CHAPTER IV

RESULT AND DISCUSSION

1. Hypertensive patients

Recruitment of patients began in October 1999 and ended on July 2000 at the out-patient department Phramongkutklao Hospital. The screening process identified 61 patients who met the screening criteria for eligibility and entered the placebo run-in period. Thirty-four patients were excluded for various reasons, i.e., thirty-one patients (about 50% of the screening recruited patients) were diagnosed to be white coat hypertension (which when closely monitored with ambulatory blood pressure monitoring machine their mean 24-hour DBP were less than 85 mmHg), two patients were consent denied and one patiented showed abnormal laboratory data. The remaining twenty-seven subjects having mean 24-hour DBP $\geq$ 85 mmHg measured by ABPM were recruited in the study.

The patients were categorized into mild and moderate hypertensive patients who then receive enalapril 5 and 10 mg per day respectively. During the study, one patient was dropped out from the study due to adverse drug reaction (cough), one patient showed higher BP level when he received the higher dose of enalapril and one patient dropped out of the study during the first period of treatment. Finally, there were twenty-four patients who completed this study and their data only were used for statistical analysis.

Demographic data

Twenty-four hypertensive patients were enrolled in the study with eleven were classified into mild while thirteen were classified into moderate hypertensive patients, respectively. Baseline demographic details are summarized in Table 7. There were fourteen males and ten females, with the average age of 59 ± 10.17 years (range 37-76 years). The average weight, height and BMI values (Mean ± SD) were 65 ± 8.14 kg., 159 ± 8.88 cm. and 26 ± 2.39 kg/m^2, respectively. One subject is currently smoking cigarettes and five subjects drank alcohol for social life.

Nine patients were new cases while fifteen had been treated for their hypertension either monotherapy or combined therapy before they entered into the study. Laboratory data at the end of the placebo run-in period are shown in table 8. Seven subjects had hyperglycemia and one subject had his serum creatinine at the high normal level. Seven subjects had high levels of cholesterol and eight subjects had high levels of triglyceride. However, the liver function tests as well as the electrolyte in all subjects were in the normal ranges. The demographic and laboratory data of each subject were demonstrate in details in Appendices A and B.

Table 7 : Demographic data of hypertensive subjects

No. of subjects	24
Sex	
Male	14
Female	10
Age (years)	
Mean ± SD	59 ± 10.17
Range	(37-76)
Weight (kg)	
Mean ± SD	65 ± 8.14
Range	(52-85)
Height (cm)	
Mean ± SD	159 ± 8.88
Range	(146-175)
BMI* (kg/m^2)	
Mean ± SD	26 ± 2.39
Range	(22-30)
Cigarettes smoking (no.)**	1
Alcoholic (no.)**	5

* BMI = Body Mass Index

** the number of patients who is currently smoking ,drink within 1 year

Table 8 : Laboratory data of hypertensive subjects

Tests	Mean ± SD	Range
Glucose (4.2-6.1 mmol/l)	5.9 ± 1.93	(2.9-10.8)
BUN (2.6-9.2 mmol/l)	5.3 ± 1.11	(3.7-7.7)
SCr (62-124 μmol/l)	106 ± 37.66	(76-259)
Uric acid (240-538 μmol/l)	302 ± 87.33	(181-524)
Cholesterol (150-250 mg/dl)	237 ± 47.62	(176-401)
Triglyceride (50-160 mg/dl)	151 ± 60.54	(62-270)
HDL (30-70 mg/dl)	51 ± 11.81	(30-74)
LDL (130-159 mg/dl)	157 ± 43.40	(69-294)
AST (0-37 U/L)	21 ± 4.73	(13-32)
ALT (0-40 U/L)	24 ± 8.75	(6-43)
Sodium (135-150 mmol/l)	142 ± 2.67	(138-146.5)
Potussium (3.5-5.5 mmol/l)	4.4 ± 0.39	(3.79-5.3)
Chloride (98-110 mmol/l)	107.4 ± 2.38	(103-111.6)
CO_2 (24-34 mmol/l)	26.3 ± 2.88	(17.3-30.9)

2. Blood pressure data at baseline of hypertensive subjects

Office blood pressure (OBP) at the screening visit and after placebo run-in period were illustrated in Table 9. BP after taking placebo was used as the baseline level for comparing the drug effects. There was an insignificant difference of BP values obtained between these two periods. When the ranges were consider and compared, the result showed that after placebo, the values of the lower end (140 mmHg) were higher than the values at the screening visit (130 mmHg) since some patients had already been treated with some antihypertensive drugs while the values of the upper end (183 mmHg) were not since these should be the values of the untreated patients. In treated patients, none of them showed state of severe hypertension (SBP $\geq$ 180 or DBP $\geq$ 110 mmHg) after placebo run-in

The office BP and 24-hour ambulatory blood pressure at baseline were shown in Table 10. Comparison of mean blood pressure between those of office BP and 24-ABP found that the mean office BP was higher than the mean BP either when considered as the average throughout 24-hour, during day-time or during night-time, however, mean office BP was closed to the day-time BP. Furthermore, ABPM could provide the frequency and magnitude of BP loads. In this study, the results showed that the frequency of SBP loads during night-time was higher than the other periods of monitoring, while the frequency of SBP loads throughout 24-hour was closed to the values during day-time. However, the frequency of DBP loads whether from 24-hour, day-time and night-time were nearly equal and all were around 58 %. When absolute SBP and DBP loads were considered, It was found that the values obtained from 24-hour, day-time and night-time were nearly equivalent and the values were approximately 20 mmHg and 10 mmHg for absolute loads of SBP and DBP respectively.

The office BP and 24-hour ambulatory blood pressure (ABP) monitoring had been used as the methods for detecting BP in hypertensive patients and also in determining the antihypertensive effect of enalapril in this study. Some of the benefits of ambulatory BP measurement over the standard clinic or office BP measurement in a clinic therapeutic trial have been well established[40-42]. These included the ability to detect white coat hypertensives during patient selection. A placebo group could be avoided and the sample size could be reduced when ABPM were used to determine the efficacy of an antihypertensive drug. Finally, 24-hour mean BP is more reproducible than clinic BP. Thus, with the 24-hour ABP measurement during patient selection, white coat hypertensive patients were not included in the antihypertensive drug trial and hypertensive patients who were eligible into this study had high BP both in the office and their daily lives.

Several studies had shown that repeated BP elevations during work stress and the overall BP load may also be an important determinant of cardiovascular risk[15-16,43]. The systolic BP load in normotensive patients increase from approximately 9 percent in young adults to 25 percent in elderly[44] . The diastolic BP load averages 3 to 4 percent and does not appear to vary sinificantly with age. Studies in untreated hypertensive patients showed that the likelihood of developing cardiac abnormalities was markedly increased when the daily BP load was 40 percents or more[45], which White et al. suggested that these patients should receive antihypertensive therapy.

From this study, it was found that night-time SBP loads was higher than day-time SBP loads which could due in part to the unfamiliar with the non-invasive BP monitoring machine which showed more pronounced effect while rest at night, and also due to the reason that there were eleven out of twenty-four patients who showed small BP reduction during night-time as compared to those of the day-time.

However, BP level during night-time was lower than day-time. It was demonstrated that the falling in BP at night was the result of sleep and inactivity rather than the time of the day. In both normotensive and hypertensive individuals, BP varies according to mental status and physical activity level which are usually different during wakefulness and during sleep. Furthermore, in this study about 45 % of subjects who normotensive (24-hour DBP < 85 mmHg at baseline) and were exclude from the study when monitored with 24-hour ABPM showed SBP load of more than 40 %.

With the categorization of hypertensive patients as "dipper" or "non-dippers" according to the percentage of BP reduction during night-time as compared to day-time. Dippers were patients who had BP fall during the night by more than 10 % compared to day-time BP while others whose BP fall less than 10 % were non dippers. With this criteria, thirteen patients participated in this study were dipper (54%) while eleven patients were non dipper(46%).

There is evidence that failure of the BP to fall during sleep may be an additional risk factor for the development of left ventricular hypertrophy and other cardiovascular complication[18,46-48]. This effect appeared to be more prominent in women, diabetics with renal insufficiency, and blacks. However, other studies had found that nondippers including women and blacks, showed no increase in left ventricular geometry[49].

Concerning the mean 24-hour BP profile (Figure 5.), it was found that BP was stayed at high level during day-time and was reduced to lower level during night-time as shown in Figure 1. BP decreased to its lowest point (nadir) at approximately 12.00 PM. The nadir BPs were 132/78 mmHg of SBP / DBP which corresponded to the MAP value of 96 mmHg. After nadir , BP tended to increase throughout the

early morning hours and was further increase when they woke up (approximately 05.00 AM) to a high level of 156 / 98mmHg for SBP / DBP at 9.00AM.

Table 9 : Office BP at the screening visit and after placebo run-in period or at baseline

Office BP at the screening visit*		
SBP (mmHg)	158 ± 15.95	(130-183)
DBP (mmHg)	99 ± 8.52	(80-110)
MAP (mmHg)	119 ± 9.78	(97-133)
HR (bpm)	77 ± 9.99	(60-94)
Office BP after placebo (at baseline)		
SBP (mmHg)	155 ± 8.87	(140-173)
DBP (mmHg)	97 ± 5.00	(89-107)
MAP (mmHg)	116 ± 4.68	(107-126)
HR (bpm)	79 ± 9.70	(62-96)

*data are shown as mean ± SD (range)

Table 10 : Office BP and 24-hour ABP of hypertensive patients after placebo run-in period or at baseline

	Office BP* (mmHg)	24-hour ABP*								
		Average BP (mmHg)			BP loads**					
		24-hour BP	day-time BP	night-time BP	24-hour BP		daytime BP		nighttime BP	
					frequency[a] (%)	absolute[b] (mmHg)	frequency[a] (%)	absolute[b] (mmHg)	frequency[a] (%)	absolute[b] (mmHg)
SBP	155 ± 8.87	146 ± 9.47	151 ± 9.87	137 ± 14.35	69 ± 21.48	20 ± 5.45	65 ± 23.77	19 ± 6.67	79 ± 20.79	20 ± 11.08
DBP	97 ± 5.00	89 ± 4.18	93 ± 4.33	82 ± 6.90	58 ± 17.67	10 ± 2.30	58 ± 19.03	10 ± 3.15	55 ± 25.78	10 ± 3.91
MAP	116 ± 4.68	108 ± 4.74	112 ± 5.23	100 ± 8.07						
HR(bpm)	79 ± 9.70	76 ± 6.81	80 ± 6.43	67 ± 8.33						

* data are shown as mean ± SD

** BP loads were BP values that higher than 140 or 120 mmHg for SBP and 90or 80 mmHg for DBP during day-time, night-time respectively

[a] frequency of BP load in percentage

[b] absolute of pressure of BP loads in mmHg

24-hour BP= average BP during 24-hour, day-time BP=average BP during 06.00 am –10.00 pm, night-time BP=average BP during 10.00 pm – 06.00 am by ambulatory blood pressure monitoring machine

SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, HR=heart rate respectively

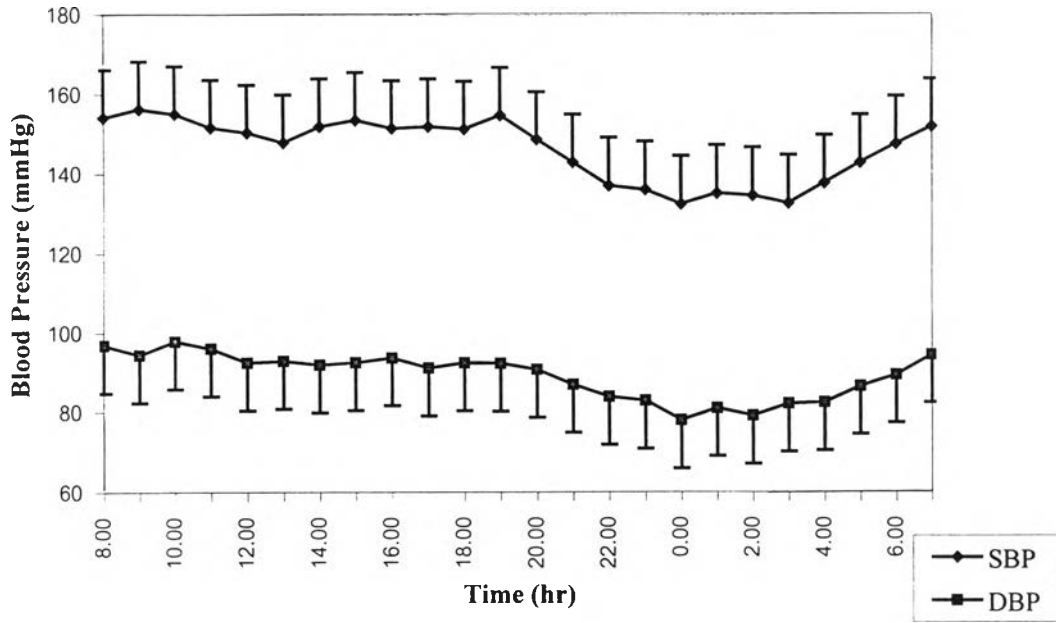


Figure 5 : Ambulatory hourly blood pressure data of hypertensive patients (n=24) at baseline

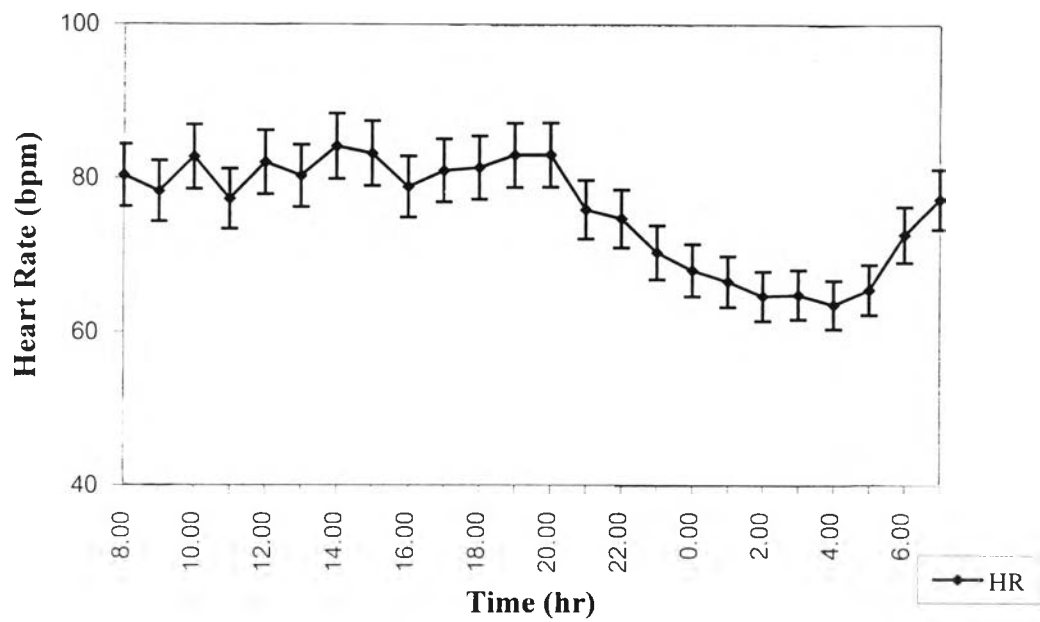


Figure 6 : Ambulatory hourly heart rate of hypertensive patients (n=24) at baseline

3. Antihypertensive effect evalution.

There were twenty-four hypertensive patients entered and completed in this study and they were classified by office blood pressure into eleven of mild and thirteen of moderate hypertensive patients and had been assigned to received enalapril 5 mg or 10 mg per day as the starting dose, respectively, for 4 weeks. In mild hypertensive group, three patients achieved the target BP (office SBP < 140 and DBP <90 mmHg) after 4 weeks of treatment and their doses were decreased to 2.5 mg per day (Figure 7) which further evaluation showed that these lowered doses were also able to keep their BP within the normalized range, one patient was nearly normalize with his SBP / DBP achieved 140 /88 mmHg and was normalize when titrated dosage to 7.5 mg per day. However, seven mild hypertensive patients were remained non normalized with their values of office SBP ≥ 140 or DBP ≥ 90 mmHg, therefore, their daily doses were increased to 10 mg and found that three patients were normalize while remaining four patients were non normalize at the end of treatment period. However in moderate group, after 4 week treatment with 10 mg per day of enalapril, nine patients whose office SBP remained ≥ 140 or DBP remained ≥ 90 mmHg were assigned to receive the higher dose of 20 mg OD and found that five patients were normalize whereas four were non normalize. The office BP of one patient in this group was nearly normalize with his SBP/ DBP achieved of 140 / 70 mmHg and his dose was therefore titrated to 15 mg per day of enalapril. Furthermore he was normalize when completed the study.

Note :- Besides the ten moderate hypertensive patients mentioned above, there were three more moderate hypertensive patients who completed the two dose study but did not follow the same pattern as those aforementioned according to different physician's decision, i.e,one moderate hypertensive patient was started with 5 mg per

day enalapril, after 4 weeks, her blood pressure was still not reduced to normal, therefore the physician decided to give her 10 mg per day for another 4 weeks and her BP was again monitored. Two moderate hypertensive patients were started with 20 mg per day dose for 4 weeks, then their BP were monitored and were found to be normalised, therefore their doses were reduced to 15 mg per day for another 4 weeks and their BP were then monitored. The BP of these three patients were evaluate separately

In this study, one of these twenty-four hypertensive patients was receiving enalapril concomitant with naproxen. Concerning on the drug-drug interaction between enalapril and NSAIDs which might antagonize the hypotensive effect of enalapril[34], finally the results shown that he was normalize with 15 mg per day of enalapril. It was suggested that the patients who taking drugs which interfere with the antihypertensive effect such as steroids, NSAIDs, and drugs that are enzyme inducers or enzyme inhibitor should exclude from this study

Office Blood Pressure

The effects of 5-20 mg dosage of enalapril on the office BP reduction of both mild and moderate hypertensive patients were shown in Table 11-13. The office BP monitoring couldn't detect any BP reduction effect in both SBP and DBP after 5 mg dosage of enalapril either considered by include the three patients who achieved the target BP with 5 mg or focus only on the seven patients were non normalize with this dose, the means office BP at baseline and after treated with 5 mg per day of enalapril were nearly equal. The mean differences were around 1-2 mmHg only for both SBP and DBP. However, the reduction in office DBP were all statistically significant when treated with higher dose of 10 mg/day or 20 mg/day of enalapril, while office SBP showed statistically significant reduction only after treatment with

20 mg/ dose of enalapril. These resulted in office MAP which showed significantly reduction after both10 mg/day and 20 mg/day dose of enalapril in either mild or moderate hypertensive groups of the patients. Although the difference in BP reduction was quite large in magnitude (12 mmHg for SBP after 5 mg vs 10 mg), but it was found to be non statistically significant since the fluctuation among subjects were also large, resulted in big standard deviation while the number of subjects was small. There were no reports of symptomatic or postural hypotension. At the same time, very little change in HR was observed this suggested the absence of reflex tachycardia by enalapril.

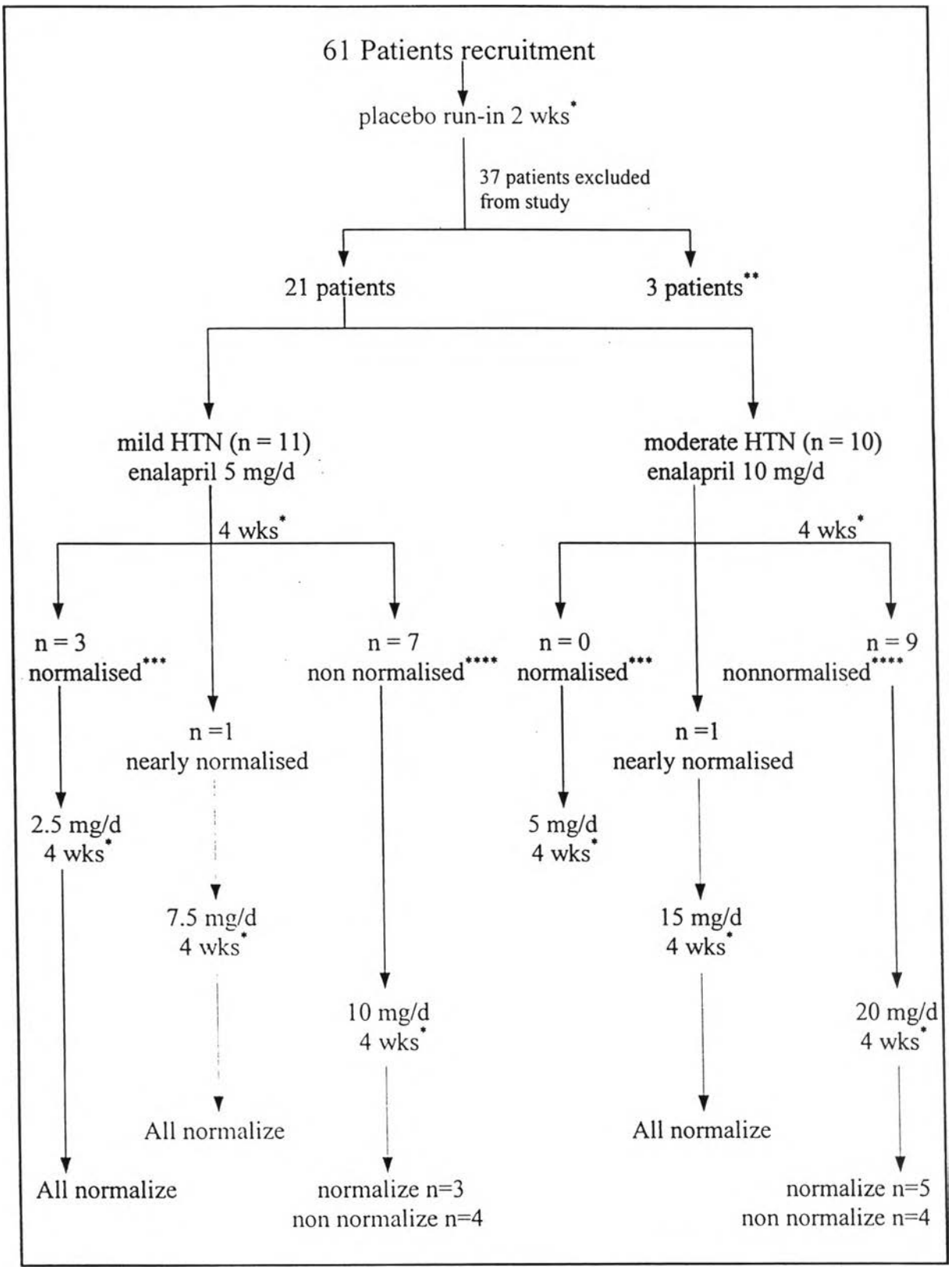
Ambulatory Blood Pressure

Table 11-12,14 showed 24-hour ABP at baseline and after taking 5-20 mg enalapril per day in mild and moderate hypertensive patients. After treatment with either dosages of enalapril, 24-hour SBP and DBP, day-time SBP and DBP and night-time SBP were all statistically significantly reduced from baseline, while night-time DBP did not reduce to the extent that showed statistically significant. The results when include all patients whose starting with 5 mg per day of enalapril were shown similar to results from seven patients. In this study, most of the comparison of BP reduction between low and high dosage of enalapril (5 vs 10 mg and 10 vs 20 mg) showed statistically significant reduction in both SBP and DBP after treatment with higher dose, except for some, such as, the difference of day-time SBP, day-time and night-time DBP between 10 and 20 mg per day doses of enalapril showed non statistically significant, since the standard deviation was large while the sample size was small. However, as a whole, it could be concluded that BP reduction was increase with increasing doses of enalapril. In this study, HR was not affected by increasing dose of enalapril.

In this study, the antihypertensive efficacy of 10 - 20 mg per day dosage of enalapril were apparent not only from office BP measurement but also better reflected from the 24-hour ABP monitoring. The parameters used to assess the antihypertensive efficacy of enalapril on 24-hour ABP were the average BP values the BP loads for day-time, night-time and over the 24-hours and area under the blood pressure curve (AUC). These parameters had been demonstrated to have some relationship with the hypertensive disease complications (eg. left ventricular enlargement and vascular compliance)[46-48]. The significant reductions of BP evaluated by these parameters therefore are essential.

In this study, enalapril in the dosage of 5-20 mg per day could significantly reduced the average BP of 24-hour, day-time and night-time SBP and DBP. These reductions were increased with higher dosage. However, in this study, the highest dose was 20 mg per day. Since few studies had suggested that enalapril exhibits shallow, or flat, dose-response relationship,[12-13] therefore an increase in dosage further than the dosage used in this study may result in an extension of the duration of action without any increase in the magnitude of the antihypertensive effect.

The ambulatory BP profiles throughout 24 hours before and after treatment with 5, 10 and 20 mg per day of enalapril in mild and moderate hypertensive patients were reduce in both SBP and DBP. This study found that the circadian BP rhythm especially during night-time was changed in some patients after treatment period with 10 mg of enalapril as indicated by the increase in the number of patients who were non-dipper. However, the same was not found after treatment with 5 and 20 mg per day of enalapril.



* Office BP & 24-hour measurements

** patients weren't started enalapril dosage according to protocol, data described in in page 60

*** office SBP < 140 mmHg and DBP < 90 mmHg

**** office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg

Figure 7 : Flow chart of dose titration

Table 11 : Office BP and 24-hour ABP of hypertensive patients[a] at baseline and after first period of enalapril treatment

Parameter	Mild HTN (n = 11)			Moderate HTN (n = 10)		
	Baseline	Dosage$_1$ (5 mg/day)	Difference	Baseline	Dosage$_2$ (10 mg/day)	Difference
Office BP[a] (mmHg)						
SBP	148 ± 6.92	141 ± 14.47	7.82 ± 6.92 (p=0.156)	157 ± 9.24	145 ± 15.03	11.80 ± 12.94* (p=0.018)
DBP	94 ± 3.08	90 ± 7.71	4.18 ± 6.88 (p=0.072)	100 ±5.46	92 ± 7.02	8.10 ± 4.82* (p<0.001)
MAP	112 ± 4.22	107 ± 9.35	5.54 ± 9.54 (p=0.083)	119 ± 4.20	110 ± 8.08	9.40 ± 7.12* (p=0.002)
HR (bpm)	83 ± 6.25	81 ± 7.61	2.09 ± 9.29 (p=0.473)	76 ± 11.87	73 ± 9.31	3.30 ± 11.78 (p=0.399)
24-hour ABP[a] (mmHg)						
- average 24-hour						
SBP	142 ± 7.09	129 ± 10.81	13.09 ± 10.11* (p=0.002)	149 ± 10.74	135 ± 10.83	13.40 ± 8.34* (p=0.001)
DBP	88 ± 3.59	82 ± 6.30	5.18 ± 6.48* (p=0.024)	92 ± 4.14	85 ± 7.30	6.20 ± 5.00* (p=0.004)
MAP	106 ± 4.06	98 ± 7.50	7.82 ± 7.18* (p=0.005)	111 ± 4.70	102 ± 7.42	8.60 ± 5.85* (p=0.001)
HR (bpm)	78 ± 5.87	73 ± 7.49	5.18 ± 11.02 (p=0.150)	75 ± 7.95	74 ± 8.75	0.60 ± 8.23 (p=0.823)
- average day-time						
SBP	149 ± 8.94	135 ± 13.06	14.00 ± 12.41* (p=0.004)	152 ± 11.25	139 ± 9.75	12.90 ± 9.04* (p=0.001)
DBP	91 ± 3.44	85 ± 7.53	6.09 ± 5.34* (p=0.004)	95 ± 4.37	88 ± 7.17	7.20 ± 4.71* (p=0.001)
MAP	111 ± 4.72	102 ± 9.04	8.91 ± 7.16* (p=0.002)	114 ± 5.02	105 ± 7.05	9.10 ± 5.47* (p=0.001)
HR (bpm)	82 ± 5.73	78 ± 7.70	3.36 ± 5.77 (p=0.082)	79 ± 7.87	79 ± 8.37	0.60 ± 6.50 (p=0.777)
- average night-time						
SBP	128 ± 8.80	119 ± 10.56	8.54 ± 9.44* (p=0.013)	142 ± 15.68	127 ± 15.33	14.70 ± 13.08* (p=0.006)
DBP	80 ± 7.69	78 ± 6.53	2.54 ± 7.31 (p=0.275)	85 ± 6.54	80 ± 8.60	4.70 ± 7.02 (p=0.063)
MAP	96 ± 7.48	92 ± 7.52	4.46 ± 7.65 (p=0.082)	104 ± 8.36	96 ± 9.61	7.90 ± 8.58* (p=0.017)
HR (bpm)	70 ± 7.31	65 ± 6.81	5.09 ± 5.92* (0.017)	66 ± 9.70	65 ± 10.14	1.00 ± 12.55 (p=0.807)

[1, 2, 3] after treatment with 5, 10, 20 mg /day of enalapril

[a] data are shown as mean ± SD

* $p < 0.01$, ** $p < 0.05$ versus baseline, ns = not significant

Table 12 : Office BP and 24-hour ABP of hypertensive patients[a] at baseline and after enalapril treatment

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	Baseline	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	Baseline	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)
Office BP[a] (mmHg)						
SBP	148 ± 6.13	146 ± 10.39 [ns]	133 ± 13.26 [ns]	156 ± 9.03	146 ± 15.84 [ns]	134 ± 16.47 **
DBP	94 ± 2.99	93 ± 4.39 [ns]	85 ± 8.08 **	101 ± 5.11	94 ± 5.90 **	84 ± 8.70 **
MAP	112 ± 3.98	111 ± 4.86 [ns]	101 ± 8.85 **	119 ± 4.42	111 ± 7.75 **	100 ± 9.68 **
HR (bpm)	81 ± 7.35	79 ± 5.22 [ns]	69 ± 13.9 [ns]	78 ± 11.56	75 ± 6.85 [ns]	76 ± 8.73 [ns]
24-hour ABP[a] (mmHg)						
- average 24-hour						
SBP	144 ± 7.60	133 ± 7.84 **	128± 9.20 **	148 ± 11.36	136 ± 11.08 **	130 ± 12.97 **
DBP	88 ± 4.39	85 ± 4.73 *	80 ± 5.06 *	92 ± 4.39	86 ± 7.38 **	82 ± 9.39 **
MAP	107 ± 4.60	101 ± 4.98 **	96 ± 5.35 **	110 ± 4.72	103 ± 7.52**	98 ± 9.82 **
HR (bpm)	77 ± 7.30	73 ± 8.41[ns]	69 ± 10.92 [ns]	76 ± 7.26	74 ± 9.17 [ns]	74 ± 7.14 [ns]
- average day-time						
SBP	150 ± 9.51	139 ± 8.85**	135 ± 9.43 **	151 ± 11.54	139 ± 10.34 **	135 ± 12.67**
DBP	92 ± 3.58	88 ± 4.61**	85 ± 4.50 **	95 ± 4.56	88 ± 7.48 **	85 ± 8.76 **
MAP	111 ± 5.15	105 ± 5.51**	101 ± 5.02 **	114 ± 5.15	105 ± 7.52 **	101 ± 9.12 **
HR (bpm)	80 ± 6.74	77 ± 9.46 [ns]	72 ± 10.21 [ns]	80 ± 7.02	79 ± 8.83 [ns]	77 ± 6.87 [ns]
- average night-time						
SBP	132 ± 8.32	122 ± 9.28 **	115 ± 13.71**	142 ± 16.39	129 ± 14.09**	121 ± 16.42 **
DBP	82 ± 7.81	79 ± 7.16 [ns]	73 ± 8.60 **	85 ± 6.61	81 ± 7.75 [ns]	77 ± 12.08 [ns]
MAP	98 ± 7.87	93 ± 7.55 [ns]	87 ± 10.24 **	104 ± 8.52	98 ± 8.28 [ns]	91 ± 13.05**
HR (bpm)	70 ± 8.73	65 ± 7.86 [ns]	61 ± 12.08 **	67 ± 9.60	66 ± 10.53 [ns]	68 ± 9.60 **

[1, 2, 3] after treatment with 5, 10, 20 mg /day of enalapril

[a] data are shown as mean ± SD

* $p < 0.01$, ** $p < 0.05$ versus baseline, ns = not significant

Table 13 : The effect of dosage of enalapril on the magnitude reduction of office BP in hypertensive patients.

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	difference	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)	difference
Office BP (mmHg)**						
SBP	2.00 ± 11.72 (p= 1.000)	14.29 ± 11.57 (p=0.051)	12.29 ± 14.53 (p=0.200)	10.11 ± 12.50 (p=0.124)	21.78 ± 13.32 (p = 0.004)	11.67 ± 9.72 (p = 0.021)
DBP	1.14 ± 3.44 (p=1.000)	9.71 ± 6.62 (p = 0.025)	8.57 ± 6.02 (p = 0.028)	7.56 ± 4.77 (p = 0.004)	17.44 ± 9.08 (p = 0.001)	9.89 ± 6.70 (p = 0.007)
MAP	1.71 ± 4.68 (p=1.000)	11.29 ± 7.54 (p = 0.022)	9.57 ± 5.13 (p = 0.008)	8.44 ± 6.84 (p = 0.018)	19.00 ± 10.06 (p = 0.001)	10.56 ± 6.89 (p = 0.005)
HR (bpm)	2.71 ± 9.54 (p=1.000)	12.29 ± 16.73 (p=1.000)	9.57 ± 11.33 (p=1.000)	2.67 ± 12.32 (p=1.000)	2.33 ± 13.96 (p=1.000)	-0.33 ± 8.09 (p=1.000)

difference are differ between two dosage

** data are shown as mean ± SD

[1, 2, 3] after treatment with 5, 10, 20 mg /day of enalapril

Table 14 : The effect of dosage of enalapril on the magnitude of ABP reduction in hypertensive patients.

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ (5mg/day)	$dosage_2$ (10 mg/day)	difference	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)	difference
*- average 24-hour**						
SBP	11.00 ± 6.98 (p = 0.018)	15.86 ± 7.73 (p = 0.005)	4.86 ± 2.41 (p = 0.005)	12.22 ± 7.92 (p = 0.005)	18.00 ± 9.00 (p = 0.001)	5.78 ± 4.74 (p = 0.019)
DBP	3.27 ± 0.95 (p < 0.001)	8.00 ± 1.63 (p < 0.001)	4.71 ± 2.06 (p = 0.003)	5.56 ± 4.85 (p = 0.027)	9.44 ± 7.09 (p = 0.012)	3.89 ± 3.62 (p = 0.037)
MAP	5.71 ± 2.63 (p = 0.004)	10.57 ± 3.41 (p = 0.001)	4.86 ± 1.68 (p= 0.001)	7.78 ± 5.72 (p = 0.011)	12.67 ± 7.88 (p= 0.004)	4.89 ± 3.92 (p = 0.17)
*- average daytime**						
SBP	11.29 ± 7.14 (p = 0.017)	15.29 ± 7.16 (p = 0.004)	4.00 ± 2.00 (p = 0.006)	11.89 ± 8.96 (p = 0.012)	16.00 ± 10.05 (p = 0.004)	4.11 ± 6.39 (p=0.269)
DBP	3.57 ± 2.64 (p = 0.035)	7.14 ± 3.76 (p = 0.007)	3.57 ± 2.76 (p = 0.042)	6.56 ± 4.50 (p = 0.007)	10.00 ± 7.23 (p = 0.010)	3.44 ± 3.64 (p=0.066)
MAP	6.29 ± 3.45 (p = 0.009)	10.00 ± 4.08 (p = 0.002)	3.71 ± 1.98 (p = 0.008)	8.56 ± 5.66 (p = 0.006)	12.44 ± 8.13 (p = 0.005)	3.89 ± 3.65 (p = 0.038)
*- average nighttime**						
SBP	10.43 ± 7.07 (p = 0.024)	16.86 ± 10.42 (p = 0.016)	6.43 ± 6.05 (p=0.092)	13.11 ± 12.81 (p = 0.046)	21.67 ± 14.24 (p = 0.006)	8.56 ± 7.84 (p = 0.034)
DBP	3.00 ± 3.56 (p=0.202)	8.57 ± 5.22 (p = 0.015)	5.57 ± 2.37 (p = 0.002)	3.89 ± 6.94 (p=0.393)	8.33 ± 9.90 (p=0.107)	4.44 ± 6.58 (p=0.232)
MAP	5.29 ± 4.42 (p=0.059)	11.14 ± 6.74 (p=0.014)	5.86 ± 3.48 (p=0.013)	6.22 ± 8.83 (p=0.202)	12.67 ± 10.84 (p=0.024)	6.44 ± 6.71 (p=0.061)

[1, 2, 3] after treatment with 5, 10, 20 mg /day of enalapril
difference are differ between two dosage
* data are shown as mean ± SD

The results in Table 15 showed seated SBP and DBP reduction after 3 weeks of original enalapril treatment in Bergstrand's study compared with the results in this study (4 weeks of each treatment period). The difference result could due in part to the difference design, the number of evaluable subjects, and BP monitoring method.

Table 15 : Mean change from baseline in office seated SBP and DBP (mmHg) after treatment with enalapril from Bergstrand et al. (3 weeks) compared with this study (4 weeks).

Treatment	dose	Baseline		3 weeks		Baseline		4 weeks	
	(mg/day)	n	S/D	S	D	n	S/D	S	D
Placebo	0	27	157/96	1	-1	-	-	-	-
Enalapril	2.5	32	157/96	-10*	-5*	3	153/95	-21*	-9*
Enalapril	5	27	155/97	-4	-4	11	148/94	-7	-4
Enalapril	10	27	161/98	-15*	-8*	17	153/98	-13*	-9*
Enalapril	20	28	159/95	-13*	-4	9	156/101	-22*	-17*
Enalapril	40	29	159/96	-20*	-10*	-	-	-	-

* significant decrease from baseline, $p < 0.05$
Data shown as mean of SBP and DBP

Rate of blood pressure reduction

Office Blood Pressure

Rate of blood pressure reduction was calculated from the magnitude of BP reduction after treatment with different doses of enalapril divided by the dosage of administration and also calculated from the different in magnitude of BP reduction after treatment with the low dose and higher doses divided by the different in dosage of administration . These result in the magnitude of BP reduction per mg of enalapril. The results of this study indicated that the rate of office BP reduction in mild and moderate hypertensive patient groups was tended to increase with the higher dose of enalapril whether they are SBP, DBP or MAP (Table 16, Figure 8-9) especially the increase in rate between treatment with 5 and 10 mg per day of enalapril administration in mild hypertensive patients were statistically significant.

24-hour Ambulatory Blood Pressure

In contrary, the different from office BP results found in 24-hour ABPM (Table 16, Figure 8-9) The result showed that the rates of BP reduction tended to decrease even though non statistically significant when the patients received higher dosage of enalapril either considered only during daytime, night-time or as the whole 24-hour with the rate of SBP reduction showed most prominent. The average rate of BP reduction per mg of enalapril administration was approximately 1-2 mmHg for SBP and 0.7 mmHg for DBP in both mild and moderate hypertensive patients 5-20 mg per day dosage was administered. When the rate of BP reduction during day-time and night-time were compared their values were quite similar between monitoring periods.

Table 16 : The effect of dosage administration on rate of BP reduction in hypertensive patients

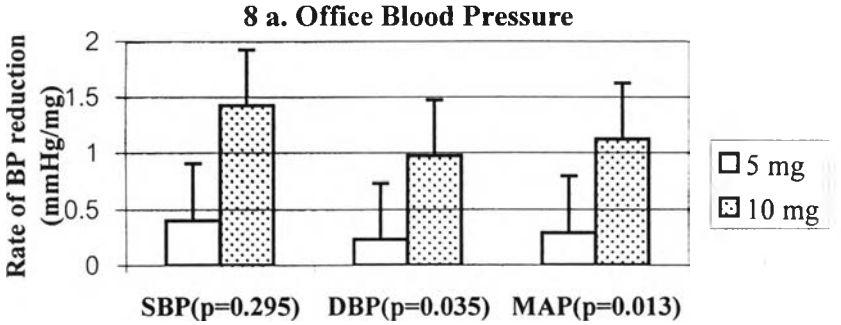
Rate of response (Δ BP/mg)	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	difference	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)	difference
*Office BP**						
SBP	0.4 ± 2.34	1.42 ± 1.16	-1.03 ± 2.37	1.01 ± 1.25	1.09 ± 0.66	- 0.02 ± 0.9
DBP	0.23 ± 0.69	0.97 ± 0.66	-0.74 ± 0.72**	0.75 ± 0.48	0.87 ± 0.45	-0.12 ± 0.36
MAP	0.29 ± 0.92	1.12 ± 0.73	-0.83 ± 0.63**	0.84 ± 0.67	0.94 ± 0.50	-0.10 ± 0.47
*Average 24-hour BP**						
SBP	2.2 ±1.39	1.58 ± 0.77	0.61 ± 0.70	1.22 ± 0.79	0.9 ± 0.45	0.32 ± 0.47
DBP	0.66 ± 0.19	0.8 ± 0.16	-0.14 ± 0.28	0.55 ± 0.48	0.47 ± 0.35	0.02 ± 0.24
MAP	1.14 ± 0.52	1.06 ± 0.34	0.02 ± 2.8	0.78 ± 0.57	0.63 ± 0.39	0.14 ± 0.29
*Average day-time**						
SBP	2.26 ± 1.43	1.53 ± 0.72	0.73 ± 0.76**	1.19 ± 0.89	0.8 ± 0.50	0.39 ± 0.59
DBP	0.71 ± 0.53	0.71± 0.38	0.0 ± 0.39	0.65 ± 0.45	0.5 ± 0.36	0.15 ± 0.19**
MAP	1.26 ± 0.69	1.0 ± 0.41	0.26 ± 0.39	0.85 ± 0.56	0.62 ± 0.41	0.23 ± 0.25**
*Average night-time**						
SBP	2.08 ± 1.41	1.68 ± 1.04	0.4 ± 0.80	1.31 ± 1.28	1.08 ± 0.71	0.23 ± 0.26
DBP	0.6 ±0.71	0.86 ± 0.52	-0.26 ± 0.30	0.39 ± 0.69	0.42 ± 0.50	-0.03 ± 0.46
MAP	1.06 ± 0.88	1.11 ± 0.67	-0.03 ± 0.42	0.62 ± 0.88	0.63 ± 0.54	0.00 ± 0.57

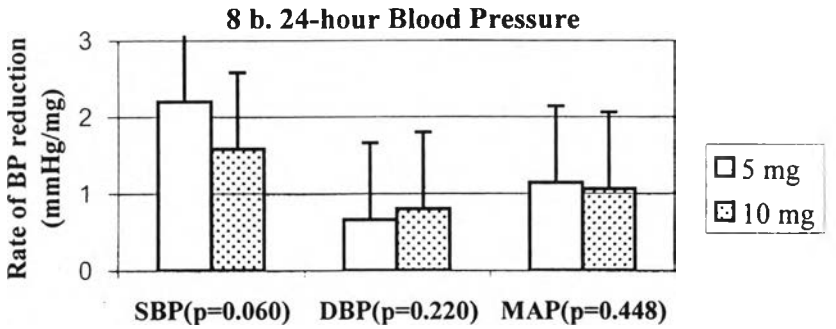
difference are differ between two dosage

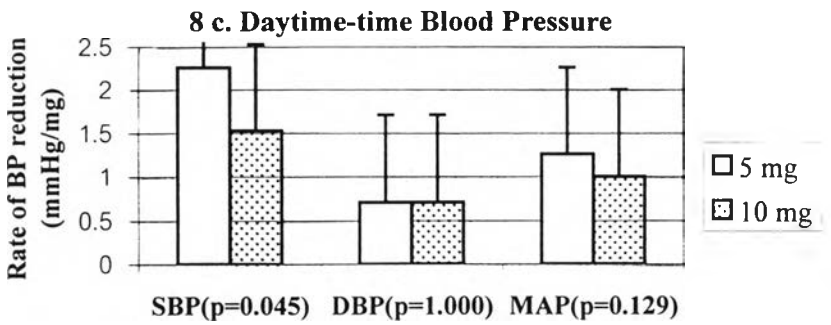
* data are shown as mean ± SD,

** $p < 0.05$ versus lower dose

Figure 8 : Comparison rate of blood pressure reduction between dosage of administration in mild hypertensive patients (n=7)







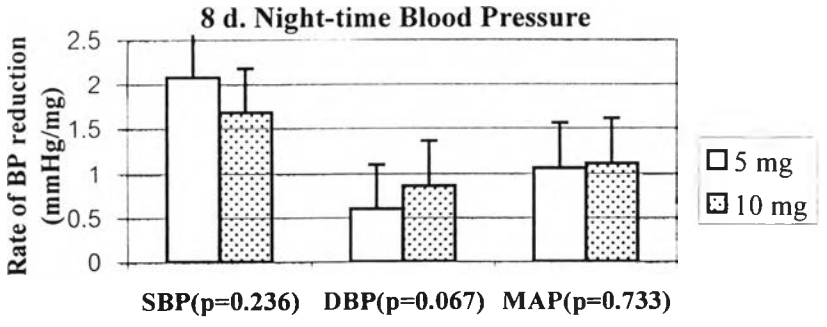
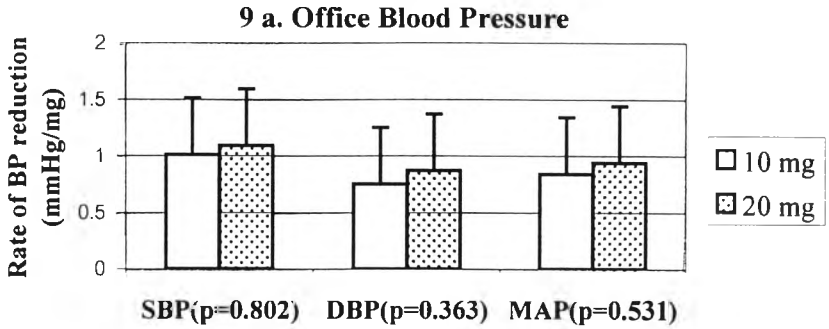
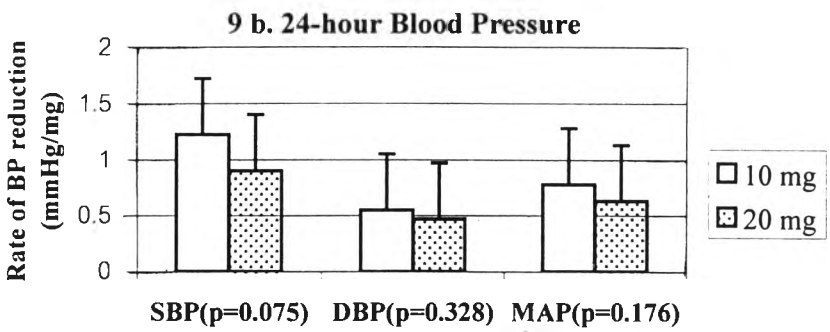
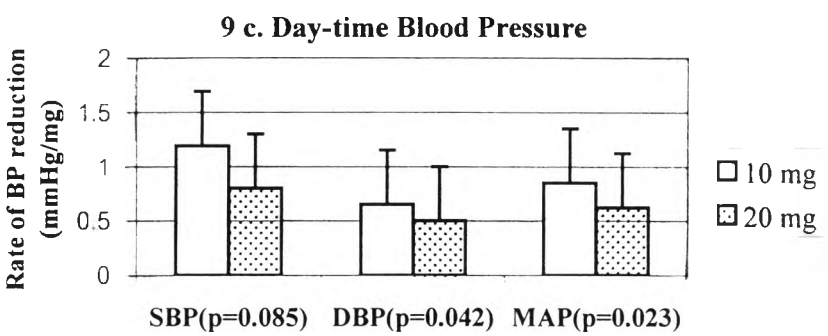
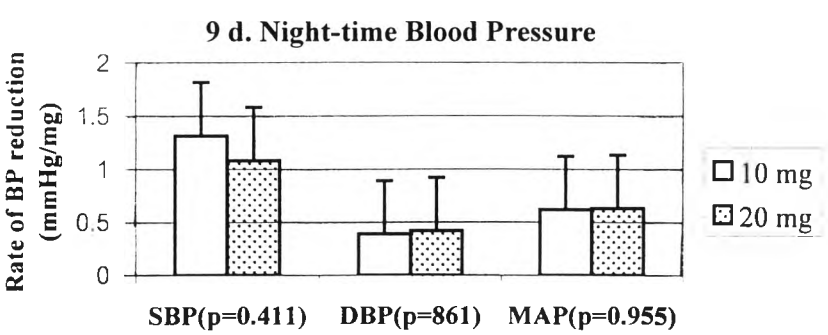


Figure 9 : Comparison rate of blood pressure reduction between dosage of administration in moderate hypertensive patients. (n=9)









Rate of BP reduction and individual factors of patients.

Age

When the relationship between the rate of BP reduction and the age of patients were considered, it was found that the rate of mean MAP reduction in mild and moderate hypertensive patients after treated with equal dosage of 10 mg per enalapril day showed tendency to decrease with older patients when office BP were to evaluation (Figure 10 a). In contrary, rate of BP reduction obtained from 24-hour, day-time and night-time showed slightly increase in higher age (Figure 10 b-d). However , the R^2 obtained was so small that no relationship between age and rate of MAP reduction was concluded.

Sex

From this study, when focus was especially put on sex of patients and rate of BP reduction, there were nine males and seven females hypertensive patients included in the consideration. Comparison of rate of BP reduction between male and female patients after receiving 10 mg per day enalapril was shown in Figure 11. shown that The results from office BP and 24-hour ABPM were different. However, no significant relationship between sex and the rate of reduction of SBP, DBP or MAP could be found no matter the BP monitoring parameters considered were 24-hour BP, day-time BP or night-time BP. Therefore, it could be concluded that there was no significant relationship between sex and the rate of BP reduction.

Body Mass Index(BMI)

When the relationship between BMI of patient and the rate of MAP reduction in mild and moderate hypertensive patients after receiving enalapril 10 mg per day was considered (Figure 12), the results obtained from office BP were similar to the night-time BP, i.e, that it seem to be slightly higher rate with increasing BMI. On the

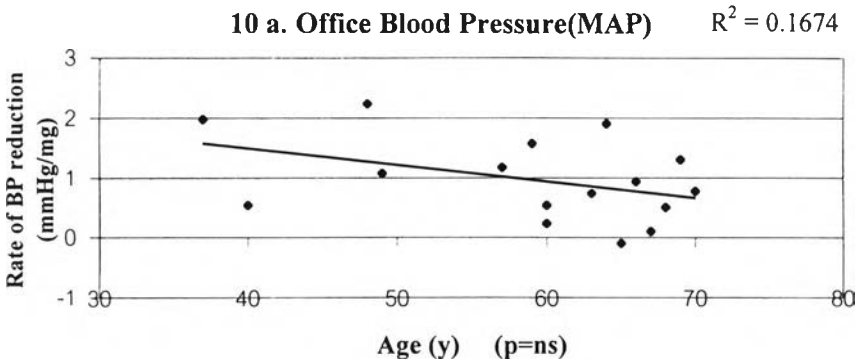
other hand, 24-hour BP and day-time BP showed that the rate of BP reduction was decreased with higher patient's BMI. Since these relationships were very small and inconsistent, the conclusion of no relationship between patient's BMI and rate of MAP reduction was made.

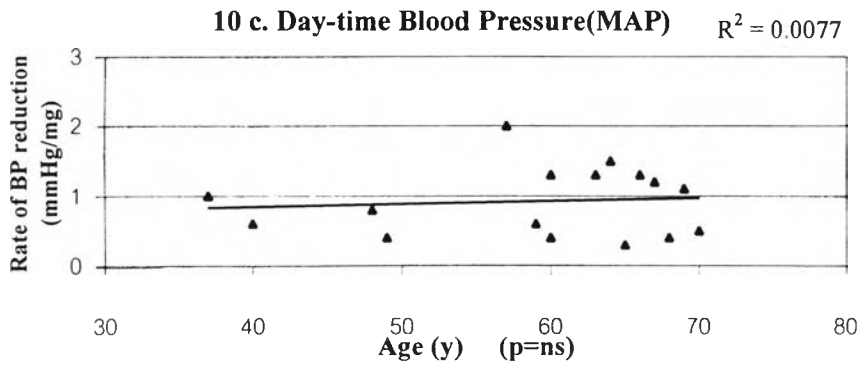
Pretreatment Blood Pressure & Stage of hypertension

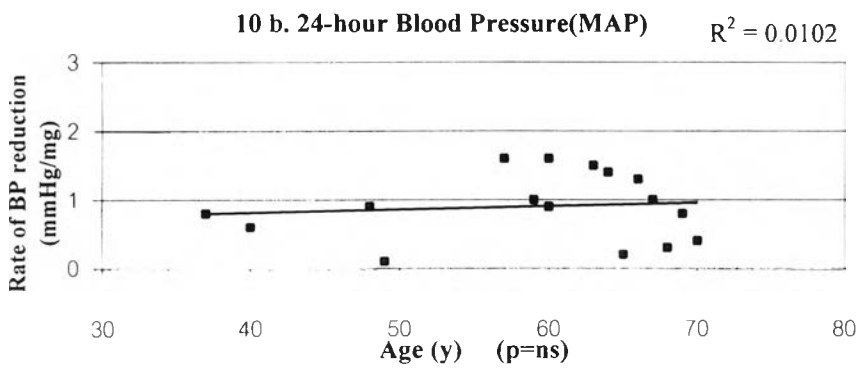
No relationship between pretreatment blood pressure and his response to antihypertensive drugs (by focus on the rate of BP reduction) was found when the relationship between stage of hypertension and rate of MAP reduction after treatment with 10 mg per day of enalapril (Figure 13-14) was considered. Similar results were obtained from office BP and 24-hourABP monitoring. It was shown that mild hypertensive patients have higher rate of SBP, DBP and MAP reduction than moderate hypertensive patients in all monitoring periods. However, these relationships were not statistically significant.

The results from Figure 10-14 showed that there were no relationship between patient's factors that were age, sex, BMI, pretreatment BP, stage of hypertension and the rate of BP reduction. The results are differ from some previous studies which showed that there was a significant positive correlation between BP reduction and the pretreatment BP[50-51], but no relation between the responsiveness to enalapril and patient's age[38,51]. Finally, we cannot exclude the possibility that the difference in 24-hour antihypertensive action could partially attribute to effects other than ACE inhibition. A different modulation of enalapril action on bradykinin breakdown inhibition, prostaglandin synthesis, or sympathetic activity could also account for the observed treatment difference in the blood pressure lowering effect.

Figure 10 : Relationship between age VS rate of mean MAP reduction in mild and moderate hypertensive patients after administration 10 mg enalapril. (n=16)







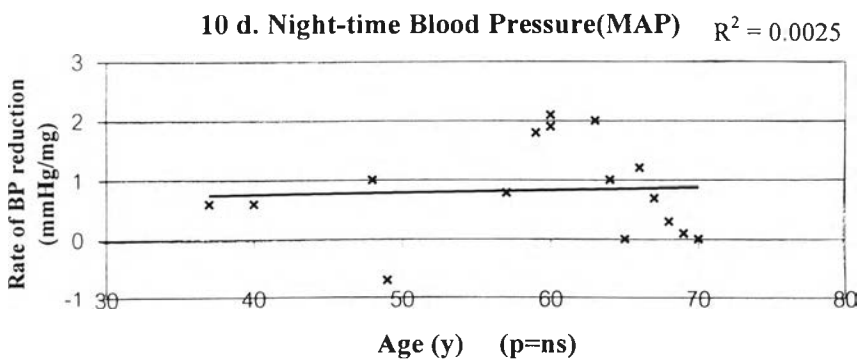


Figure 12 : Relationship between BMI VS rate of mean MAP reduction in mild and moderate hypertensive patients after administration 10 mg enalapril. (n=16)

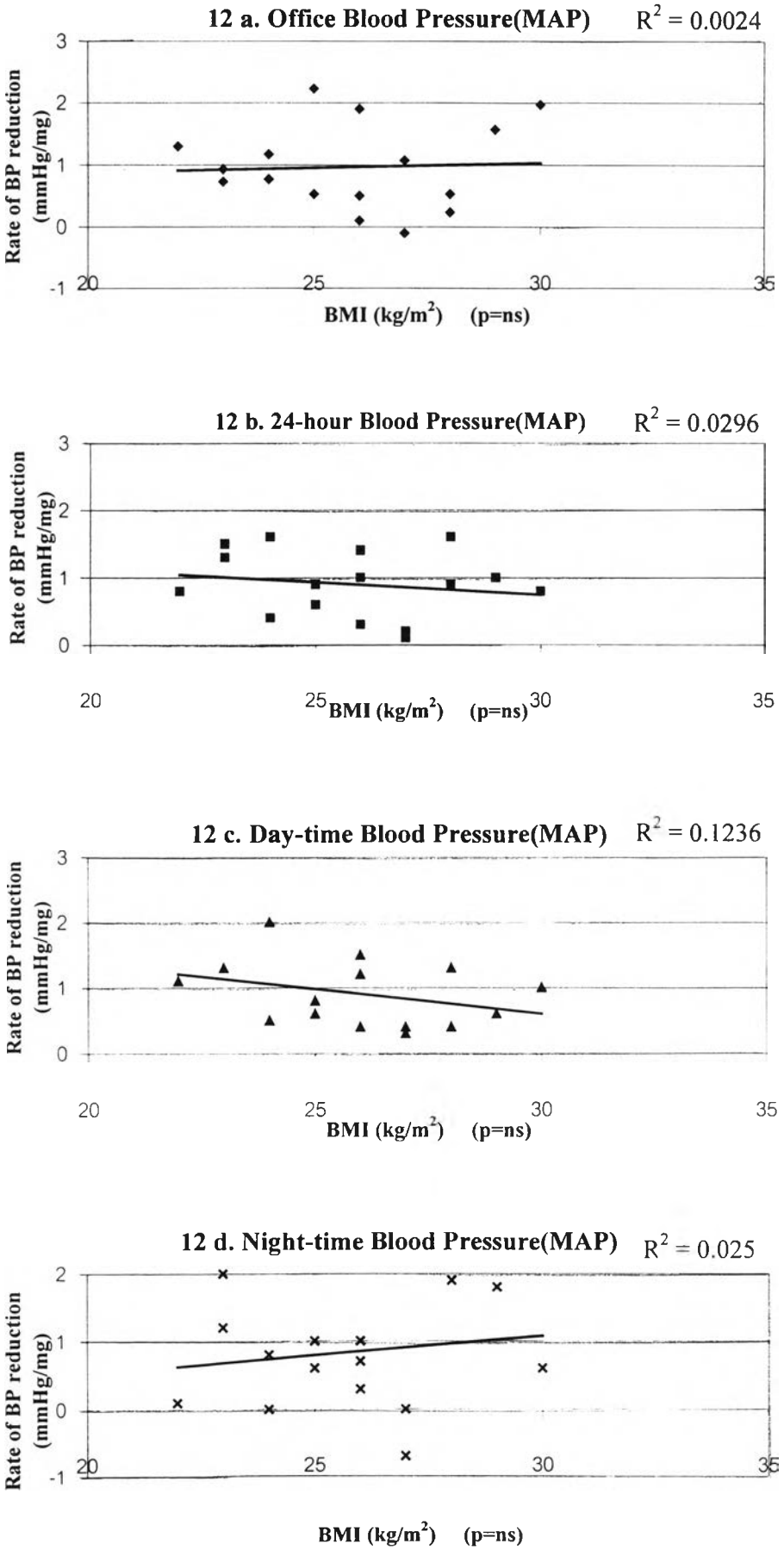
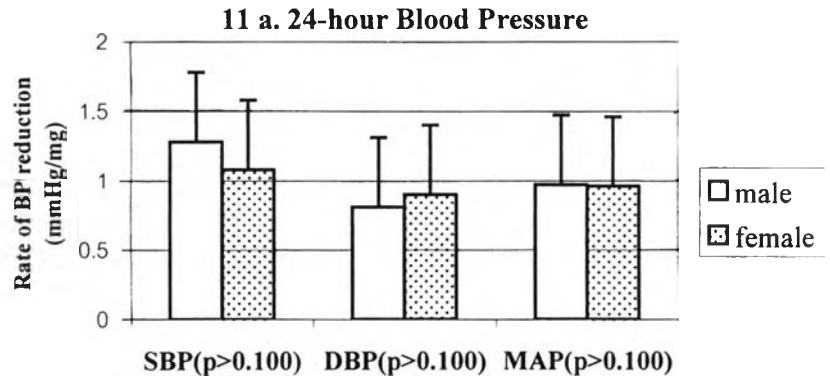
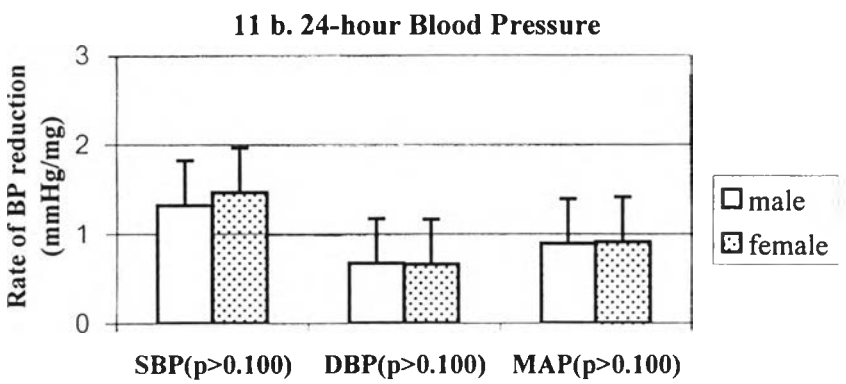
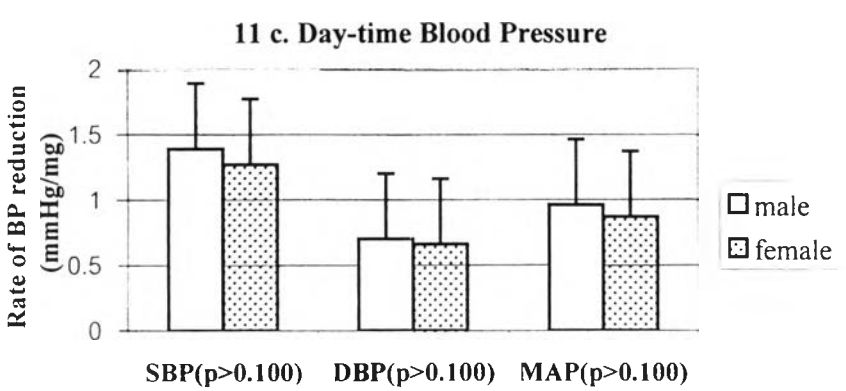


Figure 11 : Comparison rate of blood pressure reduction between male and female hypertensive patients after administration 10 mg enalapril (M=9, F=7)







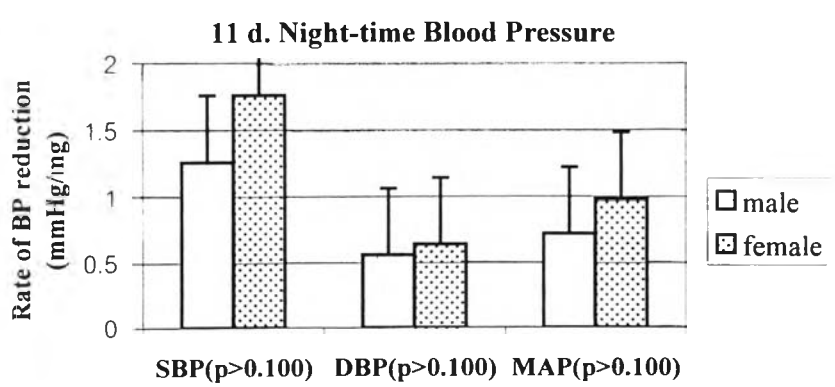
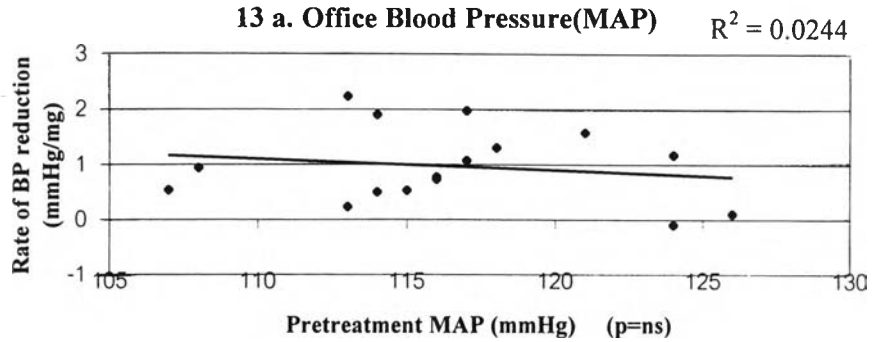
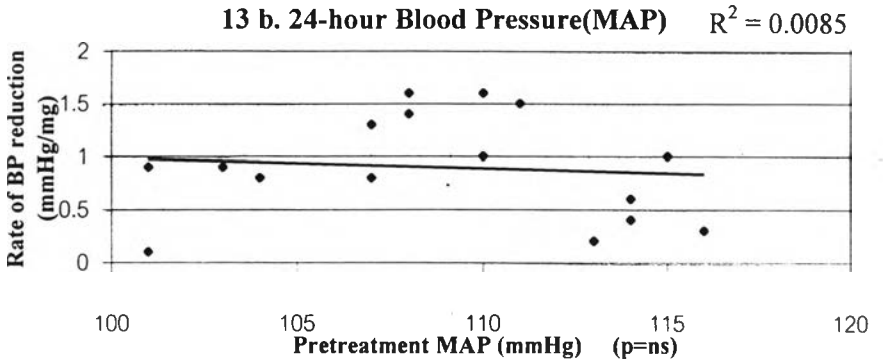
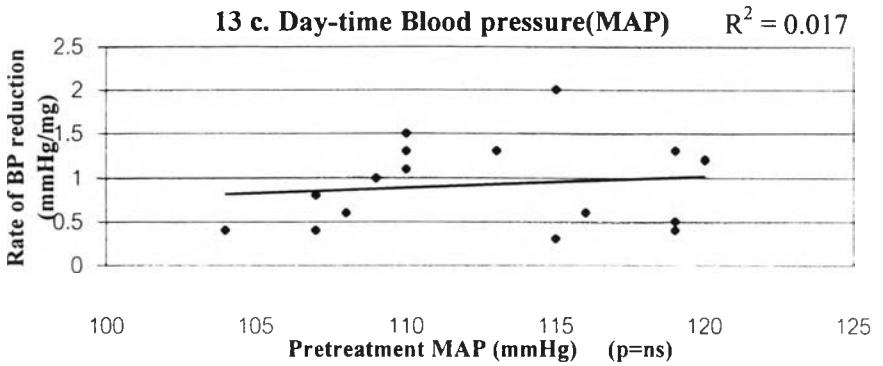


Figure 13 : Relationship between pretreatment BP VS rate of mean MAP reduction in mild and moderate hypertensive patients after administration 10 mg enalapril. (n=16)







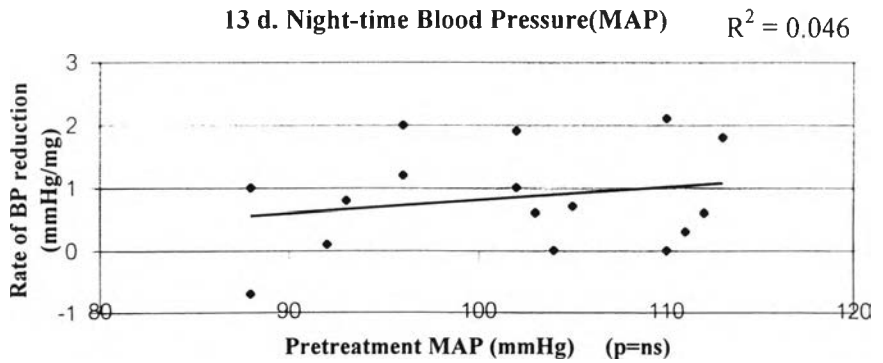
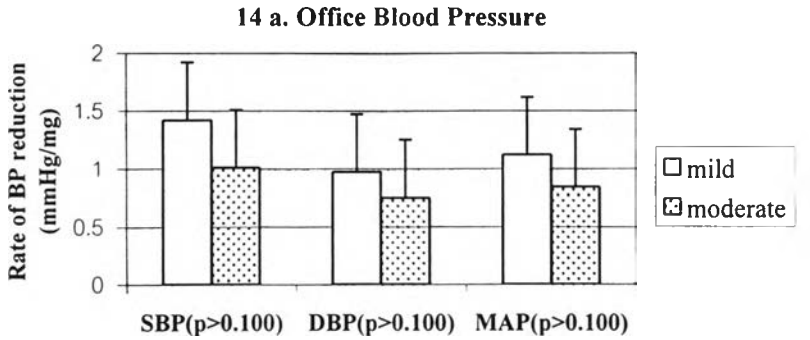
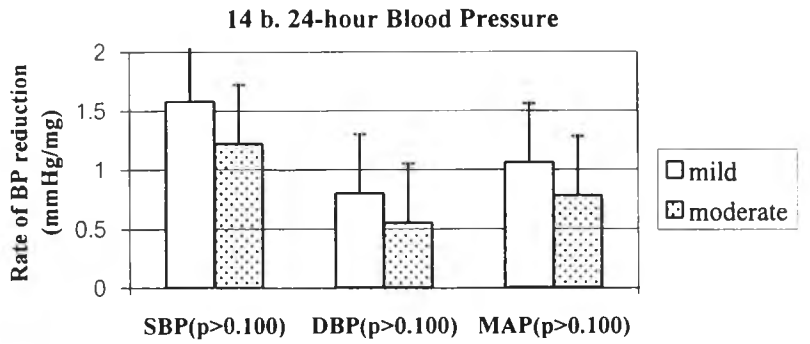
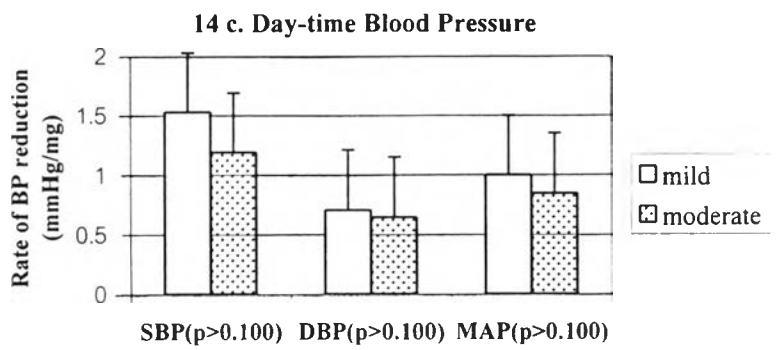
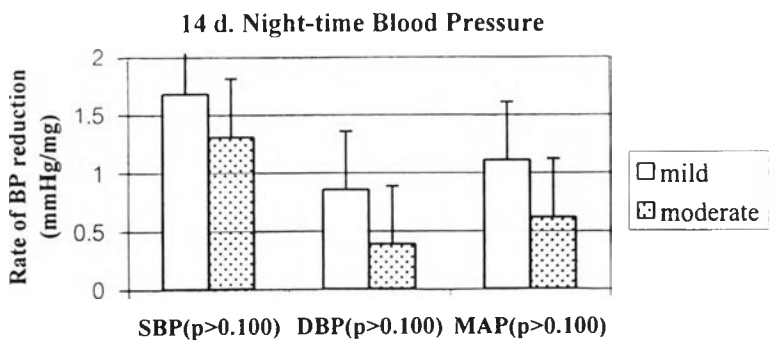


Figure 14 : Comparison rate of blood pressure reduction between mild and moderate hypertensive patients after administration 10 mg enalapril. (mild=7, moderate=9)









Area under the blood pressure curve (AUC)

AUC was one of the parameters which was used to evaluated efficacy of antihypertensive drugs[52]. It could represent both frequency and magnitude of abnormal BP. AUC was calculated by using area under the systolic or diastolic BP curve, with cutoff values of 140 mmHg during day-time and 120 mmHg during night-time for SBP and cutoff values of 90 mmHg during day-time and 80 mmHg during night-time for DBP. Figure 15 showed evaluation of antihypertensive therapy by using the area under the systolic blood pressure curve.

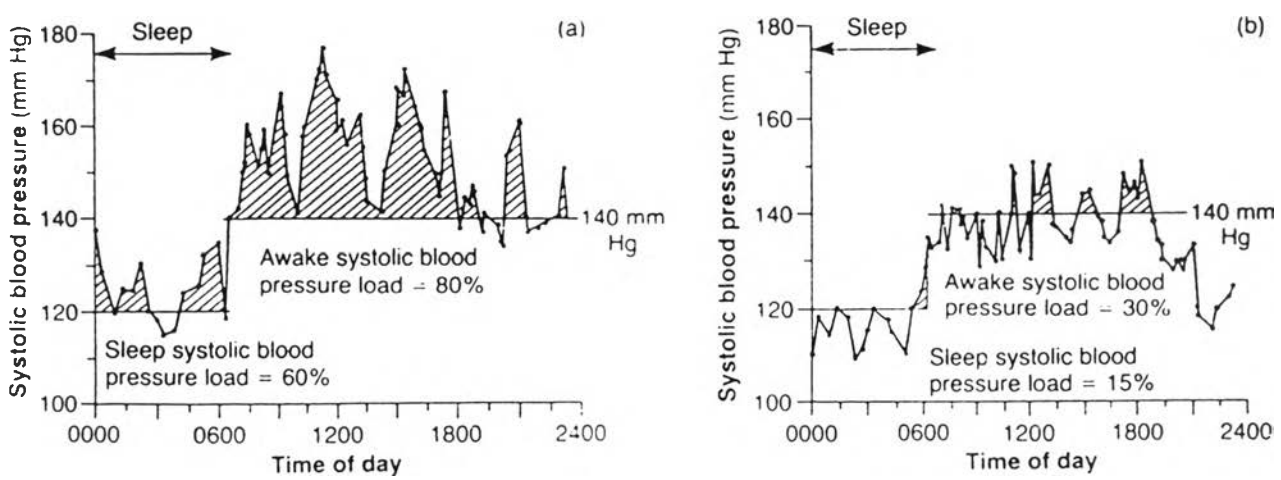


Figure 15 : Evaluation of antihypertensive therapy using the area under the systolic blood pressure curve with cutoff values of 140 mmHg during waking hours and 120 mmHg during sleeping for (a) placebo and (b) antihypertensive therapy.

Data obtained from this study (Table 17) showed that the initial dosage could produce a more pronounced effect on the reduction in the AUC of SBP and DBP (above normal blood pressure) than the consecutive dosages. Most of the AUC reduction were approximately 180-250 mmHg.h for SBP and 45-80 mmHg.h for DBP

Even though the results indicated that each dosage of enalapril could induce significantly reduction in area under the SBP and DBP curve when compared to baseline ($p < 0.05$), either in mild or moderate hypertensive patients. However, the difference of AUC reduction between 5 versus 10 mg per day in mild hypertensive patients and 10 versus 20 mg in moderate hypertensive patients were not statistically significant.

By using AUC for assessing effect of the antihypertensive drug over time, several conclusions could be drawn[52]. First, the effect and duration of effect of the drug over the entire 24-hour period can be immediately visualized. Second, the blood pressure load can be calculated in mmHg.h or, in mild hypertensives, as a percentage of the blood pressure distribution. Thus, data removal or smoothing method is unnecessary and quite simple statistical tests can be used to compare the treatment groups.

The area under the SBP and DBP curves were significantly decreased after treatment with enalapril as compared to baseline. These decreasing in areas were increased with increasing doses of enalapril. However, comparisons between the increasing area of 5 mg and 10 mg per day dose of enalapril in the mild hypertensive group and between the decreasing areas after 10 and 20 mg per day doses of enalapril in the moderate hypertensive group all showed no statistically significant.

According to J-shape curve, the reduction in BP that is too extreme can produce signs and / or symptoms of organ damage because a rapid and extreme

reduction in BP below the limits of the autoregulatory curve may compromise perfusion of vital structures such as the brain and heart. Some evidence showed the preference of BP reduction which is not lower than 30 % from baseline[52]. The area of BP curve throughout 24-hour after treatment with enalapril was therefore classified into 5 intervals, that were, area above baseline, area 0-10 % below baseline, 10-20 % below baseline, 20-30 % below baseline and area more than 30 % below baseline.

The results shown in Table 18 indicated that the areas of BP above baseline were reduced with increased dosage of enalapril either from 5 to 10 mg per day or from 10 to 20 mg per day. After treatments the AUC of SBP and DBP fell mostly in the 0-10 % and 10-20 % below baseline intervals respectively. Very few percentage of AUC were fell in the interval of > 30 % below baseline indicated that the dose range 5-20 mg of enalapril did not reduce the BP beyond the extreme rang (just one patients accidentally take the double the dose resulted in more percentage of AUC reduction from baseline.

Thus from the data obtained, it was shown that enalapril can produce some evident of BP reduction > 30 % from baseline and percentage was increased when treated with higher dose.

Table 17 : The effect of dosage administration of enalapril on area above the normal blood pressure versus time curve

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	baseline	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	baseline	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)
AUC (mmHg.h)						
SBP*	294 ± 130.82 (82-496)	107 ± 104.50 (16-291)	99 ± 99.70 (14-267)	376 ± 225.46 (101-714)	167 ± 175.96 (21-580)	116 ± 122.83 (0-355)
DBP*	106 ± 59.20 (55-233)	58 ± 64.17 (8-184)	46 ± 53.77 (0-157)	138 ± 67.70 (44-243)	80 ± 87.26 (0-252)	60 ± 62.50 (0-167)

	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ vs B (5 mg/day)	$dosage_2$ vs B (10 mg/day)	$dosage_1$ vs $dosage_2$	$dosage_2$ vs B (10 mg/day)	$dosage_3$ vs B (20 mg/day)	$dosage_2$ vs $dosage_3$
ΔAUC (mmHg.h)						
SBP*	186 ± 104.20 (p = 0.010)	194 ± 107.67 (p = 0.009)	8 ± 33.71 (ns)	209 ± 154.21 (p = 0.011)	259 ± 139.65 (p = 0.002)	51 ± 72.27 (ns)
DBP*	47 ± 21.25 (p = 0.003)	60 ± 22.90 (p = 0.001)	12 ± 27.32 (ns)	58 ± 49.70 (p = 0.024)	78 ± 48.36 (p = 0.004)	19 ± 35.33 (ns)

Δ BP = difference in BP between dosage

* data are shown as mean ± SD

[1, 2, 3] after treatment with 5, 10, 20 mg /day of enalapril

B = baseline

Table 18 : % reduction of area under the curve after treatment of enalapril in hypertensive patients

Mean % AUC reduction (Frequency)	Mild HTN (n=7)				Moderate HTN (n=9)			
	AUCs		AUCd		AUCs		AUCd	
	$dosage_1$	$dosage_2$	$dosage_1$	$dosage_2$	$dosage_2$	$dosage_3$	$dosage_2$	$dosage_3$
> Baseline %	22 ± 15.85	13 ± 11.72	38 ± 6.00	22 ± 6.08	19 ± 17.81	10 ± 10.45	27 ± 21.39	20 ± 17.27
(range)	(4-48)	(0-30)	(26- 43)	(17-35)	(0-43)	(0-30)	(0-52)	(0-43)
0 – 10 %	36 ± 12.00	35 ± 15.47	35 ± 9.39	30 ± 7.29	41 ± 19.27	38 ± 23.71	40 ± 10.07	31 ± 20.75
(range)	(22-57)	(13-52)	(22-52)	(22-43)	(17-61)	(0-74)	(26-57)	(0-65)
10 – 20 %	27 ± 10.90	30 ± 13.75	20 ± 4.24	35 ± 12.04	31 ± 20.60	26 ± 13.92	25 ± 11.08	29 ± 13.92
(range)	(3-48)	(4-48)	(13-26)	(17-52)	(4-61)	(9-43)	(9-39)	(9-48)
20 – 30 %	14 ± 16.24	20 ± 18.76	6 ± 4.24	9 ± 6.64	9 ± 10.20	22 ± 21.63	7 ± 9.22	12 ± 10.65
(range)	(0-43)	(0-48)	(0-13)	(4-22)	(0-30)	(0-70)	(0-26)	(0-26)
> 30 %	1 ± 3.29	2 ± 3.42	1 ± 3.29	3 ± 5.45	0 ± 0.00	4 ± 7.35	1 ± 3.07	8 ± 18.50
(range)	(0-9)	(0-9)	(0-9)	(0-13)	(0)	(0-22)	(0-9)	(0-57)
Total (%)	100	100	100	100	100	100	100	100

* AUCs, AUCd mean area under the curve of systolic and diastolic blood pressure

[1, 2, 3] after treatment with 5, 10, 20 mg enalapril

The Blood Pressure loads

Table 19-21 showed the frequency and the absolute value (the magnitude) of BP loads at baseline and after treatment with of different dosage ranged from 5-20 mg enalapril per day. When frequency of BP loads were considered, it was found that higher doses resulted in higher reduction in frequency of BP loads but these reductions were not linearly proportioned to the dosage administered. The reduction in frequency for SBP ranged from 10 % to 50 % with the doses of 5-20 mg per day. The reduction in frequency for DBP were approximately 10 % to 30 % with the doses of 5-20 mg per day. When, the magnitude of BP loads were considered, the results showed that higher doses resulted in higher reductions in the magnitude of SBP loads but these reductions were not linearly proportion with dose. The reduction of the magnitude BP loads in majority of the patients were around 6 mmHg for SBP and 2 mmHg for DBP with 5-20 mg per day dose of enalapril.

The result showed that BP loads were significantly reduced after enalapril treatment compared to baseline. The reduction in BP load (both frequency and magnitude) was important because several data support the view that BP load is a better determinant of cardiac and vascular abnormalities than either casual or mean 24-hour ABPM values[14-16].

Table 18 : The frequency and the magnitude of BP loads at baseline and after enalapril treatment

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	Baseline	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	Baseline	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)
Frequency of BP loads (%)[1]						
24-hour BP load						
SBP	60 ± 25.27	50 ± 24.66 ns	32 ± 20.58*	74 ±24.27	51 ± 22.32*	42 ± 26.34**
DBP	54 ± 13.94	39 ± 21.03 ns	27 ± 16.27*	66 ± 18.21	39 ± 25.35*	35 ± 24.84*
daytime BP load						
SBP	60 ± 22.63	42 ± 26.66*	32 ± 18.82*	72 ± 27.29	50 ± 27.83*	39 ± 24.54**
DBP	53 ± 12.40	43 ± 17.06 ns	27 ± 16.07*	65 ± 20.39	35 ± 24.16*	36 ±2 4.57*
nighttime BP load						
SBP	79 ± 18.81	39 ± 32.15 ns	30 ± 33.91*	85 ± 20.42	71 ± 28.70 ns	42 ± 37.10*
DBP	54 ± 26.88	41 ± 33.64 ns	25 ± 28.03 *	68 ± 25.78	51 ± 26.14 ns	39 ± 31.45 ns
Absolute value of pressure of BP loads (mmHg)[1]						
24-hour BP load						
SBP	19 ± 4.34	14 ± 2.69 ns	12 ± 7.14 ns	19 ± 6.29	13 ± 4.31*	11 ± 4.22*
DBP	10 ± 2.79	8 ± 2.12 ns	8 ± 2.97 ns	10 ± 2.06	8 ± 3.3 ns	7 ± 2.89*
daytime BP load						
SBP	20 ± 5.76	13 ± 22.36*	13 ± 6.88 ns	17 ± 6.06	12 ± 3.42 ns	10 ± 4.46*
DBP	10 ± 2.79	8 ± 2.12 ns	8 ± 2.64 ns	10 ± 3.58	13 ± 15.92 ns	7 ± 3.97 ns
nighttime BP load						
SBP	15 ± 5.06	17 ± 4.99 ns	7 ± 8.58*	24 ± 13.71	17 ± 8.82 ns	13 ± 6.79*
DBP	11 ± 3.26	6 ± 3.41 ns	5 ± 4.71*	9.4 ± 3.47	8 ± 5.45 ns	7 ± 5.61 ns

[1] data are shown as mean ± SD

* $p < 0.05$ versus baseline, ** $p < 0.001$ versus baseline

ns = not significant

Table 19 : The effect of dosage administration of enalapril on the reduction in frequency of BP loads

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ (5 mg/day)	$dosage_2$ (10 mg/day)	Δ BP	$dosage_2$ (10 mg/day)	$dosage_3$ (20 mg/day)	Δ BP
*- average 24-hour**						
SBP	10.86 ± 12.54 (p=0.185)	28.14 ± 20.32 (p = 0.032)	17.29 ± 23.57 (p=0.302)	23.67 ± 18.75 (p = 0.016)	32.78 ± 13.98 (p < 0.001)	9.11 ± 12.30 (p=0.171)
DBP	15.00 ± 12.22 (p=0.053)	26.29 ± 10.58 (p = 0.002)	11.29 ± 10.90 (p=0.101)	26.44 ± 19.96 (p = 0.012)	30.67 ± 19.24 (p = 0.004)	4.22 ± 5.00 (p=0.105)
*- average day-time**						
SBP	18.57 ± 14.09 (p = 0.039)	28.00 ± 13.32 (p = 0.006)	9.43 ± 10.16 (p=0.148)	22.00 ± 21.69 (p = 0.048)	32.89 ± 14.91 (p < 0.001)	10.89 ± 15.66 (p=0.211)
DBP	9.57 ± 11.28 (p=0.198)	25.43 ± 16.14 (p = 0.018)	15.86 ± 12.94 (p=0.053)	29.89 ± 21.39 (p = 0.009)	28.67 ± 19.38 (p = 0.007)	-1.22 ± 6.22 (p=1.000)
*- average night-time**						
SBP	39.43 ± 32.20 (p=0.053)	48.29 ± 34.52 (p = 0.030)	8.86 ± 27.98 (p=1.000)	14.11 ± 32.33 (p=0.680)	42.56 ± 31.15 (p = 0.010)	28.44 ± 35.44 (p=0.128)
DBP	13.43 ± 17.54 (p=0.268)	29.57 ± 18.2 (p = 0.015)	16.14 ± 20.24 (p=0.238)	16.78 ± 30.65 (0.418)	29.56 ± 32.40 (p=0.077)	12.78 ± 18.92 (p=0.232)

* data are shown as mean ± SD

Δ BP = difference in BP between dosage

Table 20 : The effect of dosage of enalapril on the reduction in absolute BP loads

Parameter	Mild HTN (n=7)			Moderate HTN (n=9)		
	$dosage_1$ (5 mg/d)	$dosage_2$ (10 mg/d)	Δ BP	$dosage_2$ (10 mg/d)	$dosage_3$ (20 mg/d)	Δ BP
*- average 24-hour**						
SBP	5.14 ± 4.34 (p=0.060)	6.29 ± 6.52 (p=0.131)	1.14 ± 5.40 (p=1.000)	6.22 ± 5.63 (p = 0.032)	8.33 ± 5.24 (p = 0.004)	2.11 ± 3.72 (p=0.382)
DBP	2.29 ± 3.20 (p=0.323)	2.00 ± 1.63 (p=0.053)	-0.29 ± 3.74 (p=1.000)	1.78 ± 3.74 (p=0.573)	2.56 ± 2.45 (p = 0.043)	0.78 ± 3.31 (p=1.000)
*- average day-time**						
SBP	7.14 ± 5.40 (p = 0.038)	7.57 ± 6.29 (p=0.057)	0.43 ± 5.09 (p=1.000)	4.33 ± 4.87 (p=0.085)	6.44 ± 5.53 (p = 0.024)	2.11 ± 5.23 (p=0.782)
DBP	2.0 ± 3.21 (p=0.453)	1.42 ± 2.15 (p=0.387)	-0.57 ± 3.10 (p=1.000)	-3.67 ± 15.57 (p=1.000)	2.22 ± 4.18 (p=0.447)	5.89 ±17.66 (p=1.000)
*- average night-time**						
SBP	-1.43 ± 5.38 (p=1.000)	8.71 ± 5.12 (p = 0.012)	10.14 ± 7.34 (p = 0.032)	6.89 ± 11.74 (p=0.349)	10.67 ± 10.57 (p = 0.049)	3.78 ± 5.19 (p=0.182)
DBP	5.00 ± 4.54 (p=0.081)	5.86 ± 4.14 (p = 0.029)	0.86 ± 4.67 (p=1.000)	1.78 ± 4.35 (p=0.766)	2.67 ± 4.87 (p=0.418)	0.89 ± 3.06 (p=1.000)

* data are shown as mean ± SD

** Δ BP = difference in BP between $dosage_1$ and $dosage_2$

[1, 2, 3,] after treatment with 5, 10, 20 mg /day enalapril

Trough to peak ratio

From the 24 hour ABP profile of each patient, individual trough and peak antihypertensive effects were obtained (Table 22). The time to peak antihypertensive effects or maximal BP fall was approximately 4 to 8 hours post-dose for enalapril. When the T :P ratios for SBP after taking 5-20 mg enalapril per day were considered, it was found that the reduction of SBP at trough was approximately 13 mmHg while the reduction was around 30 mmHg at peak for either dosages. The T : P ratio of mean SBP was nearly equal to the mean T : P ratio of individual patients which was around 40-50 %. The T : P ratio was likely to increase with increased dose. For DBP, it was found that the reduction in DBP at trough was around 6-10 mmHg while the reduction was about 17 mmHg at peak resulted in the T : P for DBP to be around 40-60 %. Higher doses are likely to result in higher T : P ratio either calculated from the mean DBP or evaluated as the mean of the individual T : P ratios.

Based on the assumption that patients with hypertension are likely to receive the greatest benefit from therapy when the antihypertensive effects do not fluctuate greatly during the dosing interval, the FDA guidelines indicate that the effect of an antihypertensive drug at the end of the dose interval (trough) should be no less than half to two-thirds of the peak effect.[53] Thus, a trough : peak ratio of 50-66 % is required for the efficacy of an antihypertensive agent to be considered satisfactory to its proposed dosage interval.

In this study, the average T : P ratio of SBP and DBP after administered 5 and 10 mg per day dosage of enalapril in mild hypertensive patients were lower than 50 %, only two of seven patients had T : P ratios which were higher than 50 % except for the T : P ratio of DBP after 10 mg administration of enalapril which the T :P was estimated from the mean DBP, was found to be 50 % and number of patients whose T

: P ratio values were > 50 % were 4 out of 7 patients. This means that with low dosages the enalapril induced BP lowering effect might not be sufficient in the last few hours of the once daily dosing interval. It was suggest that 5 mg of enalapril should administer twice daily to obtain 24-hour blood pressure control. However, the result obtained from moderate hypertensive patients showed the mean T : P ratios which were > 50% and the percent of patients whose T: P ratios were > 50 % were also increased: Zannad had reviewed the literature from 1986 to 1992 and reported that a wide range of T : P ratio values ranged from 50-80 % was found with dosage of 5 – 20 mg OD of enalapril and concluded that the aforementioned dosage regimen of enalapril could control the BP for 24-hour. Some other studies showed that after 4-weeks treatment with 10-20 mg enalapril OD, the T : P ratio was found to be above 50 %[54].

Concerning on the adverse effects of enalapril in hypertensive patientd whose complete the study we found that three of twenty-four hypertensive patient reported cough (12.5%), five of twenty-four were repeated laboratory monitoring, no patients whose had elevated in serum creatinine or potassium level. One patient on enalapril 5 mg per day had mild orthostatic symptom and had not symptom when titrated dose to 2.5 mg per day.

Table 22 : The trough and peak BP changes and the T:P ratio after enalapril treatment

Parameter	Mild HTN (n=7)		Moderate HTN (n=9)	
	$dosage_1$ (5 mg/d)	$dosage_2$ (10 mg/d)	$dosage_2$ (10 mg/d)	$dosage_3$ (20 mg/d)
SBP[1]				
Δ BP at Trough (mmHg)	13 ± 4.46	13 ± 3.09	14 ± 5.17	12 ± 5.38
Δ BP at Peak (mmHg)	31 ± 7.92	28 ± 6.68	32 ± 9.80	23 ± 9.72
T:P ratio of mean (%)	42	46	44	52
T:P ratio of individual (%) (range)	41 ± 9.54 (31 - 55)	47 ± 10.14 (37 - 65)	43 ± 10.56 (22 - 55)	51 ± 12.68 (34 - 76)
DBP[1]				
Δ BP at Trough (mmHg)	6 ± 2.37	8 ± 2.98	10 ± 3.67	10 ± 4.37
Δ BP at Peak (mmHg)	17 ± 5.00	16 ± 4.10	18 ± 5.83	17 ± 5.81
T:P ratio of mean (%)	35	50	56	59
T:P ratio of individual (%) (range)	43 ± 4.86 (38 - 50)	49 ± 13.16 (33 - 72)	54 ± 12.98 (33 - 74)	59 ± 11.76 (42 - 76)

1 data are shown as mean ± SD

[1, 2, 3,] after treatment with 5, 10, 20 mg/day enalapril