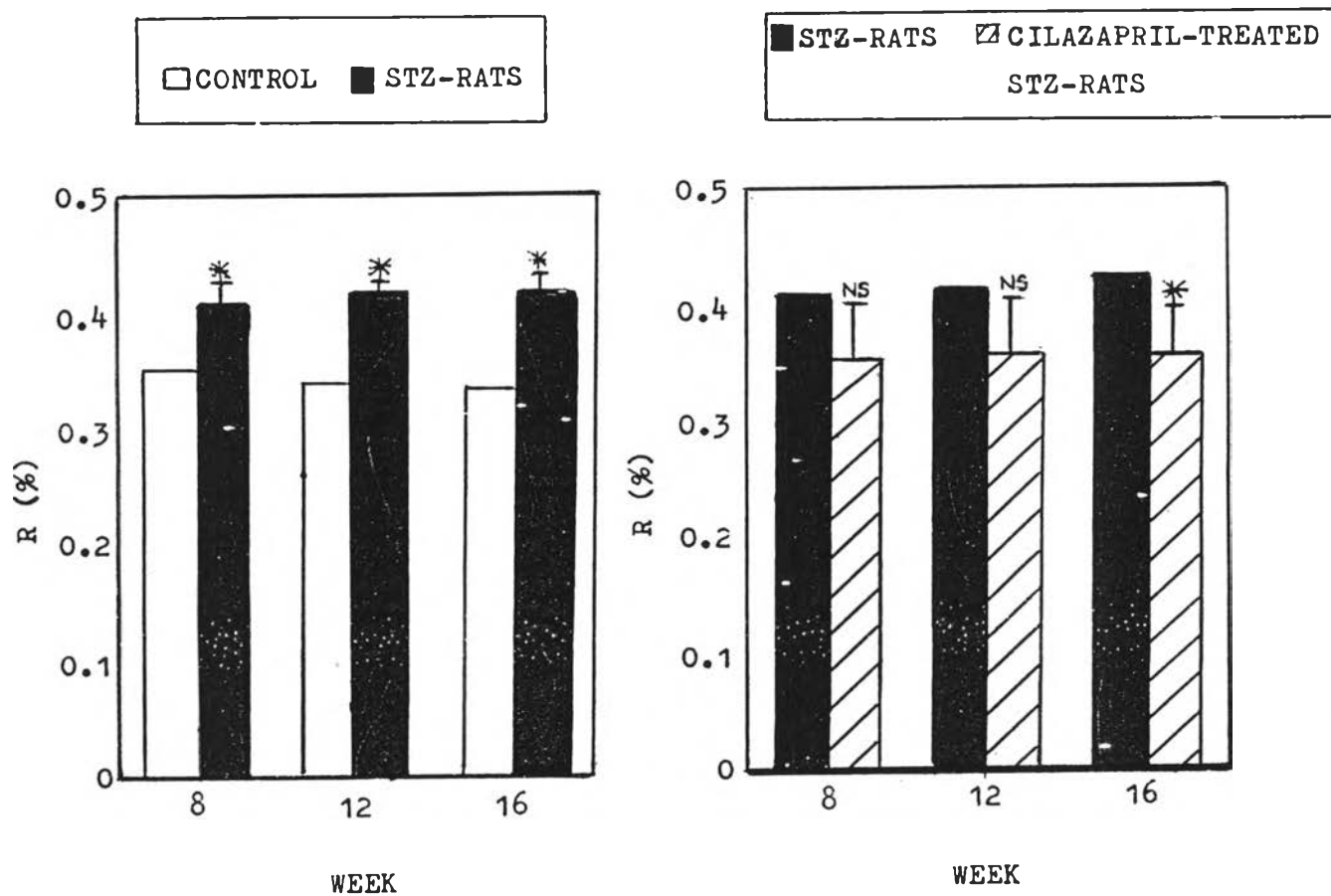


Figure 4.6 Means and SD of ratio heart weight per 100 gm body weight (R, %) of 5 control (□), 5 STZ-rats (■), 5 cilazapril-treated STZ rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference (p < 0.05).

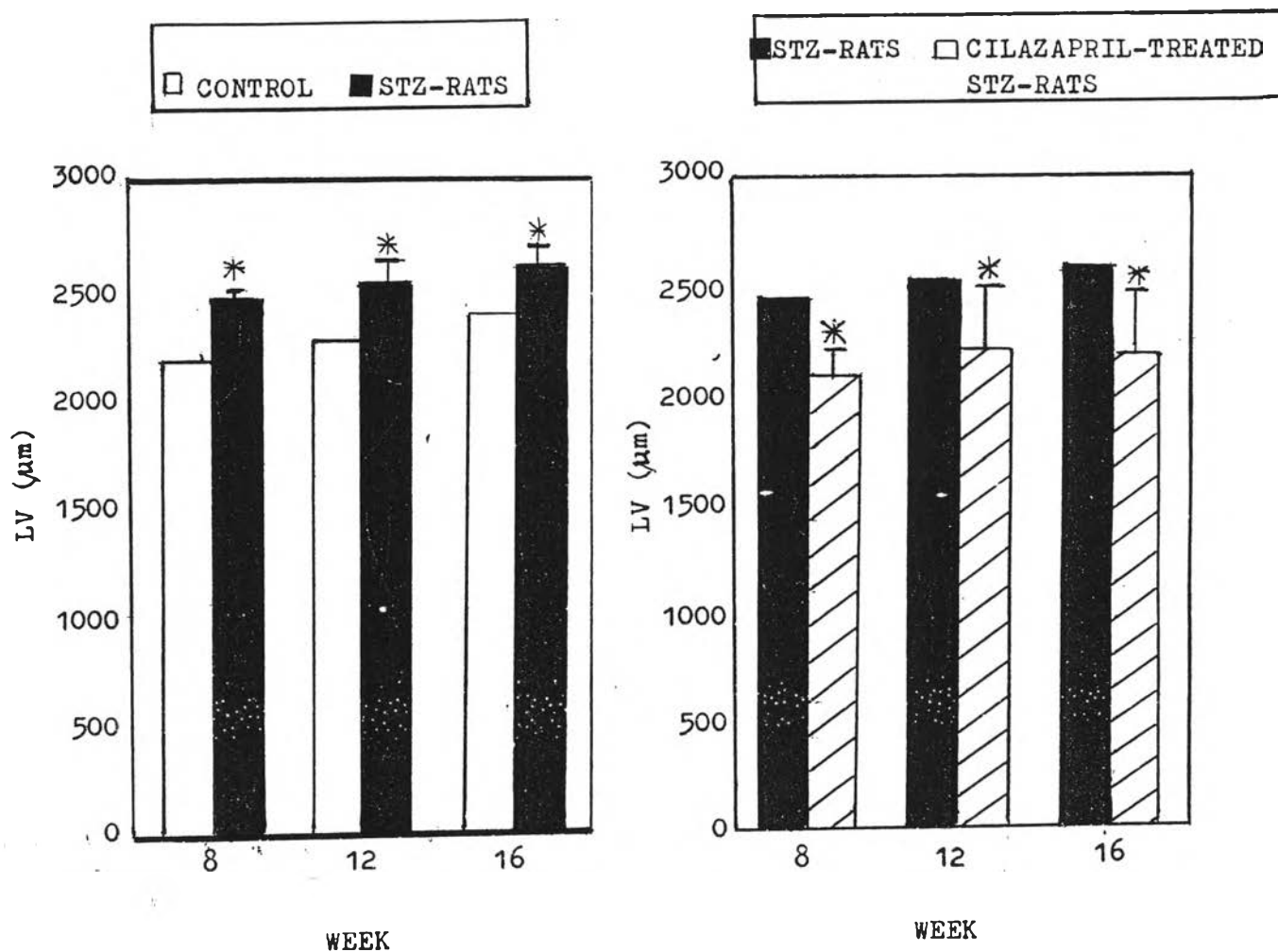


Figure 4.7 Means and SD of thickness of left ventricular wall (LV, μm) of 3 control (\square), 3 STZ-rats (\blacksquare), 3 cilazapril-treated STZ rats (\square) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

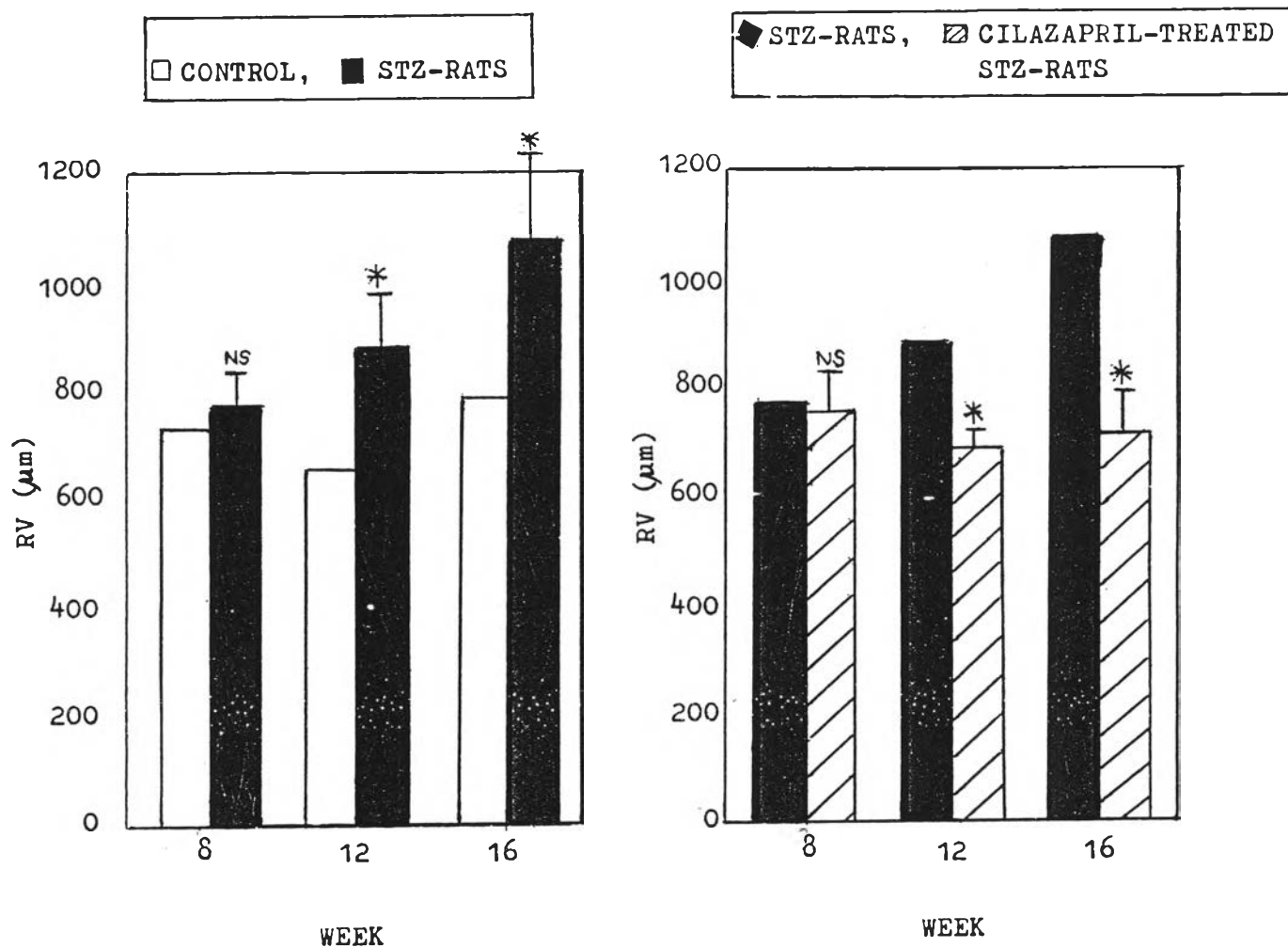


Figure 4.8 Means and SD of thickness of right ventricular wall (RV, μm) of 5 control (\square), 3 STZ-rats (\blacksquare), 3 cilazapril-treated STZ rats (\square) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).

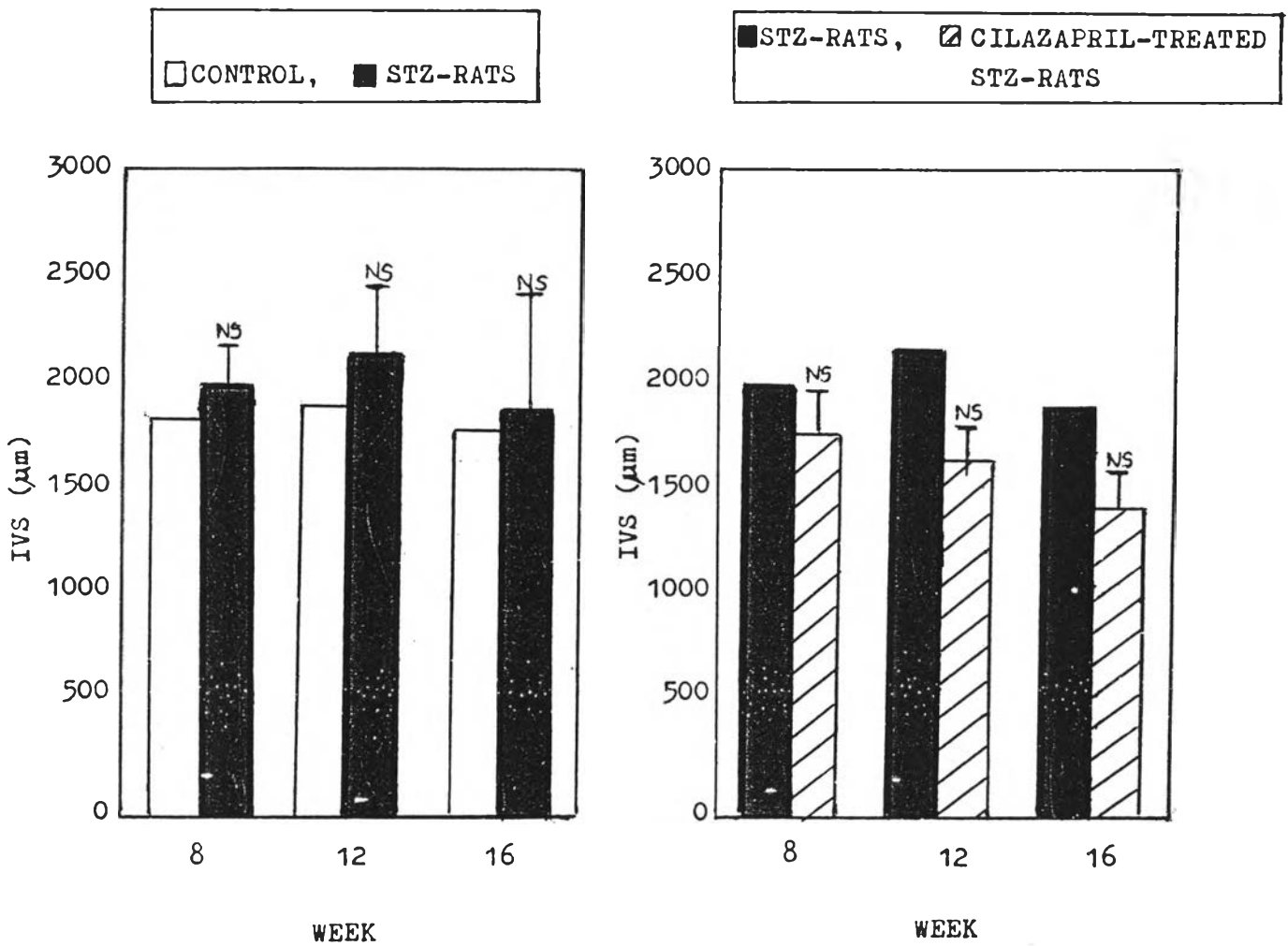


Figure 4.9 Means and SD of thickness of interventricular septum (IVS, μm) of 3 control (□), 3 STZ-rats (■), 3 cilazapril-treated STZ rats (▨) were showed.

* Statistical difference, NS = nonsignificant difference ($p < 0.05$).



Figure 4.10 The cross-section of 8 - week control heart showed left (LV) and right ventricle (RV) and interventricular septum (IVS).
(Eosin & Hematotoxylin X4)

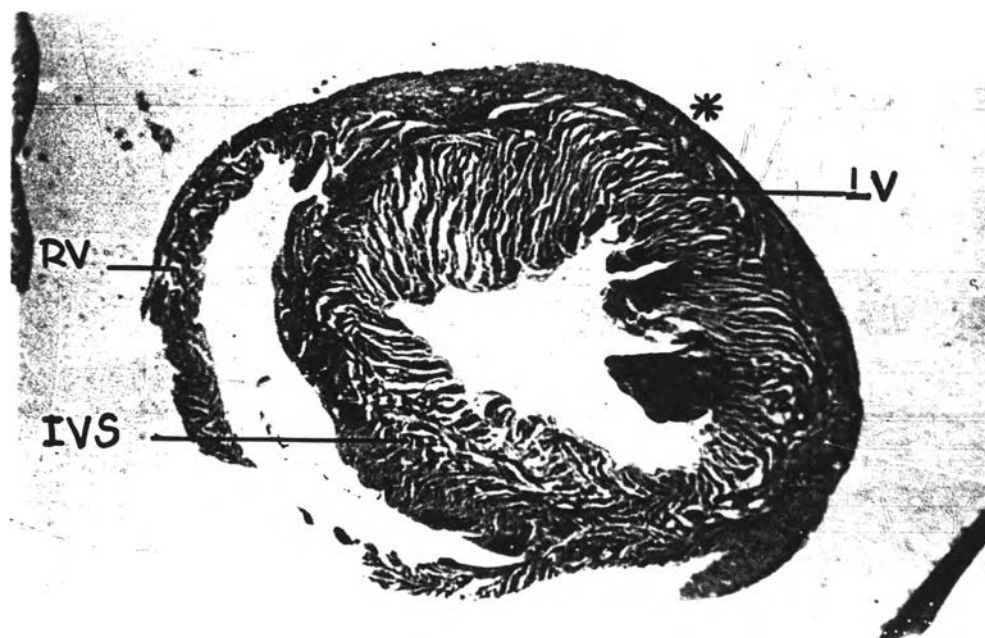


Figure 4.11 Light photo micrograph from 8 - week STZ- rat heart. It is indicated that the wall of left ventricle of this STZ-rat was thicker than the control (Figure 4.10) (Eosin & Hematotoxylin X4)



Figure 4.12 Light photo micrograph from 8 - week cilazapril-treated STZ-rat heart.

It is indicated that the thickness of left ventricular wall was less than the STZ-rat showed in Figure 4.11.

(Eosin & Hematotoxylin x4)

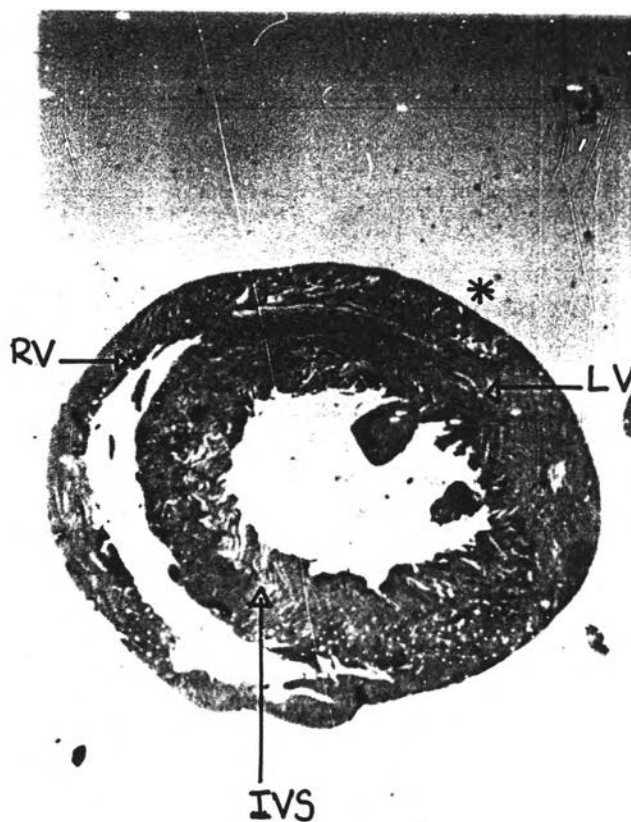


Figure 4.13 The cross-section of 12 - week control heart showed left (LV) and right ventricle (RV) and interventricular septum (IVS). (Eosin & Hematotoxylin X4)



Figure 4.14 Light photo micrograph from 12 - week STZ-rat heart. It is indicated that the wall of left ventricle of this STZ-rat was thicker than the control. (Figure 4.13) (Eosin & Hematotoxylin x4)



Figure 4.15 Light photo micrograph from 12 - week cilazapril-treated STZ-rat heart.
It is indicated that the thickness of left ventricular wall was less than the STZ-rat (Figure 4.14).
(Eosin & Hematotoxylin x4)

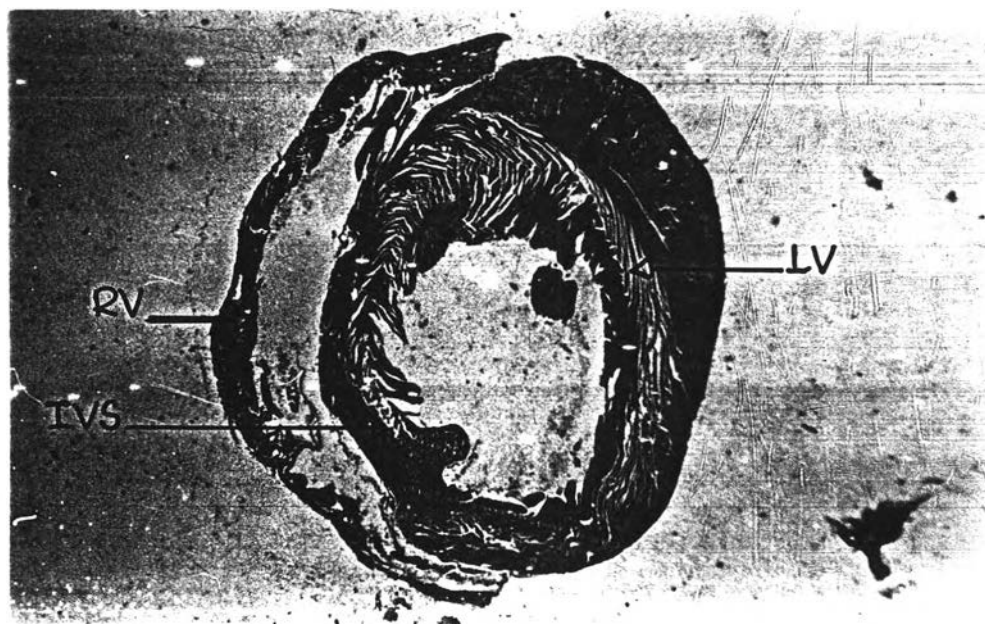


Figure 4.16 The cross-section of 16 - week control heart showed left (LV) and right ventricle (RV) and interventricular septum (IVS).
(Eosin & Hematotoxylin X4)



Figure 4.17 Light photo micrograph from 16 - week STZ-rat heart. ■ It is indicated that the wall of left ventricle of this STZ-rat was thicker than the control. (Eosin & Hematotoxylin X4)

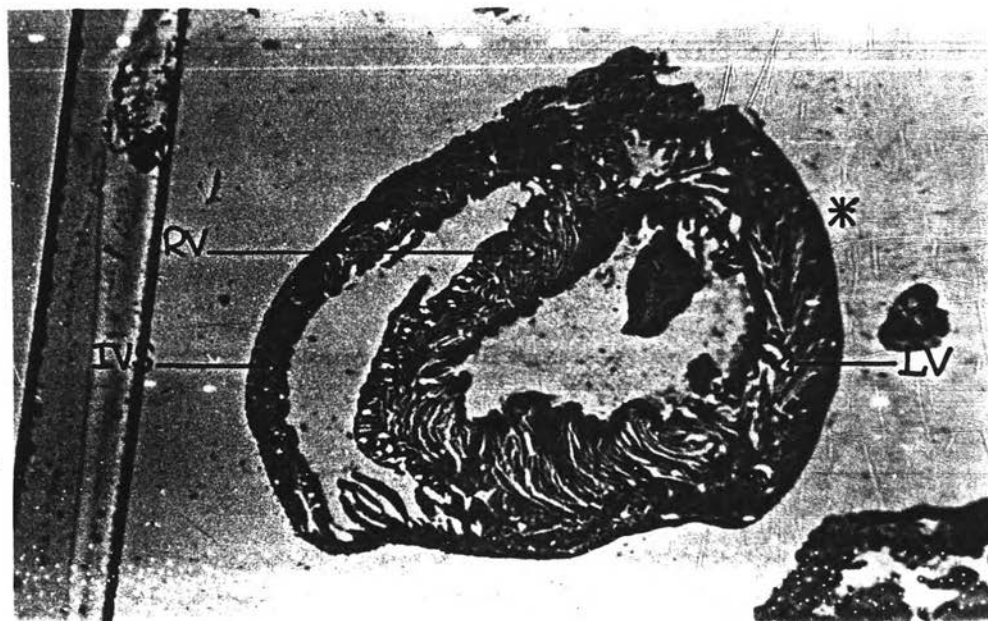


Figure 4.18 Light photo micrograph from 16 - week cilazapril-treated STZ-rat heart. It is indicated that the thickness of left ventricular wall was less than the STZ-rat (Figure 4.17). (Eosin & Hematotoxylin x4)

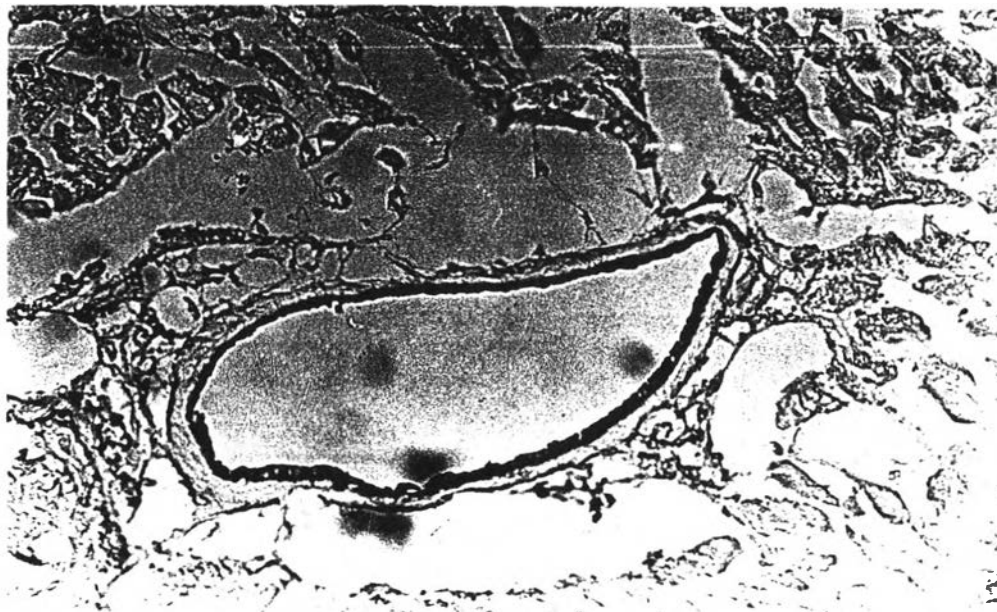


Figure 4.19 Light photo micrograph from intramural coronary artery from left ventricular myocardium of 8 week control heart. (Elastic x 40)

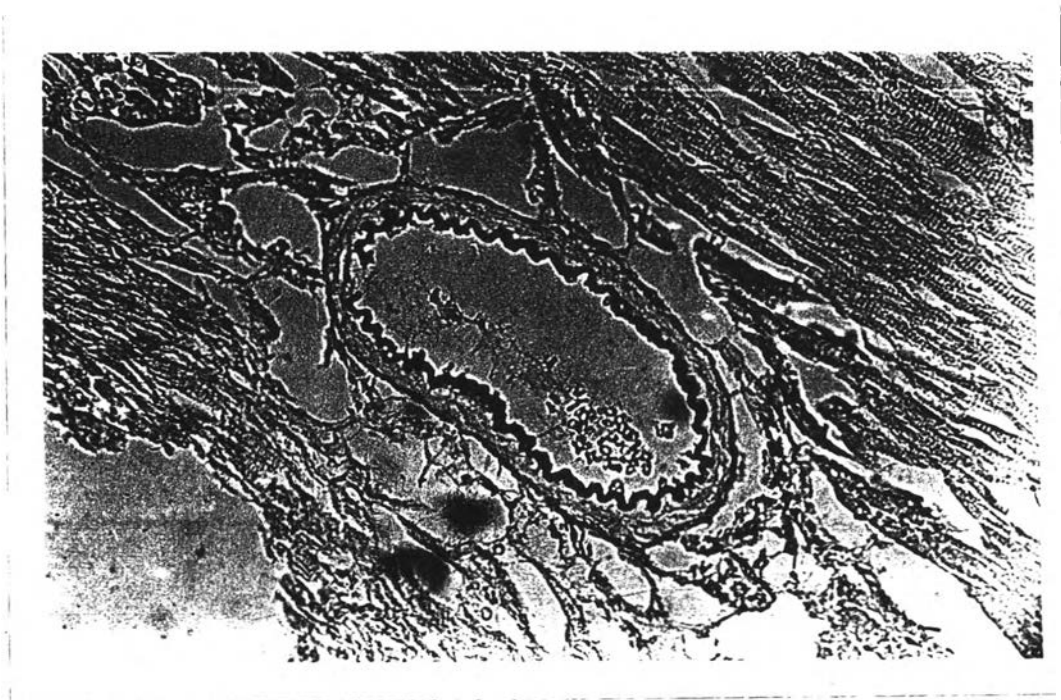


Figure 4.20 Light photo micrograph of intramural coronary artery from 8 week STZ-rat. It was observed that the arterial wall become thicker than the control (Figure 4.19). (Elastic x 40)

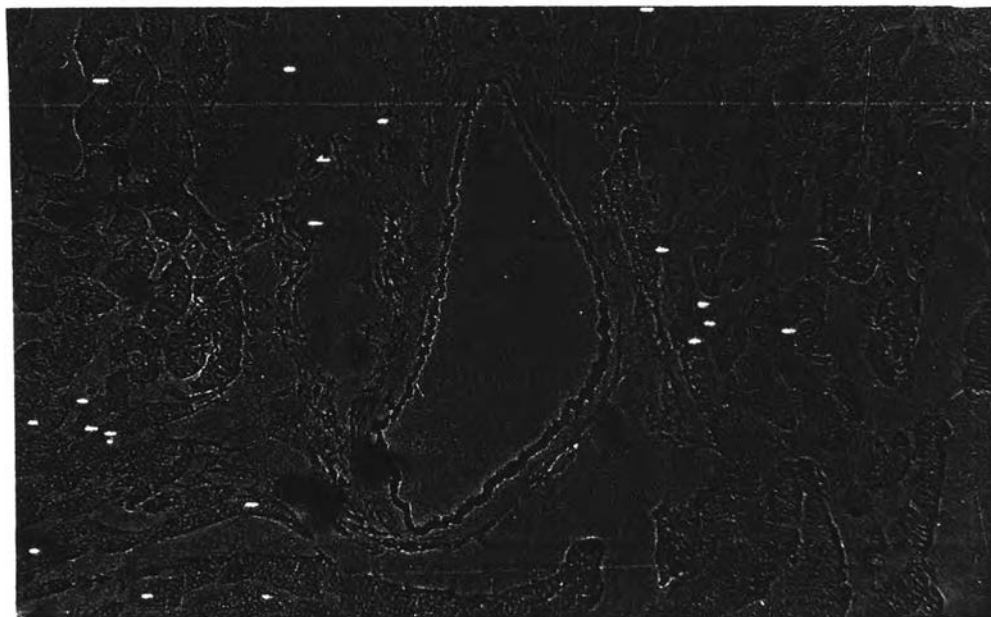


Figure 4.21 Light photo micrograph showing the thickness of intramural coronary artery wall from 8 week cilazapril-treated STZ-rat. It was observed that the arterial wall thickness was less than the STZ-rat (Figure 4.20). (Elastic x 40)

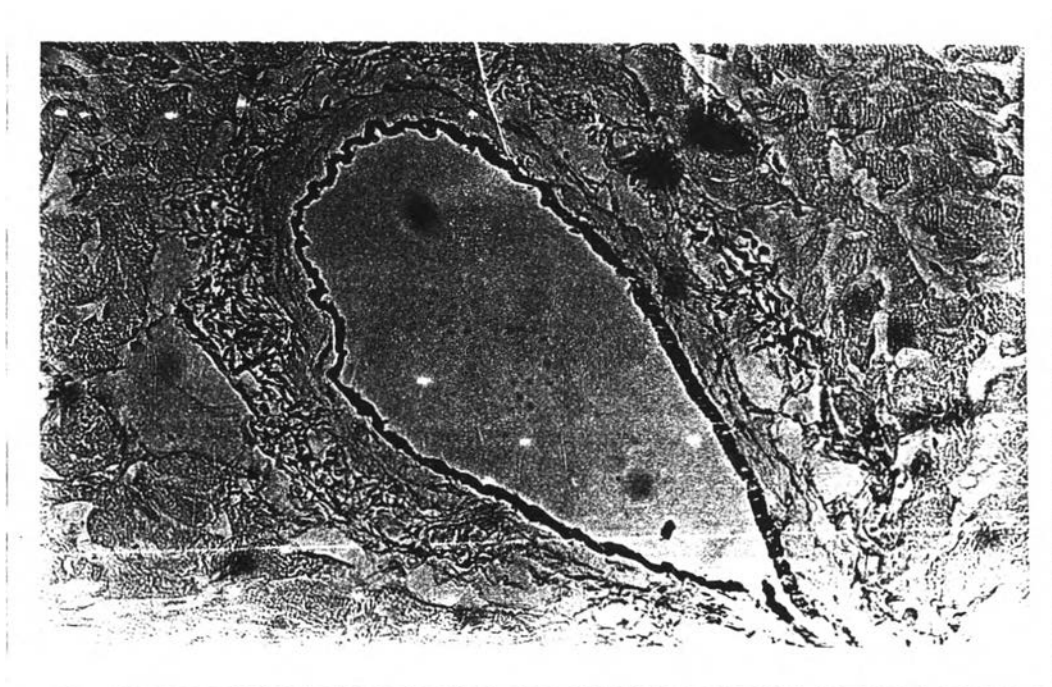


Figure 4.22 Light photo micrograph of intramural coronary artery from left ventricular myocardium of 12 week control heart. (Elastic x 40)

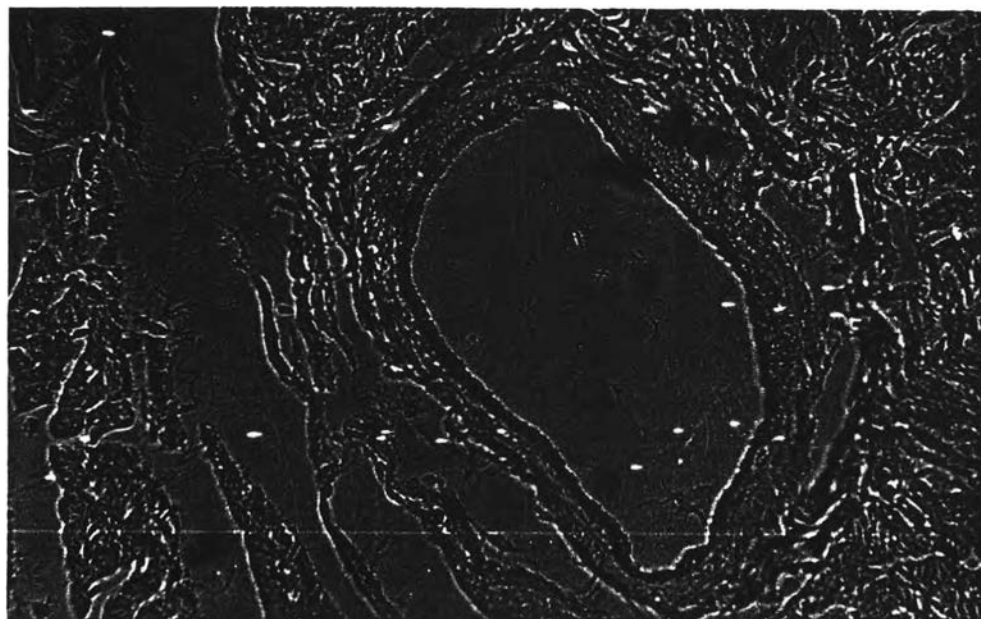


Figure 4.23 Light photo micrograph of intramural coronary artery from 12 week STZ-rat. It was observed that the arterial wall become thicker than the control (Figure 4.22). (Elastic x 40)

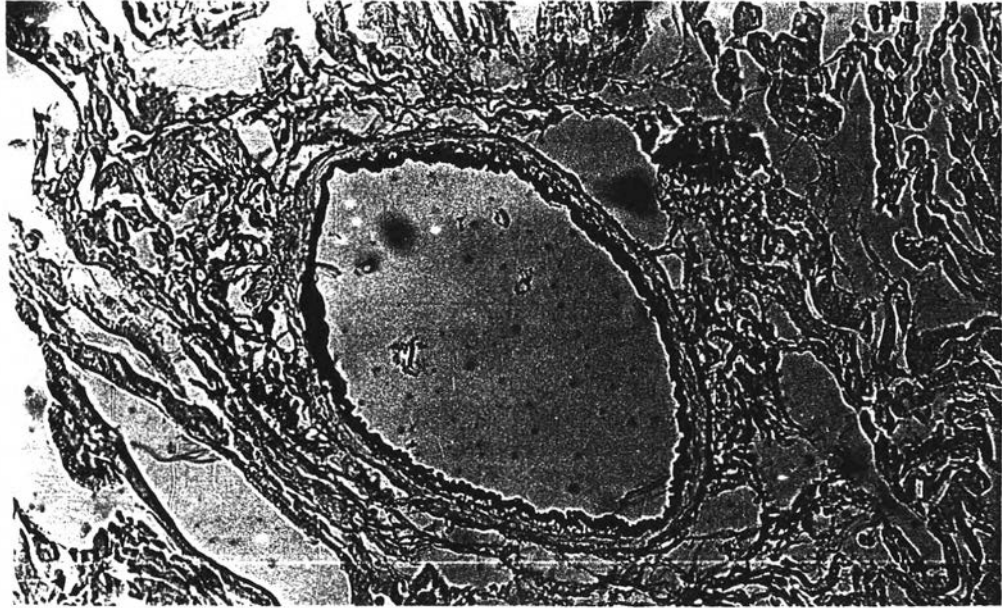


Figure 4.24 Light photo micrograph showing the thickness of intramural coronary artery wall from 12 week cilazapril- treated STZ-rat. It was observed that the arterial wall thickness was less than the STZ-rat (Figure 4.22). (Elastic x 40)



Figure 4.25 Light photo micrograph of intramural coronary artery from left ventricular myocardium of 16 week control heart. (Elastic x 40)



Figure 4.26 Light photo micrograph of intramural coronary artery from 16 week STZ-rat. It was observed that the arterial wall become thicker than the control (Figure 25). (Elastic x 40)

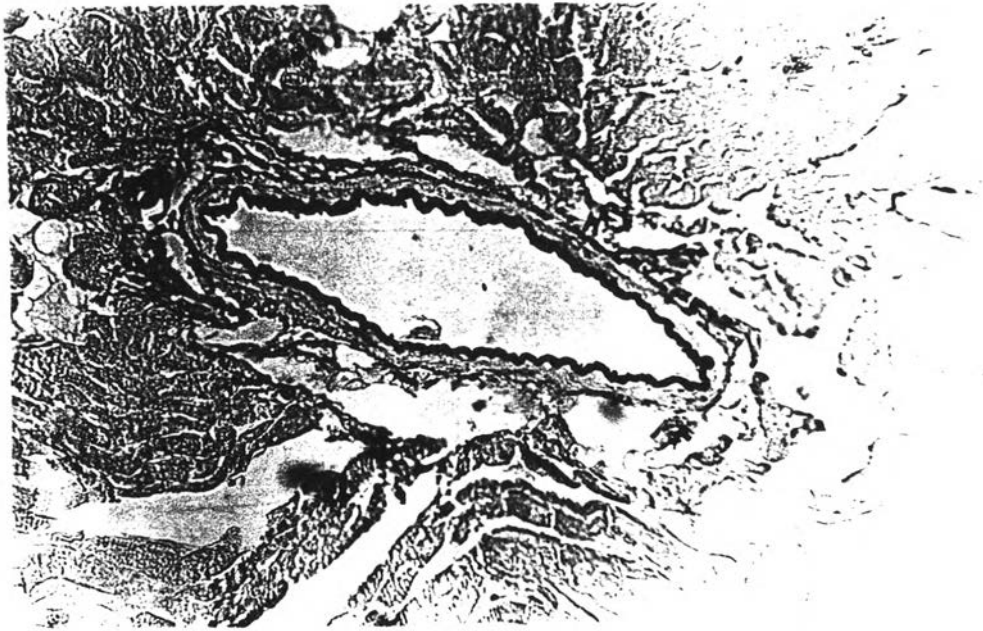


Figure 4.27 Light photo micrograph showing the thickness of intramural coronary artery wall from 16 week cilazapril-treated STZ-rat. It was observed that the arterial wall thickness was less than the STZ-rat (Figure 26). (Elastic x 40)