DIPPERS AND NON-DIPPERS : POTENTIAL CAUSES AND CLINICAL SIGNIFICANCE OF DIURNAL BLOOD PRESSURE VARIATION

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Dedicated to Sharon and Cameron

Declaration

I hereby declare and affirm that this thesis is entirely my own work and composition. Where I have received technical assistance or help in patient recruitment, this is indicated in the text.

Signature ..... Date 4/10/96

Abstract

Blood pressure varies over 24 hours with levels during sleep about 20% less than those during the day. Variations in this pattern are now recognised, and preliminary work suggests that those whose pressure does not fall at night - "*non-dippers*" - may have a greater prevalence of cardiovascular disease. This thesis, based on clinical studies utilising non-invasive ambulatory BP monitors (ABPM), explores the nature and potential clinical significance of diurnal blood pressure variation in detail.

ABPM is of proven accuracy in sinus rhythm, but its reliability has not been demonstrated in patients with cardiac arrhythmia. Validation of two commonly used ABPMs in patients with atrial fibrillation has demonstrated significant device inaccuracy, and such patients have therefore been excluded from further clinical and research study.

The optimal method for characterising the diurnal BP profile remains unknown but a change in the definition of night-time has been shown to have a major impact upon the nocturnal dip. A more physiological description, using sleep time, can be achieved using electronic activity meters to quantify sleep. The potential to improve reproducibility by correcting for day-time activity levels has also been explored.

Analysis of ABPM recordings from a large, heterogeneous population has demonstrated approximately Normal distribution of the nocturnal dip, with no evidence of bimodality. This study has also shown age, but not severity of hypertension, to be an important determinant of diurnal variability, while anti-hypertensive drug treatment, as used in normal clinical practice, appears to have no significant independent effect.

Blunting of diurnal variability in some forms of secondary hypertension has been confirmed. Study of such patients provides an insight into potential mechanisms underlying the nocturnal dip. Catecholamine excess appears to have a profound effect, confirming the importance of the autonomic nervous system in its regulation. Attenuation of the dip in those with volume mediated hypertension and those with impaired renal function suggests that hypervolaemia resulting in posture related changes in BP may also impact upon this rhythm. Glucocorticoid excess has been shown to blunt diurnal variability, but a modest increase in glucocorticoid exposure in hypopituitary patients has no effect, suggesting that pathological but not physiological quantities of corticosteroid are required to modify the diurnal rhythm.

Study of patients with accelerated phase hypertension has demonstrated loss of the diurnal rhythm which returns towards normal with successful treatment. However, such patients are commonly hospitalised and study of other groups requiring emergency hospital admission suggests that this process may in part explain this effect.

Mean wake blood pressure has been shown to be the most important predictor of target organ damage, assessed by echocardiography and microalbuminuria, but some further independent predictive information is provided by knowledge of diurnal variability.

The hypothesis that occult sleep apnoea or nocturnal hypoxia may account for loss of diurnal variability is tested. Patients with essential hypertension, sleep apnoea syndrome and chronic obstructive pulmonary disease were studied, with no direct link between nocturnal hypoxaemia and the night-time BP dip apparent.

A potential active role for the heart in the control of the diurnal rhythm is examined in a study of patients with mild cardiac failure starting treatment with an ACE inhibitor. The nocturnal dip was preserved but blunted, and was reduced still further by treatment, due to a greater fall in day than night BP.

Diurnal BP variability is a complex phenomenon which, although intrinsically related to sleep, is influenced by many other variables. Factors affecting the rise in BP during the day appear as important as those controlling its fall during sleep.

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List of Abbreviations Used in Thesis

ABPM	Ambulatory Blood Pressure Monitor
ACC	Accutracker Ambulatory Blood Pressure Monitor
ACE	Angiotensin Converting Enzyme
ACTH	Adrenocorticotrophic Hormone
AF	Atrial fibrillation
AHA	American Heart Association
Amax	Maximum Left Ventricular Inflow Velocity - Atrial Component
ANOVA	Analysis of Variance
Ao	Aorta
BMI	Body Mass Index
BP	Blood Pressure
COP	Copal Electronic Sphygmomanometer
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
DBP	Diastolic Blood Pressure
DT	Deceleration Time
ECG	Electrocardiogram
EEG	Electroencephalogram
Emax	Maximum Early Left Ventricular Inflow Velocity
GFR	Glomerular Filtration Rate
HRZ	Hawksley Random Zero Sphygmomanometer
ISH	International Society of Hypertension
IVRT	Isovolumic Relaxation Time
IVS	Interventricular Septum
LA	Left Atrium
LV	Left Ventricle
LVH	Left Ventricular Hypertrophy
LVID	Left Ventricular Internal Dimension
LVMI	Left Ventricular Mass Index
MRC	Medical Research Council
NS	Not Statistically Significant
NYHA	New York Heart Association
p	Probability
PW	Posterior Wall of Left Ventricle
RV	Right Ventricle

RWT	Relative Wall Thickness
SaO2	Oxygen Saturation
SAS	Semiautomatic Sphygmomanometer
SBP	Systolic Blood Pressure
s.d.	Standard Deviation
s.d.d.	Standard Deviation of the Difference
s.e.m.	Standard Error of the Mean
SL	SpaceLabs Ambulatory Blood Pressure Monitor
TAK	Takeda Electronic Sphygmomanometer
WHO	World Health Organisation
x^2	Chi-squared

CHAPTER 1

Introduction : The Measurement Of Arterial Blood Pressure

Historical Background

The development of methods for the measurement of blood pressure (BP) had, of necessity, to await the description of the circulation by William Harvey (1628). A further century then had to pass before the pressure exerted by the heart on the circulation was first measured by the Reverend Stephen Hales who, in 1733, cannulated the femoral artery of a horse and measured the vertical height to which blood rose in a glass tube some 9 feet in length (Hales, 1733). In 1828 this procedure was simplified by Poiseuille, who used a much shorter U-tube filled with mercury and measured arterial pressure in millimetres of mercury for the first time (Poiseuille, 1828). Poiseuille was also the first to recognise that the same pressure is maintained throughout the arterial tree. In 1847 Ludwig connected Poiseuille's manometer to a writing pen attached to a revolving smoked drum, thus enabling the recording of changes in the arterial pressure (Ludwig, 1847). This instrument was used by Faivre during a limb amputation to record the systolic blood pressure for the first time in man (Faivre, 1856).

However, routine blood pressure measurement in man required a non-invasive technique. Vierordt (1855) was the first to attempt this, in 1854, using a scale pan attached to a lever pressed on the radial pulse, to determine the weight in grams required to obliterate the radial pulse - the sphygmograph. Mahomed, working in Guy's Hospital in London, modified this device (Mahomed, 1872) and began to apply these techniques to human disease for the first time. Thus, in 1874 he described the association between high blood pressure and acute nephritis (Mahomed, 1874). The potential importance of an accurate technique for the measurement of blood pressure was beginning to be appreciated.

The sphygmograph, while capable of giving a pulse wave tracing, was not an accurate device for measuring blood pressure, largely because it took no account of the size of the arterial surface being compressed (Lawrence, 1979). Further refinement of the indirect measurement of blood pressure was described by von Basch (1880). In experiments on cadaver arteries he was able to demonstrate that the pressure required to occlude the lumen of an artery equals the pressure within the vessel plus that required to overcome wall rigidity. As the rigidity of arteries was small, the occlusion pressure was a

reasonable estimate of the intra-arterial pressure. He then developed a device - which he called the 'sphygmomanometer' - utilising a fluid-filled rubber bulb which was used to compress the radial pulse, with the pressure required to achieve this forcing water from the bulb into a manometer; the point of disappearance of the pulse being taken as the systolic pressure. Importantly, this instrument provided an estimate of pressure per unit of surface, overcoming the major limitation of the sphygmograph. Zadek (1880) used this sphygmomanometer extensively and was probably the first to observe the variability of blood pressure under different measuring conditions.

The von Basch sphygmomanometer, although the first reasonably accurate device for clinical measurement of blood pressure, was flawed in that it assumed that the artery could be uniformly compressed against underlying bone. The prototype of the modern mercury sphygmomanometer was devised by Riva-Rocci who, in 1896, placed a band around the upper arm and inflated it with air until the pressure was sufficient to obliterate the pulse (Riva-Rocci, 1896). By releasing the air gradually while observing the pressure on a manometer and palpating the pulse, he was able to record the systolic pressure, overcoming the deficiencies of von Basch's device. It was not long, however, before a serious source of error was noted with this instrument. First von Recklinghausen (1901) and then Janeway (1904) showed that the 5 cm wide cuff used by Riva-Rocci resulted in erroneously high systolic pressures, which could be corrected by using a 12 cm cuff.

Contemporaneously Hill and Barnard were developing their own sphygmomanometer, utilising an aneroid gauge connected to an arm cuff, which was the first device capable of recording both systolic and diastolic pressure (Hill & Barnard, 1897). Although Hill referred to diastolic blood pressure (Hill & Barnard, 1897), it was Janeway (1904) who described the correct use of their device, demonstrating that the point of maximum oscillation of the needle corresponded to diastolic and not, as previously thought, to mean arterial pressure.

The major disadvantage of this device was that the gauge became inaccurate with use and frequent recalibration was necessary. This led to methods of determining diastolic blood pressure by observing the oscillations in a mercury manometer, rather than on an aneroid gauge, and indirectly to the auscultatory measurement of systolic and diastolic pressure. Janeway (1901) described the occurrence of sounds during deflation of the cuff but it was Korotkoff (1905) who related these sounds to the systolic and diastolic pressure :

'The cuff of the Riva-Rocci is placed on the middle third of the upper arm; the pressure within the cuff is quickly raised up to complete cessation of circulation below the cuff. Then, letting the mercury of the manometer fall one listens to the artery just below the cuff with a children's stethoscope. At first no sounds are heard. With the falling of the mercury in the manometer down to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometric figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer one hears the systolic compression murmurs, which pass again into tones (second). Finally, all sounds disappear. The time of cessation of sounds indicates the free passage of the pulsewave; in other words, at the moment of the disappearance of the sounds the minimal blood pressure within the artery predominates over the pressure in the cuff. It follows that the manometric figures at this time correspond to the minimal pressure.' (Laher & O'Brien, 1992)

The equipment used has since been modified to improve accuracy, but the technique is essentially unchanged.

Blood Pressure Measurement and the Mercury Sphygmomanometer

In 1939, in an attempt to standardise the technique for the measurement of blood pressure, the American Heart Association and the Cardiac Society of Great Britain and Ireland issued joint recommendations on methods of blood pressure determination (American Heart Association, 1939). These have subsequently been updated at intervals as appropriate by the American Heart Association (AHA) in the US (Frohlich *et al,* 1988) and the British Hypertension Society (BHS) in the UK (Petrie *et al,* 1986) and, despite some vacillation over the issue of the diastolic end-point (Frohlich *et al,* 1988), are now in broad agreement. With careful attention to detail, the mercury sphygmomanometer provides accurate, reliable and reproducible blood pressure measurement.

In clinical practice, however, errors in blood pressure determination are common. Despite the AHA, BHS and World Health Organisation all recommending the routine use of Korotkoff sound phase V, many physicians continue to record phase IV (Manek *et al,* 1984, Padfield *et al,* 1990). As the vast majority of epidemiological data (Kannel, 1974) and the major therapeutic intervention trials (Management Committee, 1980; Medical Research Council Working Party, 1985) have used phase V readings, and as there are greater errors in the identification of phase IV (Freis & Sappington, 1968), the arguments in favour of the universal use of phase V (with the possible exception of readings in children, when sounds may persist to zero) are overwhelming.

Controversy over the appropriate cuff size continues. The AHA recommend the use of a cuff with a ratio of bladder width to upper arm circumference of 0.4 (Frohlich *et al,* 1988). The bladder length should be at least twice the width, thus ensuring that the bladder will encircle 80% of the arm, and the centre of the bladder should be over the brachial artery. A bladder which encircles the arm completely correlates better with intra-arterial recordings (Russell *et al,* 1989; Croft & Cruickshank, 1990), yet the standard adult cuff (12 by 23 cm) will encircle only 33% of adult arms. The British Hypertension Society therefore recommends the use of a standard cuff measuring 12 by 35 cm, which would encircle 99% of adult arms (Petrie *et al,* 1986). Under-estimation of pressure with larger cuffs is not a problem in practice (Croft & Cruickshank, 1990). As many as 14% of hypertensive patients may have spurious elevation of BP related to use of a standard cuff (Linfors *et al,* 1984). Pseudo-hypertension in the elderly (Messerli *et al,* 1985) is probably an artefact related to inappropriate cuff size and is not seen when larger cuffs are used (O'Callaghan *et al,* 1983; Linfors *et al,* 1984).

Observer bias, particularly when there is an arbitrary division between normal and high blood pressure, is a common cause of error in blood pressure measurement, the magnitude of which is sufficient to have important implications for both research and management (Bruce *et al,* 1988; Padfield *et al,* 1990), and the reduction in bias seen with re-training of observers is short-lived (Bruce *et al,* 1988). Terminal digit preference is also widespread, with as many as 84% of systolic and 73% of diastolic values being recorded to the nearest '0' (Hessel, 1986; Padfield *et al,* 1990). As this tendency tends to be more common around diagnostic levels for hypertension (Padfield *et al,* 1990), this could well affect the level of treatment in a population. The Hawksley random- zero sphygmomanometer, designed to reduce the effect of observer bias, introduces computational error and may also be subject to additional, systematic machine error (O'Brien *et al,* 1990b).

Problems with the equipment in common usage are also widespread, with as many as a half of hospital sphygmomanometers being defective (Burke *et al,* 1982), and regular maintenance being the exception rather than the norm. Aneroid sphygmomanometers, which are commonly used by general practitioners, are even more susceptible to failing accuracy if not regularly serviced (Burke *et al,* 1982).

Blood Pressure Variability and "White Coat" Hypertension

Ayman and Goldshine (1940) first reported that the blood pressure of hypertensive patients measured in their own home was substantially lower than that recorded in the

clinic and they suggested that home measured pressure may be a better indicator of prognosis. At around the same time Smirk and co-workers (Smirk, 1944; Smirk *et al,* 1959; Smirk, 1964) were studying casual (clinic), basal and supplemental blood pressures in essential hypertension. Basal blood pressure was that measured after subjects had spent a night in a single room under mild sedation using a barbiturate, and had been habituated to the blood pressure measuring procedure. Supplemental pressure was defined as the difference between casual and basal blood pressure and is the more variable part of the casual pressure, representing the response of the individual to the current environment (Smirk, 1944). Basal blood pressure was shown to be a strong predictor of morbidity and mortality, while supplemental pressure had little predictive value (Smirk *et al,* 1959; Smirk, 1964).

However it is only with the development of techniques for monitoring blood pressure throughout 24 hours that the extent of the variability of arterial pressure has been appreciated (Richardson *et al,* 1964; Raftery, 1983). Ambulatory intra-arterial recording of blood pressure demonstrates that it is a continuous variable with considerable beat-to-beat and minute-to-minute variation (Raftery, 1983). Consequently any non-invasive measure of BP can only be a rough estimate of a subject's true pressure, with repeated measurements over a period of time improving the precision of the estimate (Armitage & Rose, 1966; Armitage *et al,* 1966). Conventional clinic blood pressure measurement should be performed twice per visit for at least three visits (Rosner & Polk, 1981), and preferably more often (Littler & Komsuoglu, 1989), to achieve a reasonable estimate of hypertensive status, and this process should be repeated each time a change in anti-hypertensive therapy is considered.

In addition to spontaneous variability in pressure, a large proportion of subjects who come to a doctor's clinic show a transient rise in blood pressure, seen almost immediately after the arrival of the doctor, peaking within 1 to 4 minutes and averaging 27/15 mmHg in one study (Mancia *et al,* 1983a). This response is highly variable, with the rise in systolic pressure ranging from 4 to 75 mmHg, and is unrelated to age, sex, baseline blood pressure or blood pressure variability (Mancia *et al,* 1983a). It persists with repeated visits over a short time span (Mancia *et al,* 1987) and as the rise is also seen when a subject measures his own pressure in the presence of a doctor (Mengden *et al,* 1990), it is clearly due to subject-doctor interaction, rather than the measuring procedure itself. A similar but smaller rise is seen when BP is measured by a nurse (Mancia *et al,* 1987).

As a result of this "white coat" hypertension, between 20 and 50% of subjects with borderline hypertension may be misclassified as hypertensive (Laughlin *et al,* 1980; Pickering *et al,* 1988; Hall *et al,* 1990) and started on treatment, perhaps unnecessarily (O'Brien & O'Malley, 1988). In both the Medical Research Council (Medical Research Council Working Party, 1985) and Australian National Blood Pressure studies (Management Committee, 1980) a fall in blood pressure to normotensive levels was seen in up to 50% of placebo treated patients and these subjects had a similar prognosis to hypertensive subjects with the same blood pressure on anti-hypertensive therapy. This fall largely occurred in the first 3 to 4 months and, as no clinically significant placebo effect is seen when 24-hour mean ambulatory pressure is measured (Gould *et al,* 1981; Mutti *et al,* 1991) it seems likely that this fall in pressure with time is due to both diminution of the "white coat" effect and regression to the mean.

"White coat" hypertension may not be an entirely benign condition. Epidemiological studies show that a single clinic blood pressure reading is predictive of cardiovascular morbidity and mortality (Kannel, 1974). Furthermore, in the Tecumseh study subjects with "white coat" hypertension have a cardiovascular risk profile and haemodynamic parameters (vascular resistance and minimal forearm resistance) similar to those with sustained hypertension and significantly different from a normotensive group (Julius *et al,* 1990). In contrast to patients with borderline or mild hypertension, the clinic blood pressure of normotensive subjects tends to be slightly lower than the day-time average ambulatory blood pressure (O'Brien *et al,* 1991c). The "white coat" effect may, then, be one of the earliest clinical indications of the transition from a "normotensive" to a "hypertensive" state (Cox *et al,* 1991a). Thus, while such patients are probably at lower risk of hypertensive complications and may not require anti-hypertensive therapy, they should be monitored and counselled on non-pharmacological methods of blood pressure control and the modification of other cardiovascular risk factors.

Home (Self) Monitoring of Blood Pressure

In addition to the diagnosis of "white coat" hypertension, home monitoring of blood pressure by a patient or a member of the family allows more frequent readings of blood pressure over a short time period, improving diagnostic accuracy. The average home pressure over a period of three days predicts the ultimate clinic pressure of newly diagnosed hypertensives after 4 weeks with an accuracy of 79% (Padfield *et al,* 1987). Home pressure is highly reproducible (James *et al,* 1988) and remains stable over a four week period (Jyothinagaram *et al,* 1990a). It has also been shown to correlate better than

clinic BP with left ventricular hypertrophy (Kleinert *et al,* 1984) and its regression (Ibrahim *et al,* 1977).

Home measured BP is devoid of a placebo effect (Cottier *et al,* 1982) and should provide a better guide to changes in drug therapy (James *et al,* 1988). It may also be of benefit when assessing the effect of new anti-hypertensive agents in clinical trials (Gould *et al,* 1986). Blood pressure measurement with an electronic sphygmomanometer will abolish observer bias, which may be an advantage in clinical and epidemiological studies, and machines of proven accuracy are available (Jamieson *et al,* 1990).

Self-monitoring techniques can also improve patients' understanding of their disease and many patients appreciate the opportunity to participate in the management of their disease (Hunt *et al,* 1985), which may improve patient compliance (Edmonds *et al,* 1985). Conversely, other patients may become overtly conscious of minor fluctuations in pressure, which could result in anxiety and possibly inappropriate self-adjustment of therapy (Hunt *et al,* 1985). Inadequate instruction may lead to inaccurate readings, misleading both the patient and the physician. Detailed education on correct methodology is therefore of considerable importance (World Hypertension League, 1988).

At present, there is no agreed standard for the frequency or duration of self-measurement regimes, with published work ranging from blood pressure readings taken twice daily for one week to six times daily for fourteen days or longer (Julius *et al,* 1974; Laughlin *et al,* 1980; Kleinert *et al,* 1984; Padfield *et al,* 1987). A series of 5 readings a day for 3 days has been shown to be a valid (Padfield *et al,* 1987) and reproducible (Jyothinagaram *et al,* 1990a) regimen, which is well tolerated by patients.

Home or self-measured blood pressure recording remains under utilised in the UK. This may reflect concerns over the ability of patients to learn self-measurement techniques. In early studies, in which patients were taught to use a stethoscope and mercury sphygmomanometer, many patients were unable to master the technique (Julius *et al,* 1974; Burns-Cox *et al,* 1975; Laughlin *et al,* 1980). However techniques for self-monitoring have become simpler with the development of micro-electronics (Hunt *et al,* 1985) and a wide variety of semi-automated machines are now available. Virtually all use a sphygmomanometer cuff and utilise either a microphone for Korotkoff sound detection, oscillometry or ultrasound. No one technique appears to be consistently more accurate, though oscillometric machines have the advantage of not requiring accurate cuff placement. Fully automatic machines, which do not require self-inflation of a

sphygmomanometer cuff, are preferable as the isometric exercise involved in self-inflation can raise BP significantly (Veerman *et al,* 1990). Unfortunately the accuracy of these machines is variable, with many inaccurate and unreliable machines marketed (Hunyor *et al,* 1978; Pickering *et al,* 1986; O'Brien *et al,* 1990a) and it is important that any machine used is validated prior to use and at regular intervals thereafter, ideally after each set of home recordings is complete (Hall *et al,* 1990).

Despite the apparent advantages, prospective data on clinical outcome based on home monitored pressures are still lacking, and this technique therefore compliments rather than replaces clinic BP measurement.

Ambulatory Blood Pressure Monitoring

The development of devices for monitoring blood pressure over periods of 24 hours or more while subjects continue their normal daily activities has added a new dimension to the evaluation of the hypertensive patient. Early work with invasive, intra-arterial monitoring systems clearly demonstrated the extent of the variability of blood pressure throughout the day (Littler *et al,* 1978) and the extent of the diurnal variation of blood pressure (Littler *et al,* 1975). Although this technique has proved to be a valuable research tool (Raftery, 1983), it is clearly not suited to general clinical use. Consequently, a variety of non-invasive, fully automatic ambulatory blood pressure recorders have been developed, generally using oscillometric or Korotkoff sound techniques (The National High Blood Pressure Education Program Co-ordinating Committee, 1990; Meyer-Sabellek *et al,* 1990). These devices can be programmed to inflate an arm cuff automatically at pre-set intervals, typically ranging from 6 to 120 minutes, throughout a 24 to 48 hour period. Data are stored on microcomputer hardware within the monitor and down-loaded directly onto a personal computer at the end of the monitoring period. Data can then be edited and analysed according to pre-set criteria.

As with home monitors, the accuracy and reliability of ambulatory blood pressure monitors is variable (O'Brien & O'Malley, 1990) but standards for the evaluation of these devices have been agreed (Association for the Advancement of Medical Instrumentation, 1987; O'Brien *et al,* 1990c; O'Brien *et al,* 1993). When starting this work, only the SpaceLabs 90202 (O'Brien *et al,* 1989b), SpaceLabs 90207 (O'Brien *et al,* 1991b) and Medilog (Hope *et al,* 1988) systems had fulfilled the criteria of the Association for the Advancement of Medical Instrumentation for both systolic and diastolic pressure and were therefore recommended for routine use (O'Brien & O'Malley, 1990). The Accutracker

device had been validated using less stringent standards (Appel *et al,* 1990; Jyothinagaram *et al,* 1990b) and was used initially in small numbers of patients, but, in light of the results of more detailed validations, the majority of this research utilised the SpaceLabs 90207 ambulatory monitor.

Although reasonably accurate at rest, no currently available device is accurate during exercise (White *et al,* 1990) and subjects must therefore be instructed to keep their arm motionless during each BP reading. Similarly, accuracy may be significantly reduced in the presence of cardiac arrhythmias such as atrial fibrillation (Caramella & Desmonts, 1986) and at present this represents a serious deficiency in these devices.

Nonetheless, 24-hour ambulatory blood pressure records, with blood pressure readings every 30 minutes or less, correspond closely to simultaneous intra-arterial recordings (Di Rienzo *et al,* 1983) and are highly reproducible (James *et al,* 1988). No alerting reaction or pressor response is seen with intermittent cuff inflation (Parati *et al,* 1985b; Brigden *et al,* 1990), monitoring does not affect the normal haemodynamics of sleep (Parati *et al,* 1985a), and no placebo response is seen in clinical trials (Conway *et al,* 1988). Thus non-invasive ambulatory blood pressure recorders appear to accurately reflect an individual's BP over 24 hours and will provide similar information to home blood pressure monitoring, including the recognition of "white coat" hypertension (Pickering *et al,* 1988).

These machines are generally well tolerated, with less than 10% of patients being unable to tolerate the equipment or refusing to wear it in public (Meyer-Sabellek *et al,* 1990), and disturbance of sleep is less of a problem with newer, quieter devices (Meyer-Sabellek *et al,* 1989). Complications are exceptionally rare. Petechiae and oedema distal to the cuff (White, 1985), and ecchymoses (Burris *et al,* 1988) and thrombophlebitis (Creevy *et al,* 1985) at the cuff site may appear. Localised exfoliative dermatitis (Burris *et al,* 1988) and allergic reactions (Meyer-Sabellek *et al,* 1990) have also been reported. These complications appear to be more common with very frequent measuring intervals or when the equipment is malfunctioning, with delayed relaxation of the cuff.

A major disadvantage of these devices is their cost, with current machines costing over £3000 each. Computer hardware and software for analysis are also necessary, adding to the costs. As it takes around 30 minutes to fit a device and educate a subject, personnel costs also need to be considered. However, in patients with mild hypertension, ambulatory monitoring has shown that as many as 40% of patients have pressures low

enough to withhold antihypertensive treatment (Krakoff *et al,* 1988) and it has been suggested that the resultant cost savings would offset the cost of the investigation (Krakoff *et al,* 1988). By enabling the direction of treatment at those with the highest pressures, a more effective reduction in cardiovascular morbidity could be achieved, while actually lowering the cost of the drug bill.

Data Analysis

There are many different approaches to the analysis of a 24-hour ambulatory blood pressure trace, designed to provide information on blood pressure profiles over 24-hours, during day-time and night-time. The simplest and most widely used method is to calculate the 24 hour, day and night mean blood pressure values. Some workers have excluded readings in the early morning and late evening from this calculation (O'Brien *et al,* 1991c), when rapid changes in blood pressure may be taking place. However as there is an excess of cardiovascular events at these times (Mitler *et al,* 1987), important prognostic or diagnostic information may be omitted. Any arbitrary definition of day and night times may also affect the mean values calculated, and analysing wake and sleep periods may therefore be more appropriate.

Smoothing procedures, including the use of spline functions and Fourier analysis, have been developed (Streitberg *et al,* 1989; Streitberg & Meyer-Sabellek, 1990). While such methods overcome problems in analysis resulting from irregular spacing in time of blood pressure measurements and smooth the spikes inherent in blood pressure over time, they are complex to compute and assume, wrongly (Pickering, 1989), that blood pressure has a natural circadian rhythm.

An alternative method of presenting and analysing data is to calculate the blood pressure load, defined arbitrarily as the percentage of blood pressure measurements exceeding 140/90 mmHg during waking hours and 120/80 mmHg during sleep (White, 1991). While of some prognostic relevance (White *et al,* 1989), this method fails at extremes in that all normotensives will have a load of 0% and all severe hypertensives a load of 100%.

In routine clinical use, the arithmetic mean blood pressure values for wake, sleep and 24 hours remains the simplest and most appropriate way to present data.

Prognostic Value of Ambulatory Monitoring

Evidence that these readings are of prognostic importance and a better predictor than clinic BP of cardiovascular risk is growing (Pickering & Devereux, 1987). Several workers have demonstrated that mean ambulatory blood pressure is a better predictor of echocardiographically determined left ventricular mass (Rowlands *et al,* 1982; Drayer *et al,* 1983; Devereux *et al,* 1983; Gosse *et al,* 1988a; White *et al,* 1989; Verdecchia *et al,* 1990), a marker of hypertensive target organ damage. Patients whose ambulatory BP is similar to clinic pressure have a higher prevalence of target organ damage (assessed by ECG and fundal change) than those who have lower ambulatory pressure (Floras *et al,* 1981) and latent cerebrovascular disease, assessed by nuclear magnetic resonance imaging of the brain, is related to mean ambulatory BP but not clinic BP (Shimada *et al,* 1990).

There are also two prospective studies relating clinical events to ambulatory blood pressure. Perloff *et al* (1983) have followed 1076 patients for 5 years and shown that subjects whose day-time mean ambulatory blood pressure is low relative to their clinic pressure at presentation have a better prognosis, with lower mortality and lower incidence of cardiovascular events, than those whose ambulatory pressure is higher. Thus, as clinic pressures were comparable in the two groups studied, ambulatory pressure recording appeared to provide prognostic information over and above the clinic pressure. This was true particularly in younger patients and those with borderline or mild hypertension, in whom the decision to treat can be the most difficult, but also applied to patients who had already developed a cardiovascular complication (Perloff *et al,* 1989). However this study depended entirely on the initial ambulatory pressure, with no information on the change in ambulatory pressure with time, and recorded day-time pressures only.

Mann *et al* (1985) have followed 137 patients for a mean of 2 years with 14 subjects experiencing a first cardiovascular event in this time. Ambulatory pressures were better than clinic pressure at predicting these events.

Ambulatory monitoring also provides an accurate estimate of BP variability, usually taken as the 24-hour blood pressure standard deviation (Littler *et al,* 1978; Floras *et al,* 1988), provided readings are every 15 minutes or more frequently (Di Rienzo *et al,* 1983). The importance of this measurement is not clear. Early studies (Rowlands *et al,* 1982; Mann *et al,* 1985) did not find any correlation between BP variability and target organ damage or cardiovascular damage. However Parati *et al* (1987) and Palatini *et al* (1985) both

found that variability provided additional prognostic information and suggested that it may be an independent risk factor for cardiovascular disease.

Diurnal Variation in Blood Pressure

Since the introduction of techniques for ambulatory blood pressure monitoring it has been clear that blood pressure has a diurnal rhythm, with levels during sleep about 20% less than during the day (Littler *et al,* 1975). This rhythm is generally preserved in hypertensive patients, with an upward shift of the entire curve (Raftery, 1983), but in about 20% of essential hypertensives (O'Brien *et al,* 1988) this "dip" in blood pressure during sleep is reduced or absent. This observation has resulted in the suggestion that the hypertensive population can be subdivided into two broad groups, "dippers" and "non-dippers" (O'Brien *et al,* 1988; Pickering, 1990b). As preliminary work suggests that an absent or reduced nocturnal dip may impart increased cardiovascular risk, this may be of more than academic interest. O'Brien *et al* (1988) have reported the frequency of stroke in a population of non-dippers to be 23.8%, compared to a frequency of only 2.9% in age, sex and weight matched dippers with similar day-time blood pressure. Kobrin *et al* (1984) studied 21 elderly (>65 years) hypertensives and found a normal diurnal blood pressure rhythm in 14, but a reduced or absent nocturnal dip in 7. All of the non-dippers, but only 43% of the dippers, had clinical evidence of hypertensive or atherosclerotic complications.

Gosse *et al* (1988a) have found night-time BP to be the best correlate of left ventricular mass in 24 treated hypertensives and Verdecchia *et al* (1990) have published the results of a large study comparing 24 hour ambulatory blood pressure profile and echocardiographic left ventricular hypertrophy in 137 untreated hypertensives and 98 healthy normotensives. In the hypertensive group left ventricular mass correlated more closely with night-time than with day-time blood pressure. Of the hypertensive patients, 40% had a reduced nocturnal dip (< 10% of systolic and diastolic BP) and this group had a greater LV mass index. There was an inverse correlation between LV mass index and the nocturnal dip. Thus these data suggest that the nocturnal dip in BP prevents or delays the development of left ventricular hypertrophy.

Shimada *et al* (1990) have also found that hypertensive cerebrovascular disease, assessed by brain magnetic resonance imaging in 73 elderly, asymptomatic subjects, correlates more closely with night-time BP than with day-time or 24-hour BP.

Perhaps more importantly, using a retrospective case-control study, Verdecchia *et al* (1993) have recently demonstrated an association between a reduced diurnal rhythm and future cardiovascular morbid events, with the groups matched for both clinic and day time ambulatory blood pressure. Although apparent only in women, this work is the first to relate changes in diurnal variation to mortality.

Secondary Hypertension and the Diurnal Variation in Blood Pressure

Many, but not all, causes of secondary hypertension disturb the diurnal blood pressure rhythm (Baumgart *et al,* 1989a; Imai *et al,* 1990; Middeke & Schrader, 1994). An absent diurnal rhythm is seen in patients with phaeochromocytoma (Littler & Honour, 1974; Padfield *et al,* 1991), end-stage renal failure (Abel *et al,* 1990), pre-eclampsia (Oney & Meyer-Sabellek, 1990), Cushing's syndrome (Imai *et al,* 1988b) and treatment with high dose corticosteroids (Imai *et al,* 1989). Sleep apnoea syndrome, which several studies suggest is present in around 30% of treated hypertensives (Kales *et al,* 1984; Lavie *et al,* 1984; Fletcher *et al,* 1985), could also result in a non-dipping BP profile (Tilkian *et al,* 1976).

The renin-angiotensin system seems to have less influence on the blood pressure rhythm. Early reports which suggested that patients with primary aldosteronism and renovascular hypertension lost their diurnal variation studied older patients with more severe hypertension (Tanaka *et al,* 1983). Later studies have failed to confirm these observations (Munakata *et al,* 1988; Baumgart *et al,* 1989a). Younger patients with fibromuscular dysplasia have a normal diurnal rhythm; and treatment with angioplasty for renovascular hypertension or excision of an adrenal adenoma in primary aldosteronism does not affect the rhythm (Imai *et al,* 1990).

Complete reversal of the diurnal rhythm is also seen in patients with autonomic failure (Mann *et al,* 1983), and the nocturnal dip is attenuated or absent in patients with diabetic autonomic neuropathy (Reeves *et al,* 1986; Hornung *et al,* 1989) and quadriplegic spinal cord injury patients (Krum *et al,* 1991). Patients with cardiac failure (Caruana *et al,* 1988) and cardiac transplant patients (whose ventricles are denervated) (Reeves *et al,* 1986; Sehested *et al,* 1990b) also have a disturbed rhythm.

Pathophysiology of the Diurnal Variation in Blood Pressure

The normal dip in blood pressure is intrinsically related to sleep. Junior hospital doctors lose their nocturnal dip when on-call (Mehler & Anderson, 1987) and shift workers reverse their diurnal rhythm when moving from night to day shift (Baumgart, 1990). This reversal occurs immediately, without a period of adjustment, in contrast to true circadian rhythms, suggesting that there is no "internal clock" determining the diurnal variation (Baumgart, 1990). Patients on strict bed rest also exhibit a diurnal rhythm (Athanassiadis *et al,* 1969) suggesting that activity is not solely responsible. This concept is supported by the observation that many patients with secondary hypertension lose their nocturnal dip.

A reduction in sympathetic nervous system activity during sleep may be an important factor controlling the nocturnal fall (Pickering, 1990b) and would explain the absent dip in autonomic neuropathy, phaeochromocytoma and following cardiac transplantation. However urinary catecholamines do not correlate with diurnal blood pressure changes in patients with essential hypertension (Messerli *et al,* 1982), suggesting that other mechanisms are involved.

While the observation that patients with Cushing's syndrome (Imai *et al,* 1988b) or on high dose corticosteroids (Imai *et al,* 1989) have no nocturnal dip in blood pressure is intriguing, physiological doses of cortisol do not appear to influence the diurnal rhythm in patients with hypopituitarism (Jyothinagaram *et al,* 1989), and a major role for the pituitary-adrenal axis in essential hypertension seems unlikely. Similarly, conditions affecting the renin-angiotensin system do not appear to consistently alter the nocturnal blood pressure (Baumgart *et al,* 1989a), and the diurnal variation in blood pressure of essential hypertensives is not affected by treatment with an angiotensin converting enzyme inhibitor (Mejer *et al,* 1986). Thus the cause for differences in the blood pressure pattern of patients with essential hypertension remains obscure.

Clinical Relevance of the Diurnal Rhythm

Knowledge of the diurnal rhythm of blood pressure, which can only come from ambulatory monitoring, appears to provide additional prognostic and diagnostic information. Although the effect of treatment of night-time pressures on prognosis is unknown, it seems likely that, where it is high, treatment which reduces BP throughout 24 hours will be beneficial. Patients with pre-eclampsia are more susceptible to crises during

the night (Oney & Meyer-Sabellek, 1990) and treatment should be given and monitored accordingly (Oney & Meyer-Sabellek, 1990). Following heart transplantation, patients may initially have hypertension during the night only (Sehested *et al,* 1990b), and again the need for treatment needs to be assessed and given accordingly.

Conversely, dippers may drop their blood pressure to normal levels during sleep and, particularly in the presence of left ventricular hypertrophy and ischaemic heart disease, may be at further risk if drug therapy induces a further significant reduction in blood pressure (Cruickshank *et al,* 1987; Cruickshank, 1988). It has even been suggested that unrecognised nocturnal hypotension may be one reason why the reduction in the incidence of myocardial infarction with anti-hypertensive treatment has been so disappointing (Floras, 1988). Although as yet unknown, it is possible that drug therapy in such patients should be tailored to reduce BP during the day only.

Ambulatory Monitoring - Normal Reference Data

Despite the wealth of information on ambulatory blood pressure monitoring in disease, the need to determine adequate normal reference values for 24-hour ambulatory blood pressure has only recently been addressed. Initial values for ambulatory blood pressure normality were based on relatively small numbers, and groups studied were often preselected by normal clinic blood pressure (Kennedy *et al,* 1983; Weber *et al,* 1984; Drayer & Weber, 1985; de Gaudemaris *et al,* 1987). A meta-analysis of studies on non-invasive ambulatory monitoring in normal subjects determined the day-time mean to be 122/77 mmHg, night-time pressure to be 106/64 mmHg and 24-hour mean ambulatory pressure to be 117/72 mmHg (Staessen *et al,* 1990). In a large epidemiological study O'Brien *et al* (1991c) have recorded ambulatory blood pressure in 815 employees of the Allied Irish Bank, aged 17-79. This population was not pre-selected, although subjects on antihypertensive drugs were excluded, and should therefore be reasonably representative of the population. The results were similar to those of this large meta-analysis: mean day-time pressure was 124/78, night-time 106/61 and 24-hour 118/72 mmHg. Significant differences in relation to age and sex were observed and means for different age groups and sex are provided.

Baumgart *et al* (1990), performing linear regression analysis on ambulatory blood pressure records of 1039 subjects to relate ambulatory pressure to their clinic pressure, calculated that mean day-time values of 135/85 were equivalent to clinic pressures of 140/90 mmHg. Data such as these provide reference values for non-invasive ambulatory

blood pressure monitoring, but the relevance of such data to morbidity and mortality is still not proven. However at the current time a day-time mean blood pressure of > 135/85 mmHg has been suggested as representing a hypertensive condition (The Scientific Committee, 1990).

Ambulatory Monitoring in Clinical Studies

Ambulatory blood pressure monitoring, by identifying and excluding "white coat" hypertensives (Pickering *et al,* 1988) and by improving the reproducibility of the blood pressure measurement (Trazzi *et al,* 1991) can assist in clinical trials and reduce the sample size necessary to show a significant blood pressure lowering effect (Conway *et al,* 1988). A sample size of only 16 should be sufficient to detect a reduction in 8/5 mmHg in a cross-over study (Conway *et al,* 1988). In addition, as ambulatory blood pressure monitoring appears to be devoid of a clinically significant placebo effect (Conway *et al,* 1988; Mutti *et al,* 1991), studies without a placebo limb may be possible, which could simplify the design and conduct of clinical studies of anti-hypertensive drugs (O'Brien *et al,* 1989a). However, recently published data from the Syst-Eur study (Staessen *et al,* 1994) has demonstrated a small reduction in 24 hour mean systolic blood pressure in patients treated with placebo over one year, suggesting that placebo-control is necessary in long-term studies.

A further advantage of ambulatory monitoring is the ability to indicate the duration of drug effect and the influence of drugs on nocturnal blood pressure (O'Brien *et al,* 1991d). In a clinical trial comparing once daily lisinopril (a long-acting ACE inhibitor) to twice daily captopril (a short acting ACE inhibitor) blood pressure control was maintained for 9 to 10 hours after each dose of captopril but then began to return towards baseline (Whelton *et al,* 1990). As a result blood pressure reduction over 24 hours was greater with lisinopril. Similarly in a comparison of the anti-hypertensive effect of beta-blockers (Floras *et al,* 1982), atenolol was shown to reduce blood pressure throughout 24 hours, while the anti-hypertensive effect of pindolol lasted only 15 hours and metoprolol 12 hours.

Information such as this is only available from clinical trials involving ambulatory monitoring and its routine use in the evaluation of drug efficacy has been advocated (O'Brien *et al,* 1991d).

Clinical Applications of Ambulatory Monitoring

Whilst ambulatory blood pressure monitoring may not be necessary in individuals with moderate to severe hypertension or with evidence of target organ damage, in whom the benefits of treatment are clear, it is a valuable technique in the assessment of borderline hypertension (Pickering & James, 1989), to help exclude "white coat" hypertensives and target those who will benefit most from treatment (Pickering *et al,* 1988). It should also be regarded as an initial investigation in the evaluation of apparently resistant hypertension when there is no evidence of target organ damage (Pickering, 1988; Metia *et al,* 1990), both to document the size of the "white coat" response and to demonstrate the degree and duration of antihypertensive drug action.

Symptoms suggestive of hypotension due to antihypertensive medication can also be investigated, when symptomatic marked reductions in blood pressure in response to taking medication may be identified (White, 1986).

Episodic hypertension may cause concern, as it can indicate adrenergic excess. If phaeochromocytoma is suspected, ambulatory monitoring may document episodic hypertension, which could otherwise be missed by clinical evaluation (Imai *et al,* 1988a). Episodic hypertension may also be associated with anxiety syndromes, and such patients can present with a variety of cardiovascular symptoms. Ambulatory monitoring may help in the identification of such patients (White & Baker, 1986).

Ambulatory monitoring may help in the evaluation of patients with type 1 (Wiegmann *et al,* 1990) and type 2 (Hansen *et al,* 1991) diabetes mellitus, when early intervention with blood pressure lowering drugs may be of benefit. It has also been recommended for the diagnosis of hypertensive disease in pregnancy (Margulies *et al,* 1989) and particularly in pre-eclampsia (Oney & Meyer-Sabellek, 1990). However, the lack of normative data in these populations must hamper the interpretation of ambulatory blood pressure results.

More widespread use of ambulatory monitoring techniques as part of the routine evaluation of hypertensive patients cannot be recommended until more information about the relationship of data derived from ambulatory blood pressure monitoring to morbidity and mortality is available. On-going prospective studies should provide this information in the next few years (Clement, 1989).

New Methods of Blood Pressure Measurement

Application of the plethysmographic method first described by Penaz has provided a non-invasive means of measuring blood pressure continuously (the Finapres system) (Boehmer, 1987). Arterial pulsation in a finger is detected by a photoplethysmograph under a pressure cuff. The size of the artery is measured when its internal pressure (i.e. arterial pressure) equals external cuff pressure. This point, when transmural pressure equals zero, is maintained by continuous, automatic adjustments of external cuff pressure. These adjustments parallel intra-arterial pressure variations and algorithms determine the systolic, diastolic and mean arterial pressures (Boehmer, 1987). The pressures so determined appear to reflect intra-arterial pressure (Imholz *et al,* 1988), though under-estimating indirect brachial artery pressure (Takahashi *et al,* 1990).

This device appears to accurately follow pressure changes over time and as such has been of particular interest to anaesthetists (van Egmond *et al,* 1985; Gibbs *et al,* 1991) and obstetricians (Kinsella *et al,* 1989; Epstein *et al,* 1989). It is also of use in clinical research studies monitoring blood pressure changes over short time intervals (Christen *et al,* 1990). However, its accuracy in routine clinical use remains unproven and there is evidence that digital blood pressure is influenced by the severity of hypertension and anti-hypertensive drugs (Takahashi *et al,* 1990), when peripheral circulation may be impaired, and by diseases affecting the peripheral circulation (Kurki *et al,* 1990).

A prototype ambulatory version of this device has recently been developed which, although still prone to the problems detailed above, has the potential to allow continuous non-invasive blood pressure monitoring over 24 hours (Schmidt *et al,* 1992; Imholz *et al,* 1993) with less disruption of sleep and more accurate information on blood pressure variability. However, this instrument is bulky, expensive and still to be formally validated. Nonetheless if early promise is confirmed it could prove to be a valuable additional tool in the study of cardiovascular disease.

A technique for indirect blood pressure measurement based on wave form analysis of the Korotkoff signal has also been described - the K2 technique (Blank *et al,* 1988). The potential advantage of this system is its dependence on pattern recognition, rather than the absolute level of sound, which varies widely from one individual to another (Pickering, 1989). This technique is, however, still in the developmental stage.

Conclusions

Although careful measurement of blood pressure with stethoscope and mercury sphygmomanometer is a valid and accurate technique, there are many potential sources of error, due to both equipment and methodology. More importantly, the inherent variability of blood pressure itself, and its tendency to increase in the presence of medical and nursing staff, means that clinic measurement cannot reliably reflect the blood pressure load affecting the individual patient. With the development of reliable electronic sphygmomanometers which have a reasonable standard of accuracy, patients can be taught how to measure their own blood pressure in their normal environment over several days. In addition to providing information on an individual's blood pressure profile, home measurement is a valuable opportunity to educate patients and can improve compliance. By reducing observer bias electronic sphygmomanometers are also of use in clinical and epidemiological studies. Unfortunately many of the electronic devices marketed to date are unreliable and no machine should be purchased unless supported by data on its accuracy from a reliable and independent source.

Newer techniques for the non-invasive measurement of ambulatory blood pressure now allow us to obtain a large number of measurements over 24 hours, including during sleep. This technique is safe, can be repeated and is reproducible. Information on the variability, and particularly the diurnal variation, of blood pressure is also obtained. The evidence that these measurements provide prognostic information over and above the clinic pressure is growing and on-going prospective clinical trials should help delineate the place of ambulatory monitoring in the diagnosis and management of essential hypertension. Again, it is imperative that these devices are validated prior to use and the publication of guidelines on methodology for their evaluation is a great advance in this regard.

"White coat" hypertension appears to be a common phenomenon and, while not synonymous with normotension, may indicate a substantially lower cardiovascular risk. It may, therefore, be possible to target antihypertensive therapy at those who will benefit most. Although this equipment is expensive, this may well be offset by the financial, therapeutic and social advantages of not treating thousands of individuals unnecessarily.

Ambulatory or home monitoring of blood pressure should also be an integral part of the evaluation of apparently resistant hypertension, and can be valuable in the differential diagnosis of episodic hypertension.

Ambulatory monitoring has proved to be a valuable research tool. Preliminary clinical trials of new anti-hypertensive agents should be possible with smaller numbers and without a placebo limb. Information on the action of such agents over the whole 24 hours is available, and may become of increasing importance if preliminary data on the prognostic importance of an absent nocturnal dip in blood pressure is borne out in prospective studies. New methods of blood pressure measurement being developed may improve the diagnostic accuracy of such devices further, and allow continuous non-invasive ambulatory monitoring.

We have come a long way since Reverend Hales first measured blood pressure in animals, but our understanding of the significance of blood pressure measurements in man remains far from complete. In particular, the importance of blood pressure changes during sleep remains uncertain. The recent description of the non-dipping blood pressure profile, its apparent association with target organ damage, and its increased prevalence in secondary hypertension, implies that important diagnostic and prognostic information may be imparted by knowledge of the diurnal blood pressure profile. This hypothesis forms the basis of this thesis.

Outline of Thesis

The technique of ambulatory blood pressure monitoring has progressed from being predominantly a research tool to an accepted and often essential investigation in the assessment of the hypertensive patient. The development of methods of confirming the accuracy of these devices in routine clinical practice has been an essential pre-requisite of this, and protocols for validating these devices have now been agreed. Several monitors have been rigorously assessed and deemed suitable for clinical use, including the SpaceLabs 90207 used for the majority of the work described here. However, the need to validate such equipment for use in particular patient groups has recently been emphasised, yet at the outset of this study no device had been validated in the presence of cardiac arrhythmia, and, in particular, in patients with atrial fibrillation, who are known to present particular diagnostic difficulty. In Chapter 2, I compare the performance of two ambulatory blood pressure monitors and two electronic sphygmomanometers to measurements made by a trained observer with a mercury sphygmomanometer in patients with controlled atrial fibrillation, and demonstrate major errors associated with the use of electronic measuring devices.

Activity is a major determinant of blood pressure, and differences in the pattern of activity on different monitoring days can have a major impact on the reproducibility of the diurnal blood pressure profile. Moreover, the onset of sleep is probably the major factor influencing the nocturnal fall in blood pressure. A method to quantify activity, relate this to changes in blood pressure, and allow the measurement of sleep time, could therefore improve the precision with which changes in blood pressure over 24 hours are assessed. In Chapter 3, I explore the potential of wrist worn activity meters to achieve these goals. The impact of a change in the arbitrary definition of day and night periods on the determination of diurnal blood pressure variation is assessed and compared to that calculated on the basis of activity-derived sleep time. The reproducibility of ambulatory blood pressure monitoring and the ability of activity monitoring to influence this is also examined.

Blood pressure has a Gaussian distribution in the population, and the diagnosis of hypertension is dependant on an arbitrary definition of "high" blood pressure. This fact, although now accepted dogma, was the centre of a major debate amongst those at the forefront of hypertension research for many years, yet much published work on diurnal blood pressure variability relies on the division of the population into two groups, "dippers" and "non-dippers". In Chapter 4, by examining the frequency distribution of the nocturnal dip in blood pressure of all patients referred for ambulatory blood pressure monitoring over a 4 year period, I attempt to determine whether this distinction is as fallacious as that dividing the general population into "normotensive" and "hypertensive". This data is also used to study the impact of diagnosis, age, severity of hypertension and antihypertensive treatment on diurnal blood pressure variation.

One consistent observation from earlier work has been loss of the nocturnal fall in blood pressure in patients with pathological cortisol excess, but the mechanisms underlying this and the potential importance of the pituitary-adrenal axis in the control of diurnal blood pressure variability in subjects without hypercortisolaemia are not understood. The study of patients with hypopituitarism, who require lifelong cortisol replacement therapy, enables assessment of the effect of manipulation of exposure to cortisol within the physiological range. In Chapter 5, I examine the impact of modest changes in exposure to cortisol on the diurnal blood pressure profile of such patients.

Accelerated hypertension is frequently quoted as resulting in loss of the diurnal blood pressure rhythm, yet only one study, performed over 30 years ago, has studied the diurnal rhythm of such patients in any detail. Moreover, this condition normally results in

emergency or early admission to hospital, but little is known of the effect of hospitalisation *per se*. In Chapter 6, I study the ambulatory blood pressure profile of patients with accelerated phase hypertension before and after treatment, and compare this to patients with benign essential hypertension and to other patient groups requiring acute hospitalisation. The factors potentially governing changes in diurnal blood pressure variation in accelerated phase hypertension are discussed.

Both cardiac and renal target organ damage are correlated with blood pressure and the severity of hypertension, but the importance of nocturnal blood pressure elevation and blunting of diurnal blood pressure variation remains uncertain. Previous studies have either been limited in scope, or studied selected patient groups. In Chapter 7, I describe the results of a blood pressure screening exercise performed in a healthy, working population, from which a cohort of randomly selected subjects, weighted to include all those with elevated clinic pressures, were studied in detail. All underwent ambulatory blood pressure monitoring and measurement of their blood pressure response to isometric exercise. The relative importance of different measures of blood pressure and blood pressure variability is assessed by comparing each to measures of cardiac structure and function, assessed echocardiographically, and to urinary albumin excretion.

Hypertension and sleep apnoea commonly co-exist, and sleep apnoea syndrome is now known to be a common but still under-diagnosed condition in the general population. Sleep apnoea syndrome in its severe form has been shown to cause nocturnal hypertension and abolition of the diurnal blood pressure profile. In Chapter 8, the possibility that occult sleep apnoea in patients with essential hypertension accounts for attenuation of the nocturnal blood pressure dip is investigated. To determine whether nocturnal hypoxia itself influences the nocturnal dip, patients with chronic obstructive pulmonary disease were also studied.

Blunting of the diurnal blood pressure rhythm in patients left ventricular hypertrophy and in orthotopic cardiac transplant recipients has led to the suggestion that the heart has an active role in the control of blood pressure. Studies of patients with severe congestive cardiac failure, demonstrating reduction in diurnal blood pressure variability, have tended to confirm this view. In Chapter 9, I compare the blood pressure profile of patients with systolic heart failure to that of a randomly selected control group and study the impact of treatment with angiotensin converting enzyme inhibitors on the diurnal rhythm and on renal function of the heart failure patients.

In Chapter 10, these studies are considered together and the nature and potential clinical importance of diurnal blood pressure variability is discussed.

Methods and Materials

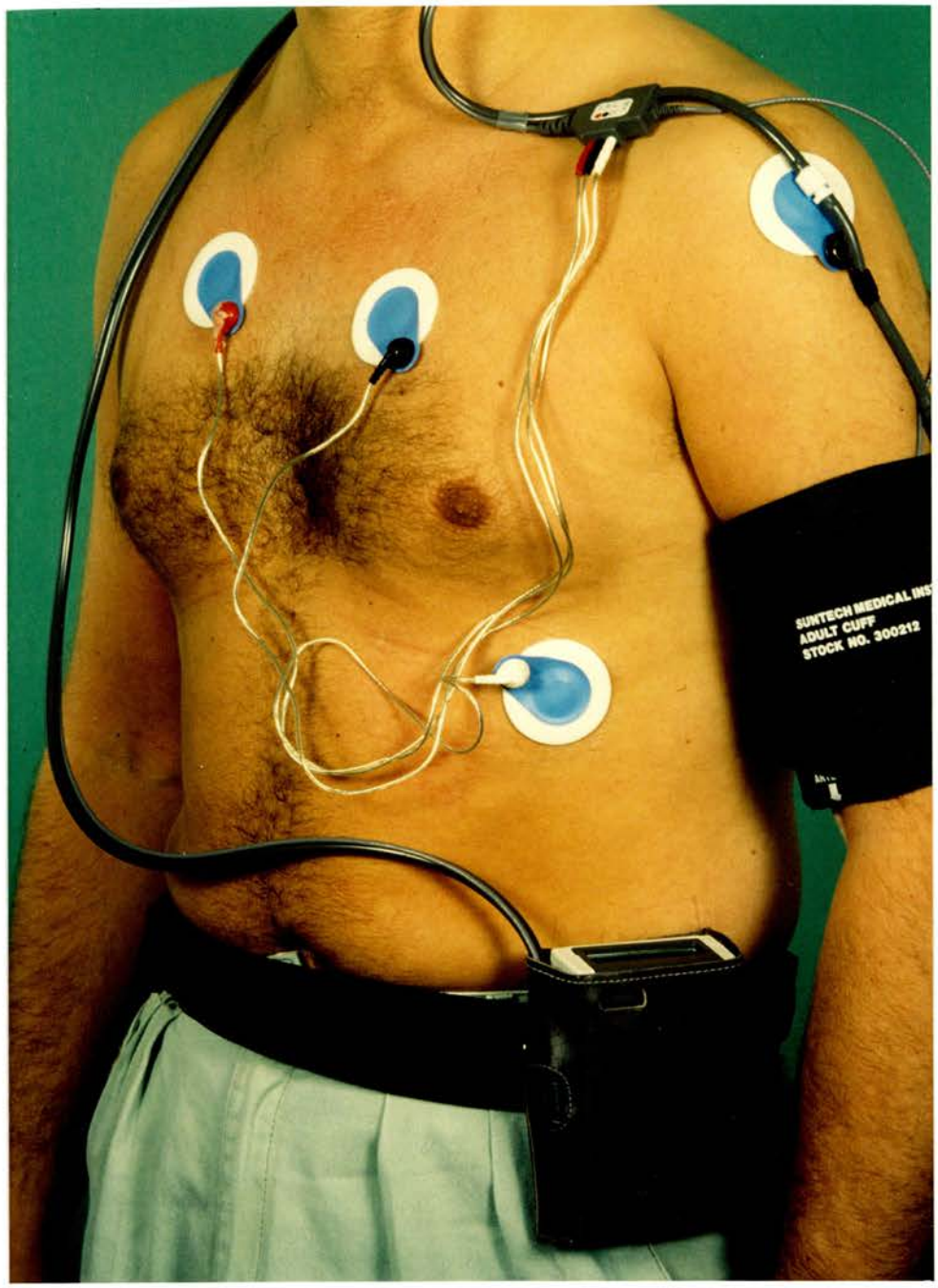
Detailed methodology is described in each chapter. Ethical approval was obtained for the individual studies from the Lothian Health Board Ethics of Medical Research Committee and informed consent was obtained from all patients prior to study. Patients described in Chapter 4 all underwent ambulatory blood pressure monitoring as part of their clinical assessment and therefore no specific consent was deemed necessary for this work.

Ambulatory blood pressure monitors were all fitted by myself or by a Research Nurse under my direction. Initial studies used the Accutracker monitor (Figure 1.1) which relies upon the detection of Korotkoff sounds via a microphone taped over the brachial artery. The auscultatory technique is prone to error resulting from extraneous noise, including muscle contraction and the transmission of noises from the motorised pump required to inflate the arm cuff. To minimise this potential source of error the Accutracker device requires the application of 3 ECG electrodes to the chest, enabling ECG gating, ensuring that only Korotkoff sounds occurring within the R-wave window are registered. This does, however, reduce the tolerability of this device.

From October 1990 the SpaceLabs 90207 monitor (Figure 1.2) was used for the majority of studies. This device uses an oscillometric technique for the recording of blood pressure, requiring application of an arm cuff only. The oscillometric technique relies upon internal algorithms to register waves generated by the brachial artery during cuff deflation. The initial wave form is taken as systolic pressure and the point of maximum oscillation mean arterial pressure. Diastolic pressure is calculated via pre- and post-maximal oscillations. Such monitors are smaller, lighter, easier to use and better tolerated than those requiring application of a microphone.

Monitors are capable of being programmed to measure blood pressure for a time interval between 6 minutes and 2 hours. In the studies described here, blood pressure readings were obtained every 30 minutes throughout the 24 hour period, or, where short-term blood pressure variability was of particular interest, every 15 minutes.

Figure 1.1 **Subject with the Accutracker 2 Ambulatory Monitor**



A microphone has been positioned under the arm cuff. ECG electrodes are required to enable R wave gating of the Korotkoff sounds, improving accuracy but reducing tolerance of the procedure.

Figure 1.2 **Subject with the SpaceLabs 90207 Ambulatory Monitor**

Blood pressure is monitored using the oscillometric technique, obviating the need for a microphone. As a result, cuff placement is less critical and accurate measurement when worn over a thin shirt, as shown here, is possible, improving tolerability. However, the equipment is normally positioned under clothing to make the procedure as unobtrusive as possible.

Blood pressure values with systolic BP of less than 70 mmHg or diastolic BP of less than 30 mmHg, or which were physiologically impossible, e.g. mean arterial pressure greater than systolic BP, were automatically rejected by monitor software. Where this occurred, or when movement artefact prevented accurate recording, a second reading was attempted after 3 minutes, minimising the number of failed readings.

Both devices are equipped with liquid-crystal displays, capable of displaying the blood pressure reading or an error signal if an erroneous reading is obtained. At the time of fitting, simultaneous measurement with a mercury sphygmomanometer, using a Y-connector attached to the monitor cuff, was performed to ensure satisfactory accuracy. Readings had to concur to within 5 mmHg to be deemed satisfactory. The device was then programmed *not* to display the blood pressure value, to remove the possibility of the subject observing blood pressure readings during the recording period and modifying behaviour as a result. Monitors were also programmed to emit a warning bleep immediately prior to each recording and subjects were instructed to keep their arm as still as possible during cuff deflation, minimising movement artefact. This facility was switched off from midnight until 7 am to minimise sleep disruption. An instruction leaflet detailing these points was supplied at the time of fitting. This incorporated a diary section where any problems encountered or unusual activity with the potential to significantly influence blood pressure were noted. Details of sleep time and quality were also requested.

At the end of the monitoring period data were downloaded onto personal computer using proprietary device interface and software. Data were then transferred to a DBase IV file, with further automatic data editing designed to eliminate physiologically implausible readings. Any value with a pulse pressure less than half the mean pulse pressure over the 24-hour period was rejected (Conway *et al,* 1988). Automatic calculation of hourly mean pressures, 24-hour mean, day-time (defined as 7 am to midnight), night-time (midnight to 7 am), wake and sleep blood pressures and diurnal blood pressure variability (percentage change from day to night or wake to sleep) was performed at the same time.

Further clinical data, including patient demographic details and other clinical information appropriate to that study, were entered into linked data base files at the time of monitor downloading.

CHAPTER 2

The Accuracy of Automated Blood Pressure Measuring Devices in Patients with Controlled Atrial Fibrillation

Background

Hypertensive patients with co-existent atrial fibrillation (AF) present particular diagnostic difficulty as there is beat to beat variation in the intensity of the Korotkoff sounds and the level at which they can be heard, increasing both intra- and inter-observer variability (Sykes *et al,* 1990). At present these patients cannot be monitored using electronic BP measuring equipment as these have not been validated in the presence of cardiac arrhythmia. In theory, by reducing observer variability and by increasing the number of available readings, these machines should be of particular value in this group of patients. However, clinical experience with these devices has suggested that they may be significantly less accurate in the presence of arrhythmia, and a single case report, in which a patient developed atrial fibrillation during the comparison of an oscillometric device to intra-arterial recording, supports this view (Caramella & Desmonts, 1986).

Introduction

The importance of properly evaluating blood pressure monitoring equipment before use is now accepted (O'Brien *et al,* 1990c) and the need to validate such equipment for use in particular patient groups recently emphasised (O'Brien *et al,* 1993). I have compared the accuracy of two electronic, semi-automatic sphygmomanometers and two ambulatory blood pressure monitors to the measurements of a trained observer using a Hawksley random zero sphygmomanometer in patients with controlled atrial fibrillation.

Patients and Methods

Thirty patients with electrocardiographically confirmed atrial fibrillation, identified as hospital in-patients, were studied. Two patients did not tolerate the repeated BP measurements required and were withdrawn, leaving 28 patients, 18 male and 10 female, mean age 72 ± 9 years, for analysis. All had a controlled ventricular rate, defined as a resting heart rate of less than 100 per minute with a pulse-apex difference of less than 10. All had normal arm circumference (less than 42 cm).

Both normotensive and hypertensive subjects were included, with blood pressures in the range 90-158/40-96 mmHg, mean $124 \pm 20/67 \pm 13$ mmHg.

Two ambulatory blood pressure monitors (ABPM) were tested: the Accutracker 1 ABPM which utilises a microphone to detect Korotkoff sounds, and the SpaceLabs 90207 ABPM which is dependant upon the oscillometric method. Two semi-automatic electronic sphygmomanometers were also tested (Table 2.1).

Table 2.1 **Devices Used in the Study**

1. Hawksley Random Zero Sphygmomanometer
2. Takeda UA-751 Digital Blood Pressure Meter (Oscillometric)
3. Copal UA-251 Auto-inflation Digital Sphygmomanometer (Korotkoff)
4. SpaceLabs 90207 Ambulatory Blood Pressure Monitor (Oscillometric)
5. Accutracker 1 Ambulatory BP Monitor (Korotkoff)

The performance of these instruments was assessed during a single sitting in all patients. Each patient had their BP measured twice with each test device and twice with the Hawksley random zero sphygmomanometer (HRZ) before and after each test device measurement. As the time taken to set up and calibrate the Accutracker ABPM is much longer than that required with the other devices, the initial measurement was made with this machine in all patients. Each patient also had three sequential measurements with the HRZ, enabling comparison of the HRZ as a "test" device to the electronic sphygmomanometers.

Statistical Analysis

The first reading obtained with each device was compared to the immediately preceding and following mercury measurements using the sequential same arm technique (Atkins *et al,* 1990). In this test, there is a basic assumption that the difference between these sequential readings may not be linear and the difference is calculated as follows: where the test device measurement lies between the first and third HRZ measurement, the difference is taken to be zero; otherwise the nearer of the HRZ readings is subtracted from the test value to give the difference. The proportion of machine readings > 5 mmHg different from the HRZ was then compared to that obtained by 3 sequential HRZ measurements, using Chi-squared test. Finally the variability of each measuring method was assessed by determining the standard deviation of the difference (s.d.d.) for the paired readings from each device, and the difference between the variability of each device was compared to that of the HRZ using Wilcoxan signed rank procedure.

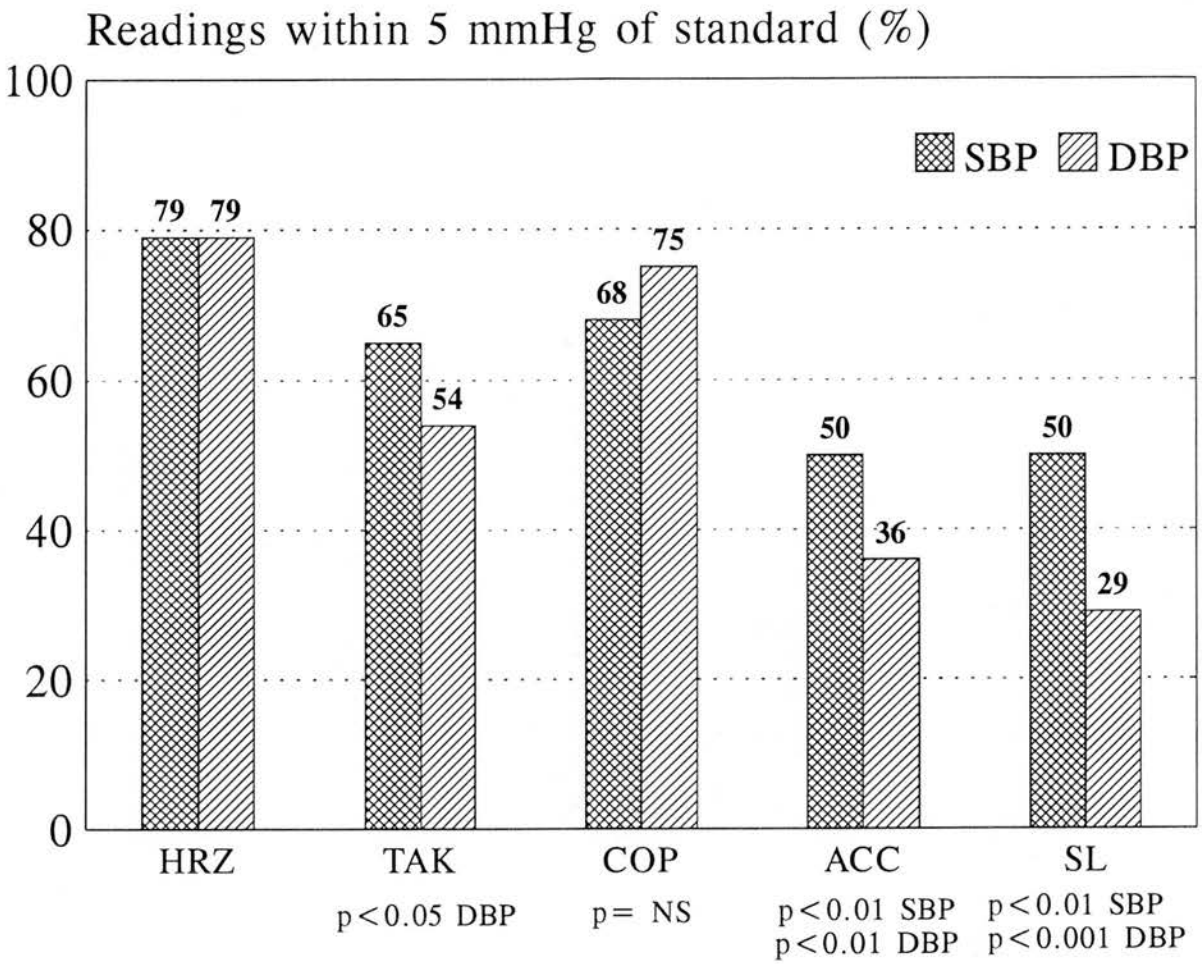
Results

Although BP readings could be obtained in all patients and on every occasion using the HRZ, readings could not be obtained with the Takeda and Copal electronic sphygmomanometers on 3 occasions each (5%), with the Accutracker on 8 occasions (14%) and with the SpaceLabs on 14 occasions (21%).

The results of sequential testing against the HRZ are given in Figure 2.1. Only the Copal electronic sphygmomanometer, which uses the Korotkoff technique, obtained a level of accuracy approaching that of three sequential HRZ measurements. The two ABPMs were markedly less accurate than the cheaper electronic sphygmomanometers.

Intra-patient variability with each device was assessed by determining the standard deviation of the difference from paired readings obtained with each device. The results are given in Figure 2.2. Although the differences observed did not achieve statistical significance, both ABPMs and the Takeda electronic sphygmomanometer demonstrated greater variability than HRZ while the Copal had a level of consistency comparable to paired HRZ readings.

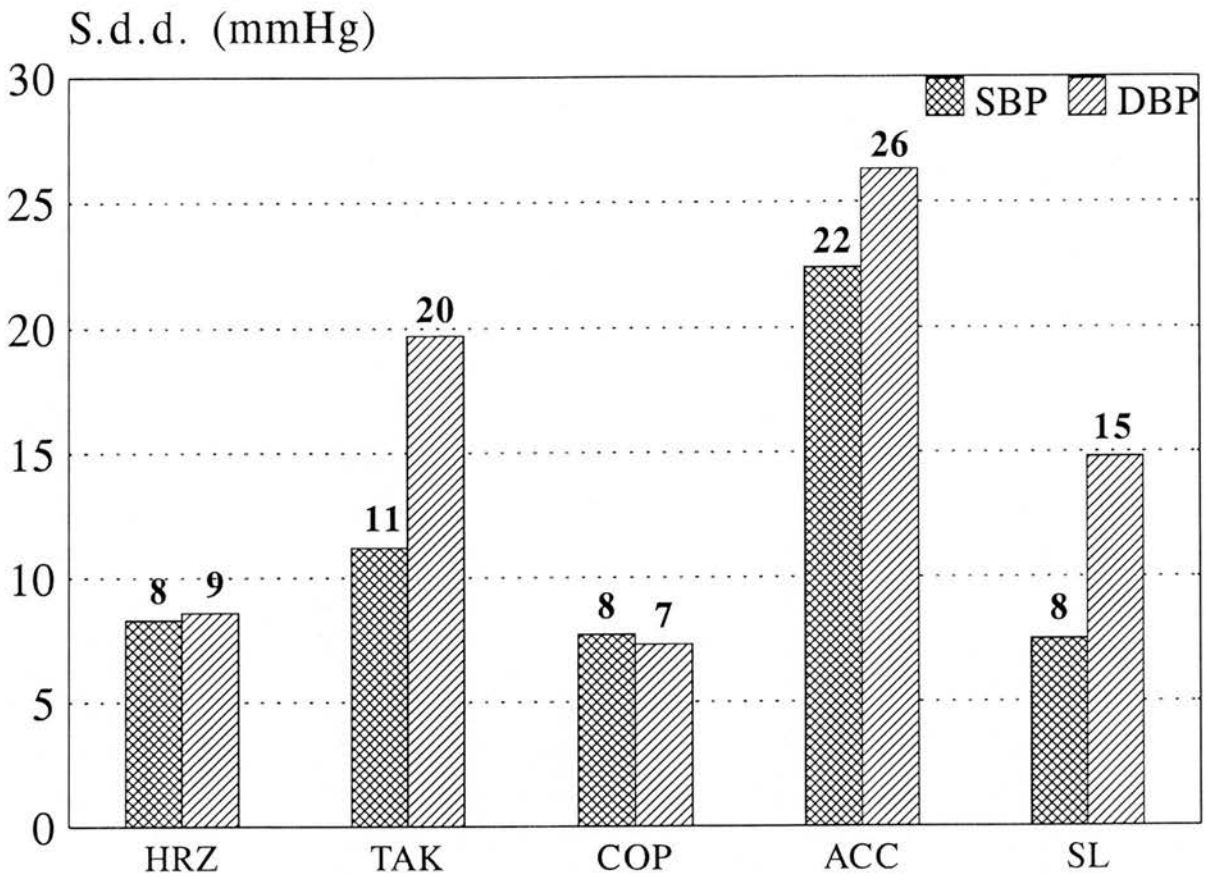
Figure 2.1 **Comparison of Blood Pressure Measuring Devices in Patients with Controlled Atrial Fibrillation**



Each device, including the Hawksley random zero sphygmomanometer, has been tested using the sequential same arm technique (Atkins *et al,* 1990). The proportion of readings falling within 5 mmHg of immediately preceding and following measurements obtained with the HRZ is expressed as a percentage for both systolic (SBP) and diastolic (DBP) blood pressure. The accuracy of each electronic device has been compared to the HRZ and statistical significance at the 5% level is given along the x-axis.

HRZ = Hawksley random zero sphygmomanometer
TAK = Takeda UA-751 Digital Blood Pressure Meter
COP = Copal UA - 251 Auto-inflation Digital Sphygmomanometer
ACC = Accutracker 1 Ambulatory BP Monitor
SL = SpaceLabs 90207 Ambulatory Blood Pressure Monitor

Figure 2.2 **Intra-patient Variability of BP Monitors in Patients with Atrial Fibrillation**



Each patient had their blood pressure measured twice with each device, both measurements being obtained within 120 seconds, leaving at least 30 seconds between readings. The standard deviation of the difference (s.d.d.) was calculated for each pair of readings for both systolic and diastolic BP. The variability of each electronic device was compared to paired readings obtained with the HRZ but did not achieve statistical significance.

Abbreviations as for Figure 2.1

Discussion

The use of semi-automatic and ambulatory BP measuring equipment is of proven benefit in the management of patients with hypertension and its use is increasing. Patients with atrial fibrillation form a group whose blood pressure is particularly difficult to assess, as beat to beat variation is much greater than normal. As such, automated BP measurement could be particularly valuable, as repeated measurements over a short time period would provide a better estimate of cardiovascular risk. However their use in such patients has not previously been validated.

I have tested 4 devices in patients with atrial fibrillation and found marked differences in their performance. One device, the Copal UA-251, appears to provide a level of accuracy equivalent to that of a trained observer using the Hawksley random zero sphygmomanometer.

While the use of the HRZ in validation studies has recently been criticised (Conroy *et al,* 1993), many workers feel that it does provide a satisfactory level of accuracy when used carefully and correctly (Various, 1993). Moreover, it does have the important advantage of reducing observer bias which, as I was also comparing intra-patient variability, was particularly important in this study.

Clearly, despite such concerns, the performance of three of these devices, all previously validated (albeit not all to current protocol standards) and shown to be accurate in patients with normal sinus rhythm (Jamieson *et al,* 1990; Appel *et al,* 1990; O'Brien *et al,* 1991b), is poor in patients with atrial fibrillation. The routine use of these devices in patients with AF cannot therefore be recommended. However, it is encouraging to note that one device, the Copal UA-251, does provide a satisfactory level of accuracy, and the use of such devices in the assessment of fibrillating patients with hypertension warrants further assessment. Unfortunately this particular device is no longer marketed.

Conclusions

Accurate measurement of BP with an electronic device is possible but the marked difference between devices and limited accuracy of the ambulatory blood pressure monitors tested here demonstrates the need to ensure that such devices are of proven accuracy in this patient group. As a result of this study, patients with atrial fibrillation have been excluded from routine clinical study and all subsequent research work.

CHAPTER 3

Simultaneous Ambulatory Blood Pressure and Activity Monitoring to Improve the Definition of The Diurnal Blood Pressure Profile

Background

Reproducibility of Ambulatory Blood Pressure Monitoring

The introduction of ambulatory blood pressure monitoring has improved our understanding of the variability of blood pressure and the nature of hypertension. Day-time mean ambulatory blood pressure is clearly more reproducible than clinic BP (Coats, 1990), presumably due to the greater number of available readings (Trazzi *et al,* 1991), and preliminary evidence suggests that it is also better able to define those at risk (Perloff *et al,* 1983), but this does little to improve the problem of separating "normal" from "high" blood pressure (Pickering, 1992b), and any cut-off value at which treatment is advised remains arbitrary. However, such improved reproducibility enables the comparison of different anti-hypertensive drugs with smaller numbers (Conway *et al,* 1988), and improves our confidence in the blood pressure lowering effect of a drug in the individual (Coats, 1990).

Unfortunately, within-subject variability is greater than that of a group mean (Pickering, 1990c; Bottini *et al,* 1992), and hence the pressure recorded in the individual is less reliable. Moreover, within-subject variability is greater still when the level of activity on two separate study days differs significantly (Pickering, 1990c). Indeed, activity (both physical and mental) is probably the main determinant of long-term blood pressure variability (Pickering, 1990d).

Diurnal Blood Pressure Variation

When deciding upon the level of cardiovascular risk in the individual, as determined by ambulatory blood pressure monitoring, physicians have traditionally relied upon the day-time mean pressure (The Scientific Committee, 1990). However, there is growing evidence that additional prognostic information is available if night-time or sleep blood pressure is also considered. Since the introduction of ambulatory blood pressure monitoring, it has been clear that blood pressure has a diurnal rhythm, with levels during sleep about 20% less than those during the day (Littler *et al,* 1975). This rhythm is generally preserved in essential hypertension, with an upward shift of the entire curve,

but has been noted to be absent in a substantial proportion of patients with secondary hypertension (Hany *et al,* 1987; Imai *et al,* 1990; Middeke & Schrader, 1994), and a minority of those with essential hypertension (O'Brien *et al,* 1988). This has led to the concept of two groups within the hypertensive population : "dippers" and "non-dippers" (O'Brien *et al,* 1988). As the potential pathological significance of a blunted nocturnal fall in blood pressure is explored, it has become clear that this distinction is of more than academic interest.

Kobrin *et al* (1984) studied 21 elderly (> 65 years) hypertensives and found a normal diurnal blood pressure in 14, but a reduced or absent fall in 7. All the non-dippers, but only 43% of the dippers, had clinical evidence of hypertensive or atherosclerotic complications (Kobrin *et al,* 1984). O'Brien *et al* (1988) later reported the frequency of stroke in a population of non-dippers to be 23.8%, compared to a frequency of only 2.9% in age, sex and weight matched dippers with a similar day-time blood pressure. Shimada *et al* (1992) have found asymptomatic hypertensive cerebrovascular disease, as assessed by brain magnetic resonance imaging, to be more closely correlated with sleep blood pressure than with wake or 24 hour blood pressure.

Hypertensive heart disease may also be influenced by the diurnal variation of blood pressure. Gosse *et al* (1988a) have found night-time BP to be the best correlate of left ventricular mass in a group of 24 treated hypertensives, while Verdecchia *et al* (1990) found greater left ventricular mass in hypertensive patients with a reduced nocturnal dip, and an inverse correlation between LV mass index and the nocturnal dip. The LV mass of hypertensive dippers was similar to that of normotensive controls, suggesting that the nocturnal dip may prevent or delay the development of left ventricular hypertrophy.

Thus knowledge of the diurnal rhythm of blood pressure may provide additional prognostic information in patients with essential hypertension.

The Definition of Dippers and Non-dippers

Despite the increasing importance given to differences in the diurnal variation of blood pressure, there is no clear consensus as to how this should be best defined. Although several complex statistical methods for describing diurnal variation have been described (Streitberg *et al,* 1989; Streitberg & Meyer-Sabellek, 1990), most workers appear to use the difference between day and night blood pressure as a measure of the nocturnal dip (The Scientific Committee, 1990), and recent papers have variously defined night for this purpose as 8 pm - 6 am (Verdecchia *et al,* 1990), 8 pm - 8 am (Hany *et al,* 1987), 10 pm

- 6 am (Middeke & Schrader, 1994), 12 midnight - 8 am (O'Brien *et al,* 1988), or sleep (Shimada *et al,* 1990).

Unfortunately, the measurement of sleep blood pressure and the day-night blood pressure dip appears to be less reproducible than the day-time mean pressure (Cox *et al,* 1991b). In part, this may be the result of this artificial divide of the hypertensive population into "dippers" and "non- dippers", which relies on an arbitrary cut-off value. As a result, relatively minor variation in the nocturnal dip of an individual whose day-night fall is close to this point can result in a change in "dipping" status. As the nocturnal dip appears to be distributed unimodally in the population (Stewart & Padfield, 1992) (see Chapter 4) any associated risk is almost certainly graduated, and hence such a division is probably inappropriate. Moreover, many studies have artificially divided the 24 hour period into day and night using fixed time periods. Variation in the chosen definition may dramatically affect the prevalence of "non-dipping" and any change in the sleeping pattern of the patient will also reduce the reproducibility of the measure. To try and overcome this problem some workers have excluded the transition periods between day and night, defining day as 10 am - 11 pm and night as 1 am - 7 am (O'Brien *et al,* 1991c), but, while possibly useful in population studies, individual exceptions to this will still exist in practice, limiting its clinical relevance. Thus, division of the 24 hour period into sleep and wake may be preferable, but the problem of defining these remains.

Electronic Activity Monitoring

There are now a variety of wrist-worn activity monitors (actigraphs) available, designed to sense gross body motion and quantify activity, which are ideally suited to the simultaneous study of activity during ambulatory blood pressure monitoring (Van Egeren, 1991). We have used the Gaehwiler actigraph (Figure 3.1), a solid state device little bigger than a wrist watch, which is unobtrusive and easily tolerated by the patient. It determines an activity value at 125 ms intervals and stores the total activity over a pre-set measuring period (typically 10 seconds) as a one-byte value, in the range 0-255.

The change in mean activity over 24 hours closely parallels that of blood pressure in a group (Van Egeren, 1990), although there is wide variation in the strength of the relationship between individuals (Van Egeren, 1991). As activity normally falls dramatically with the onset of sleep, the actigraph can also be used to objectively measure sleep time, and such devices have been shown to provide an estimation of sleep time with accuracy approaching that of EEG scoring (Mullaney *et al,* 1980).

Figure 3.1 **The Gaehwiler actigraph**

This monitor, normally worn on the wrist of the non-dominant arm, is initialised via a computer interface and is capable of storing up to 4 days of activity data. Data are downloaded directly onto computer for analysis at the end of the monitoring period.

Introduction

Criteria used for analysis of the nocturnal dip vary widely in published work and no diagnostic criteria for "dipping" have been set. However, guidelines from an International Consensus Meeting on ambulatory blood pressure monitoring have recommended that the day-time period run for 15 ± 2 hours and night-time for 9 ± 2 hours (The Scientific Committee, 1990). To determine whether the extremes of these criteria could have a significant effect on the diurnal rhythm of the population described, a cohort of patients who had undergone ambulatory monitoring for varied indications was examined retrospectively and the proportion of non-dippers calculated for each of 3 definitions of night-time : 8 pm - 7 am, 10 pm - 7 am and 12 midnight to 7 am.

A further group of patients referred for assessment of hypertension was then studied prospectively to determine whether simultaneous ambulatory monitoring of activity and blood pressure could improve the definition of the diurnal rhythm, with activity-based sleep-wake blood pressure values compared to those determined using these pre-set cut-off points for day and night.

The strength of the relationship between activity and blood pressure has also been studied in a smaller group to determine the optimal actigraphic measurement for activity-blood pressure regression analysis, with a view to adjusting blood pressure for activity, and the ability of this technique to reduce within-patient variation in ambulatory blood pressure has been assessed.

Patients and Methods

1. When is Night-time ?

Two hundred and fifty seven individual ambulatory BP recordings, performed with either the Accutracker 1 or SpaceLabs 90207 monitors, were analysed retrospectively. Eight were excluded as technically unsatisfactory, leaving 249 for final analysis. Patients age ranged from 18 - 82 years, 53 (21%) were normotensive, 114 (46%) had primary essential hypertension and the remainder a variety of causes of secondary hypertension. Non-dippers were classified as subjects whose night-time BP was $< 10\%$ lower than day-time BP for both systolic and diastolic BP. Three separate day and night blood pressure were calculated, with day-time defined as (i) 7 am - 8 pm, (ii) 7 am - 10 pm and (iii) 7 am - 12 midnight, all of which would be within the guideline limits set by the first Consensus meeting (The Scientific Committee, 1990). The change in the proportion of subjects

classified as non-dippers was then analysed using McNemar's test (with Yates' correction).

2. Analysis of Sleep Blood Pressure Using Activity Monitoring

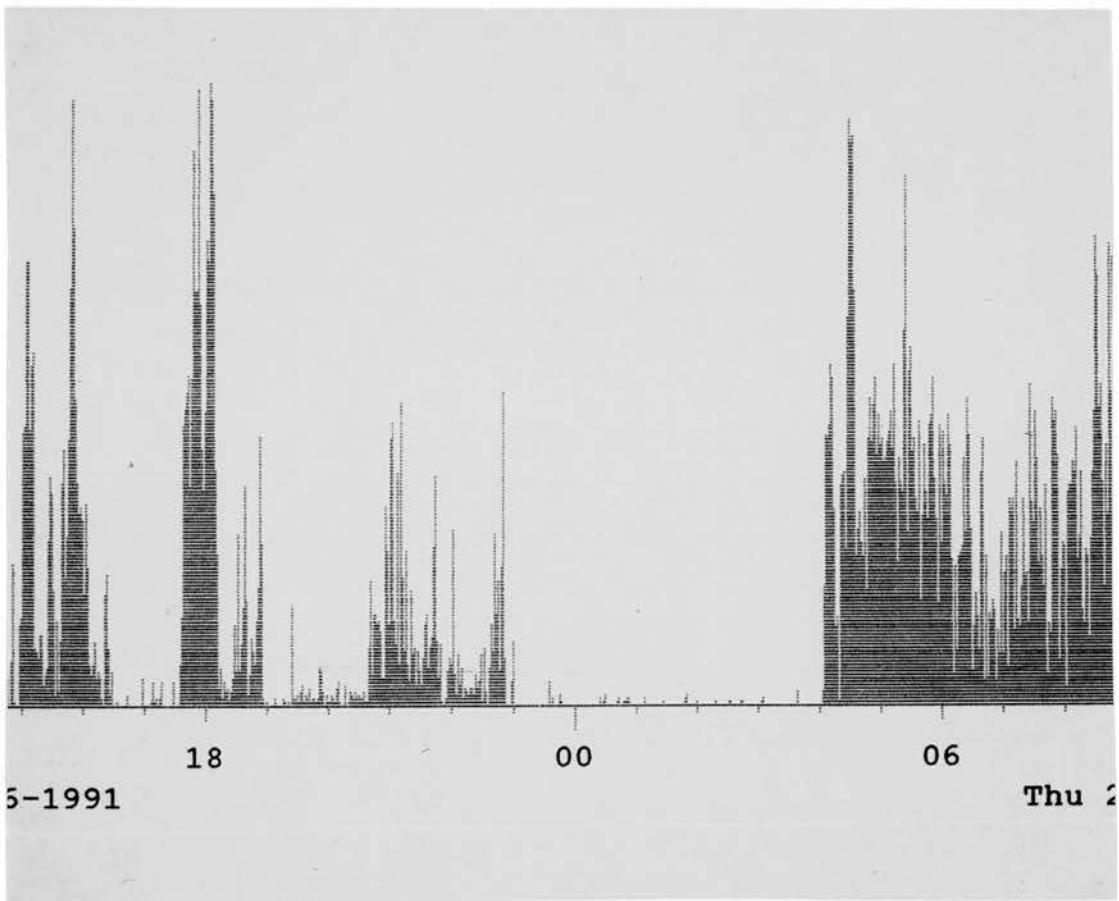
The data of all patients referred to our department for ambulatory blood pressure monitoring who had simultaneous activity monitoring using the Gaehwiler actigraph were then analysed. Three hundred and nineteen patients with technically satisfactory activity and blood pressure recordings were included in the analysis. All had ambulatory blood pressure measured using the SpaceLabs 90207 device with blood pressure recordings every 30 minutes over 24 hours. Activity was measured using the Gaehwiler wrist actigraph recording over a 10 second time period.

At the end of the recording period, data from both devices were down-loaded onto personal computer for analysis. The activity data were manually scored to differentiate wake from sleep. Total cessation of activity (score = 0) for a minimum of 300 seconds was taken as the onset of sleep, and the first prolonged (greater than 90 second) burst of activity not immediately followed by a return to "sleep" taken as wake (Figure 3.2).

Using software designed in our department, the blood pressure data were then transferred to DBase IV data base management system with automatic elimination of rogue readings according to a pre-set protocol (those which were either physiologically impossible or had a pulse pressure less than half the mean pulse pressure over the 24 hour period (Conway *et al,* 1988)) and automatic calculation of mean wake, sleep, day-time and night-time blood pressures, as defined above.

To determine which arbitrary day-night limit most closely matched the actigraph-determined wake-sleep figure, paired t-test comparison of wake and sleep blood pressure to each day and night blood pressure respectively was performed, using the Minitab statistical software package. The nocturnal dip, defined as the percentage difference between mean day-time and night-time BP, and the proportion of non-dippers, were also compared for each definition.

Figure 3.2 **Wrist Actigraph-Derived Activity Score Over 24 Hours**



Wrist actigraph data presented graphically over a 24 hour period. The abrupt fall in activity co-incident with the onset of sleep is readily appreciated, with estimated sleep period on this recording 2258 to 0405.

3. Activity Monitoring to Improve the Reproducibility of the Diurnal Rhythm

To study the relationship of activity to blood pressure in more detail and determine whether correction for activity could improve the reproducibility of ambulatory blood pressure recordings, 30 patients, 13 female, mean age 52 ± 2 years, were asked to undergo repeat monitoring 1-18 days (mean 8) apart. The monitoring procedure was performed as detailed above on both occasions. As I hoped to determine whether the technique had a potential role in routine clinical practice, no attempt was made to standardise activity on the two monitoring periods.

Ambulatory blood pressure parameters from the two monitoring days were compared and the standard deviation of the difference calculated as a measure of the reproducibility for each of the calculated methods.

Both activity and BP files were then written in ASCII format and analysed using a Fortran programme developed for the purpose. The following activity parameters were calculated and correlated to each blood pressure measurement :-

1. Mean activity in the 5, 10, 20 and 30 minutes prior to each BP measurement.
2. Maximum activity value within each of these time periods.
3. Maximum activity in any 2 minute period within each time period.
4. Maximum activity in any 4 minute period within each time period.
5. Mean weighted activity in each time period, with increasing weight given to activity values closest to the measurement.

As the resulting activity values were asymmetrically distributed, logarithmic transformation was performed before correlating each to the corresponding BP values. The marked fall in both activity and blood pressure during sleep could result in spuriously positive correlations if the entire 24 hour period was analysed, therefore wake and sleep periods were analysed separately. Correlations during sleep were very small and further analyses therefore concentrated on wake data only.

Correlation coefficients varied widely, both between patients and, to a lesser extent, within patients. Three activity features were selected as being most closely related to blood pressure in the patients taken as a whole: (i) Maximum activity within preceding 5 minutes, (ii) maximum activity over 2 minutes within the preceding 10, and (iii) mean weighted activity over the preceding 30 minutes. These features were then used to form two multiple regression models :-

(a) A model was used to adjust each individual blood pressure reading for activity within each patient record. This fitted separate slopes for each activity feature and made adjustments such that the resulting values reflected blood pressure at the mean daily activity for each patient record.

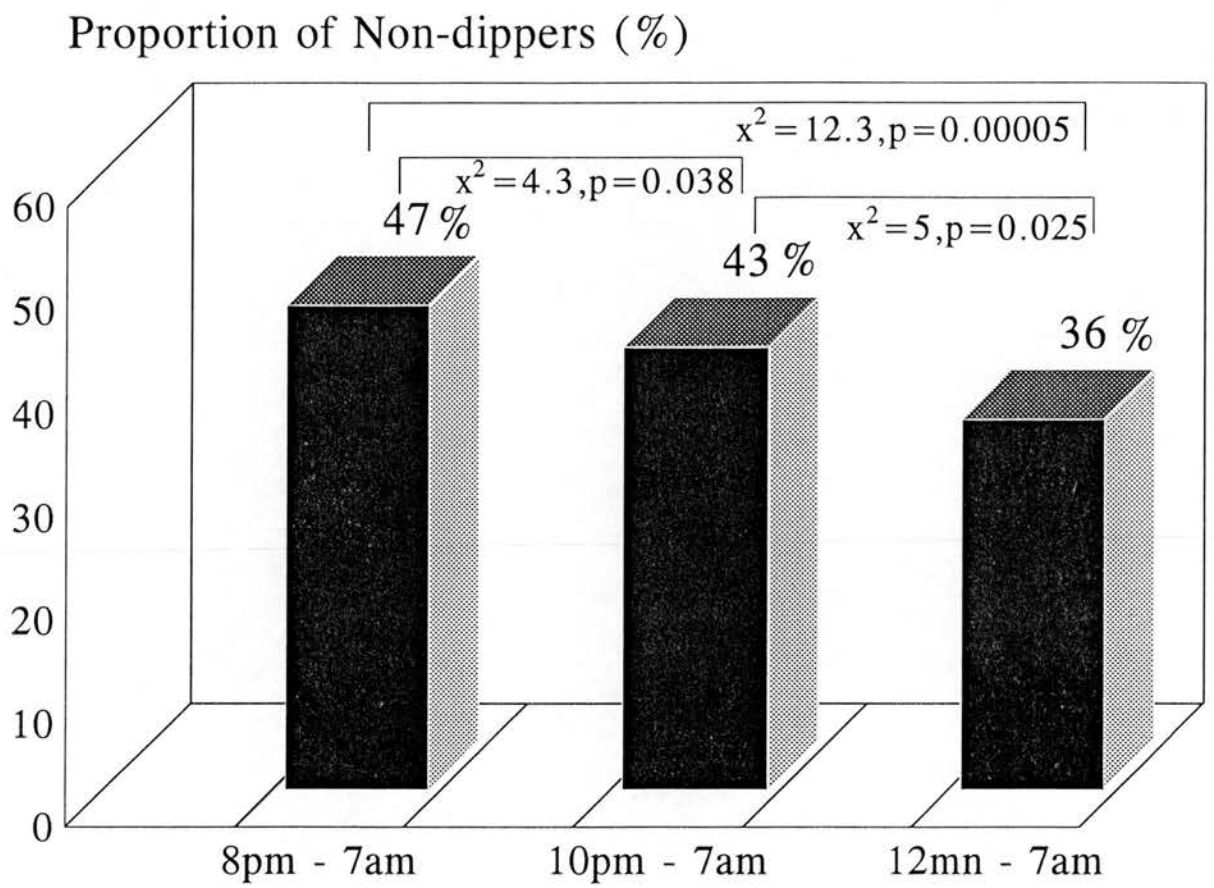
(b) A second model fitting the 3 activity features was used to model the mean wake blood pressure values. As the first two features did not significantly improve a model using the weighted mean activity value alone, this simpler model was used to adjust for activity such that the resulting blood pressure reflected that expected at the average mean daily activity for all patients.

Results

1. When is Night-time ?

The number of subjects classified as non-dippers fell progressively as the start of night-time rose, from 118 (47%) at 8 pm, to 106 (43%) at 10 pm and 91 (36%) at 12 midnight. The change in defined proportion was statistically significant for each inter-group comparison (Figure 3.3). The proportion of non-dippers defined was relatively high, reflecting the heterogeneous nature of this group, with a large number of patients with severe and/or secondary hypertension.

Figure 3.3 **The Prevalence of Non-Dipping Defined by Different Definitions of Day and Night**



The prevalence of non-dipping falls progressively as the start of night-time increases. The proportion of non-dippers described by each definition is significantly different from the other two groups.

2. Comparison of Sleep BP

The comparison of mean wake and sleep values and the nocturnal dip in the 319 patients with hypertension are detailed in Table 3.1. Wake blood pressure was most similar to day-time defined as 7 am - 10 pm, but all day-time values were similar, being within 1 mmHg of the wake value. In contrast, larger differences were seen in sleep BP, range 1-6 mmHg, and all were higher than the activity derived sleep figure, with 12 midnight - 7 am being most closely matched. The nocturnal dip for wake-sleep also matched 12 midnight - 7 am more closely (Table 3.1).

The change in the proportion of non-dippers with the varying definition of night-time was less pronounced in this population, with 21% of subjects non-dippers when relying on sleep time. A trend for the proportion to increase as the start of night-time fell was still apparent (Figure 3.4). In this analysis the proportion of non-dippers defined by 10 pm - 7 am was not statistically different from that defined by sleep.

3. Reproducibility of Diurnal Blood Pressure Variation

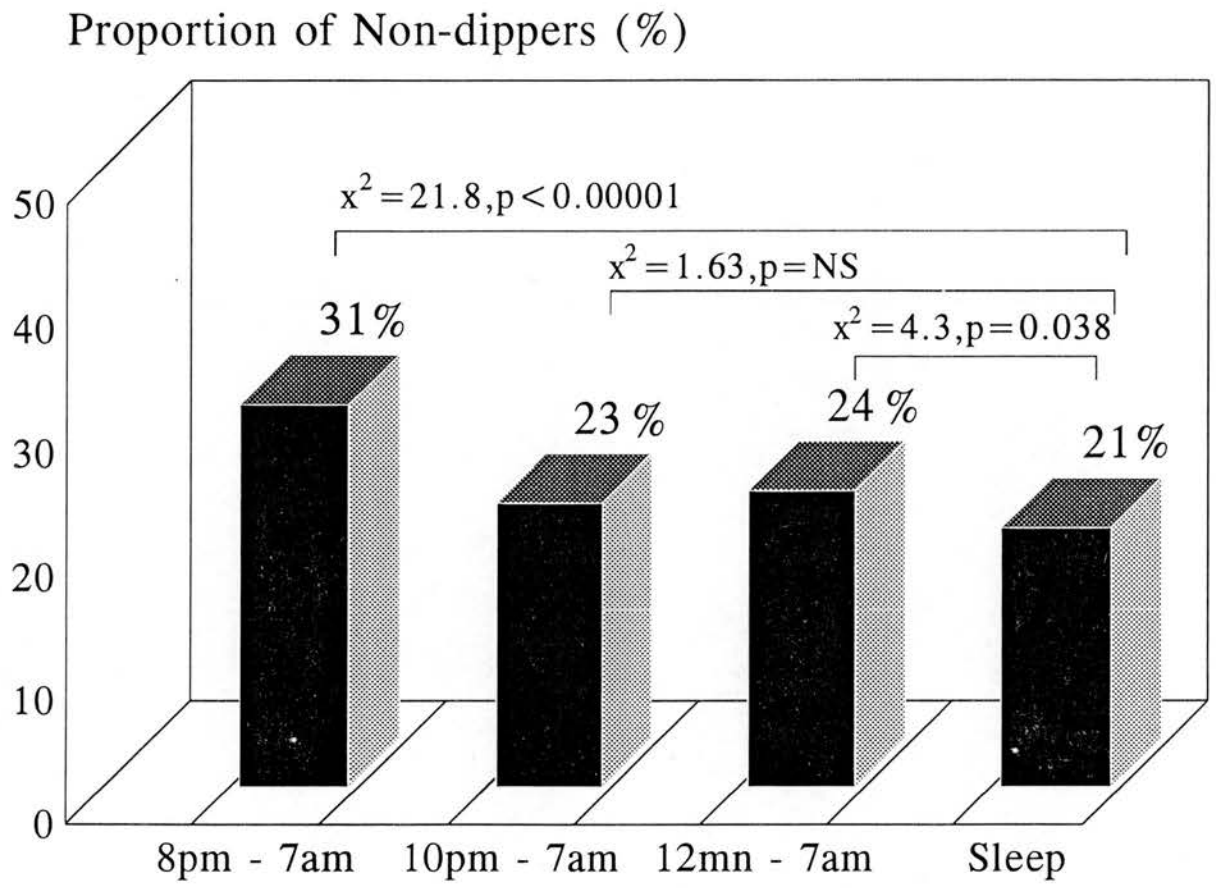
Comparative data from the 30 patients monitored on two occasions, demonstrating the effect of the differing time periods on reproducibility, is given in Tables 3.2 and 3.3. Reproducibility was similar regardless of the method used. However, absolute differences in measures of diurnal blood pressure variability were smaller when using the activity derived data, despite the nocturnal dip being largest with this method.

Table 3.1 **Comparison of Mean Wake and Sleep BP to Three Arbitrary Day-Night Values**

	Activity	BP 7am-8pm	t	BP 7am-10pm	t	BP 7am-12mn	t
Wake SBP (mmHg)	145.7	146	-2.3	145.8	-1.4	145	6.6
Wake DBP (mmHg)	89.2	89.9	-6.3	89.5	-4	88.7	6.7
Sleep SBP (mmHg)	126.7	133	-20.1	130.4	-14.7	128	-5.7
Sleep DBP (mmHg)	74.2	78.6	-19.2	76.8	-14	75	-5.6
Nocturnal Dip SBP (%)	12.9	8.8	16	10.5	12	11.7	6.8
Nocturnal Dip DBP (%)	16.6	12.3	14	14.1	10.6	15.1	6.7

The *t*-statistic reflects the result of *paired t-test* comparisons of each value to sleep/wake and is used as a measure of parity between the two values (closeness of *t* values to zero indicating the extent of agreement). All are highly statistically significant ($p < 0.01$), with the exception of 7 am - 10 pm and wake SBP.

Figure 3.4 **Prevalence of Non-Dipping Using Sleep/Wake Times and Arbitrary Definitions of Day and Night**



The proportion of non-dippers was smallest using activity-derived sleep and wake times, and this proportion was significantly different from that using night-time defined as either 8 pm - 7 am or 12 midnight - 7 am.

Table 3.2 **Reproducibility of Ambulatory Blood Pressure - Variation Dependant on Time**

Mean ± S.E.M.	Day 1	Day 2	Absolute Difference	Standard deviation of the difference (s.d.d.) mmHg.
Wake systolic BP (activity derived)	147±2.7	145±3	2.7	7.1
Wake diastolic BP (activity derived)	91±1.8	90±2	0.8	3.8
Sleep systolic BP (activity derived)	125±2.5	123±2.6	1.9	6.3
Sleep diastolic BP (activity derived)	73±1.7	73±1.9	0.7	3.9
Day systolic BP (7am - 8pm)	147±2.6	145±3	2.7	7.3
Day diastolic BP (7am - 8pm)	91±1.7	90±2	0.8	4.0
Night systolic BP (8pm - 7am)	131±2.5	129±2.7	1.5	6.4
Night diastolic BP (8pm - 7am)	78±1.7	77±1.8	0.3	3.9
Day systolic BP (7am - 10pm)	147±2.6	144±3	2.7	7.0
Day diastolic BP (7am - 10pm)	90±1.8	90±2	0.5	4.0
Night systolic BP (10pm - 7am)	128±2.5	126±2.7	1.6	6.7
Night diastolic BP (10pm - 7am)	75±1.7	75±1.8	0.6	4.0
Day systolic BP (7am - 12mn)	146±2.6	143±3	2.6	6.8
Day diastolic BP (7am - 12mn)	90±1.7	89±2	0.7	4.1
Night systolic BP (12mn - 7am)	125±2.6	124±2.7	1.6	6.7
Night diastolic BP (12mn - 7am)	74±1.8	73±1.9	0.7	3.7

Table 3.3 **Reproducibility of Diurnal Blood Pressure Variance**

Mean ± S.E.M.	Day 1	Day 2	Absolute Difference	Standard deviation of the difference (s.d.d.) %.
Nocturnal SBP dip - activity	15.1±1.4	14.8±1.2	0.25	4.7
Nocturnal DBP dip - activity	18.8±1.5	18.9±1.5	-0.09	5.1
Nocturnal SBP dip - 8pm - 7am	11.1±1.1	10.5±0.9	0.59	4.1
Nocturnal DBP dip - 8pm - 7am	14.6±1.2	14.2±1	0.37	4.5
Nocturnal SBP dip - 10pm - 7am	12.9±1.3	12.5±1.1	0.44	4.1
Nocturnal DBP dip - 10pm - 7am	16.4±1.5	16.6±1.1	-0.28	4.6
Nocturnal SBP dip - 12mn - 7am	14.1±1.3	13.7±1.2	0.41	4.1
Nocturnal DBP dip - 12mn - 7am	17.4±1.5	17.6±1.3	-0.13	5.1

In these 30 patients the average correlation between the three activity measures outlined above and blood pressure was 0.34 (range -0.4 to +0.79) for diastolic BP and 0.25 (range -0.38 to +0.75) for systolic. The relationship was statistically significant at the 5% level in over half the readings. The strength of the relationship and the optimal measure of activity varied widely between patients and, to a lesser extent, within patients.

Adjustment of the half hourly blood pressure readings for activity reduced systolic BP variation by an average of 20% (range -10 to +70%) and diastolic BP variation by an average of 26% (range -9 to +65%). The relationship between activity and blood pressure varied significantly between patients ($p < 0.0001$) and between the 2 readings in the same patient ($p=0.03$).

Correlation coefficients between mean wake activity and blood pressure were 0.24 ($p=0.07$) and 0.39 ($p=0.002$) for systolic and diastolic pressure respectively, with regression equations:

$$SBP = 102.3 + 5.67 \times Activity$$
$$DBP = 43.3 + 6.2 \times Activity$$

These were used to adjust mean wake BP for each patient to give expected BP had that patient's activity been equal to the average daily activity of the patients :-

Adjusted SBP = SBP - 5.67xActivity +41.8.
Adjusted DBP = DBP - 6.2xActivity +45.7

This adjustment reduced within-patient (i.e. between reading 1 and 2) variation by 6%/9%, which resulted in an average change in BP of 4/4 mmHg (maximum 9/10 mmHg). Thus, while the overall reduction in variation was small, the size of the change in patients with either markedly low or high activity could be clinically significant.

The standard deviation of the difference between first and second readings before adjustment was small (7/4 mmHg), indicating that reproducibility of the group mean was already good and further adjustment would therefore be hard to achieve with adjustment for activity.

Discussion

This study has shown that statistically significant, though not necessarily clinically relevant, differences exist between different definitions of day and night when compared to wake and sleep. The difference in the proportion of subjects classified as non-dippers was still more striking, particularly in a heterogeneous population with a large number of non-dippers. The definition of night-time varies widely in the literature (O'Brien *et al,* 1988; Verdecchia *et al,* 1990; Shimada *et al,* 1992) and current recommendations remain imprecise (The Scientific Committee, 1990).

I have found wake/sleep data, with sleep time objectively measured using a wrist actigraph, simple to perform and compute. The additional monitoring procedure was well tolerated by the vast majority of patients, causing minimal additional discomfort. This technique overcomes some of the disadvantages inherent in relying on patient diaries, where sleep time may not be accurately recorded. In addition, simultaneous initialisation of the two instruments ensures that there is no discrepancy in the timing due to watch or clock inaccuracy.

Three different definitions of day-time all approximate closely to wake, while larger and potentially clinically significant differences exist when comparing sleep, with 12 midnight

- 7 am best approximating to the sleep value. I would suggest that more rigid criteria for the description of 24 hour blood pressure profiles are required, and as no one time period is clearly "right", would strongly recommend the use of wake and sleep as both physiologically and scientifically more sound. To be accurate, this should entail a constant sampling interval throughout the monitoring period. If an arbitrary cut-off value for day and night must be used, a definition of 7 am - 10 pm may be preferred when day-time BP is the main end-point, while if diurnal variation and the nocturnal dip are the main indications for the study, 7 am - 12 midnight is preferable.

Reproducibility of the ambulatory blood pressure parameters and of diurnal blood pressure variation was good and was similar regardless of the method used. However, the absolute difference in the nocturnal dip was smallest when using the activity derived method, despite a larger recorded dip, suggesting that this may be more accurately defining the true fall in blood pressure during sleep.

I have also tried to define which actigraph activity measure most closely relates to wake blood pressure variability, and determine whether adjustment of mean wake blood pressure for activity could improve within-patient reliability. Several different time periods and activity measures were considered but it was clear that no one measure was ideal, with wide variation in the strength of the relationship between individuals and, to a lesser extent, within individuals. This fact alone must limit the potential for this technique as a method of improving the definition of blood pressure in routine clinical practice. However, with a multiple regression technique, using the three activity features most closely related to blood pressure in the group as a whole, I was able to show that on average 20% of systolic and 26% of diastolic day-time variability could be accounted for by wrist actigraph-measured activity, which is similar to the value previously reported by Van Egeren (1991) for variability over 24 hours.

Regression analysis, using a simpler model, dependent on weighted mean activity over 30 minutes only, was also used to adjust mean wake BP for activity, such that the activity value of each BP record was equal to the group mean. On average, this resulted in a 4/4 mmHg change in mean BP, with a maximum change of 9/10 mmHg. This did not significantly improve the reproducibility of the mean group wake blood pressure. However, this was relatively good before adjustment (standard deviation of the difference for day mean BP 7/4 mmHg), with the result that any further improvement was always going to be difficult to achieve. Correcting mean BP for activity may be of more importance when baseline reproducibility is poorer. Moreover, at either extreme in

activity, change in blood pressure of as much as 9/10 mmHg was seen, which could significantly improve within-patient variation in some individuals. Such an alteration could be clinically relevant and help, for example, in the assessment of the blood pressure response to anti-hypertensive therapy in the individual. However, the precise effect on within-patient variation and any possible clinical role for this technique requires further study.

Conclusions

Any change in the definition of day and night can affect the diurnal blood pressure profile described, with the potential to effect major differences in the proportion of non-dippers defined. The use of sleep time to define diurnal variability appears more physiologically sound and may be more reproducible than any arbitrary definition of night-time. The use of activity monitors can provide an objective measurement of sleep time. Although such devices also allow a correction to be made for day-time activity levels the overall effect on reproducibility is modest and unlikely to be widely applicable in routine clinical practice.

CHAPTER 4

The Distribution of Diurnal Blood Pressure Variation in Patients Attending a Hypertension Clinic : Impact of Age, Treatment and Cause

Background

Unimodality versus Bimodality - The "Normal" Distribution of Blood Pressure

Hypertension research was enlivened and changed for ever by the historic debate between Sir George Pickering and Sir Robert Platt on the fundamental nature of hypertension which raged throughout the 1950's and 60's (Swales, 1985). The conventional view, as espoused by Platt, was that of essential hypertension as a distinct disease entity, inherited as a Mendelian dominant trait, and hence distributed bimodally in the population (Platt, 1947; Platt, 1959). Pickering, however, argued that arterial blood pressure was distributed continuously, with a skew at the upper end of the curve, and as such any separation between normotension and hypertension was arbitrary (Oldham *et al,* 1960; Pickering, 1961). He was the first to express the view that the sharp distinction between hypertension and normotension was a medical artefact (Pickering, 1955). He therefore felt that hypertension should be defined and analysed quantitatively and not qualitatively (Pickering, 1961) and deplored the continuing tendency of doctors to divide the population in two - normotensive and hypertensive (Pickering, 1978). Indeed he felt that this attitude had hindered research in the field for decades (Pickering, 1961).

Pickering eventually won the day and, although recent complex statistical analyses have suggested that the two populations may indeed be distinct (McManus, 1983; Julius *et al,* 1991), few would argue today that there is any clear dividing line between them, and the problem of defining hypertension remains.

Despite the pivotal role of this debate in hypertension research, early work on the potential importance of diurnal blood pressure variation has concentrated on differences between the two extremes - "Dippers" and "Non-dippers" (O'Brien *et al,* 1988; Pickering, 1990b). This distinction is based on an arbitrary division to separate them, commonly a day-night difference of < 10% (Verdecchia *et al,* 1991). The distribution of the nocturnal dip has not been studied in detail, but preliminary observations have failed to reveal any evidence of bimodality (Stewart & Padfield, 1992), suggesting that such a definition may be erroneous and potentially misleading.

Ambulatory Blood Pressure and Blood Pressure Variation

The introduction of ambulatory blood pressure monitoring has improved our understanding of the variability of blood pressure and the nature of hypertension. Day-time mean ambulatory blood pressure is clearly more reproducible than clinic BP (Conway *et al,* 1988; Coats, 1990; Bottini *et al,* 1992), largely due to the greater number of available readings (Trazzi *et al,* 1991). Preliminary evidence suggests that this measurement also better defines those at risk (Perloff *et al,* 1983), but this does little to improve the problem of separating "normal" from "high" blood pressure (Pickering, 1992b), and any cut-off value at which treatment is advised remains arbitrary.

The variation in blood pressure in different clinical situations has been appreciated since the earliest days of blood pressure measurement (Zadek, 1880) and differences in blood pressure during the day and the night appreciated for the most of this century (Janeway, 1904). However, it is only with widespread use of ambulatory blood pressure monitoring that the extent of the variation from day to night has been realised (Richardson *et al,* 1964; Littler *et al,* 1975). From the early days of this technique it was appreciated that the diurnal variation present in normotensive subjects persisted in most hypertensive patients, with an upward shift of the entire curve (Littler *et al,* 1975; Raftery, 1983; Mancia *et al,* 1983b). Thus, the nocturnal fall, when expressed as a percentage, is approximately 20% in both normotensives and hypertensives, although the fall in absolute terms is greater at higher pressures. Differences to this pattern are now recognised (O'Brien *et al,* 1988) but factors which may alter this are not well understood, although the apparent excess of altered diurnal variation in patients with some forms of secondary hypertension has provided some clues.

Diurnal Blood Pressure Variation in Secondary Hypertension

Several workers have noted that the nocturnal fall in blood pressure is less marked in most patients with secondary hypertension (Hany *et al,* 1987; Imai *et al,* 1990; Middeke & Schrader, 1994), and have argued that this observation could aid the differential diagnosis of secondary hypertension. However, there is marked variation in the pathophysiology of these different forms of hypertension and in the reported effect on diurnal blood pressure variation (Padfield & Stewart, 1991).

Primary aldosteronism or Conn's syndrome is the archetypal form of volume mediated hypertension (Fraser *et al,* 1989) and as such, if volume changes related to posture were important in the pathophysiology of the nocturnal dip, might be expected to have a pronounced effect on the diurnal rhythm. However, data in the literature is conflicting,

with two reports suggesting loss of the diurnal rhythm (Tanaka *et al,* 1983; Baumgart *et al,* 1989a) not being confirmed by further work (Munakata *et al,* 1988).

Hypertension is common in Cushing's syndrome, occurring in 80% of cases (Fraser *et al,* 1989) and attenuation of the diurnal rhythm has been found both with the pituitary dependent form, primary adrenal glucocorticoid excess (Imai *et al,* 1988b), and when glucocorticoids are given exogenously in large doses (Imai *et al,* 1989).

Renal disease is thought to raise blood pressure via a complex interaction between sodium or volume status and inappropriate production of renin and angiotensin II (Davies *et al,* 1973). Attenuation of the nocturnal dip in chronic renal failure appears to be a consistent observation (Baumgart *et al,* 1989b; Imai *et al,* 1990; Portaluppi *et al,* 1990), and may be directly related to the severity of renal dysfunction (Imai *et al,* 1988b; Baumgart *et al,* 1989a). In contrast, studies of renovascular disease vary, with Tanaka *et al* (1983) suggesting an altered blood pressure rhythm in middle aged and elderly patients, while Imai *et al* (1990) have found the rhythm of younger patients with fibromuscular hyperplasia to be normal, suggesting that the observation in older patients, in whom atherosclerotic disease predominates, may be an epiphenomenon, rather than a cause and effect relationship. Baumgart *et al* (1989a), while demonstrating loss of the nocturnal dip in chronic renal disease, only noted abnormal rhythms in renovascular disease when overall renal function was compromised. Abel *et al* (1990) have suggested that the autonomic neuropathy seen in chronic renal failure is responsible for the altered diurnal rhythm in such patients.

The importance of the autonomic nervous system, and particularly the sympathetic nervous system, is demonstrated by studies of varied clinical conditions. Complete reversal of the diurnal rhythm is seen in autonomic failure (Mann *et al,* 1983) and the nocturnal dip is attenuated or absent in diabetic autonomic neuropathy (Liniger *et al,* 1987; Hornung *et al,* 1989), and in cardiac transplant recipients, whose ventricles are denervated (Reeves *et al,* 1986). An abnormal diurnal rhythm is also seen in patients with phaeochromocytoma (Littler & Honour, 1974; Padfield *et al,* 1991), but detailed analysis reveals that this is only the case in those with paroxysms of hypertension, suggesting that the level of noradrenaline may be of more importance than that of adrenaline (Imai *et al,* 1988a; Imai *et al,* 1990). Despite these observations, there is no evidence to support the view that the diurnal blood pressure variation in normotensive and essential hypertensive subjects is entrained to sympathetic nervous system activity (Messerli *et al,* 1982).

Limited studies on patients with coarctation of the aorta have shown normal diurnal blood pressure variation whether untreated (Middeke & Schrader, 1994) or after surgical correction (Sehested *et al,* 1990a) suggesting that this is a purely mechanical form of hypertension.

Impact of Age and Severity of Hypertension on the Diurnal Rhythm

Blood pressure increases with age and several studies have shown the prevalence of hypertension in an elderly population to be as high as 50% (The Working Group on Hypertension in the Elderly, 1986; Vokonas *et al,* 1988). Vascular changes associated with ageing lead to a decrease in vascular compliance and predominant systolic hypertension in many elderly patients (Messerli & Schmieder, 1991). This, together with changes in vascular responsiveness associated with ageing (Messerli & Schmieder, 1991), results in an increase in short term blood pressure variability in elderly patients (Mancia *et al,* 1980; Drayer *et al,* 1982). However, the effect on long term, or diurnal, variability appears less pronounced (Drayer *et al,* 1982; Munakata *et al,* 1991) and the nocturnal fall in blood pressure appears to persist in older age in population studies (Staessen *et al,* 1991; O'Brien *et al,* 1991c), although the haemodynamic components responsible may differ (Minamisawa *et al,* 1994).

Short term blood pressure variability has also been shown to higher in hypertensives than in normotensives (Watson *et al,* 1979; Mancia *et al,* 1980; Floras *et al,* 1988), although when variability is corrected for the mean blood pressure this difference disappears (Mancia *et al,* 1980). Gosse *et al* (1988b) have suggested that the diurnal variation in blood pressure is determined more by the severity of the hypertension than by cause but this has not been confirmed by other workers (Reeves *et al,* 1984) and was not apparent in a study of patients with accelerated hypertension (Shaw *et al,* 1963).

Antihypertensive Treatment and the Diurnal Rhythm

The improved reproducibility (Trazzi *et al,* 1991) and possible lack of any placebo effect (Conway *et al,* 1988; Mutti *et al,* 1991) has led to the rapidly increasing use of ambulatory blood pressure monitoring in clinical trials of new anti-hypertensive drugs (Conway *et al,* 1990; O'Brien *et al,* 1991a; White, 1992). Furthermore ambulatory monitoring has the ability to indicate the duration of drug effect and the influence of drugs on nocturnal blood pressure (O'Brien *et al,* 1991d) and on blood pressure variability (Pickering, 1990e).

There are now many published studies utilising ambulatory monitoring in the assessment of antihypertensive drugs, but few compare the effect of drugs from different class. In a retrospective survey of 2859 patients O'Brien *et al* (1991a) found that the nocturnal dip in blood pressure was accentuated in subjects given angiotensin converting enzyme inhibitors as compared to both untreated essential hypertensives and subjects given beta blockers. Floras *et al,* (1982) have studied the duration of action of 4 different beta blockers, all given in once daily dosage, and found that pindolol, the only drug with intrinsic sympathomimetic activity, failed to lower blood pressure during sleep, thus attenuating the nocturnal dip. However, reviews of the differing effects of antihypertensive drugs conclude that the majority have little effect on the diurnal rhythm (Sirgo *et al,* 1988; Pickering, 1990e) but there is a tendency to lower pressure more during the day. Pickering (1990e) concludes that two agents, labetolol and methyl dopa, may have preferential effects on day-time blood pressure, leading to a relative attenuation of the nocturnal dip, and speculates that this is because these agents block both limbs of the sympathetic nervous system, thus preventing the increase in blood pressure during day-time seen in response to sympathetic stimulation.

Introduction

In this study, the nature of the diurnal rhythm in patients with hypertension is explored in detail. The distribution curve of the nocturnal dip from a large cohort of patients has been analysed and examined for evidence of bimodality. The impact of age, severity of hypertension, and antihypertensive treatment on the diurnal curve has been assessed and long-term blood pressure variability of patients with secondary hypertension compared to that of essential hypertensives.

Methods

This is a retrospective analysis of all patients referred for ambulatory blood pressure monitoring over a 4 year period, from 1989 - 1993. Patients with both primary essential and secondary hypertension, and normotensive subjects were included. As many patients had multiple ambulatory recordings over this time period, only the first recording was included in analyses of the pattern of diurnal rhythm. A separate analysis then studied diurnal blood pressure parameters of those whose treatment had changed over time.

Data from every patient referred for ambulatory blood pressure monitoring were stored on a DBase IV programme developed for the purpose. This enabled automatic editing of data

in a standardised manner (readings which were either physiologically impossible or had a pulse pressure less than half the mean pulse pressure over the 24 hour period (Conway *et al,* 1988) were eliminated) and the concurrent storage of other demographic and treatment details. A coding system was used to record the diagnosis of essential hypertension or of a secondary cause where appropriate.

Mean twenty-four hour, day (defined as 7 am - 12 midnight) and night (12 midnight to 7 am) blood pressures, and the change in blood pressure from day to night expressed as a percentage were automatically calculated and stored at the time of data entry. The mean of all blood pressure readings obtained in each one hour period was also calculated and stored.

Only patients in whom > 80% of readings had been successfully obtained were included in the analysis.

The distribution curve of the nocturnal dip in patients with essential hypertension, treated or untreated, was plotted and analysed for Normality using Shapiro-Wilks' W test (Altman, 1991).

The influence of age and of severity of hypertension on diurnal blood pressure variation in patients with essential hypertension was assessed by dividing the study group into quartiles based on age and blood pressure level respectively. Differences in the nocturnal dip were then analysed using analysis of variance.

Differences in blood pressure variation across different classes of anti-hypertensive drugs have also been sought, with the absolute level across treatment groups compared, and the impact of treatment on the dip analysed in patients in whom readings were available before and after a change in therapy, using Student's paired t-test or analysis of variance as appropriate.

Diurnal blood pressure variation in patients with secondary hypertension has been compered to that of the essential hypertensive population using analysis of variance, with age as a possible confounding co-variate. The impact of renal function on the nocturnal dip has also been assessed in patients with essential hypertension. Diurnal blood pressure variation in patients with normal serum creatinine was compared to that of patients with mildly elevated (140 - 200 μmol/l) and more significantly elevated (> 200 μmol/l) creatinine levels using analysis of variance.

Results

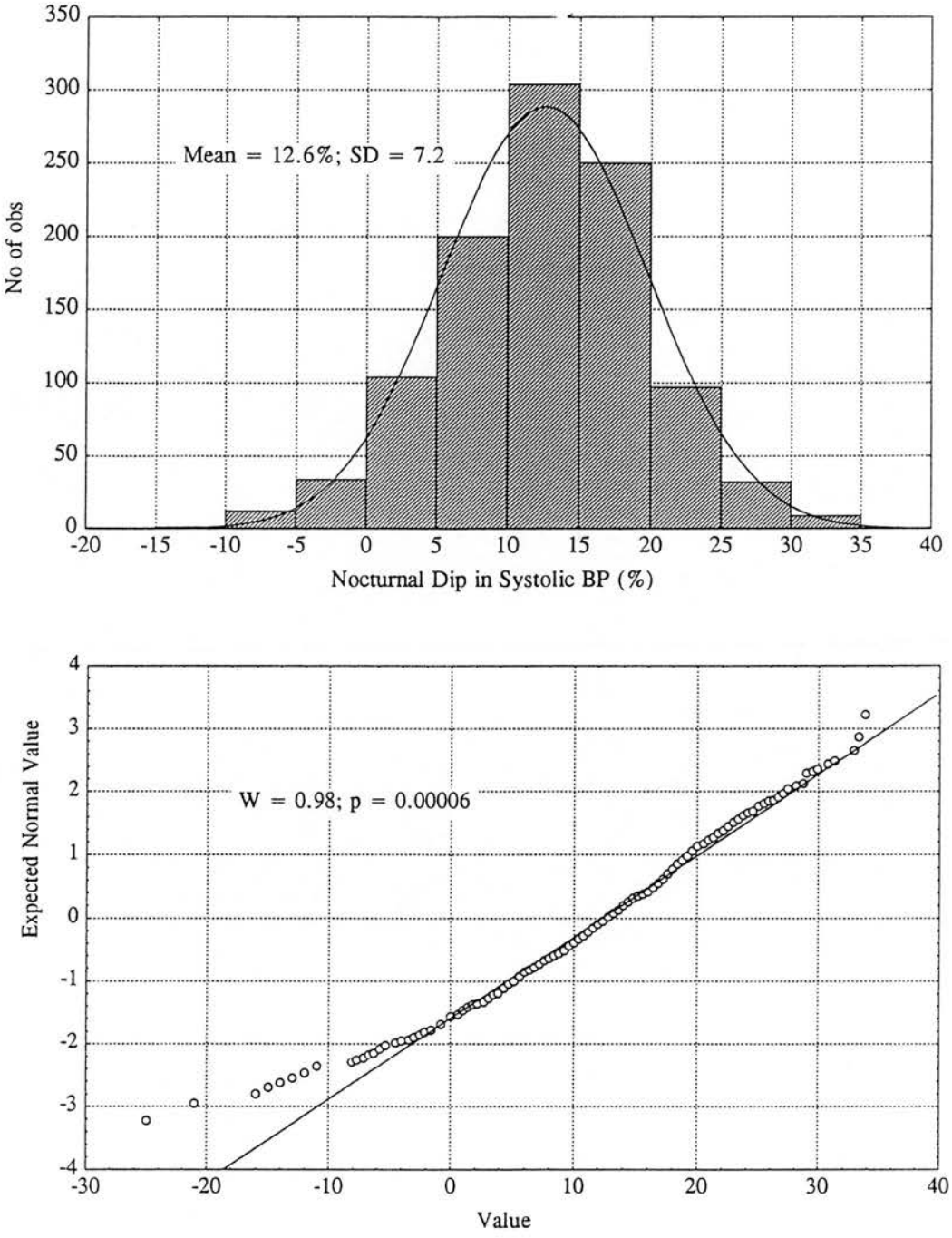
1. Diurnal Blood Pressure Variation in Essential Hypertension

From a data base of 2635 records, 1053 individual records from subjects with primary essential hypertension (both treated and untreated) were identified, with a mean age of 51 ± 0.44 years and clinic blood pressure of 153 ± 0.7/95 ± 0.4 mmHg. Five hundred and sixty four (54%) were male and 489 (46%) female. Mean day-time BP was 146 ± 0.6/89 ± 0.4 mmHg (range 215/132 to 106/56 mmHg) and night-time BP was 128 ± 0.6/74 ± 0.4 mmHg (range 204/138 to 82/42 mmHg). Nocturnal dip averaged 12.3 ± 0.2/16.2 ± 0.3 % (range 33.8/40.9 to -24/-38%).

Frequency histograms of the nocturnal dip were plotted for both systolic and diastolic BP (Figures 4.1 and 4.2) and the data used to construct Normal plots (Altman, 1991) (Figures 4.1 and 4.2). In such plots, the horizontal axis shows the numerical value of the observation, and the vertical axis gives the relative frequency in terms of the number of standard deviations from the mean. Data which has a Normal distribution should create a straight line, with departures of the sample data from Normality easily seen as departures from this line.

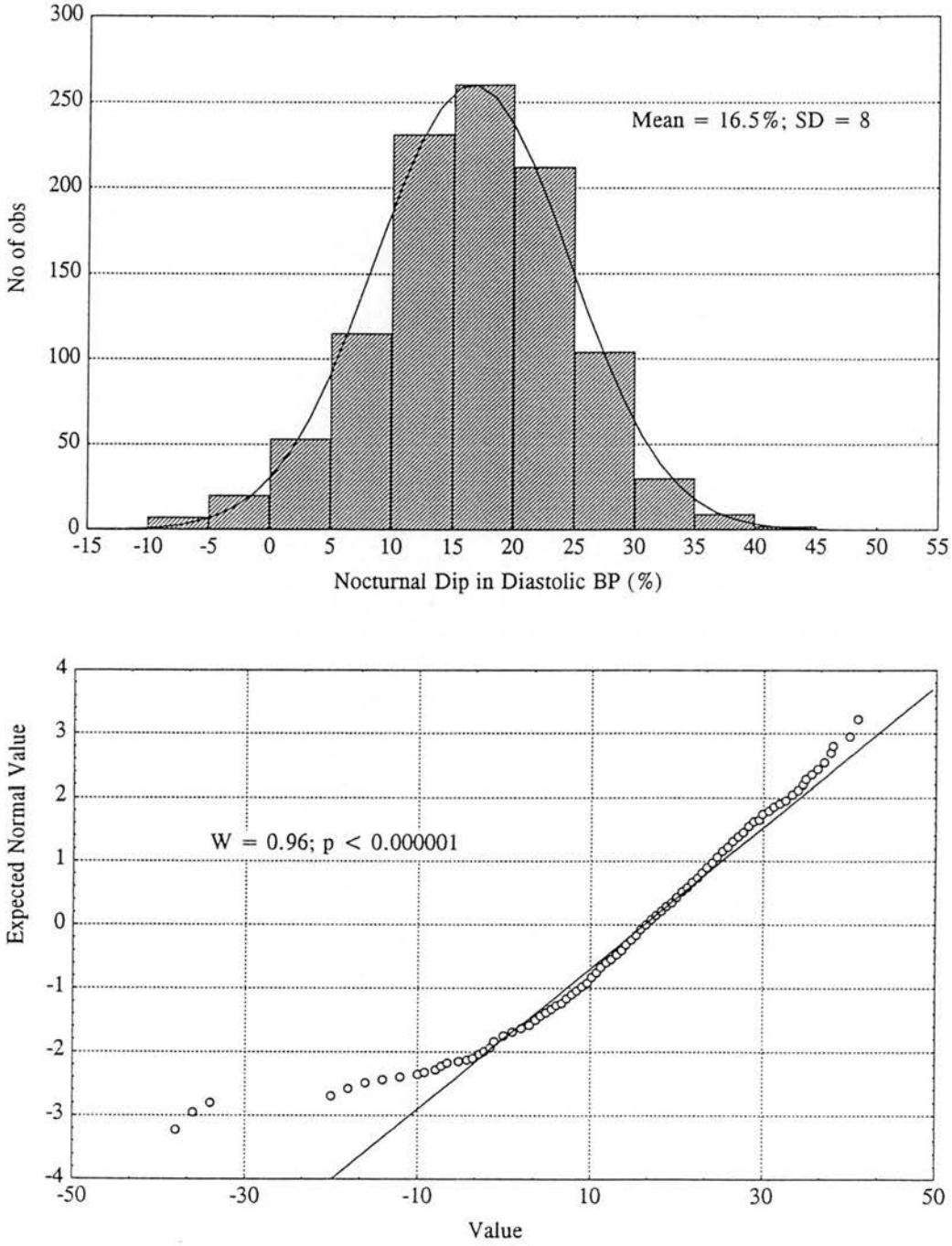
Data were then analysed using the Shapiro-Wilk's W test for Normality. In this analysis, the closer the W statistic is to unity the more Normal the distribution. On initial analysis, W was 0.98 for the systolic dip and 0.96 for the diastolic, but with very small probability values, indicating clear deviance from Normality. Inspection of the Normal plots suggested that this was due to small numbers of subjects with marked ***increase*** in nocturnal BP (Figures 4.1 and 4.2). From clinical experience, some individuals demonstrate artefactual reversal of the normal day-night blood pressure dip due to factors such as shift work, complete disruption of sleep or, in one case, an attack of renal colic during the night. The analysis was therefore repeated with the lowest 1% of readings (n = 10) excluded. Repeat Normal plots then confirmed Normality, with little change in W but high probability values (Figure 4.3).

Figure 4.1 **The Distribution of the Nocturnal Dip in Systolic Blood Pressure**



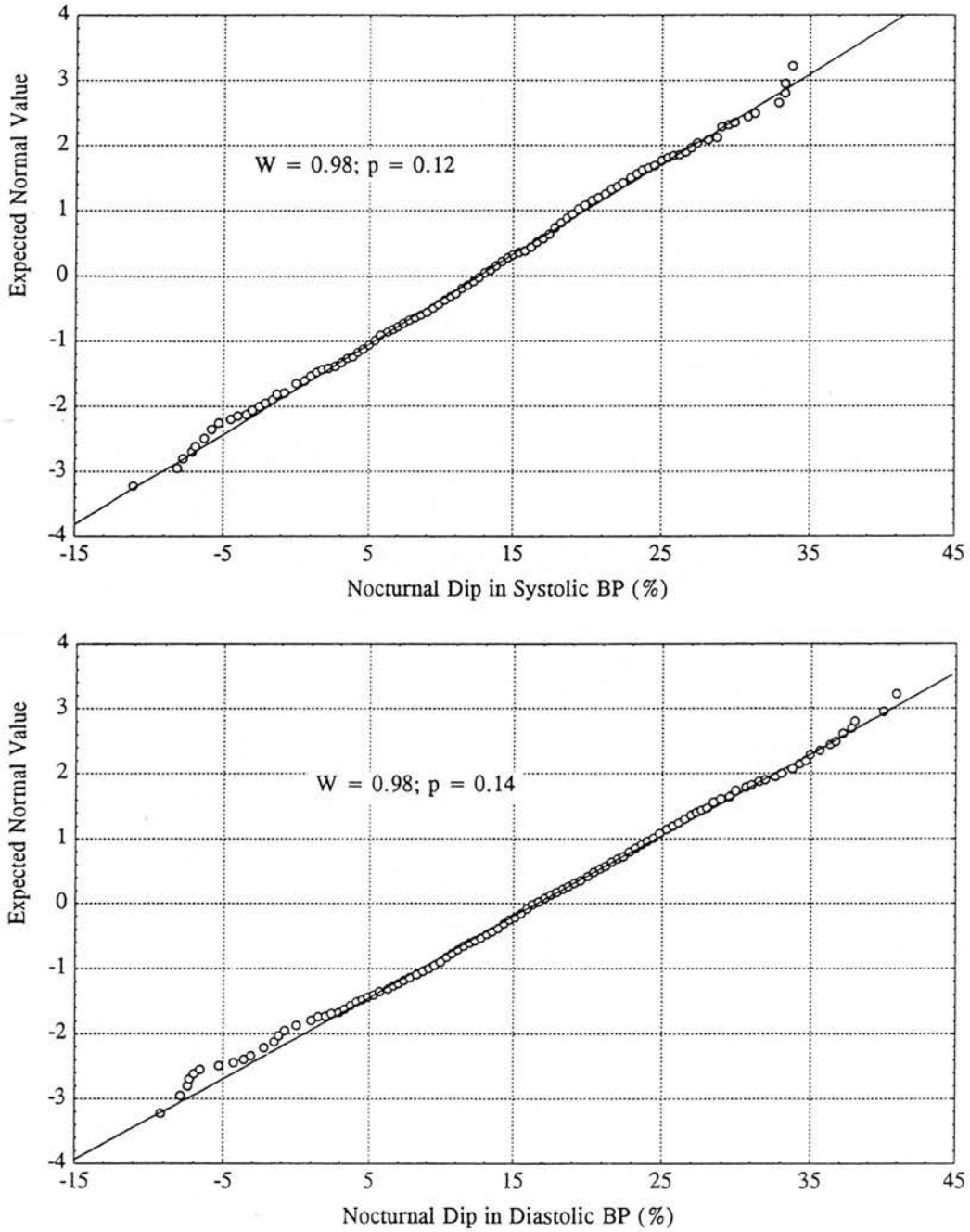
Frequency histogram (upper panel) and Normal plot (lower panel) for diurnal variation in systolic blood pressure. The frequency distribution is approximately Normal but, although the W statistic is close to 1.0, the Normal plot demonstrates significant deviation from Normality, predominantly due to outliers with extreme negative values.

Figure 4.2 **The Distribution of the Nocturnal Dip in Diastolic Blood Pressure**



Frequency histogram (upper panel) and Normal plot (lower panel) for diurnal variation in diastolic blood pressure. Again, the distribution appears approximately Normal but with significant deviation from Normality due to negative outliers.

Figure 4.3 **Normal Plots of Diurnal Blood Pressure Variance**



Normal plot for systolic (upper panel) and diastolic (lower panel) blood pressure after removal of potentially erroneous outliers. The W value has not changed significantly but the population is now shown to be Normally distributed.

2. Effect of Age on Blood Pressure and Diurnal Blood Pressure Variation

The population described above was then divided into quartiles based on age (Table 4.1) and the change across the groups analysed using analysis of variance (Figure 4.4).

Table 4.1 **Quartiles based on age**

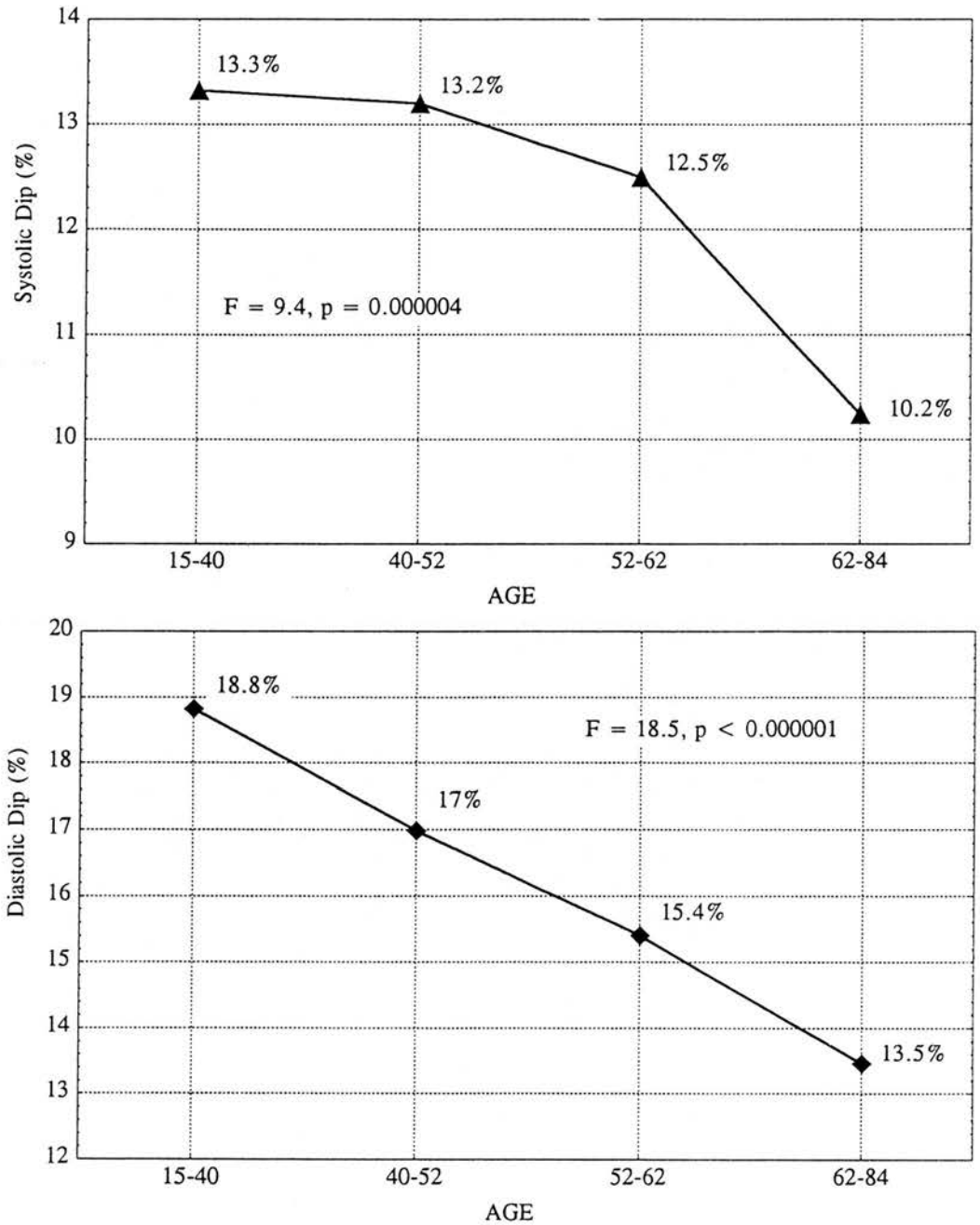
Mean ± SEM	**15 - 40**	**40 - 52**	**52 - 62**	**62 - 84**
Number	263	263	263	264
Age	32 ± 0.4	47 ± 0.2	58 ± 0.2	69 ± 0.3
Day SBP	139 ± 1	144 ± 1	150 ± 1.2	152 ± 1.1
Day DBP	88 ± 0.7	93 ± 0.7	91 ± 0.7	84 ± 0.7
Night SBP	121 ± 1	125 ± 1.1	131 ± 1.3	136 ± 1.3
Night DBP	71 ± 0.7	77 ± 0.7	77 ± 0.7	73 ± 0.8
Nocturnal Dip SBP (%)	13.3 ±0.38	13.2 ± 0.43	12.5 ± 0.48	10.2 ± 0.56
Nocturnal Dip DBP (%)	18.8 ± 0.48	17 ± 0.47	15.4 ± 0.53	13.5 ± 0.62

As expected from previous epidemiological work, systolic blood pressure rises progressively with age, while diastolic blood pressure increases to middle age but then falls at the extreme. However, a clear effect of age on the nocturnal dip in blood pressure was apparent, with a progressive fall in each age range.

3. Effect of Severity of Hypertension on Diurnal Blood Pressure Variation

The data were then re-analysed after sub-dividing the population into quartiles based on the severity of hypertension, as indicated by level of mean day-time blood pressure (Tables 4.2a and 4.2b), and the change across the groups analysed using analysis of variance (Figure 4.5).

Figure 4.4 **The Impact of Age on Diurnal Blood Pressure Variation**



ANOVA plot demonstrating the effect of age on systolic (upper panel) and diastolic (lower panel) diurnal blood pressure variation. The nocturnal dip fall progressively with increasing age.

Table 4.2a **Quartiles based on severity of systolic hypertension**

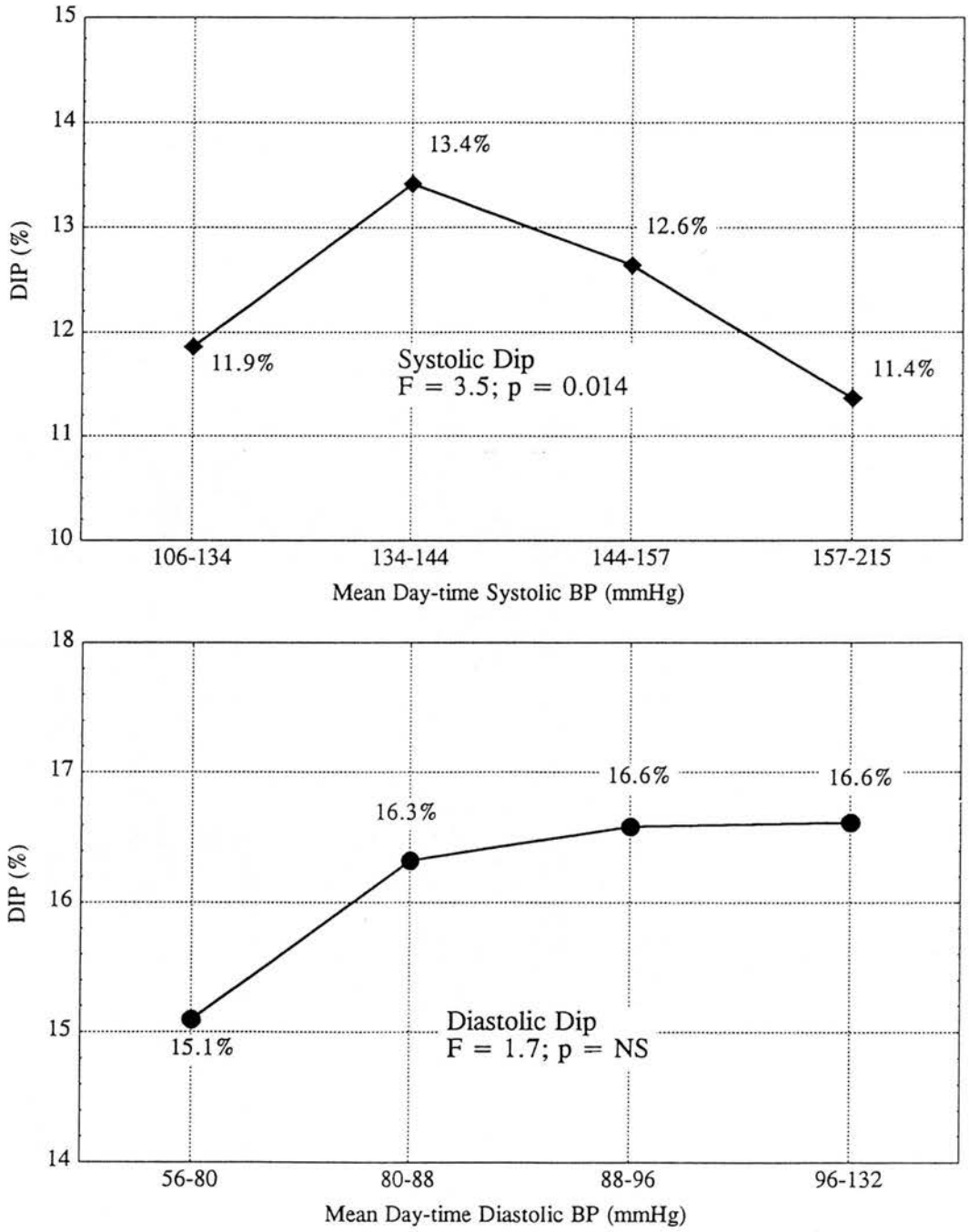
Mean ± SEM	**106 - 134**	**134 - 144**	**144 - 157**	**157 - 215**
Number	283	253	265	252
Age	46 ± 0.8	49 ± 0.9	53 ± 0.8	57 ± 0.8
Day SBP	126 ± 0.4	139 ± 0.2	150 ± 0.2	172 ± 0.7
Night SBP	111 ± 0.6	121 ± 0.6	131 ± 0.8	152 ± 1.1
Nocturnal Dip SBP (%)	11.9 ± 0.44	13.4 ± 0.44	12.6 ± 0.49	11.4 ± 0.52

Table 4.2b **Quartiles based on severity of diastolic hypertension**

Mean ± SEM	**56 - 80**	**80 - 88**	**88 - 96**	**96 - 132**
Number	253	265	272	263
Age	53 ± 1.1	50 ± 0.9	52 ± 0.8	50 ± 0.7
Day DBP	74 ± 0.3	85 ± 0.1	92 ± 0.1	104 ± 0.4
Night DBP	62 ± 0.5	71 ± 0.5	77 ± 0.5	87 ± 0.7
Nocturnal Dip DBP (%)	15.1 ±0.63	16.3 ± 0.55	16.6 ± 0.51	16.6 ± 0.48

There appeared to be no relationship between severity of diastolic hypertension and the night-time dip in diastolic pressure. A statistically significant effect of day-time systolic blood pressure on the dip was apparent, accounted for in part by an excess of elderly subjects in the group with the highest systolic pressure. Correcting for this, the statistical significance is less ($F = 3.1$, $p = 0.03$). Moreover, the relationship is non-linear and as such unlikely to be of any clinical significance.

Figure 4.5 **The Effect of Severity of Hypertension on Diurnal Blood Pressure Variation**



ANOVA plots demonstrating the effect of the level of wake systolic BP on systolic diurnal variation (upper panel) and wake diastolic BP on diastolic blood pressure variation (lower panel). Although there is a statistically significant difference across quartiles of systolic BP, this is non-linear and unlikely to be clinically relevant.

Effect of Anti-hypertensive Treatment on Diurnal Blood Pressure Variation

Data on drug therapy at the time of the ambulatory blood pressure recording were available in 1029 of this patient group. To determine whether anti-hypertensive treatment can influence diurnal blood pressure variation, an initial analysis compared treated patients with untreated, regardless of drug class, quantity or dose. Six hundred and two patients were untreated and 427 on treatment. The two groups were compared using Student's t-test for unpaired data (Table 4.3). In view of the marked difference in age between the two groups, data were re-analysed using analysis of variance, correcting for age (Table 4.3).

Table 4.3 **Effect of Drug Therapy on Diurnal Blood Pressure Variation**

Mean ± SEM	Untreated	Treated	P (t test)	P - Age Corrected (ANOVA)
Number	602	427		
Age	47 ± 0.6	58 ± 0.6	< 0.000001	
Day SBP	145 ± 0.7	148 ± 0.9	0.004	NS
Day DBP	90 ± 0.5	87 ± 0.6	0.0001	0.003
Night SBP	125 ± 0.8	132 ± 1	0.000001	NS
Night DBP	74 ± 0.5	75 ± 0.6	NS	NS
Nocturnal Dip SBP (%)	13.4 ± 0.27	11.5 ± 0.42	0.000005	0.005
Nocturnal Dip DBP (%)	17.8 ± 0.31	14.2 ± 0.47	< 0.000001	0.0001

Even after correcting for age diurnal blood pressure variation appears less pronounced in treated patients.

Subjects on monotherapy were then examined separately in an attempt to determine whether there was any difference in the effect of anti-hypertensive drugs. The nocturnal dip of patients treated with beta blockers, diuretics, angiotensin converting enzyme inhibitors and calcium antagonists were compared and analysed using analysis of variance (Table 4.4 and Figure 4.6). A significant difference across treatment groups was apparent, with calcium antagonist therapy apparently associated with attenuation of the nocturnal dip. However, a difference in age across treatment groups was also apparent and data was therefore re-analysed allowing for age as a covariate, following which the effect of therapy on the systolic dip was just significant and that on the diastolic dip no longer so. Moreover, both day and night systolic pressures were markedly higher in the

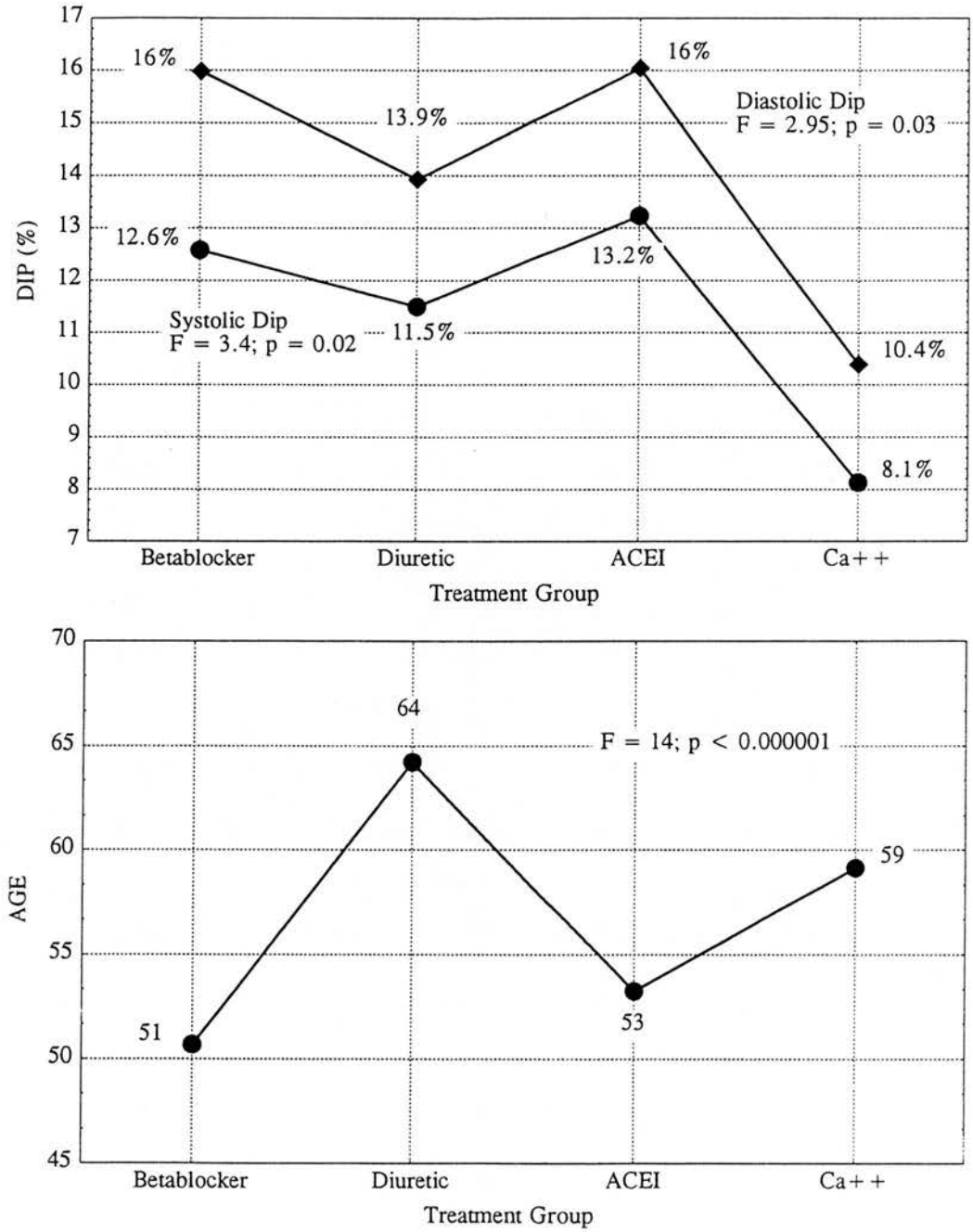
calcium blocker group, suggesting that baseline hypertension may have been more severe in this group. Although, as shown above, the blood pressure level *per se* does not influence the diurnal variation, this may indicate that these groups are not strictly comparable.

Table 4.4 **Effect of Drug Mono-therapy on Diurnal Blood Pressure Variation**

Mean ± SEM	Beta Blocker	Diuretic	ACE Inhibitor	Calcium Antagonist
Number	45	53	44	42
Age	51 ± 2.1	64 ± 1.4	53 ± 1.6	59 ± 1.5
Day SBP	141 ± 2.7	144 ± 2.1	146 ± 2.5	155 ± 3.4
Day DBP	87 ± 1.5	84 ± 1.5	90 ± 1.4	90 ± 1.7
Night SBP	124 ± 2.9	127 ± 2.3	126 ± 2.9	142 ± 3.5
Night DBP	73 ± 1.9	72 ± 1.7	75 ± 1.7	80 ± 1.6
Nocturnal Dip SBP (%)	12.6 ± 1.27	11.5 ± 1.02	13.2 ± 1.2	8.1 ± 1.29
Nocturnal Dip DBP (%)	16 ± 1.41	13.9 ± 1.57	16 ± 1.27	10.4 ± 1.63

The entire data base was then examined to identify those patients whose treatment had changed over time. Due to the relatively small numbers involved, no attempt was made to examine each class of drug independently. The change in blood pressure and in diurnal blood pressure variation has been assessed using Student's paired t test (Table 4.5a). For comparison, those subjects who had undergone repeat monitoring at a different time point with no change in treatment were subjected to the same analysis (Table 4.5b). The standard deviation of the difference between the two measurements has been calculated as a measure of the repeatability.

Figure 4.6 **The Effect of Drug Therapy on Diurnal Blood Pressure Variation**



ANOVA plot comparing diurnal blood pressure variation in patients treated with monotherapy by drug class (upper panel). The difference in age across drug class has also been examined (lower panel). After correcting for age, the influence of drug class is less significant, with F = 2.8, p = 0.004 for systolic BP and F = 2.2, p = 0.09 for diastolic BP. ACEI = Angiotensin converting enzyme inhibitor. Ca++ = Calcium antagonist.

Table 4.5a **Change in Ambulatory Blood Pressure Parameters After a Change in Antihypertensive Treatment**

Cohort includes subjects whose treatment has been increased or decreased

Mean ± SEM	Ambulatory BP 1	Ambulatory BP 2	Mean Difference	SD of the Difference (s.d.d.)	p
Number	137	137			
Day SBP	154 ± 1.6	145 ± 1.4	9.1	17.3	< 0.0000001
Day DBP	93 ± 1.1	88 ± 0.9	5.8	10.7	< 0.0000001
Night SBP	136 ± 1.9	129 ± 1.6	8	19.4	0.000004
Night DBP	80 ± 1.2	75 ± 0.9	4.9	11.7	0.000002
Nocturnal Dip SBP (%)	11.4 ± 0.68	11.2 ± 0.63	0.2	7.9	NS
Nocturnal Dip DBP (%)	14.6 ± 0.8	14.4 ± 0.73	0.2	9.2	NS

Table 4.5b **Change in Ambulatory Blood Pressure Parameters Over Time With No Change in Antihypertensive Treatment**

Cohort includes untreated subjects and treated patients whose treatment is unchanged.

Mean ± SEM	Ambulatory BP 1	Ambulatory BP 2	Mean Difference	SD of the Difference (s.d.d.)	p
Number	164	164			
Day SBP	142 ± 1.4	140 ± 1.3	2.1	11	0.014
Day DBP	88 ± 0.9	87± 0.9	1.7	6.8	0.002
Night SBP	126 ± 1.5	123 ± 1.4	2.3	13.4	0.03
Night DBP	75 ± 1	73 ± 0.8	2.4	8.7	0.0006
Nocturnal Dip SBP (%)	11.4 ± 0.59	11.9 ± 0.53	-0.4	7.2	NS
Nocturnal Dip DBP (%)	14.8 ± 0.68	15.8 ± 0.64	-1	9.1	NS

As expected, the change in both day and night blood pressure over time was highly significant in those whose treatment had changed. However, diurnal blood pressure variation did not change significantly. Smaller, statistically but not clinically significant changes in day and night blood pressure were seen in those whose treatment did not change. Again, there was no significant difference in the nocturnal dip.

5. Diurnal Blood Pressure Variation in Secondary Hypertension

Patients with secondary hypertension were identified and their initial ambulatory blood pressure data compared to that of the essential hypertensive population (Table 4.6). Most patients were on no therapy or conventional antihypertensive treatment (i.e. not specific therapy aimed at the cause of secondary hypertension) at the point of study. Patients with coarctation of aorta had all been operated on in childhood and were investigated as part of follow-up review. Initial analysis indicated a significant difference in age between groups and age was therefore included as a covariate.

Diurnal blood pressure variation is significantly attenuated in patients with phaeochromocytoma, Cushing's syndrome and acromegaly. In contrast, diurnal variation in patients with coarctation of the aorta is normal. Patients with hypothyroidism, now recognised as treatable, secondary cause of hypertension (Bing *et al,* 1980; Streeten *et al,* 1988), also had relatively normal diurnal blood pressure variation.

Table 4.6 **Comparison of Ambulatory Blood Pressure Parameters in Essential and Secondary Hypertension**

Mean ± SEM	Essential Hypertension	Hypo-thyroidism	p	Phaeochromo-cytoma	p
Number	1053	21		15	
Age	51 ± 0.4	49 ± 3.7	NS	43 ± 3	0.02
Day SBP	146 ± 0.6	137 ± 3.6	0.03	139 ± 3.4	NS
Day DBP	89 ± 0.4	75 ± 1.4	0.000001	83 ± 2.9	0.03
Night SBP	128 ± 0.6	124 ± 4.8	NS	132 ± 6.4	NS
Night DBP	74 ± 0.4	63 ± 1.3	0.00001	75 ± 4.7	NS
Nocturnal Dip SBP (%)	12.3 ± 0.24	9.7 ± 1.78	NS	5.2 ± 4	0.0003
Nocturnal Dip DBP (%)	16.2 ± 0.27	16.1 ± 1.84	NS	9.2 ± 4.85	0.0001

Cushing's Syndrome	p	Acromegaly	p	Coarctation of Aorta	p
8		11		18	
35 ± 4.5	0.001	53 ± 3.7	NS	22 ± 2.5	0.000001
137 ± 6	NS	139 ± 4.8	NS	131 ± 3.2	NS
84 ± 4.2	NS	85 ± 4.1	NS	74 ± 1.7	0.000001
127 ± 8.4	NS	130 ± 5.5	NS	112 ± 3	NS
74 ± 5.5	NS	76 ± 3.8	NS	59 ± 1.7	0.000006
7.6 ± 2.52	0.03	7 ± 1.52	0.024	14.5 ± 1.65	NS
12.3 ± 3.1	0.04	10.7 ± 1.68	0.046	20.2 ± 1.97	NS

Each secondary hypertension parameter has been compared to that of essential hypertension, correcting for age, using one way analysis of variance. The p statistic in the column following each cause of secondary hypertension refers to this analysis.

6. Influence of Renal Function on Diurnal Blood Pressure Variation

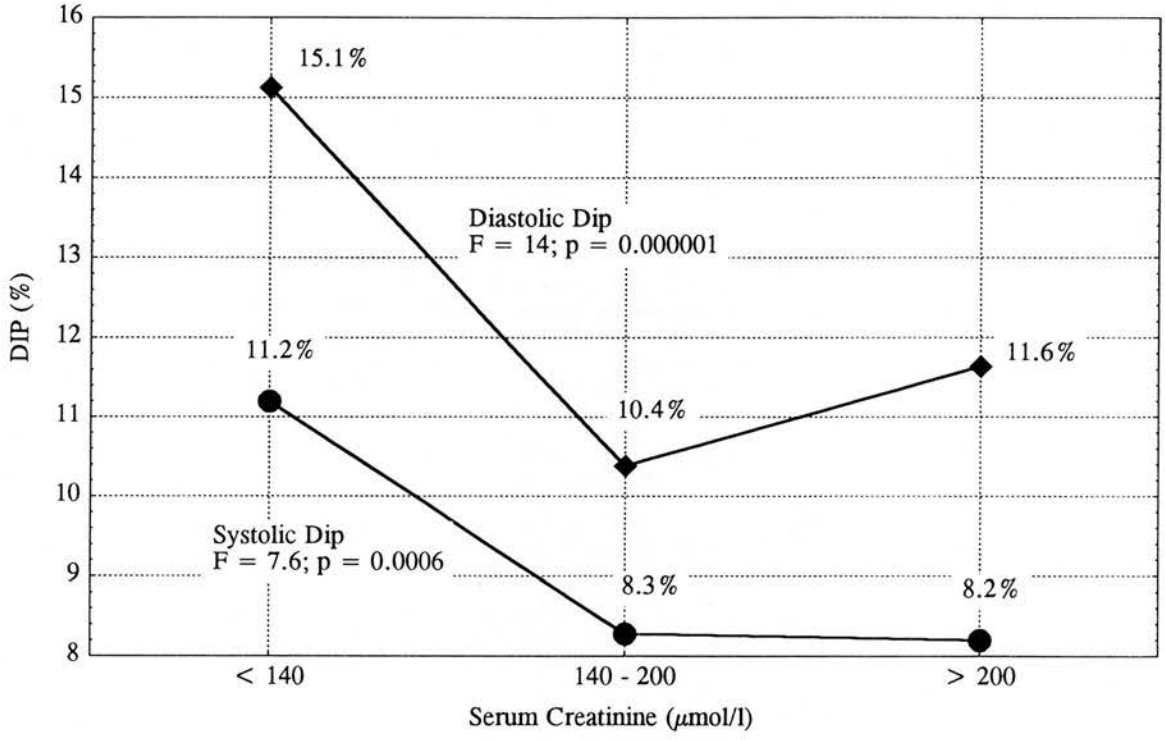
Results of serum biochemistry, including urea and creatinine, usually performed at the Hypertension clinic within 1 month of blood pressure monitoring, were available in 688 patients. This population was subdivided on the basis of a normal, mildly elevated (140 - 200 μmol/l) or more severely elevated (> 200 μmol/l) serum creatinine (Table 4.7) and mean blood pressure parameters compared using analysis of variance, again allowing for age as a co-variate (Figure 4.7). Although day-time mean BP was similar in the three groups, diurnal blood pressure variability was significantly attenuated in those with abnormal serum creatinine. However, there was no evidence of a linear relationship, with a similar reduction in the nocturnal dip of those with mildly and severely impaired renal function, and correlation coefficients for serum creatinine and the nocturnal dip of -0.05 for systolic BP and -0.09 for diastolic BP.

Table 4.7 **Blood Pressure in Essential Hypertension in Patients with Normal, Mildly Impaired and Severely Impaired Renal Function**

Mean ± SEM	Creatinine < 140	Creatinine 140 - 200	Creatinine > 200	F	p
Number	564	88	36		
Age	58 ± 0.5	57 ± 1.2	64 ± 1	5.4	0.005
Day SBP	152 ± 0.8	151 ± 2.4	160 ± 3.9	2.7	NS
Day DBP	89 ± 0.5	91 ± 1.5	89 ± 1.2	1.4	NS
Night SBP	135 ± 1	139 ± 2.4	148 ± 4.7	5.3	0.005
Night DBP	75 ± 0.5	81 ± 1.4	79 ± 1.6	9.2	0.0001
Nocturnal Dip SBP (%)	11.2 ± 0.33	8.3 ± 0.76	8.2 ± 0.98	7.6	0.0006
Nocturnal Dip DBP (%)	15.1 ± 0.4	10.4 ± 0.81	11.6 ± 1.07	14	<0.00001
Urea (mmol/)l	6.4 ± 0.1	9.4 ± 0.3	14.7 ± 1.2	194	<0.00001
Creatinine (μmol/l)	99 ± 0.8	159 ± 1.7	510 ± 170	54	<0.00001

Parameters have been compared using analysis of variance, allowing for age as a co-variate.

Figure 4.7 **The Impact of Renal Dysfunction on Diurnal Blood Pressure Variation**



ANOVA plot comparing diurnal blood pressure variation in patients with normal (creatinine < 140 μmol/l), mildly impaired (creatinine 140 - 200 μmol/l) and severely impaired (creatinine > 200 μmol/l) renal function. Diurnal variation appears blunted in those with impaired renal function but this is non-linear.

Discussion

This detailed analysis of over 1000 individual patients referred for ambulatory blood pressure monitoring over a four year period has demonstrated Normal distribution of the nocturnal dip of both systolic and diastolic blood pressure. This accords with an earlier observation from a limited patient sample (Stewart & Padfield, 1992) and suggests that any division of the hypertensive population into "Dippers" and "Non-dippers" must rely on an arbitrary definition. Undue emphasis on populations so defined risks recreating some of the errors inherent in the early days of hypertension research, when, as a result of the belief that essential hypertension was a distinct disease entity, work concentrated on trying to find the defect underlying hypertension. Referring to this propensity of physicians to treat hypertension as a qualitative rather than quantitative phenomenon Sir George Pickering damned the practice :

> *"It is .. fallacious and .... a hindrance to the true understanding of the facts with which we are concerned. It is a perfect example of ....the mysterious viability of the false."* (Pickering, 1978)

Despite his efforts, the practice of dividing a population in two - normal and abnormal, physiologic and pathologic - has persisted, other examples including low renin hypertension (Padfield *et al,* 1975) and idiopathic hyperaldosteronism (Padfield *et al,* 1981). This may arise from clinicians need to make a fundamental decision when dealing with patients: ill or healthy; treatment or no treatment. In the face of such training, it should not surprise us that any new observation or abnormality leads to patients being classified separately. The danger is that once misclassified and having received a name, they come to be seen as an entity, a fault recognised in the last century by John Stuart Mill :

> *"The tendency has always been strong to believe that whatever receives a name must be an entity or being, having an independent existence of its own; and if no real entity answering to the name could be found man did not for that reason suppose that none existed, but imagined that it was something peculiarly abstruse and mysterious, too high to be an object of sense."* (Mill, 1869)

Having recognised the quantitative nature of the nocturnal dip, it becomes clear that any study of the differences between different populations should concentrate on the absolute figure rather than the qualitative study of dippers and non-dippers. Moreover, the recognition that the frequency distribution of diurnal blood pressure variation

approximates to Normality allows the use of parametric statistics in such analyses, improving the power of the studies.

This observation has a further important consequence. Several authors have suggested that ambulatory blood pressure monitoring could improve the diagnosis of secondary hypertension (Hany *et al,* 1987; Imai *et al,* 1990; Middeke & Schrader, 1994), and this study has confirmed that diurnal variation is attenuated in certain forms of secondary hypertension when compared to essential hypertension. However, in any given population of essential hypertensives, a substantial proportion will be classified as non-dippers, the precise number being heavily dependent on the definition chosen, but averaging at 20 - 40% (Verdecchia *et al,* 1991). As secondary hypertension occurs in only 5 - 10% of patients with hypertension, it is clear that the absence of a nocturnal fall in blood pressure in any undiagnosed individual is much more likely to be associated with essential hypertension than with a secondary cause. Moreover, the fall in blood pressure during the night in patients with hypothyroidism and previously treated coarctation of the aorta is similar to that of patients with primary essential hypertension, indicating that the absence of a nocturnal dip is neither a sensitive nor a specific indicator of secondary hypertension.

Nonetheless, the study of patients with secondary hypertension does provide some clues as to possible mechanisms involved in the control of the nocturnal fall in blood pressure. Endocrine hypertension related to an excess of glucocorticoid or catecholamine appears to be associated with blunting of the dip, while that related with deficiency of a hormone, thyroxine, is not. Data in the literature relating to a further condition of hormone excess, hyperaldosteronism, are inconsistent, with some (Tanaka *et al,* 1983; Baumgart *et al,* 1989a) but not all (Munakata *et al,* 1988) studies suggesting that it is related to absence of the nocturnal dip. Although I did not have a sufficient number of patients with hyperaldosteronism to warrant separate study here, the hypertension seen in a further condition of hormone excess, acromegaly, was also associated with attenuation of the blood pressure fall at night. Such hypertension involves the effects of excess growth hormone on sodium balance, the renin-angiotensin system and the adrenal cortex (Fraser *et al,* 1989) and is therefore likely to behave similarly, as a form of volume mediated hypertension. It is thus possible that volume changes related to posture are partially involved in the pathophysiology of the nocturnal dip.

Glucocorticoid excess, whether due to Cushing's syndrome (Imai *et al,* 1988b) or exogenous glucocorticoid excess (Imai *et al,* 1989) is associated with loss of the nocturnal fall in blood pressure, and we have confirmed this in a small group of patients with

Cushing's syndrome. However, in patients with hypopituitarism who are taking glucocorticoid replacement therapy the diurnal blood pressure profile is not altered by reversing the pattern of therapy (Jyothinagaram *et al,* 1989) or by doubling the dose of hydrocortisone given (see Chapter 5). Thus, it appears that only pathological quantities of corticosteroid are capable of modifying the diurnal rhythm, making a physiological role for cortisol less likely.

Blunting of the nocturnal dip was most pronounced in patients with phaeochromocytoma and this is in accord with other work (Littler & Honour, 1974; Padfield *et al,* 1991), although one study has failed to reveal any difference compared with essential hypertension (Imai *et al,* 1988a). However, many of these patients were on treatment and those with marked nocturnal spikes of pressure were excluded from the analysis. Nonetheless, the marked impact on diurnal rhythm in most patients with catecholamine excess, together with observations made in patients with autonomic failure (Mann *et al,* 1983) or neuropathy (Liniger *et al,* 1987; Hornung *et al,* 1989) argues in favour of the autonomic nervous system having an important role in control of the diurnal blood pressure pattern.

Attenuation of diurnal blood pressure variability associated with renal dysfunction was striking and, unexpectedly, apparent in those with even mildly impaired renal excretory function. In patients with established kidney disease, the prevalence of hypertension increases as renal failure progresses, with hypervolaemia resulting from salt and water retention the predominant cause (Raine, 1994), and hyper-reninaemia an important additional factor in a minority (Vertes *et al,* 1969). Previous studies have suggested that loss of the nocturnal dip in chronic renal failure is related to severity of disease (Imai *et al,* 1988b; Baumgart *et al,* 1989a), with one study of patients with chronic glomerulonephritis suggesting that the diurnal blood pressure rhythm in patients not treated with glucocorticoid remains normal until the glomerular filtration rate is below 20 ml/min. (Imai *et al,* 1988b). Clearly, however, the impact of renal function in patients with essential hypertension may be very different from that in primary renal disease. Although primary renal disease was not completely excluded in the patients studied here, the majority were thought to have primary essential hypertension, with renovascular disease present in some.

The interplay between blood pressure regulation, the development of hypertension and the development of renal dysfunction is complex and still not completely understood. Essential hypertension results in a fall in renal blood flow and a rise in renal vascular

resistance, yet glomerular filtration rate generally remains normal (Raine, 1994). Although accelerated hypertension can cause significant renal damage (Kincaid-Smith *et al,* 1958), the extent to which renal impairment develops in less severe hypertension remains controversial (Raine, 1994), but renal failure due solely to benign hypertension appears rare (Brown & Whitworth, 1992).

Hypertension and a gradual decline in renal function due to glomerulosclerosis are both common accompaniments of ageing. However, the age of patients with mildly impaired renal function in this study was similar to those with normal renal function, and the statistical analysis corrected for age. The effect of age on diurnal blood pressure variation is therefore unlikely to account for the differences observed here.

Hypertension is a a major risk factor for both large and small vessel atherosclerosis and much of the renal dysfunction associated with benign hypertension is likely to be ischaemic origin. No attempt was made in this study to exclude those with proven or suspected reno-vascular disease, and several of the patients with the most profound reduction in renal function are likely to have had reno-vascular disease. Data on diurnal blood pressure variability in hypertension associated with renal artery stenosis are conflicting. Two studies have suggested a negative association with diurnal blood pressure variation (Tanaka *et al,* 1983; Middeke & Schrader, 1994), but neither gave data on renal function in these patients. Baumgart *et al (*1989a) found diurnal blood pressure variation in reno-vascular disease to be attenuated only in patients whose renal function was compromised, while a study of patients with fibromuscular hyperplasia, in whom there is no doubt that the arterial stenosis underlies the elevation in blood pressure, demonstrated normal diurnal variation (Imai *et al,* 1990). This latter observation argues strongly against any independent influence from reno-vascular disease *per se.* Nonetheless, as I do not have data on the renal vasculature of all of our patients, I cannot exclude the possibility that the presence of reno-vascular disease, with the profound elevation of renin and angiotensin II associated with this condition, accounts for the observed effect.

I have observed attenuation of diurnal blood pressure variation in patients with essential hypertension and both modestly and severely impaired renal function. While factors such as autonomic neuropathy (Abel *et al,* 1990) and sympathetic overactivity (Converse *et al,* 1992) may contribute to this in advanced renal failure, they are unlikely to account for this observation in those with only mild disease. Mild hypervolaemia related to early renal excretory dysfunction therefore seems the most plausible explanation for this effect.

However, prospective study with well matched groups and full investigation of renal and blood volume status would be needed to confirm this hypothesis.

A further possible explanation for the reduced nocturnal dip in blood pressure in secondary hypertension is that such patients tend to have more severe hypertension, which Gosse *et al* (1988b) suggested was an important determinant of the nocturnal fall. However, I have found no evidence to support this in my study population, with similar nocturnal fall in different quartiles of blood pressure.

Although study of patients with secondary hypertension has provided insight into the pathophysiology of the nocturnal dip in blood pressure, the most noteworthy determinant of diurnal blood pressure in this analysis was age, with a clear inverse linear relationship between age and the nocturnal fall. Previous studies have suggested that the diurnal blood pressure rhythm is similar in younger and older subjects (Drayer *et al,* 1982; Kennedy *et al,* 1983; Munakata *et al,* 1991) but these are in relatively small patient groups, with less variation in age between groups.

Reduction in diurnal blood pressure variation with age could have several potential mechanisms. Older subjects tend to sleep less and have more fragmented sleep pattern (Feinberg *et al,* 1967). One third of people over the age of 65 report waking too early several times per week (Mant & Eyland, 1988). Particularly when relying on an arbitrary definition of day and night, the shorter sleep period could result in some wake readings being included in the night value, artefactually raising this. Moreover, the more fragmented sleep pattern may attenuate the associated fall in blood pressure, and result in greater sleep disruption from the monitoring process.

Studies of American Negroes have suggested that diurnal blood pressure variation is smaller than in Caucasian controls (Harshfield *et al,* 1990; Murphy *et al,* 1991), but African Negroes have a similar profile to American Caucasians (Murphy *et al,* 1991). Detailed analysis of these ethnic differences have suggested that the effect is likely to be environmental and largely accounted for by differences in the extent and nature of physical activity in the different groups (Murphy *et al,* 1991). Similar mechanisms may explain the decline in diurnal blood pressure variation with age. Older patients are less likely to engage in strenuous physical activity and so, if matched for nocturnal pressure, will have relatively lower day-time blood pressure.

Assessment of the effect of antihypertensive treatment on blood pressure can only be accurately assessed in a blinded prospective study but analysis of our data base has enabled a search for potentially important differences between drugs. Clearly, if a potent, short acting drug was given on retiring to bed, lowering blood pressure during this period only, an accentuation of the diurnal rhythm could be achieved. However, all patients analysed here were treated with conventional therapy, consisting either of a single agent known to influence blood pressure over 24 hours, or divided doses of shorter acting agents. When comparing treated to untreated patients, regardless of treatment type, diurnal blood pressure variability was less in the treated group. Day-time systolic pressure was similar in the two groups, but diastolic pressure higher in the untreated patients. Differences in night time pressures could largely be accounted for by age, suggesting that the effect on the diurnal rhythm is due predominantly to relatively lower pressure during wake hours in the treated patients. This hypothesis would accord with Pickering's conclusion from a review of studies of anti-hypertensive studies using ambulatory monitoring (Pickering, 1990e). As drug therapy is still largely monitored and adjusted using clinic or day-time blood pressure values, treatment will not have been increased in those whose pressure was not reduced at night, and this observation may therefore reflect a less pronounced effect of some agents on night-time pressure. Against this, however, is the observation that in patients who had undergone repeat monitoring after a change in treatment, there was a marked decrease in both day and night blood pressure, with no overall effect on the diurnal rhythm.

Study of patients treated with a single drug only demonstrated attenuation of the nocturnal dip predominantly in patients treated with a calcium antagonist. However such patients were also older and had higher blood pressure on treatment, suggesting that their baseline hypertension was more severe. As such, the groups are not strictly comparable and we must be wary of drawing erroneous conclusions, particularly as prospective studies of drugs in this class have shown no effect on the diurnal rhythm (Gould *et al,* 1982; Lacourciere *et al,* 1990). Nonetheless, a recent case control study of patients treated with different anti-hypertensive drugs found an increased risk of myocardial infarction in those treated with calcium antagonists, suggesting that these drugs could have different and potentially adverse effects on the cardiovascular system (Psaty *et al,* 1995). If such patients had less blood pressure reduction during the night, this would be one potential mechanism to explain this effect. However, a more plausible explanation is that selection bias resulted in patients at more risk of cardiovascular disease receiving calcium channel blockers, both in Psaty's study and in our own. This would explain both the excess of

myocardial infarction associated with use of these drugs, and the reduced nocturnal dip, if we accept this as a marker of cardiovascular risk.

Conclusions

This study has confirmed that the nocturnal fall in blood pressure is a Normally distributed phenomenon in the population. It has also shown an inverse linear relationship between age and diurnal blood pressure variability. There is no evidence that the dip is related to severity of hypertension, and a significant effect related to anti-hypertensive drug therapy appears unlikely. Attenuation of the nocturnal dip is common in secondary hypertension, but not universal. Study of those conditions in which this is most apparent suggests an important role for the autonomic nervous system, with the condition of catecholamine excess, phaeochromocytoma, having a marked effect on the diurnal rhythm. The possibility that volume changes related to posture also play a role is raised by the observation that the diurnal rhythm is blunted in the volume mediated hypertension of acromegaly and in patients with mildly impaired renal function. The nocturnal fall in blood pressure is a complex, multifactorial process, but this study has provided important insights into some of these mechanisms.

CHAPTER 5

Cortisol as a Potential Modulator of the Diurnal Rhythm

Background

The secretion of corticosteroid has a circadian rhythm in normal individuals (Akerstedt & Levi, 1978; Desir *et al,* 1980), and is thought to control the circadian variation of other biological variables (Desir *et al,* 1980). The potential for a role of this hormone in the control of the diurnal variation of blood pressure is therefore apparent. Studies of patients with Cushing's syndrome (Imai *et al,* 1988b; Munakata *et al,* 1988) and on large doses of exogenous steroids (Imai *et al,* 1989) have demonstrated the ability of corticosteroids to abolish this rhythm. However, the mechanism of this is uncertain, and the extent to which endogenous steroids are involved in the physiological control of blood pressure is not clear.

The nocturnal fall in blood pressure is multifactorial, but withdrawal of sympathetic tone is likely to have a major role. Plasma adrenaline and noradrenaline levels are influenced by the circadian rhythm of cortisol (Akerstedt & Levi, 1978) and by glucocorticoid administration (Stene *et al,* 1980). Moreover, glucocorticoids can influence the vascular responsiveness to catecholamines (Kalsner, 1969; Krakoff *et al,* 1975) and may also act centrally to increase sympathetic activity (Takahashi *et al,* 1983).

Excess glucocorticoid can also disturb normal sleep patterns. Up to two thirds of patients with Cushing's syndrome complain of insomnia (Starkman *et al,* 1981). Sleep studies in patients with endogenous cortisol excess have demonstrated decreased or no slow wave sleep (Krieger *et al,* 1976; Fehm *et al,* 1986) and exogenous glucocorticoid can alter the amount of rapid eye movement sleep (Gillin *et al,* 1972; Fehm *et al,* 1986) and increase intermittent wakefulness (Fehm *et al,* 1986). As blood pressure changes according to sleep phase (Khatri & Freis, 1969), the effect of steroid on blood pressure may be enacted indirectly via its effect on sleep.

Patients with secondary adrenocortical insufficiency require exogenous replacement of steroid with hydrocortisone. It is conventional to administer a twice daily regime which usually involves a larger dose in the morning with a smaller dose in the evening in an attempt to mimic the circadian rhythm of cortisol production. A typical schedule is 20 mg

taken on rising and 10 mg taken in the evening. However it is likely that individual dose requirement varies. Under replacement may cause vague symptoms of ill health or fatigue, while mild over-replacement, although clinically silent, may produce metabolic complications over the longer term. Unlike primary adrenocortical insufficiency (Addison's disease), where plasma ACTH serves as a marker for cortisol over-replacement, such over-replacement is difficult to detect.

Jyothinagaram *et al* (1989) have shown that reversing the periodicity of a normal replacement regime in such patients, with the higher dose given at night, has no effect on the diurnal blood pressure rhythm, suggesting that the blood pressure rhythm is not closely entrained to physiological cortisol levels.

Introduction

With the premise that pathological, but not physiological, doses of hydrocortisone may significantly influence the blood pressure profile, this study was designed to ascertain whether modest changes in exposure to corticosteroid can influence the diurnal rhythm. This work was performed with the assistance of Mr. David Leitch, a medical student working on a Scottish Home and Health Department Vacation Grant, who helped with patient recruitment and biochemical analyses.

Patients and Methods

This study was conducted in compliance with ethical committee review and all patients gave written informed consent.

Fifteen hypopituitary patients requiring hydrocortisone replacement therapy under regular review in the local Pituitary clinic were studied (Table 5.1). All had had pituitary neoplasms and all but two became hypopituitary secondary to tumour resection. No patient was on cardio-active medication. Three patients were unable to tolerate overnight blood pressure monitoring and were therefore excluded from further study.

Table 5.1 **Demographic details**

Subject	Age	Sex	Normal dose of Hydrocortisone
1	53	M	20 mg + 10 mg
2	48	M	20 mg + 10 mg
3	57	M	20 mg + 10 mg
4	31	F	5 mg + 2.5 mg
5	61	M	20 mg + 10 mg
6	53	M	30 mg + 10 mg
7	42	F	20 mg + 10 mg
8	52	M	10 mg + 10 mg
9	54	F	10 mg + 5 mg + 5 mg
10	59	M	20 mg + 10 mg
11	32	F	20 mg + 10 mg
12	27	M	15 mg + 5 mg
Mean (± S.D.)	47 ± 12	75% M 25% F	17.5 + 8.5

This was a 2 week, open, randomised, two period study. Patients were randomised to initial study on their normal maintenance dose of hydrocortisone, followed by repeat study after one week on double their normal steroid dose, or to initial study after taking the increased dose for one week, with repeat study one week after dosing was returned to normal. All medication, other than the hydrocortisone, was kept constant throughout the study period.

All subjects had their blood pressure monitored over 24 hours, with readings every 30 minutes, using the SpaceLabs 90207 ambulatory monitoring system (O'Brien *et al,* 1991b). Patients were also fitted with a wrist activity meter to enable accurate quantification of sleep time (Webster *et al,* 1982). In light of the known effects of corticosteroids on sleep, patients were also asked to comment on their quality of sleep, using a visual analogue scale to quantify this. This consisted of a 20 cm line, with subjects asked to mark with a cross a value between zero and ten, where a value of 10 was taken to be a normal night's sleep and zero to be no sleep whatsoever. Percentage sleep disturbance was then calculated by measuring the distance along the scale from zero to the cross to the nearest centimetre.

Two 12 hour urine samples were collected during each period of ambulatory monitoring to measure day (8 am - 8 pm) and night (8 pm - 8 am) free cortisol excretion. An aliquot of each sample was then analysed using the Amerlex cortisol radio-immunoassay.

Statistical Analysis

Differences between day, night and 24-hour cortisol excretion on the two different doses of hydrocortisone were compared using Wilcoxan rank sum test for paired data. Linear analogue scale sleep scores were also analysed using Wilcoxan's method.

Changes in ambulatory blood pressure parameters were examined using Student's paired t-test.

Pearson's correlation coefficient was used to assess the strength of the association between exposure to glucocorticoid and the nocturnal blood pressure fall, expressed as percentage change from day to night. The blood pressure dip was correlated with both day and night cortisol excretion.

Results

Cortisol excretion was significantly higher on the larger dose of hydrocortisone, confirming increased exposure to cortisol (Table 5.2).

Table 5.2 **Urinary free cortisol**

	Normal Dose (nmol/l)	**High Dose (nmol/l)**	**p**
Day	263	463	0.02
Night	99	229	0.01

Although subjects reported greater than 25% sleep disturbance on 13 of the 24 (54%) visits, using their normal night's sleep as a standard for comparison, sleep time and quality were unaffected by the change in hydrocortisone dosage (Table 5.3). However, an order effect was apparent, with sleep quality on linear analogue scale increasing from a mean of 65% to 77% ($p = 0.047$) from the first to the second ambulatory recording period.

Table 5.3 **Sleep time measured by wrist actigraph and sleep quality measured by linear analogue scale**

	Normal Dose		High Dose		
	Mean	**Median**	**Mean**	**Median**	**p**
Sleep Time (Minutes)	447	436	436	442	NS
Sleep Quality (% score on linear scale)	72	78	70	72	NS

Neither total blood pressure nor the diurnal blood pressure profile was significantly affected by the increased dose of steroid (Table 5.4, Figure 5.1).

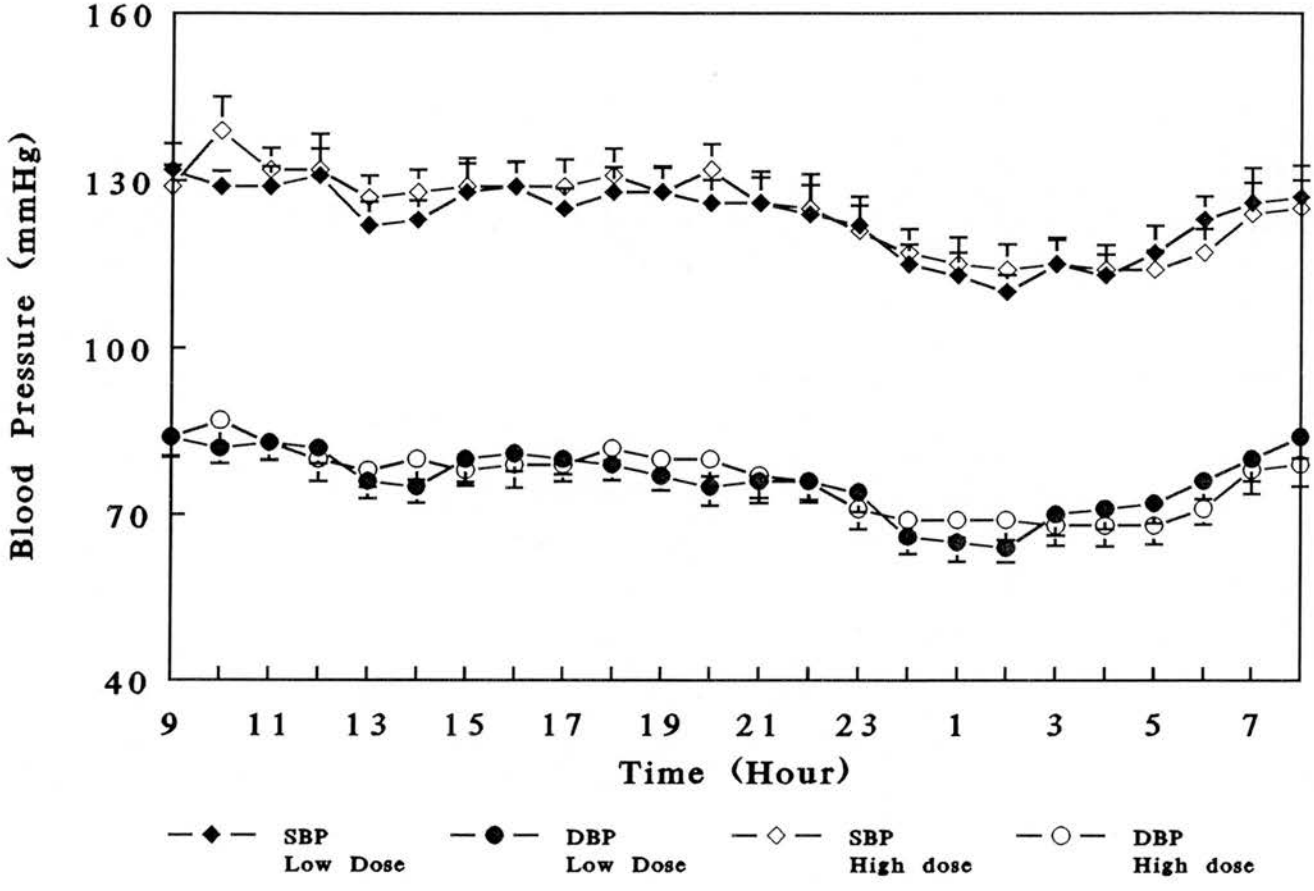
Day-time cortisol excretion appeared to be negatively correlated with the nocturnal dip, with Pearson's correlation coefficient -0.45/-0.5 for systolic and diastolic blood pressure (Figure 5.2), although this was not statistically significant. The strength of association fell on the higher dose of hydrocortisone to -0.23/-0.46. There was no evidence of any association with night-time cortisol, with correlation coefficient ≤ 0.1.

Table 5.4 **Ambulatory blood pressure profile.**

Variable (Mean $\pm$ S.E.M.)	**Normal Dose**	**High Dose**
24-hour Systolic BP	123 ± 4	124 ± 4
24-hour Diastolic BP	76 ± 3	76 ± 3
Mean Wake Systolic BP	127 ± 4	129 ± 4
Mean Wake Diastolic BP	80 ± 3	80 ± 3
Mean Sleep Systolic BP	115 ± 4	114 ± 4
Mean Sleep Diastolic BP	69 ± 3	68 ± 3
Nocturnal SBP Dip (%)	10.9 ± 1.7	11.2 ± 1.9
Nocturnal DBP Dip (%)	14.1 ± 2.2	14.5 ± 2.2

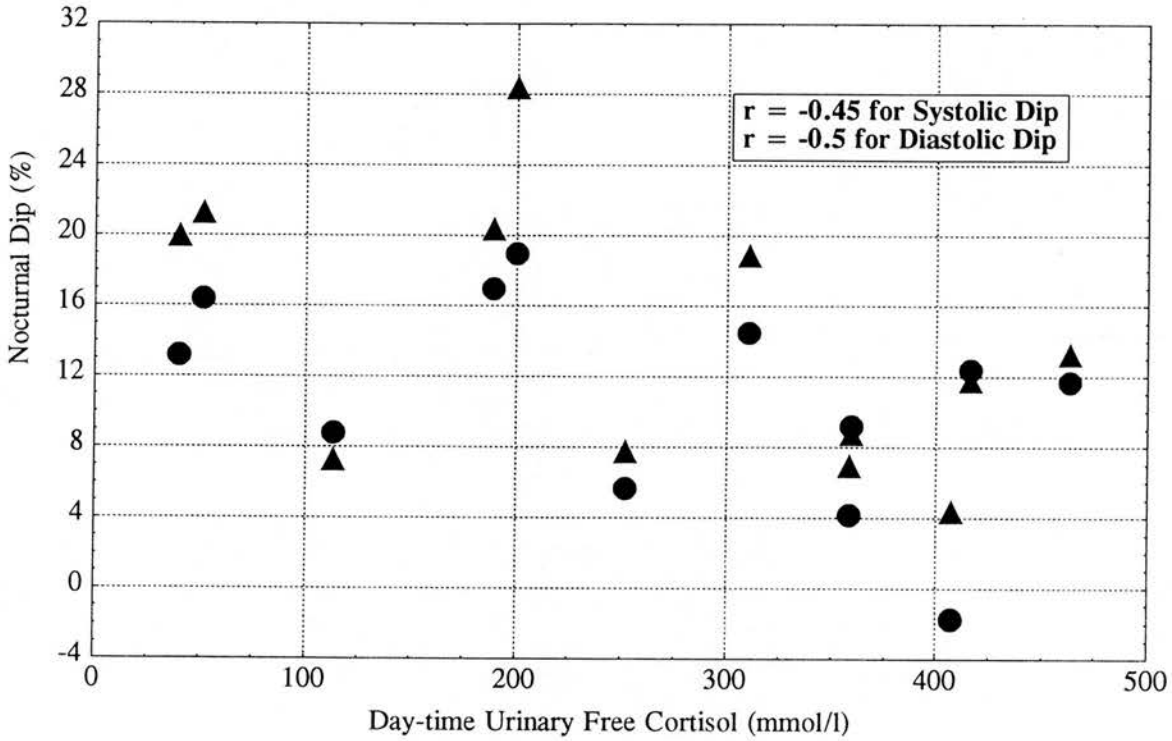
There was no significant difference between blood pressure on normal and high dose hydrocortisone.

Figure 5.1 **The Impact of Increased Steroid Exposure on Ambulatory Blood Pressure in Hypopituitary Patients**



Ambulatory blood pressure profile of patients on normal dose (solid symbols) and high dose (open symbols) hydrocortisone. Hourly mean BP ± S.E.M. has been plotted against time. The curves are almost identical indicating no effect on either the level or diurnal variation of BP.

Figure 5.2 **Relationship of Cortisol Exposure to Diurnal Blood Pressure Variation**



Correlation of urinary free cortisol and the nocturnal dip in blood pressure with diurnal variation in systolic BP indicated by circles and diastolic BP by triangles. There is an apparent negative correlation between the nocturnal dip and day-time cortisol exposure but this is not statistically significant.

Discussion

An effect on the blood pressure profile has only been demonstrated with hugely pharmacological doses of exogenous glucocorticoid (Munakata *et al,* 1988; Imai *et al,* 1989) or in untreated Cushing's disease or syndrome (Imai *et al,* 1988b). That such pathological exposure to glucocorticoid can influence the diurnal rhythm is not questioned, but the dose level and duration at which this first occurs remains unknown and the mechanism uncertain.

In this study, despite a significant increase in exposure to corticosteroid over 24 hours, this modest increase in hydrocortisone (which remains within the range seen physiologically) did not influence the diurnal blood pressure rhythm in hypopituitary patients in the short term. While it is possible that the neutral effect of hydrocortisone on blood pressure demonstrated here represents a type 1 statistical error related to the small number of patients studied, the fact that there was a slight *increase* in the nocturnal dip on the higher dose of steroid makes this less likely. This, together with the observation that reversing the day and night dose of hydrocortisone has no impact on diurnal variation in a similar group of patients (Jyothinagaram *et al,* 1989), makes a role for cortisol in the physiological control of blood pressure variability unlikely. However, the negative correlation seen between day-time cortisol excretion and the nocturnal dip, although not statistically significant, makes it impossible to exclude such a relationship altogether.

In addition, patients with hypopituitarism may not be entirely representative of a healthy population. They suffer from multiple hormone deficiencies which are incompletely replaced. In particular, most are deficient in growth hormone which is also known to influence blood pressure (Fraser *et al,* 1989). They are also deficient in adrenocorticotrophic hormone which has a modulating influence on cortisol metabolism at tissue level in addition to its principal action on the adrenal gland, and may have independent effects on blood pressure regulation (Fraser *et al,* 1989). Nonetheless, such patients provide the only means by which changes in cortisol exposure within the physiological range can be explored, and any difference in the blood pressure response would be controlled for in a cross-over study. Moreover, the patients studied here had all been maintained on hormone replacement therapy and been stable and clinically well for a period of years. As such, we would have expected cardiovascular responsiveness to glucocorticoid to be little different from the normal population.

The influence of corticosteroid on sleep pattern is a possible explanation for the modulating effect on blood pressure. To allow for this we measured sleep time objectively with wrist activity meters and sleep quality subjectively by linear analogue scale, and found these parameters unaffected by the increased dose of hydrocortisone. However, self-reported monitoring of sleep quality is relatively insensitive and minor effects on the pattern of sleep can only be detected by continuous EEG monitoring during sleep (Fehm *et al,* 1986). Thus, it is not possible to completely exclude an effect of glucocorticoid on sleep pattern in this or other studies. Clearly, if this is the mechanism by which higher doses of steroid influence the nocturnal blood pressure fall, the increased exposure to hydrocortisone obtained in this study was not sufficient to influence the sleep pattern.

Conclusions

Increased exposure to cortisol occurring within the physiological range does not appear to have any significant effect on the diurnal blood pressure rhythm, making a physiological role for cortisol in the control of the nocturnal dip unlikely.

CHAPTER 6

Diurnal Blood Pressure Variation in Accelerated Phase Hypertension and Following Acute Hospitalisation

Background

Diurnal blood pressure curves appear sinusoidal when presented graphically. However, when the effects of environmental stimuli and physical activity are reduced to a minimum, the profile becomes relatively flat, with the fall during sleep persisting, making the curve appears as a square wave (Athanassiadis *et al,* 1969; Mann *et al,* 1979). Blood pressure changes also appear less pronounced in hospitalised patients when compared to patients studied in their natural environment (Young *et al,* 1983), with higher levels of blood pressure and of blood pressure variability seen at home. Both the average level of blood pressure and blood pressure variability have been shown to fall during periods of bed rest as compared to activity (Rowlands *et al,* 1980) but the effect of acute hospitalisation on nocturnal blood pressure and on diurnal blood pressure variability has not been studied previously. As many of the conditions commonly quoted as being associated with abolition of diurnal blood pressure variability have been studied only in hospitalised patients, this potential confounding factor is clearly of some importance.

Information on blood pressure variability in malignant or accelerated hypertension is particularly lacking, with only one study in the literature examining the diurnal rhythm in patients hospitalised with this condition. As the blood pressure of such patients frequently falls significantly following hospital admission and bed rest, before the use of anti-hypertensive drugs, the potential for hospitalisation to influence the diurnal rhythm is marked.

Malignant Hypertension

Malignant hypertension was originally defined by Volhard and Fahr (1914) as a condition characterised by severe hypertension, impaired renal function and rapid progression to uraemic death, associated with fibrinoid necrosis and intimal proliferation of renal arterioles. This definition was later refined by Keith *et al* (1939) when they identified the importance of retinal haemorrhages, exudates and papilloedema in hypertensive patients. Possibly due to better detection of hypertension and improved treatment of mild and moderate disease, malignant phase hypertension is now a relatively rare disease (Kincaid-Smith, 1985).

While effective treatment for malignant hypertension is now available, the pathophysiology is still incompletely understood. Although a complication of established hypertension, the height of the blood pressure alone does not distinguish benign from malignant phase. Prior to the introduction of effective anti-hypertensive therapy, there was little difference between the blood pressure levels of patients with severe benign hypertension and malignant hypertension (Kincaid-Smith *et al,* 1958). Malignant hypertension is an angiotensin dependent form of hypertension with high renin and angiotensin II levels (Laragh *et al,* 1960). The initial elevation in angiotensin II may in part result from renal arterial narrowing and, once initiated, a vicious circle develops in which increasing renal damage results in increased release of renin and a consequent further rise in blood pressure (Kincaid-Smith, 1980). Although it can arise from hypertension of any cause providing the pressure rises high enough or increases rapidly, there is underlying renal disease in at least 50% of cases (Kincaid-Smith, 1991).

Malignant hypertension is characterised by fibrinoid necrosis of small arterioles of the kidney and throughout the body. Fibrinoid necrosis in the retina results in the development of soft exudates, flame-shaped haemorrhages and, eventually, papilloedema. It is now appreciated that there is a spectrum of severe hypertension and the term accelerated hypertension is used to describe the clinical condition of severe hypertension associated with exudates and/or haemorrhages in the retinal fundus, encompassing both malignant phase hypertension (traditionally diagnosed only in the presence of papilloedema), which may be associated with encephalopathy and renal failure, and lesser degrees of severe hypertension (Ahmed *et al,* 1986). Untreated, this condition has a mortality of around 80% at two years (Leishman, 1959).

In a study of hospitalised patients on bed rest Shaw *et al* (1963) found that patients with malignant hypertension, diagnosed on the basis of fundal changes, had no nocturnal fall in blood pressure, while a control group of patients with benign essential hypertension had a normal nocturnal fall. This study utilised a static automatic blood pressure monitor which measured blood pressure at half hourly intervals for 24 hours and subjects were therefore confined to bed for the period of study. The average blood pressure of patients with benign hypertension (217/127 mmHg) was similar to those with malignant (238/135 mmHg) and there was no correlation between the severity of hypertension and the change in blood pressure during sleep. The authors concluded that the severity of the hypertension did not account for the difference between the two groups and hypothesised that the pathological changes in small vessels in malignant phase hypertension resulted in a

relatively fixed peripheral vascular resistance, preventing the fall in blood pressure during sleep. This remains the only study examining nocturnal blood pressure in patients with malignant or accelerated hypertension.

Introduction

Accelerated hypertension is said to abolish the normal diurnal variation in blood pressure but the only study to examine this phenomenon was performed over 30 years ago, using a newly developed automatic blood pressure monitor which tied patients to their beds, preventing full mobility. To confirm this observation, determine whether it is a specific phenomenon related to the pathophysiology of the accelerated phase, and assess the extent to which acute hospitalisation and bed rest could account for any abnormality in diurnal blood pressure variability, patients with accelerated hypertension have been studied as soon as practicable following diagnosis. The ambulatory blood pressure profile has been compared to that of patients with benign essential hypertension and to patients admitted to hospital with other acute medical conditions. Two such control groups were studied: (i) patients with acute stroke who were hypertensive on admission to hospital, and (ii) a random selection of patients admitted with other acute medical problems.

Patients and Methods

Accelerated hypertension was defined as severe hypertension, with grade III or IV retinopathy (haemorrhages and exudates $\pm$ papilloedema). Eleven such patients were identified within 24 hours of diagnosis and agreed to undergo ambulatory blood pressure monitoring. Nine were studied as hospital in-patients and two as out-patients. All received routine medical and nursing care but were not on strict bed rest. Ten were either already on anti-hypertensive medication or were started on treatment during the recording period. Demographic details are given in Table 6.1. All underwent full investigation to look for a secondary cause of their hypertension. Six patients had renovascular hypertension (atheromatous renal artery stenosis), one renal parenchymal disease and 4 essential hypertension. Renal function as assessed by serum biochemistry was normal in 3 (urea 5 ± 0.8 mmol/l, creatinine 111 ± 6.1 μmol/l), borderline high in 3 (urea 8.9 ± 1.7 mmol/l, creatinine 145 ± 4.7 μmol/l) and significantly abnormal in 4 (urea 21.6 ± 7.6 mmol/l, creatinine 448 ± 184 μmol/l) with no result available from one patient.

Six patients underwent repeat ambulatory blood pressure monitoring after treatment, when fundal signs had resolved, 1 to 15 months (mean 5) after the initial diagnosis.

Out-patients attending the Hypertension Clinic with benign essential hypertension who had been referred for ambulatory blood pressure monitoring (n = 135) were used as the out-patient control group. Ninety (67%) were on anti-hypertensive treatment. Demographic details are given in Table 6.1a.

Sixteen patients with acute stroke found to be hypertensive on admission to hospital (ward BP > 160/90 mmHg) also agreed to undergo ambulatory blood pressure monitoring within 24 hours of admission. Five of the 16 were on anti-hypertensive treatment which was continued after admission. A further group of 10 patients admitted to the acute medical wards were also studied shortly after admission. Any patient who was haemodynamically stable, not requiring emergency drug treatment likely to influence blood pressure, and fit to give informed consent, was considered for this study group. Three patients were admitted with non-specific chest pain, 2 with suspected pulmonary thrombo-embolism, 2 with congestive cardiac failure, 2 with urinary tract infection and one with Wernicke's encephalopathy. Three were on drugs which could affect blood pressure. Demographic details are given in Table 6.1b.

Data acquisition and statistical analysis

Ambulatory blood pressure monitoring was performed using the Accutracker 1 monitor in 6 patients and the SpaceLabs 90207 in 5 patients with accelerated hypertension. All control group recordings were obtained with the SpaceLabs 90207. Blood pressure readings were obtained at least every thirty minutes for 24 hours in every patient. In stroke patients, the monitor was fitted to the non-paretic arm (Yagi *et al,* 1986). Day-time blood pressure was defined as 7 am to 12 midnight and night-time as midnight to 7 am. The prevalence of non-dipping in patients with accelerated hypertension, defined as night-time BP < 10% lower than day-time BP for both systolic and diastolic pressure, was compared to that of the control groups using the Chi squared test. Diurnal blood pressure variation, defined as the mean day-night BP difference expressed as a percentage, was also analysed, using Student's t-test. The change in diurnal variation in those patients with accelerated hypertension in whom a second recording was available after treatment was assessed using Student's paired t-test.

Table 6.1a **Demographic Details - Accelerated and Essential Hypertension**

Mean ± S.E.M.	Accelerated Hypertension	Essential Hypertension	p
Number	11	135	
Age	61±12	53±1.2	NS
Sex	6 M, 5F	63M, 72F	NS
Clinic systolic BP	192±9.1	172±1.7	0.003
Clinic diastolic BP	115±8.7	105±1.1	0.025

Table 6.1b **Demographic Details - Control Groups**

Mean ± S.E.M.	Accelerated Hypertension	Acute Stroke	p	Medical Admissions	p
Number	11	16		10	
Age	61±12	66±3.4	NS	59±2.8	NS
Sex	6 M, 5F	9 M, 7F	NS	7M, 3F	NS
Clinic systolic BP	192±9.1	176±4.8	NS	138±4.9	0.00007
Clinic diastolic BP	115±8.7	101±3.4	NS	86±4.2	0.0008

The age and initial blood pressure of the accelerated hypertension group has been compared to each of the control groups using Student's t-test and the proportion of patients in each sex compared using Chi squared.

Results

Ambulatory blood pressure parameters for patients with accelerated hypertension and for each control group are given in Tables 6.2a and 6.2b.

Eight of the 11 (73%) patients with accelerated hypertension were non-dippers, compared to only 33 of the 135 (24%) with essential hypertension (x^2 = 11.7, p = 0.0006). Diurnal blood pressure was blunted in patients with accelerated phase hypertension (Figure 6.1), with a nocturnal dip of 1.7/5.5% compared to 10.2/15%. There was no significant correlation between the severity of the hypertension and the nocturnal dip in either patient group: correlation coefficients for day mean BP and nocturnal dip were -0.28/-0.12 in accelerated hypertension and -0.11/0.01 in benign essential hypertension.

Table 6.2a **Ambulatory BP Data in Accelerated and Benign Hypertension.**

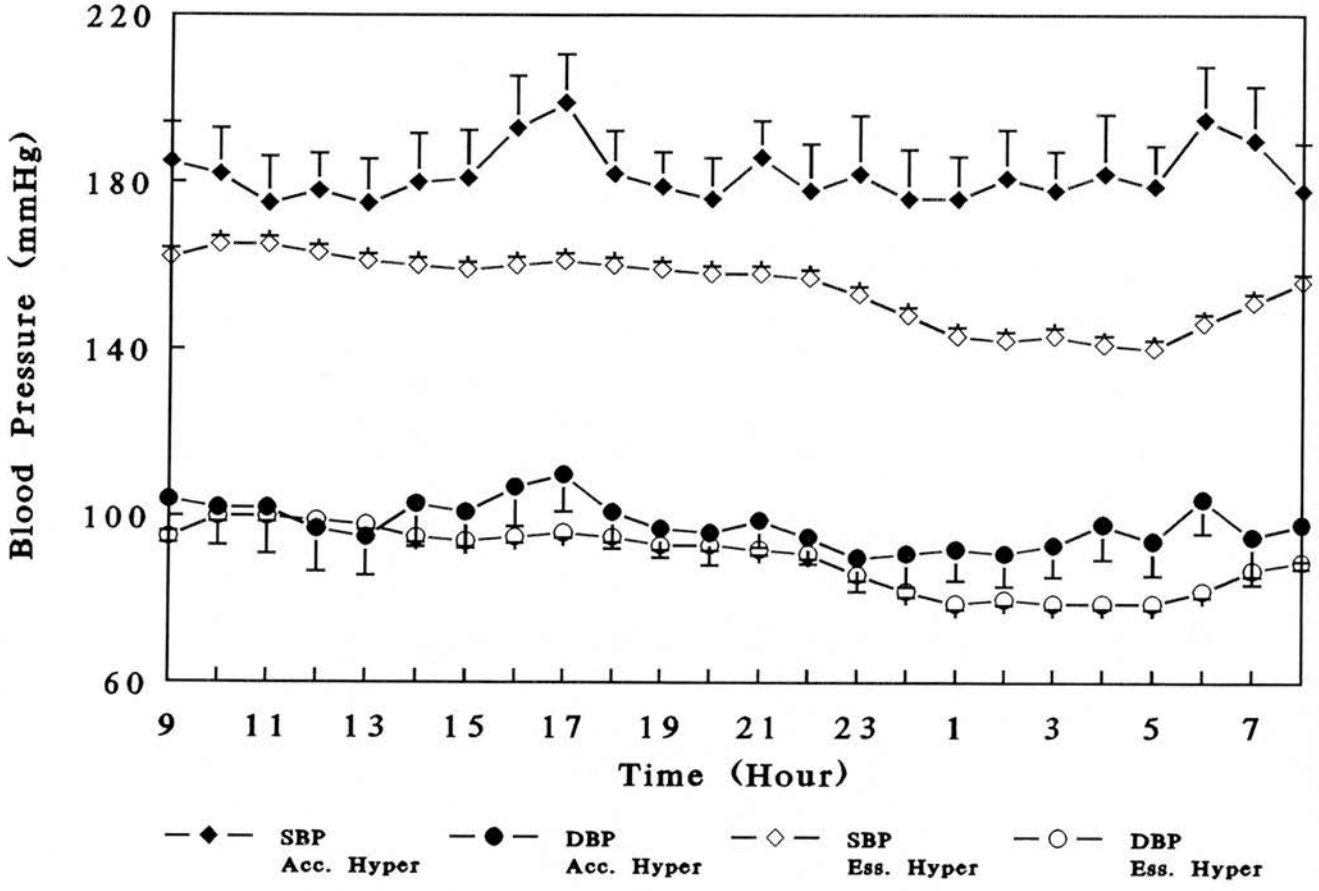
Mean ± S.E.M.	Accelerated Hypertension	Essential Hypertension	p
24 hour Systolic BP	183±10.1	155±1.4	0.00001
24 hour Diastolic BP	98±7.3	90±0.9	0.04
Day mean Systolic BP	184±9.9	160±1.5	0.0001
Day mean Diastolic BP	100±7.4	95±1	NS
Night mean Systolic BP	181±10.9	144±1.9	0.000001
Night mean Diastolic BP	94±7.4	80±1.1	0.002
Nocturnal Dip - Systolic BP (%)	1.7±1.8	10.2±0.7	0.0008
Nocturnal Dip - Diastolic BP (%)	5.5±2.2	15±0.8	0.0008

Table 6.2b **Ambulatory BP Data in Accelerated Hypertension Compared to Acute Hospital Admissions**

Mean ± S.E.M.	Accelerated Hypertension	Acute Stroke	p	Medical Admissions	p
24 hour Systolic BP	183±10.1	163±3.9	0.04	130±4	0.0001
24 hour Diastolic BP	98±7.3	96±3.3	NS	80±3.2	0.04
Day mean Systolic BP	184±9.9	165±3.8	0.049	133±3.8	0.0002
Day mean Diastolic BP	100±7.4	97±3.4	NS	82±3.2	0.048
Night mean Systolic BP	181±10.9	158±4.8	0.04	123±4.8	0.0001
Night mean Diastolic BP	94±7.4	92±3.6	NS	74±3.8	0.03
Nocturnal Dip - Systolic BP (%)	1.7±1.8	4.4±1.7	NS	7.2±2.1	NS
Nocturnal Dip - Diastolic BP (%)	5.5±2.2	5.1±2.2	NS	9.2±2.1	NS

Ambulatory blood pressure parameters of the accelerated hypertension group have been compared to each of the control groups using Student's t-test.

Figure 6.1 **Ambulatory Blood Pressure of Patients with Accelerated and Benign Hypertension**



Ambulatory blood pressure profile in patients with accelerated phase hypertension (solid symbols) and benign essential hypertension (open symbols). Mean hourly blood pressure ± S.E.M. has been plotted against time for each group. The curve from patients with accelerated phase hypertension is seen to be relatively flat, while the normal nocturnal fall in blood pressure can be appreciated in patients with benign essential hypertension.

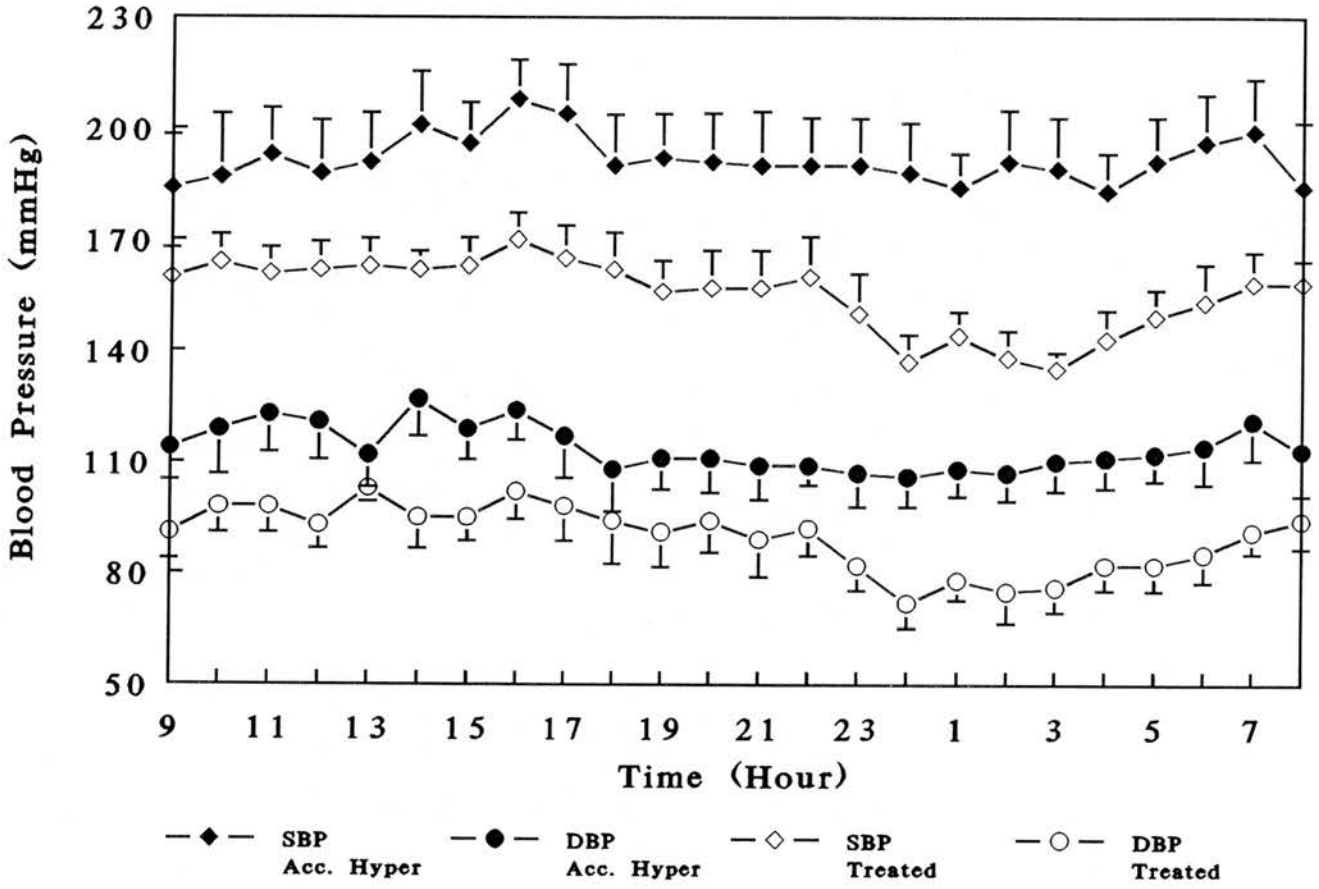
In the 6 patients with repeat ambulatory monitoring, day mean BP had fallen from 194/114 to 161/94 and diurnal blood pressure variation increased from 2/4.1% to 10.2/15.9% (Table 6.3, Figure 6.2).

Nine of the 16 stroke patients (56%) and 5 of the 10 (50%) hospital admissions were non-dippers, which is similar to the prevalence seen in the patients with accelerated hypertension (x^2 = 0.4, NS, Figure 6.3). Diurnal blood pressure variation in both stroke patients and acute admissions was more pronounced than in those with accelerated hypertension (Table 6.2b, Figure 6.4) but this difference was not statistically significant in either group.

Table 6.3 **Ambulatory blood pressure data from patients with accelerated hypertension after treatment**

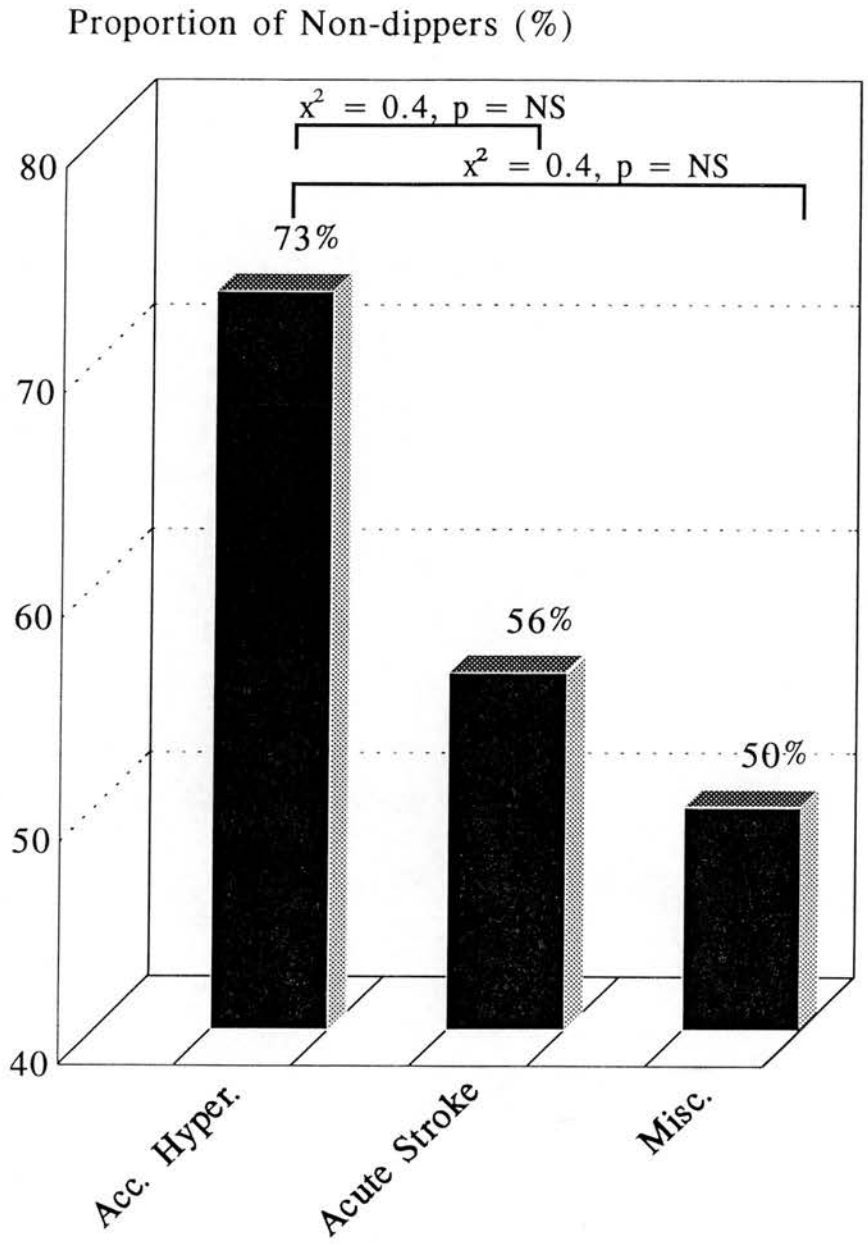
Mean ± S.E.M.	**Accelerated Hypertension - Baseline**	**Accelerated Hypertension - Treated**	**p**
24 hour Systolic BP	193±11.6	157±6.8	NS
24 hour Diastolic BP	113±7.7	90±6.7	NS
Day mean Systolic BP	194±11.9	161±6.4	NS
Day mean Diastolic BP	114±8.2	94±6.8	NS
Night mean Systolic BP	190±11.6	145±7.5	0.04
Night mean Diastolic BP	109±7.3	79±6.3	0.04
Nocturnal Dip - Systolic BP (%)	2±2.7	10.2±1.6	0.02
Nocturnal Dip - Diastolic BP (%)	4.1±3.6	15.9±2	0.04

Figure 6.2 **Effect of Successful Treatment of Accelerated Phase Hypertension on Diurnal Blood Pressure Variation**



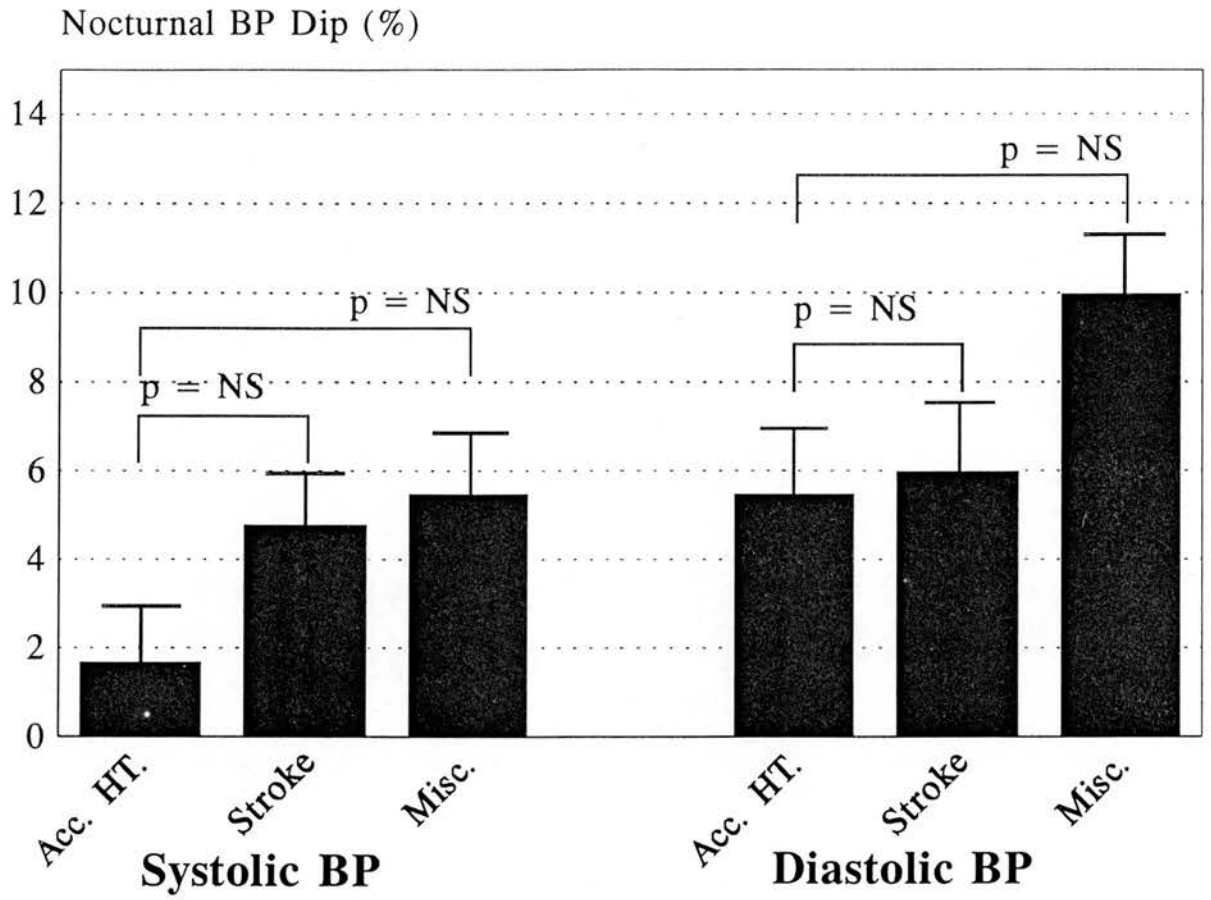
Hourly mean blood pressure ± S.E.M. in patients with accelerated hypertension before (solid symbols) and after (open symbols) treatment. Return of the normal nocturnal drop in blood pressure is readily appreciated.

Figure 6.3 **Proportion of Non-Dippers in Accelerated Hypertension and After Acute Hospitalisation**



The proportion of non-dippers in patients with accelerated hypertension (acc. hyper), acute stroke and miscellaneous other medical conditions (misc.) are compared. Although the proportion of non-dippers in patients with accelerated hypertension is greater, this is not statistically significant.

Figure 6.4 **Diurnal Blood Pressure Variation in Accelerated Hypertension and After Acute Hospitalisation**



Diurnal blood pressure variation, expressed as the percentage change from day to night, is compared in patients with accelerated hypertension (acc. HT), acute stroke and miscellaneous other medical conditions (misc.). Again, although diurnal variation is less in patients with accelerated hypertension, the difference is not statistically significant.

Discussion

Significant blunting of the diurnal blood pressure profile in patients with accelerated phase hypertension has been confirmed, and the observation that this profile returns towards normal with successful treatment of the accelerated phase, as demonstrated by resolution of fundal changes, suggests that it may be a specific complication of this condition. Renal impairment is a common complication of accelerated hypertension (Kincaid-Smith, 1991) and was the most common cause of death in such patients before successful treatment was available (Kincaid-Smith *et al,* 1958). Moreover, seven of the 11 patients studied here had renal disease complicating their hypertension and possibly contributing to the development of the accelerated phase. As renal impairment *per se* appears capable of influencing the diurnal rhythm (Baumgart *et al,* 1989b; Abel *et al,* 1990) (Chapter 4) this may be the mechanism by which diurnal blood pressure variability is modified in a relatively short time frame. However, with the small numbers studied here, and without more accurate measurement of renal function, this hypothesis could not be tested further in this patient group.

Nine of the 11 patients studied were admitted to hospital with some urgency to receive treatment of severe hypertension and have therefore been studied in unfamiliar circumstances. Whilst not on strict bed rest, activity during day-time is also likely to have been significantly reduced. Comparing blood pressure variability to out-patients undertaking normal activity may therefore be inappropriate and two further control groups were studied - patients admitted to hospital acutely with common medical conditions and patients with acute stroke.

Study of blood pressure changes in patients requiring acute medical care is hampered by the potential for emergency therapy to influence the blood pressure. Patients chosen for study were all therefore relatively stable, admitted primarily for further investigation or for treatment unlikely to influence blood pressure acutely. Two patients with congestive cardiac failure were included in this group but neither required intra-venous therapy to control their symptoms. This group was normotensive but blunting of the diurnal blood pressure rhythm was still apparent, albeit less pronounced. The prevalence of non-dipping and the amplitude of the diurnal rhythm did not differ significantly from that of patients with accelerated hypertension.

The impact of hospitalisation on blood pressure may be more pronounced in patients with elevation of blood pressure on arrival. As over 80% of stroke patients are hypertensive

on admission to hospital (Wallace & Levy, 1981; Loyke, 1983; Oppenheimer & Hachinski, 1992) such patients were also studied here. Any patient admitted with acute stroke and found to have a blood pressure over 160/90 mmHg on arrival on the receiving ward was considered for study. Patients so gravely ill that they were not expected to survive 24 hours were not included.

Study of the blood pressure changes at the time of acute stroke is complex. Hypertension is the major risk factor for cerebrovascular disease (MacMahon *et al,* 1990) and many patients presenting with a cerebrovascular accident will therefore have pre-existing hypertension. Moreover, stroke itself results in acute changes in blood pressure, with an acute rise in the first few days (Wallace & Levy, 1981) followed by a gradual fall over subsequent weeks (Wallace & Levy, 1981; Loyke, 1983; Britton *et al,* 1986). The impact of stroke on ambulatory blood pressure and the diurnal blood pressure rhythm is less clear. However, Shimada *et al* (1990) have recently shown that ambulatory blood pressure better predicts asymptomatic cerebrovascular disease detected by magnetic resonance scanning and that such disease is more common in non-dippers (Shimada *et al,* 1992). Thus, patients with stroke resulting from hypertension may be expected to have reduced diurnal blood pressure variation. In keeping with this, patients in this study admitted to hospital with stroke had significant attenuation of diurnal blood pressure variability. The extent attributable to acute hospitalisation and reduced activity, rather than reflecting the pathophysiology of acute stroke, cannot be determined by this study.

Conclusions

Blunting of the diurnal blood pressure rhythm is common in accelerated phase hypertension and returns towards normal with successful treatment. However, similar changes are seen in other acute hospital admissions. This observation is thus likely to be multifactorial, related in part to the stress of hospitalisation, reduced activity during day-time, and poorer sleep in an unusual environment, in addition to the effect of the underlying illness.

CHAPTER 7

Diurnal Blood Pressure Variation in a Healthy Working Population and its Influence on Target Organ Damage

Background

Although hypertension is an important risk factor for stroke (Medical Research Council Working Party, 1985) and ischaemic heart disease (Kannel, 1987), the benefits of treating mild hypertension in the individual patient are small: in the MRC trial of mild hypertension 850 patient years of treatment were required to prevent 1 stroke (Medical Research Council Working Party, 1985). As anti-hypertensive treatment may even be harmful (MRC Working Party on mild to moderate hypertension, 1981), targeting those individuals who will benefit most from therapy is desirable. One of the major perceived advantages of ambulatory blood pressure monitoring is that it may provide a more accurate estimate of an individual's cardiovascular risk. However, the measure best able to achieve this remains unresolved. Exercise blood pressure, whether measured as the response to static or dynamic exercise, has also been shown to relate to hypertensive target organ damage.

When assessing the importance of risk factors or the impact of an intervention on risk we are primarily interested in clinical outcome, particularly mortality. However, this is often impractical and cross-sectional and epidemiological studies frequently use surrogate measures of disease. Several methods of assessing the extent of hypertensive target organ damage have been developed, including the assessment of vascular changes in the retina (Parati *et al*, 1987), protein excretion in the urine (Opsahl *et al,* 1988), changes in cardiac structure and function (Devereux *et al,* 1983; Parati *et al*, 1987, White, 1990), and, more recently, ultrasonic assessment of carotid artery morphology (Salonen & Salonen, 1991; Roman *et al,* 1992) and nuclear magnetic resonance imaging of brain (Shimada *et al,* 1990). Of these, assessment of left ventricular size is by far the best validated and most widely used, while the measurement of urinary microalbuminuria is perhaps the most widely available.

<u>Measurement of left ventricular mass (LV Mass)</u>

Left ventricular hypertrophy (LVH) is one of the major biological responses to chronic pressure overload (Badeer, 1964) and its development has long been known to indicate an

adverse prognosis (Sokolow & Perloff, 1961). Although severe LVH can be determined from the electrocardiogram, providing a powerful predictor of future cardiovascular morbidity and mortality (Kannel *et al,* 1969; Kannel *et al,* 1970), this is a specific but insensitive measure (Reichek & Devereux, 1981) and does not accurately quantify cardiac mass. The development of a simple non-invasive method of assessing LV mass was therefore a major advance, and while several alternative approaches to the measurement have been assessed, a calculation based on M-mode measurements of left ventricular dimensions at end-diastole according to the Penn convention (Devereux & Reichek, 1977) remains the best validated and most widely used measure. This convention, contrary to conventional measurement criteria, dictates that the thickness of the endocardial lines are excluded from wall thickness measurement and included in the assessment of left ventricular internal diameter. LV mass is then calculated using cube function geometry according to the equation -

$$LV\ Mass = 1.04[(LVIDd + PWTd + IVSTd)^3 - (LVID)^3] - 13.6\ g.$$

where LVIDd = left ventricular internal diameter at end-diastole, PWTd = posterior left ventricular wall thickness at end-diastole and IVSTd = intra-ventricular septal thickness at end-diastole.

As sex and body size significantly influence body size, LV mass should be corrected for body size, conventionally by indexing for body surface area (Devereux *et al,* 1984). Sex specific criteria for the diagnosis of LVH have been developed from population studies, with cut-off values of 134 g/m^2 for men and 110 g/m^2 for women (Hammond *et al,* 1986). Age may also influence left ventricular mass but data from the Framingham study suggests that this may not be an important effect in otherwise healthy individuals free of cardiovascular disease (Dannenberg *et al,* 1989).

This methodology appears to provide an anatomically valid measure of LV mass (Devereux & Reichek, 1977; Devereux *et al,* 1986) with acceptable reproducibility (Wallerson & Devereux, 1987) and has been shown to predict future cardiovascular events and mortality (Casale *et al,* 1986; Levy *et al,* 1990). Its accuracy is however dependant on assumptions about left ventricular geometry and it is less accurate in abnormally shaped ventricles (Devereux, 1987), particularly when major regional wall motion abnormalities are present following myocardial infarction.

However, the pattern of left ventricular hypertrophy can vary (Grossman *et al,* 1975; Savage *et al,* 1987; Ganau *et al,* 1992) and recent work using both LV mass and relative wall thickness (Reichek & Devereux, 1982) has suggested that the variable geometric adaptation of the left ventricle in patients with hypertension can be matched to systemic haemodynamics and ventricular loading conditions (Ganau *et al,* 1992). The typical pattern of concentric hypertrophy (increased left ventricular mass and increased relative wall thickness) appears to be less common than either concentric left ventricular remodelling (normal LV mass index with increased relative wall thickness) or eccentric hypertrophy (increased LV mass index but normal relative wall thickness) (Ganau *et al,* 1992; Devereux *et al,* 1993). As left ventricular mass may be more closely related to ventricular cavity size than systolic blood pressure, and as many other factors influence cardiac hypertrophy (Ganau *et al,* 1990), it is possible that these alternative patterns of ventricular remodelling (particularly concentric remodelling) provide a more sensitive and precise index of hypertensive target organ damage.

Relationship of Left Ventricular Mass to Ambulatory Blood Pressure

Clinic BP is only weakly correlated with LVH (Savage *et al,* 1990) and it is now clear that average blood pressure obtained over 24 hours is a better predictor of LV mass (Rowlands *et al,* 1982; Drayer *et al,* 1983; Devereux *et al,* 1983; White *et al,* 1989; Gosse *et al,* 1989; Verdecchia *et al,* 1990). However, these studies disagree as to which component of the 24 hour profile correlates most closely with LVH (Table 7.1). Devereux *et al* (1983) found that day-time pressure, particularly during working hours, correlated more closely than BP during sleep, while Rowlands *et al* (1982), using an invasive, intra-arterial monitoring system, and White *et al* (1989) found similar correlations during the day and the night. Drayer *et al* (1983) analysed night-time, defined as 10 pm - 6 am, rather than sleep, and found a closer relationship with day-time pressures. Gosse *et al* (1989), with a larger number of patients, found similar correlations. In contrast, Verdecchia *et al* (1990), in the largest study to date, also analysed night (8 pm - 7 am) rather than sleep, but showed a closer correlation with this period. Indeed, in this study hypertensive patients whose BP during the night fell by more than 10% had similar LV mass to normotensive subjects, suggesting that changes in BP during sleep may be of greater importance than the level of pressure throughout the day.

Table 7.1 **Major Studies Examining the Relationship Between Day and Night Ambulatory Blood Pressure and Left Ventricular Hypertrophy (Correlation Coefficients)**

Drayer used left ventricular mass as a measure of LVH. All other studies used the left ventricular mass index (LV mass/body surface area).

Author	n	Clinic BP	Day BP	Night BP	24-hour BP
Rowlands (1982)	50	0.45***	0.57***	0.56***	0.6***
Drayer (1983)	12	0.55	0.82**	0.7*	0.81**
Devereux (1983)	100	0.24*	0.5***	0.1	0.38***
White (1989)	30	0.13	0.39	0.42*	0.54**
Gosse (1989)	23	0.6**	0.72***	0.56**	
Verdecchia (1990)	150	0.44***	0.51***	0.54***	0.57***

Correlation coefficients indicating the strength of association between systolic blood pressure and left ventricular mass. The correlation coefficient for diastolic BP was less in each case, but followed the same pattern.

*p < 0.05, **p < 0.05, ***p, < 0.005

As anti-hypertensive drugs can induce regression of LVH (Rowlands *et al,* 1982) these studies did not include subjects with more severe hypertension, on treatment, in whom it was judged unethical to discontinue therapy. As a result only patients with relatively mild hypertension were studied; average clinic BP in Verdecchia's study was 160/98 (Verdecchia *et al,* 1990). These results are not therefore truly representative of a hypertensive population.

Monitors used in earlier studies were bulky and noisy compared to current equipment and it is therefore possible that disturbance to sleep was greater in these studies, providing a less reliable estimate of sleep pressure. In addition, the method of analysing the 24 hour profile in these studies differed. Some relied on patient reporting of sleep time, which is likely to be imprecise, while others arbitrarily divided the 24 hours into "day" and "night". It is therefore not possible to draw definite conclusions about the possible predominance of day-time or night-time BP on the development of LVH from these studies.

Relationship of Exercise Blood Pressure to LV Mass

Several studies have also demonstrated that left ventricular size correlates more closely to exercise BP than to resting BP (Table 7.2). In Ren's study of hypertensive patients, not only was the relationship of LV mass to exercise BP better than to clinic BP, but in addition all subjects found to have an exercise BP greater than 190 mmHg also had left ventricular hypertrophy (Ren *et al,* 1985). Ferrara and colleagues (1989) used an electronic sphygmomanometer to measure BP and found a marked difference in the strength of the relationship between resting and exercise BP. Nathwani *et al* (1985) measured the response to sub-maximal exercise in young subjects with mild hypertension and also found exercise BP to be a better predictor of LV mass. They also noted that the this relationship was independent of, and additive to, the effect of regular physical activity. Gottdiener *et al* (1990) studied normotensive subjects and found left ventricular hypertrophy in 14 of 22 subjects with an excessive BP response (systolic BP $>$ 210 mmHg) compared to only 1 of 22 with a normal response. Subjects in this study who had a marked BP response to exercise and large left ventricles were found to consume no more oxygen (an objective measure of fitness and conditioning) than those with a normal BP response and normal ventricle. One interpretation of these latter two studies is that the close relationship between exercise BP and left ventricular enlargement reflects the role of the heart in generating maximal haemodynamic force, rather than simply indicating the effect of raised BP during exercise on cardiac structure (Devereux, 1990). In other words, the left ventricular hypertrophy may precede, and be a prerequisite for, the exaggerated BP rise with exercise. This view remains theoretical only.

Table 7.2 **Major Studies Examining the Relationship Between Exercise BP and Left Ventricular Mass (Correlation Coefficients)**

Author	n	Exercise Methodology	Resting Blood Pressure	Exercise Blood Pressure
Ren (1985)	67	Treadmill	0.16	0.58***
Nathwani (1985)	20	Treadmill	0.21	0.57**
Gosse (1986)	61	Bicycle	0.40**	0.53***
Gosse(1989)	23	Bicycle	0.60**	0.67***
Ferrara (1989)	16	Bicycle	0.20	0.52*
Gottdiener (1990)	39	Treadmill	0.40**	0.65***

* $p < 0.05$, ** $p < 0.01$, *** $P < 0.001$

Further Echocardiographic Measurements

In addition to left ventricular size, echocardiography can provide an estimate of both systolic and diastolic function. Providing that left ventricular geometry is normal, a reasonable estimate of systolic function is provided from M-mode measurement of the left ventricle by calculating fractional shortening (McDonald *et al,* 1972) using the formula :

$$\textit{Fractional shortening (\%)} = \frac{\textit{LVIDdiastole - LVIDsystole}}{\textit{LVIDdiastole}}$$

Although more complex formulae using two-dimensional echocardiographic data provide more accurate estimates of left ventricular ejection fraction (Schiller *et al,* 1989), their use is of most value when left ventricular geometry is distorted, particularly in the assessment of systolic function in patients with ischaemic heart disease.

Diastolic function can also be assessed from careful M-mode study (St.John Sutton *et al,* 1982) but this is complex and has largely been superseded by Doppler echocardiographic assessment of left ventricular inflow velocities (Taylor & Waggoner, 1992). While the simple ratio of peak early (E) and atrial (A) filling velocities has been used by many investigators to indicate diastolic function, its complexity is such that this is a gross over simplification (Appleton *et al,* 1988) and full Doppler evaluation should therefore include the E velocity and A velocity, the E/A ratio, deceleration time of the peak velocity and the isovolumic relaxation time (Taylor & Waggoner, 1992).

Diastolic dysfunction appears to be an important early consequence of hypertensive left ventricular hypertrophy, preceding the development of LVH (Fouad *et al,* 1984). Clinic BP is related to measures of left ventricular filling (Genovesi-Ebert *et al,* 1991), although less predictably than to left ventricular mass (Genovesi-Ebert *et al,* 1991). There is little information on the relationship of ambulatory blood pressure data or the diurnal BP rhythm to diastolic filling parameters. However two small studies have suggested that the 24 hour ambulatory BP is related to left ventricular filling characteristics (Phillips *et al,* 1989; White, 1990), although a more recent study found no relationship (Prisant *et al,* 1992).

Measurement of Urinary Protein Excretion (Microalbuminuria)

Overt proteinuria, which occurs in up to 16% of middle-aged patients with hypertension (Samuelsson *et al,* 1985; Bulpitt *et al,* 1986) is associated with increased cardiovascular morbidity and mortality (Kannel *et al,* 1984; Samuelsson *et al,* 1985; Bulpitt *et al,* 1986).

More sensitive methods of detecting urinary albumin have now been developed and microalbuminuria is defined as urinary excretion of albumin which is persistently above normal although below the sensitivity of conventional urine test strips, in the absence of infection or structural abnormalities in the renal tract (Winocour, 1992).

Wider clinical use of microalbuminuria as a potential marker of cardiovascular risk has been hampered by lack of consensus over methods of collecting the urine sample and expressing the result (Hutchison *et al,* 1988; Marshall, 1991). Furthermore, there is considerable postural and diurnal variation in individual subjects (Marshall, 1991). Twenty-four hour, timed, and early morning urine samples have all been used, and the results expressed as an absolute value or as an albumin/creatinine ratio (Hutchison *et al,* 1988; Marshall, 1991). Measurement of a timed urine sample remains the most accurate measurement but is bedevilled by problems with inaccurate collection, and it is clearly not an ideal screening test. Using timed overnight urine collection, an albumin excretion rate of greater than 20 μg/min is diagnostic of microalbuminuria and an early morning urine albumin:creatinine ratio of greater than 3.0 reliably predicts an overnight excretion rate of greater than 30 μg/min (Marshall, 1991). Measurement of this ratio therefore appears to be a reliable screening test (Marshall, 1991). If the ratio is $<$ 3.5 mg/mmol, the patient can be classified as normoalbuminuric, while a ratio greater than 10 mg/mmol indicates significant albuminuria which, in a diabetic, warrants further investigation (Marshall, 1991).

In diabetes mellitus, the occurrence of microalbuminuria predicts the development of nephropathy (Mogensen & Christensen, 1984) and early mortality from cardiovascular disease (Mogensen, 1984). The importance of blood pressure in the development and progression of renal disease is now appreciated (Mathiesen *et al,* 1990) and early control of hypertension is the mainstay of management.

The clinical relevance of microalbuminuria in normotensive subjects and patients with essential hypertension is less clear. However, its presence appears to predict death from cardiovascular disease in elderly subjects (Damsgaard *et al,* 1990) and possibly also coronary and peripheral vascular disease in the general population (Yudkin *et al,* 1988). This could indicate either that microalbuminuria and proteinuria reflect generalised cardiovascular disease, or that it is associated with an excess of cardiovascular risk factors, or both (Winocour, 1992).

Microalbuminuria is more common in a hypertensive population (Yudkin *et al,* 1988; Giaconi *et al,* 1989; Gosling & Beevers, 1989) and, in some studies, is linearly related to the level of blood pressure (Parving *et al,* 1974; Opsahl *et al,* 1988; Yudkin *et al,* 1988; Damsgaard *et al,* 1990; Winocour *et al,* 1992), suggesting a causal relationship. Winocour (1992) has suggested that the presence of microalbuminuria in essential hypertension should lead to more active management of the hypertension.

There is some evidence that ambulatory blood pressure better correlates with microalbuminuria in essential hypertension (Opsahl *et al,* 1988; Giaconi *et al,* 1989) but little is known about the impact of the diurnal blood pressure rhythm. However, loss of the nocturnal dip is associated with higher prevalence of microalbuminuria in diabetics (Bauduceau *et al,* 1991; Lindsay *et al,* 1995) and patients with advanced renal disease have blunting of their diurnal BP rhythm (Abel *et al,* 1990; Middeke & Schrader, 1994).

Introduction

Both cardiac target organ damage, as assessed by echocardiography, and renal damage, as assessed by urinary microalbuminuria, are correlated with blood pressure, but the importance of nocturnal blood pressure elevation and the diurnal rhythm remains uncertain. In this study all members of a large, heterogeneous working population were asked to attend for blood pressure screening and both exercise BP response and the 24 hour ambulatory blood pressure profile of all hypertensive subjects and a randomly selected group taken from the whole population were compared to left ventricular anatomy and function, and to urinary albumin excretion.

Patients and Methods

With the co-operation of a large electronics group based locally (GEC-Ferranti), the entire working population of approximately 1300 was invited to attend for blood pressure screening. Employing both manual and professional staff, across all social strata, this population should have provided a cohort representative of the general working population. All subjects found to be hypertensive and a randomly selected subset were then invited to attend for more detailed study.

Stage 1 - Screening

A trained nurse co-ordinated a screening programme based in the company medical centre. Every employee based locally was invited to attend via department newsletters and notices posted throughout the factory.

Each individual had their age, sex, height and weight recorded. A note of any current medication was made and subjects on anti-hypertensive medication excluded from further study. After 5 minutes rest, blood pressure was measured in the right arm with the subject sitting and arm resting on a desk. The blood pressure was measured three times, using a semi-automatic electronic sphygmomanometer (Takeda UA-751) and the mean of these measurements recorded as the clinic blood pressure. These machines have been shown to be reliable and valid instruments (Bruce *et al,* 1988) and have the advantage of removing observer bias from the measurement procedure (Jamieson *et al,* 1990). Subjects were deliberately not given the results of screening, but were told that all subjects found to have high blood pressure would be notified at the end of the study.

Stage 2 - Randomisation

A randomly selected sub-group, weighted to include all hypertensive subjects, was then invited to attend for further study. Assuming the standard deviation for the measurement of LV mass index to be 30 g/m^2 (Verdecchia *et al,* 1990) and a difference of 20 g/m^2 to be clinically significant, I estimated that 110 randomly selected subjects would be needed to detect a statistically significant difference ($p < 0.05$) in the LV mass between those whose pressure falls during sleep and those who fail to "dip", with 80% power.

This protocol was designed to overcome some of the disadvantages of previous studies which, by not including subjects with more severe hypertension, were not representative of an entire hypertensive population. Most previous studies have consisted largely of patients referred to hypertension clinics with known or suspected hypertension. As knowledge of blood pressure level or a previous diagnosis of hypertension may influence the clinic pressure (Rostrup *et al,* 1988), possibly due to modification of the "white coat" response (Pickering, 1992a), I wished to ensure that we were studying subjects blinded to their own blood pressure level. Thus I hoped to be studying a "virgin" population, with no known history of cardiovascular disease or hypertension.

I was concerned that it may be unethical not to inform the subject or his general practitioner of the result of screening if they were found to have moderate to severe hypertension (diastolic BP > 110). To overcome this problem, the only subject in this

category was invited to attend for ambulatory monitoring and echocardiography shortly after the screening visit, and then informed of the diagnosis. To try and ensure that the investigator remained blinded to the results of the screening, a randomly selected subject was invited to attend for further investigation at the same time as the newly-diagnosed hypertensive.

Stage 3 - Detailed Investigation

Each randomised subject was invited to attend for more detailed investigation, consisting of 24-hour ambulatory blood pressure monitoring, measurement of blood pressure in response to sustained hand grip, collection of early morning urine sample for microalbuminuria, and two-dimensional, M-mode and Doppler echocardiography.

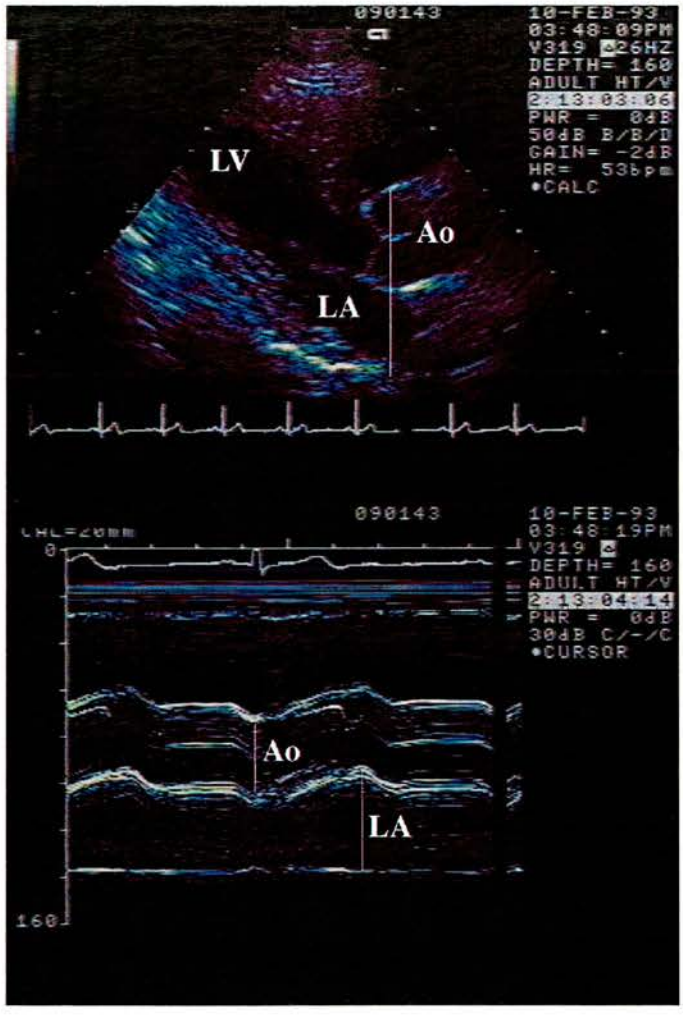
Ambulatory blood pressure monitoring was performed using the SpaceLabs 90207 monitor, programmed to measure BP at 30 minute intervals throughout 24 hours, with simultaneous wrist activity monitoring to allow an objective measurement of sleep time. All subjects returned to work after the monitor was fitted and were asked to continue with normal activities.

A urine sample was collected immediately after rising the next day and urinary albumin/creatinine ratio was estimated using an in-house radio-immunoassay.

Exercise blood pressure was measured after removal of the monitor 24 hours later. Blood pressure was measured at rest, using the Takeda UA-751 semi-automatic electronic sphygmomanometer and again after three minutes of isometric exercise, using the protocol described by Lenders *et al* (1988). Isometric exercise was performed using a calibrated strain gauge hand grip dynamometer. Each subject's maximal voluntary strength was ascertained at the outset as the maximum force achieved on three attempts. The subject was then asked to maintain sustained hand grip to 30% of maximum for three minutes and blood pressure measurement was repeated on completion.

Echocardiography was performed the same day using an Acuson XP/10 with 2.5 to 3.5 MHz probe. All studies were performed with subjects in the left lateral decubitus position. Standard two-dimensional parasternal and apical views were obtained to ensure normal left ventricular geometry and systolic function in all subjects. A two-dimensionally guided M-mode echocardiogram of the aortic valve and left atrium was recorded from the parasternal long axis view (Figure 7.1), and of the left ventricle from the short axis view just below the mitral valve apparatus (Figure 7.2).

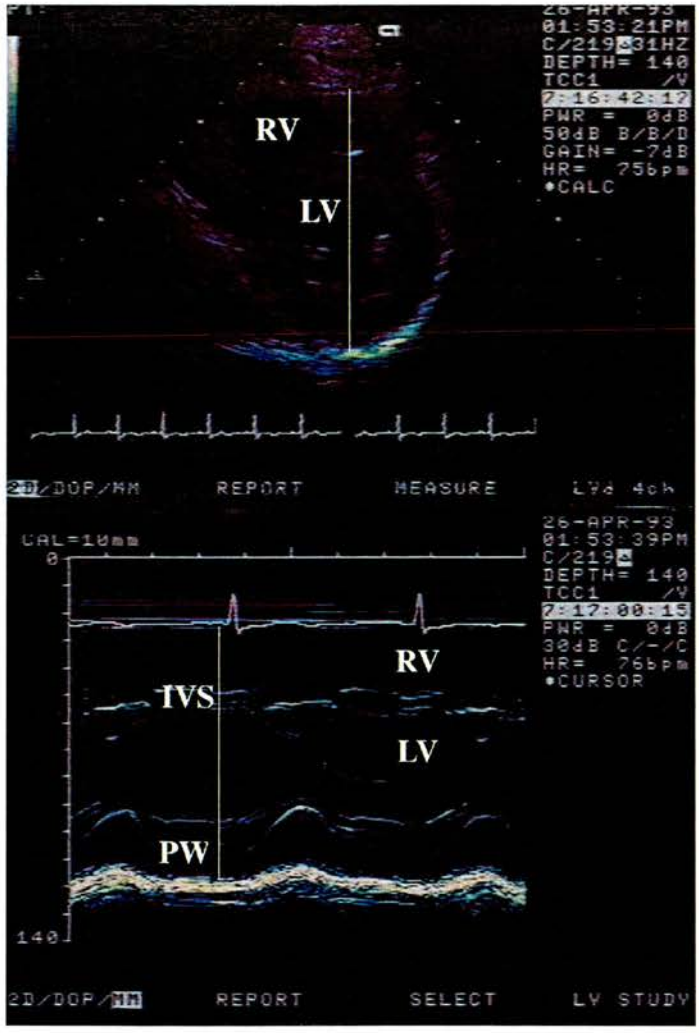
Figure 7.1 **Echocardiographic Measurement of the Aorta and Left Atrium**



The M-mode cursor was positioned at the level of the aortic valve on the two-dimensional long axis view (upper panel, M-mode cut indicated by the white line). Aortic root diameter and left atrial size were then measured from the M-mode following ASE recommendations (lower panel). The Acuson B-mode modality, shown here, which colours the image and accentuates endocardial boundaries, was used for most measurements.

LV = left ventricle, LA = left atrium; Ao = ascending aorta.

Figure 7.2. **Echocardiographic Measurement of Left Ventricular Mass**



The M-mode cursor was positioned across the left ventricular cavity at the level of the papillary muscles on the two-dimensional short axis view (upper panel, M-mode cut indicated by the white line). Septal and posterior wall thickness and left ventricular cavity dimension in diastole were measured from the M-mode, using the Penn convention (lower panel).

RV = right ventricle, LV = left ventricle, IVS = interventricular septum, PW = posterior wall of left ventricle.

Colour Doppler study of the left ventricular outflow tract and mitral valve was performed to exclude significant aortic or mitral regurgitation and a two-dimensionally guided pulsed Doppler examination of left ventricular inflow velocities was made from the apical four chamber view with the Doppler sample volume positioned at the level of the mitral leaflet tips in diastole (Figure 7.3). Studies were stored on video for later analysis using Acuson proprietary software. To minimise the effect of respiratory variation each measurement was averaged over 6 frames. All M-mode measurements were made according to the guidelines of the American Society of Echocardiography (Sahn *et al,* 1978), with the exception of the parameters used to calculate left ventricular mass, which were calculated at end-diastole using the Penn convention (Devereux & Reichek, 1977; Devereux *et al,* 1986).

All echocardiograms were performed by myself or by an experienced technician, and all were analysed by myself.

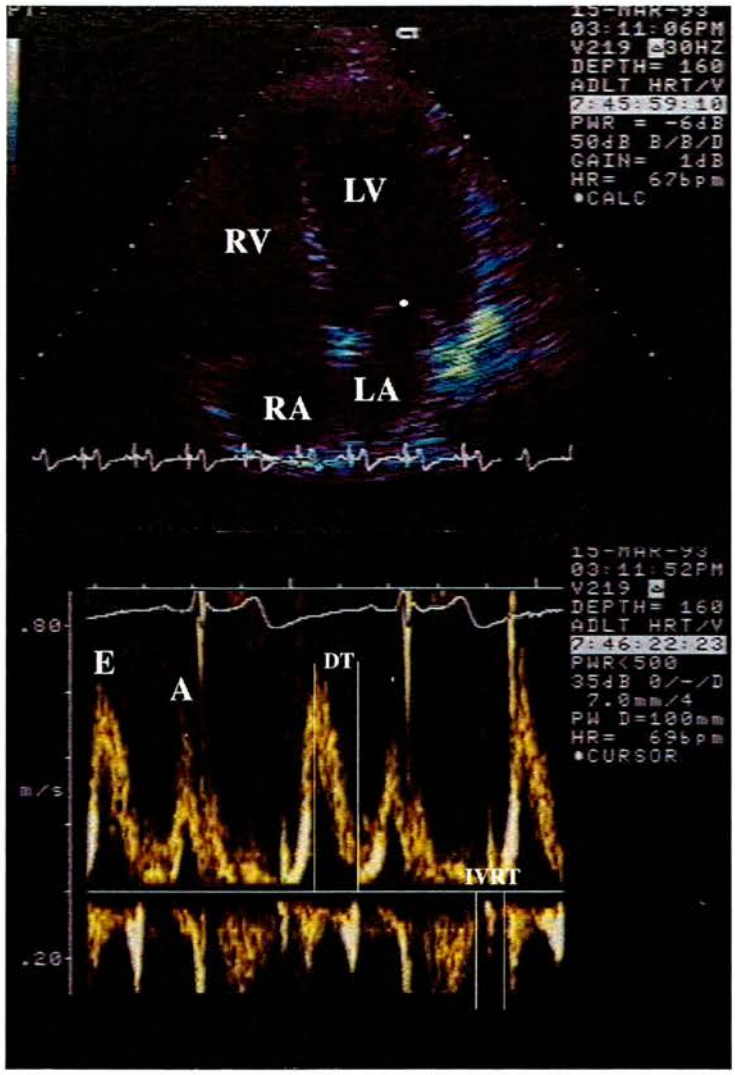
Statistical Analysis

Baseline demographic parameters from the screening population and the groups studied were compared using Student's t-test or Chi squared test as appropriate.

For simplicity of presentation, groups were then divided into dippers and non-dippers, defined as those with less than 10% drop in both systolic and diastolic BP from wake to sleep, and the two sub-groups compared by parametric or non-parametric analysis as appropriate.

The blood pressure profile of subjects found to have left ventricular hypertrophy (defined as left ventricular mass index $>$ 110 g/m^2 for women and $>$ 134 g/m^2 for men (Hammond *et al,* 1986)) was also compared to those with normal LV mass. Left ventricular geometry was further defined using the method described by Ganau *et al* (1992), and the ambulatory BP profile in each subset compared to that of the normal group.

Figure 7.3 **Doppler Measurement of Left Ventricular Diastolic Function**



The Doppler cursor was positioned at the level of the mitral leaflet tips in the left ventricular cavity from the two-dimensional apical four chamber view (upper panel, pulsed wave sample volume location is indicated by the white dot). Maximum early (E wave) and late (A wave) left ventricular inflow velocities were then measured from the pulsed Doppler flow profile (lower panel). Deceleration time (DT, time period indicated by vertical white lines) and, when it was possible to simultaneously visualise left ventricular inflow and outflow, isovolumic relaxation time (IVRT, time period again indicated by white lines) were also measured (lower panel).

RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium.

Pearson correlation coefficients were calculated to determine the extent to which each BP measure relates to target organ damage. Stepwise multiple regression models were used to determine which BP measures predicted target organ damage, taking account of the other BP measures. The criteria used for entry and retention into the models was $p < 0.10$.

Principal components analysis is a method of data reduction which produces a small number of derived variables (the principal components) from a larger number of originals, such that these principal components are uncorrelated and retain most of the varance of the originals (Everitt, 1994). This analysis was performed on all blood pressure measurements to determine which accounted for the majority of the variance and the extent of additional information provided by each measure.

Results

Population Screened

The entire workforce of GEC Ferranti on two local sites was invited to attend for screening between February and May 1992. One thousand and five subjects from a workforce of approximately 1300 were screened (response rate 77%) of whom 35 were known hypertensives on treatment and three were receiving beta-blockers for ischaemic heart disease. The baseline data from the remaining 967 subjects, used for this study, is given in Table 7.3. The distribution of clinic BP is shown in Figure 7.4 and is seen to be approximately Normally distributed, with minor positive skew.

One hundred and sixty-two subjects (110 randomly selected + all subjects with screening diastolic BP > 95 mmHg) were invited to attend for more detailed study. One hundred and thirty four (83%) completed the analysis phase. The baseline parameters of the randomly selected subgroup were not significantly different from that of the total population (Table 7.3) although, as expected, blood pressure was higher in the study population which included all hypertensives. None of the 28 patients who failed to attend were female but otherwise their demographic details were not significantly different from the group studied, with a mean age of 37 $\pm$ 2, body mass index of 26.5 $\pm$ 0.8 and mean clinic BP of $142 \pm 2.8/89 \pm 2.4$ mmHg.

Table 7.3 **Baseline Demographic Parameters - The GEC Ferranti Work Force**

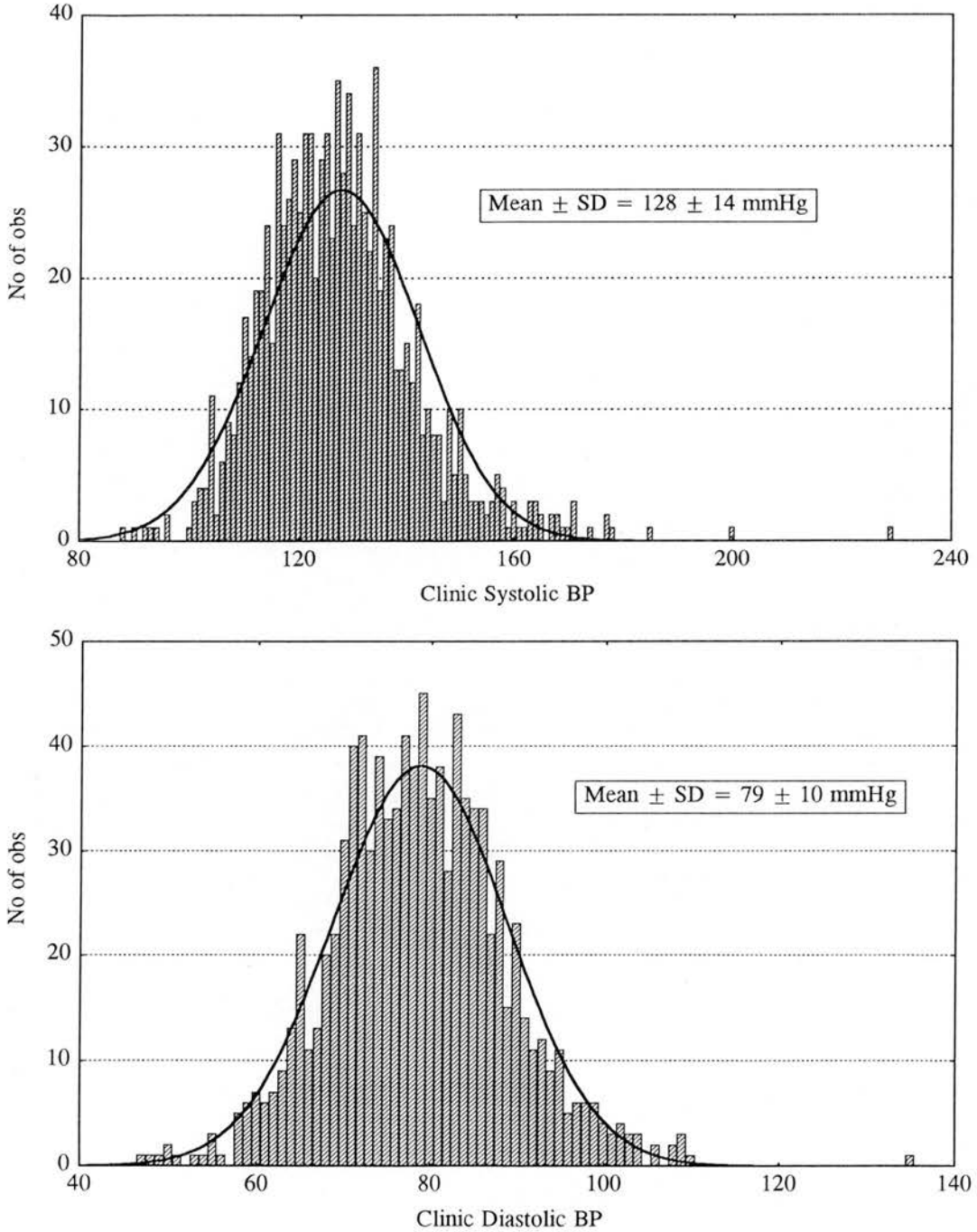
Variable (± S.E.M.)	Screened Population	Random Subgroup	Weighted Subgroup	Population Studied
Number	967	110	162	134
Age	37±0.4	36±1	38±0.9	39±1
Female sex (%)	182 (19%)	19 (17%)	21 (13%)*	20 (15%)
Height (cm)	173±0.3	173±0.8	173±0.6	172±0.7
Weight (kg)	76±0.4	75±1.2	77±1	76±1.1
Body mass index (g/m^2)	25.3±0.1	24.9±0.4	25.7±0.3	25.5±0.3
Clinic Systolic BP	128±0.5	128±1.3	136±1.5***	135±1.7***
Clinic Diastolic BP	79±0.3	78±0.9	85±1.1***	84±1.2***
Pulse Rate	69±0.4	69±1.1	71±1**	69 ±1

Each subgroup has been compared to the screening population to ensure comparability.
* $p < 0.05$, ** $p = 0.02$, *** $p < 0.00001$

Eight subjects from the randomly selected subgroup would be classified as hypertensive on the basis of their clinic BP, using World Health Organisation (WHO) Criteria of BP $\geq$ 160/95 (Subcommittee of WHO/ISH Mild Hypertension Liaison Committee, 1993).

As baseline parameters in the total population studied were no different from the random subgroup (other than for BP), and as the number of subjects with significant hypertension or left ventricular hypertrophy in the random subgroup would be limited, all further analyses were performed on the total population studied. Forty-five (34%) of this group were classified as hypertensive using the WHO criteria.

Figure 7.4 **Frequency Distribution of Clinic Blood Pressure in GEC Ferranti Workers**



The distribution of clinic blood pressure in a working population. Both systolic blood pressure (upper panel) and diastolic blood pressure (lower panel) are seen to be approximately Normally distributed, with slight positive skew indicating a small excess of subjects with raised blood pressure.

Ambulatory BP Monitoring

Data from 24-hour ambulatory blood pressure recording was available in 132 subjects from the entire cohort, of whom 94 had been randomly selected from the complete population (Table 7.4). Ambulatory BP monitoring was not available from two subjects. One was markedly obese with short arms and even an obese cuff could not be comfortably fitted to her arm. Blood pressure monitoring was not tolerated by the remaining subject, who complained of arm pain and removed the monitor shortly after leaving the clinic. The number of patients classified as hypertensive using ambulatory BP of $\geq$ 140/90 was 38 (29%). Only six subjects (5%) were classified as non-dippers.

Table 7.4 **Ambulatory BP Monitoring**

Variable	Mean ± S.E.M.
24 hour Mean Systolic BP	126±1.1
24-hour Mean Diastolic BP	79±0.9
Mean Wake Systolic BP	132±1.2
Mean Wake Diastolic BP	84±0.9
Mean Sleep Systolic BP	112±1
Mean Sleep Diastolic BP	67±0.9
Nocturnal Dip (%) SBP	14.9±0.5
Nocturnal Dip (%) DBP	20.4±0.6

Exercise BP Response

Exercise blood pressure data was obtained in 115 subjects (Table 7.5). In the remainder the electronic sphygmomanometer failed to measure BP at peak exercise. As this device can take up to 20 seconds to obtain a reading only one attempt at a reading was obtainable in each subject. A rest period of at least 30 minutes would have been required before repeating this study which was not feasible within the time frame of this study.

Where peak BP after exercise was less than that baseline, the BP difference was scored as zero.

Table 7.5 **Blood Pressure Response to Isometric Exercise**

Variable	Mean ± S.E.M.	Range
Exercise Systolic BP - Peak	156±2.2	102 - 216
Exercise Diastolic BP - Peak	104±1.5	68 - 159
Systolic BP Difference	22±1.4	0 - 66
Diastolic BP Difference	19±1.1	0 - 63

Outcome Variables

Technically adequate echocardiograms were obtained in 120 subjects (88%) which is comparable to other population based studies (Levy *et al,* 1987; Pearce *et al,* 1992). Details are given in Tables 7.6a and 7.6b. Twelve (9%) had left ventricular hypertrophy by conventional criteria.

Urine samples were returned by 129 subjects (Table 7.6c). Two subjects (1.6%) had an albumin/creatinine ratio > 3.5 consistent with possible significant microalbuminuria. No subject had a ratio greater than 10. Both subjects with significant microalbuminuria had significantly elevated ambulatory blood pressure (mean wake BP 154/103 and 155/99 mmHg) but with the diurnal rhythm preserved (nocturnal dip 10.4/11.7 and 27.3/22.9 %).

Table 7.6a **Results of M-mode Echocardiography**

Variable	Mean ± S.E.M.
Intraventricular Septum - Systole (cm)	1.24±0.02
Intraventricular Septum - Diastole (cm)	0.79±0.02
LV Posterior Wall - Systole (cm)	1.52±0.02
LV Posterior Wall - Diastole (cm)	0.9±0.02
LV Internal Diameter - Systole (cm)	3.45±0.06
LV Internal Diameter - Diastole (cm)	5.12±0.05
Fractional Shortening (%)	33.5±0.6
Left Ventricular Mass (g)	180.5±6
Left Ventricular Mass Index (g/m^2)	94.7±2.8
Relative Wall Thickness	0.36±0.01
Aorta (cm)	3±0.04
Left Atrium (cm)	3.6±0.04

Table 7.6b **Results of Doppler Echocardiography**

Variable	Mean ± S.E.M.
Peak Early LV Filling (Emax)	0.67±0.01
Peak Atrial Filling (Amax)	0.51±0.01
E/A ratio	1.38±0.04
Isovolumic Relaxation Time	113.5±2.3
Deceleration Time	149.1±2.1

Table 7.6c **Results of Urine Analysis**

Variable	Mean ± S.E.M.
Albumin (mg)	11.4±1.9
Creatinine (mmol)	14.2±0.5
Albumin/Creatinine Ratio	0.8±0.08

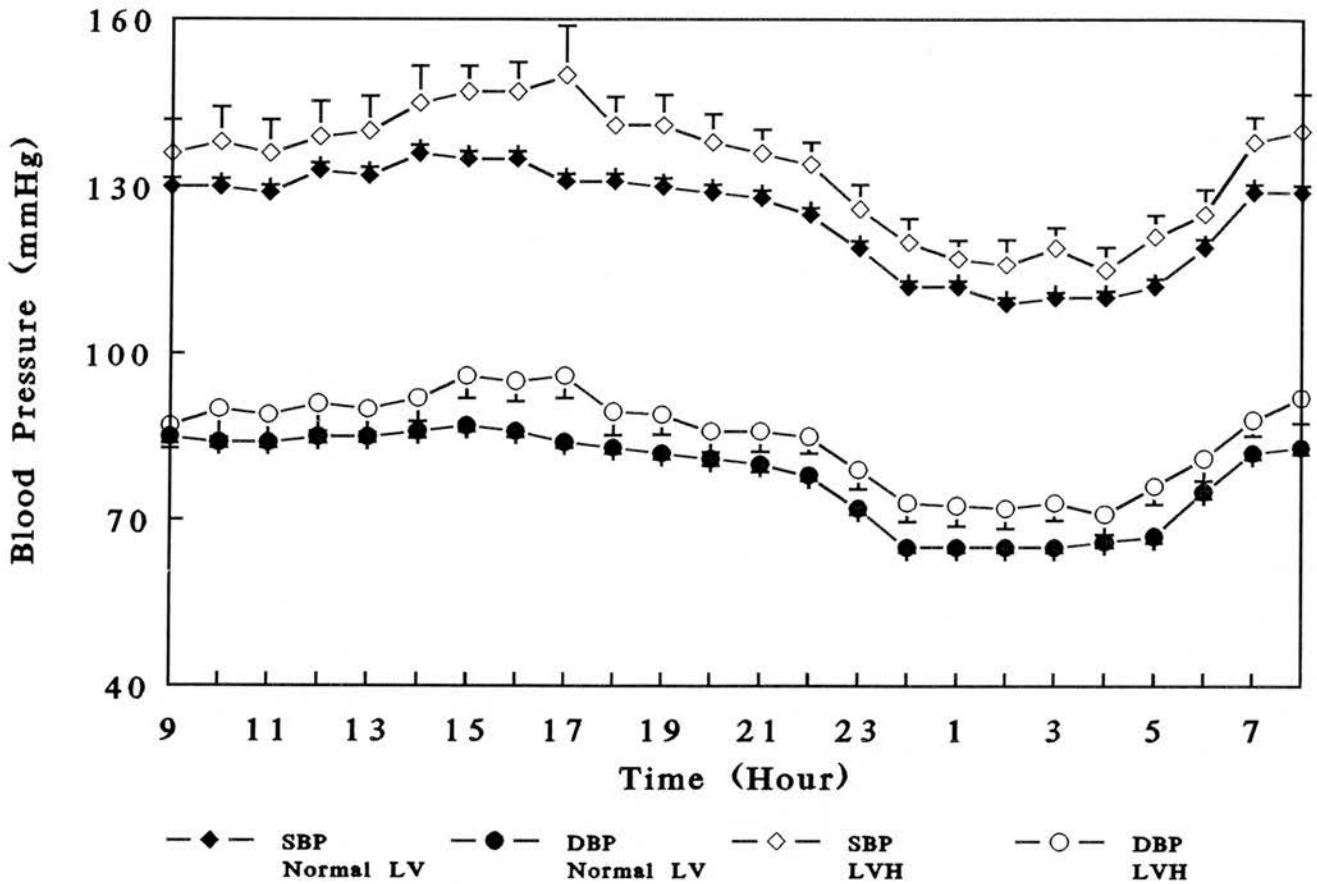
The blood pressure profile and outcome variables of the patients classified as non-dippers were compared to that of the dippers (Table 7.7). Blood pressure was higher throughout the 24 hours in the non-dippers, although this reached statistical significance during the night only. Left ventricular mass index was also higher in non-dippers, but this difference was not statistically significant.

Table 7.7 **Dippers and Non-Dippers Compared**

Variable ± S.E.M.	Dippers	Non-Dippers	p
Number	128	6	
Age	39 ± 1	45 ± 5	NS
24-h Mean Systolic BP	125 ± 1	138 ± 9.6	0.01
24-h Mean Diastolic BP	78 ± 0.8	89 ± 6.4	0.01
Mean Wake Systolic BP	131 ± 1.1	141 ± 9.8	NS
Mean Wake Diastolic BP	83 ± 0.9	90 ± 6.4	NS
Mean Sleep Systolic BP	111 ± 0.9	133 ± 8.3	< 0.00001
Mean Sleep Diastolic BP	66 ± 0.8	95 ± 5.6	< 0.00001
Nocturnal Dip (%) SBP	15.3 ± 0.4	4.9 ± 2.4	< 0.00001
Nocturnal Dip (%) DBP	21 ± 0.5	5.9 ± 1.5	< 0.00001
Exercise Systolic BP -Peak	155 ± 2.3	165 ± 9	NS
Exercise Diastolic BP - Peak	103 ± 1.5	106 ± 4.6	NS
LVMI	93 ± 2.9	125 ± 24.3	NS
E/A Ratio	1.4 ± 0.04	1.4 ± 0.3	NS
Fractional Shortening	33.7 ± 0.6	26.9 ± 0.6	NS
Albumin/Creatinine Ratio	0.8 ± 0.09	0.9 ± 0.1	NS

Patients with LVH, who also had lower E/A ratios in keeping with early diastolic dysfunction, were slightly older than those with normal left ventricles, and had higher BP during the day and night (Table 7.8). However no difference in the diurnal blood pressure profile was apparent, with similar fall in BP during sleep in each group (Figure 7.5, Table 7.8).

Figure 7.5 **Comparison of Diurnal Blood Pressure Variation in Subjects with and without Left Ventricular Hypertrophy**



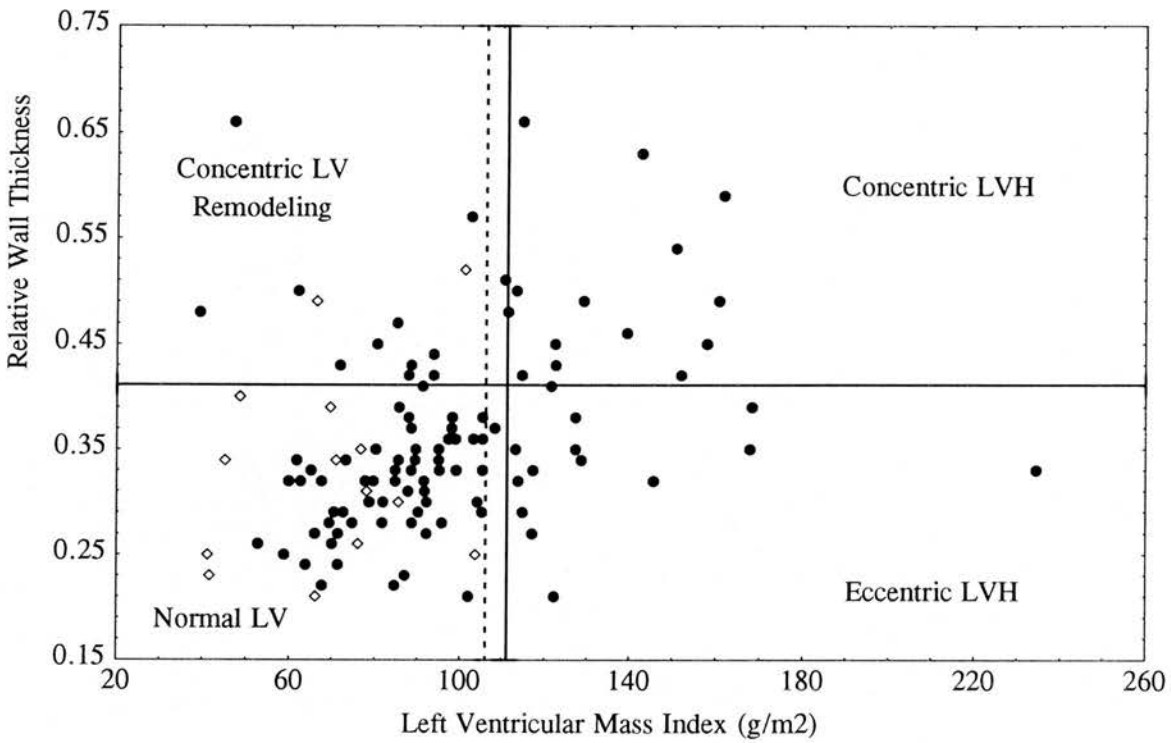
Ambulatory blood pressure profile of subjects with normal (solid symbol) and increased (open symbol) left ventricular mass. Ambulatory BP is seen to be higher in those with increased LV mass but the diurnal profile is similar.

Table 7.8 **Blood Pressure Parameters in Left Ventricular Hypertrophy**

Variable ± S.E.M.	Normal	LVH	p
Number	108	12	
Age	38 ± 1	45 ± 4.3	0.04
LVMI	88 ± 2.1	162 ± 4.3	< 0.00001
Fractional Shortening	33.8 ± 0.64	30.7 ± 2.5	NS
E/A Ratio	1.4 ± 0.04	1.1 ± 0.17	0.04
24-h Mean Systolic BP	125 ± 1	134 ± 4.3	0.01
24-h Mean Diastolic BP	78 ± 0.9	85 ± 3.3	0.015
Mean Wake Systolic BP	130 ± 1.1	141 ± 5.1	0.006
Mean Wake Diastolic BP	83 ± 0.9	90 ± 3.7	0.016
Mean Sleep Systolic BP	110 ± 1	119 ± 3.7	0.01
Mean Sleep Diastolic BP	65 ± 0.8	73 ± 3.2	0.003
Nocturnal Dip (%) SBP	15.1 ± 0.5	15.2 ± 1.6	NS
Nocturnal Dip (%) DBP	20.8 ± 0.6	18.5 ± 2.3	NS
Exercise Systolic BP - Peak	155 ± 2.4	168 ± 8.2	NS
Exercise Diastolic BP - Peak	103 ± 1.6	113± 5.9	NS

Left ventricular mass index was then plotted against relative wall thickness (Figure 7.6) to further stratify LV geometry. The scattergram was then divided into four fields using upper 95% confidence limits for LVMI, quoted by Ganau *et al* (1992), of 111 g/m^2 for men and 106 g/m^2 for women, and for relative wall thickness of 0.41 for both men and women. This is therefore a less restrictive definition of left ventricular hypertrophy. Seventy-four subjects (63%) had normal left ventricular geometry, 15 (13%) had concentric left ventricular hypertrophy, 14 (12%) had eccentric left ventricular hypertrophy and 15 (13%) had concentric left ventricular remodelling. Again, no difference in the diurnal BP profile was apparent, despite higher BP with each pattern of abnormal LV geometry (Table 7.9).

Figure 7.6 **Left Ventricular Geometry in a Working Population**



Scatter plot of left ventricular mass against relative wall thickness, with solid symbols indicating male and open symbols female subjects. The diagram has been divided into four fields by upper 95% confidence limits of left ventricular mass index (111 g/m^2 in men and 106 g/m^2 for women, solid and dashed vertical lines respectively) and of relative wall thickness (0.41 for men and women, horizontal line).

Table 7.9 **Patterns of Abnormal LV Geometry**

Variable ± S.E.M.	Normal	Concentric LVH	Eccentric LVH	Concentric Remodelling
Number	76	15	14	15
Age	36 ± 1.2	43 ± 2.8*	44 ± 3*	37 ± 2.8
24-h Mean Systolic BP	121 ± 1	133 ± 3.4**	134 ± 2.7***	127 ± 2.8*
24-h Mean Diastolic BP	75 ± 0.9	85 ±2.7**	86 ± 2.4***	81 ± 2.2*
Mean Wake Systolic BP	127 ± 1.1	140 ± 4***	140 ± 2.8***	133 ± 3.2*
Mean Wake Diastolic BP	79 ± 0.9	90 ± 3.1**	91 ± 2.1***	86 ± 2.4
Mean Sleep Systolic BP	108 ± 1	117 ± 3.2*	119 ± 2.6**	113 ± 2.3*
Mean Sleep Diastolic BP	63 ± 0.9	72 ± 2.6**	72 ± 2.4**	68 ± 1.9*
Nocturnal Dip (%) Systolic BP	14.8 ± 0.6	16.2 ± 1.6	15.2 ± 1.4	14.6 ± 1.2
Nocturnal Dip (%) Diastolic BP	20.7 ± 0.7	20.1 ± 2.1	21.1 ± 1.5	20.6 ± 1.5

Abnormal geometry has been compared to the normal group, with statistical significance indicated by asterisks : *$p < 0.05$, **$p < 0.0001$, ***$p < 0.00001$.

Relationship of Blood Pressure to Outcome Variables

The major outcome variables were correlated to the BP measurements to determine which had the greatest impact on cardiac and renal target organ damage. Results are detailed in Table 7.10.

Table 7.10 **Strength of Relationship of BP Measurements to Outcome Variables**

Variable	LVMI	E/A Ratio	Albumin/ Creatinine Ratio
Clinic Systolic BP	0.44*	-0.41*	0.16
Clinic Diastolic BP	0.37*	-0.54*	0.21*
24 hour Mean Systolic BP	0.48*	-0.41*	0.26*
24-hour Mean Diastolic BP	0.42*	-0.58*	0.27*
Mean Wake Systolic BP	0.48*	-0.45*	0.24*
Mean Wake Diastolic BP	0.42*	-0.59*	0.26*
Mean Sleep Systolic BP	0.41*	-0.25*	0.28*
Mean Sleep Diastolic BP	0.39*	-0.47*	0.30*
Nocturnal Dip (%) SBP	0.07	-0.28*	-0.07
Nocturnal Dip (%) DBP	-0.04	-0.09	-0.12
Exercise Systolic BP - Peak	0.44*	-0.28	0.12
Exercise Diastolic BP - Peak	0.46*	-0.36*	0.03
Systolic BP Difference	0.23*	0.04	-0.03
Diastolic BP Difference	0.23*	0.13	-0.07

Pearson's correlation coefficient. Values marked * are significant at $p < 0.05$.

Correlation coefficients for alternative measures of left ventricular diastolic function (isovolumic relaxation time and deceleration time) were all less than 0.25.

Left atrial size and the diameter of the left ventricular outflow tract appeared unrelated to the BP level, with no significant correlation apparent (all < 0.1).

Multiple linear regression analysis was then performed to determine which BP measures predicted each measure of major target organ damage. For this analysis, a diagnosis of hypertension on the basis of clinic, ambulatory or exercise BP, or of non-dipping, were included as BP measures, in addition to the qualitative measures, and are selected in preference to the quantitative measure when seen to have a more direct influence on the outcome measure. The following definitions were used :-

H1. - Clinic BP > 160/95 mmHg

H2. - Mean wake ambulatory BP > 140/90 mmHg

H3. - Exercise systolic BP > 190 mmHg

H4. - Non-Dipper = Nocturnal dip in BP form wake to sleep < 10% for both systolic and diastolic BP.

The most important predictor variables for each target organ measure are listed, with p-values in brackets.

1. Left ventricular mass index : H2 (0.021), H4 (0.006), Exercise systolic BP peak (0.0001)

2. E/A ratio : H4 (0.038), 24-h mean systolic BP (0.075), Mean sleep systolic BP (0.001), 24-h mean diastolic BP (0.0001)

3. Isovolumic relaxation time : H4 (0.007), 24-h mean systolic BP (0.0001), clinic diastolic BP (0.006), 24-h mean arterial pressure (0.0001)

4. Deceleration time : H1 (0.003), H2 (0.004), Clinic systolic BP (0.0001), Exercise systolic BP difference (0.018)

5. Albumin/Creatinine ratio : H4 (0.054), Exercise diastolic BP peak (0.023), Mean sleep mean arterial pressure (0.0001)

The analysis was then repeated after adjusting the measures of target organ damage for age, sex and body mass index, giving the following results :

1. Left ventricular mass index : H2 (0.038), Exercise systolic BP peak (0.0005), Clinic diastolic BP (0.0001)

2. E/A ratio : H2 (0.025), H4 (0.062), 24-h mean systolic BP (0.001), Exercise systolic BP peak (0.081), 24-h mean diastolic BP (0.0001)

3. Isovolumic relaxation time : H4 (0.007), 24-h mean systolic BP (0.0001), clinic diastolic BP (0.006), 24-h mean arterial pressure (0.0001)

4. Deceleration time : H4 (0.02), Mean sleep systolic BP (0.045), Exercise systolic BP difference (0.0007), nocturnal dip in diastolic BP (0.0007), 24-h mean arterial pressure (0.0001), sleep mean arterial pressure (0.066)

5. Albumin/Creatinine ratio : Mean sleep systolic BP (0.0001), nocturnal dip in systolic BP (0.011), clinic diastolic BP (0.011), 24-h mean diastolic BP (0.022), mean sleep diastolic BP (0.006), 24-h mean arterial pressure (0.0007).

Thus, while conventional or ambulatory BP values are most closely related to target organ damage, the diurnal BP profile, particularly when designated as being a non-dipper, does appear to have an independent influence on target organ damage, particularly on the indices of diastolic dysfunction. Sleep BP appears to be the most important predictor of microalbuminuria.

Principal Components Analysis of BP Measures

This analysis is used to summarise the variation in all the blood pressure measurements in fewer dimensions. Each dimension is independent and is calculated as a linear sum of the measures. Principal components were calculated for every BP measurement parameter (18 in total). Ninety-five per cent of the information was contained in the first 5 principal components Fifty-seven per cent of the variation was accounted for by all measures of ambulatory blood pressure, except the nocturnal dip, with less emphasis on the exercise BP value. Nineteen per cent was accounted for by the nocturnal dip, 10% by the peak exercise BP, 4% by the increase in BP on exercise, and 4% by clinic BP. Thus, while the ambulatory BP values are most closely related to the extent of target organ damage, almost a fifth of the remaining variation is accounted for by the nocturnal dip. A small amount of additional information is provided by exercise BP data and the clinic BP, presumably because each provides an additional measure of blood pressure reactivity.

Discussion

The relative importance of different blood pressure measurements in predicting cardiovascular morbidity has been debated for many years. Blood pressure and its variability can be considered as consisting of two basic components : the basal level, and the phasic fluctuations which take place around this (Pickering, 1991). The relative importance of each, both regarding prediction of future hypertension and in predicting outcome in those with hypertension remains uncertain. Sir Horace Smirk (1944) pioneered the concept of basal blood pressure, arguing that it was this, rather than blood pressure reactivity which predicted outcome (Smirk *et al,* 1959; Smirk, 1964). At the other extreme several workers have found exercise blood pressure, i.e. the response of blood pressure to physical stress, to correlate better than casual blood pressure with left ventricular hypertrophy (Ren *et al,* 1985; Nathwani *et al,* 1985; Ferrara *et al,* 1989;

Gottdiener *et al,* 1990) suggesting that this measure of blood pressure reactivity is a better indicator of cardiovascular risk.

Clinic blood pressure, although ideally representing basal blood pressure, has a significant phasic component - the "white coat" effect (Mancia *et al,* 1983a). The variation in the extent of this, together with the imprecision inherent in a technique which allows relatively few measurements to be made, probably accounts for its poorer relationship with target organ damage. Ambulatory blood pressure is a mixture of both components, with sleep blood pressure approximating to basal, and wake blood pressure representing the mean of the basal pressure and tonic reactions throughout the day. The possible importance of the latter has been emphasised by Devereux *et al* (1983), who found the ambulatory blood pressure during work to be more closely related to LV mass than either total 24-hour or sleep BP. Other workers, although not separating "day" from "work" have found "day" to more closely relate to LV mass (Drayer *et al,* 1983; Gosse *et al,* 1989). In contrast, in the largest such study published, Verdecchia *et al* (1990) found night-time BP to more closely relate to LV mass, with an inverse correlation between the nocturnal BP decline and cardiac size. Later work by the same author has suggested that this may be the case predominantly in women (Verdecchia *et al,* 1995) but, due to the relatively small number of female subjects in the current study, I have not been able to test this hypothesis further here.

Many earlier studies have had small sample sizes and/or included convenient, rather than representative, samples. Most have included subjects referred to a hypertension clinic with a diagnosis based on repeated clinic measurement, and some have included patients on anti-hypertensive treatment or after a period of weeks off treatment. Thus, the relationship between blood pressure and target organ effects may have been blurred by patient risk factor modification in light of their diagnosis of hypertension, and by current or residual treatment effects. This study, by including randomly selected subjects (weighted to include all those with raised clinic BP) from a large population base, who were unaware of their blood pressure level and who had never received anti-hypertensive medication, should have avoided this potential problem.

In previous studies there has also been wide variation in the blood pressure monitoring equipment used, in the number of readings taken, and in the definition of day and night. All these factors may affect the relative importance of differing parts of the ambulatory blood pressure profile. In this study, blood pressure has been measured every 30 minutes throughout the 24 hours, which has been shown to provide an accurate estimate of true BP

when compared to intra-arterial values (Di Rienzo *et al,* 1983), and activity meters have been used to obtain an objective estimate of sleep time. This technique, which appears physiologically more sound than choosing an arbitrary definition of day and night, has been shown to result in a greater nocturnal drop in blood pressure (Stewart *et al,* 1993), and may be more reproducible (see Chapter 3).

Earlier studies have also tended to concentrate on one measure of blood pressure and compare this to the clinic pressure, making an appreciation of other alternative measures impossible. In this study, by performing multivariate analysis which includes clinic, ambulatory and exercise blood pressure I have attempted to assess the relative importance of each. This work is unique in measuring both ambulatory blood pressure and exercise blood pressure. In addition, all subjects wore wrist activity monitors, allowing objective definition of wake and sleep, so allowing more accurate assessment of the diurnal blood pressure profile. Although I made no attempt to separately measure blood pressure at work, all subjects were studied on a normal working day, and returned to work after being fitted with their monitor. Furthermore, all subjects had had casual blood pressure measured during the screening phase, using an electronic sphygmomanometer to remove observer bias (Bruce *et al,* 1988), by a trained nurse, minimising the white coat response (Mancia *et al,* 1987).

Echocardiographic left ventricular mass, Doppler indices of diastolic function, and urinary albumin/creatinine ratios were used as measures of target organ damage. To improve the sensitivity of the analysis of cardiac target organ damage, left ventricular structure was further subdivided on the basis of left ventricular geometry (Ganau *et al,* 1992).

By screening a local working population and studying a random subset in detail, previously undiagnosed and untreated subjects, who remained unaware of their blood pressure level throughout the study, were examined. As such, a major potential source of bias has been removed. Although a relatively young and healthy population, and therefore not typical of the general population, subjects studied were from all social groups, involving both manual and professional workers. There was a satisfactory response rate, both to the original screening programme (77%) and for more detailed study (83%), suggesting that the group studied was representative of the entire working population.

Thirty-six of 134 subjects studied were classified as hypertensive based on a clinic BP of $>$ 160/95 mmHg, while 38 had an ambulatory blood pressure greater than 140/90 mmHg. Only six were non-dippers and they were significantly more hypertensive than the dippers,

particularly during the night. Indices of target organ damage were not significantly different between the groups, although left ventricular mass index was higher in the non-dippers. Exercise blood pressure was also slightly higher in the non-dippers, arguing against the view that the greater diurnal blood pressure variation in dippers is due to larger increases in blood pressure with exercise during the day (Fumo *et al,* 1992). An absolute difference in the level of activity cannot however be excluded.

Using criteria suggested by Hammond *et al* (1986), based on a population survey of working adults, 12 subjects had left ventricular hypertrophy. These were slightly older and had lower E/A ratios, suggesting early diastolic dysfunction and therefore haemodynamically important LVH. Wake blood pressure was slightly, but not significantly, higher in this group, while sleep blood pressure was significantly increased. The diurnal profile was almost identical. With further subdivision of subjects based on more detailed analysis of left ventricular geometry, a similar pattern was apparent, with significantly higher pressures during wake and sleep in those with abnormal geometry, and no difference in the nocturnal dip.

In keeping with earlier studies, ambulatory blood pressure was more closely related to LV mass, although the difference between clinic BP and ambulatory BP was less pronounced than that noted by others (Devereux *et al,* 1983; Verdecchia *et al,* 1990). There are several possible explanations for this. Blood pressure was measured by a nurse in subjects' work environment, minimising the pressor effect related to the measuring procedure. Indeed, recent studies have suggested that nurse-measured BP may be more reproducible than ambulatory BP (Reeves *et al,* 1992) and, when measured electronically, better predict an increase in left ventricular mass over time (Spence *et al,* 1991). Furthermore, all subjects in this study were unaware of their blood pressure level and none had previously been diagnosed as hypertensive. As the white coat response may be a reflex learnt in response to the measuring procedure and the diagnosis of hypertension (Pickering, 1990a), this confounding variable may have had little impact in this study. Thus, the clinic BP measurement in this study may have been representative of that individual's true BP level, approximating to the basal value, and as such providing a better measure of cardiovascular risk than the clinic BP referred to in other work.

Relying on an objective measure of sleep time, mean wake BP was most closely related to both left ventricular mass and the E/A ratio, a measure of diastolic function. The relationship with sleep blood pressure was less marked but remained significant. In contrast, the albumin/creatinine ratio, an alternative measure of target organ damage, was

more closely related to sleep blood pressure. Interestingly, this is in accord with data which we have obtained from patients with non-insulin dependant diabetes mellitus (Lindsay *et al,* 1995) and may indicate differences in the relationship between the blood pressure profile and target organ damage in different systems. In keeping with this possibility, sleep blood pressure has also been shown to be a more important predictor of cerebral target organ damage (Shimada *et al,* 1990; Shimada *et al,* 1992). However, as microalbuminuria was measured from an early morning urine sample, that is from urine produced overnight, an alternative explanation for the higher correlation with sleep blood pressure may be that this was the blood pressure to which the system was exposed at the time of urine production.

The nocturnal dip, used as a measure of diurnal blood pressure variation, correlated only with the E/A ratio. However, on multiple linear regression analysis, the diurnal rhythm was shown to be independently associated with target organ damage, and accounted for 19% of the variation in the blood pressure measurements.

Conclusions

This study has demonstrated that, even when clinic BP is measured carefully, using every possible method to reduce observer bias and the white coat effect, ambulatory blood pressure measurements are more closely related to hypertensive target organ damage. While wake BP appears to be the major determinant of cardiac hypertrophy, an independent effect of sleep blood pressure is apparent. Knowledge of the diurnal blood pressure rhythm also appears to impart additional prognostic information. In contrast, exercise blood pressure, once the effect of ambulatory blood pressure has been allowed for, imparts relatively little additional information.

The use of ambulatory blood pressure monitoring appears capable of improving the precision of the estimate of an individual's cardiovascular risk. Mean wake blood pressure is probably the best single measure, but knowledge of sleep blood pressure and the diurnal blood pressure rhythm imparts additional prognostic information.

CHAPTER 8

Sleep Apnoea and Nocturnal Hypoxia : Possible Modulators of Diurnal Blood Pressure Variation in Essential Hypertension

Background

Hypertension and sleep apnoea commonly co-exist; 60% of patients with sleep apnoea syndrome are hypertensive (Guilleminault *et al,* 1976) and around 30% of treated hypertensives have apnoic episodes during normal sleep (Kales *et al,* 1984; Lavie *et al,* 1984; Fletcher *et al,* 1985). Sleep apnoea is now known to be a common condition, affecting 2-4% of middle-aged men and 1-2% of middle aged women (Jennum & Sjol, 1992; Young *et al,* 1993). Previously thought to be a disease of the obese, it is now recognised that only about 50% of patients have a body mass index of > 30 kg/m^2 (Douglas, 1994). Thus, many people with mild sleep apnoea are at present undiagnosed and unaware of their condition.

Patients with sleep apnoea experience hundreds of apnoic episodes throughout sleep and each episode is associated acutely with an initial fall in blood pressure, followed by a gradual rise as the oxygen desaturation falls. On average systolic blood pressure rises about 1 mmHg for every 1% fall in SaO2 (Stradling, 1989a; Parish & Shepard, 1990). The fall in SaO2 is associated with a rise in catecholamine production resulting in vasoconstriction and a rise in total peripheral resistance which may account for the rise in BP (Tilkian *et al,* 1976; Fletcher *et al,* 1987). Not surprisingly therefore sleep apnoea has been identified as a condition in which diurnal blood pressure variation is reduced or absent (Tilkian *et al,* 1976).

Severe sleep apnoea appears to cause significant day-time hypertension in some patients and, particularly in younger patients, the hypertension can be "cured" when the sleep apnoea is treated effectively (Burack *et al,* 1977; Lund-Johansen & White, 1990). However the majority of patients will remain hypertensive during the day despite effective treatment of their apnoea (Guilleminault *et al,* 1981). In a recent trial of nasal continuous positive airway pressure (CPAP) treatment in hypertensive patients with sleep apnoea, a fall in blood pressure was more closely linked to weight loss than to elimination of sleep apnoea by CPAP (Rauscher *et al,* 1993). Smoking, alcohol abuse and particularly obesity

are all risk factors for both hypertension and sleep apnoea syndrome and the association may simply reflect co-morbidity (Jeong & Dimsdale, 1989).

Occult sleep apnoea has been proposed as a possible cause of some cases of "essential" hypertension but this suggestion remains much more controversial. Snoring, a predominant symptom in sleep apnoea syndrome and a possible marker for occult cases, has also been proposed as a possible risk factor for hypertension and vascular disease (Hoffstein *et al,* 1988; Waller & Bhopal, 1989). Hoffstein (1994) has recently demonstrated that snoring is a marker for sleep apnoea but has no independent association with blood pressure.

If hypoxaemia due to sleep apnoea is implicated in the pathogenesis of systemic hypertension, other conditions causing hypoxaemia would also be expected to result in hypertension. The one study to look specifically at this question compared patients with sleep apnoea and restrictive chest wall disease and demonstrated a significantly greater incidence of day-time hypertension in the sleep apnoea group (Shiner *et al,* 1990). They did not however measure nocturnal blood pressure.

A more common cause of hypoxaemia in the general population is chronic obstructive pulmonary disease (COPD) and some of these patients experience transient hypoxaemia during sleep which is not due to sleep apnoea (Catterall *et al,* 1983). Patients who experience nocturnal oxygen desaturation have higher BP than those who do not, and a hypoxic challenge will increase the BP in the former group only (Fletcher *et al,* 1989). There is also some evidence that COPD patients have significantly greater rates of systemic hypertension and left ventricular hypertrophy than controls (Kassis, 1977). Some patients in this study had evidence of LVH but not hypertension and it may be that significant nocturnal hypertension accounted for this.

Patients with COPD have a greater than expected mortality during sleep (McNicholas & Fitzgerald, 1984) and episodes of nocturnal oxygen desaturation have been shown to increase myocardial oxygen demand, as measured by the heart rate-blood pressure product, by as much as maximal exercise in patients with severe disease (Shepard *et al,* 1984). Although not a primary end-point, this study compared mean intra-arterial blood pressure during the night to the resting BP but not the average day-time ambulatory BP : nocturnal BP was lower than resting day-time BP but by less than 20% (Shepard *et al,* 1984).

Introduction

In light of these observations, I hypothesised that any causal link between occult sleep apnoea and essential hypertension would act primarily on the nocturnal blood pressure and could therefore account for the attenuated diurnal blood pressure rhythm seen in a proportion of essential hypertensives. If nocturnal hypoxia, rather than apnoea, was the stimulus to the blood pressure rise, loss of the nocturnal dip should also be present in patients with COPD. I have therefore examined the inter-relationship between nocturnal oxygen saturation, blood pressure and diurnal blood pressure variation in essential hypertension and in patients with COPD. Diurnal blood pressure variability was also examined in patients known to have symptomatic sleep apnoea syndrome.

Patients and Methods

This was a cross-sectional observational study. It was conducted in compliance with ethical committee review and all patients gave written informed consent.

Three groups of patients were studied. Demographic details are given in Table 8.1.

1. Essential Hypertension

Sixty-eight patients referred from the hypertension clinic for ambulatory blood pressure monitoring were studied, of whom 66, 45 male, successfully completed the overnight monitoring. Twelve (18%) subjects were classified as obese (BMI > 30). Thirty-five were untreated and 31 treated with a variety of anti-hypertensive drugs, the majority taking 2 or more agents.

To determine whether this patient group was representative of the hypertensive clinic population I compared their characteristics to those of all patients attending our clinic with a diagnosis of essential hypertension (n=362). The control group was older (55 ± 14) with a similar systolic but lower diastolic BP ($157 \pm 23/91 \pm 12$). However BMI was almost identical (27 ± 4.6 g/m^2), with a similar proportion of obese individuals (24%). Thus the group studied appears to be representative of a hypertensive population with, in particular, no excess of obese individuals.

2. Chronic Obstructive Pulmonary Disease

Twenty patents with moderate or severe COPD were invited to participate, of whom 14, 9 male, completed the study. These patients were older and smaller but of similar body

mass index to the hypertensive patients. Only two (14%) were obese. No patient was on anti-hypertensive drug therapy but 8 (57%) were on diuretics and 6 (43%) on maintenance, low-dose oral corticosteroid. All patients were studied when clinically stable, with no acute exacerbation requiring hospitalisation or an increase in oral steroid in the previous three months. Any patient with access to domiciliary oxygen was asked not to use it during the study period.

3. Sleep Apnoea Syndrome

Ten patients, 8 male, with known moderate or severe sleep apnoea were also studied as part of a placebo-controlled cross-over study of continuous positive airway pressure ventilation. Data from the placebo limb (which consisted of a single tablet taken at night) are included here. These patients were of similar age but significantly more obese (BMI 36 ± 11, 60% obese) than the hypertensives. Three were on anti-hypertensive medication at the time of study and 6 of the remaining 7 had significantly elevated clinic pressures.

Table 8.1 **Demographic details of patient groups studied**

Variable (Mean ± S.E.M.)	Hypertensive	COPD	p	Sleep Apnoea	p
Number	66	14		10	
Age	50 ± 1.5	68 ± 1.8	$<.00001$	50 ± 3.4	NS
Height (cm)	171 ± 1.1	164 ± 3.2	0.02	174 ± 2.5	NS
Weight (kg)	80.5 ± 1.9	68.9 ± 5	0.015	108.8 ± 10.9	0.00003
BMI (kg/m^2)	27.5 ± 0.6	25.3 ± 1.4	NS	36 ± 3.4	0.04
Clinic Systolic BP	154 ± 2	134 ± 3	0.0002	152 ± 5	NS
Clinic Diastolic BP	100 ± 1	78 ± 2	$<.00001$	96 ± 5	NS

P values refer to comparison of each group to the hypertensive control population.

Methods

As hospitalisation may influence sleeping habit and diurnal blood pressure patterns (see Chapter 6), all patients were studied in their own homes.

In all essential hypertensives and COPD patients a full drug history, a history of snoring, both from the patient and, where applicable, from their partner, and details of current smoking habit and alcohol consumption were noted. Height and weight were recorded and neck circumference (a measure of upper body obesity) was measured at the level of

the crico-thyroid membrane. Spirometry was also performed in the hypertensive patients to ensure that no patient had hypoxaemic pulmonary disease.

All patients then underwent 24 hour ambulatory BP monitoring using the SpaceLabs 90207 monitor, which has been extensively validated by others (O'Brien *et al,* 1991b; Groppelli *et al,* 1991). BP was measured every 30 minutes throughout the 24 hours.

To study changes during sleep accurately a method to discriminate between sleep and wake is needed as patients' reporting of sleep time may be unreliable. The only certain method of doing this is to study patients in a sleep laboratory with continuous EEG monitoring. However this is labour intensive and the patient is not sleeping in his/her natural surroundings and may not therefore sleep properly. To overcome this problem all patients were fitted with a wrist activity meter (Gaehwiler), a solid state device worn on the wrist like a watch which records activity at pre-set intervals (e.g. 30 sec.). Activity values were determined at 125 ms. intervals and the total activity over the measuring interval stored as a one-byte word. After completion of the recording data are down-loaded onto a personal computer. As activity normally falls dramatically with the onset of sleep, sleep time can be determined. Such devices have been shown to provide an accurate estimation of sleep time (Mullaney *et al,* 1980). The activity derived sleep time was then used to determine mean blood pressure during wake and sleep, and the diurnal blood pressure variation, defined as the percentage change in BP from wake to sleep. This method has been shown to be both more physiologically sound and possibly more reproducible that reliance upon any arbitrary definition of day and night (see Chapter 3).

After fitting the ambulatory monitoring equipment patients were instructed in the use of a pulse oximeter (Ohmeda 3740, modified to disable all alarms). This machine is portable and easy to use. Its sister device, the Ohmeda 3700, which has identical internal software but a larger case and display panel, has been evaluated previously and shown to be suitable for unattended overnight recording of oxygen saturation (Warley *et al,* 1987). On retiring to bed, the oximeter was switched on and a finger clip was positioned on the middle or index finger of the hand, using the arm which did not have the blood pressure cuff attached. The machine display was then checked to ensure that there was an adequate signal. On waking, the device was switched off and returned. Up to 8 hours of data were stored in the internal memory of the device. This was down-loaded onto personal computer and analysed using a DBase IV programme developed for the purpose. Median oxygen saturation (SaO2) and the number of dips in SaO2 during sleep were calculated. Using the limits described by Stradling & Crosby (1990), a dip was counted as significant

when SaO2 fell by more than 4% below the previous updated high. No further dip could then be scored until the saturation subsequently rose by more than 3%. Thus no assumptions are made about baseline but any new fall greater than 4% is scored as a dip. The number of dips is then divided by the duration of the monitoring period to give the hourly dip rate. This has been shown to correlate closely with the apnoea index as measured by polysomnography, with a dip rate of greater than 5 per hour suggestive of sleep apnoea.

All hypertensive patients found to have nocturnal hypoxaemia suggestive of sleep apnoea were invited to attend for formal polysomnography. Age and sex matched controls with normal nocturnal saturation patterns were also invited to attend.

Patients with previously diagnosed sleep apnoea underwent 24 hour ambulatory BP and activity monitoring only.

Analysis

All data were analysed on a personal computer using the Minitab statistical software package.

The inter-relation among the continuous variables in the hypertensive patients was first examined with Pearson's correlation coefficients. The influence of median oxygen saturation, SaO2 dip rate, age, height, weight and neck circumference, alcohol consumption, smoking habit and snoring history on the BP profile was then assessed by multiple linear regression analysis, using wake BP, sleep BP and diurnal BP variation as dependent variables.

Ambulatory blood pressure data was used to determine diurnal BP variation and classify patients as dippers or non-dippers, with a normal BP dip defined as a fall of $>$ 10% of mean wake BP during sleep for both systolic and diastolic BP. The proportion of non-dippers in the hypertensive, COPD and sleep apnoic groups was then compared using the Chi-squared test. The absolute nocturnal dip was also analysed using Student's t-test.

Pulse oximetry data was compared using the Mann Whitney U test.

Results

1. Diurnal Blood Pressure Variation

Ambulatory blood pressure data from the three groups studied is given in Table 8.2. Five of the 66 essential hypertensives (8%) were non-dippers. Three of the COPD patients (21%) (Yates corrected Chi-sq. = 1.16, NS) and 2 of the sleep apnoea patients (20%) (Yates corrected Chi-sq. = 0.07, NS) were classified as "non-dippers". The nocturnal dip in blood pressure of the patients with sleep apnoea was slightly reduced but not significantly different from the essential hypertensives (Figure 8.1). The diurnal blood pressure profile was maintained in COPD, but with nocturnal dip less than that of patients with essential hypertension (Figure 8.2).

Table 8.2 **Ambulatory Blood Pressure Data.**

Variable (Mean ± S.E.M.)	Hypertensive	COPD	p	Sleep Apnoea	p
Wake Systolic BP	150±1.9	133±4.2	0.0003	137±3.8	0.01
Wake Diastolic BP	96±1.3	76±2.3	<0.00001	87±3.2	0.01
Sleep Systolic BP	129±1.8	119±4.7	0.04	122±5.6	NS
Sleep Diastolic BP	79±1.2	66±2.7	0.00006	72±4.3	NS
Nocturnal Dip (%) SBP	14.4±0.6	10.5±1.6	0.015	11.1±2.3	NS
Nocturnal Dip (%) DBP	17.9±0.8	13.3±1.9	0.015	17.2±3.1	NS

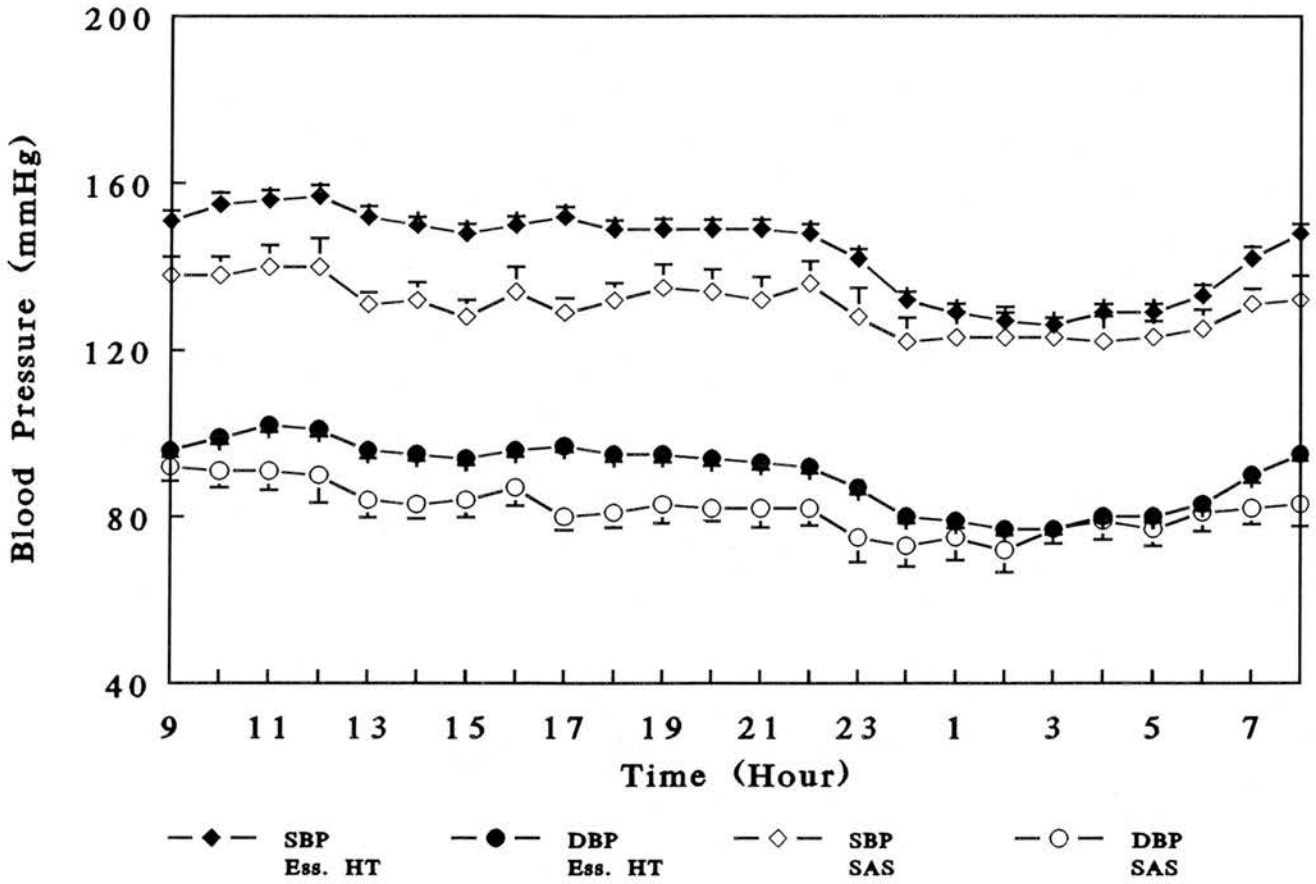
P values refer to the comparison of the hypertensive patients to the other two groups.

2. Oxygen saturation

Median oxygen saturation of the 66 patients with essential hypertension was 95%, with a mean SaO2 dip rate of 2.4/hour (range 0.1 - 24.7/hour). Seven patients (11%) had SaO2 dip rates > 5/hour, suggestive of significant sleep apnoea (Figure 8.3). Of these, 6 were on anti-hypertensive treatment and 6 were male. All had normal diurnal BP variation, with a mean drop in BP during sleep of 16.1/19.1%. All patients classified as non-dippers had normal oxygen saturation patterns, with mean SaO2 dip rate 1/hour (range 0.14 - 2.65).

Oxygen saturation of the COPD patients was lower, although the dip rate was not significantly different (Table 8.3) Two patients (14%) with SaO2 dip rates > 5/hour both had normal diurnal BP variation with nocturnal dips of 8.9%/19.5% and 11.5%/13.7%.

Figure 8.1 **Diurnal Blood Pressure Variation in Essential Hypertension and Sleep Apnoea Syndrome**

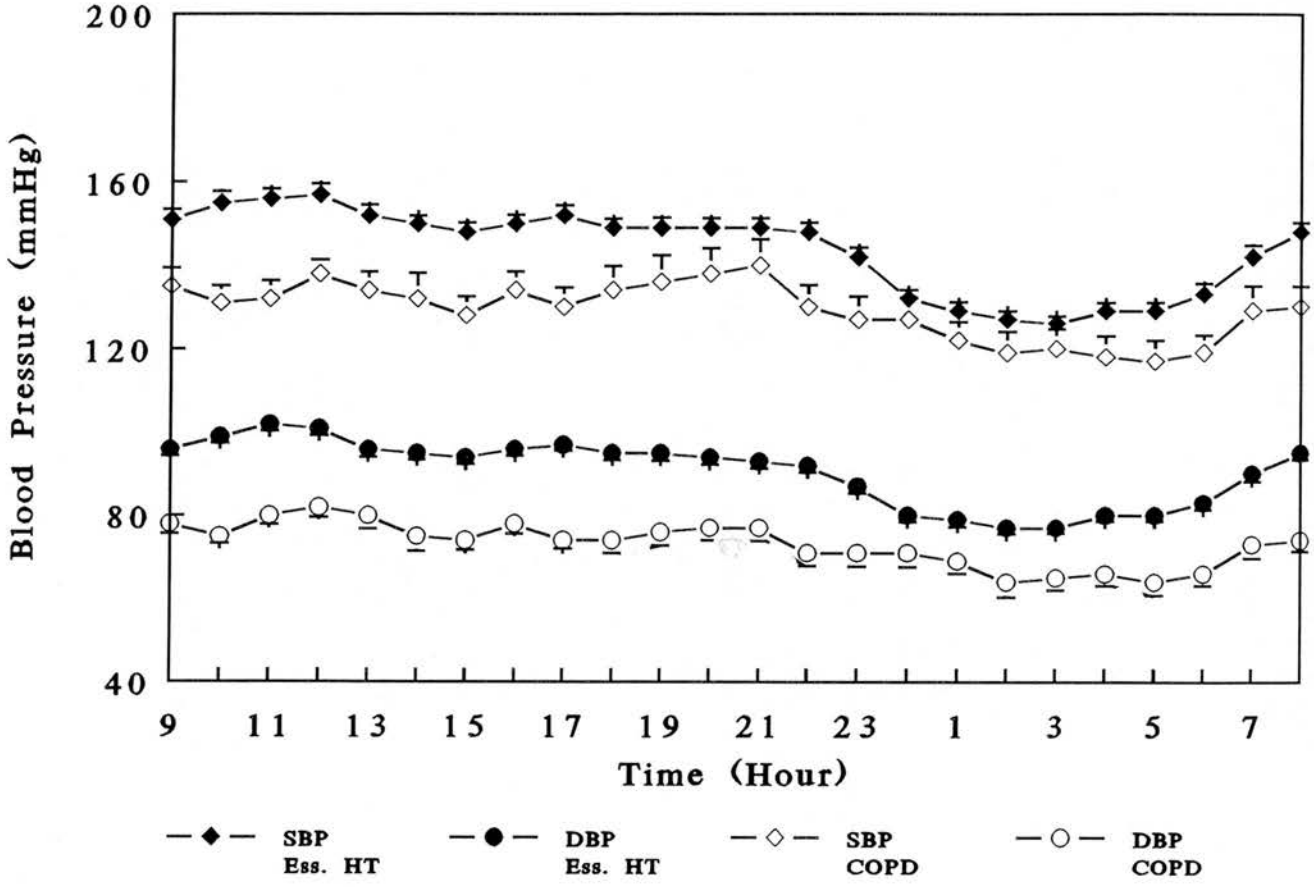


Twenty-four hour ambulatory blood pressure profile of patients with essential hypertension (Ess. HT = solid symbols) compared to those with symptomatic sleep apnoea (SAS = open symbols).

Hourly average blood pressure ± S.E.M. is plotted against time.

The normal diurnal blood pressure is apparent in the essential hypertensives but appears mildly blunted in sleep apnoea (though not statistically significant).

Figure 8.2 **Diurnal Blood Pressure Variation in Essential Hypertension and COPD**

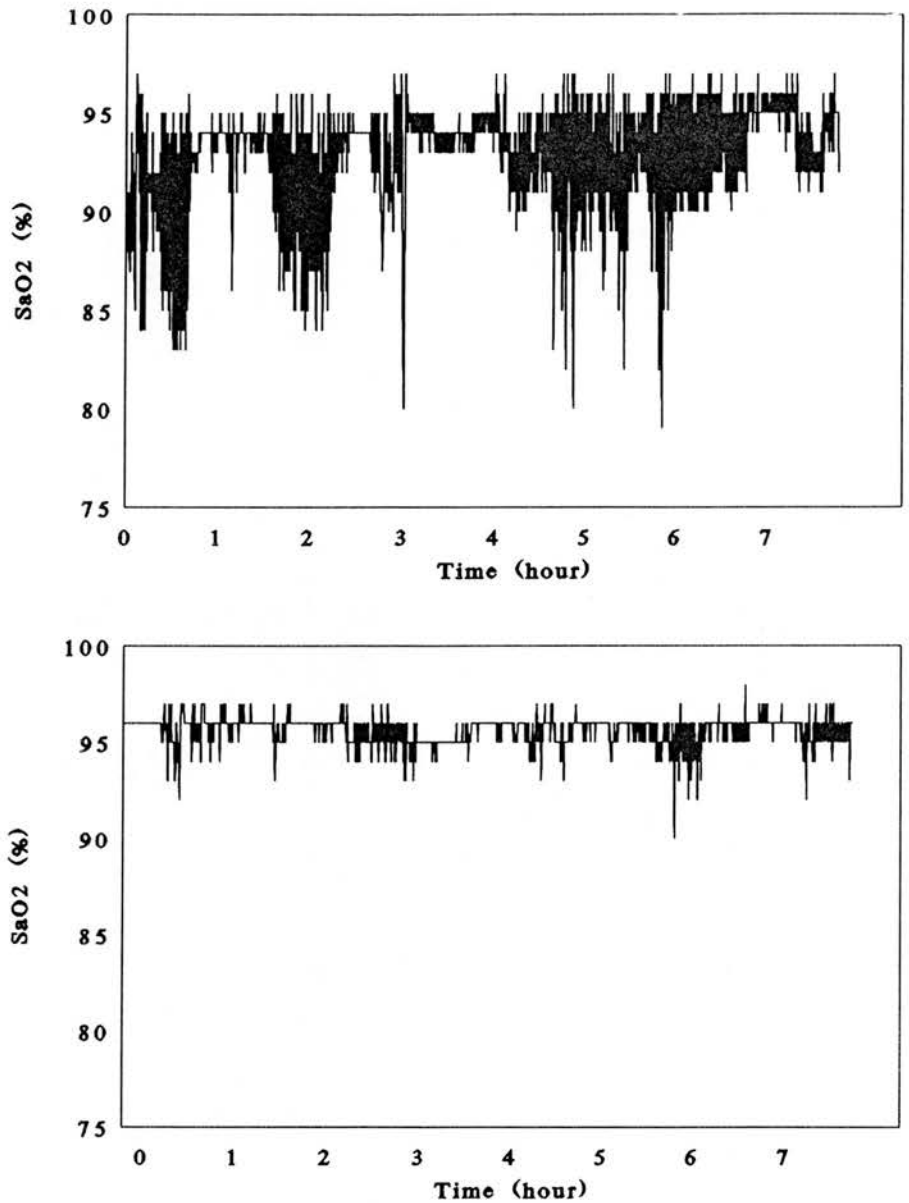


Twenty-four hour ambulatory blood pressure profile of patients with essential hypertension (Ess. HT = solid symbols) compared to those with chronic obstructive pulmonary disease (COPD = open symbols).

Hourly average blood pressure ± S.E.M. is plotted against time.

The normal diurnal blood pressure is apparent in the essential hypertensives but appears blunted in COPD.

Figure 8.3 **Nocturnal Pulse Oximetry**



Linear representation of overnight pulse oximetry studies. Each SaO2 measurement, representing the lowest SaO2 detected during the preceding 12 seconds, is plotted against time.

The marked variability of the subject in the upper panel (who is subject 1 in Table 8.4), with frequent drops in oxygen saturation, is readily appreciated. This subject had 195 dips in SaO2 > 4%. The lower panel (from Control Subject 1 in Table 8.4) illustrates a normal recording, with some baseline variability, but almost all in the range 92-96%. There were, however, 5 dips in SaO2 > 4%.

Table 8.3 **Overnight Pulse Oximetry Data**

	Essential Hypertension		COPD		
Variable (%)	**Median**	**Mean**	**Median**	**Mean**	**p**
Median SaO2	95	95	90	89	<0.00001
Max. SaO2	98	98	95	94	<0.00001
Min. SaO2	89	88	79.5	76	0.0001
No. of Dips SaO2> 4%/hour	0.92	2.4	1.3	2.6	NS

3. Linear Regression Analysis - Essential Hypertension

Using single Pearson correlation coefficient analysis, only age and wake systolic BP were significantly correlated ($r = 0.28$, $p = 0.02$), with the correlation coefficients for SaO2 and the BP parameters all less than 0.06. On multiple linear regression analysis, there was a strong relationship between age and the SaO2 dip rate (0.34, $p < 0.005$), and a relationship between neck circumference and SaO2 which approached significance ($r = 0.22$, $p = 0.08$). No relationship between blood pressure and nocturnal hypoxaemia could be demonstrated.

4. Linear Regression Analysis - COPD

There was no significant correlation between either demographic parameters or oximetry data, with only BMI and wake diastolic BP approaching significance ($r = 0.37$, $p = 0.19$).

5. Polysomnography

Six of the 7 patients found to have an SaO2 dip rate > 5/hour and 3 of 7 matched controls agreed to attend for formal polysomnography using the standard methods of the Scottish National Sleep Laboratory (Douglas *et al,* 1992). Results are given in Table 8.4. Lower minimum SaO2 and more hypopnoeas were detected by polysomnography, in keeping with its greater sensitivity. All but one patient who had a positive domiciliary study had witnessed apnoeas, while no patient with a negative study had a witnessed apnoea. Subject 3, who had a negative polysomnography study, slept for only 42% of the study night (less than 3 hours), and spent only 6% of the night in deep (slow wave) sleep The accuracy of this study is therefore questionable. An apnoea/hypopnoea index of > 15 during formal polysomnography is characteristic of sleep apnoea (Douglas *et al,* 1992), thus, excluding subject 3, 4/5 (80%) of domiciliary studies were true positives, with one false positive (note that the domiciliary study was borderline positive and

polysomnography borderline negative). One of 3 control studies (33%) appears to have been a false negative, but again polysomnography was borderline positive. Thus, while far from 100% accurate, the domiciliary pulse oximetry study appears to have achieved a satisfactory standard for the purposes of this study.

Table 8.4 Results of Overnight Sleep Study

The first two columns give the data from the domiciliary study and the following columns the result of polysomnography.

Subject	Min. SaO2 - Home	SaO2 Dips - Home	Min. SaO2	Apnoeas	Hypo-pnoeas	Apnoea Index (/hour)	Apnoea/ Hypopnoea Index (/hr)
1	79	24.7	61	33	175	7.5	47.1
2	76	18.3	69	34	186	9.2	59.8
3	73	12.4	78	0	25	0	8.9
4	84	5.2	88	8	53	1.9	14.4
5	82	6.1	91	26	170	4.9	37
6	78	5.3	65	27	100	5.4	25.5
Control 1	90	0.63	83	0	67	0	13.2
Control 2	89	1.27	85	0	67	0	12.9
Control 3	89	1.65	88	0	94	0	16

Discussion

By obtaining 24 hour BP profiles in patients' own home, with simultaneous monitoring of oxygen saturation during sleep, I have overcome some of the limitations of previous studies examining the possible association of hypertension and sleep apnoea. The use of ambulatory BP monitoring removes any potential observer bias, and confirmed that all patients had sustained hypertension. Furthermore, by using activity monitors to measure sleep time objectively, I have been able to differentiate wake and sleep BP, and thus examine the potential relationship of sleep apnoea to both sustained diurnal hypertension and to the diurnal BP rhythm. Finally, this methodology was designed to enable all investigations to be performed in patients' own home. As there is evidence that hospitalisation *per se* may have an effect on diurnal blood pressure variation, this removed a further potential source of error inherent in studies performed in a hospital ward or sleep laboratory.

I have relied upon pulse oximetry for the diagnosis of sleep apnoea. While recognising that this provides information on hypoxaemia alone, with no information on apnoeas, this approach has been shown to be valid (Stradling *et al,* 1989b) and is approved by the British Thoracic Society (British Thoracic Society, 1990). However, as up to one third of patients with sleep apnoea may have significant apnoea without hypoxia (Douglas *et al,* 1992), and as such apnoeas may be responsible in part for the blood pressure elevation, full polysomnography studies were arranged in a subset of patients and appear to validate our results. The advantages of being able to study blood pressure changes in a subject's own environment may outweigh the loss of sensitivity inherent in my method.

Ambulatory non-invasive blood pressure monitoring is, of necessity, intermittent and in this study blood pressure was recorded every 30 minutes. Thus, it is possible that acute, transient elevations in blood pressure during the night, associated with apnoeas, were missed. Nonetheless, intermittent recording, with measurements every 30 minutes or less, has been shown to correspond closely to beat-to-beat intra-arterial recording (Di Rienzo *et al,* 1983), suggesting that this estimate of mean blood pressure during sleep is accurate. Non-invasive measurement of blood pressure variability is less accurate and I am not able to exclude a significant increase in nocturnal blood pressure variability in the patients with apnoea.

Nocturnal hypoxaemia does not appear to be associated with the level of either wake or sleep BP nor to blunting of the diurnal BP profile in essential hypertensives. Hypertension and the apnoea index are both positively correlated to age. Furthermore, the correlation of neck circumference to apnoea, while not achieving statistical significance, is similar to that previously reported as the strongest independent predictor of sleep apnoea in middle aged men (Stradling & Crosby, 1991). Whilst related to generalised obesity (Stradling & Crosby, 1991), neck circumference appears to be a stronger marker for the pattern of obesity most closely related to sleep apnoea (Davies & Stradling, 1990; Stradling & Crosby, 1991). Although not clearly demonstrated here, obesity is also associated with both hypertension (Levy & Kannel, 1988) and attenuation of the diurnal BP profile (Jamerson & Julius, 1991). Thus, the increased prevalence of sleep apnoea in hypertensive patients may simply reflect the presence of the confounding variables of age and obesity.

If there was a causal association between sleep apnoea and hypertension, this would have to act primarily via an effect on BP during sleep and a blunting of the normal diurnal BP profile would be expected. The absence of such a relationship, both in a group of

essential hypertensives and in patients with symptomatic sleep apnoea, argues strongly against any such association.

Patients with COPD, who were significantly more hypoxic overnight, did appear to have minor blunting of the diurnal blood pressure profile, and the prevalence of non-dipping was higher than that seen in essential hypertension, though not significantly so. There were however several potential confounding variables in this group. They were significantly older that the hypertensive patients, and there is some evidence that the diurnal rhythm may attenuate with age (Munakata *et al,* 1991) (see Chapter 4). Almost half were on long-term oral corticosteroid which may also influence blood pressure variability (Munakata *et al,* 1988). Patients with COPD may not sleep as soundly as normal subjects (Catterall *et al,* 1983) and, anecdotally, monitoring was less well tolerated in these patients, with 6 of 20 subjects unable to tolerate the domiciliary sleep study. Perhaps most importantly, these patients had markedly limited activity during the day and failure of blood pressure to rise normally during wake hours could account for the smaller diurnal variation. The small sample size makes it difficult to determine the extent to which these factors have biased our results, but the absence of any clear relationship between oxygen saturation and blood pressure argues against a pathophysiological link.

Despite the absence of any association between the apnoea index and the blood pressure profile, I have found the prevalence of sleep apnoea in hypertensive patients to be over double that seen in a random male population sample (10.6% vs 4.6% (Stradling & Crosby, 1990)), although substantially less than the 22-35% previously reported in male hypertensives (Kales *et al,* 1984; Lavie *et al,* 1984; Fletcher *et al,* 1985; Williams *et al,* 1985). I have included both male and female patients in this study but, as the prevalence in male patients was only marginally higher (13.3%), this is unlikely to account for this difference. However, most patients with nocturnal hypoxaemia were on drug treatment, and the prevalence in treated, male, hypertensives (23.8%) is similar to that previously reported.

This apparent discrepancy in the prevalence of sleep apnoea in treated and untreated patients has been noted previously (Warley *et al,* 1988; Hirshkowitz *et al,* 1989) and an adverse effect of anti-hypertensive drugs on ventilatory control remains a possible mechanism for the observed apparent excess of sleep apnoea which cannot be excluded by this work. Patients in early studies were mainly treated hypertensives (Kales *et al,* 1984; Lavie *et al,* 1984; Fletcher *et al,* 1985) and three more recent studies of untreated patients found the prevalence of nocturnal hypoxaemia and/or apnoea in hypertensive patients to be

no higher than in a control group (Warley *et al,* 1988; Hirshkowitz *et al,* 1989; Stradling & Crosby, 1990). One of these (Hirshkowitz *et al,* 1989) also studied treated hypertensives and found that they did have a higher incidence of sleep apnoea. The earlier reports may therefore have been finding an artefactually raised prevalence of sleep apnoea due to the effects of anti-hypertensive drugs.

Diuretics, particularly in the face of inadequate potassium replacement, can cause a mild metabolic alkalosis. Such alkalosis has been shown to decrease ventilation in dogs (Sullivan *et al,* 1985), though the effect in man is unknown. Beta-blockers (Boudoulas *et al,* 1983) and methyl-dopa (LaHive *et al,* 1988) have both been postulated to cause a reduction in upper airway patency due to effects on smooth muscle tone. A direct central depressant effect on ventilatory centres is also a possibility.

Przybylski *et al* (1986) hypothesised that hypertension and sleep apnoea syndrome are both manifestations of arterial chemoreceptor hyper-responsiveness and that increased chemoreceptor activity may lead to both increased sympathetic outflow and instability of ventilatory control. If true, it may be that some patients are particularly vulnerable to the effects of blood pressure lowering drugs on ventilation. As an angiotensin converting enzyme inhibitor has been reported to cause a reduction in apnoic episodes (Peter *et al,* 1989), determining which hypertensive patients are in this category could have important therapeutic implications.

Since starting this work, two studies analysing ambulatory blood pressure data in patients with sleep apnoea have been published. Noda *et al* (1993) studied 21 men with known sleep apnoea and found 9 (43%) to have normal diurnal blood pressure, 8 (38%) to have mildly attenuated blood pressure variability and 4 (19%) to have significantly reduced diurnal blood pressure variability. The latter group had the most severe sleep apnoea. They compared this data to a control group of normotensive male subjects and concluded that the blood pressure profile was significantly different in those with most severe sleep apnoea. No attempt was made to control for obesity or other potential confounding variables. This and the small numbers in each sub-group make this difficult to interpret.

The study of Hla *et al* (1994) is more important. This was a population based study of 147 subjects, including a subset whose medical history suggested a high likelihood of sleep apnoea. Although not clearly stated, it appears that ambulatory BP monitoring and polysomnography were performed on two separate occasions. Designed predominantly to determine whether sleep apnoea was independently associated with hypertension, no

parameter of the diurnal BP rhythm was studied. Blood pressure was higher in subjects with sleep apnoea (though still in the normal range) but the diurnal rhythm was maintained and almost identical in the two groups. Nocturnal blood pressure variability, defined as the co-efficient of variation of the mean arterial pressure, was higher in those with sleep apnoea. The association between sleep apnoea and hypertension persisted after correction for age, sex and obesity. However, obesity was defined simply as BMI > 27 kg/m^2 with no attempt made to correct for the type of obesity. This is of potential importance as Stradling & Crosby (1991) have previously shown neck circumference to be the single most important predictor of sleep apnoea in a large community based survey, and different patterns of obesity are known to impart different levels of cardiovascular risk. Thus, while appearing to show an independent association between sleep apnoea and hypertension, the potential for obesity as a major confounding variable persists.

Conclusions

The absence of any association between sleep apnoea and nocturnal hypertension or diurnal blood pressure variation in essential hypertension, and normal diurnal variation in BP in patients with symptomatic sleep apnoea, makes any pathophysiological link between the two conditions unlikely. Minor blunting of the diurnal blood pressure rhythm in COPD patients with significant hypoxia makes it impossible to exclude an effect of hypoxia on nocturnal BP but there was no clear linear relationship. The increased prevalence of sleep apnoea in essential hypertension is probably caused by the confounding variables of age and obesity. A potential adverse effect of anti-hypertensive drugs on ventilatory controls remains a further possible mechanism which may warrant further study.

CHAPTER 9

Diurnal Blood Pressure Variation in Patients with Left Ventricular Dysfunction and Effect of Treatment with Long and Short-acting ACE Inhibitors

Background

Potential Role of the Heart as a Modulator of Diurnal Blood Pressure Variation

An active role for the heart in the control of blood pressure has been suggested by the observation that left ventricular mass may become elevated before blood pressure rises in individuals destined to become hypertensive with time (Mahoney *et al,* 1988; de Simone *et al,* 1991). Studies of patients with established left ventricular hypertrophy have also suggested blunting of the diurnal rhythm independent of the level of blood pressure (Gosse *et al,* 1988a; Verdecchia *et al,* 1990; Kuwajima *et al,* 1992). Moreover, the diurnal rhythm is modified in cardiac transplant recipients (Reeves *et al,* 1986; Sehested *et al,* 1990b), whose ventricles are denervated, and in patients with central autonomic denervation (Shy-Drager syndrome) (Mann *et al,* 1983). Autonomy of the blood pressure rhythm from other physiological cardiac rhythms has been confirmed by the observation that day-night blood pressure variation persists in patients with ventricular demand pacemakers (Davies *et al,* 1984), whose heart rates are constant.

Thus, the heart may have an independent role in the control of the diurnal blood pressure rhythm, and if so, an altered rhythm in patients with left ventricular dysfunction may be expected. In keeping with this hypothesis, in a study of normotensive patients with moderate-to-severe, chronic congestive cardiac failure secondary to ischaemic heart disease, Caruana and colleagues (1988) demonstrated a reduction in blood pressure variability, and suggested that the amplitude of the 24-hour blood pressure curve was related to the degree of left ventricular functional impairment, such that those with worst left ventricular function have the smallest day-night BP variation. Similarly, in a study of patients with end-stage heart failure, referred for cardiac transplantation, van de Borne *et al* (1992) found that severity of heart failure correlated with a reduction in the amplitude of both heart rate and blood pressure diurnal rhythm.

Angiotensin Converting Enzyme Inhibitors - Efficacy, Effect on Diurnal Rhythm and Potential Adverse Effects

Both long- and short-acting angiotensin converting enzyme (ACE) inhibitors are effective therapy for the treatment of heart failure and have been shown to improve prognosis (The SOLVD Investigators, 1991; Fonarow *et al,* 1992). However there appear to be important clinical differences, regarding both efficacy and side-effect profile, between different ACE inhibitors. Lisinopril (a long-acting ACE inhibitor) has been shown to result in a statistically greater increase in both exercise duration and left ventricular ejection fraction than captopril (a short-acting ACE inhibitor) (Giles *et al,* 1989). Lisinopril does however also cause a larger increase in blood urea, but not creatinine, the significance of which is uncertain (Giles *et al,* 1989). Packer *et al* (1986), using large, fixed doses of ACE inhibitors in patients with severe heart failure, found more prolonged hypotension and a deterioration in creatinine clearance in patients treated with enalapril (duration of action between that of lisinopril and captopril) than with the shorter-acting captopril. Enalapril and captopril can both cause a reduction in glomerular filtration rate (GFR), despite an increase in effective renal plasma flow, and the decline in GFR correlates with the chronic fall in BP seen in these patients (Cleland & Dargie, 1987), suggesting that a prolonged fall in BP may be deleterious.

A comparative study of lisinopril and captopril using ambulatory monitoring in hypertensive patients has shown significantly greater blood pressure reduction with lisinopril, not apparent on clinic blood pressure measurement (Whelton *et al,* 1990), with blood pressure tending to rise between doses of captopril. Unlike hypertensive patients, such prolonged reduction may be deleterious in a patient with heart failure. The only study to examine the effect of ACE inhibition on the diurnal blood pressure profile of patients with heart failure studied small numbers of patients and was uncontrolled (Osterziel *et al,* 1992). In this study there was a tendency (albeit non-significant) for the diurnal curve to flatten on treatment, and this effect was greater with the long-acting drug, lisinopril. This study also examined the effect of treatment on biochemical indices of renal function, demonstrating a small, though non-significant, reduction in creatinine clearance with lisinopril.

Introduction

While it appears likely that severe left ventricular impairment is associated with blunting of the diurnal blood pressure profile, the mechanism remains uncertain and it is not clear whether those with mild or moderate heart failure are similarly affected. Moreover, the

effect of treatment with ACE inhibitors on the diurnal rhythm, and the importance of such effects on renal function, is not known. In this study the 24 hour blood pressure profile of patients with mild to moderate cardiac failure was studied before and after therapy with a long- and a short-acting angiotensin converting enzyme inhibitor, and the influence of severity of heart failure on diurnal profile was assessed. The effect of such treatment on glomerular filtration rate was also studied.

Methods

This study was conducted in compliance with ethical committee review and all patients gave written informed consent.

Study Design

This was a 15 week, prospective, double blind, randomised, two-period cross-over study with single-blind run-in and washout periods to compare the effect of lisinopril and captopril on the 24 hour blood pressure profile and on renal function in patients with heart failure. Although originally conceived as a single-centre study, problems with recruitment of suitable patients led to two other centres taking part. However, all data was collected in an identical manner and analysed by myself.

All patients had a clinical diagnosis of heart failure, in NYHA functional class I, II or III, treated with loop diuretic (>40 mg frusemide per day or equivalent) and were in sinus rhythm. The diagnosis of heart failure was confirmed by a radionuclide ejection fraction < 35% in all patients. Patients with recent myocardial infarction (< 2 months), cardiac surgery (< 3 months) or stroke (< 6 months) were excluded, as were patients with valvular heart disease or predominant cor pulmonale. Those with renal dysfunction, defined as serum creatinine > 250 μmol/l, GFR < 35 ml/min/1.73m^2 or > 0.5 g/l proteinuria, or clinically significant hepatic or haemopoietic disorders were also excluded.

Patients already taking an ACE inhibitor or other vasodilator (unless used for the treatment of chronic stable angina), beta-blockers, or non-steroidal anti-inflammatory drugs (other than low dose aspirin) were also excluded. All other drug therapy was kept constant throughout the study period.

Drug Administration

After a one week placebo run-in period, eligible patients were randomised and received either a test dose of lisinopril 2.5 mg and placebo, or a test dose of captopril 6.25 mg and

placebo. Patients who developed symptomatic hypotension after test dosing were excluded from further study. If the test dose was tolerated, patients were then discharged on lisinopril 10 mg once daily and placebo matching captopril three times daily, or captopril 25 mg three times daily and placebo matching lisinopril once daily. After 6 weeks treatment active treatment was changed to placebo and continued for a two week washout period. Patients then received a further test dose of the alternative therapy and, if tolerated, were maintained on that therapy for a further 6 weeks.

Patient Evaluation

All patients underwent radionuclide ventriculography prior to or during the initial placebo run-in phase providing an objective index of left ventricular function. The primary variables evaluated were non-invasive 24-hour ambulatory blood pressure profiles and glomerular filtration rate measured isotopically. Secondary end-points included patients' responses to a symptom questionnaire and change in New York Heart Association functional status. Serum biochemistry, haematology and urine dipstick analysis of proteinuria were measured at each visit for safety analysis.

Ambulatory blood pressure was measured non-invasively using the SpaceLabs 90207 monitor (O'Brien *et al,* 1991b), with blood pressure readings made every 30 minutes throughout the monitoring period. For the purposes of analysis, day-time was defined as 7 am-12 midnight (Stewart *et al,* 1993) and the 24-hour, day-time and night-time mean blood pressures calculated, excluding biologically impossible or implausible readings (Conway *et al,* 1988). Diurnal blood pressure variation was expressed as percentage change from day to night for each of systolic, diastolic and mean arterial pressure. Blood pressure was monitored for the 24 hours immediately prior to test dosing and for a further 24 hours after test dose. Further 24 hour BP monitoring was then undertaken after each 6 week treatment period.

Glomerular filtration rate was measured radio-isotopically after a single intra-venous injection of ^{99m}technetium diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA), followed by repeated blood sampling over 4 hours (Fawdry *et al,* 1985), in the week before each test dose and at the end of each 6 week treatment period.

Control Group

The diurnal blood pressure profile at baseline was compared to that of a normal, healthy, working population studied previously (see Chapter 7).

Statistical Methods

An estimate of the sample size required to demonstrate a clinically significant difference in blood pressure was made using the method of Donner (1995) for crossover studies, assuming the most conservative situation, i.e. that there is no correlation between measurements within an individual between the two treatment periods. Using data from earlier studies indicating the standard deviation of systolic blood pressure to be 6.99 mmHg, it was estimated that 24 patients would be required to complete the study, with 80% power at the 5% level of significance.

The blood pressure profile was compared to that of the control group using Student's t-test for independent samples. Baseline comparability and between group differences were assessed using Student's paired t-test or Wilcoxan matched pairs test as appropriate.

The strength of association between left ventricular ejection fraction and measures of blood pressure were examined using Pearson's correlation coefficient. The change in renal function over the period of study was compared to the change in blood pressure using Spearman's rank correlation coefficient.

Statistical significance was taken as $p < 0.05$.

Results

Patient characteristics

Forty-eight patients were screened for entry into the study, 41 of whom completed the one week placebo run-in period and entered the cross-over phase of the study. Of the patients not randomised 3 had an ejection fraction > 35%, 3 withdrew consent and one developed atrial fibrillation. Of the 41 patients entering the cross-over phase, 21 were randomised to Sequence L (Lisinopril → Captopril) and 20 were randomised to Sequence C (Captopril → Lisinopril). In total, 13 patients failed to complete the study, seven patients in Sequence L and six patients in Sequence C. Two patients were withdrawn because of worsening or inadequately controlled heart failure, one patient died suddenly, with the death ascribed to ischaemic heart disease, one patient died after acute myocardial infarction, and one patient sustained a disabling stroke. Two patients withdrew complaining of side effects from medication and one patient withdrew after an acute anxiety attack. Five patients were withdrawn for other reasons.

Thus, 28 patients completed the study, 14 in each sequence group. The results presented here are for these patients only. Baseline demographic details are given in Tables 9.1 and 9.2.

Although there were minor differences between the two sequence groups in terms of demographic parameters, these were not statistically significant and, as this was a cross-over study, should have no influence on the analysis of the study.

Four patients had a history of chronic ischaemic heart disease, 3 a history of previous myocardial infarction and 2 patients had undergone coronary artery by-pass surgery. One patient was hypertensive.

All patients were treated with the loop diuretic frusemide, 22 (79%) maintained on 40 mg daily and 6 (21%) on 80 mg daily. Twenty patients (71%) were on low dose aspirin therapy, 11 (39%) on isosorbide mononitrate, 4 (14%) on digoxin and 5 (18%) on a calcium antagonist.

Table 9.1 **Baseline Demography**

Variable (mean ± S.E.M.)	Sequence L	Sequence C	Total
Number of Patients	14	14	28
Age	63±2.6	64.4±1.7	63.7±1.5
Gender - male	11 (79%)	10 (71%)	21 (75%)
Gender - female	3 (21%)	4 (29%)	7 ((25%)
Height	171±2.6	167.9±2.5	169.4±1.8
Weight	80.3±4.2	71.6±3	75.9±2.7
Ejection fraction	24.7±1.9	23.5±2	24.1±1.4
Duration of heart failure (months)	13.2±6.3	11±5.3	12.1±4.1
NYHA Grade I	6 (43%)	4 (29%)	10 (36%)
NYHA Grade II	7 (50%)	7 (50%)	14 (50%)
NYHA Grade III	1 (7%)	3 (21%)	4 (14%)

There were no significant differences between groups.

Table 9.2 **Baseline Outcome Variables**

Variable (mean ± S.E.M.)	Sequence L	Sequence C	Total
Clinic Systolic BP	124±5	134±4.7	128±3.5
Clinic Diastolic BP	72±3.2	81±2.5	76±2.1
24-hour Mean Systolic BP	116±4.4	119±2.9	117±2.6
24-hour Mean Diastolic BP	72±2.6	72±2.1	72±1.6
Day-time Mean Systolic BP	120±4.4	123±3	121±2.7
Day-time Mean Diastolic BP	75±2.6	75±2.3	75±1.7
Night-time Mean Systolic BP	110±4.5	110±3.3	110±2.8
Night-time Mean Diastolic BP	67±2.7	66±2.3	66±1.8
Nocturnal SBP Dip (%)	9±1.8	11.4±2	10.1±1.3
Nocturnal DBP Dip (%)	12.1±2.2	13.9±2.2	13±1.6
GFR (ml/min/1.73m^2)	81.6±5.8	71±5	75.8±3.9

There were no significant differences between the groups.

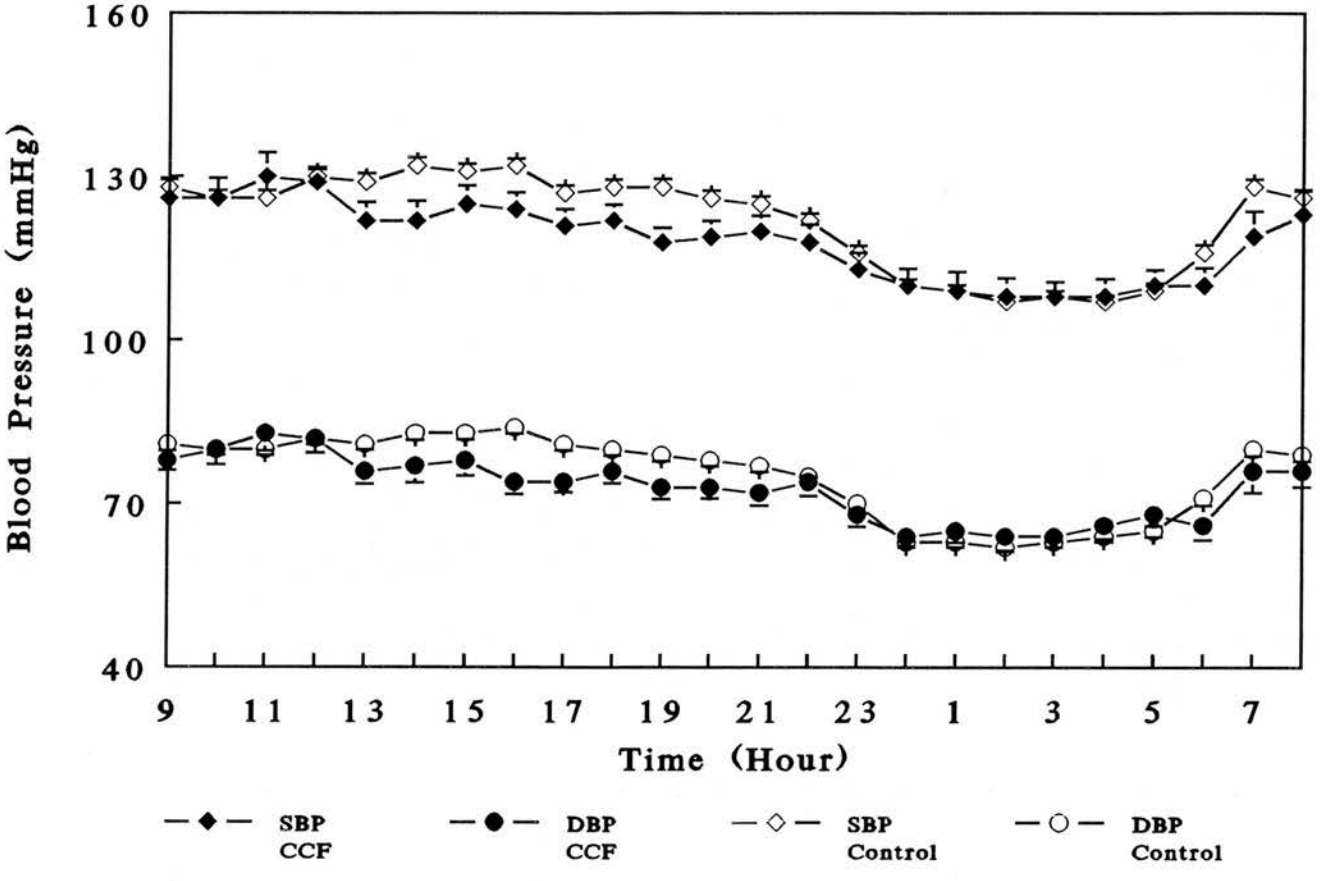
Outcome Measures

Diurnal blood pressure variation was preserved in the patients with heart failure, but appeared blunted in comparison to a healthy population (Table 9.3, Figure 9.1). Night-time blood pressure in the two groups was remarkably similar, with the greater nocturnal dip in the control group predominantly due to higher day-time pressure. The working population was significantly younger than those with heart failure (36±1.1 vs 64 ± 1.5 years) which is likely to partially, but not completely, explain this difference.

Table 9.3 **Comparison of Ambulatory BP Profile in Heart Failure Patients to a Healthy, Working Population.**

Variable (mean ± S.E.M.)	Control (n=94)	Heart failure (n=28)	p
Day-time Mean Systolic BP	127±1.1	121±2.6	0.02
Day-time Mean Diastolic BP	79±0.9	75±1.7	0.02
Night-time Mean Systolic BP	109±1	109±2.6	NS
Night-time Mean Diastolic BP	64±0.8	65±1.7	NS
Nocturnal SBP Dip (%)	13.9±0.5	10.1±1.3	0.003
Nocturnal DBP Dip (%)	19.1±0.7	13±1.5	0.0006

Figure 9.1 **Diurnal Blood Pressure Variation in Heart Failure**



Twenty-four hour blood pressure profile of patients with heart failure (CCF, solid symbols) compared to that of a healthy, working population (Control, open symbols). Hourly average BP ± S.E.M. is plotted against time. Day-time BP is seen to be lower in the heart failure population, with night-time values similar to controls.

In this population, left ventricular ejection fraction appeared to have no significant association with diurnal blood pressure variation, either at baseline or after treatment (Figure 9.2).

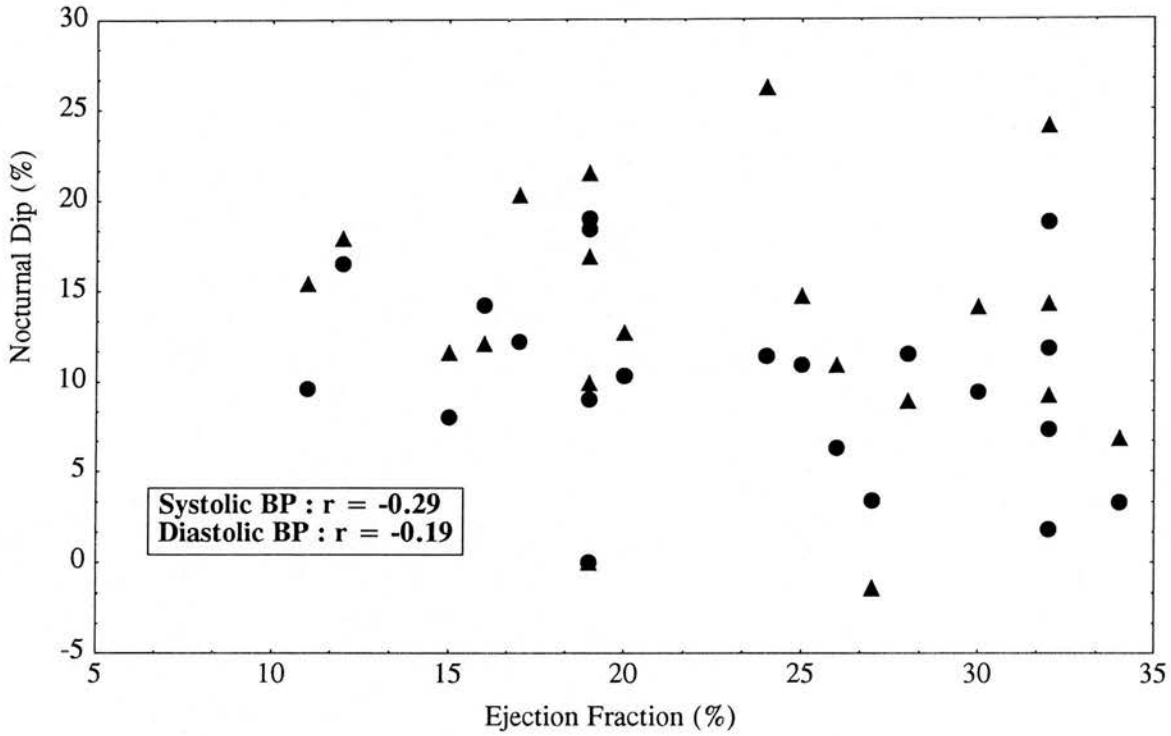
Following treatment, blood pressure fell significantly in both treatment groups, predominantly due to a reduction in day-time pressure (Table 9.4, Figures 9.3 and 9.4). However, the blood pressure reduction was greater in the lisinopril group, with a significant fall during the night in this group only. Predominantly as a result of the greater fall in day-time pressures, diurnal blood pressure variation was significantly reduced in the lisinopril group only. Despite this, comparison of the final blood pressure in each treatment group reveals significantly lower blood pressures in the lisinopril group during day-time only (Table 9.5, Figure 9.5). The nocturnal dip was lower in the lisinopril group but not significantly so.

Glomerular filtration rate did not change significantly in either group (Tables 9.4 and 9.5). However, there was a small fall in the lisinopril group and a small increase in the captopril group, possibly suggesting a trend towards greater deterioration in renal function in the lisinopril group. There was no significant correlation between the change in blood pressure and that of GFR (Table 9.6).

Table 9.4 **Change in Blood Pressure and GFR After 6 Weeks Treatment with an ACE Inhibitor**

	Lisinopril			Captopril		
Variable (mean)	**pre**	**post**	**p**	**pre**	**post**	**p**
Clinic Systolic BP	130	120	0.0002	128	128	NS
Clinic Diastolic BP	76	72	NS	76	76	NS
24-hour Systolic BP	118	110	0.00001	117	113	0.006
24-hour Diastolic BP	72	66	0.00001	72	69	0.002
Day-time Systolic BP	122	113	0.000003	121	117	0.002
Day-time Diastolic BP	75	69	0.000001	75	72	0.001
Night-time Systolic BP	109	105	0.01	109	105	NS
Night-time Diastolic BP	64	61	0.02	65	62	NS
Nocturnal Dip SBP(%)	10.2	6.9	0.01	10.1	9.5	NS
Nocturnal Dip DBP(%)	14.4	10.6	0.03	13.2	12.7	NS
GFR (ml/min/1.73m^2)	77.4	73	NS	74.3	76.3	NS

Figure 9.2 **Relationship of Diurnal Blood Pressure to Ejection Fraction in Heart Failure**



Ejection fraction, measured radio-isotopically, has been correlated with systolic (circles) and diastolic (triangles) diurnal blood pressure variation. The apparent negative correlation is not statistically significant.

Table 9.5 **Comparison of Blood Pressure and GFR after Treatment**

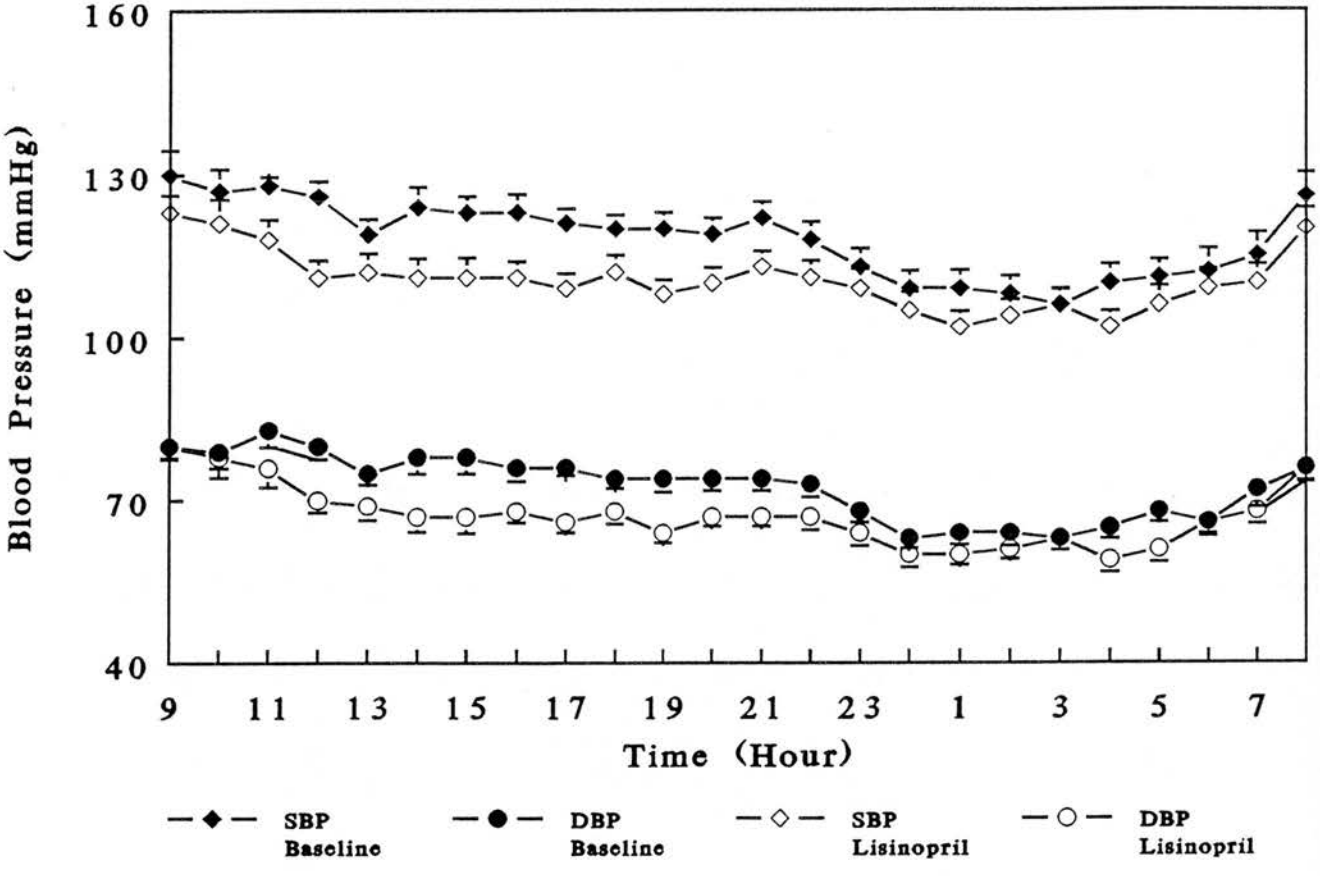
Variable (mean ± S.E.M.)	Lisinopril	Captopril	p
Clinic Systolic BP	120±3.6	128±4.3	0.002
Clinic Diastolic BP	73±2.1	76±2.1	NS
24-hour Systolic BP	110±2.3	113±2.6	0.007
24-hour Diastolic BP	66±1.5	69±1.7	0.005
Day-time Systolic BP	113±2.3	117±2.6	0.003
Day-time Diastolic BP	69±1.5	72±1.7	0.003
Night-time Systolic BP	105±2.6	106±2.8	NS
Night-time Diastolic BP	61±1.7	63±1.9	NS
Nocturnal Dip SBP(%)	6.9±1.6	9.2±1.6	NS
Nocturnal Dip DBP(%)	10.6±1.8	12.4±2	NS
GFR (ml/min/1.73m^2)	73±4.3	76±5.1	NS

Table 9.6 **Strength of Association Between Change in Blood Pressure and Change in GFR**

	Lisinopril	Captopril
BP Variable	Spearman Rank Correlation	Spearman Rank Correlation
Clinic Systolic BP	0.15	-0.1
Clinic Diastolic BP	-0.9	-0.11
24-hour Systolic BP	0.13	-0.18
24-hour Diastolic BP	0.14	-0.01
Day-time Systolic BP	0.11	-0.16
Day-time Diastolic BP	0.12	0.14
Night-time Systolic BP	0.15	-0.16
Night-time Diastolic BP	0.09	-0.12
Nocturnal Dip (%)	-0.19	0.04
Nocturnal Dip (%)	-0.06	0.21

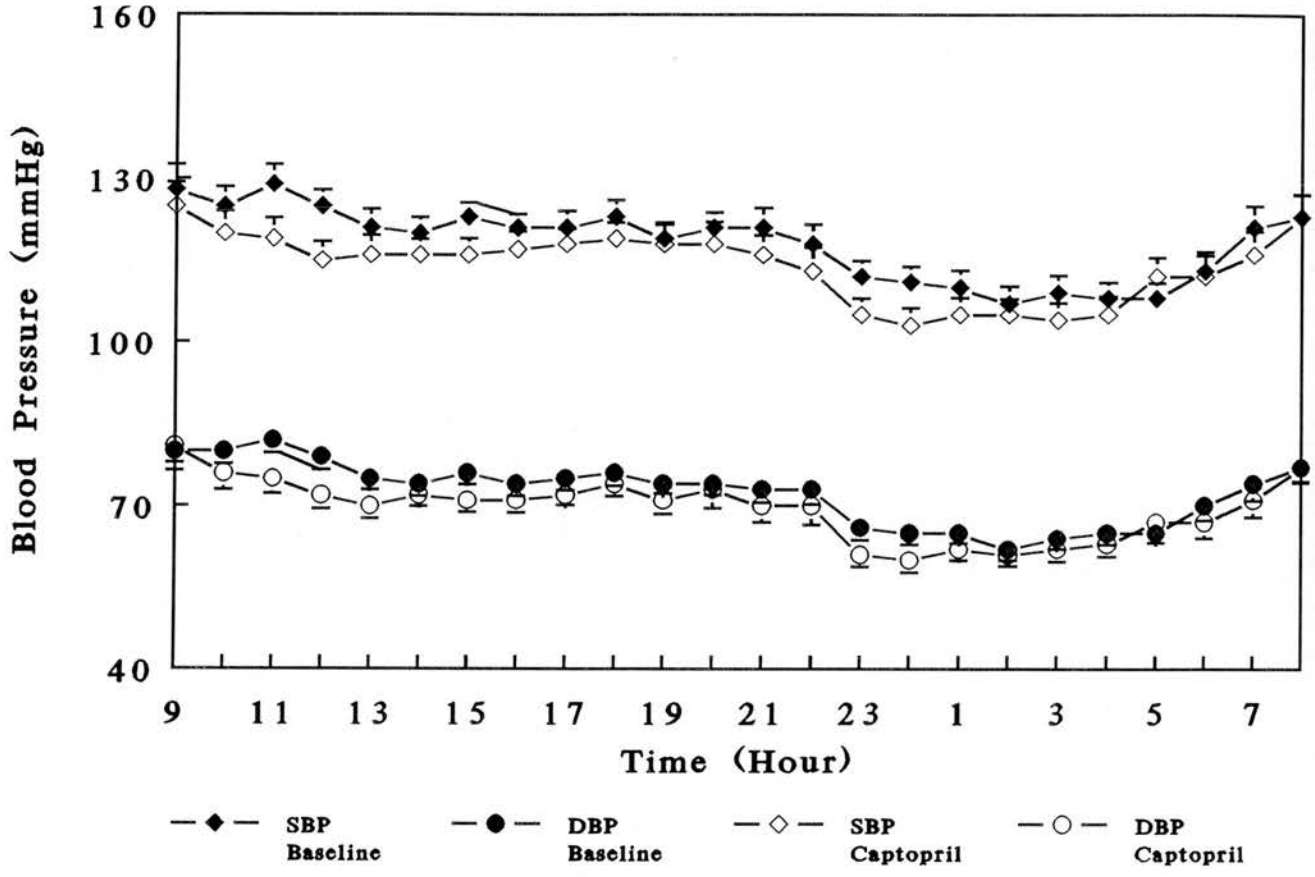
No correlation was significant at the 5% level.

Figure 9.3 **Change in the Diurnal Blood Pressure Profile After Treatment with Lisinopril**



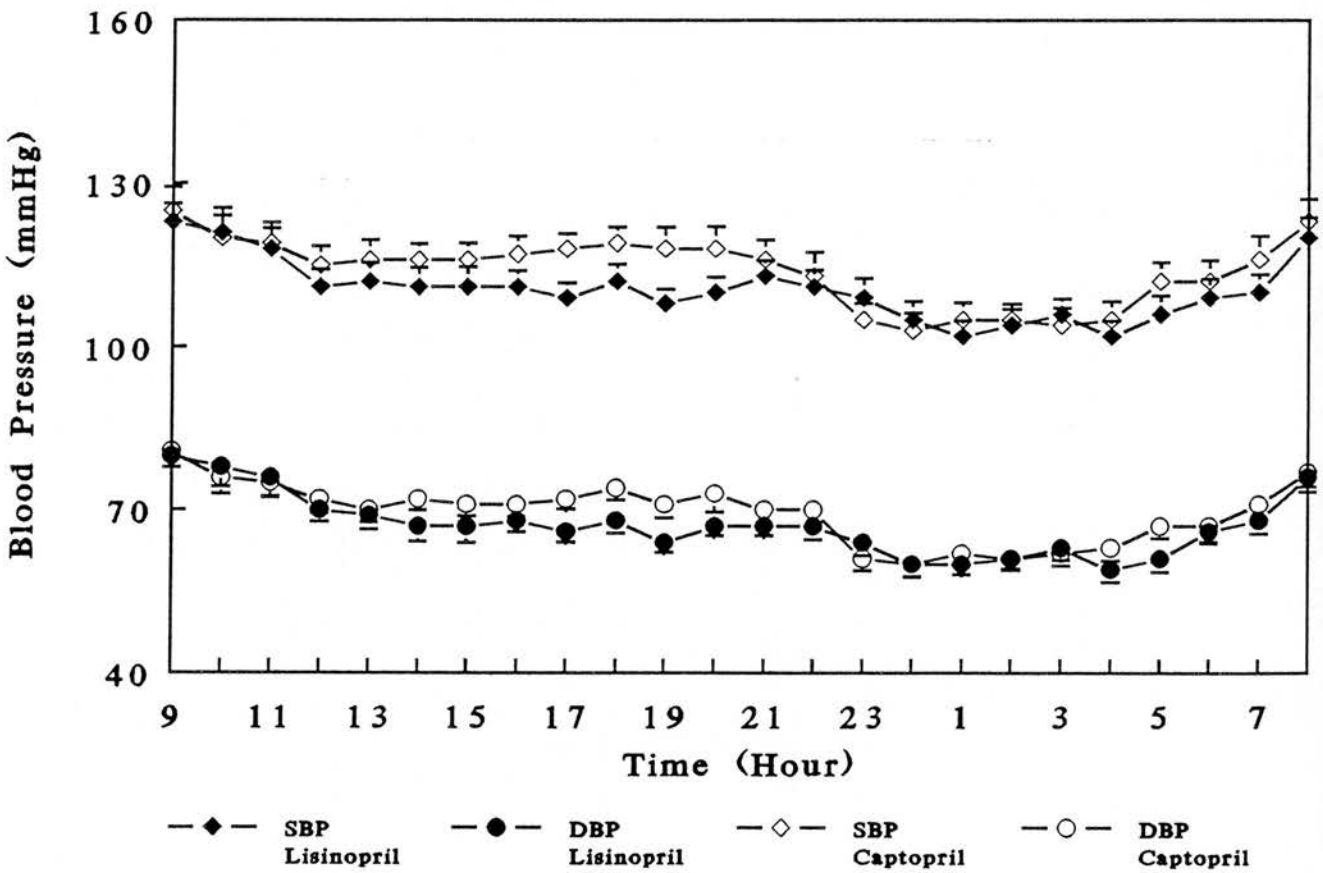
Twenty-four hour blood pressure profile of patients with heart failure at baseline (solid symbols) and after 6 weeks treatment with lisinopril (open symbols). Hourly average BP ± S.E.M. is plotted against time. The reduction in BP with lisinopril treatment, predominantly in day-time, is readily appreciated. The greater reduction in day-time than night-time BP results in some attenuation of the diurnal variability.

Figure 9.4 **Change in the Diurnal Blood Pressure Profile After Treatment with Captopril**



Twenty-four hour blood pressure profile of patients with heart failure at baseline (solid symbols) and after 6 weeks treatment with captopril (open symbols). Hourly average BP ± S.E.M. is plotted against time. There is a slight reduction in the ambulatory BP curve with captopril, but diurnal variability is preserved.

Figure 9.5 **Comparison of Diurnal Variation in Blood Pressure after 6 Weeks Treatment with Lisinopril and Captopril**



Twenty-four hour blood pressure profile of patients with heart failure after 6 weeks treatment with the long-acting ACE inhibitor, lisinopril (solid symbols), and the short-acting agent, captopril (open symbols). Hourly average BP ± S.E.M. is plotted against time. Day-time pressures are seen to be lower on lisinopril, while night-time values are similar.

Secondary Outcome Measures

There was a small but statistically significant increase in serum creatinine in patients treated with lisinopril only (Table 9.7).

Table 9.7 **Change in biochemical indices of renal function after treatment.**

	Lisinopril			Captopril		
Variable (Mean ± S.E.M.)	**pre**	**post**	**p**	**pre**	**post**	**p**
Creatinine (μmol/l)	102±3.2	109±3.6	0.01	107±4.2	107±3.2	NS
Urea (mmol/l)	6.1±0.3	6.5±0.5	NS	5.9±0.4	6.3±0.4	NS

There was no statistically significant difference between the variables in the two treatment groups at baseline or after treatment.

Median NYHA grade was 2 in both treatment groups at baseline, falling to 1.5 in the captopril-treated group and unchanged in the lisinopril-treated patients. This difference was not statistically significant. Responses to the patients questionnaire were broadly similar.

Discussion

This study has demonstrated persistence of the diurnal blood pressure profile in patients with mild to moderate heart failure, and this profile was maintained after treatment with an ACE inhibitor. The amplitude of the nocturnal dip was reduced when compared to that of a normal, working population. However, as no attempt was made to match these populations, this observation must be treated with some caution. In this study, the amplitude of diurnal blood pressure variation did not appear to be related to the severity of heart failure as measured by radionuclide ventriculography. This contrasts with two earlier studies (Caruana *et al,* 1988; van de Borne *et al,* 1992) both of which studied patients with more severe heart failure. Thus, it is possible that this relationship is only manifest in end-stage heart failure, when activity levels are significantly reduced, and where the influence of cardiac output on blood pressure is likely to be greater. Moreover, sleep patterns are disturbed in the later stages of heart failure (Dowell *et al,* 1971; Hanly *et al,* 1989) and this may lead to higher pressures during the night in those most severely affected.

In keeping with previous studies (Packer *et al,* 1986; Oster & Materson, 1992) blood pressure fell in most patients when treated with an ACE inhibitor. Potentially important

differences in the blood pressure profile between treatments were apparent, with lower clinic and day-time mean BP on lisinopril, confirming the observation of others (Giles *et al,* 1989; Osterziel *et al,* 1992). This presumably reflects the much shorter plasma half-life of captopril (about 1 hour) compared to that of lisinopril (about 12 hours). However, against initial expectations, there was only a modest decrease in the night-time blood pressure, which, although significant for lisinopril only, was similar for both drugs. Thus the fall in day-time BP led to a reduction in the nocturnal dip in both groups, reaching statistical significance with lisinopril only. If the reduced diurnal profile was a function of left ventricular function *per se*, we might have expected the converse with treatment known to have a beneficial effect on haemodynamics (Chatterjee *et al,* 1985; Fonarow *et al,* 1992), ejection fraction (Giles *et al,* 1989), and prognosis (The SOLVD Investigators, 1991). This would appear to argue against the view that the left ventricle contributes directly to the maintenance of the normal blood pressure profile. The greater reduction in pressure over 24 hours with lisinopril may indicate greater reduction in left ventricular after-load, explaining the improved exercise performance in patients treated with this agent (Giles *et al,* 1989).

Renal blood flow appears to be the principal determinant of glomerular filtration in patients with congestive cardiac failure (Cody *et al,* 1988). Thus, there is a concern that the fall in blood pressure may have deleterious effects in some patients. Indeed, several workers have noted that there is a greater deterioration in renal function with the longer acting ACE inhibitors, which are associated with a larger fall in blood pressure (Packer *et al,* 1986; Giles *et al,* 1989; Osterziel *et al,* 1992). The clinical significance of this is uncertain (Oster & Materson, 1992). Many studies have relied upon serum creatinine or creatinine clearance as measures of renal function, which are unreliable: it has been estimated that a 28% difference between results is needed to detect a change in renal function (Brochner-Mortensen, 1978). In this study glomerular filtration rate has been monitored isotopically, using a method shown to be both accurate and reliable (Fawdry *et al,* 1985). To determine whether the fall in blood pressure seen with ACE inhibition is directly related to change in GFR, ambulatory blood pressure parameters have been compared to the change in GFR. In particular, as lowest blood pressures are normally attained during sleep, the hypothesis was that a fall in nocturnal blood pressure would lead to a fall below renal perfusion pressure and consequent deterioration of GFR. However, there was no significant change in GFR in either group, and no evidence of any clear relationship in change in GFR to any measure of blood pressure or to the diurnal rhythm. As noted previously, the fall in pressure during the night was much less than that seen during the day and is unlikely to be primarily responsible for the change in renal function.

The renal effects of ACE inhibitors in heart failure are dependant upon inhibition of both the circulating and tissue renin-angiotensin systems (Hirsch *et al,* 1990). The initial decline in renal function seen after starting an ACE inhibitor in the patient with heart failure may be related to a transient fall in renal blood flow (Mujais *et al,* 1984), related to the fall in blood pressure, which corrects over the course of the first few days of treatment (Mujais *et al,* 1984), perhaps because of less constriction of the afferent arteriole. During long-term therapy renal plasma flow actually increases and GFR remains stable (Mujais *et al,* 1984; Cleland *et al,* 1986). However this will not occur if the blood pressure decreases to the level at which renal blood flow becomes directly proportional to perfusion pressure, that is if the renal perfusion pressure is reduced to the range in which auto-regulation becomes dependant on an intact tissue renin-angiotensin system (Hricik & Dunn, 1990). This has been estimated to occur at a mean arterial pressure below 60 mmHg (Cleland *et al,* 1984). In this study, the night-time mean arterial pressure averaged 78 mmHg in the captopril-treated patients and 77 mmHg in the lisinopril-treated patients, remaining well above critical perfusion pressures. It is possible that part of the explanation for the relatively higher pressures during sleep in patients with severe heart failure, and for the smaller than expected fall in nocturnal pressures seen after treatment in this study, is auto-regulation independent of the renin-angiotensin system, designed to prevent a fall in blood pressure below critical perfusion pressure.

Conclusions

The diurnal blood pressure rhythm is preserved but blunted in patients with mild-to-moderate congestive cardiac failure, and the amplitude of day-night variation is not related to severity of left ventricular dysfunction. The nocturnal dip in blood pressure is reduced further by angiotensin converting enzyme inhibition, largely as a result of a greater decrease in day-time than night-time blood pressure. This change in the blood pressure profile is greater with the longer acting drug, lisinopril, possible indicating greater off-loading of the left ventricle. There was no evidence of a clinically important effect on renal function after ACE inhibition with either drug, and no obvious relationship between change in the diurnal blood pressure rhythm and change in renal function.

CHAPTER 10

Summary and Conclusions

It is almost a century since Hill (1898) described the variability of blood pressure over the course of a day, noting the nocturnal fall in pressure with sleep, yet the clinical importance of the nocturnal pressure remains uncertain. Early work by Perloff *et al* (1983), using a prototype non-invasive ambulatory blood pressure monitor, demonstrated that ambulatory readings provide prognostic information over and above the clinic pressure, but this device required subjects to self-inflate the arm cuff, preventing nocturnal measurement. The development of a technique for monitoring ambulatory pressure continuously over 24 hours using an indwelling intra-arterial catheter - the Oxford technique (Bevan *et al,* 1969) - soon led to the description of the dramatic change in blood pressure during sleep (Littler *et al,* 1975). However the invasive nature of this technique limited it to small numbers of research studies. It is only in the last decade that technological advances have led to the development of monitors which are sufficiently miniaturised and reliable to allow routine monitoring of non-invasive blood pressure over 24 hours in large numbers of patients. In this period the technique has rapidly moved from research tool to accepted clinical procedure.

Clinical acceptance of this technique has in part depended upon demonstration of the accuracy of these monitors, and the development of protocols for device validation (O'Brien *et al,* 1990c) has been an essential component of this. However, when starting this work, a major limitation of these protocols, emphasised subsequently (O'Brien *et al,* 1993), was the lack of device validation in specific patient groups. In particular, the impact of cardiac arrhythmia on the accuracy of electronic blood pressure measuring equipment had never been tested. As atrial fibrillation, the commonest clinically significant arrhythmia in the community (Lip & Beevers, 1995), is known to make conventional blood pressure measurement more difficult (Sykes *et al,* 1990), knowledge of monitor accuracy in this patient sub-group is of some importance. The study of 30 patients with chronic, controlled atrial fibrillation described in Chapter 2 confirmed these reservations. Neither the SpaceLabs 90207 nor the Accutracker ambulatory monitor achieved a satisfactory level of accuracy, and both devices failed to register any pressure in a substantial proportion of patients. One semi-automatic electronic sphygmomanometer, the Copal UA-251, did achieve reasonable accuracy, but clearly such devices are of no value in the monitoring of nocturnal blood pressure. As a result of this

work, patients with atrial fibrillation were excluded from both routine clinical study with ambulatory monitors and from the subsequent studies described here.

With the more widespread application of ambulatory blood pressure monitoring, different patterns of diurnal blood pressure variability have come to be recognised. In particular, a substantial proportion of subjects have been found not to have the normal nocturnal fall in blood pressure, leading O'Brien *et al* (1988) to coin the term "*non-dippers*" to differentiate this sub-group from the more common "*dippers*". The same authors noted an apparent excess of stroke in the former group, suggesting that this distinction may be of prognostic importance (O'Brien *et al,* 1988). Subsequent work has suggested that left ventricular hypertrophy (Gosse *et al,* 1988a; Verdecchia *et al,* 1990) and cerebrovascular disease (Shimada *et al,* 1992) are also more common in non-dippers. Moreover, several authors have noted that the phenomenon appears more common in patients with secondary hypertension (Hany *et al,* 1987; Imai *et al,* 1990; Middeke & Schrader, 1994).

These initial clinical observations made no attempt to standardise the monitoring procedure, and methods for calculating the nocturnal dip in blood pressure and classifying patients as dippers or non-dippers varied widely, with several different definitions of day and night used to define the diurnal profile. In Chapter 3, I have examined the ambulatory blood pressure profile of 249 subjects and shown the profound effect which a change in the start of night-time can have, with the proportion of subjects classified as non-dippers varying from 47% (night-time = 8 pm to 7 am) to 36% (night-time = midnight to 7 am). I have then explored the potential for wrist worn activity meters to improve the definition of the diurnal profile by allowing the accurate quantification of *sleep* time, rather than relying on an arbitrary definition of night. Prospective study of 319 patients who underwent simultaneous activity and blood pressure monitoring confirmed that the nocturnal fall was greater when defined on the basis of sleep. As inclusion of wake readings in the night-time value will erroneously increase this value in most patients, this observation suggests that the activity-derived sleep time is more physiologically sound. Night-time blood pressure defined as midnight to 7 am was most similar to sleep blood pressure. On the basis of this study, I have recommended that wake and sleep blood pressure be used in clinical studies whenever possible, and 12 midnight to 7 am used for the arbitrary definition of night-time where sleep times are not known (Stewart *et al,* 1993).

Activity is a major determinant of blood pressure and differences in the pattern of activity on different monitoring days can reduce the reproducibility of the ambulatory blood

pressure profile (Pickering, 1990c). Activity monitoring has the potential to assess change in activity pattern and so correct for this. A subset of the patients studied in Chapter 3 were therefore asked to undergo repeat monitoring and the strength of the relationship between activity and blood pressure was studied to determine the optimal actigraphic measurement for activity-blood pressure regression analysis and determine whether such adjustment could improve reproducibility. While there was wide variation between patients in the activity measure most closely related to blood pressure, mean weighted activity over the 30 minutes prior to each blood pressure monitoring proved to be the most useful value for modelling the wake blood pressure value. On average, actigraph measurements accounted for 20% of systolic and 26% of diastolic blood pressure variability, but with marked intra- and inter-individual variation, limiting the applicability of this technique to routine clinical practice. The impact on reproducibility, while marked in some individuals, was limited and not clinically significant when applied to the group as a whole. At the present time, while worthy of further study and refinement, this technique has not been applied to continued clinical work.

Blood pressure is Normally distributed in the population and the distinction between normotension and hypertension is now known to be a medical artefact dependant upon the definition chosen for hypertension. In Chapter 4, I have demonstrated that the same tendency to divide the population in two has been erroneously applied to the nocturnal dip. Analysis of the diurnal blood pressure pattern of over 1000 individual subjects referred for ambulatory monitoring over a 4 year period found no evidence of significant deviation from Normality and, more particularly, no evidence of bimodality. This important observation means that the nocturnal dip should be treated as a continuous variable, using parametric statistics. The absolute change in blood pressure variation is more important than classification as a dipper or non-dipper.

Analysis of this same data set allowed study of other extraneous variables with the potential to influence the nocturnal dip. Age was shown to be an important determinant of the dip, with a progressive decline in diurnal blood pressure variability as the age range increased. Severity of hypertension did not, however, appear to have any important impact. When studying different population groups it is therefore important to allow for age as a possible confounding variable.

The effect of anti-hypertensive drug therapy on any blood pressure variable ideally requires double blind, controlled study, but the numbers required for study of each different class of anti-hypertensive drug prevented such analysis here. However

retrospective analysis of this database has enabled some conclusions to be drawn. Treated patients tended to have a smaller nocturnal dip than untreated and, after correcting for age, this appeared to reflect lower day-time pressure in the treated group. This may be because decisions about drug treatment continue to be based solely on blood pressure measurements made during the day, with sub-optimal wake blood pressure prompting a change in therapy, while an inadequate effect on nocturnal pressure is either not noticed or ignored. Analysis by drug class revealed blunted diurnal variability in those treated with calcium channel antagonists, but as such patients were older with more severe hypertension it is difficult to determine whether this is a specific effect of these agents. Diurnal variability in the other major classes of drug were, allowing for age, similar. Study of those patients who had undergone repeat monitoring after a change in treatment found similar lowering of day and night pressure with no overall impact on diurnal variability. Thus, it appears unlikely that anti-hypertensive drug treatment, as used in normal clinical practice, has a major independent effect on the nocturnal dip.

Several authors have suggested that knowledge of the nocturnal dip could aid the differential diagnosis of secondary hypertension (Hany *et al,* 1987; Imai *et al,* 1990; Middeke & Schrader, 1994). The data in Chapter 4, while confirming that diurnal variability is attenuated in certain forms of secondary hypertension, suggests that this effect is non-specific, and, as the number of patients with essential hypertension far outweighs those with secondary, blunting of the diurnal profile will be more commonly found in primary than secondary hypertension. As such, knowledge of the ambulatory blood pressure profile does little to aid the diagnosis of secondary hypertension. However study of such patients does provide some insight into possible mechanisms underlying the nocturnal dip. Catecholamine excess appears to have the most profound impact on diurnal variability, suggesting an important role for the autonomic nervous system. Attenuation of the nocturnal dip in patients with acromegaly, whose hypertension is thought to be volume mediated, and in those with both mildly and severely impaired renal function leads me to speculate that hypervolaemia resulting in posture related changes in blood pressure also plays a role in diurnal blood pressure variability.

Blunting of the nocturnal fall in blood pressure in patients suffering from glucocorticoid excess, whether due to Cushing's syndrome (Imai *et al,* 1988b) or exogenous glucocorticoid excess (Imai *et al,* 1989), has been a consistent finding in published work and I have confirmed this in a small group of patients with Cushing's syndrome. The study of patients with hypopituitarism who require glucocorticoid replacement therapy permits study of change to glucocorticoid exposure within the physiological range. Study

of such patients has previously shown that the diurnal blood pressure profile is not altered by reversing the pattern of therapy (Jyothinagaram *et al,* 1989). In Chapter 5, I examined the effect of a doubling of the dose of hydrocortisone given and, although achieving a significant increase in exposure to glucocorticoid, found no evidence of any effect on the diurnal blood pressure profile. Thus, it appears that pathological, but not physiological, quantities of corticosteroid are capable of modifying the diurnal rhythm, making a physiological role for cortisol in the control of the nocturnal dip unlikely.

Data on the ambulatory blood pressure profile of patients with accelerated phase hypertension is surprisingly limited, with the study most frequently quoted as demonstrating loss of diurnal variability in such patients actually referring to a group studied with a stationary monitor which tied patients to their beds (Shaw *et al,* 1963). In Chapter 6 I have studied patients with accelerated hypertension before and after treatment, and confirmed blunting of the diurnal profile, as compared to essential hypertensives, which returns towards normal after successful treatment of the accelerated phase. Seven of the 11 patients studied had impaired renal function which, as described in Chapter 4, has the potential to influence the nocturnal dip, and it is not possible to determine the extent to which this contributes to the observed effect. Nonetheless, the normalisation of the diurnal profile, which was pronounced, does imply that the accelerated phase per se may influence the nocturnal dip.

However, 9 of the 11 patients were hospital in-patients when first studied. To determine the potential importance of this I have also studied two control groups requiring emergency hospitalisation: patients with acute stroke who were hypertensive, and a mixed group of emergency hospital admissions who were normotensive. Although blunting of the diurnal profile was more pronounced in the patients with accelerated hypertension, there was no statistically significant difference between the three groups. The blood pressure changes which occur following acute stroke are complex, and it is possible that loss of the nocturnal dip is part of this pathophysiological process. However, taken together, these data suggest that emergency hospitalisation itself may result in an initial loss of the diurnal rhythm.

Both cardiac and renal damage are correlated with blood pressure and the severity of hypertension but, while it is clear that ambulatory blood pressure is a better predictor than clinic pressure, debate as to which blood pressure measure is most important has not been resolved. Previous work has tended to concentrate on one blood pressure measure and has frequently studied selected patient subgroups. In an attempt to overcome some of

these limitations, I have studied a randomly selected group of healthy, working volunteers, with no previous history of hypertension or cardiovascular disease. By undertaking a screening study prior to randomisation it was possible to weight this cohort such that most subjects with an elevated clinic pressure were included. Comprehensive blood pressure assessment included nurse-measured clinic pressure, blood pressure response to isometric exercise, and 24 hour ambulatory blood pressure monitoring with activity derived sleep/wake indices. Target organ damage was assessed by echocardiographic measurement of cardiac structure, Doppler assessment of left ventricular haemodynamics and by measurement of urinary albumin excretion. In multiple linear regression analysis I have found wake blood pressure to be the most consistent predictor of both left ventricular mass and diastolic function, while sleep pressure was the better predictor of urinary albumin excretion. While 57% of the predictive information was attributable to the ambulatory blood pressure, knowledge of diurnal blood pressure rhythm accounted for a further 19%. Peak exercise blood pressure accounted for 10% and the increase in blood pressure with exercise and clinic blood pressure a further 4% each. This work, described in Chapter 7, suggests that the mean blood pressure from ambulatory monitoring is the best single predictor of target organ damage, but with additional information imparted by knowledge of diurnal variability. Exercise and clinic blood pressure appear relatively less useful measurements.

Hypertension and sleep apnoea commonly co-exist but the pathophysiological relationship remains unclear. In Chapter 8, I have investigated the possibility that occult sleep apnoea accounts for nocturnal hypertension and loss of diurnal blood pressure variability in patients with essential hypertension. Patients with proven, symptomatic sleep apnoea and with chronic obstructive pulmonary disease, who experience profound nocturnal hypoxia but not apnoea, were also studied. There was no evidence of any association between sleep apnoea and nocturnal hypertension or diurnal blood pressure variation in essential hypertension, and normal diurnal variation in BP in those with symptomatic sleep apnoea, making any pathophysiological link between the two conditions unlikely. Minor blunting of the diurnal blood pressure rhythm in COPD patients with significant hypoxia makes it impossible to exclude an effect of hypoxia on nocturnal BP but there was no clear linear relationship, and reduced day-time activity, with consequent failure of blood pressure to rise during wake hours, appears a more likely explanation for this observation. The increased prevalence of sleep apnoea in essential hypertension is probably caused by the confounding variables of age and obesity. There was, however, a greater prevalence of sleep apnoea in treated subjects, and a potential adverse effect of anti-hypertensive drugs

on ventilatory control remains a plausible mechanism for the previously observed excess of sleep apnoea in a hypertensive population, with possible therapeutic implications.

The heart has a central, active role in haemodynamic regulation and is no longer thought of as a simple pump. An independent role for the heart in the control of the diurnal blood pressure rhythm has been suggested by studies of orthotopic cardiac transplant recipients (Sehested *et al,* 1990b), patients with left ventricular hypertrophy (Verdecchia *et al,* 1990) and those with systolic dysfunction (Caruana *et al,* 1988). In Chapter 9, I have studied patients with mild to moderate congestive cardiac failure before and after the introduction of ACE inhibitor therapy, known to improve haemodynamics, ejection fraction and prognosis. The diurnal rhythm was preserved but blunted in such patients, with no evidence of any relationship between severity of left ventricular dysfunction and the nocturnal dip. Diurnal blood pressure variation was reduced further by active treatment, largely due to a greater decrease in day-time than night-time blood pressure, arguing against a significant role for the left ventricle in the maintenance of the normal diurnal blood pressure profile. Concern that excessive reduction in blood pressure may have an adverse effect on renal function proved unfounded, with no significant change in glomerular filtration apparent.

Arterial blood pressure is a complex physiological variable, controlled by an interplay between anatomical factors which vary with age (i.e. length and structure of the resistance vessels), autonomic nervous system function, baroreceptor reflexes, and both tissue and plasma hormone levels. As such, it should come as no surprise that one measure of blood pressure variability, the day-night rhythm, should prove so difficult to define accurately, with multiple confounding factors and causality. Whilst intrinsically related to sleep, the nocturnal dip varies widely in the population, with multiple additional factors determining the extent of the fall. This work has clearly demonstrated that classification of an individual as *dipper* or *non-dipper* is no more physiologically sound than the classification into normotensive and hypertensive. Indeed, study of the relationship of the dip to age, and of diurnal blood pressure variation in patients with chronic lung disease or heart failure, suggests that the day-time rise is as important as the night-time fall in many subjects - *blippers* and *non-blippers* ? Nonetheless, knowledge of diurnal variability does appear to provide additional prognostic information over and above the ambulatory mean, and as such could aid the characterisation of the risk profile in the individual patient.

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PUBLICATION OF DATA FROM THIS THESIS

Original Papers

1. M.J. Stewart, H. Brown, P.L. Padfield. Can simultaneous ambulatory blood pressure and activity monitoring improve the definition of blood pressure ? *Am J Hypertension* 1993; **6**: 174S - 178S.

2. M.J. Stewart, K Gough, P.L. Padfield. The accuracy of automated blood pressure measuring devices in patients with controlled atrial fibrillation. *J Hypertens* 1995; **13:** 297-300.

Published Abstracts

1. Analysis of ambulatory blood pressure profiles - when is night-time? MJ Stewart, IM McGinley, PL Padfield. *J Hypertens* 1991; **9**:1094.

2. What causes 'non-dipping' in accelerated phase hypertension ? MJ Stewart, K Gough, G Kane, PL Padfield. *J.Hypertens* 1992;**10**:1436.

3. Can changes in glucocorticoid replacement alter ambulatory BP or nocturnal BP reductions? MJ Stewart, DL Leitch, K Gough, IM McGinley, BC Williams, PL Padfield. *J Hypertens* 1992;**10(Suppl.4)**:s22.

4. Does sleep apnoea cause "non-dipping" in essential hypertension ? MJ Stewart, K Gough, IM McGinley, PL Padfield. *J Hypertens* 1993; **11 (Suppl.)**: 727.

5. Impact of diurnal blood pressure variation on target organ damage in a healthy working population. MJ Stewart, G Kane, GR Sutherland, PL Padfield. *Eur Heart J* 1996, **17 (Abstract Suppl.)** 769.

6. A comparison of the effect of long and short acting ACE inhibitors on diurnal blood pressure variation and on renal function in heart failure. MJ Stewart, PL Padfield, L O'Toole, KS Channer. *Eur Heart J* 1996, **17 (Abstract Suppl.)** P409.

7. Frequency distribution of day-night blood pressure variation and the impact of age, severity and treatment of hypertension. MJ Stewart, K Gough, PL Padfield. *J Hypertens* 1996; **14**: 5.

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ERRATUM

Attention is drawn to the following typographical errors in the text of this work :

p29 p 83	Paragraph 1 and Paragraph 1	*Wilcoxon* misspelled as Wilcoxan
p46	Title of Table 3.2	*Dependent* misspelled as dependant
p54	Paragraph 3	The first sentence should read "Short term blood pressure variability has also been shown to *be* higher in hypertensives than in normotensives ..."
p56	Paragraph 7	*Compared* misspelled as compered
p69	Paragraph 3	The final sentence should read "Patients with hypothyroidism, now recognised as *a* treatable, secondary cause of hypertension ..."
p76	Paragraph 3	The first sentence should read "....benign hypertension is likely to be ischaemic *in* origin."
p103	Paragraph 3	The first sentence should read "As sex and body size significantly influence *LV size*,..."
p119	Paragraph 3	This sentence should read "Where peak BP after exercise was less than that *at* baseline, the BP difference was scored as zero."
p126	Paragraph 3	In the second sentence, qualitative should be replaced with *quantitative.*
p128	Paragraph 3	In this paragraph, variation should be replaced with *variance.*
p133 p133	Paragraph 1 and Paragraph 2	*Apnoeic* misspelled as apnoic.