ผลของเวลาในการบริหารยาอีนาลาพริล ต่อการควบคุมความดันเลือด 24 ชั่วโมง เปรียบเทียบเช้า – เย็น

นางสาวรุ่งทิวา เลาหเธียรประธาน

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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EFFECT OF TIMING OF ENALAPRIL ADMINISTRATION ON 24 - HOUR BLOOD PRESSURE CONTROL : MORNING VERSUS EVENING

Miss Roongtiwa Laohathienpratan

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รุ่งทิวา เลาหเธียรประธาน : ผลของเวลาในการบริหารยาอีนาลาพริลต่อการควบคุมความดันเลือด 24 ชั่วโมง เปรียบเทียบ เช้า – เย็น (EFFECT OF TIMING OF ENALAPRIL ADMINISTRATION ON 24 -HOUR BLOOD PRESSURE CONTROL: MORNING VERSUS EVENING) อ. ที่ปรึกษา : รศ. ดร.ดวงจิต พนมวัน ณ อยุธยา, อ. ที่ปรึกษาร่วม : น.พ. สมเกียรติ แสงวัฒนาโรจน์ : 105 หน้า. ISBN 974-346–180-9

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาถึงผลของเวลาในการบริหารยาอีนาลาพริลต่อการควบคุมความดันเลือดตลอด 24 ชั่วโมงเปรียบเทียบระหว่างการบริหารยาในตอนเช้าและตอนเย็น โดยใช้เครื่องมือวัดความดันเลือดอัตโนมัติชนิดพกพา (24-hour ambulatory blood pressure monitoring machine) ศึกษาผลในผู้ป่วยที่เป็นความดันเลือดสูงชนิดปฐมภูมิ 25 ราย ณ แผนกผู้ป่วยนอกโรงพยาบาลจุฬาลงกรณ์ ผู้ป่วยที่มีค่าความดันเลือด diastolic(DBP)ขณะนั่ง 90 – 110 มิลลิเมตรปรอท และค่าความดันเลือด diastolic) เฉลี่ย 24 ชั่วโมง ≥ 85 mmHg หลังจากรับประทานยาหลอกเป็นเวลา 2 สัปดาห์ถูกนำเข้าสู่การศึกษา โดยผู้ป่วยที่มีความดันเลือดสูงอยู่ในขั้นอ่อน(จำนวน 15 คน) จะให้รับประทานยา enalapril ในขนาดยา 10 mg ต่อวันและผู้ป่วยที่มีความดันเลือดสูงอยู่ในขั้นปานกลาง(จำนวน 10 คน) จะให้รับประทานยา enalapril ในขนาดยา 20 mg ต่อวันโดยใช้วิธีการสุ่มให้ผู้ป่วยรับประทานยาในตอนเช้าหรือรับประทานยาในตอนเย็นก่อนเป็นเวลา 4 สัปดาห์ จากนั้นผู้ป่วยที่ได้ยาในตอนเช้าจะเปลี่ยนไปรับประทานยาในตอนเย็น ขณะที่ผู้ป่วยที่เคยรับประทานยาในตอนเย็น จะสลับไปรับประทานยาในตอนเช้าแทน เป็นเวลา 4 สัปดาห์ เช่นกัน เมื่อรับประทานยาจนครบเวลาที่กำหนดแล้วจะทำการวัดความดันเลือดทั้งที่คลินิกและด้วยเครื่องวัดความดันเลือดอัตโนมัติชนิดพกพาทุกครั้ง

ภายหลังการรับประทานยา enalapril ในขนาด 10 และ 20 มิลลิกรัมต่อวัน จนครบ 4 สัปดาห์ พบว่า office blood pressure, ความดันเลือดโดยเฉลี่ย 24 ชั่วโมง และ ความดันเลือดเฉลี่ยช่วงเวลากลางวัน ลดลงอย่างมีนัยสำคัญทางสถิติ($p<0.01$) เมื่อเทียบกับก่อนได้รับยาไม่ว่าจะบริหารยาในตอนเช้าหรือตอนเย็น และพบว่าการบริหารยาในเวลาที่ต่างกันไม่ส่งผลให้ความดันเลือดดังกล่าวข้างต้นลดลงต่างกันอย่างมีนัยสำคัญทางสถิติ อย่างไรก็ตามความดันเลือดเฉลี่ยช่วงเวลากลางคืนถึงแม้ว่าจะลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับก่อนได้รับยาไม่ว่าจะบริหารยาที่เวลาใด แต่พบว่าการบริหารยาในมื้อเย็นมีแนวโน้มที่จะทำให้ระดับความดันเลือดในช่วงเวลากลางคืนลดลงมากกว่าเมื่อให้ยาในตอนเช้า นอกจากนี้พบว่า enalapril ในขนาด 10 และ 20 มิลลิกรัมต่อวัน สามารถลดความดันเลือดในช่วงเช้าได้อย่างมีนัยสำคัญทางสถิติ และเช่นเดียวกันมีแนวโน้มที่การบริหารยาในมื้อเย็นจะสามารถลดความดันเลือดในช่วงเช้าได้มากกว่าการบริหารยาในมื้อเช้า ($p=0.05$-0.10) Trough:Peak ratio ที่คำนวณได้จากการรับประทานยา enalapril ในขนาด 10 และ 20 มิลลิกรัมต่อวันทั้งในตอนเช้าและตอนเย็นพบว่ามีค่าประมาณ 60% สำหรับ SBP และ 55 % สำหรับ DBP โดยเวลาในการบริหารยาที่ต่างกันไม่ส่งผลกระทบต่อ Trough:Peak ratio นอกจากนี้ BP loads ทั้งในช่วงเวลากลางวันและตลอด 24 ชั่วโมง ลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับก่อนได้รับยาเช่นกันไม่ว่าจะบริหารยาในตอนเช้าหรือตอนเย็น ($p<0.01$) ในขณะที่ BP loads ในช่วงเวลากลางคืนลดลงอย่างมีนัยสำคัญทางสถิติ($p<0.05$)เมื่อเทียบกับก่อนได้รับยาเฉพาะเมื่อบริหารยาในตอนเย็นเท่านั้น ผลการลดความดันเหล่านี้ไม่ได้ทำให้เกิดภาวะหัวใจเต้นเร็วกว่าปกติ หรืออาการข้างเคียงอย่างอื่น

เมื่อทำการบริหารยา enalapril แบบวันละครั้งไม่ว่าจะให้ยาในตอนเช้าหรือตอนเย็น สามารถลดความดันเลือดได้อย่างมีนัยสำคัญ อย่างไรก็ตามพบว่าการบริหารยาในตอนเย็นสามารถลดความดันเลือดในช่วงเวลากลางคืนและช่วงเวลาในตอนเช้า ได้มากกว่าเมื่อบริหารยาในตอนเช้า อย่างไรก็ตามการพิจารณาเวลาในการบริหารยาที่เหมาะสมต้องคำนึงว่าการที่ความดันเลือดลดลงได้มากกว่าในช่วงเวลาดังกล่าวข้างต้นนี้ จะส่งผลดีหรือเพิ่มความเสี่ยงต่อผู้ป่วยแต่ละรายไป

ภาควิชา.....เภสัชกรรม..... **ลายมือชื่อนิสิต**.....

สาขาวิชา.....เภสัชกรรม..... **ลายมือชื่ออาจารย์ที่ปรึกษา**.....

ปีการศึกษา.....2543..... **ลายมือชื่ออาจารย์ที่ปรึกษาร่วม**.....

4176578233: MAJOR HOSPITAL AND CLINICAL PHARMACY
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ROONGTIWA LAOHATHIENPRATAN: EFFECT OF TIMING OF ENALAPRIL ADMINISTRATION ON 24 - HOUR BLOOD PRESSURE CONTROL: MORNING VERSUS EVENING. THESIS ADVISOR: ASSOC. PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D. THESTS CO-ADVISOR: Dr. SOMKIAT SANGWATTANAROJ, M.D. 105 PP. ISBN 974-346-180-9

The purpose of this study was to determine the effect of timing of enalapril administration (morning or evening) on the 24-hour blood pressure control by using 24-hour monitoring ambulatory blood pressure (ABP) in mild to moderate primary hypertensive patients in out-patients department at King Chulalongkorn Memorial Hospital. Twenty-five patients with seated diastolic blood pressure 90-110 mmHg and 24-hour mean ambulatory diastolic blood pressure $\geq$ 85 mmHg after 2 weeks of placebo were allocated into the study. The dosage administered were 10 mg and 20 mg enalapril in mild (n=15) and moderate (n=10) hypertensive patients, respectively. They were randomly assigned to consume the drug either in the morning or in the evening time. After 4 weeks, the times for administering the drug were crossover. The office blood pressure and the ambulatory blood pressure were monitored at the end of each period.

It was found that office BP, 24-hour BP and day-time BP were significantly reduced from baseline with either morning or evening administration with 10 mg or 20 mg per day dose of enalapril($p<0.01$) but there were no statistically significant differences in the reduction of these BP between morning and evening administration, while the night-time BP was reduced by both regimens but the BP tended to be reduced to a greater extent with the evening administration as compared to the morning administration. Enalapril in the dose of 10 and 20 mg significantly reduced the early morning peak BP and the effect tended to be greater with the evening administration($p=0.05$-0.10). Trough:Peak ratios calculated for SBP and DBP were approximately 60% and 55% respectively with either morning or evening administration. The different time of administration did not effect the Trough:Peak ratios of the patients. Enalapril also induced significant reduction in BP loads during day-time and the whole 24-hour with either morning or evening administration($p<0.01$), while night-time and peak morning BP loads were significantly reduced from baseline with evening administration($p<0.05$) only. The antihypertensive effect was generated without the reflex tachycardia or other intolerance effects.

Enalapril administered once daily either in the morning or in the evening could significantly reduce the blood pressure to nearly the same extent during day-time. However, evening administration showed a more pronounced effect in the reduction of the blood pressure during nighttime and during peak morning time as compared to the effect caused by the morning administration. It is therefore depend on whether these pronounced effects are of benefit or risk to the individual patient in order to decide the best time of administration for each patient.

Department……..Pharmacy…… **Student's signature**……..

Field of study……...Pharmacy…… **Advisor's signature**…….

Academic year…….2000…… **Co-advisor's signature**……...

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Roongtiwa Laohathientpratan

CHAPTER I

INTRODUCTION

Hypertension is a major cardiovascular disorder and remains one of the leading causes of cardiovascular morbidity and mortality. Efforts to prevent, diagnose, and treat hypertension remain an important concern of national healthcare.

The goal of hypertension treatment is to achieve optimal or normal blood pressure (BP) and to minimize end-organ damage which can lead to kidney failure, stroke, and coronary heart disease (CHD)[1]. The pharmacological treatment of hypertension clearly has improved the prognosis for strokes, heart failure, renal failure and reduced cardiovascular mortality and morbidity.

The modern approach to pharmacological management is to use drug once a day with the concept that this is more convenient for the patient and will improve compliance [2]. Since the treatment of hypertension is considerably lifelong, this is an important consideration. The evidence that once daily therapy achieves better compliance than twice a day dose therapy is still not conclusive. However, most recently developed drugs, particularly the angiotensin converting enzyme inhibitors (ACEI) are all aim for once daily use [3-9].

However, cardiovascular events, such as myocardial infarction and stable angina pectoris, sudden cardiac death, have repeatedly been shown to exhibit a circadian variation with a higher incidence during the morning hours. Increasing in cardiovascular morbidity and mortality is also seen at times of stressful physical or mental activity, especially when their activities are undertaken after rising in the morning. With once a day therapy, the drugs are usually ingested in the morning, thus the lowest drug level and probably the least pharmacological effect might occur in the early morning time, in consequence with the increase in heart rate, blood pressure,

peripheral resistance, thrombotic events and a decrease in fibrinolytic activity leading to an increase in myocardial oxygen consumption.

At the time of this early morning rise in blood pressure, there is a twofold increased in the incidence of myocardial infarction and sudden death compared with other time intervals [10-11]. Contradictory findings have been reported concerning the time of onset of ischemic stroke with a maximum during the night or in the early morning hours. For this reason, antihypertensive treatment in primary hypertension should aim to reduce blood pressure during day-time without leading to a too pronounced decrease in the night time values.

There are several solutions for treatment failure. First, by using once daily drugs at a dose that can control blood pressure throughout the day or have a trough to peak ratio for the dosing interval is close to 100 %. Second, by decreasing the dosing interval so that the trough to peak ratio for the dosing interval is close to 100 %. An alternative solution is to change timing of administration by administration daily doses of drug at night time. Recently, a few studies have evaluated the effects of timing of the dose of the conventional antihypertensive agents on circadian blood pressure, for example, morning versus evening administration of a once-daily agent [12-16]. However, the results were relatively inconsistent. As a class, the angiotensin converting enzyme (ACE) inhibitors demonstrate a blood pressure response that appears to be agent specific. Accumulating data indicated that most angiotensin converting enzyme (ACE) inhibitors were able to lower blood pressure levels for 24- hours when given as a single daily dose [17-20] and some data appear to suggest that time of administration may play a role in the 24- hour efficacy of these agents [17].

Enalapril is a non-sulfhydryl angiotensin converting enzyme (ACE) inhibitors product which is deesterified to its active metabolite enalaprilat. This drug was clearly established as an effective and well tolerated monotherapy for the treatment of hypertension and congestive heart failure.

The antihypertensive efficacy of enalapril has been demonstrated in hypertensive patients in many studies (as either non-comparative studies or comparative to other antihypertensive drug) [21-24]. However, the question of whether ACE inhibitors should be taken in the evening rather than in the morning is not yet clearly determined, therefore further studies are needed.

Since ambulatory blood pressure monitoring (ABPM) offers the possibility of obtaining reliable, reproducible and detailed information on the time-course and magnitude of the effect of antihypertensive treatment on blood pressure over 24- hour [25-28]. Moreover, it is not affected by the alerting reaction usually observed during the doctor visit. ABPM is therefore particularly useful when testing the efficacy of new antihypertensives agents on 24- hour blood pressure control.

This study was undertaken to determine whether enalapril given once daily in the morning or in the evening could influence the 24- hour blood pressure pattern and peak morning blood pressure differently by using ambulatory blood pressure monitoring.

Objectives

1. To assess the effect of timing of administration , morning and evening , on 24- hour blood pressure control of enalapril particularly during early morning blood pressure rise.

2. To find out the appropriate time of administration for enalapril in order to achieve optimal 24-hour blood pressure control.

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Significance of the study

1. This study will provide information about the effect of administration time on 24- hour blood pressure control

2. This study will provide information about the best time administered enalapril in order to achieve the optimal blood pressure.

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CHAPTER II

REVIEW OF LITERATURE

1. Hypertension [29]

Hypertension is a very common chronic medical disorder. Despite its widely recognized high prevalence and associated danger, remains inadequately treated in the majority of patients. In the representative sample of the U.S. population examined in the 1988-1991 National Health and Nutrition Examination Survey (NHANES III), only 21 percent of hypertension had their blood pressure well controlled, as defined by a reading below 140/90 mmHg. Although most hypertension had been identified previously, only about half of hypertensives were currently being treated.

A. Prevalence of hypertension [29,30]

Blood pressure increases with age, but the onset of hypertension most often occurs during the third, fourth, and fifth decades of life. The incidence of hypertension among blacks is greater at every age beyond adolescence, they have a higher proportion of more severe disease with a higher mortality rate than whites at every level of income. The National Health and Nutrition Examination Survey (NHANES III)found that the prevalence of hypertension decreased from approximately 58 million in the period between 1976 and 1980 to around 50 million in the period between 1988 and 1991, recently published results of the 1988-1991.

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B Etiology and Pathogenesis of hypertension [29-31]

No single or specific cause is known for most hypertension, referred to as primary in preference to essential. Since persistent hypertension can develop only in response to an increase in cardiac output or a rise in peripheral resistance, defects may be present in one or more of the multiple factors that affect these two forces. The interplay of various derangements in factors affecting cardiac output and peripheral resistance may precipitate the disease, and these may differ in both type and degree in different patients. Secondary hypertension is arterial hypertension of known cause, fewer than 5 percent of all cases of systemic hypertension are in this category. The importance of identifying patients with secondary hypertension is that they sometimes can be cured by surgery or can be easily controlled by specific medical treatment.

Primary hypertension tends to cluster in families and represents a collection of genetically based diseases and/or syndromes with a number of underlying inherited biochemical abnormalities. Pathophysiologic factors that have been implicated in the genesis of primary hypertension include increased sympathetic nervous system activity, overproduction of an unidentified sodium-retaining hormone, chronic high sodium intake, inadequate dietary intakes of potassium and calcium, increased or inappropriate renin secretion, deficiencies of vasodilators such as prostaglandins, congenital abnormalities of the resistance vessels, diabetes mellitus, insulin resistance, obesity, increased activity of vascular growth factors, and altered cellular ion transport.

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B.1 The neural mechanisms [29-30]

Both the central (CNS) and the autonomic nervous systems are intricately involved in the maintenance of arterial blood pressure. Stimulation of certain areas within the CNS (nucleus tractus solitarius, vagal nuclei, vasomotor center) can result in either an increase or a decrease in blood pressure. The α and β receptors located on the presynaptic surface of sympathetic terminals play a role in negative and positive feedback to the norepinephrine-containing vesicles located near the neuronal ending.

These receptors are also located on the surface of effector cells innervated by sympathetic neuronal fibers. Stimulation of postsynaptic α_1 receptors on arterioles and venules results in vasoconstriction and that of β_2 receptors in the arterioles and venules results in vasodilation. When β_1 receptors in the heart are stimulated, an increase in heart rate and contractility occurs.

The major negative-feedback mechanism controlling sympathetic activity is the system of baroreceptor reflexes. In this reflex system, an acute elevation in arterial pressure increases the rate of baroreceptor discharge, which results in vasodilation throughout the peripheral circulatory system and a decrease in heart rate and contractility. Conversely, the low blood pressure has the opposite effect. A pathologic disturbance in any of these neural components that modulate arterial blood pressure could conceivably lead to a sustained elevation in blood pressure. A defect in one component may disturb the normal function in another, and the combined abnormalities may then cause hypertension.

B.2 The humoral mechanisms

The renin-angiotensin-aldosterone system (RAS)

The renin-angiotensin-aldosterone system (RAS) plays an important role in the regulation of sodium, potassium, and fluid balance, and it significantly influences vascular tone and sympathetic nervous system activity. Of course, all of these factors contribute to blood pressure homeostasis.

In the kidney, renin is synthesized and stored in the juxtaglomerular cells which are located primarily in the wall of the afferent arteriole. Several factors are known to control renin release, these are intrarenal factors (such as perfusion pressure, catecholamines, and angiotensin II) and extrarenal factors (such as sodium, chloride, and potassium). The juxtaglomerular cell functions as a baroreceptor sensing device in the afferent arteriole, decreased perfusion pressure leads to an increase in renin secretion. In addition, the juxtaglomerular apparatus also contains a group of specialized distal tubule cells referred to collectively as the macula densa. The flux of

sodium and chloride across the cells influences renin release. A decrease in the amount of sodium and chloride delivered to distal tubule stimulates renin release.

In blood, renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme. An increase in circulating angiotensin II can cause an elevation in blood pressure through both pressor and volume effects. The pressor effects of angiotensin II include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and a centrally mediated increase in sympathetic nervous system activity. Angiotensin II also stimulates the release of aldosterone from the adrenal gland, which lead to retention of both sodium and fluid, with a resultant increase in plasma volume and blood pressure.

Various components of the RAS have been demonstrated in blood vessels, heart and brain. High concentrations of ACE, for example, occur in the epithelial cells of the gastrointestinal and reproductive tracts, choroid plexus, in fibroblasts and differentiated macrophages. It is possible that tissue ACE provides an additional mechanism and step controlling the rate of formation of angiotensin II in the interstitial compartment of peripheral tissues. Local formation of angiotensin II in the interstitium of blood vessels controlled by ACE may provide further regulation of regional blood flow, facilitate the release of noradrenaline and prevent its reuptake from sympathetic nerve terminals. Moreover, angiotensin II may act as a mitogen to stimulate vascular hypertrophy and neointimal hyperplasia. In the heart, angiotensin II has direct inotropic and chronotropic actions in the heart and decreases vagal tone. Similar to the blood vessels, angiotensin II is also postulated to have growth-modulating effects and may be involved in cardiac hypertrophy.

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Natriuretic hormone

Another humoral factor that may be involved in the development of primary hypertension is the increased concentration of natriuretic hormone. The proposed role of natriuretic hormone is to inhibit Na^+ / K^+ATPase and, thus, to interfere with sodium transport across cell membranes. This hormone is thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium would ultimately lead to increased vascular tone and hypertension.

B.3 Insulin resistance and hyperinsulinemia

Insulin resistance and consequent hyperinsulinemia are present in as many as half of nonobese patients with primary hypertension and in virtually all patients with two conditions that are commonly accompanied by hypertension: obesity and adult-onset, non-insulin-dependent diabetes mellitus. Over the past few years, an "insulin hypothesis" has evolved, attributing the development of hypertension to the effects of hyperinsulinemia. Several mechanisms have been hypothesized to explain the relationship between hyperinsulinemia and blood pressure elevation: Hyperinsulinemia could elevate blood pressure by increasing sodium reabsorption in the distal nephron and possibly in the proximal tubule as well, thus expanding plasma and extracellular fluid volume. Hyperinsulinemia in the presence of normal blood glucose levels increases sympathetic nervous system activity, which can, in turn, elevate blood pressure. Insulin is a potent stimulus for receptor-mediated growth of vascular endothelial and smooth muscle cells, thus leading to increased peripheral vascular resistance and blood pressure. Insulin, by altering plasma free fatty acid levels, modulates Na^+ / K^+ -ATPase activity, thus altering cellular cation transport in a manner that could increase peripheral vascular tone and blood pressure. Furthermore, other mechanisms have been proposed and having experimental support. Interventions that reduce insulin resistance, such as weight loss, diets low in carbohydrates and high in unsaturated fats, and aerobic exercise, reduce both blood pressure and insulin

resistance, supporting the concept that primary hypertension is an insulin-resistant state. Additional evidence in favour of a hypertension-inducing effect of hyperinsulinemia is the lowering of blood pressure by the use of agents that increase insulin sensitivity and lower insulin levels, accomplished in humans with the biguanide metformin. In total, the evidence for a pressor effect of hyperinsulinemia seems impressive. Nonetheless, Anderson and Mark conclude that "Despite the recent surge of interest, it is not yet clear whether insulin resistance and hyperinsulinemia promote hypertension or whether these are secondary to abnormal skeletal muscle sympathetic and vascular mechanisms in obesity and hypertension.

B.4 The vascular mechanisms

The abnormalities in the structure and function of the vasculature are increasingly recognized as contributing to the hypertensive state by increasing total peripheral resistance. During the past decade, it has become obvious that the endothelium, the single cell, innermost layer of blood vessels, is more than a passive barrier between the blood and the vascular smooth muscle. We now know that the endothelium plays a crucial role in circulatory homeostasis responding not only to humoral and chemical signals, but also to changes in the haemodynamics of blood flow such shear stress. Endothelial cells release chemical mediators that modulate the responses of numerous cells including vascular smooth muscle, platelets, and leucocytes. The endothelium serves a dual role in the control of vascular tone, endothelial cells produce and release a variety of vasoactive substances. These include both vasodilators, such as endothelium-derived relaxing factor (EDRF) which has now been identified as nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin, and vasoconstrictors, such as thromboxane A_2 and prostaglandin H_2, endothelin, and angiotensin II. The interaction between these vasodilators and vasoconstrictors provides a local control mechanism that regulates vascular tone. Alterations in the production of these mediators are involved in the induction and persistence of hypertension in both experimental models and humans, in addition this endothelial cell dysfunction has been reported in various forms. Plasma

levels of endothelin, for example, have been reported to be significantly higher in patients with primary hypertension. In addition, both chemical-stimulated and basal release of EDRF has been shown to be severely attenuated in hypertensive patients as well as in experimental models of hypertension. Another abnormality in the biology of vascular smooth muscle cells that may account for increased vasotone of hypertensives, is a disturbance in the physico-chemical properties of the cell membrane leading to abnormalities in ion handling. Reported abnormalities of cellular electrolyte homeostasis, for example, increased sodium influx due to elevation of sodium-hydrogen exchange activity, decreased sodium-potassium cotransport, increased lithium-sodium countertransport and decreased red cell membrane binding of calcium.

In parallel with studies on the function of vascular smooth muscle in the hypertensive state, considerable attention has been given to the importance of structural changes. The change in the geometry of the vessel wall that results in an increased vasocontrictor response with the same degree of shortening of vascular smooth muscle in hypertensive patients is a decrease in the lumen (internal radius of the vessed). In studies of small resistance vessels from subcutaneous tissue from hypertensive subjects, an average 29% increase in the media thickness: lumen diameter ratio was found, closely matching the 32% elevation in blood pressure. The increase in the media thickness: lumen diameter ratio can resulf from an increase in wall thickness either due to medial smooth muscle cell proliferation, accumulation of glycoaminoglycans, or from the increasing evident support to the role of rearrangement of a normal amount of tissue around a small lumen, a process known as remodelling.

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C. Clinical Presentation [30]

Patients with uncomplicated, primary hypertension are usually asymptomatic initially. While a complete history and physical examination may help identify concerns that warrant further evaluation, a few basic tests should be performed in all hypertensive patients prior to initialing drug therapy. These include hemoglobin and hematocrit, urinalysis, serum potassium and creatinine, liver function tests, and electrocardiogram. Total and high –density-lipoprotein cholesterol, plasma glucose, and serum uric acid are indicated to assess other risk factors and to develop baseline data for monitoring drug-induced metabolic changes. As the hypertension progresses, however, symptoms characteristic of cardiovascular, cerebrovascular, or renal disease may occur as the patient develops target organ damage. Patients with secondary hypertension usually complain of symptoms suggestive of the underlying disorder. More than half of the patients with this form of secondary hypertension suffer episodes of orthostatic dizziness or syncope. In primary aldosteronism, hypokalemic symptoms usually manifest including muscle cramps and muscle weakness. Patients who present with hypertension secondary to Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness. The most common causes of secondary hypertension are summarized in table 1.

Frequently, the only sign of primary hypertension is an elevated blood pressure. The rest of the physical examination may be completely normal. Again, as the hypertension progresses, signs of end-organ damage begin to appear. These are chiefly related to pathologic changes in the eye, brain, heart, kidneys, and peripheral blood vessels.

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Table 1. Causes of secondary hypertension.[31]

Systolic and diastolic hypertension

Renal
- Renal parenchymal disease
  - Chronic nephritis
  - Polycystic disease
  - Collagen vascular disease
  - Diabetic nephropathy
  - Hydronephrosis
  - Acute glomerulonephritis
- Renal vascular disease
- Renal transplantation
- Renin-secreting tumors

Endocrine
- Adrenal
  - Primary aldosteronism
  - Overproduction of 11-deoxycorticosterone (DOC), 18-OH-DOC, and other mineralocorticoids
  - Congenital adrenal hyperplasia
  - Cushing's syndrome
  - Pheochromocytoma
- Extra-adrenal chromaffin tumors
- Hyperparathyroidism
- Acromegaly

Pregnancy-induced hypertension

Coarctation of the aorta

Neurologic disorders
- Dysautonomia
- Increased intracranial pressure
- Quadriplegia
- Lead poisoning
- Guillain-Barre syndrome

Postoperative

Drugs and chemicals
- Cyclosporine
- Oral contraceptives
- Glucocorticoids
- Mineralocorticoid, including licorice and carbenoxolone
- Sympathomimetics
- Tyramine and MAO inhibitors

Isolated systolic hypertension
- Aging with associated aortic rigidity
- Increased cardiac output
  - Thyrotoxicosis
  - Anemia
  - Aortic valvular insufficiency

Decreased peripheral vascular resistance
- Arteriovenous shunts
- Paget's disease of bone
- Beriberi

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D. Definition and classification of hypertension [1,32]

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitrary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international authorities and particularly by the Joint National Committee (JNC) in the United State and the WHO-ISH Guidelines committee. Hypertension is therefore defined as a SBP of 140 mmHg or greater and/or a DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adults over the age of 18 is provided in table 2.

Table 2. Definitions and classification of blood pressure levels (mmHg) [32]

Category	Systolic	Diastolic
Optimal	< 120	< 80
Normal	<130	< 85
High-normal	130-139	85-89
Grade 1 hypertension(mild)	140-159	90-99
Subgroup: borderline	140-149	90-94
Grade 2 hypertension(moderate)	160-179	100-109
Grade 3 hypertension(severe)	> 180	> 110
Isolated systolic hypertension	> 140	< 90
Subgroup: borderline	140-149	< 90

New (1999) WHO/ISH definitions and classification of BP levels

When a patient's systolic and diastolic blood pressure fall into different categories, the higher category should apply

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk factors, concomitant diseases such as diabetes, target organ damage and cardiovascular or renal disease, as well as other aspects of the patient's personal, medical and social situation. To provide a simple method by which to estimate the combined effect of several risk factors and conditions on the future absolute risk of major cardiovascular events. The estimates are based on age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular disease, the presence of target-organ-damage and history of cardiovascular or renal disease. They were calculated from data on the average 10 year risk of cardiovascular death, nonfatal stroke and nonfatal myocardial infarction among participants (average initial age of 60 years; range 45-80 years) in the Framingham Study.

Four categories of absolute cardiovascular risk are defined (low, medium, high and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors presents. Individuals with other risk factors listed in table 3 may also have absolute risk levels that are towards the higher end of the range for the category. The risk factors used to stratify risk in table 4 should also be useful in stratifying the risk of these diseases.

Low- risk group

The low-risk group includes men below 55 and women below 65 years of age with grade 1 hypertension and no other risk factors. Among individuals in this category, the risk of a major cardiovascular event in the next 10 years is typically less than 15 %. The risk will be particularly low in patients with borderline hypertension.

Medium - risk group

This group includes patients with a wide range of blood pressure and risk factors for cardiovascular disease. Some have lower blood pressures and multiple risk factors, whereas others have higher blood pressures and no or few other risk factors. This is the patient group for which the clinical judgement of the responsible doctor will be

paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next 10 years is typically about 15 – 20 % The risk will be closer to 15 % in those patients with grade I (mild) hypertension and only one additional risk factor.

High- risk group

This group includes patients with grade I or grade 2 hypertension who have three or more risk factors listed in Table 3, diabetes or target – organ damage and patients with Grade 3 (severe) hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in following 10 years is typically about 20 – 30 %.

Very-high-risk group

Patients with grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease (as defined in Table 3) carry the highest risk of cardiovascular events, of the order of 30 % or more over 10 years, and thus qualify for the most intensive and rapidly instituted therapeutic regimens.

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Table 3. Factors influencing prognosis [32]

Risk Factors For Cardiovascular Diseases	Target Organ Damage (TOD)	Associated Clinical Conditions (ACC)
I. Used for risk stratification ● Levels of systolic and diastolic blood pressure (Grades 1-3) ● Men >55 years ● Women >65 years ● Smoking ● Total cholesterol >6.5 mmol/L (250 mg/dl) ● Diabetes ● Family history of premature cardiovascular disease **II. Other factors adversely influencing prognosis** ● Reduced HDL cholesterol ● Raised LDL cholesterol ● Microalbuminuria in diabetes ● Impaired glucose tolerance ● Obesity ● Sedentary lifestyle ● Raised fibrinogen ● High risk socioeconomic group ● High risk ethnic group ● High risk geographic region	● Left ventricular hypertrophy (elec-trocardiogram, echocardiogram, or radiogram) ● Proteinuria and/or slight elevation of plasma creatinine concentration 106-177 mmol/l (1.2-2.0 mg/dl) ● Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) ● Generalised or focal narrowing of the retinal arteries	**Cerebrovascular disease** ● Ischaemic stroke ● Cerebral haemorrhage ● Transient ischaemic attack **Heart disease** ● Myocardial infarction ● Angina pectoris ● Coronary revascularisation ● Congestive heart failure **Renal disease** ● Diabetic nephropathy ● Renal failure (plasma creatinine con-centration >177 mmol/L) (>2.0 mg/dl) **Vascular disease** ● Dissecting aneurysm ● Symptomatic arterial disease **Advanced hypertensive retinopathy** ● Haemorrhages or exudates ● Papilloedema

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Table 4. Stratifying risk and quantifying prognosis [32]

	BLOOD PRESSURE (mmHg)		
Other risk factors & disease history	**Grade1** (mild hypertension) SBP 140-159 or DBP 90-99	**Grade 2** (moderate hypertension) SBP 160-179or DBP 100-109	**Grade 3** (severe hypertension) SBP ≥ 180 or DBP ≥110
I. no other risk Factors	low risk	medium risk	high risk
II. 1-2 risk factors[1]	medium risk	medium risk	v high risk
III. 3 or more risk factors or TOD[2] or diabetes	high risk	high risk	v high risk
IV. ACC[3]	v high risk	v high risk	v high risk

[1] See table 3

[2] TOD – target organ damage (see table 3)

[3] ACC-associated clinical conditions, including clinical cardiovascular disease or renal disease (see table 3)

Cardiovascular disease risk in hypertensive patients

Stroke

Blood pressure levels, both systolic (SBP) and diastolic (DBP), have been shown to be positively and continuously related to the risk of stroke across a wide range of levels in populations from both Western and Eastern hemispheres [33-34]. Among individuals of mostly middle age, a prolonged 5 mmHg lower level of usual DBP was shown to be associated with a 35-40% lower risk of stroke, with no lower level identified below which the risk of stroke did not continue to decline. The slope of the association appears to decline somewhat with increasing age [35]; however, because the incidence of stroke increases so rapidly with age, the elderly still suffer the large majority of blood pressure related cerebrovascular disease. Blood pressure levels are positively related to both cerebral haemorrhage and cerebral infraction, but the association appears to be somewhat steeper for haemorrhage than infarction [33].

Coronary heart disease

Blood pressure levels have also been shown to be positively and continuously related to the risks of major CHD events (CHD death or nonfatal myocardial infarction) [34]. The strength of this association is about two-thirds is steep as that for stroke, and appears to be similar across a broad range of blood pressure levels, that includes both hypertensive and normotensive individuals. Once again, no lower level has been identified below which the risks do not continue to decline.

Heart failure and renal disease

The risks of heart failure and of renal disease have been observed to be related to blood pressure levels, but the sizes of the relationships are less well established than those for stroke and CHD. Nevertheless, there is evidence that patients with a history of hypertension have at least six times greater risk of heart failure than do individuals without such a history [36], and that each 5 mmHg lower level of DBP is associated with at least a one-quarter lower risk of end-stage renal disease [37].

Recurrent cardiovascular events

Among individuals with a history of cerebrovascular disease or previous myocardial infarction, there have been reports of both linear [38-39] and non- linear (J-curve) [40-41] associations between blood pressure levels and the risks of recurrent events. However, the associations in patients with prior cardiovascular disease are subject to confounding as a consequence of the effects of disease (or its treatment) on blood pressure and, independently, on the risks of recurrence. Studies that have attempted to control for this (either by excluding patients with more severe disease or by excluding early recurrent events) have consistently demonstrated continuous positive associations between blood pressure levels and the longer-term risks of stroke and CHD recurrence [38-39].

Pulse pressure and arterial distensibility

There is evidence that pulse pressure (the difference between SBP and DBP) is also positively associated with a variety of cardiovascular disease[42-43]. However, there remains uncertainly as to whether pulse pressure predicts disease risk independently of either SBP or DBP. Pulse pressure is one index of arterial distensibility. While there are theoretical reasons for expecting arterial distensibility to be

independently predictive of cardiovascular disease risk, there are still few data demonstrating such an association.

2. Chronotherapy of cardiovascular diseases [44-49]

Continued characterization of the relationship between time - dependent effects of endogenous biological processes and exogenous stimuli or triggers on cardiovascular function is helping to elucidate the mechanisms influencing patterns of cardiac events. By understanding circadian patterns of risk of cardiac events and by developing individualized therapeutic strategies to reduce this risk, clinicians may be better able to optimize preventive and treatment therapies for cardiovascular conditions.

Patterns of endogenous process that affect cardiovascular function

There is complex, dynamic relationship between fluctuations in some biological processes and the rhythmic patterns of cardiovascular function. Many biological processes and markers of cardiovascular function (heart rate, blood pressure, vasomotor tone, platelet aggregation, and blood viscosity) exhibit distinct patterns of activity over a 24-hour cycle.

Neurohumoral activity is a major biological determinant of circadian variation in cardiovascular function. In general, sympathovagal tone varies cyclically over a 24-hour period, with sympathetic activity highest during the day and parasympathetic activity more pronounced during the night. The earliest evidence for circadian variation in blood pressure and heart rate was documented in 1978 with the advent of 24-hour blood pressure is observed during the night and is followed by an early – morning surge in blood pressure and an increase in heart rate that correspond to the time of awakening. Vasomotor tone is another neurohumoral variable that influences cardiovascular function. It is enhanced in the morning, a time when sympathetic tone is also augmented. A direct functional relationship between circadian variation in renin – angiotensin –aldosterone activity and blood pressure and an inverse correlation with atrial natriuretic peptide have also been reported. The activity of both of these counterregulatory processes of cardiovascular function is modulated by the autonomic nervous system. Although there is significant variability in renin-angiotensin –aldosterone

activity, such activity usually peaks during the day and reaches a nadir at night. Early-morning elevations in activity correlate with the observed early-morning increase in blood pressure. The circadian rhythm of atrial natriuretic peptide, in contrast, is exactly opposite to that of blood pressure. The responsiveness of platelets to the aggregation agents adenosine diphosphate and epinephrine generally follows a circadian pattern, with increased aggregation in the morning. two endogenous counterregulartory processes of fibrinolysis- the activity of tissue plasminogen activator (TPA) and the activity of tissue plasminogen activator inhibitor-1(PAI-1)- exhibit inverse circadian patterns. Tissue plasminogen activitor activity is lowest in the morning and peaks in the evening; PAI-1 displays a reverse pattern. Plasma euglobulin fibrinolytic activity also exhibits circadian peaks in the evening, contributing further to the decrease in morning fibrinolytic activity. Evidence also suggests an increased risk of thrombogenesis in the morning. Both activated partial thromboplastin time and thrombin time are decreased in the morning.

Relationship between circadian patterns in cardiovascular function, alterations in endogenous chronobiological patterns and the occurrence of cardiac events

Epidemiologic studies have revealed a circadian variation in the occurrence of many cardiovascular condition, such as myocardial ischemia, stroke, ventricular arrhythmia, and sudden cardiac death, with peak occurrences between 06.00 and 12.00. These circadian patterns display a marked temporal association, with the general patterns of circadian variation observed for biological processes influencing cardiovascular function and for the markers of cardiovascular function.(figure 1).

The general pattern of chronobiological processes related to cardiac function may be altered by acute or chronic conditions of stimuli. In addition to normal shifts in circadian patterns, certain conditions or diseases, such as left ventricular dysfunction (LVD) and diabetes mellitus, may affect chronobiological processes that influence circadian patterns of cardiovascular function. Age, patients with a history of acute myocardial infartion, smoking, or peripheral vascular disease may also contribute to alterations in circadian patterns.

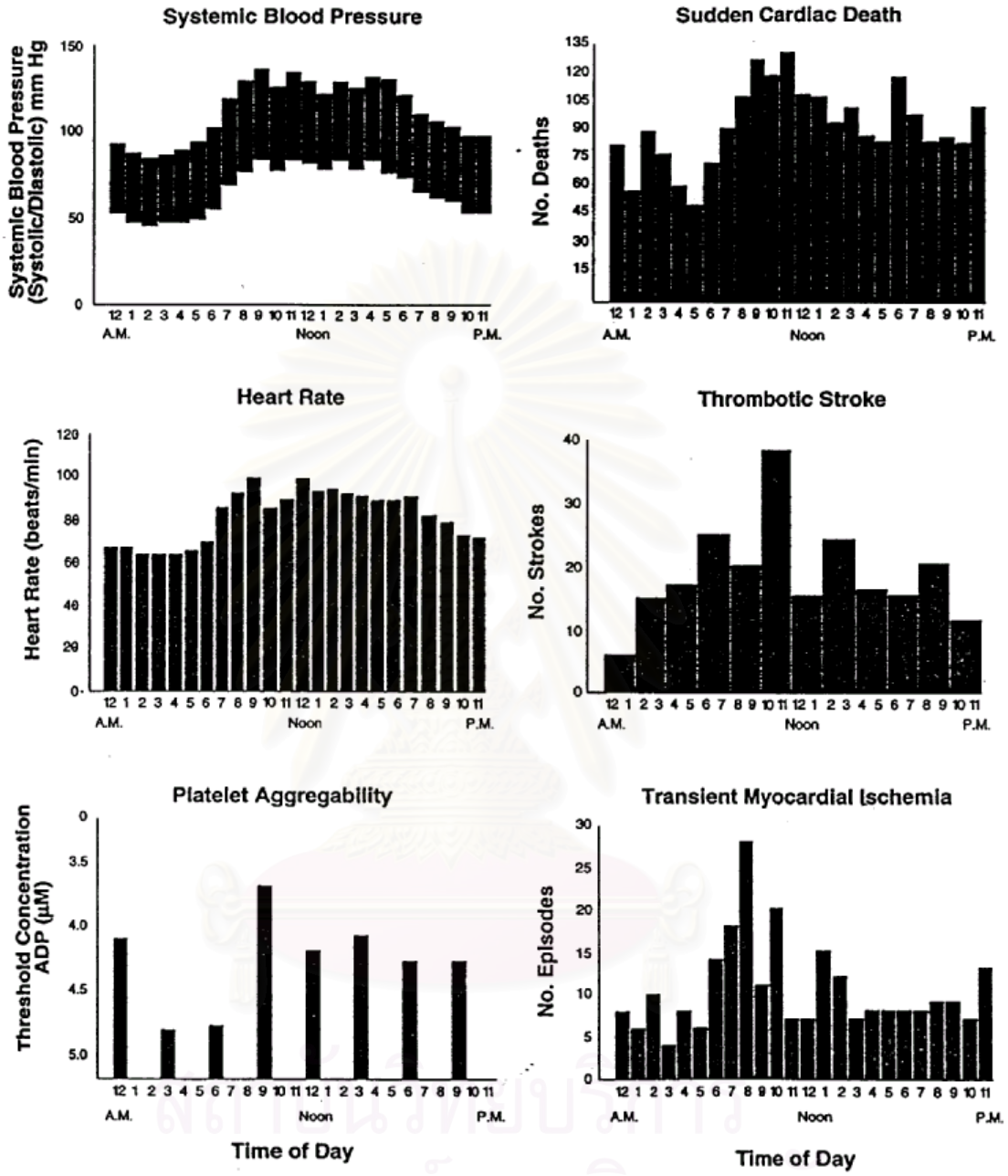
Exogenous triggers of cardiac events

The association between endogenous chronobiological processes and cardiovascular function is just one facet of investigation into patterns of the occurrence of cardiac events. Researchers involved in epidemiologic studies evaluating patterns of cardiac events have also suggested that external stimuli or triggers may contribute to the timing of these events. Two commonly reported possible triggers were mental stress and physical stress. Continued analysis of triggering and increased awareness of factors that may act as potential triggers will promote improvements in the prevention of cardiac conditions.

The contribution of endogenous chronobiological processes and exogenous stimuli or triggers to cardiovascular function and patterns of occurrence of cardiac events follow the natural fluctuations in endogenous physiological processes, with a vulnerable period consistently observed in the early-morning hours. Certain triggers, such as physiological or emotional stressors, may also contribute to the timing of cardiac events. The importance of 24-hour assessment of fluctuations in markers of cardiovascular function, such as blood pressure and heart rate, is clearly illustrated. Dynamic assessment of such markers may assist in determining the extent of disease progression and thereby provide prognostic information. It may also assist in optimizing the selection and evaluation of cardiovascular therapeutics as more agents designed to influence the circadian pattern of disease expression become available to clinicians.

A majors objective of chronotherapy for cardiovascular diseases would be to deliver the drug in higher concentrations during the time of greatest need, e.g. the early morning post awakening period, and in lesser concentrations when the need is less, e.g. during the middle of the sleep cycle. Recently, a few studies have evaluated the effects of the timing of the dose of a conventional antihypertensive agent on circadian BP- for example, morning versus evening administration of a once-daily agent. However, the results of these relatively small studies have been inconsistent.

Figure 1. variation over 24-hour period in three physiological processes that effect cardiovascular function and circadian patterns in the onset of cardiac events.



3. Blood pressure measurement [25-28,30]

Accurate blood pressure (BP) measurement is essential to the reliable assessment of antihypertensive drugs. The casual office or clinic method of measuring BP has been used routinely in clinical trials of antihypertensive agents. The usual, indirect of measuring blood pressure is with the sphygmomanometer cuff on the patient's arm at the level of the heart. It is important to use a proper size cuff to avoid over estimating the actual pressure when the cuff is too small. It has become common practice to use duplicate or triplicate measurements during a 1- to 4 – week placebo period and then again during the treatments period, although multiple casual BP measurements are not required by the Food and Drug Administration (FDA) and apparently do not offer information different from a single measurement.

Although it may be practical to streamline data collection as much as possible during clinical antihypertensive drug trials, data reduction also may result in potential deficits in important information about an antihypertensive agent before it is marketed. For example, there is great interest in the duration of an antihypertensive drug's pharmacodynamic activity because once-daily dosing has become a sought-after property of most new agents. It is impossible to establish duration of antihypertensive activity accurately with simple, casual measurements. Potential alternatives for assessing antihypertensive efficacy over time include (1) taking frequent casual BP measurements in clinical research units, (2) having patients take doses in outpatient clinics, wait in the facility for peak effects, and return later for trough measurements (peak-trough effects), or (3) use of noninvasive automatic ambulatory BP monitoring after dosing.

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Casual (clinic or office) BP determinations. [50]

The causal BP measurement is of value in that it is reasonably replicable as long as the conditions in which the measurements are made are similar. However, although the level of arterial pressure as measured at the clinic is an important risk factor in populations, its predictive value in individual patients is poor. This poor predictive power of clinic pressure readings may be due to the multifactorial nature of

the pathogenesis of cardiovascular damage. Moreover, clinic blood pressure measurements are often affected by the alerting reaction induced in patients by the doctor's presence, and this reaction causes a rise in blood pressure which may be both large and unpredictable. Also known as the 'white-coat-effect', this alerting reaction interferes with the evaluation of antihypertension treatment by clinic readings in two ways. Firstly, due to the associated pressor response, the alerting reaction may cause an overestimates of the initial blood pressure levels. Secondly, it may lead to an underestimate of the reduction in blood pressure achieved with treatment.

Automatic ambulatory monitoring of the BP (ABPM) [25-28,50-53]

For the past several years, portable recorders have been used for the study of BP over prolonged periods. This uses a portable device with an inflatable cuff, a compressor, an oscillometric or sphygmomanometric guage and an electronic recorder. In order to avoid misuse, it is essential that all operators have an understanding of the normal ranges of ambulatory blood pressure variabilities and usual circadian rhythms. In addition, the operator must be familiar with the equipment and with the calibration procedures. Subjects for ambulatory blood pressure measurement must be capable of coping with and caring for the recorder. The conditions of measurement for the subject should be standardized as far as possible in relation to activity; in particular the arm should be held still during each measurement. The subjects should be asked to keep a diary of activities during the recording period, unless motion-logging, as an objective assessment of activity, is available.

Comparing casual BP measurements with ambulatory BP measurements.

In most clinical antihypertensive drug trials, the causal BP measurement is determined with two goals in mind. The first, and more scientific goal, is to calculate the actual reduction of BP in mmHg after drug administration. A second parameter to be evaluated is"BP control" or the clinical response to the study drug, that is, the number of patients who achieved a particular goal of therapy. ambulatory blood pressure monitoring offers a number of advantages over clinic readings. For example, automates or semi-automated blood pressure measurements delivered by non-invasive monitors

do not elicit an alerting reaction and a rise in blood pressure. Furthermore, ambulatory blood pressure monitoring allows the effectiveness of a given antihypertensive drug to be tested not just in the artificial environment of the physician's office, but under exposure to the variable physical and psychological stimuli in daily life. By using ambulatory monitoring, precise and detailed information can be obtained on the time-course of the blood pressure fall induced by antihypertensive drugs. With this technique the exact time of the real daily life, peak antihypertensive drug effect can be identified and the persistence of the reduction can be followed over 24 hour. A further advantage is that there is no placebo effect to modify the 24-h average blood pressure. There are two limitations of ambulatory blood pressure monitoring. (1) average hourly values are not reproducible as average 24-h values, and this varies between different hours. This means that the number of study patients cannot be reduced from the number required. (2) the discontinuous nature of the measurement delivered by ambulatory monitoring does not allow a precise estimate of the variability in blood pressure.

ABPM can improve and simplify clinical trials of anti-hypertensive drugs in a number of ways.

Reliable identification of the target population

Antihypertensive therapeutic effects can be demonstrated only in hypertensive patients. Thus their correct identification is of utmost importance. Only ABPM allows for the correct diagnosis 'hypertension' as there is no white-coat hypertension. ABPM does so within on measurement day. With home measurement about three days are needed while, with casual clinic measurement, up to three or four months are needed to achieve a similar correct diagnosis. Thus the use of ABPM will shorten considerably the time necessary to identify suitable patients. There is an ethical reason for the use of ABPM to ensure a correct diagnosis. Patients who are not really hypertensive cannot benefit from antihypertensive treatment but they may be exposed to possible adverse drug reactions, which are not balanced by therapeutic benefit.

Reduction of sample size

ABPM does not respond to placebo and is highly reproducible. Thus the sample size required to show efficacy of an antihypertensive treatment can be reduced markedly. Two studies have shown independently almost identical effects of repeated

measurements on the standard deviation of the difference on sample size. Probably these computations are over-optimistic as one has to allow for losses resulting from drop-outs and technical failures. Nevertheless, a reduction of the required sample size of about 50% seems realistic.

Assessment of non-drug therapies

The effect of non-drug therapies on lowering arterial pressure lies in the range of 3-6 mmHg. Such differences have been assumed by many as clinically not relevant. Recent attempts to adjust the data of the Framingham study with regard to regression dilution bias because of casual clinic measurements at baseline indicate strongly that the regression for diastolic pressure and relative risk of stroke is much steeper than had been assumed until then. Thus, a decrease of 5 mmHg in diastolic pressure, for example, can equal a 75% reduction of the relative risk of stroke.

Assessment of dose-reponse relationship and duration of drug action

The proper assessment of the dose-response curve is easier with ABPM. There is less variability, thus smaller sample sizes and a shorter period of time may suffice. ABPM is a truly elegant way to assess a drug's duration of action and this is not only important for drugs given once daily.

Assessment of night-time blood pressure

There are reports that night-time arterial pressure correlates more closely with target organ damage than daytime pressure. If these observations can be confirmed in prospective studied, arterial pressure control during night- time will become an important therapeutic objective

There are concerns among clinicians that night-time arterial pressure could fall too much with antihypertensive treatment so that regional blood flow, especially in patients with arteriosclerosis, is insufficient .Thus, ABPM at night-time also serves a safety purpose.

A third indication for measuring night-time pressure is the evaluation of drug given once daily. Drugs with a once-a-day regimen have to demonstrate that there is adequate arterial pressure control during night-time and especially in the early morning hours before the effect of the next dose is seen.

Prognostic Significant of 24-hour Blood Pressure (BP) Variables [54-56]

Several studies have shown that various measures of organ damage associated with hypertension correlate to a greater degree with 24-h average arterial blood pressure than with clinic blood pressure. Many types of information can be obtained by using 24-hour ABPM device, including an individual's true blood pressure level, amplitude of diurnal variation, short-term blood pressure variability and blood pressure load, all of which might have prognostic significance.

Prognostic significance of average 24-hour and daytime blood pressure

Average daytime blood pressure values obtained non-invasively by a semi-automatic measuring device were correlated more closely with the overall end-organ damage in patients with hypertension than clinic blood pressure values. This finding was later confirmed by other investigators who provided the following additional evidence : (1) both the daytime blood pressure and the 24-hour average blood pressure are correlated more closely with end organ damage in hypertensive patients than clinic blood pressure; (2) the close correlation between 24-hour average blood pressure and end-organ damage can be seen when organ damage is measured by a comprehensive score based on patient history and clinical and laboratory examinations, and when different (and sometimes more sensitive) measures of individual end organ damage are considered. Thus, albuminuria, cerebral lacunae, left ventricular hypertrophy and retinopathy have all shown a greater correlation with 24-hour average values than with clinic values.

Prognostic significance of blood pressure variability

Blood pressure variations over 24 hour are correlated with end organ damage in hypertensive patients. The greater incidence and severity of end-organ damage was seen in the classes with greater blood pressure variability. Another support was shown by the study in 73 hypertensive patients using intra-arterial ambulatory monitoring. It was found that among the blood pressure readings taken at baseline, the short-term variability (defined as the standard deviation of consecutive half-hourly values during the daytime) was the best predictor of subsequent left ventricular mass. The other significant predictor was an aggregate measure of target-organ damage based on the ECG, chest X-ray, examination of the fundus and the serum creatinine concentration.

The variability in blood pressure also predicted aggregate target organ damage at follow-up, but blood pressure level was not a predictor.

Prognostic significance of the diurnal rhythm of blood pressure

Blood pressure usually follows a circadian rhythm with pressure levels higher during the day and lower at night. In most people, blood pressure falls during the night by more than 10%, such people are often referred to as dippers. But there are others (non-dippers) in whom the fall in blood pressure is smaller. This blunted circadian pattern has been reported to be associated with increased prevalence of left ventricular hypertrophy, atherosclerosis and stroke. In addition, a few cross-sectional studies have indicated that target organ damage is more pronounced in non-dippers than in dippers with comparable clinic blood pressure. It has also been suggested that this difference applies to women but not to men.

Prognostic significance of the daily blood pressure load

A study by White et al. in 30 never previously treated patients with mild to moderate essential hypertension via 24-hour ambulatory BP monitoring indicated that percentage of elevated BP values that includes both the awake and asleep periods is predictive of cardiac target organ involvement. Elevated BP values during the awake hours (> 140/90 mmHg) and sleeping hours (> 120/80 mmHg) were used to calculate the total percentage of abnormal BP values (load) in each patient. It was found that the BP loads were related to left ventricular mass index and left atrial index more strongly than were the mean 24-hour BP values. Moreover, if > 40% of the ambulatory BP values were elevated, the likelihood of increased mass or decreased filling was greater than 61%, whereas if< 40% of the BP values were elevated, the incidence of an abnormal cardiac test result decreased to less than 17%.

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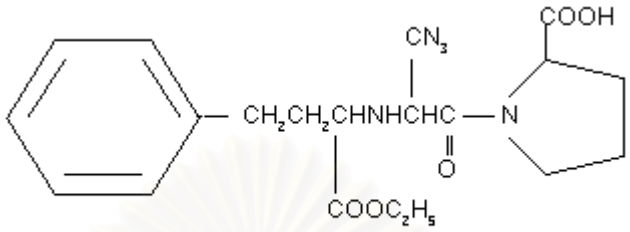
4. Enalapril [21-21,24,57-63]

enalapril was the second orally active angiotensin converting enzyme (ACE)inhibitor drug to become widely available for therapeutic use. Enalpril is administered as a maleate salt and is the monoethyl ester of enalaprilat



Enalapril

Figure 2 : Chemical structure of enalapril [57]

Pharmacokinetic and Pharmacodynamic properties. [64]

Following oral administration, enalapril is rapidly and well absorbed (60 to 70 %) from the gastrointestinal tract.Peak plasma concentrations(C_{max}) are attained about 1 hour after drug administration. After absorption, enalapril is rapidly de-esterified (hydrolysed) by carboxylesterase to from enalaprilat. As a result, plasma concentrations of parent drug are virtually undetectable about 4 hours after administration. In humans this metabolic transformation occurs almost exclusively in the liver. The parent drug has an elimination half-life of about 2 hours. Unchanged enalapril and enalaprilat are excreted both in urine and feces, with the urinary route predominating.

Enalaprilat undergoes polyphasic elimination with an initial elimination phase half-life of approximately 5 hours but a prolonged terminal phase of 30 to 35 hours, reflecting the strong binding of enalaprilat to plasma ACE. Enalaprilat appears to penetrate most tissues (kidneys and vascular tissue in particular). Enalapril has been shown, however, to decrease circulating plasma catecholamine levels and the turnover of brain tissue catecholamines. The bioavailability of enalapril is not affected by food but predictably, is affected by hepatic function. Clearance is reduced only in advanced uncompensated hepatic impairment.

Effects on Renin-Angiotensin-Aldosterone System

Enlapril prevents the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor) through inhibition of ACE. The drug completes with physiologic substrate (angiotensin I) for the active site of ACE. Inhibition of ACE initially results in decreased plasma angiotensin II concentrations and, consequently, blood pressure may be reduced in part through decreased vasoconstriction. Plasma renin activity (PRA) increases, possibly as a result of loss of feedback inhibition (mediated by angiotensin II) on the release of the renin from the kidneys and/or stimulation of reflex mechanisms via baroreceptors (as a result of the decrease in blood pressure). By decreasing local angiotensin II production, ACE inhibitors may decrease vascular tone by reducing direct angiotensin II-induced vasoconstriction and/or angiotensin II-induced increases in sympathetic activity.

Enalapril alone may be more effective in reducing blood pressure in patients with high or normal renin hypertension, but the drug may also lower blood pressure in patients with low renin hypertension. Initial decreases in plasma angiotensin II concentrations lead to decreased aldosterone secretion from the adrenal cortex and therefore, to decreased plasma concentrations and urinary excretion of aldosterone; however, plasma aldosterone concentrations may not decrease during enalapril therapy in some patients and may return to pretreatment levels in others during prolonged therapy.

Effects on catecholamines and autacoids

Circulating plasma norepinephrine concentration generally is not affected by enalapril, but the drug has reduced these concentrations in some patients with hypertension or congestive heart failure. In addition, the drug has attentuated the increase in plasma norepinephrine concentration that results from orthostatic reflexs. By inhibiting angiotensin II formation, ACE inhibitors may effect catecholamine release and reuptake by noradrenergic nerve endings and /or may decrease vascular sensitivity to vasopressors. Because ACE also degrades the vasodilator bradykinin, it has been suggested that inhibition of ACE may cause accumulation of bradykinin in plasma or

tissues with resultant vasodilation; however, plasma and/or urinary concentrations of bradykinin and/or its metabolites have been unchanged in enalapril responsive patients.

Cardiovascular effects

In hypertensive patients, enalapril reduced blood pressure by decreasing total peripheral resistance with a slight increase or no change in heart rate, stroke volume, or cardiac output. The drug causes arterial and possibly venous dilation. Enalapril generally decreases systolic and diastolic blood pressure by approximately 10-15%. In pateints with congestive heart failure, enalapril, usually in conjunction with cardiac glycosides and diuretics, decreases total peripheral resistance, pulmonary capillary wedge pressure, heart size, and mean arterial and right atrial pressures.

Renal and electrolytes effects

Renal blood flow may increase, but glomerular filtration rate is usually unchanged during enalapril therapy. BUN and serum creatinine concentrations have occasionally increased during long-term enalapril therapy. Enalapril's effects on renal blood flow and glomerular filtration in patients with renovascular hypertension appear to be similar to those in hypertensive patients with normal renal function. Increases in serum potassium concentration may occur secondary to enalapril – induced decreases in aldosterone secretion, especially in patients with impaired renal function. The hypothesis effects of enalapril may also result in part from decreased sodium and water retention secondary to reduced aldosterone secretion; however, decreases in aldosterone secretion during enalapril therapy are generally small.

There is also a chronopharmacological effect, presumably reflecting differential rates of absorption and hepatic function. Evening administration leads to a significant prolongation of time to C_{max} (t_{max}) for enalapril, with apparently no significant consequences for the disposition of enalaprilat.

Therapeutic use in hypertension [23,60]

Enalapril is used in the management of mild to severe hypertension. This drug has been used as monotherapy or in combination with other classes of antihypertensive agents. Enalapril provides effective 24-hour blood pressure control whether administered once or twice daily. Titrated dose of enalapril, 5 to 40 mg / day as monotherapy, reduce mean SBP and DBP by 15% to 25 % with adequate control (DBP < 90 mmHg) in approximately 50% to 75% of patients, depending on the initial severity of hypertension. The general lack of drug interactions with most other agents (with the exception of potassium-sparing diuretics and lithium) makes enalapril particularly suitable for patients with concomitant illness requiring long-term medication. Enalapril also has been effective in the management of renovascular or malignant hypertension, renal hypertension secondary to renal artery stenosis, and, in some patients, hypertension associated with chronic renal failure. however, enalapril should be used with caution in patients with impaired renal function, especially those with bilateral renal –artery stenosis or with renal artery stenosis in a solitary kidney.

Tolerance to the hypotensive effect of enalapril apparently does not occur during long-term administration, particularly if the drug is used with a diuretic. As with other hypotensive agents, treatment with enalapril or enalaprilat is not curative; after withdrawal of the drug, blood pressure returns to pretreatment levels. Abrupt withdrawal of enalapril or enalaprilat therapy results in a gradual return of hypertension; rapid increases in blood pressure have not been reported to date.

For the patients not receiving a diuretic, the usual initial adult dosage of enalapril maleate is 2.5-5 mg daily. Dosage of the drug should be adjusted according to the patient's blood pressure response. The usual maintenance dosage of enalapril maleate is 10-40 mg daily, given as a single dose or in 2 divided doses daily.

Therapeutic use in congestive heart failure [23,60]

Several studies clearly demonstrate that enalapril is important for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In these patients, enalapril improves symtoms, increases survival, improved function capacity and decrease the frequency of hospitalization. The recommended starting dose is 2.5 mg administered once or twice daily, titration up to a target dose of 10 mg twice daily in several weeks. The usual therapeutic dosing or two divided doses; most clinical studies have used twice –daily dosing

Myocardial infarction and left ventricular Dysfunction.

Numerous trials involving almost 100,000 patients have demonstrated a reduction in morbidity and mortality associated with ACE inhibitor therapy administered after MI. In these trials, ACE inhibitors were added to traditional therapy, such as nitroglycerin, thrombolysis, aspirin, or B-blockers. Data obtained from the PRACTICAL trial shown that enalapril can improve LV function and prevent LV dilation when administered with 24 hour after the onset of chest pain and was continued for three months.

Enalapril is used in clinically stable asymptomatic patients with left ventricular dysfunction (manifested as an ejection fraction of 35% or less) in an effort to decrease the rate of development of overt heart failure and subsequent hospitalizations for heart failure in these patients.

Enalapril and enalaprilat, also have been used to minimize or prevent the development of left ventricular dilatation and dysfunction following acute myocardial infarction. However, evidence regarding the efficacy of such therapy has been somewhat conflicting, particularly when parenteral therapy was initiated early (within 24-48 hours) and included patients with no evidence of baseline dysfunction.

Adverse effects

Adverse reactions to enalapril are usually mild and transient but have required discontinuance of therapy in about 3 or 6 % of patients receiving the drug for management of hypertension or congestive heart failure, respectively. Enalapril usually is well tolerated. The frequency of adverse experiences was not related to total daily dosage within usual ranges. In patients with hypertension, the overall percentage of patients treated with enalapril reporting adverse experiences was often comparable with the percentages of those receiving placebo. Adverse nervous system effects (e.g., headache, dizziness, fatigue) occur most frequently during enalapril therapy for hypertension, although adverse effects of enalapril generally are mild, discontinuance of the drug has been necessary in about 6% of patients, principally because of dizziness, headache, hypotension, or rash.

Cough has been reported in 1.3 or 3.5 % of patients receiving enalapril alone or in fixed combination with hydrochlorothiazide for hypertension, respectively. Nonproductive cough, particularly at night, may occur more frequently, especially in patients with chronic obstructive pulmonary disease. The cough generally is persistent, is not associated with other respiratory symptoms, and is reversible following discontinuance of the drug. Nasal congestion also has been reported. It has been suggested that accumulation of kinins in the respiratory tract secondary to ACE inhibition may in part be responsible for cough and nasal congestion. Concomitant therapy with a nonsteroidal anti-inflammatory agent (i.e., sulindac) appeared to minimize cough in a few patients, but additional study of the safety (e.g., effects on renal function) of such combined therapy is necessary. If cough develops in a patient receiving enalapril, ACE inhibitor-induced cough should be considered as part of the differential diagnosis.

CHAPTER III

PATIENTS AND METHODS

The study was conducted from June 1999 to March 2000 at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Patients

This study was designed as a randomized, double-blind, run-in placebo, crossover trial to assess the effect of enalapril administration time on 24- hour blood pressure control (morning versus evening), particularly in the early morning blood pressure. The study was approved by the ethics committee of King Chulalongkorn Memorial Hospital. All patients entering the study gave their informed consent. The patients with mild to moderate essential hypertension were recruited for this study based on the following criteria :

Inclusion criteria

- primary hypertensive patients with the office sitting diastolic blood pressure (DBP) in the range of 90-109 mmHg at the end of an initial 2 weeks placebo run-in period (at baseline)
- an age of 18 years or older
- mean 24- hour ambulatory blood pressure (ABP) of DBP $\geq$ 85 mmHg

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Exclusion criteria

- hypersensitivity to enalapril or other ACE inhibitors
- secondary hypertension of any etiologies
- chronic diseases such as other cardiovascular disease (eg. congestive heart failure,
- myocardial infarction, angina pectoris)
- significantly impaired liver function (AST, ALT $\geq$ 2 time of normal value)
- significantly impaired renal function (Scr $\geq$ 3.0 mg/dl)
- pregnancy or lactation
- night shift worker patients
- target organ damage [1]
- office systolic blood pressure (SBP) $\geq$ 180 mmHg

note : [1] = heart disease (angina, prior myocardial infarction, prior coronary revascularization), heart failure, stroke or transient ischemic attack, nephropathy, peripheral arterial disease, retinopathy)

- written informed consent had to be given by the patients
- concomittant therapy with drugs that interfere with the antihypertensive effects such as steroids, non- steroids antiinflammatory, etc. were not allowed to this study

Materials

1. drug : enalapril (enaril®) 5,20 mg (as enalapril maleate specially prepared for the study)
2. Instruments
   : Mercury Sphygmomanometer
   : 24- hour Ambulatory blood pressure monitoring machine (TM - 2421, A&D Company Limited , JAPAN)
   : 24 - hour Ambulatory blood pressure monitoring machine (90207 ABP report generator, Spacelab Medical Company Limited, Redmond, Washington, USA)

Method

Study design

After a washout and placebo run-in period from any previous antihypertensive therapy for 2 weeks, 24-hour ABP was measured. If the patients had previously been treated, all antihypertensive medication was stopped before the patients entered a 2 – week placebo run-in period. At visits after 2 weeks of placebo, the patients were eligible for the study if their office diastolic blood pressure measured in triplicate by mercury sphygmomanometer after sitting quietly for 5 minutes was 90-109 mmHg. A further eligibility criterion was a mean 24- hour diastolic blood pressure $\geq$ 85 mmHg measured by an ambulatory blood pressure monitor.

Eligible patients were randomly assigned to single daily dose of 10 mg enalapril for mild hypertension (DBP 90-99 mmHg or SBP 140-159 mmHg), 20 mg for moderate hypertension (DBP 100-109 mmHg or SBP 160-179 mmHg) either 10.00 am or 10.00 pm with matching placebo in a crossover design. Each treatment period lasted 4 weeks and the order for taking the tablets in the morning or at night was also randomized . At the end of placebo run – in and of each enalapril treatment period, office BP and 24- hour blood pressure monitoring were performed. The patients were requested to record times both their sleep and got up , as well as their activities while the monitoring was going on. Study flow chart is shown in figure 3

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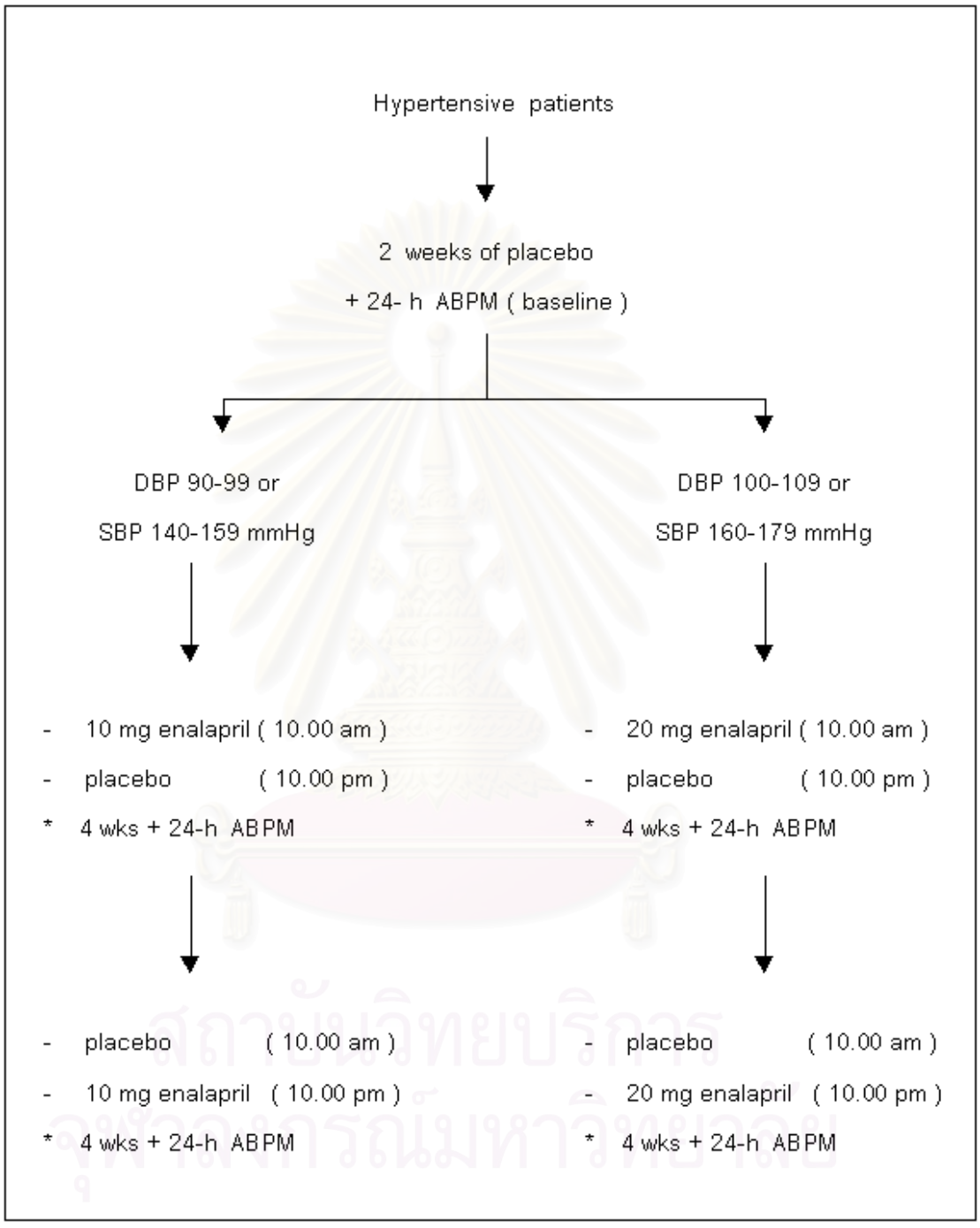
Figure 3. Study flow chart



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Procedures

- office blood pressure measurement

Sitting SBP and DBP were measured with a mercury sphygmomanometer (Korotkoff I and V for SBP and DBP, respectively) on the left arm after patients had been resting in the sitting position for 5 minutes. Four consecutive BP readings were recorded (three taken in the sitting and one in the standing position). HR was measured in sitting position for 3 times.

- 24- hour ambulatory BP measurement

24- hour ambulatory BP and HR were measured with a portable, non-invasive, fully automatic BP recorder which can be used alternately both auscultatory and oscillometric methods. The adult cuff (range :20-31 cm) was applied to the left arm of each patient and recordings were started shortly before the patients took enalapril. The device was programmed to provide a blood pressure and heart rate measurement every 20 minutes during the day-time (06.00 am-10.00 pm),in particularly every 15 minutes during 06.00am-09.00am and every 60 minutes during night-time (10.00 pm-06.00 am). Subjects were allowed to have their normal daily activities. However, they were to remain motionless each time a reading was taken.

Data analysis

- office blood pressure measurement

The average of three BP and HR measurements was used for the analysis. Sitting DBP was employed as an index of treatment with a DBP at the end of the test treatment > 90 mmHg were defined as non

– normalized. The mean arterial pressure (MAP) was calculated as DBP plus 1/3 of the difference in pressure (SBP-DBP).

24- hour ambulatory BP measurement

BP was detected by oscillometric method, except when oscillometric measurement was failure then the korotkoff BP will be used for the analysis instead. Raw data of ambulatory BP and HR were transferred to a computer programme. Systolic reading > 280 or < 60, diastolic readings > 160 or < 40 and pulse > 200 or < 35 bpm were deleted. SBP, DBP, MAP and HR values which were out of the range of $\pm$ 2 SD (standard deviation) of each parameter were excluded.

The following specific parameters were extracted from the data, evaluated for each therapeutic regimens and compared with placebo.

Mean values of SBP, DBP, MAP and HR

were calculated for each hour, for the whole 24- hour, as well as during day-time hour only, during night-time hour only and also concentrated on peak morning hour only. Mean hourly values derived from the average of 3 reading obtained in each hour ,such as the value at 8.40, 9.00, 9.20, were used for the calculation of BP value at 9.00. the day-time and night-time were defined as time between 6.00 am to 10.00 pm and 10.00 pm to 06.00 am, respectively.

Peak morning blood pressure

Peak morning blood pressure was defined as the blood pressure in the 2 hours starting from 30 min after the patient had got out of bed.

BP loads

BP loads were BP values that were higher than 140 or 120 mmHg for SBP and 90 or 80 mmHg for DBP during day-time and night-time, respectively. In addition, BP loads were expressed as the frequency or percentage as well as the absolute or magnitude value of blood pressure loads (mmHg).

Trough to peak ratio (T:P ratio)

Trough to peak ratio (T:P ratio) was the ratio between the antihypertensive effect at the end of the interval between doses (trough) and at the time of its maximum effect (peak). For each 24- hour ABP recording, trough SBP and DBP effects were taken as the reductions in blood pressure achieved between the 23 and the 24 hours after the dose, while peak SBP and DBP effects were maximum BP reduction occurred within 2-6 hours after the dose. T:P ratio were presented both as the mean of the individual T:P ratios and that resulted from using mean trough and peak values.

Dippers and Non- dippers

Dippers were defined as those who had the reduction in the night-time SBP and DBP $\geq$ 10 % of their day – time values. Those whose night-time BP were reduced less than 10 % of their day – time values were defined as non-dippers.

Statistical analysis

The OBP, 24- hour ABP measurements before and after each treatment period (morning and evening) with 10 or 20 mg enalapril were compared by using repeated analysis of variance (repeated ANOVA) and then followed by the Bonferroni correction to calculate the significance of pairwise differences (SPSS 9.0 program). Trough to peak ratio were calculated using both mean and the individual data.

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CHAPTER IV

RESULT AND DISCUSSION

1. Hypertensive patients

From June 1999 to March 2000, total of 44 patients with mild to moderate hypertension (office DBP > 90 and < 110 mmHg) were screened at out – patient department, King Chulalongkorn Memorial Hospital. At the end of placebo run – in period, only 35 patients with mean 24- hour DBP $\geq$ 85 mmHg measured by ABPM recruited in this study.

They were allocated randomly to the study therapy regimens, 10 or 20 mg enalapril in morning and evening regimen. During the study, 10 patients drop out from the study due to adverse drug reaction(3 patients with cough), concomitant illness (1 patient with pyroxymal atrial fibrillation and 2 patients with migrane) and 4 patients lost of following up . Finally there were 25 patients who were completed the study (figure 4).

Demographic data

Characteristics of the 25 patients enrolled in the study are reported in table 5. Eight males and seventeen females, with an average age of 57 years (range 42-71 years). The average weight, height and BMI values (mean $\pm$ SD) were 63 $\pm$ 9.29 kg, 161 $\pm$ 7.59 cm. and 24 $\pm$ 3.90 kg/m^2, respectively. Two patients were currently smoking cigarettes (1 pack per day) and four patients drink alcohol for social life. Two patients had a history of smoking cigarettes. Laboratory data at the end of the placebo run-in period or at baseline are shown in table 6. Majority of these patients had normal

Figure 4 study flow chart of enalapril treatment

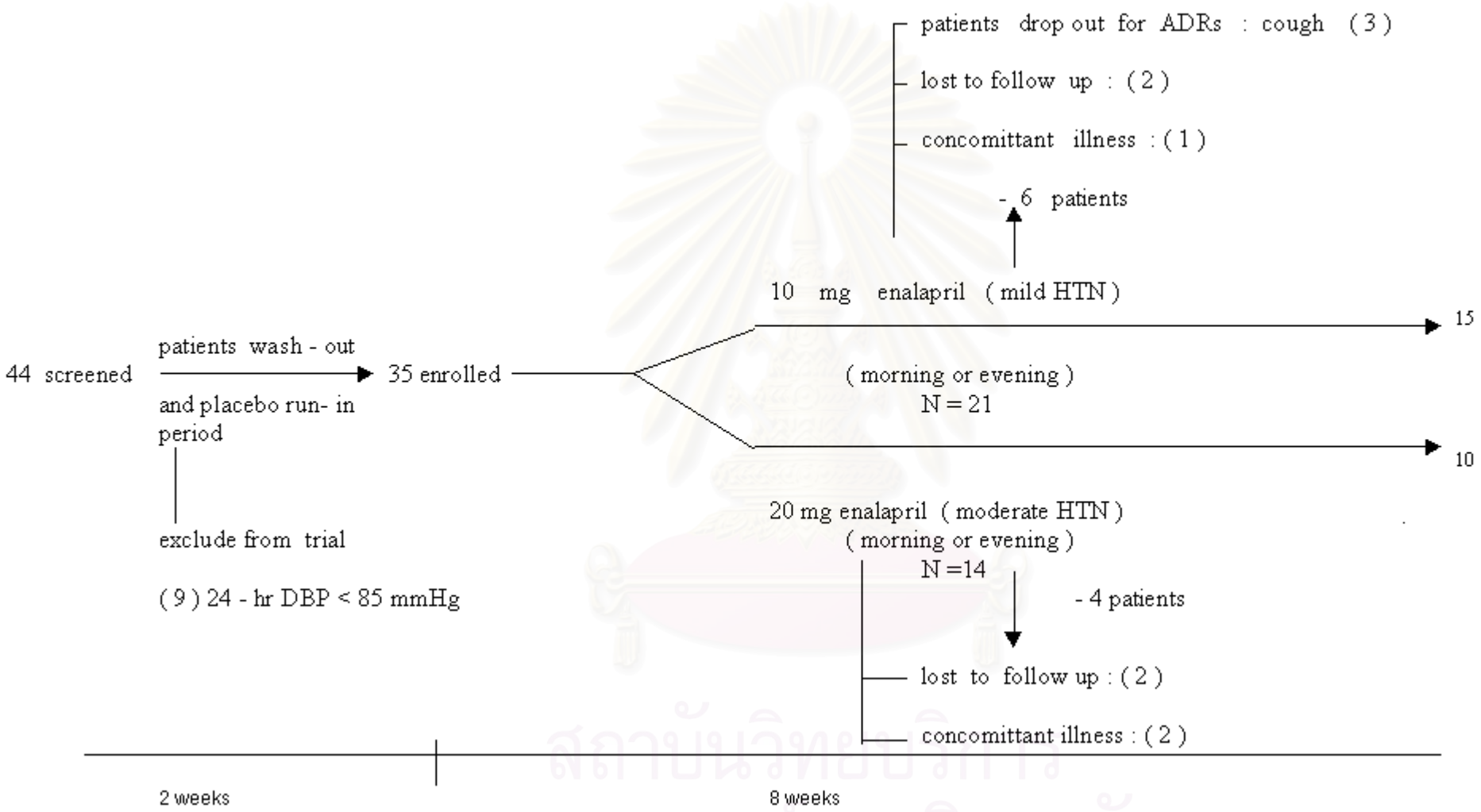

Table 5 : Demographic data of the subjects at baseline

No. of subjects	25
Age (years)	
Mean ± SD	57 ± 9.05
Range	42-71
Weight (kg)	
Mean ± SD	63 ± 9.29
Range	47-81
Height (cm)	
Mean ± SD	161 ±7.59
Range	152-180
BMI (kg/m^2)*	
Mean ± SD	24± 3.9
Range	17-33
SEX (no.)	
Male	8
Female	17
Cigarettes smoking (no.)	2
Alcoholic (no.)	4

* BMI : body mass index = $\frac{\text{weight}}{(\text{height})^2}$

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Table 6 : Labolatory data of the subjects at baseline (n = 25)

Test (normal range)	Mean ± SD	range
FPG (70-110 mg/dl)	104.60 ± 22.06	(79- 176)
BUN (10-20 mg/dl)	14.72 ± 2.48	(11- 19)
Cr (0.5-2.0 mg/dl)	0.96 ± 0.28	(0.5-1.6)
Uric acid (2.0-7.0 mg/dl)	5.2 ± 1.31	(3.8-8.1)
Cholesterol (150-240 mg/dl)	213.52 ± 36.01	(166-279)
Triglyceride (40-155 mg/dl)	107.84 ± 54.87	(0-234)
HDL (0-100 mg/dl)	52.52 ± 10.74	(35-74)
AST (0-38 u/l)	21.20 ± 5.32	(14-36)
ALT (0-38 u/l)	23.40 ± 11.29	(12-61)
Sodium (135-150 mEq/l)	140.64 ± 3.82	(131-147)
Potassium (3.8-5.5 mEg/l)	4.19 ± 0.38	(3.1-4.7)
Chloride (98-110 mEq/l)	107.32 ± 3.73	(96-112)
CO_2 (22-32 mEq/l)	24.64 ± 2.41	(20-29)

FPG = fasting plasma glucose

BUN = blood urea nitrogen

Cr = creatinine clearance

AST = alanine aminotranferase

ALT = aspartate aminotranferase

CO_2 = carbondioxide

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levels of laboratory data. Six patients had high cholesterol levels (> 240 mg/dl) and five patients had high triglyceride level (> 155 mg/dl), among of them two patients had both high levels of cholesterol and triglyceride. Two patients showed hyperglycemia while four other patients showed hyperuricemia. However, the kidney and liver function as well as the electrolyte of all subjects were in the normal ranges. The demographic and laboratory data of each patients were demonstrated in Appendix A and B.

2. Blood pressure data of the patients at baseline

Office blood pressure (OBP) at the screening visit and after placebo run -in period are illustrated in Appendix C. BP after taking placebo was used as the baseline level for comparing the drug effects. Five patients had never been treated for their hypertension while twenty of them had been administered with antihypertensive drug either monotherapy or combined therapy. There were little differences in BP between screening visit and after placebo run –in in new onset patients. In treated patients, none of them showed state of severe hypertension (SBP $\geq$ 180 or DBP $\geq$ 110 mmHg) after placebo run-in.

Some of the benefits of ambulatory BP measurement over the standard clinic or office BP measurement in a clinical therapeutic trial have been well established [50-52]. First, it is not substantially affected by the administration of placebo over several weeks. This means that when ambulatory blood pressure is used to determine the efficacy of an antihypertensive drug , a placebo group can be avoided, reducing the study size. Second, it also avoid the error arising as the white – coat effect. Third, 24-hour mean blood pressure is more reproducible than clinic blood pressure. Thus, white – coat hypertensive patients could be identified and excluded from the antihypertensive drug trial with 24- hour ABP measurement.

Table 7. showed BP at baseline measured both by office BP and 24- hour ABPmeasurement. The mean Office BP was 155 $\pm$ 8.64 / 95 $\pm$ 4.96 mmHg while the mean 24- hour BP was 145 $\pm$ 8.09 / 89 $\pm$ 5.98 mmHg and the mean day-time BP was

148 ± 8.29 / 92 ± 6.51 mmHg. The mean night - time BP or during sleep was 138 ± 9.72 / 84 ± 6.51 mmHg. The mean night-time BP were 10.72 ± 7.42 and 9.32 ± 6.16 mmHg less than the mean day-time BP for SBP and DBP, respectively.during day- time. It was day-time SBP and DBP, respectively. BP during early morning time was 151 ± 10.67/ 94 ± 6.98 mmHg which was higher than BP averaged from all period of day-time.

Hypertensive subjects who were recruited into this study had high BP both in the office and in their daily life. The average 24- hour BP value was lower than that of office BP. This was essentially due to the large reduction in BP during the night. It was demonstrated that the fall in BP at night was the result of sleep and inactivity rather than the time of the day.

By using the 24- hour BP monitoring, BP variability throughout the day could be observed. It was found that BP was maintained at a high level during awakening especially in the early morning, this is called the " morning surge " and was reduced to a lower level during sleeping time. This early morning rise in BP could contribute to the occurrence of cardiovascular events, such as acute myocardial infarction, sudden cardiac death, stable angina pectoris in the early morning hours [14-15]. Furthermore, these events also had been assumed to be associated with the rapid morning increase in sympathetic activity, peripheral resistance leading to an increased myocardial oxygen consumption, together with an increase in thrombotic events and a decrease in fibrinolytic activity at that time [12-15]. However, concerning to individual data, it was found that some patients did not show pattern of rising BP in the early morning when compared to day-time BP. According to the categorization of hypertensive patients as dippers or non- dippers with the percentage of BP reduction of night –time BP compared to day-time BP. Dippers were patients who had BP fall during the night by more than 10 % compared to day-time BP, but others in whom the fall in BP was less than 10 % were non- dippers. With this criterion, Eight patients were dippers (32 %) while seventeen patients were non- dippers (68 %).

The non – dipping or flat pattern of circadian BP variability is clinically important since recent studies suggest that these patients appear to have an

Table 7 : Office BP and ABP of the subjects at baseline

	Office BP* (mmHg)	24 – hour ABP * Average BP (mmHg)			
		24- hour BP	Day-time BP	Night-time BP	Peak morning BP
SBP	155 ± 8.64	145 ± 8.09	148 ± 8.29	138 ± 9.72	151 ± 10.67
mild	149 ± 4.53	142 ± 4.78	147 ± 4.70	133 ± 7.21	150 ± 10.67
moderate	163 ± 6.37	149 ± 10.49	150 ± 11.89	145 ± 8.31	154 ± 14.50
DBP	95 ± 4.96	89 ± 5.98	92 ±6.51	84 ±6.51	94 ± 6.98
mild	93 ± 2.94	87 ± 4.40	90 ±4.81	82 ±5.52	92 ± 5.62
moderate	98 ± 6.05	92 ± 6.92	95 ±8.02	87 ±6.82	97 ± 8.02
MAP	115 ± 4.90	107 ± 5.82	111 ± 6.13	101 ± 6.83	106 ± 6.78
mild	112 ± 2.79	106 ± 3.48	110 ± 4.10	98 ± 5.43	112 ± 1.48
moderate	120 ± 3.41	111 ± 7.24	113 ± 8.08	106 ± 6.30	116 ± 7.64
HR	81± 9.24	79 ± 6.53	83 ± 7.41	70 ± 7.56	82 ± 9.85
mild	80 ± 9.23	80 ± 6.11	84 ± 6.39	73 ± 7.25	84 ± 7.95
moderate	84 ± 9.10	77 ± 7.08	82 ± 8.98	67 ± 6.54	79 ± 11.93

* data are shown as mean ± SD

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

24- hour ABP = average BP in 24 – hour by ambulatory blood pressure monitoring machine

day-time BP = average BP during day-time (06.00 am -10.00 pm) by ambulatory blood pressure monitoring machine

night – time BP = average BP during night-time (10.00 pm - 06.00 am) by ambulatory blood pressure monitoring machine

peak morning BP = average BP during time intervals (06.00 am – 09.00 am) by ambulatory blood pressure monitoring machine

mild = subjects who had SBP 140-159 or DBP 90-99 mmHg

moderate = subjects who had SBP 160-179 or DBP 100-109 mmHg

increase in cardiovascular morbidity. In addition, there is some evidence that non-dippers have a greater left ventricular mass than dippers [(44,46-47)].

Furthermore, with the observation of BP measured throughout the day, the SBP/DBP value that were higher than 140/90 mmHg during day-time and 120/80 mmHg during night-time were judged as anomalous values or elevated values or BP loads. The frequency and absolute value of BP loads are presented in table 8. It was found that the hypertensive subjects possessed high percentage of BP loads which was presented both during day-time and night-time. About 65 % of all SBP, 50 % of DBP obtained during day-time were anomalous value which were higher than 140/90 by 17 $\pm$ 17.31 and 9 $\pm$ 7.85 mmHg for SBP and DBP, respectively. Even higher percentage of anomalous values (SBP/DBP) of 83 $\pm$ 26.88 / 46 $\pm$ 35.72 % were observed during nighttime. In addition, those BP loads during night-time were 20 $\pm$ 8.65 / 8 $\pm$ 6.20 mmHg higher than 120/ 80 mmHg. When 24- hour BP was evaluated, the percentage of elevated BP values were 67 $\pm$ 22.82 / 49 $\pm$ 28.12 % while the magnitude of absolute deviated BP were 15 $\pm$ 6.52 / 13 $\pm$ 16.39 mmHg.

The high percentage of BP loads confirmed that these hypertensive patients required antihypertensive therapy. White et al suggested that patients with BP loads of more than 40 % should receive antihypertensive therapy. From this study, it was found that night – time BP loads was higher than day – time BP loads which might be the effect of unfamiliar with the non – invasive BP monitoring machine.

In both normotensive and hypertensive individuals, BP varies according to both mental and physical activity levels which are usually different during wakefulness and during sleep. As shown in figure 5, it was found that BP and HR were at their highest levels during the period when the patient was awaked and active (eg. work) and at their lowest levels during the sleeping

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Table 8 : Blood Pressure loads of the subjects at baseline

	BP loads (mmHg)**							
	24- hour BP*		Day-time BP*		Night-time BP*		Peak morning BP*	
	frequency [1] (%)	absolute [2] (mmHg)	frequency [1] (%)	absolute [2] (mmHg)	frequency [1] (%)	absolute [2] (mmHg)	frequency [1] (%)	absolute [2] (mmHg)
SBP	67 ± 22.82	15 ± 6.52	63 ± 24.52	17 ± 17.31	83 ± 26.88	20 ± 8.65	64 ± 30.72	14 ± 10.89
mild	63 ± 24.01	13 ± 4.78	61 ± 24.47	13 ± 5.29	71 ± 29.74	14 ± 8.40	63±29.79	12 ± 5.65
moderate	73 ± 20.62	18 ± 8.05	67 ± 25.40	24 ± 25.84	100 ± 0.00	25 ± 8.26	68±33.48	17 ± 15.72
DBP	49 ± 28.12	13 ± 16.39	49 ± 28.29	9 ± 7.85	46 ± 35.72	8 ± 6.20	46 ± 30.77	8 ± 5.43
mild	40 ± 26.83	12 ± 20.24	40 ± 26.60	6 ± 3.20	39 ± 35.62	6 ± 6.01	40 ± 28.25	7 ± 4.39
moderate	62 ± 25.46	14 ± 8.60	63 ± 26.01	14 ± 10.13	57 ± 35.10	11 ± 5.55	57 ± 32.96	10 ± 6.42

* data are shown as mean ± SD

** BP loads were BP values that higher than 140/90 mmHg (SBP/DBP) during day time and 120/80 mmHg (SBP/DBP) during nighttime

1. frequency of BP loads in percentage

2. absolute value of pressure of BP loads in mmHg

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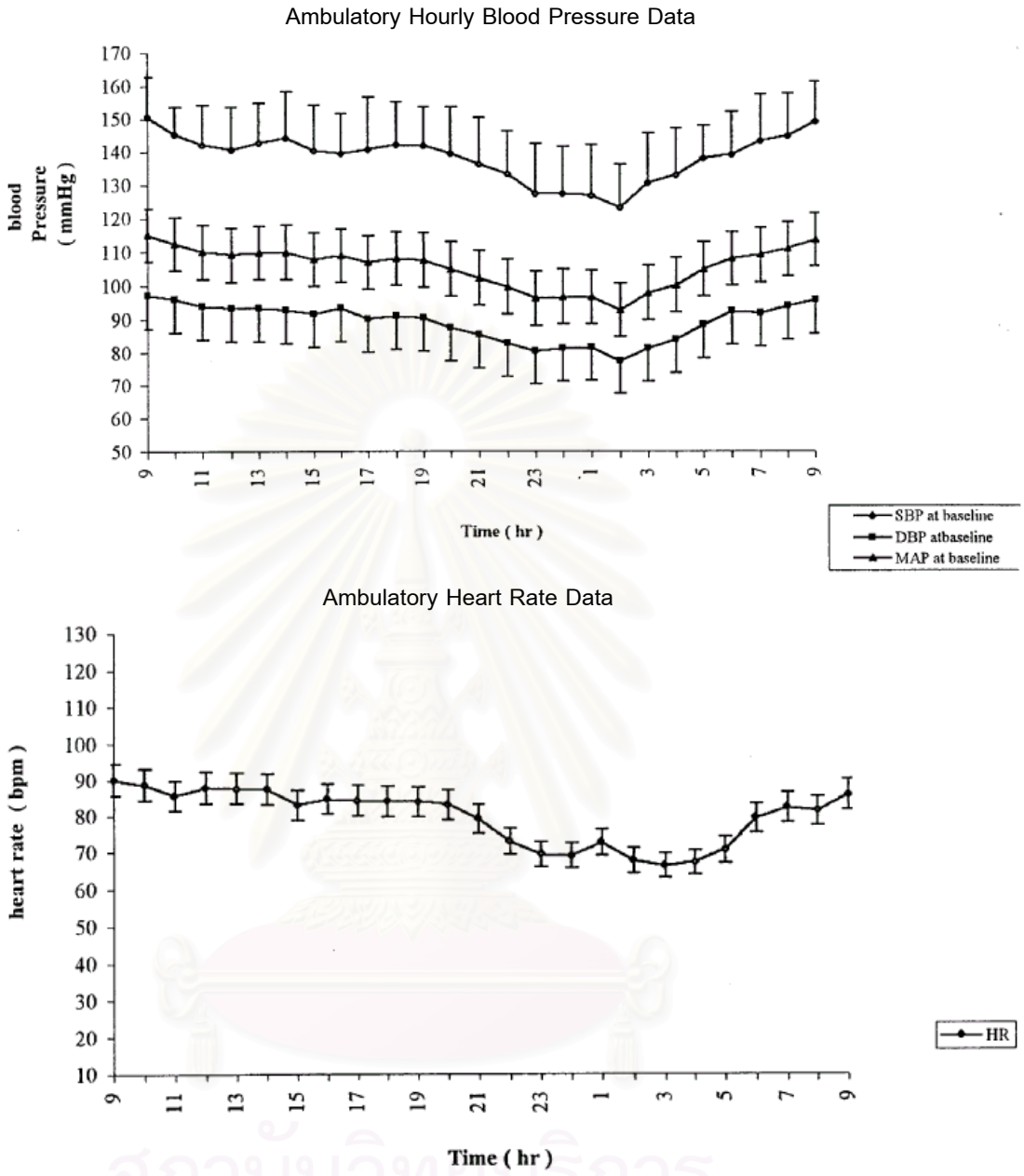
Figure 5. Blood Pressure and Heart Rate Profiles at baseline of patients



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period. BP started to decline when subjects went to bed (approximately at 10.00 pm) and continued decreasing to the lowest point(nadir) at approximately 02.00 am. The nadir BPs were 123/77 mmHg for SBP and DBP which corresponded to MAP value of 102 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 day- time BP. The change in heart rate was similar to that of the BP profile.

3. Antihypertensive effect evaluation (morning versus evening)

Office BP

After treatment with enalapril 10 mg per day form either regimen, morning or evening, it was found that office SBP and DBP significantly decreased, passing from 149 $\pm$ 4.53 / 93 $\pm$ 2.94 mmHg to 135 $\pm$ 9.16 / 82 $\pm$ 6.13 mmHg with the morning administration and to 134 $\pm$ 6.06 / 82 $\pm$ 5.62 mmHg with the evening administration (these BP were significantly differences from the pre-treat values at $p< 0.001$ level). MAP was also significantly lowered from 112 $\pm$ 2.79 to 100 $\pm$ 6.48 with morning administration and to 99 $\pm$ 5.01 mmHg with evening administration ($p<0.001$). However, there were no significant changes in HR after either regimen which the HR was recorded to be 80 $\pm$ 9.23 before treatment while the HR was 77 $\pm$ 7.45 bpm with morning administration and was 74 $\pm$ 6.06 bpm with evening administration (table 9).

At the same time, office SBP and DBP were significantly reduced from 163 $\pm$ 6.37 / 98 $\pm$ 6.05 mmHg to 144 $\pm$ 6.96 / 88 $\pm$ 7.33 mmHg with morning administration and to 142 $\pm$ 6.69 / 88 $\pm$ 7.85 mmHg with evening administration when 20 mg per day of enalapril had been used for one month ($P<0.001$). MAP was also significantly lowered from 120 $\pm$ 3.41 to 107 $\pm$ 6.27 with morning administration and to 106 $\pm$ 6.77 mmHg with evening administration ($p<0.001$). HR decreased from 84 $\pm$ 9.10 to 79 $\pm$ 10.63 and to 76 $\pm$ 7.89 bpm with morning and evening administration respectively. However, there were no significant differences in the reduction of SBP, DBP,

Table 9 : the mean office BP and ABP of the subjects after placebo and after enalapril treatments

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Placebo	Morning dose	Evening dose	Placebo	Morning dose	Evening dose
	(2 weeks)	(4 weeks)	(4 weeks)	(2 weeks)	(4 weeks)	(4 weeks)
Office BP (mmHg) [1]						
SBP	149± 4.53	135 ± 9.16*	134±6.06*	163±6.37	144±6.96*	142±6.69*
DBP	93± 2.94	82 ± 6.13*	82±5.62*	98±6.05	88±7.33*	88±7.85*
MAP	112±2.79	100 ± 6.48*	99±5.01*	120±3.41	107±6.27*	106±6.77*
HR (bpm)	80±9.23	77 ± 7.45 ns	74±6.06 ns	84±9.10	79 ±10.63 ns	76±7.89 ns
24 – hour ABP (mmHg) [1]						
- average 24 hour						
SBP	142 ± 4.78	136 ± 9.36**	130 ± 8.93*	149 ±10.49	137 ± 8.75*	135 ± 9.00*
DBP	87 ± 4.40	77 ± 7.46*	77 ± 8.15*	92 ± 6.92	83 ± 9.31*	81 ± 8.52*
MAP	106 ± 3.48	96 ± 6.75*	95 ± 6.81*	111 ± 7.24	101 ± 8.16*	99 ± 8.04*
HR (bpm)	80 ± 6.11	77 ± 9.10 ns	81 ± 8.18 ns	77 ± 7.08	78 ± 8.21 ns	75 ± 6.13 ns
- average day – time						
SBP	147 ± 4.70	137 ± 9.15*	136 ± 10.16*	150 ±11.89	139 ±10.50**	138 ± 8.99*
DBP	90 ± 4.81	79 ± 8.23*	80 ± 8.86*	95 ± 8.02	85 ±10.80*	84 ± 9.30*
MAP	110 ± 4.10	99 ± 7.26*	99 ± 7.95*	113 ± 8.08	102 ± 9.82*	102 ± 8.27*
HR (bpm)	84 ± 6.39	81 ± 9.53 ns	83 ± 6.50 ns	82 ± 8.98	82 ± 8.80 ns	79 ± 7.61 ns
- average night-time						
SBP	133 ± 7.21	129 ±11.80 ns	123 ± 12.01*	145 ± 8.31	135 ± 8.88*	129 ± 9.48*+
DBP	82 ± 5.52	73 ± 7.77*	70 ± 7.04*	87 ± 6.82	80 ± 7.76*	77 ± 7.36*
MAP	98 ± 5.43	92 ± 7.86*	88 ± 6.89*	106 ± 6.30	98 ± 6.96*	94 ± 7.10*+
HR (bpm)	73 ± 7.25	69 ± 9.96 ns	73 ± 9.51 ns	67 ± 6.54	72 ± 8.00 ns	67 ± 7.38 ns
- peak morning BP						
SBP	150 ± 7.22	138 ± 8.54*	132 ± 9.64*	154 ±14.50	143 ±11.69 ns	137 ±13.11**
DBP	92 ± 5.62	81 ± 7.94*	77 ± 8.37*#	97 ± 8.02	91 ± 9.69*	83 ± 9.16*+
MAP	112 ± 1.48	100 ± 6.95*	95 ± 6.67*+	116 ± 7.64	108 ± 8.91*	101 ± 9.07*+
HR (bpm)	84 ± 7.95	80 ±11.20 ns	83 ±10.57 ns	79 ±11.93	82 ± 9.55 ns	81 ± 8.82 ns

1 data are shown as mean ± SD

* p < 0.01, ** p < 0.05 versus placebo

\+ p < 0.05, # p = 0.05-0.10 versus morning dose , ns = not significant

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Table 10 : The effect of administration time (morning versus evening) on the reduction of office BP

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Morning	Evening	ΔBP**	Morning	Evening	ΔBP**
Office BP (mmHg)*						
SBP	14.53 ± 8.17	14.93 ± 6.78	-0.40 ± 9.10	18.60 ± 10.56	20.80 ± 10.02	-2.20 ± 5.34
	(P < 0.001)	(P < 0.001)	(ns)	(P = 0.001)	(P < 0.001)	(P = 0.672)
DBP	10.67 ±5.12	11.33 ± 6.14	0.67 ± 5.62	10.10 ± 4.79	9.50 ± 5.06	0.60 ± 4.79
	(P < 0.001)	(P < 0.001)	(ns)	(P < 0.001)	(P < 0.001)	(ns)
MAP	11.87 ± 5.81	12.47 ± 5.48	-0.60 ± 5.99	12.80 ±4.69	13.10 ±5.13	-0.30 ± 2.83
	(P < 0.001)	(P < 0.001)	(ns)	(P < 0.001)	(P < 0.001)	(ns)

* data are shown as mean+ SD

** ΔBP = difference in BP between morning and evening treatment

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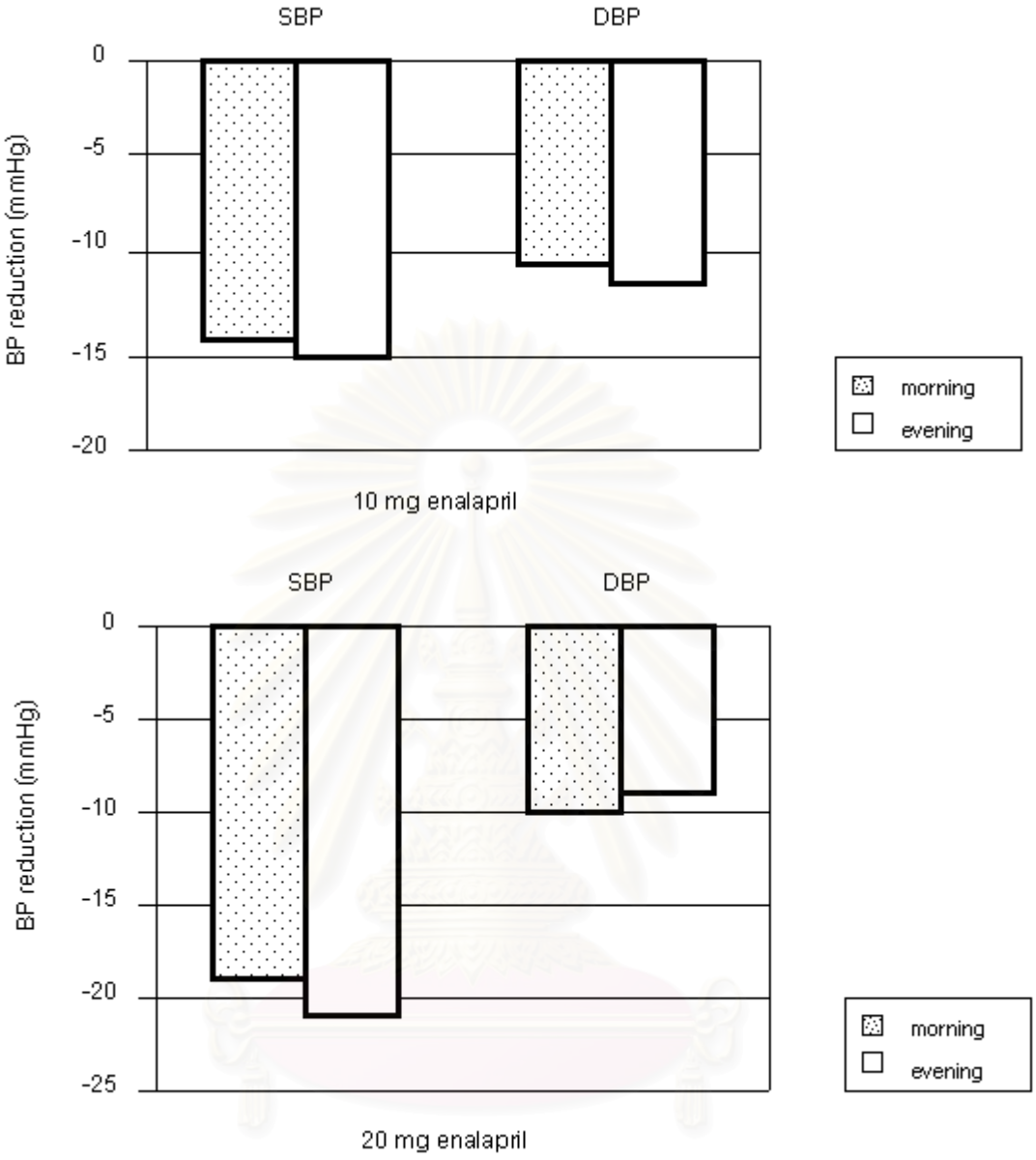
Figure 6. Office blood pressure reduction



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MAP and HR between morning and evening administration of either 10 mg or 20 mg dose of enalapril (table 10, figure 6). Neither symptomatic nor postural hypotension were reported during treatment with these dose.

Ambulatory BP

Average 24-hour BP

Using 24 – hour BP evaluation, SBP and DBP were also significantly reduced from 142 ± 4.78 / 87 ± 4.40 to 136 ± 9.36 / 77 ± 7.46 mmHg with morning administration ($p<0.05$) and to 130 ± 8.93 / 77 ± 8.15 mmHg with evening administration ($p<0.01$) when 10 mg per day of enalapril was used. The reduction in DBP was similar whether the time of administration was in the morning or in the evening, whereas the reduction in SBP was a little greater with the evening administration (table 9). Similar results were obtained with 20 mg per day of enalapril , SBP and DBP were significantly reduced from 149 ± 10.49 / 92 ± 6.92 mmHg to 137 ± 8.75 / 83 ± 9.31 mmHg with morning administration ($p<0.01$) and to 135 ± 9.00 / 81 ± 8.52 mmHg with evening administration ($p<0.01$). MAP was also significantly lowered from 111 ± 7.24 to 101± 8.16 with morning administration ($p<0.01$) and to 99 ± 8.04 mmHg with evening administration ($p<0.01$). HR was recorded to be 77 ± 7.08 bpm before treatment and was 78 ± 8.21 bpm and 75 ± 6.13 bpm with the morning and the evening administration respectively(table 9).

Comparison between the effect of morning and evening time of administration showed that whether 10 mg or 20 mg per day of enalapril were used, there were no statistically significant differences in the reduction of the 24 hour average SBP, DBP, MAP and HR between morning and evening administration (table 11, figure 7) even though the evening administration showed a little bit greater average reduction values of SBP, DBP and MAP.

Average day-time BP

When the BP during day – time hours only were considered, the mean day-time SBP and DBP were significantly dropped from 147 ± 4.70 / 90 ± 4.81 to 137 ± 9.15 / 79 ± 8.23 mmHg with morning administration and to 136 ± 10.16

Table 11 : The effect of administration time (morning versus evening) on the reduction of ABP

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Morning	Evening	ΔBP	Morning	Evening	ΔBP
*- average 24 hour**						
SBP	6.87 ± 8.09	11.93 ± 8.18	-5.07 ± 8.45	11.70 ± 8.89	13.50 ± 8.87	-1.80 ± 2.70
	(P =0.016)	(P < 0.001)	(P =0.108)	(P = 0.007)	(P = 0.003)	(P = 0.193)
DBP	10.07 ± 5.20	10.13 ± 5.94	-0.06 ± 3.54	9.50 ± 5.30	11.20 ± 2.74	-1.70 ± 4.06
	(P < 0.001)	(P < 0.001)	(ns)	(p = 0.01)	(P < 0.001)	(P =0.653)
MAP	9.20 ± 5.84	10.80 ± 6.34	-1.60 ± 4.81	10.00 ± 5.44	11.70 ± 4.62	-1.70 ± 3.37
	(P < 0.001)	(P < 0.001)	(P =0.655)	(P = 0.001)	(P < 0.001)	(P = 0.435)
*- average day – time **						
SBP	9.53 ± 8.46	11.27 ± 9.15	-1.73 ± 10.55	11.80 ±10.13	12.00 ± 9.31	-0.20 ± 5.35
	(P = 0.002)	(P = 0.002)	(ns)	(P = 0.015)	(P = 0.008)	(ns)
DBP	10.73 ± 5.92	9.87 ± 6.17	0.867 ± 3.87	9.90 ± 6.21	10.90 ± 3.38	-1.00 ± 5.42
	(P < 0.001)	(P < 0.001)	(ns)	(P = 0.002)	(P < 0.001)	(ns)
MAP	10.87 ± 7.08	10.87 ± 8.18	0.00	10.80 ± 6.48	11.40 ± 5.10	-0.60 ± 5.25
	(P < 0.001)	(P < 0.001)	(ns)	(P = 0.002)	(P < 0.001)	(ns)
*- average night-time**						
SBP	4.00 ± 8.93	10.27 ±10.94	- 6.27 ± 10.85	10.10 ± 9.04	15.9 ± 10.47	-5.80 ± 5.58
	(P = 0.315)	(P = 0.008)	(P =0.127)	(P = 0.019)	(P = 0.003)	(P = 0.028)
DBP	9.07 ± 8.08	11.67 ± 7.49	-2.60 ± 6.07	7.80 ± 4.10	10.60 ± 2.63	-2.80 ± 4.52
	(P = 0.002)	(P < 0.001)	(P = 0.358)	(P = 0.001)	(P < 0.001)	(P = 0.245)

* data are shown as mean ± SD

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Table 11 : The effect of administration time (morning versus evening) on the reduction of ABP (continue)

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Morning	Evening	Δ_{BP}	Morning	Evening	Δ_{BP}
MAP	6.73 ± 7.30	10.60 ± 7.67	-3.87 ± 7.06	7.90 ± 3.54	11.90 ± 4.25	-4.00 ± 4.24
	(P = 0.009)	(P < 0.001)	(P = 0.157)	(P < 0.001)	(P < 0.001)	(P = 0.046)
peak morning *						
SBP	11.67 ± 9.60	17.47 ± 9.80	-5.80 ± 12.19	11.40 ± 14.42	16.70 ± 18.34	- 5.30 ± 6.80
	(P =0.001)	(P < 0.001)	(P =0.260)	(P = 0.101)	(P = 0.054)	(P = 0.107)
DBP	11.60 ± 8.37	15.87 ± 6.47	-4.27 ± 6.39	6.90 ± 5.79	14.00 ± 2.66	-7.10 ± 5.12
	(P < 0.001)	(P < 0.001)	(P = 0.064)	(p = 0.013)	(P < 0.001)	(P =0.005)
MAP	11.87 ± 8.44	16.80 ± 6.53	-4.93 ± 6.45	8.20 ± 5.94	15.10 ± 6.50	-6.90 ± 4.33
	(P < 0.001)	(P < 0.001)	(P =0.031)	(P = 0.005)	(P < 0.001)	(P = 0.002)

* data are shown as mean ± SD

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/ 80 ± 8.86 mmHg with evening administration when 10 mg per day of enalapril was used (these differences were statistically significant at $p < 0.01$). At the same result was obtained, with 20 mg per day dose of enalapril, mean day-time SBP and DBP were decreased from 150 ± 11.89 / 95 ± 8.02 to 139 ± 10.50 / 85 ± 10.80 mmHg and to 138 ± 8.99 / 84 ± 9.30 mmHg with morning and evening administration, respectively (table 9).

These day – time hours BP reduction in SBP, DBP and MAP were not statistically significant differences between morning and evening administration whether 10 mg or 20 mg per day dose of enalapril were used(figure 8).

Average night-time BP

With 10 mg enalapril per day dose, even though the evening time of administration resulted in a greater extent of BP reduction in SBP, DBP and MAP but these values were not statistically significantly different(table 9,11). With 20 mg per day dose of enalapril statistically significantly greater reduction of SBP and MAP when compared to the morning administration ($p<0.05$).

When the BP reduction during day-time and during night – time were considered separately, it was found that morning administration of either 10 mg or 20 mg per day dose of enalapril could decrease the day-time mean values of SBP,DBP and MAP in a higher extent when compared to the night-time mean values. In contrary, the evening administration decreased the night-time mean values DBP than day-time mean for 10 mg and more decreased the night-time mean values only in SBP than day-time mean for 20 mg (figure 9,11).

Peak morning BP

When focus was especially put on peak morning hours, it was found that peak morning SBP / DBP and MAP were significantly reduced from 150 ± 7.22 / 92 ± 5.62 / 112 ± 1.48 mmHg to 138 ± 8.54 / 81 ± 7.94 / 100 ± 6.95 mmHg with morning administration and to 132 ± 9.64 / 77 ± 8.37 / 95 ± 6.67 mmHg with evening administration for 10 mg enalapril (these reduction in BP values were all statistically significant at $p < 0.01$). With 20 mg enalapril, SBP / DBP / MAP were lowered from 154 ± 14.50 / 97 ± 8.02 / 116 ± 7.64 to 143 ± 11.69 / 91 ± 9.69 / 108 ± 8.91 with morning administration and to 137 ± 13.11 / 83 ± 9.16 / 101 ± 9.07 mmHg with evening administration. However, the reduction values of DBP

and MAP were statistically significant at $p < 0.05$ with either time of administration but the SBP values showed significant reduction at $p \leq 0.05$ only with evening administration while the morning administration indicated significant level at $p \leq 0.01$ only 10 mg per day dose of enalapril. hen the effect of administration time (morning versus evening) were considered, it was shown that the extents of reduction in DBP and MAP by evening dose were statistically greater than the morning dose at $p < 0.05$ while the SBP was significantly greater at $p < 0.1$(table 9, table 11, figure 10).

The antihypertensive effect of enalapril with the dose of 10 mg and 20 mg per day was apparent not only from office BP measurement but also evident from the 24- hour ABP monitoring. The parameters used to assess the antihypertensive efficacy of enalapril using 24- hour ABP could be the averages BP value and the BP loads calculated over 24-hours, during day-time hour only, night-time hour only, and during peak morning time. These parameters had been reported to have relationship with indices of the hypertensive disease processes (eg. left ventricular hypertrophy)[27-28]. The significant reductions of BP from either antihypertensive drugs evaluated by these parameters therefore is essential.

Several pressing studies have shown that enalapril is effective in lowering blood pressure levels for 24 hours with single daily and twice daily dose.[24]

In agreement with those studies, our findings obtained with clinic and ambulatory monitoring showed that enalapril (10 and 20 mg) administered once daily either the morning or in the evening could significantly reduced the SBP / DBP no matter the values were evaluated for the total 24- hour, during day-time hour only or during night-time hour only. However, the response profile showed that the antihypertensive action of once-daily doses either 10 mg or 20 mg with morning administration was less effective during night-time and early morning hours. Three other studies have examined morning and night doses of ACE inhibitors. The study of Witte et al assessed the cardiovascular effects of 10 mg enalapril administered at morning and evening.[18] The mean effect was similar but the evening administration had a sustained effect over 24 hour whereas the effect of the morning administration had lost during 02.00 and 07.00 am. The same result was obtained from a study with quinapril which reported that the responses to the drugs administered at night-time and of morning time were different possibly due to

circadian variation affecting the pharmacodynamics of the drug.[17] In a study with perindopril, the result indicated that administered the drug in the morning showed no significant effect during the interval between 18 and 24 hour after the dose. While the evening administration resulted in significant effect throughout the dosing interval. The same situation was obtained in this study. Even though either the morning or evening administration of 10 mg or 20 mg enalapril showed antihypertensive effect throughout 24 hours but the evening administration pronounced more significantly decrease in BP than morning administration between the peak morning time.

These data indicated that timing of administration may influence the antihypertensive effect of ACE inhibitors given once daily. Differences in the rates of onset of the effect of the various drugs and in their individual duration of action would depend upon the rate of absorption and conversion to the active agent, the rate of tissue penetration, through with chronic administration this is less of a problem. An increase in gastric emptying time [66], a reduced velocity of drug absorption [66] in the evening compared with the morning administration would chiefly account for this difference along with the circadian variation in blood pressure of the patients.

Most of ACE inhibitors are administered as a pro-drug and are deesterified by the liver to their active form. [23] Therefore, in the case of ACE inhibition hepatic bioactivation could represent another important factor in affecting their pharmacokinetics. In fact, both gastrointestinal and hepatic perfusion change with time, tending to decline during night -time hours. [44-46] Thus it seems to plausible to assume that absorption and biotransformation of pro-drug into active metabolite are slowed down when it is taken in the evening.

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Figure 7. 24 – hour Ambulatory blood pressure reduction

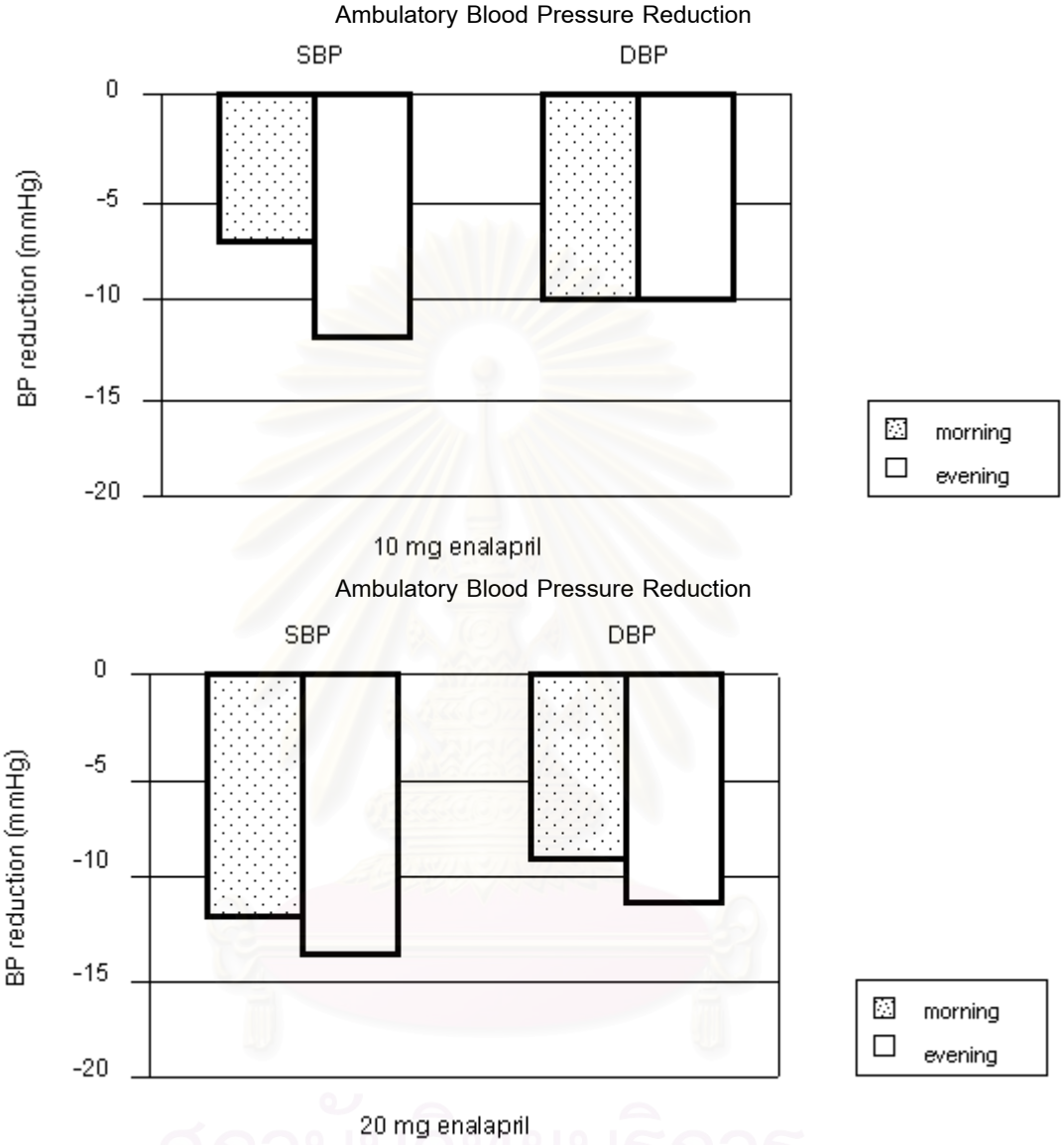

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Figure 8. Day-time blood pressure reduction

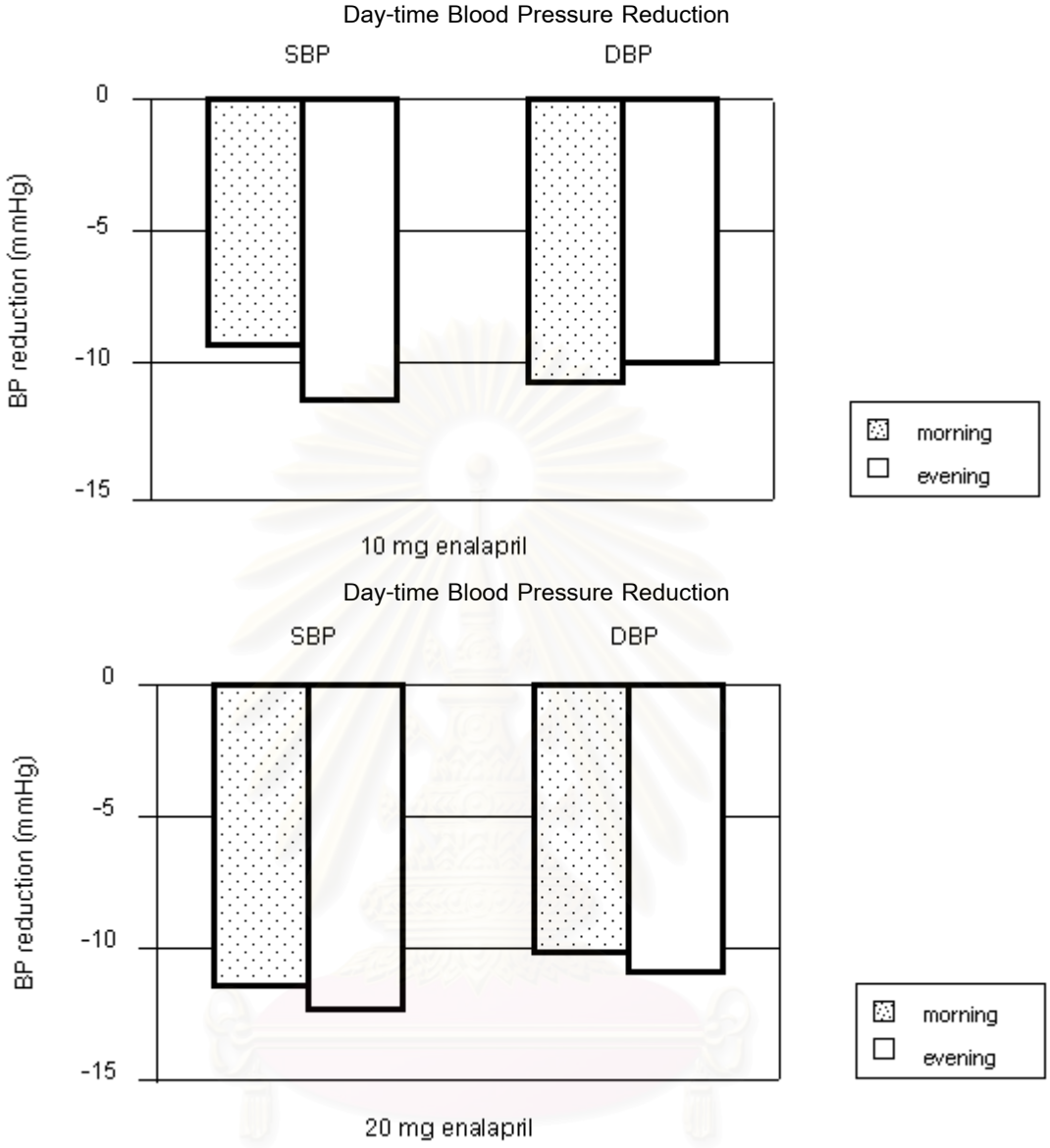

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Figure 9. Night – time blood pressure reduction

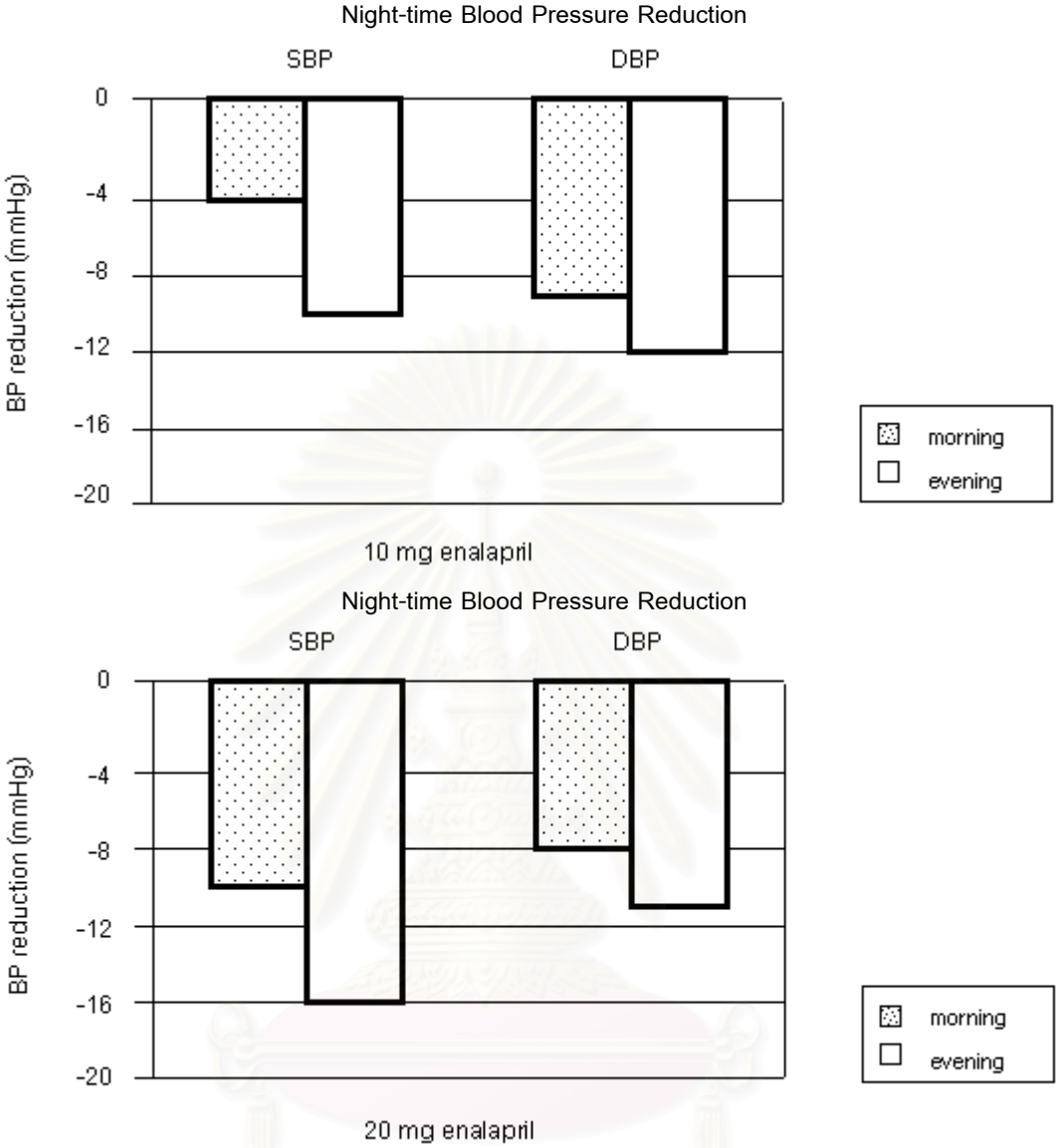

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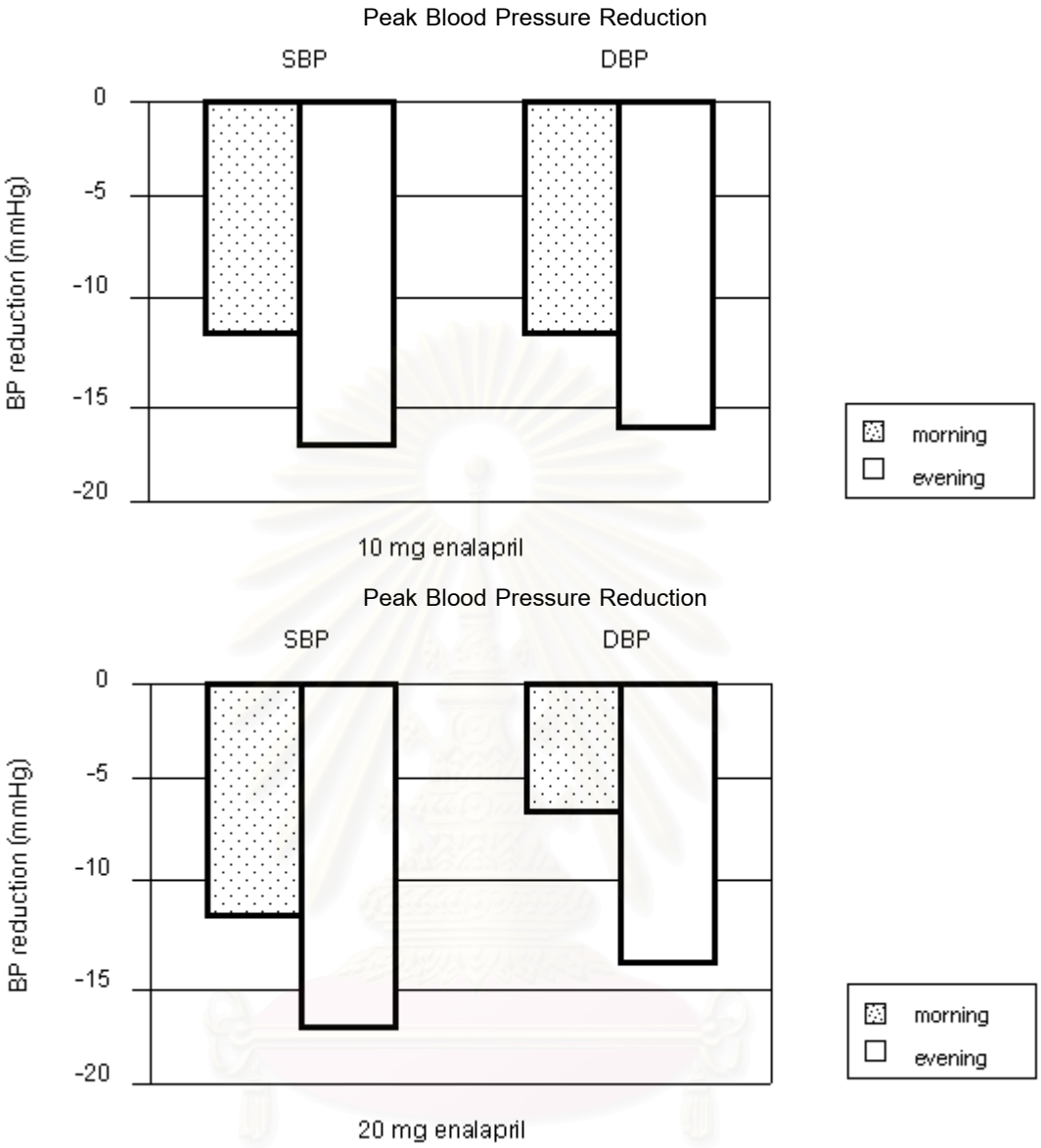
Figure 10. Peak morning blood pressure reduction



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The T:P ratio

From the 24 hour ABP profile of each patients, individual trough and peak antihypertensive effects were obtained. The time to peak antihypertensive effect or maximum BP fall was approximately 4 to 8 hours post-dose, morning and evening. When 10 mg per day dose of enalapril was considered, it was found that the magnitude of the SBP and DBP falls at peak were 22 ± 7.31 and 17 ± 4.62 mmHg respectively with morning administration and were 27 ± 6.11 and 17 ± 5.43 mmHg respectively with evening administration without producing the adverse hypotensive effect. The trough SBP and DBP falls induced by antihypertensive treatment were 12 ± 4.35 and 9 ± 2.47 mmHg respectively with morning administration and were 15 ± 5.08 and 10 ± 3.48 mmHg respectively with evening administration. By dividing the average change in trough BP with the average peak BP change, the T: P ratio of 54 % for SBP and 53 % for DBP with morning administration were obtained. With evening administration, T : P ratio of SBP was 55 % and was 59 % for DBP (table 12). The results were also calculated as the average of individual T: P ratio for SBP was 58 ± 13.05% and ranged from 34 to 84 % while for DBP, the T: P ratio was 53 ± 8.64 % and ranged from 42 to 67 % with morning administration. With evening adminstration, the average of individual T: P ratios for SBP was 59 ± 11.01 % and ranged from 41 to 74 % while T: P ratio for DBP was 56 ± 11.08 % and ranged from 38 to 75 %.

The same results were obtained for 20 mg enalapril. The magnitude of the SBP and DBP falls at peak were 21 ± 6.91 and 18 ± 5.32 mmHg respectively with morning administration and were 25 ± 13.49 and 19 ± 4.90 mmHg respectively with evening administration without producing the adverse hypertensive effect. The trough SBP and DBP falls induced by antihypertensive treatment were 12 ± 5.27 and 10 ± 3.35 mmHg, respectively with morning administration and were 14 ± 7.06 and 12 ± 3.06 mmHg respectively with evening administration. By dividing the average change in trough BP with the average peak BP change, the T: P ratio of 57 % for SBP and 55 % for DBP with morning administration were obtained. With evening administration, T: P ratio of SBP 56 % and was 63 % for DBP (table 12).

Table 12 : The trough and peak BP changes and the T:P ratio of the subjects between the morning and evening dose of 10 mg and 20 mg enalapril treatment

	10 mg enalapril [1] (n = 15)		20 mg enalapril [1] (n = 10)	
	Morning	Evening	Morning	Evening
SAB [1]				
Trough	12 ± 4.35	15 ± 5.08	12 ± 5.27	14 ± 7.06
Peak	22 ± 7.31	27 ± 6.11	21 ± 6.91	25 ± 13.49
T:P ratio (%)	54	55	57	56
T:P ratio (%)	58 ± 13.05	59 ± 11.01	59 ± 12.87	58 ± 9.38
(range)	(34-84)	(41-74)	(40-75)	(41-71)
DBP [1]				
Trough	9 ± 2.47	10 ± 3.48	10 ± 3.35	12 ± 3.06
Peak	17 ± 4.62	17 ± 5.43	18 ± 5.32	19 ± 4.90
T:P ratio (%)	53	59	55	63
T:P ratio (%)	53 ± 8.64	56 ± 11.08	55 ± 8.85	60 ± 10.09
(range)	(42-67)	(38-75)	(44-70)	(47-74)

1 data are shown as mean ± SD

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The results were also calculated as the average of individual T: P ratio for SBP was 59 $\pm$ 12.87 % and ranged from 40 to 75 % while for DBP, the T: P ratio was 55 $\pm$ 8.85 % and ranged from 44 to 70 % with morning administration. With evening administration, the average of individual T: P ratios for SBP was 58 $\pm$ 9.38 % and ranged from 41 to 71 % while T: P ratio for DBP was 60 $\pm$ 10.09 % and ranged from 47 to 74 %.

With the T: P ratios of >50% as evaluated from 10 and 20 mg per day dose of enalapril, it was demonstrated that enalapril of the dose of 10 mg and 20 mg administered once daily could maintain the antihypertensive effect through the end of the dosing interval according to the minimum requirement of US. FDA. This finding is consistent with those previous research and indicated that the long duration of action of enalapril could provide the BP control over the night.

When taking the range into consideration, it was found that there were some patients whose T: P ratios were lower than 50%, therefore, it could be concluded that enalapril administered once daily with either 10mg or 20mg per day were the suitable dosage regimens for majority of the patients with mild to moderate hypertension with the exception of a few patients who might response better with a more frequent dosage regimens such as twice daily.

Data from this study suggest that different time of administration did not effect the T: P ratios of the patients to any significant extent.

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The BP loads

Enalapril induced significant reductions in the frequency (percentage) of abnormal BP values in comparison to baseline whether the values were concentrated for day-time hours only or the whole 24 hours values were taken in to consideration (table 13). During day – time, the frequency of SBP / DBP loads after treatment were dropped from 61 ± 24.47 / 40 ± 26.60 % to 43 ± 25.33 / 21 ± 21.87 % with morning administration and to 38 ± 20.74 / 24 ± 23.25 % with evening administration. When the whole 24-hour BP were considered, SBP / DBP loads were dropped from 63 ± 24.01 / 40 ± 26.83 % to 47 ± 26.43 / 19 ± 22.26 % with morning administration and to 39 ± 19.78 / 24 ± 21.74 % with evening administration.

However, when the night – time or peak morning hours only were considered, the reduction in frequency of BP loads were not statistically significant with morning administration while the frequency of SBP loads only during night - time hour were significantly reduced with evening administration ($p < 0.05$) whether 10 mg or 20 mg per day dose of enalapril had been used. When peak morning hours was considered, the significant reduction in BP load were achieved with evening administration of 10 mg per day of enalapril ($p < 0.01$) while the reduction in DBP loads were significant with 20 mg of enalapril (table 13,14).

On the other hand, the magnitudes of BP loads were not significantly reduced from those obtained at baseline after treatment with 10 mg or 20 mg of enalapril whether the drug was administered in the morning or in the evening when the data was evaluated for the whole 24 hours or during the day time hours only. However, when the BP loads during night - time hours only were considered, the result showed that after treatment with 10 mg enalapril there were no significant reduction in the magnitude of BP loads with either morning or evening administration but the reduction in magnitude of BP loads were significant with 20 mg dose of enalapril except for the DBP load after morning administration. At the same time, while the magnitude of SBP loads during morning hours showed no significant reduction after treatment with either dosage and time of administration, the magnitude of DBP loads during morning hours showed significant reduction after treatment with either dosage pattern except after 20 mg morning dose(table 13,15).

Table 13 : The frequency and the magnitude of BP loads after placebo and at the end of enalapril treatments

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Placebo	Morning dose	Evening dose	Placebo	Morning dose	Evening dose
	(2 weeks)	(4 weeks)	(4 weeks)	(2 weeks)	(4 weeks)	(4 weeks)
Frequency of BP loads (%) [1]						
- 24 hour BP loads						
SBP	63 ± 24.01	47 ± 26.43**	39 ± 19.78*	73 ± 20.62	49 ± 21.28*	45 ± 19.30*
DBP	40 ± 26.83	19 ± 22.26*	24 ± 21.74*	63 ± 25.46	41 ± 31.51*	31 ± 24.92*
- day – time BP loads						
SBP	61 ± 24.47	43 ± 25.33*	38 ± 20.74*	67 ± 25.40	44 ±24.47**	40 ± 20.44*
DBP	40 ± 26.60	21 ± 21.87*	24 ± 23.25*	63 ± 26.01	39 ±33.12*	30 ± 25.83*
- night-time BP loads						
SBP	71± 29.74	69 ± 34.33 ns	46 ± 28.25** +	100 ± 0.00	81 ± 25.16 ns	73 ± 23.96*
DBP	39± 35.62	22 ± 27.23 ns	20 ± 23.60 ns	57 ± 35.10	48 ± 34.73 ns	33 ± 28.59 ns +
- peak morning BP						
SBP	63 ± 29.79	34 ± 36.49 ns	26 ± 21.72*	68 ± 33.48	52 ±30.86 ns	36 ±28.78 ns +
DBP	40 ± 28.25	26 ± 6.94 ns	15 ± 16.91*	57 ± 32.16	50 ± 31.35 ns	31 ± 32.64*
Absolute value of BP loads						
(mmHg) [1]						
- 24 hour BP loads						
SBP	13 ± 4.78	12 ± 5.28 ns	13 ± 4.67 ns	18 ± 8.05	13 ± 4.99 ns	13 ± 6.10 ns
DBP	12 ± 20.24	5 ± 3.06 ns	6 ± 2.67 ns	14 ± 8.60	8 ± 3.97 ns	10 ± 11.87 ns
- day – time BP loads						
SBP	13 ± 5.29	17 ± 23.07 ns	16 ± 22.14 ns	24 ± 25.84	10 ± 5.89 ns	12 ± 5.85 ns
DBP	6 ± 3.20	5 ± 3.52 ns	6 ± 2.87 ns	14 ± 10.13	7 ± 4.95 ns	7 ± 3.35 ns
- night-time BP loads						
SBP	16 ± 7.16	15 ± 8.40 ns	11 ± 7.59 ns	25 ± 8.26	15 ± 6.33**	11 ± 5.27*
DBP	6 ± 6.01	4 ± 3.75 ns	4 ± 4.49 ns	11 ± 5.55	8 ± 4.38 ns	5 ± 3.92*
- peak morning BP						
SBP	12 ± 5.65	9 ± 5.34 ns	12 ± 9.93 ns	17 ±15.72	11± 7.80 ns	14 ±13.92 ns
DBP	7 ± 4.39	3 ± 3.61**	4 ± 3.00**	10 ± 6.42	8± 4.47	5 ± 5.53**

1 data are shown as mean ± SD

* $p < 0.01$, ** $p < 0.05$ versus placebo

\+ $p < 0.05$ versus morning dose , ns = not significant

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Table 14 : Percentage reduction in frequency of BP loads compared between morning and evening administration

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Morning	Evening	ΔBP loads**	Morning	Evening	ΔBP loads**
*- average 24 hour**						
SBP	15.53 ± 20.06	23.33 ± 21.20	-7.08 ± 21.41	23.80 ± 20.21	27.80 ± 16.59	-4.00 ± 14.55
	(P =0.029)	(P = 0.002)	(P =0.541)	(P = 0.014)	(P = 0.001)	(ns)
DBP	20.73 ± 16.61	15.60 ± 5.94	5.13 ± 11.97	21.80 ± 16.70	31.50 ± 14.30	- 9.70 ± 14.63
	(P = 0.001)	(P < 0.001)	(p = 0.357)	(p = 0.008)	(P < 0.001)	(P =0.196)
*- average day – time *						
SBP	18.47 ± 20.61	23.07 ± 22.15	-4.60 ± 22.12	23.70 ± 22.13	27.80 ± 18.08	-4.10 ± 18.02
	(P = 0.011)	(P = 0.004)	(ns)	(P = 0.024)	(P = 0.002)	(ns)
DBP	18.60 ± 14.70	15.60 ± 11.57	3.00 ± 12.16	23.60 ± 20.71	32.60 ± 14.97	-9.00 ± 16.28
	(P = 0.001)	(P < 0.001)	(ns)	(P = 0.017)	(P < 0.001)	(p=0.343)
*- average night-time**						
SBP	2.27 ± 29.97	25.47 ± 3.47	- 23.20 ± 29.50	19.50 ± 25.16	27.20 ± 23.96	-7.70 ± 30.62
	(ns)	(P = 0.039)	(P =0.026)	(P = 0.110)	(P = 0.018)	(ns)
DBP	17.40 ± 25.97	19.20 ± 28.32	-1.80 ± 31.90	8.60 ± 40.36	23.70 ± 30.39	-15.10 ± 15.99
	(P = 0.064)	(P =0.06)	(ns)	(ns)	(P = 0.107)	(P = 0.046)
*- peak morning *						
SBP	29.13 ± 47.22	36.53 ± 22.08	-7.40 ± 45.52	15.60 ± 40.61	31.70 ± 36.21	-16.10 ± 17.13
	(P =0.094)	(P < 0.001)	(ns)	(P = 0.766)	(P = 0.065)	(P = 0.047)
DBP	13.93 ± 29.84	25.07 ± 18.92	-11.13 ± 19.82	6.6.0 ± 31.09	25.00 ± 9.06	-18.40 ± 25.67
	(P =0.276)	(P < 0.001)	(P = 0.142)	(ns)	(P <0.001)	(P =0.149)

* data are shown as mean ± SD

** ΔBP = difference in BP loads between morning and evening treatment

Table 15 : Reduction in absolute (magnitude) of BP loads compared between morning and evening administration

Parameter	Enalapril 10 mg (n = 15)			Enalapril 20 mg (n = 10)		
	Morning	Evening	ΔBP**	Morning	Evening	ΔBP**
*- average 24 hour**						
SBP	1.40 ± 6.38	0.93 ± 7.88	0.47 ± 6.86	5.30 ± 6.13	5.20 ± 6.55	0.10 ± 2.47
	(ns)	(ns)	(ns)	(P = 0.069)	(ns)	(ns)
DBP	6.93 ± 21.67	5.67 ± 20.47	1.27 ± 3.68	6.20 ± 10.28	4.10 ± 16.29	2.10 ± 11.42
	(P =0.707)	(P =0.905)	(p = 0.609)	(p = 0.267)	(ns)	(ns)
*- average day – time *						
SBP	4.47 ± 23.16	3.87 ± 22.29	0.60 ± 31.07	13.70 ± 24.37	11.80 ± 23.35	1.90 ± 4.01
	(ns)	(ns)	(ns)	(P = 0.328)	(P = 0.434)	(p=0.506)
DBP	1.53 ± 4.91	0.20 ± 3.01	1.33 ± 4.22	7.30 ± 11.64	7.30 ± 10.35	0.00
	(P =0.740)	(ns)	(p=0.724)	(P = 0.236)	(P =0.158)	(ns)
*- average night-time**						
SBP	1.20 ± 7.83	5.00 ± 9.78	- 3.80 ± 8.83	9.70 ± 9.75	14.00 ± 9.56	- 4.30 ± 6.98
	(ns)	(P = 0.203)	(P =0.355)	(P = 0.035)	(P = 0.005)	(P = 0.0249)
DBP	2.40 ± 6.42	1.93 ± 3.55	0.467 ± 1.81	3.30 ± 4.19	6.20 ± 4.52	-2.90 ± 4.68
	(P = 0.510)	(P = 0.161)	(ns)	(P = 0.103)	(P < 0.006)	(P = 0.245)
*peak morning **						
SBP	3.40 ± 7.41	0.20 ± 12.57	3.20 ± 10.93	6.60 ± 14.77	3.70 ± 10.88	2.90 ± 10.22
	(P = 0.292)	(ns)	(P = 0.828)	(p = 0.574)	(P = 0.930)	(ns)
DBP	3.27 ± 4.71	3.00 ± 3.74	- 0.267 ± 4.60	2.20 ± 4.87	5.00 ± 4.64	-2.80 ± 4.73
	(P =0.053)	(P = 0.023)	(ns)	(P = 0.561)	(P = 0.023)	(P = 0.283)

* data are shown as mean ± SD

** ΔBP = difference in absolute value BP loads between morning and evening treatment

BP loads was used as one parameter to assess the antihypertensive efficacy of enalapril. In this study, after treatment with 10 and 20 mg enalapril, significant reduction of the percentage of abnormal BP values occurred during day –time with either morning or evening administration. However, only evening administration showed significant reduction in the percentage of abnormal values during night – time and the peak morning hours.

The 24-hour ABP profile after treatment with 10 and 20 mg enalapril once daily either in the morning or in the evening were shown in figure 11-14 which demonstrated that the BP were reduced for both SBP and DBP throughout 24 hour. The evening administration of enalapril showed a consistency blood pressure control throughout the 24-hours while the morning administration of enalapril showed good control during day-time only then the blood pressure lowering effect tended to decline after 12.00 am. There was no significant change in HR after treatment, this suggested the absence of reflex tachycardia by enalapril.

The data obtained from the study showed that , eight patients were dipper and seventeen patients were non-dipper before treatment. After treatment with enalapril, it was found that the ratio of patients who were classified as dipper and non-dipper were changed to 6 / 19 with morning administration and to 10 / 15 with evening treatment.

When considering individual subject data on 24 hour BP, it was found that the lowest SBP and DBP values were 114 and 65 mmHg respectively with evening administration. Furthermore, when the night- time hour was considered, it was found that the lowest SBP and DBP values were 107 and 59 mmHg respectively with evening administration (appendix F). However, none of the 25 patients showed the mean night-time BP which was too pronounced decrease from the mean day-time BP (mean day-time BP – mean night-time BP < 20 % of mean day-time BP). 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. Thus from the data obtained, it was suggest that enalapril administered in evening regimen could provide the optimal BP control throughout 24 hours only in

some subjects such as non-dippers and morning administration was preferable to the patients who have the state of coronary heart disease.

Concerning on the antihypertensive effect of the drug based on the office BP, 10 mg doses of enalapril produced the normalized rate of 93 % and 100 % with morning and evening administration respectively, while enalapril in the doses of 20 mg produced the normalized rate of 70 % and 60 % with morning and evening administration, respectively. The normalized rate obtained from 10 mg doses in this study was quite high when compared to those reported by other studies of 70 –80 %[24, 64-65] . This might due in part to the reason that the subjects evaluated in our study were subjects which could complete through the study which might have already excluded those patients who might not response to enalapril (figure 4).

Some other aspects from the design of our study that should bring into consideration included the proposed dose of 10 mg and 20 mg of enalapril for the mild and moderate hypertensive subjects respectively, the non-repeated measurement of ABP after each treatment, the unequal time after drug administration to measure office BP, the small number of subjects, the number of evaluable subjects compared with the number of subjects when start with, the compounding factors, such as, environment, physical activity, mental status, life style. These were all provided some part in the explanation for any different results that might occur in the future study.

The drug administered once daily either in the morning or in the evening could significantly reduced the blood pressure to nearly the same extent during daytime (which include the office blood pressure which are normally evaluated during daytime). However, the drug given once daily in the evening showed a more pronounced effect in the reduction of the blood pressure during nighttime and during peak morning time as compared to the effect caused by the drug given once daily in the same dosage in the morning it is therefore depend on whether these pronounced effects are of benefit or risk to the individual patient in order to decide the best time of administration for each patient.

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 during morning and evening hours could also account for the observed treatment difference in the blood pressure lowering effect. Clinical studies in larger populations to investigate the benefit or risk of different circadian dosing schedules in patients with hypertension are still required to confirm what we had found in this study.

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Figure 11. Blood Pressure and Heart Rate Profiles after treatment with 10 mg enalapril in the morning

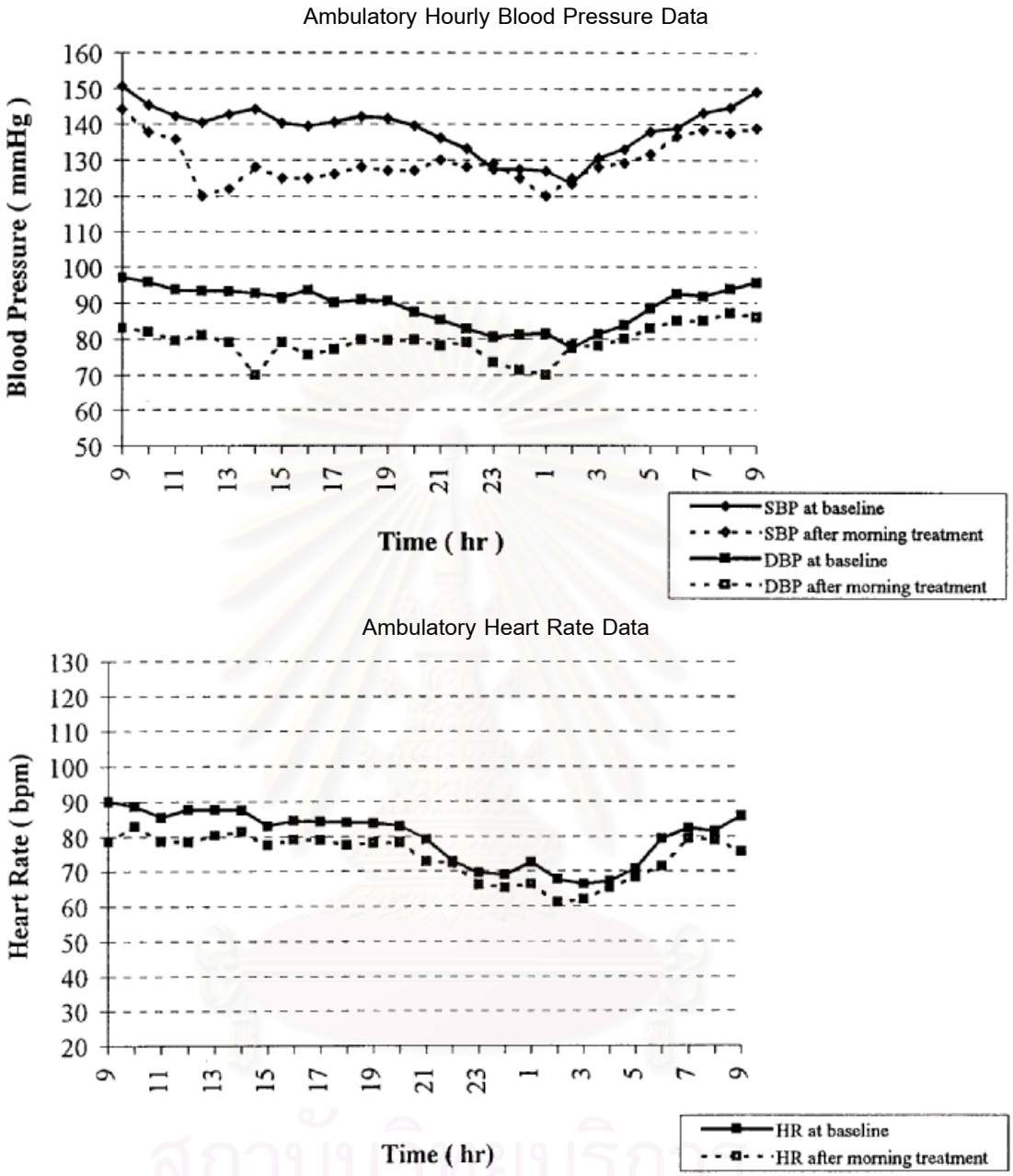

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Figure 12. Blood Pressure and Heart Rate Profiles after treatment with 10 mg enalapril in the evening

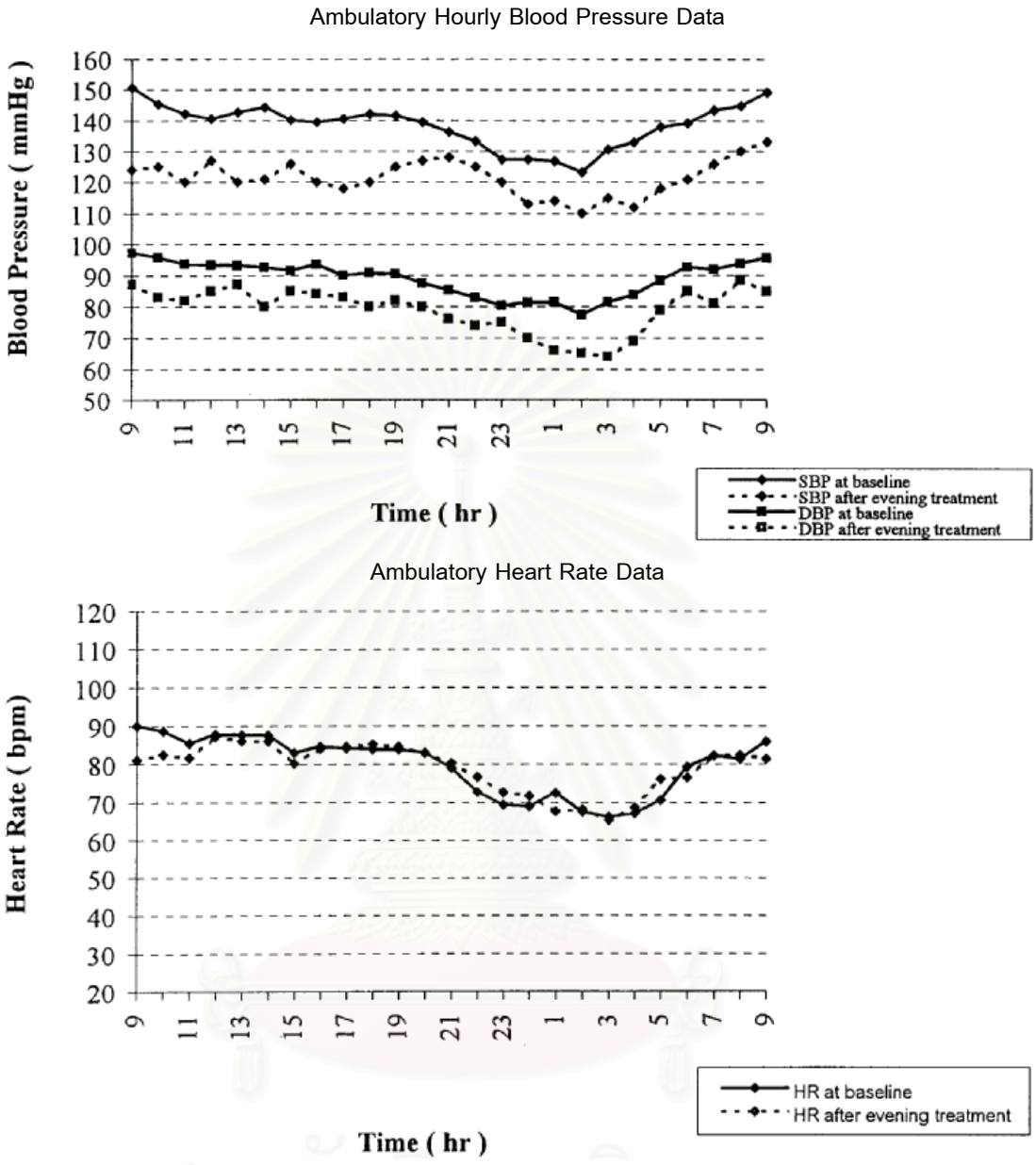

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Figure 13. Blood Pressure and Heart Rate Profiles after treatment with 20 mg enalapril in the morning

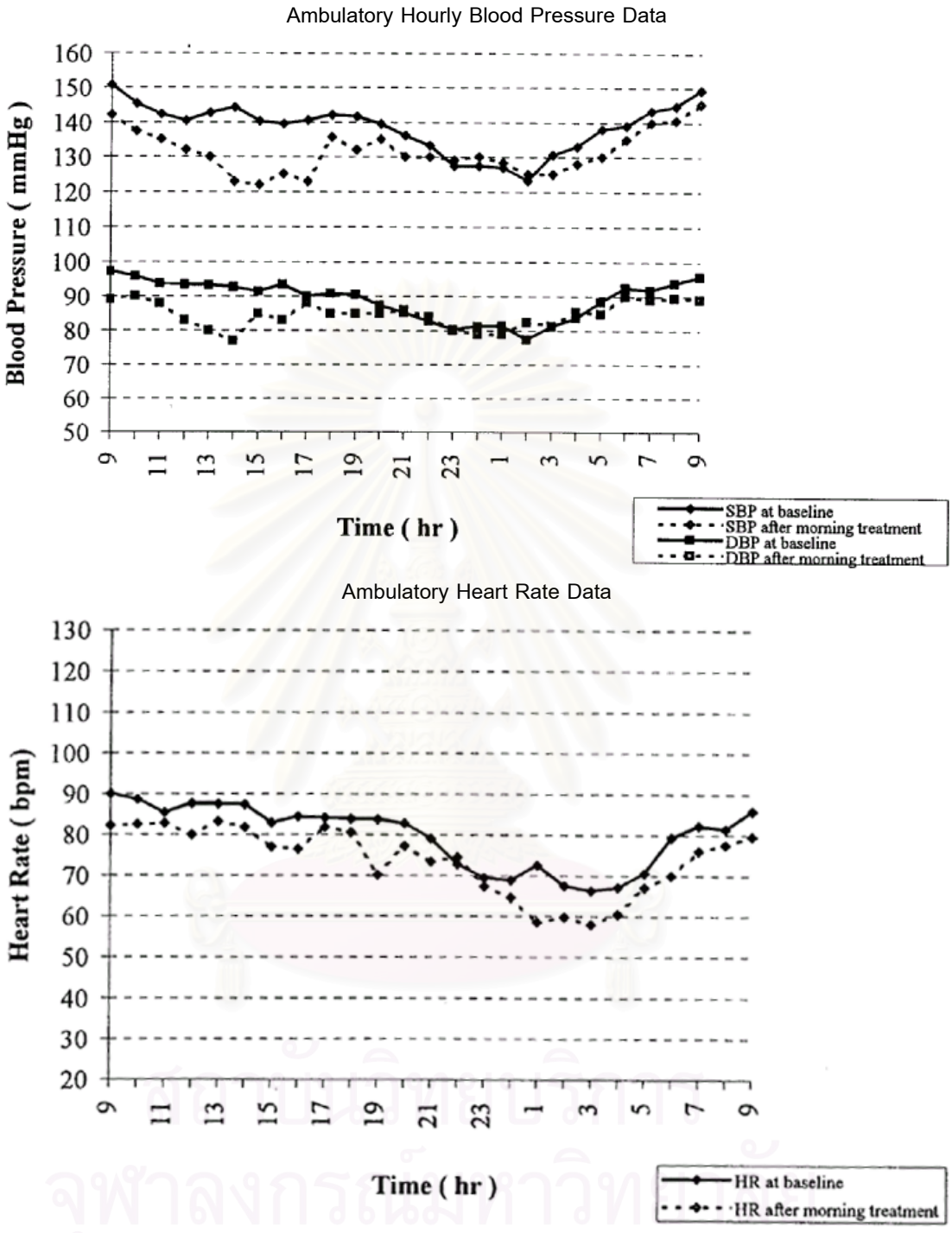
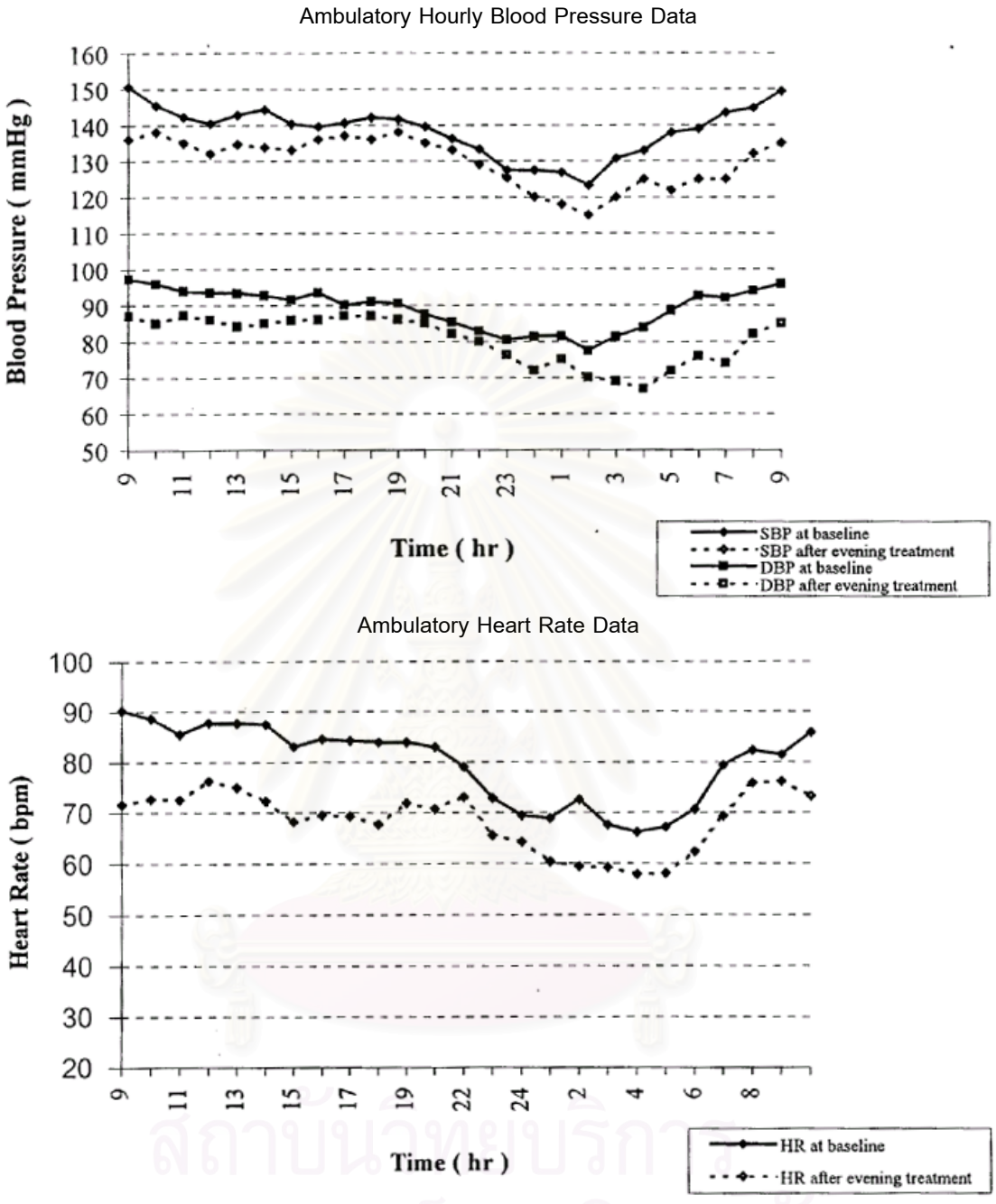


Figure 14. Blood Pressure and Heart Rate Profiles after treatment with 20 mg enalapril in the evening



CHAPTER V

CONCLUSION

1. Through intensive monitoring on the 24-hour BP after administration of placebo for the period of 2 weeks and enalapril for the period of 4 weeks in 25 mild to moderate hypertensive subjects, it could be conclude that enalapril in the dosage of 10 mg administered once daily in mild hypertensive subjects either in the morning or in the evening produced the normalized rate (office DBP $\leq$ 90 mmHg) of 93 % and 100 % respectively while enalapril in the dosage of 20 mg administered once daily in moderate hypertensive subjects either in the morning or in the evening produced the normalized rate of 70 % and 60 % respectively.

2. Enalapril administered once daily in the dosage of either 10 mg or 20 mg per day was effective in reducing office SBP, DBP and MAP whether the drug was given in the morning or in the evening. There were no significant changes in HR after either regimens. Comparison between the effect of morning and evening time of administration showed no statistically significant differences in the reduction of SBP, DBP, MAP and HR measured as the office BP and HR with either 10 mg or 20 mg dose of enalapril.

3. The average 24-hour ABP and the average of day - time hours BP after treatment was significantly reduced from baseline with either 10 mg or 20 mg per day dose of enalapril with either morning or evening regimen. These average 24-hours and day - time hours BP reduction in SBP, DBP and MAP were not statistically significant difference between morning and evening administration whether 10 mg or 20 mg per day dose of enalapril were used.

4. When the BP during night-time hour were considered, it was found that enalapril administered in the evening time resulted in a greater extent of BP reduction in SBP, DBP and MAP when compared to the morning administration but only the differences in SBP and MAP when 20 mg enalapril only was used were statistically significant. Morning administration of either 10 mg or 20 mg per day dose of enalapril could decrease the day - time mean values of SBP, DBP and MAP to a greater extent when compared to the reduction in the night - time mean values. While the evening administration seems to be able to decrease the night-time BP to the same extent as the decrease in day-time blood pressure.

5. The peak morning blood pressure was significantly reduced from baseline when either 10 mg or 20 mg per day dose of enalapril were used. However, the greater extent of reduction in SBP, DBP and MAP during the early morning hours were achieved when enalapril was administered in the evening time. Thus the evening administration seems to be preferable because it may prevent dangerous cardiovascular catastrophes, including stroke, myocardial infarction, and sudden death, known to occur more often during the morning surge of blood pressure.

6. T: P ratios derived from the average trough and peak changes in both SBP and DBP were higher than the minimum requirement of 50% no matter the drug was administrated in the morning or in the evening. In addition, the mean T: P ratios derived from the average of each individual T: P ratios also provided the values which were higher than the minimum requirement. This means that at least 50% of the peak BP reduction effect induced by enalapril was maintained until the last of the 24-hours or indicating a long enough duration of action of once daily regimen. There were no significant difference in the mean T: P ratios of the patients obtained after between morning and evening administration. This means that different time of administration did not effect the T: P ratios of the patients. However, since wide range of T: P ratio values were also observed and there were few patients whose T:P ratio values were lower than 50 %, it was suggested that once daily regimen was not suitable for these patients and twice daily regimen should be treated instead.

7. Calculation of the frequency and absolute values of BP loads during day – time, night – time, early morning and all over 24 – hour after treatment indicated that either 10 mg or 20 mg per day dose of enalapril induced significant reductions in the percentages of SBP and DBP loads for 24 – hour and during day – time hours whether the drug was administered in the morning or in the evening. However, night – time BP loads or peak morning BP loads were significantly reduced from baseline with evening administration only with either10 mg or 20 mg per day dose of enalapril.

The magnitudes of BP loads were not significantly reduced after treatment with 10 mg or 20 mg of enalapril whether administered in the morning or in the evening when the value of the whole 24 – hour and during day – time hours only were considered. However, enalapril 20 mg per day dose significantly reduced the magnitudes of BP loads during night – time hours. During morning hours, 10 mg per day dose of enalapril significantly reduced the magnitudes of DBP loads from baseline with either morning or evening administration.

8. Enalapril reduced BP without producing the reflex tachycardia since the 24 – hour HR was not changed with either 10 mg or 20 mg per day dose of enalapril. The 24-hour blood pressure profiles showed a more sustained antihypertensive action with the evening administration compared with the morning administration of either 10 mg or 20 mg per day dose of enalapril.

9. The drug administered once daily either in the morning or in the evening could significantly reduced the blood pressure to nearly the same extent during day-time (which include the office blood pressure which are normally evaluated during day – time). However, the drug given once daily in the evening showed a more pronounced effect in the reduction of the blood pressure during night –time and during peak morning time as compared to the effect caused by the drug given once daily in the same dosage in the morning0 it is therefore depend on whether these pronounced effects are of benefit or risk to the individual patient in order to decide the best time of administration for each patient.

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APPENDICES

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APPENDIX A : Demographic data of individual subjects

Subject no.	Age (years)	Wt (kg)	Ht (cm)	BMI (kg/m^2)	Smoking	Alcohol	DM
1	55	81	156	33	-	-	-
2	48	48	156	20	-	-	-
3	46	74	170	26	/	/	-
4	68	64	154	27	-	-	/
5	57	60	152	26	-	-	-
6	45	59	154	25	-	-	-
7	48	73	180	23	-	-	-
8	59	69	156	28	-	-	-
9	61	56	158	22	-	-	-
10	54	51	158	20	-	-	-
11	70	66	164	25	-	/	-
12	67	68	164	25	-	-	-
13	47	58	160	23	-	-	/
14	63	55	152	24	-	-	-
15	63	60	154	25	-	-	-
16	71	57	170	20	-	-	-
17	62	76	154	32	-	-	-
18	44	47	164	17	-	-	-
19	67	55	152	24	-	-	-
20	52	61	170	20	-	/	-
21	58	50	160	20	-	-	-
22	42	74	154	31	-	-	-
23	52	72	170	25	/	/	-
24	66	66	166	24	-	-	-
25	67	66	169	23	-	-	-

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APPENDIX B: Laboratory data of individual subjects

Subjects no.	Glucose (70-110mg/dl)	BUN (10-20mg/dl)	Cr (0.5-2.0mg/dl)	Uric acid (2.0-7.0mg/dl)	CHO (150-240mg/dl)	TG (40-155mg/dl)	HDL (0-100mg/dl)	AST (0-38u/l)	ALT (0-38u/l)	Sodium (135-150mEq/l)	Potassium (3.8-5.5mEq/l)	Chloride (98-110mEq/l)	CO_2 (22-32mEq/l)
1	104	14	0.5	5.1	261	157	50	22	35	135	4.2	111	21
2	99	12	0.7	3.9	266	127	62	18	21	140	4.5	107	24
3	104	11	1.0	7.8	180	125	41	23	23	144	4.5	104	25
4	176	16	1.3	5.6	166	81	51	20	12	131	4.4	112	22
5	88	18	0.7	4.5	192	81	49	23	19	142	4.1	107	26
6	95	15	1.1	5.1	260	82	70	21	20	142	3.1	109	24
7	100	13	0.7	5.0	189	75	45	21	17	143	4.3	109	25
8	100	18	0.8	6.1	218	178	41	17	23	139	4.7	110	26
9	101	18	0.7	4.5	202	82	74	22	19	137	4.6	112	26
10	98	12	0.8	4.0	230	227	40	20	16	137	3.8	103	27
11	100	11	1.5	4.0	192	73	52	15	17	141	4.3	107	23
12	90	12	0.7	3.9	170	82	58	17	19	140	3.8	107	26
13	173	12	0.8	5.1	279	234	42	36	61	147	4.2	112	23
14	101	17	1.1	5.1	235	75	60	29	23	139	4.0	103	25
15	90	15	1.2	4.1	185	85	35	27	29	144	4.1	109	24
16	99	14	1.6	8.1	198	124	60	17	15	141	4.6	102	28
17	100	17	0.7	3.8	272	97	68	19	23	141	3.9	109	26
18	104	16	0.8	5.2	180	76	48	30	37	134	4.2	96	22
19	79	13	0.9	6.9	194	78	38	21	15	145	4.6	106	21
20	100	15	0.9	7.3	193	138	48	23	47	142	4.7	104	20
21	105	18	1.0	4.2	175	75	54	17	19	143	4.1	108	22
22	114	16	1.0	3.9	270	148	60	14	16	143	3.9	109	26
23	100	19	1.1	7.1	187	65	51	15	17	140	3.5	107	27
24	97	13	1.1	5.6	217	69	69	16	13	147	4.2	110	28
25	98	13	1.4	4.3	227	187	47	27	29	139	4.4	110	29

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APPENDIX C: Office BP measurements of the screening visit and after placebo

Subject no.	Office BP at the screening visit				Office BP at placebo			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	160	90	113	85	153	99	117	88
2	135	80	98	75	149	90	110	80
3	148	87	107	85	145	97	113	82
4	145	85	105	74	153	91	112	72
5	140	80	100	75	147	90	109	72
6	145	80	102	75	153	97	116	70
7	150	95	113	95	151	96	114	92
8	150	90	110	85	159	93	115	80
9*	172	90	117	72	150	90	110	72
10	152	103	119	80	144	92	109	80
11	145	80	102	80	145	93	110	84
12	140	80	100	60	150	90	110	64
13	160	80	107	82	160	100	120	82
14*	160	98	119	80	160	95	117	75
15	154	90	111	85	160	100	120	88
16*	162	100	121	80	173	103	126	80
17	155	85	108	85	166	90	115	84
18	150	98	115	95	153	107	122	100
19	148	82	104	90	173	91	118	72
20	150	92	111	90	152	92	112	90
21	130	82	98	80	149	94	112	72
22	145	82	103	92	142	92	109	96
23	140	80	100	90	159	103	122	92
24*	167	95	119	85	165	90	115	74
25*	159	102	121	90	160	100	120	92

* new onset

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APPENDIX D: Office BP and 24-hour ABP measurements after placebo(at baseline)

Subject no.	BP measurements at baseline (mmHg)									
	Office BP		24 – hour ABP							
			Average 24- hour		Average day time		Average night - time		Peak morning	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1	153	99	148	86	150	89	142	81	150	95
2	149	90	137	85	141	88	129	80	145	88
3	145	97	134	85	142	91	118	72	149	87
4	153	91	147	85	150	86	142	82	157	91
5	147	90	148	85	154	88	134	78	161	91
6	153	97	140	85	147	89	125	88	140	89
7	151	96	144	100	148	103	136	96	152	105
8	159	93	144	85	150	87	135	79	148	90
9	150	90	151	85	154	88	144	81	151	93
10	144	92	139	88	143	90	132	85	140	91
11	145	93	138	85	143	87	126	77	159	91
12	150	90	144	85	150	88	132	78	156	94
13	160	100	154	92	156	94	149	88	161	89
14	160	95	157	89	159	91	151	84	169	92
15	160	100	130	92	130	92	128	92	121	93
16	173	103	142	90	144	92	139	87	147	100
17	166	90	146	85	147	88	143	80	154	92
18	153	107	151	103	151	106	150	97	160	112
19	173	91	146	85	146	87	145	79	162	93
20	152	92	142	95	150	100	126	84	155	105
21	149	94	140	88	141	89	136	85	139	87
22	142	92	139	87	141	89	137	83	142	89
23	159	103	166	106	169	111	158	98	160	108
24	165	90	158	90	164	94	145	80	168	95
25	160	100	139	92	139	93	139	88	147	103

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APPENDIX E: Office BP at baseline and after morning and evening administration of 10 or 20 mg enalapril

OFFICE BP

Subject no.	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	153	99	117	88	146	89	108	88	134	85	101	60								
2	149	90	110	80	129	80	96	75	120	80	93	84								
3	145	97	113	82	132	84	100	72	130	77	95	78								
4	153	91	112	72	145	77	100	72	131	78	96	72								
5	147	90	109	72	117	69	85	84	131	84	100	75								
6	153	97	116	70	125	80	95	76	128	72	91	72								
7	151	96	114	92	135	89	104	72	140	90	107	75								
8	159	93	115	80	145	83	104	80	145	80	102	72								
9	150	90	110	72	130	75	93	72	138	80	99	72								
10	144	92	109	80	123	82	96	72	134	82	99	68								
11	145	93	110	84	130	80	97	80	139	80	100	80								
12	145	90	108	64	140	80	100	70	131	73	92	72								
13	160	100	120	82									137	90	106	72	140	89	106	75
14	160	95	117	75									145	80	102	70	140	82	101	72
15	160	100	120	88									136	85	102	88	138	81	100	72
16	173	103	126	80									149	90	110	64	147	93	111	64
17	166	90	115	84									145	77	100	92	145	80	102	72
18	153	107	122	100									152	94	113	95	150	97	115	80
19	173	91	118	72									140	80	100	70	139	79	99	72
20	152	92	112	90	140	89	106	96	138	90	106	72								
21	149	94	112	72	147	91	110	72	135	89	104	84								
22	142	92	109	96	135	88	104	72	139	86	104	72								
23	159	103	122	92									154	97	116	72	154	101	119	80
24	165	90	115	84									135	87	103	80	134	87	103	92
25	160	100	120	92									150	98	115	84	134	95	108	84

APPENDIX F : Average ABP at baseline and after morning and evening administration of 10 or 20 mg enalapril

Subject no.

AVERAGE 24 – HOUR ABP

	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	BP	DBP	MAP	HR
1	148	86	107	82	141	82	102	80	137	86	103	79								
2	137	85	110	79	122	73	89	70	122	73	89	71								
3	134	85	101	82	129	82	97	81	117	80	92	82								
4	147	85	104	73	130	65	87	78	126	65	85	76								
5	148	85	106	82	151	71	98	61	139	68	92	70								
6	140	85	103	73	130	71	90	73	130	71	90	77								
7	144	100	115	86	153	94	113	78	134	89	104	91								
8	144	85	105	80	136	73	94	73	114	68	84	72								
9	151	85	107	80	137	77	97	78	133	75	94	94								
10	139	88	105	73	120	77	91	71	123	81	95	71								
11	138	85	102	74	132	76	95	75	129	72	91	80								
12	144	85	104	73	138	68	91	70	145	71	96	78								
13	154	92	113	87									132	79	96	82	134	79	97	75
14	157	89	112	73									136	75	95	77	137	77	97	71
15	130	92	104	81									137	89	105	86	136	86	103	75
16	142	90	108	67									135	84	101	57	130	77	95	63
17	146	85	103	69									134	66	89	77	136	69	91	79
18	151	103	119	79									138	96	110	86	135	92	106	77
19	146	85	105	75									132	74	93	76	128	73	91	72
20	142	95	108	95	130	82	98	101	134	89	104	91								
21	140	88	104	81	142	83	102	84	143	84	104	88								
22	139	87	104	84	141	84	103	86	130	85	100	89								
23	166	106	126	88									161	93	116	75	159	97	118	82
24	158	90	113	72									137	87	104	78	132	79	97	74
25	139	92	107	78									130	86	101	81	127	83	98	85

AVERAGE DAY – TIME BP

Subject no.	Baseline	10 mg enalapril OD		20 mg enalapril OD	
		Morning	Evening	Morning	Evening

	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	AP	HR	SBP	DBP	MAP	HR
1	150	89	109	84	143	84	103	84	144	92	109	81								
2	141	88	116	85	125	74	91	75	120	75	90	76								
3	142	91	108	89	137	87	104	87	122	83	96	88								
4	150	86	107	74	127	64	85	80	131	67	89	79								
5	154	88	110	85	150	69	96	62	137	70	92	75								
6	147	89	108	78	136	77	97	79	135	76	95	82								
7	148	103	118	90	157	95	116	82	141	94	110	92								
8	150	87	108	84	139	75	96	77	116	70	85	75								
9	154	88	110	83	139	78	98	78	147	81	103	85								
10	143	90	107	78	122	81	95	77	130	83	99	74								
11	143	87	106	79	134	79	97	79	135	75	95	85								
12	150	88	109	73	138	70	93	73	150	73	99	81								
13	156	94	115	91									131	77	95	88	140	80	100	75
14	159	91	113	76									134	74	94	81	139	79	99	75
15	130	92	104	86									137	89	105	91	136	88	104	79
16	144	92	110	72									137	87	104	60	132	77	96	66
17	145	85	105	68									133	67	89	78	139	71	94	81
18	151	106	121	85									141	99	113	90	138	96	110	82
19	146	87	107	80									131	75	93	80	131	76	94	76
20	150	100	117	96	136	86	103	103	141	94	110	92								
21	141	89	105	84	145	87	106	87	144	86	105	90								
22	141	89	106	91	133	85	101	95	142	85	104	91								
23	169	111	130	98									166	98	120	83	162	101	121	92
24	164	94	118	77									143	92	109	83	135	82	99	76
25	139	93	109	84									132	88	102	85	131	86	101	90

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PEAK MORNING BP

Subject no.	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	150	95	114	85	143	85	104	77	139	86	103	81								
2	145	88	116	78	129	78	95	71	121	74	90	74								
3	149	87	107	90	136	86	103	95	123	78	93	92								
4	157	91	110	81	130	73	92	77	134	69	91	77								
5	161	91	114	88	146	64	91	65	131	72	92	67								
6	140	89	106	82	129	73	92	71	126	68	87	80								
7	152	105	122	86	155	94	114	86	134	90	104	99								
8	148	90	109	88	145	79	101	69	119	64	83	68								
9	151	93	112	81	136	79	98	75	134	77	96	92								
10	140	91	107	73	125	82	96	74	122	78	92	70								
11	159	91	114	89	146	89	108	87	135	79	98	88								
12	156	94	115	71	131	72	92	67	154	66	95	78								
13	161	89	113	90									127	84	98	72	110	73	85	86
14	169	92	118	77									154	86	109	67	141	78	99	84
15	121	93	102	87									130	93	105	91	132	79	96	77
16	147	100	116	67									140	90	107	72	134	85	101	65
17	144	89	107	69									138	69	92	79	142	71	94	79
18	160	112	128	88									142	102	115	95	138	97	110	85
19	162	93	116	76									144	90	108	90	135	78	97	71
20	155	105	122	104	133	83	100	98	134	90	104	99								
21	139	87	104	80	145	86	106	93	129	72	91	88								
22	142	89	104	89	140	89	106	94	147	85	105	89								
23	160	108	125	101									168	103	125	85	164	94	117	90
24	168	95	119	64									138	94	109	78	140	85	103	76
25	147	103	117	72									144	94	111	89	136	94	108	94

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APPENDIX G : Average BP loads at baseline and after morning and evening administration of 10 or 20 mg enalapril

Subject no.	AVERAGE 24 – HOUR BP LOADS																			
	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	79	18	37	6	63	14	30	7	43	17	40	11								
2	21	10	25	6	10	8	2	7	5	16	2	4								
3	14	9	51	7	7	3	3	5	30	14	24	8								
4	76	18	12	84	36	14	-	-	19	11	4	5								
5	88	16	22	4	76	21	2	2	52	14	-	-								
6	64	17	40	7	32	15	8	1	36	10	15	7								
7	84	11	96	13	94	19	85	8	61	10	67	8								
8	63	21	9	6	52	10	10	3	4	1	4	5								
9	75	6	37	2	64	17	16	10	44	12	18	5								
10	59	10	47	6	4	2	13	4	27	11	27	7								
11	33	7	15	3	36	12	19	4	39	20	5	3								
12	71	19	14	6	53	13	-	-	70	18	15	7								
13	86	21	74	17									31	11	22	8	41	15	22	6
14	84	24	52	7									36	11	2	9	55	13	22	43
15	37	6	71	8									38	12	58	7	43	13	40	4
16	57	12	65	10									48	9	40	7	28	10	16	4
17	75	13	16	34									36	13	-	-	46	14	4	4
18	93	15	98	17									56	9	83	11	51	7	76	8
19	62	19	30	7									37	13	19	7	24	9	4	5
20	89	15	94	12	45	8	39	5	60	10	64	9								
21	79	9	55	8	71	12	27	8	58	15	38	5								
22	44	15	44	4	63	12	33	6	41	8	41	5								
23	96	32	94	22									98	26	93	16	90	28	71	13
24	89	26	58	11									72	12	52	8	46	10	25	7
25	47	10	67	9									36	9	38	7	24	7	30	7

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DAY – TIME BP LOADS

Subject no.	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	74	16	37	6	57	13	29	7	42	16	42	12								
2	21	12	25	6	10	6	-	-	-	-	2	4								
3	17	9	61	7	5	3	36	4	28	13	25	9								
4	73	15	7	3	28	98	-	-	17	13	4	5								
5	95	15	25	4	72	19	2	2	43	94	-	-								
6	64	18	47	7	31	16	9	5	40	11	18	7								
7	81	10	96	13	93	18	83	7	65	9	73	8								
8	61	21	7	8	45	8	7	2	3	1	3	6								
9	71	3	37	1	53	20	18	13	39	10	14	4								
10	53	8	42	5	3	2	13	5	27	11	27	7								
11	30	6	15	3	31	12	20	5	44	20	6	3								
12	71	20	17	6	44	8	-	-	70	19	11	7								
13	84	19	84	18									29	5	19	7	42	16	21	6
14	81	22	52	7									38	12	-	-	49	14	23	4
15	19	4	65	5									25	7	50	9	29	8	35	4
16	50	8	59	8									43	6	34	5	22	10	8	11
17	71	93	16	38									24	12	-	-	36	17	5	4
18	91	12	98	17									48	6	83	10	47	7	77	9
19	54	18	32	7									26	9	14	9	17	9	4	5
20	93	15	88	12	43	9	36	5	64	9	70	8								
21	73	7	53	7	66	13	32	8	51	11	32	5								
22	37	13	39	4	56	10	32	6	35	9	35	4								
23	96	31	96	23									97	25	97	17	88	25	73	14
24	87	27	60	12									76	13	58	8	43	10	27	7
25	40	6	67	9									30	8	38	6	22	6	30	7

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จุฬาลงกรณ์มหาวิทยาลัย

NIGHT – TIME BP LOADS

Subject no.	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	100	26	38	9	100	20	33	8	50	14	25	5								
2	25	19	25	3	13	15	13	7	38	16	-	-								
3	-	-	-	-	13	3	25	9	25	5	13	4								
4	88	29	38	7	75	22	-	-	33	3	-	-								
5	50	21	-	-	100	32	-	-	100	24	-	-								
6	63	12	-	-	38	10	-	-	13	3	-	-								
7	100	15	100	14	100	21	100	11	38	11	25	13								
8	75	18	25	4	88	15	25	6	13	1	13	3								
9	100	19	38	6	88	14	13	1	75	15	38	5								
10	88	12	75	6	13	1	13	3	25	10	25	6								
11	50	8	13	5	63	12	13	2	13	10	-	-								
12	75	12	-	-	100	24	-	-	75	14	-	-								
13	100	28	83	12									78	21	33	9	38	4	38	4
14	100	34	50	10									25	5	13	9	88	12	-	-
15	100	8	10	15									100	18	100	5	100	18	63	5
16	100	24	88	15									88	15	75	10	63	8	63	6
17	100	31	3	2									100	16	-	-	100	8	-	-
18	100	29	100	15									100	17	88	13	75	8	63	6
19	100	21	22	5									89	17	44	3	63	10	-	-
20	67	21	100	22	56	4	56	3	38	11	25	13								
21	100	15	63	10	88	17	-	-	88	28	75	5								
22	88	19	75	5	100	18	38	5	63	6	63	8								
23	100	36	88	20									100	27	75	10	100	22	63	11
24	100	22	50	6									50	8	13	4	63	12	13	10
25	100	19	71	9									75	11	38	13	38	10	25	5

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จุฬาลงกรณ์มหาวิทยาลัย

PEAK MORNING BP LOADS

Subject no.	Baseline				10 mg enalapril OD								20 mg enalapril OD							
					Morning				Evening				Morning				Evening			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	42	10	33	10	33	12	25	4	8	8	25	6								
2	15	10	23	3	11	9	-	-	-	-	-	-								
3	23	4	38	5	-	-	80	3	33	13	17	7								
4	82	20	9	4	25	13	0	0	15	8	8	4								
5	100	17	50	2	9	12	-	-	62	14	-	-								
6	55	12	9	4	8	9	-	-	9	11	-	-								
7	100	11	100	14	100	15	73	10	40	7	50	8								
8	67	15	8	5	75	9	38	2	7	1	9	6								
9	77	16	38	7	-	-	-	-	23	8	8	5								
10	50	5	33	5	9	2	36	5	15	11	8	1								
11	23	2	23	2	58	13	42	8	15	13	15	2								
12	100	18	54	5	10	12	-	-	77	19	-	-								
13	85	22	23	12									11	2	33	10	-	-	-	-
14	100	55	55	4									85	15	17	3	44	20	22	4
15	-	-	8	4									11	5	67	4	-	-	-	-
16	50	8	75	13									56	6	33	9	50	4	40	4
17	80	4	30	2									30	17	-	-	30	22	-	-
18	100	15	100	20									40	4	80	9	44	10	77	7
19	85	24	31	4									45	16	36	12	17	7	8	2
20	100	19	100	16	-	-	-	-	40	7	50	8								
21	50	7	33	12	100	9	45	10	14	43	-	-								
22	58	13	42	4	67	13	25	4	36	13	27	3								
23	90	25	100	19									100	27	100	15	100	29	87	18
24	25	9	60	9									85	7	77	9	42	10	25	5
25	62	11	85	12									58	8	58	6	33	8	58	9

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APPENDIX H : Trough and peak antihypertensive effects and T: P ratio of 10 or 20 mg enalapril

Subject no.	Morning						Evening					
	SBP reduction			DBP reduction			SBP reduction			DBP reduction		
	trough (mmHg)	peak (mmHg)	T:P ratio (%)	trough (mmHg)	peak (mmHg)	T:P ratio (%)	trough (mmHg)	peak (mmHg)	T:P ratio (%)	trough (mmHg)	peak (mmHg)	T:P ratio (%)
1	-5.5	-9.5	58	-5.5	-12	46	-15	-36.5	41	-5	-13	38
2	-11.5	-34	34	-10	-16	63	-15	-21	71	-8	-19	42
3	-14	-23.5	60	-9	-18.5	49	-12.5	-21	60	-4	-10	40
4	-16.5	-31.5	52	-12	-28	43	-27	-36.5	74	-13	-22	59
5	-18	-21.5	84	-12	-21	57	-22.5	-35.5	63	-9	-12	75
6	-19	-31	61	-9	-14.5	62	-18	-31.5	57	-14	-26	54
7	-11	-21.5	51	-6	-11	55	-16	-26	62	-13	-20	65
8	-9	-18	50	-10	-15	67	-9	-33.5	63	-14	-24	58
9	-10.5	-13.5	78	-10	-16.5	61	-17	-23.5	72	-15	-23.5	64
10	-16	-25	64	-7	-16.5	42	-10	-24	42	-8	-12	67
11	-12	-20.5	59	-8	-17.5	46	-9	-20.5	44	-11	-18	61
12	-10	-16.5	61	-11	-20	55	-11	-24	46	-9.5	-18.5	51
13*	-18	-24	75	-13	-24.5	53	-31	51	54	-17	-26	65
14*	-22.5	-35.5	63	-9	-17.5	51	-16	-30.5	52	-10.5	-16.5	64
15*	-8	-14.5	55	-6.5	-14	46	-9	-13.5	67	-8.5	-18	47
16*	-5	-11	45	-6	12	50	-12.5	-17.5	71	-11.5	-18.5	62
17*	-10	-25	40	-16	-25.5	63	-10.5	-20	53	-16.5	-27.5	60
18*	-12	-17	71	-7	-11	64	-19	-39	49	-14	-23	61
19*	-12.5	-17	74	-11	-25	44	-15.5	-37	41	-9	-19	47
20	-10.5	-22.5	47	-5	-19	63	-12.5	-22.5	56	-8.5	-18	47
21	-4	-10	40	-9	-20	45	-18.5	-27	69	-8.5	-15	57
22	-16	-24	67	-4	-9	44	-12	-20.5	59	-5.5	-8	69
23*	-16.5	-24	69	-12	-17	70	-7.5	-13	58	-10	-15	67
24*	-11.5	-20.5	56	-12	-20	60	-8.5	-13	65	-10	-14	71
25*	-8	-17.5	46	-7	-16.5	47	-10	-15.5	65	-10	-13.5	74

* 20 mg enalapril

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จุฬาลงกรณ์มหาวิทยาลัย

BIOGRAPHY

NAME	Miss Roongtiwa Laohathienpratan
DATE OF BIRTH	March 26, 1973
PLACE OF BIRTH	Kanchanaburi
INSTITUTION ATTENDED	Chiangmai University, 1991-1995: Bachelor of Science in Pharmacy Chulalongkorn University, 1997-1999 Mater of Science in Pharmacy (Clinical and hospital pharmacy)

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