

HEMODYNAMIC PARAMETERS OF PATIENTS WITH TREATED
HYPERTENSION AND CORONARY ARTERY DISEASE

By

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by

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This dissertation is dedicated to my brother, Beau, who has been my best friend since as long as I can remember and also to my lovely wife, Jen, without whom I would be much more annoying and not have eaten nearly as well as I have this past year.

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Central elastic arteries are very different from the more peripheral muscular arteries. It has long been argued that the research and management of hypertension should not be based on blood pressures (BP) measured in the brachial artery (a muscular artery). Moreover, BP is a dynamic physiologic function that changes with the demands placed on the body and mind throughout the day. It has been argued that ambulatory BP (average of multiple BP readings over the course of a given period—usually 24 hours) is a better assessment of true BP than traditional clinic BPs. The purpose of this study is to demonstrate the differences, if any, among BPs measured by conventional methods, ambulatory BP, and aortic blood measured noninvasively by applanation tonometry and a generalized transfer function. BP measurements using all three techniques were taken on 30 subjects from the INternational VErapamil/TRandolapril STudy (INVEST).

There is a highly linear relationship between central and clinic BPs in regards to systolic BP, diastolic BP, mean arterial BP, and pulse pressure (PP). Systolic BP and PP

are significantly different using the two methodologies. It is not known whether central BP changes linearly with changes in clinic pressure. There was no difference between ABP and clinic BPs, which demonstrated a weak but significant linear relationship. A significant drop in nocturnal BP was demonstrated, but the drop was not large enough to classify the subjects as dippers. No conclusions could be made about differences between the INVEST treatment groups due to the small sample size. Systolic augmentation by wave reflection accounted for more than 30% of systolic pressure. The increased pressure was not likely to cause subendocardial ischemia according to the average subendocardial viability ratio.

This was the first study that assessed both ambulatory BP and noninvasively measured central hemodynamic parameters. Areas of both technologies are identified that will help future studies to avoid certain pitfalls. The largest area for improvement is in the database systems that each device uses to store subjects' results. The largest barrier to widespread use in either clinical or research settings remains price.

CHAPTER 1 INTRODUCTION

This chapter introduces the main variables under investigation including pulse wave velocity, aortic wave reflection, arterial elastance, applanation tonometry, and ambulatory blood pressure. It states the background and main research problem to be investigated as well as the hypotheses to be tested. The definitions of the major terms, assumptions, limitations, and significance of the study also are described.

Background and Problem Statement

Traditional hypertensive theory has been that increased peripheral resistance caused elevated blood pressure (BP). Diastolic pressure was seen as the direct reflection of peripheral resistance, while elevated systolic pressure was seen as the sign of a healthy and vigorous heart (Nichols & Edwards, 2001; Nichols & O'Rourke, 1998). Thus, most hypertension treatments and research studies targeted diastolic pressure. Ironically, the treatments studied—diuretics and beta-blockers—lowered diastolic BP, not by targeting peripheral resistance, but by decreasing preload and contractility. Their efficacy was established in reducing mortality, even though the mechanism did not fit the theory. In time, it became apparent that low diastolic pressures were not desirable (Benetos et al., 2000; Cruikshank, 1992; Franklin, Khan, Wong, Larson & Levy, 1999) and that elevated systolic pressure was not the benign sign of a vigorous heart as it was thought to be. Two other classes of antihypertensive drugs that did not have the benefit of large clinical trial evidence—angiotensin converting enzyme inhibitors (ACE Inhibitors) and calcium

channel antagonists—began to be seen as effective due to their theoretical models of action (Nichols & O'Rourke, 1998).

Recent years have shown the first results of large clinical trials with ACE Inhibitors to be overwhelmingly positive in their benefits not only for patients with hypertension but with other cardiovascular risk factors such as diabetes, renal disease, and heart failure (Song & White, 2002). Meanwhile, there had been no published data from large clinical trials comparing calcium channel antagonists to beta blockers in patients with coronary artery disease and hypertension; previous trials had studied either beta blockers or calcium antagonists alone versus placebo. With this in mind, the International Verapamil/Trandolapril Study (INVEST) was designed to compare the effect of the two strategies for BP control—calcium antagonist based versus noncalcium antagonist based therapy—on mortality and morbidity in patients with both coronary artery disease and hypertension (Pepine et al., 1998). (During the investigation period of INVEST, the results of the ALLHAT study showed no difference in mortality between patients initially treated with either an ACE inhibitor, diuretic, or dihydropyridine calcium channel blocker [ALLHAT Collaborative Research Group, 2002; Kaplan, 2003].) Patients in INVEST have been randomized to one of two treatment strategies. One is calcium-antagonist based, while the other is noncalcium channel-antagonist based. Both strategies provide three medications to be used in a stepped care approach to achieve Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of Hypertension goals for hypertension treatment (JNC VI, 1997). The calcium channel antagonist based strategy started with verapamil SR, followed by the ACE inhibitor trandolapril, and if BP was not controlled with the two-drug combination, a thiazide

diuretic, HCTZ, could be added. The noncalcium antagonist strategy started with the beta blocker, atenolol, followed by HCTZ. If BP was not controlled, then trandolapril was recommended.

Although patients are being treated and monitored according to JNC VI standards, there is growing understanding in the scientific and medical community that traditional BP measurements are not the best way to diagnose or treat hypertension. Ambulatory blood pressure (ABP) measurements are 3 times more reproducible than traditional BP measurements, more highly correlated with target organ damage, and allow for measurement of BP and heart rate (HR) throughout the day and night (Mancia & Parati, 2000). Applanation tonometry allows for the estimation of aortic BP and measurements of arterial elastance, which are highly correlated with mortality and myocardial damage (Nichols & Edwards, 2001; Nichols & O'Rourke, 1998).

With these differences in mind, this study was undertaken with a subpopulation of INVEST subjects to compare these BP methodologies. INVEST patients have two clinic blood pressures taken with the traditional cuff measurements at every visit. The subjects of this study wore an ambulatory BP monitor that takes measurements every 20 minutes for a 24-hour period and arterial tonometry measurements were taken. For the BPs of the three methodologies—traditional clinic BPs, ABP, and tonometry-derived measures—various measures of arterial elastance are reported for the substudy population as a whole.

Purposes of the Study

The purposes of the study are as follows:

1. To determine the difference between the clinic measurements, ABPM measurements, and calculated central BPs in patients participating in the INVEST.

2. To determine the circadian systolic and diastolic BP parameters of INVEST patients.
3. Characterize the central hemodynamic parameters for patients participating in INVEST augmentation index and of patients participating in INVEST.
4. To compare the two treatment strategies in INVEST in terms of differences between 24-hour, daytime, and nighttime BP values and BP variability.

Hypotheses

The following hypotheses are investigated in this dissertation:

Hypothesis 1: There is no difference between clinic BP, ambulatory BP, and calculated aortic BP.

Hypothesis 2: There is no difference between Daytime and Nighttime values for systolic and daytime blood pressures.

Hypothesis 3: There are no differences between the two treatment strategies in INVEST in terms of differences between daytime and nighttime BP values and BP variability.

Definition of Terms

Ambulatory Blood Pressure (ABP)

Ambulatory blood pressure is defined as the average of a number of BP readings taken throughout a given time period while the subject goes about his or her daily activities. A small automatic oscillometric BP monitor is worn for a length of time (24 hours for this study), and brachial measurements are taken at regular intervals (every 20 minutes) (Yucha, 2001). These may be reported as awake, asleep, and 24 hour SBP and DBP.

Aortic Wave Reflection Amplitude

In this study, radial pulse waves were obtained via applanation tonometry and aortic pressure waveforms were then derived using a transfer function. Augmentation Index (Aix) was calculated as an index of aortic wave reflection amplitude (Kelly, Hayward, Avolio, & O'Rourke, 1989). As arterial elastance increases, Aix increases.

Aortic Blood Pressure

BP in the ascending aorta can only be measured directly by using invasive methods. For this study aortic BP is estimated using applanation tonometry and a validated generalized transfer function (Pauca et al., 2001).

Augmentation Index (AIx)

The augmentation index is the proportion of systolic pressure due to wave reflection. It is measured as the difference between the systolic peak and the pressure at the first inflection point of the pulse wave contour divided by the pulse pressure and is expressed as a percentage.

Subendocardial Viability Ratio (SEVR)

The subendocardial viability ratio is the ratio of mean diastolic pressure times diastolic duration divided by mean systolic pressure times systolic duration (Buckberg, Fixler, Archie, & Hoffman, 1972a). It is a measure of how well the subendocardium can be perfused by hemodynamic parameters. In this study SEVR is estimated as the integral of the aortic pressure wave under diastole divided by the integral of the same wave under systole (Nichols & O'Rourke, 1998).

Limitations

The primary limitation of the proposed study is its observational nature. While the patients studied are participating in a randomized controlled clinical trial, all patients have been randomized to their treatment group at least one and a half years prior to data collection. This precludes the collection of baseline data for ambulatory BP and tonometry-derived hemodynamic parameters. Thus, while comparisons can be made between the two groups, conclusions as to the nature of the changes under treatment cannot be verified.

The second limitation of the study is geographical in nature. INVEST is an international, multi-site study, but to carry out ABP and tonometry measurements on all 22,576 patients would prove prohibitively expensive and is probably unnecessary. Thus, this study was limited to the geographical area of Gainesville, FL, and surrounding areas.

Significance of the Study

Cardiovascular disease is the leading cause of morbidity and mortality in the Western nations (American Heart Association [AHA], 2001). Additionally, it has been the leading cause of mortality for Americans since 1900, except for 1918—when the leading cause of death was World War I. In 1999, coronary artery disease claimed the lives of almost a million Americans. More than 12 million Americans have coronary artery disease, and more than 6 million have angina pectoris, that is, chest pain caused by coronary ischemia. High BP is associated with or is a contributing factor to vascular diseases such as coronary artery disease, stroke, heart failure, and kidney disease (Mancia & Parati, 2000). Twenty-five percent of American adults and 20% of all Americans (50 million) have hypertension (AHA, 2001). In the year 1999, hypertension was the primary cause of death of 42,000 Americans and listed as the primary or contributing cause of death for 200,000 more Americans.

However, various methodologies used to measure BP often do not correlate with each other or with organ damage (Mancia & Parati, 2000). The need to accurately assess BP and its relationship to disease processes is vital to both the management of hypertension and the research that assesses hypertension's relationship to the different diseases. This study compared three different methods of BP assessment in patients with both coronary artery disease and hypertension who are currently being treated according to JNC-VI (1997) guidelines. Furthermore, this study also collected additional hemodynamic

parameters, which may be useful in interpreting the results of the larger clinical trial. The HOPE study (Ramipril) showed that reductions in BP of only 2-3 mmHg dramatically reduced mortality rate (Dagenais et al., 2001). Traditional theory cannot explain this improvement, although elastance and wave reflection improvements might be able to. However, the HOPE study used cuff-based clinic measurements and did not measure augmentation index, ambulatory BP, or calculated aortic BP, so valuable data were lost. This study represents the only collection of augmentation index and calculated aortic BP in INVEST patients.

Furthermore, in their meta-analysis, Mancia and Parati (2000) found that BP variability is a key indicator of cardiac damage and mortality. The medical field is moving toward once-daily dosing medications because of convenience to the patient and adherence issues (Claxton, Cramer, & Pierce, 2001; JNC VI, 1997). The collection of ambulatory BP may allow an assessment of the efficacy of the once-daily dosing medications used in INVEST.

CHAPTER 2 LITERATURE REVIEW

This chapter presents a literature review of the following areas of research: BP measurement—dilemmas and history—including ambulatory blood pressure and ambulatory blood pressure monitoring as well as the noninvasive measurements of aortic blood pressure; pulse wave velocity; wave reflection amplitude; and subendocardial viability ratio by pulse wave analysis, cardiovascular disease, coronary perfusion, pulse wave contour, large artery elastance, and vascular-ventricular interaction. A summary linking these areas together to provide the research rationale for this study concludes this chapter.

Dilemmas in BP Measurement

There are four central dilemmas concerning blood pressure measurements. The first is whether the measurement methodology is continuous or intermittent. The second is whether the method is invasive or noninvasive. The third is whether the measurement site is central or peripheral. The weaknesses and benefits inherent to the various methodologies are discussed. The fourth is not a question of methodology but of interpretation of the measurements. Each of these dilemmas is examined along with three common noninvasive methods of blood pressure measurement.

Continuous vs. Intermittent

The first dilemma of blood pressure—continuous versus intermittent measurement—concerns the quality and quantity of information obtained. Because the human body is not a static entity, the dynamic nature of blood pressure cannot be captured in a single

reading. The heart generates pressure by pumping, which provides a pulsatile wave through the arteries. Continuous methods can provide information about the contour of the entire pulse wave, while intermittent measurements only provide information about the peak and trough values (Drzewiecki, Melbin, & Noordergraaf, 1983). Peak and trough values are systolic and diastolic pressures respectively; mean pressure and pulse pressure can be interpolated. The quantity of information concerns the body's cyclical nature. Blood pressure varies with circadian rhythm in response to varying amounts of endogenous biochemicals. Therefore, a blood pressure measurement, whether taken continuously or intermittently, does not provide a full picture of blood pressure load, unless taken for a 24-hour period. Thus, 24-hour monitoring provides a more complete and accurate representation of the body's circadian blood pressure load (Mancia & Parati, 2000).

Invasive vs. Noninvasive

The second issue concerns the invasiveness of the methodology. Invasive blood pressure measurement is the gold standard by which all other methods are compared (Bos et al., 1992; Drzewiecki, Melbin, & Noordergraaf, 1983). It involves placing a probe into the lumen of the artery in question and directly measuring the hydrostatic forces present. In addition to monitoring blood pressure directly, invasive blood pressure measurement can be used to measure both peripheral and central pressures. Invasive methods also have the advantage of being able to record the entire pulse wave. Thus, invasive blood pressure measurement provides the most reliable and complete information possible to clinicians and researchers. However, because of the increased risk for infection, embolic events, hemorrhage, and pain associated with intra-arterial techniques, invasive methodologies have substantial disadvantages as well. Furthermore, invasive techniques

require expensive equipment and highly trained personnel, resulting in significant cost. Therefore, despite the enormous benefits of invasive measures, quick and accurate noninvasive blood pressure measurements are highly desired (Noordergraaf, 1978).

Central vs. Peripheral

The third issue involves the location of the measurements. Peripheral measurements are often used because they are more convenient. However, peripheral arteries are inherently muscular, whereas the central arteries are more elastic, causing pressure amplification in the peripheral arteries (Nichols & O'Rourke, 1998). Moreover, due to their muscular nature, peripheral arteries do not have a large change in elastance with age, while the elastance (stiffness) of central arteries tends to increase with age, changing the peripheral/central pressure gradient. Because of the changing gradient and wave reflections with age, central pressures are more closely related to aortic stiffness, a predictor of mortality (Laurent, Boutouyrie, Asmar, Gautier, Laloux, Guize, Ducimetiere, & Benetos, 2000). Accordingly, central pressures have greater relation to heart disease than peripheral measurements (Waddell, Dart, Medley, Cameron, & Kingwell, 2001) and are more useful in the assessment of cardiovascular risk.

Which Parameter Is the Most Useful?

The final dilemma is a question of interpretation. Blood pressure measurements yield a variety of parameters such as systolic, diastolic, and pulse pressure. Additionally, continuous methods record the contour of the pulse wave generating even more parameters. With all the information that can be obtained from a given blood pressure measurement, the following questions concerning the relationship of these parameters to actual clinical outcomes should be considered:

1. Which parameter is most important in the prediction of mortality and morbidity?
2. Which parameter should antihypertensive therapies target?

Historically, it has been thought and widely accepted that diastolic blood pressure correlated most closely with end organ damage (Swales, 2000). This theory, however, has recently been challenged by new findings suggesting that pulse pressure and systolic blood pressure are more important indicators of disease in the elderly (Swales, 2000). The elderly are also more likely to have hypertension than the young. Arterial wall stiffening offers one explanation for such age-related differences. Unfortunately, arterial stiffening is not uniform; while it does increase with age, it does not increase uniformly throughout the body or with regard to gender. For example, aortic elastance increases with age, while brachial artery elastance does not. In fact in women, brachial artery elastance actually decreases with age (van der Heijden-Spek, Staessen, Fagard, Hoeks, Struijker Boudier, & Van Bortel, 2000).

The differences between brachial and aortic artery compliance can seriously confound the validity of brachial blood pressures as a predictor for organ damage. Moreover, they emphasize the need for central pressure measurement methodologies. In the meantime, care must be taken by the researcher to stratify patients according to their age and for the clinician to treat them accordingly. The younger patient requires therapy targeting diastolic pressure, while the elderly patient requires therapy targeting systolic and pulse pressure (Mourad, Blacher, Blin, & Warzocha, 2000).

History of Blood Pressure Measurement

Sphygmogram

The interpretation of the arterial pulse has been of great importance to both Western and Eastern medicine from ancient times (Lee & Porcello, 1993; O'Rourke & Gallagher,

1996;). The first graphic recordings of pulse waves date back to the late 1800s. Marey in Paris and Mahomed in London separately developed sphygmographs capable of recording a patient's pulse wave but not capable of recording actual pressure. Using his device, Frederick Akbar Mahomed was able to diagnose asymptomatic hypertension, describe essential hypertension's natural history, and distinguish between essential and renal-induced secondary hypertension (O'Rourke, 1992). He noted that essential hypertension could end in nephrosclerosis and renal failure. With the aid of his sphygmograph, he described the pulse wave contours of various stages of hypertension and was able to describe age related changes. One of these first descriptions was the observation that in patients with hypertension "the tidal wave is prolonged and too much sustained" (Nichols & O'Rourke, 1998, p. 426). This statement would not be corroborated fully for almost a hundred years. Unfortunately, Mahomed would die an early death from typhoid fever at the height of his career in 1885, prematurely ending this line of scientific and medical inquiry.

Riva-Rocci-Korotkoff Cuff Based Measurement

The other contributor to the demise of the sphygmogram's popularity was the development of the cuff-based sphygmomanometer. In 1896, Riva and Rocci developed a cuff-based method of determining absolute systolic pressure. In itself, the Riva-Rocci technique was not all that useful, but it set the stage for a young Russian named Korotkoff. In 1905, Sergei Korotkoff used a Riva-Rocci device, consisting of an inflatable cuff attached to a sphygmomanometer. The cuff encircles the upper arm and is inflated until it occludes blood flow of the brachial artery. A stethoscope is applied to the brachial artery just below the cuff. The pressure is released from the cuff. As the cuff pressure lowers and blood flow returns to the artery, the researcher listens for a pulsing

sound caused by turbulent blood flow. These so-called Korotkoff sounds trail off, as the cuff pressure reaches the resting pressure of the artery and blood flow becomes laminar. The beginning of the Korotkoff sounds denotes the systolic blood pressure, and the end of the sounds denotes diastolic blood pressure. This technique is often referred to as the Riva-Rocci-Korotkoff (RRK) method (Shevchenko & Tsitlik, 1996).

The RRK method of blood pressure was useful because the equipment needed was not very expensive and it allowed researchers and clinicians to measure absolute systolic and diastolic blood pressures. For a while cuff-based measurement complemented sphygmograms. Sir James MacKenzie warned in his first text (1917) against uncritical acceptance of cuff-based measurements and short-cuts in scientific reasoning, but the posthumous publication of the third edition (1926) of his text contained the same uncritical acceptance of these shortcuts (Nichols & O'Rourke, 1998). Life insurance companies played a role in popularizing cuff-based measurements by promoting them as a screening tool. The sphygmogram began to be left behind.

As it became apparent that there were discrepancies in the measurement technique and reproducibility of cuff-based measurement, several organizations including the AHA and NIH's National High Blood Pressure Education Program (NHBPEP) released recommendations to standardize the collection of blood pressure (Perloff et al., 1993); these recommendations have changed several times since the inception of the NHBPEP in 1972. The current JNC VI guidelines (1997) are based on the 1993 AHA guidelines (Perloff, et al). Table 2-1 contains these recommendations.

Any deviation from these guidelines invites errors to blood pressure measurements. Even if the guidelines are followed, RRK blood pressures are subject to a variety of

errors. Aural acuity and quality of stethoscope are immediately identifiable as potential sources for error. Additionally, the clinician's mood and perception of the subject may also influence the blood pressure reading. If the clinician measures an obese or elderly patient, he may "hear" higher values of Korotkoff signs, while "hearing" lower values for a small or younger person based on prejudices as to who should have high blood pressure. Alternatively, if the clinician is in a hurry or has a heavy patient load, he may interpret the Korotkoff sounds more loosely, allowing higher blood pressures to be recorded as normal (Cranney, Warren, Barton, Gardner, & Walley 2001).

Table 2-1: JNC VI Recommendations for Blood Pressure Measurement

<ol style="list-style-type: none"> 1. Patients should be seated in a chair with their backs supported and arms supported at heart level. 2. Patients should not smoke or take caffeine for at least thirty minutes prior. 3. Patients should rest for at least five minutes. 4. The cuff should be of appropriate size. (The bladder should encircle at least 75% of the circumference of the arm, and the width should be approximately 1/3 the circumference of the arm.) 5. Two or more readings separated by two minutes should be averaged; if the readings differ by more than 5 mm mercury, then additional readings should be taken and averaged (JNC VI, 1997).

The RRK method of blood pressure can be automated, removing many of the above errors. Automated blood pressure machines have sensors that record the blood pressure and display it digitally. The clinician then only has to ensure proper cuff size (Alexander, Cohen, & Steinfeld, 1979) and that the patient has rested and not smoked or ingested caffeine (JNC VI, 1997). Automated blood pressure machines are currently used

throughout the United States in diverse settings such as hospitals, private practices, pharmacies, grocery markets, and private homes.

Automated blood pressure machines use one of two different technologies. The first is an auscultatory technology, in which a mechanical “ear” listens for Korotkoff sounds in the same way that a human would. The second method is called oscillometric, in which a sensor measures minute movements in the arm to determine when blood flow begins and returns to normal. Both methods take most of the subjectivity out of reading blood pressures. They do, however, introduce new sources of error. Machines must be periodically calibrated. Auscultatory monitors can be influenced by outside noises, while external vibrations and arm movements or tremor can influence oscillometric measurements (Prisant, Bottini, & Carr, 1996).

Ambulatory Blood Pressure

The culmination of RRK blood pressure is ambulatory blood pressure. Instead of averaging two readings over 2 to 5 minutes, it averages 20 to 50 measurements over the course of an entire day. Ambulatory blood pressure monitoring (ABP) uses automated cuff devices to measure blood pressure at a given interval for a specified period of time—often 24 hours. Monitors are typically small, battery-powered, automatic blood pressure machines that can be worn while the subject goes about his ordinary daily routine. The monitor can be programmed to take blood pressure readings at various intervals and record them in its memory. At the end of the recording session, the blood pressure monitors are returned to the clinician or researcher who can then download the readings for analysis (Yucha, 2001). This methodology limits threats to external validity and the effects on observers of psychological and physiological response. Ambulatory blood pressure monitoring provides various useful parameters, including the average 24-hour

BP (SBP, DBP, MAP, and PP) and HR, BP variability (the standard deviation of the average 24-hour, daytime, and nighttime measures), diurnal BP and HR changes (day-night BP and HR differences), and BP load (percentage of systolic and diastolic readings greater than 140 and 90 mmHg, respectively, during the day or greater than 120 and 90 mmHg during the night).

In their meta analysis, Mancia and Parati (2000) concluded that the correlation coefficient between office systolic and diastolic readings and their corresponding 24-hour averages is rarely greater than 0.5. This discrepancy occurs in patients with normal blood pressure (normotensives) as well as hypertensive patients. Cross-sectional studies have shown that 24-hour averages are more closely associated with target organ damage than office blood pressures. This is true of the heart (left ventricular hypertrophy), kidneys (proteinuria), brain (cerebral lacunae or white matter lesions identified by magnetic resonance imaging), and arteries.

In the Hypertension and Ambulatory Recording Venetia Study (HARVEST), the rate of excretion of albumin was highly related to 24-hour BP (Palatini, 1999). In the European Lacidipine Study on Atherosclerosis trial (ELSA), the intima-media thickness of the common carotid artery correlated significantly with average 24-hour SBP ($r = .22$, $p < .0001$), average 24-hour PP ($r = .31$, $p < .0001$), 24-hour SBP variability ($r = .11$, $p < .0001$), and 24-hour PP variability ($r = .23$, $p < .0001$) (Mancia, Giannattasio, Failla, Sega, & Parati, 1999). Verdecchia (2000) also indicated that ambulatory SBP, DBP, and PP were independently and directly associated with cardiovascular risk. The European Lacidipine Study on Atherosclerosis (Zanchetti et al., 1998) showed in 2,200 patients that 24-hour average systolic blood pressure and pulse pressure are more highly correlated

with carotid intimal wall thickening and number of carotid plaques. Twenty-four hour average systolic pressure is second only to age in correlation to carotid intima thickness.

The Study on Ambulatory Monitoring of Pressure and Lisinopril Administration (SAMPLE) (Mancia et al., 1997) showed that left-ventricular hypertrophy regression was more closely associated with controlled 24-hour averages than with office blood pressures. Before treatment, left ventricular mass index (LVMI) did not correlate with clinic BP, but it showed a correlation with systolic and diastolic 24-hour average BP ($r = .34/.27$, $P < .01$). The LVMI reduction was not related to the reduction in clinic BP, but it was related to the reduction in 24-hour average BP ($r = .42/.38$, $P < .01$). Treatment-induced changes in average daytime and nighttime BPs correlated with LVMI changes as strongly as 24-hour BP changes. No substantial advantage over clinic supine BP was shown by clinic orthostatic, random-zero, and home BP. Daytime and nighttime pressures were also significantly correlated with hypertrophy regression, indicating that a monitoring period of fewer than 24 hours may be adequate for diagnostic and management purposes. Finally, the European Study on Isolated Systolic Hypertension in the Elderly (Staessen, 1999) showed that 24-hour averages are more closely associated with cardiovascular events than office blood pressures.

Ambulatory blood pressure monitoring can provide more than just 24-hour average blood pressures. Additional measures that can be obtained include daytime average pressure, nighttime average pressure, morning rise in blood pressure, and blood pressure variability. Typically, a decrease in blood pressure is seen at night due to decreased sympathetic activity and increased vagal tone (Mancia & Parati, 2000). Those subjects in whom a nocturnal BP reduction (BP reduction from day to night) is 10% or greater are

classified as dippers, whereas nondippers are defined as those who show a reduction in BP of less than 10% between the day and night (Mallion, Baguet, Siche, Tremel, & de Gaudemaris, 1999). It has been postulated that the absence of nocturnal BP reduction is related to more severe target organ damage, either left ventricular hypertrophy or disease of major arteries, though the data remain inconclusive (Mallion et al., 1999). In the study by Mallion et al., nondippers had a significantly higher frequency of stroke and higher urinary excretion of albumin. The degree of nocturnal BP was inversely related to cardiovascular morbidity (Verdecchia et al., 1997).

May, Arildsen, and Damsgaard (1998) demonstrated that the nocturnal BP reduction calculated from individually defined day and night times was larger than the fall calculated from every possible fixed day/night definitions and concluded that the assessment of the nocturnal BP dipping should be based on individually defined periods of day and night. Blunting of the nocturnal drop is not necessarily correlated with organ damage, although severe organ damage may obliterate nighttime decreases. Studies have shown that nocturnal variation is highly individual, even within diseased populations, and the results are also mixed with regard to correlating nighttime BP fall with organ damage (compare Verdecchia et al., 1990 & 1993, with Mancia et al., 1995; Omboni, 1998). This makes the 10% drop classification somewhat arbitrary and supports the view of Nichols and O'Rourke (1998) and Thomas Pickering (1982) that hypertension is not an absolute disease but one of magnitude.

Arterial physical properties have also been studied to determine their association with nocturnal BP reduction. Arterial compliance as indexed by aortic pulse wave velocity predicts nocturnal SBP reduction in normotensives (Asar et al., 1996). Arterial

compliance, as estimated by pulse wave velocity measurement and its relationship to nocturnal BP reduction, has been studied in a group of treated hypertensive patients on hemodialysis (Amar et al., 1997). Results from this study indicated that pulse wave velocity was significantly higher in nondippers. A stepwise regression analysis further revealed that pulse wave velocity was one of the independent variables related to the lack of inverse nocturnal BP reduction.

Despite these data, nighttime blood pressure cannot be considered a reliable indicator of disease because blood pressure may vary as much as 10 mmHg when the patient is sleeping with the monitored arm above the level of the heart as compared to when lying on the other side (Schwan & Pavlek, 1989). There is no way to guarantee position of the monitored arm while sleeping unless a researcher monitors patients while they sleep; thus, night time average pressure is inherently unreliable. Additionally, the SAMPLE study found the repetition of ABP measurement in patients on stable therapy or with no therapy showed a 40% change in dipping status, indicating that the measure is either nonreproducible or highly influenced by individual sleeping patterns and physiology (Omboni et al., 1998).

Blood pressure tends to rise in the early morning and corresponds with an increased incidence of cardiovascular events. However, it is not possible to tell whether morning rise is causal or coincidental. Theory suggests that attempts to blunt the morning rise in blood pressure may make successive morning rises in blood pressure even more abrupt (Mancia & Parati, 2000). Therefore, morning blood pressure is not a useful parameter for diagnostic or management purposes. Blood pressure variability, on the other hand, has been highly correlated with organ damage. Of patients with identical 24-hour blood

pressure averages, those with greater variability have consistently suffered greater organ damage (Mancia & Parati, 2000). However, continuous monitoring must be used to demonstrate this relationship most accurately.

According Mancia and Parati (2000), ambulatory blood pressure monitoring has several advantages in addition to its higher correlation to organ damage. First, measurements are not significantly affected by the white coat effect hypertension phenomenon. Over weeks or months, ambulatory values are not substantially altered by placebo. Twenty-four hour average blood pressure values are three times more reproducible than office blood pressure values. Finally, 24-hour blood pressure monitoring enables researchers to determine whether a once-daily dosing drug lowers blood pressure consistently throughout the day and night. Inconsistent lowering may inhibit organ perfusion and adversely affect organ damage by increasing variability.

Applanation Tonometry

Despite the advances in cuff-based measurement, RRK can never reveal more information about blood pressure than gross systolic and diastolic pressure. Moreover, it is limited to a peripheral measurement site. Arterial tonometry is a method of recording arterial pulse waves noninvasively. Tonometry measures the pressure of an artery as it is deformed between the tonometer and a bony structure. It can measure the pressure and pulse wave contour of any superficial artery supported by a bony structure, such as radial, brachial, femoral, and carotid arteries (Drzewiecki, Melbin, & Noordergraaf, 1983). In theory, tonometry does not need to be calibrated, but in practice “hold down” pressure needed to deform the artery is not constant from one person to another. Calibration can take place by the RRK method. It is assumed that diastolic pressure is identical between brachial and radial measurement sites and that mean arterial pressure is identical between

brachial and carotid sites (Nichols & O'Rourke, 1998). Sato, Nishinaga, Kawamoto, Ozawa and Takatsuji (1993) found that the JENTOW continuous blood pressure monitor based on applanation tonometry was highly correlated to intra-arterial pressures, with a flat response ratio. Beat-to-beat variability was recorded almost perfectly. Slight limitations were found in recording higher frequency intra-arterial waveforms and during Valsalva maneuver, but not during tilt-table testing.

While the ability to measure peripheral arterial pressure noninvasively is impressive, it is of limited usefulness in and of itself. A truly useful application is the generation of a calculated ascending aortic pulse waveform, but even this would be of limited use if the transfer function were required to be individualized, because that would require catheterization in order to approximate aortic pressure noninvasively. So the quest began to derive a generalized transfer function that would be applicable across a diverse array of people. At first glance, the idea seems ludicrous. However, in practice, generalized transfer functions have been remarkably accurate, largely because the errors involved in biological measurement are relatively large, and the smallest meaningful frequency range in human pulse waves is also quite large (Nichols & O'Rourke, 1998). Two different generalized transfer functions have been developed independently (Chen et al., 1996; Kelly et al., 1989). The process of recording pulse waveforms peripherally and transforming them to derive an aortic pulse waveform has been christened pulse wave analysis (PWA).

While there has been some debate as to the validity of calculated aortic blood pressure using a generalized transfer function (Lehmann, 2001), a recently published study has shown that for patients with coronary artery disease in need of revascularization, the

comparison of radial to derived aortic blood pressure meets the Association for the Advancement of Medical Instruments SP10 criteria for validity with regard to mean, diastolic, systolic, and pulse pressures (Pauca, O'Rourke, & Kon, 2001). Furthermore, the validity of the derived pressure values was established both under baseline conditions and under nitroglycerine infusion but was only established while patients were lying supine. In a separate validation study of 25 healthy subjects, the SEVR measurements ranged from 119% to 254%; the inter-operator measurement difference was only 2.7% (s.d. 15.4); and the augmentation index (AIx) by applanation tonometry and PWA has excellent interobserver reproducibility, with the interobserver measurement difference being only 2.7% (Seibenhofer, Kemp, Sutton, & Williams, 1999).

Results of a study by Karamanoglu et al. (1993) using a generalized transfer function in adult humans indicate acceptable accuracy (> 90 %) in generating an aortic waveform from the pressure wave in the radial or brachial artery. In healthy adult subjects with a wide age range, Liang et al. (1998) demonstrated that measurement of AIx with applanation tonometry is highly reproducible and precise, with a correlation coefficient of .98 between visits and a coefficient of variation of 1.3%.

The reproducibility of AIx measurements via applanation tonometry has also been tested on subjects with cardiovascular risk factors. Wilkinson et al. (1998) demonstrated in a group of 33 subjects (12 diabetes, 16 hypertensives, and 5 controls) that PWA using a radial applanation tonometry is a highly reproducible method for determining AIx. They observed a low standard deviation for within-observer and between-observer measurement differences (5.37% and 3.80 %, respectively).

The first experiments with PWA used the carotid artery because there is a closer agreement between carotid and aortic blood pressures and than between radial and aortic pressures. However, in practice, carotid measurements proved to be more difficult. The carotid artery is not well supported by bony structure and measurement can be very uncomfortable for the patients who described feeling choked; measurements sometimes also caused coughing reflex. Moreover, external calibration is more difficult with carotid measurement, because neither brachial systolic nor diastolic can be assumed to be equal to their carotid counterparts. Thus, radial measurements are more useful because the radial artery is better supported by bony structure and are more comfortable for the patient. The assumption that diastolic pressure is equal between brachial and radial sites is accurate (Nichols & O'Rourke, 1998).

Cardiovascular Disease

Cardiovascular disease is the leading cause of morbidity and mortality in the Western nations (American Heart Association, 2001). More than 12 million Americans have coronary artery disease, and more than 6 million have angina pectoris, that is, chest pain caused by coronary ischemia. Given its notoriety, coronary circulation is the most studied system of arteries in the human body (Nichols & O'Rourke, 1998).

Despite the heart's intimate relationship with blood, the myocardium does not receive any oxygen from the blood that is pumped through its chambers. Rather, the myocardium's demand for oxygen is met by an elaborate and extensive network of arteries that enshrine and penetrate the heart's muscle. Many diseases of the heart have their root cause in myocardial ischemia, that is, an imbalance between myocardial oxygen demand and coronary blood flow.

Myocardial Oxygen Demand

Myocardial oxygen demand has been divided into three parts: basal energy necessary for myocyte life in the absence of activity, energy needed for the electrical activation of muscle, and the energy needed for contraction. Of these components, contraction has been estimated to take up 60% of total demand. In hypertrophy or exercise the contractile demand also increases (Nichols & O'Rourke, 1998). Two models of demand have been developed to help determine the oxygen demand of the working heart. One model, developed by Suga (1990), focuses on tension development and ventricular dimensions. The other model, developed by Sarnoff (1958), shows oxygen demand to be related to pressure generation (tension) and the time under pressure, known as the time-pressure index or tension-time index (TTI). Buckberg et al. (1972a) showed that the aortic time-pressure index is an appropriate approximation of ventricular time-pressure index in most situations but prefer the term systolic pressure time index (SPTI) because tension is not actually being measured. The SPTI from a peripheral artery, however, is not an adequate approximation due to differences in pressure augmentation.

Factors Contributing to Coronary Blood Flow

Lumen diameter

Coronary blood flow is dependant on several factors, including time, pressure gradient, and artery caliber. The major factor in coronary blood flow is vessel caliber, especially of the epicardial vessels. The larger coronary arteries have very little to no resistance in comparison to total coronary resistance. The most common cause of lumen stenosis is atherosclerosis. Coronary spasm may also completely occlude an artery but is relatively rare compared to atherosclerosis. Many clinicians dealing with coronary disease focus on lumen occluding lesions almost exclusively (Nichols & O'Rourke,

1998). A major focus of interventional cardiology is maintaining and restoring coronary artery lumen diameter. According to the American Heart Association (2001) there were more than a million angioplasties and more than half a million coronary artery bypass grafts performed in the United States in 1999. Unfortunately, the focus on artery caliber often causes clinicians to ignore the other factors of coronary blood flow. Coronary stenosis and plaques are outside the scope of this study.

Diastolic pressure-time index

The other major determinant of coronary blood flow is time-pressure index under diastole. Because of the heart's contractile nature, it can only be perfused during diastole. Blood is compressed out of the myocardial arteries during systole (Nichols & O'Rourke, 1998). Thus, increasing heart rate reduces the amount of the time the heart has to perfuse between beats. Increasing the time under systole, as often happens during heart failure and hypertension, can also result in decreased coronary blood flow. Blood flow is determined by the pressure gradient between aorta and ventricles during diastole. If diastolic pressure in the aorta falls or if systolic pressure in the ventricle remains high longer than usual, coronary artery perfusion is compromised.

This problem is further exacerbated by blood viscosity. At low flow rates, the viscosity of blood is higher than at high flow rates. Thus, even when the pressure gradient may be adequate for perfusion, there may not be adequate perfusion because there is not enough time for the gradient to overcome the higher viscosity of blood. As with the tension-time index, the diastolic pressure-time index can be measured directly or approximated from aortic values (Buckberg et al. 1972a; Buckberg, Towers, Paglia, Mulder, & Maloney, 1972b).

Benetos et al. (2000) reported the results of two French longitudinal studies of untreated subjects—Investigations Préventives et Cliniques (IPC), studying 15,000 men for an average of 13 years, and the Paris Prospective Study, following 6,000 men for an average of 17 years. After adjusting for other major risk factors, those whose diastolic pressure lowered during the study and whose systolic pressures rose (increased pulse pressure) had a risk ratio greater than two when compared to those whose blood pressure remained constant. This suggests that pulse pressure is more important than either systolic BP or diastolic BP.

Subendocardium

The deeper layers of the heart's muscle, the subendocardium, are particularly susceptible to ischemia for two reasons. The first reason is anatomic in nature. The major coronary arteries are epicardial and run along the surface of the heart. As arteries branch from these major vessels to penetrate the myocardium and perfuse the deeper layers of muscle, they become narrower and offer more resistance. As they penetrate the subendocardium, the caliber is not only reduced, but also the arteries become fewer in number with little collateral circulation. There is little collateral circulation in the subendocardium. The second factor contributing to subendocardial ischemic risk is its contractile nature. Force generation is greatest in the subendocardium, causing the compression of blood out of the arteries to be greatest in the subendocardium. This combination of anatomic and functional factors makes the subendocardium extremely sensitive to deficits in blood flow (Nichols & O'Rourke, 1998).

The ischemic susceptibility of the endocardium is exaggerated by arterial rarefaction in hypertension and/or aging. A further complication of hypertension is left ventricular hypertrophy without concomitant hyperplasia. The end result is that myocytes are larger

and have more oxidative demand; the muscle wall is thicker; and there is no corresponding enlargement of the coronary system to make up for the increased demand. The theoretical model of the subendocardium's propensity for ischemia has been confirmed in experimental models with dogs (Buckberg et al., 1972a) and demonstrated in humans (Buckberg et al., 1972b). Further, the ratio of diastolic pressure time index to tension time index has been shown to be an accurate indicator of subendocardial risk. As long as the ratio is close to 1 or above 1, blood flow is not impeded, but when the ratio falls below 0.7, coronary blood flow is compromised even in the absence of normal vessels (Buckberg et al., 1972a). This finding was further corroborated by Ganz and Marcus (1972) who found that nitroglycerine did not relieve angina induced by atrial pacing.

More recently, it has been shown that in patients with coronary stenosis diastolic perfusion time consistently correlates with coronary artery stenosis at the ischemic threshold throughout five different stress tests (Ferro et al., 1995). Ferro et al. concluded that at a given degree of stenosis, once compensatory mechanisms are spent, the diastolic perfusion time becomes the limiting factor in determining the ischemic threshold. Moreover, patients seemed to be stratified into two groups. Those with greater stenosis (lumen < 1 mm) required only a slight decrease in diastolic perfusion time to induce angina, whereas those with less stenosis (lumen > 1 mm) required a significantly higher reduction in diastolic perfusion time before reaching angina.

While diastolic perfusion time significantly correlated to coronary stenosis and ischemic threshold, raw heart rate did not correlate with either diastolic perfusion time or stenosis at ischemic threshold. The underlying reason for this anomaly is that diastolic

perfusion time is determined by heart rate and systolic duration together. At rest, heart rate strongly correlates with diastolic perfusion time, but at higher heart rates, systolic duration and heart rate are not necessarily related. This prevents heart rate alone from being used as a predictor of ischemic threshold (Ferro et al., 1995).

Buckberg subendocardial viability ratio (SEVR)

$$\text{SEVR} = \frac{\text{Diastolic Perfusion Time Index}}{\text{Systolic Pressure Time Index}}$$

From the above discussion, it has been established that the Systolic Pressure Time Index (systolic duration time index) is a reliable and accurate method of approximating the heart's oxygen demand. The Diastolic Perfusion Time Index is a reliable measure of the heart ability to perfuse the subendocardium in the absence of coronary stenosis (Baller et al., 1978). Buckberg et al. (1972a) have shown that the ratio of these two parameters is indicative of the subendocardium's risk of ischemia, with subendocardial ischemia apparent at ratios below 0.7 even with normal coronary arteries. It is important to note that this finding only holds in the case of maximal coronary dilation. If the coronary arteries are not maximally dilated, then subendocardial flow may be improved by coronary dilation. There is some confusion in the literature as this relationship has been called various names. The following names all refer to this index: (a) DPTI/TTI ratio, (b) Subendocardial Viability Ratio (SEVR), (c) Endocardial Viability Ratio (EVR), (d) Subendocardial Flow Index, (e) Buckberg SEVR, and simply (f) Buckberg ratio (Dubiel, Dubiel, Frendo, Zmudka, & Horzela, 1986; Geitan, Martucci, & Levine, 1986; Goran, 1996; Nichols & O'Rourke, 1998; Sphygmocor px, 2001).

Buckberg et al (1972a) also established that aortic pressure is an accurate substitute ventricular pressure in the determination of subendocardial risk. Nevertheless, whether

measured via ventricle or aorta, assessment of the Buckberg ratio required arterial catheterization with all the inherent risks that it involves, making it relatively difficult to use in clinical diagnosis. Indeed, his original critical value of 0.7 has been called into question. As clinical experience grew, the critical value was lowered by up to 50%. Most of the clinical data were obtained by indwelling radial artery catheters (Reitan, Martucci, & Levine, 1986). As was previously noted, peripheral arteries do not offer an accurate assessment of diastolic pressure time index or tension time index because of inconsistent pressure amplification. Reitan et al. (1986) demonstrated this phenomenon clearly in their experiments with dogs. They measured the Buckberg ratio from aortic readings and peripheral readings. Discrepancies of up to 25% were found. The authors concluded that much of the controversy surrounding the critical value of the subendocardial viability ratio is due to a lack of rigor in its calculations.

Sphygmocardiography

Pulse Wave Contour

Despite the pervasiveness of cuff-based methods, cuff measurements were never meant to be a holy grail of diagnosis and management. In fact, Sir James Mackenzie's first text on blood pressure and hypertension warned against the blind use of cuff-based methods (Nichols & O'Rourke, 2001). Thus, it is ironic that the third edition of his work (published posthumously by his editor) contained part of the foundation for the eventual dominance of cuff-based measurements and an incorrect understanding of blood pressure. Indeed, hypertension theory has always trailed the techniques used to measure blood pressure, and in the early 1900s pulsatile pressure could be measured invasively, but flow could not. From early experiments in animals by Earnest Starling, it was assumed that flow followed a pulse curve similar to pressure, but arterial flow was rarely measured

directly in humans. Why bother when absolute systolic and diastolic pressures could be measured noninvasively by RRK method? And so, the older form of blood pressure measurement used by Mahomed faded into the background. Almost a hundred years later, Murgo et al. (1980) would corroborate Mahomed's descriptions of pulse wave contour in their seminal paper.

Murgo et al. (1980) described three types of aortic pulse wave contours, which they termed Types A, B, and C. The curves were classified by the location of their inflection point and the relative magnitude of the pulse wave above the inflection point. The inflection represents the return of the reflected wave (see Figure 2-1). In Type C waves, the inflection point occurs after systole, indicating a slow return of the reflected wave. In Type A and Type B waves, the reflected wave returned early during systole, causing an augmentation in systolic pressure and a prolongation of systole (similar to Mahomed's finding). In addition to the location of the inflection point, Murgo et al. calculated the relative intensity of the reflected wave. This calculation is the pressure difference above the inflection point ($P_s - P_i$) divided by the pulse pressure ($P_s - P_d$). When this relationship is expressed as a percentage, it is known as *Augmentation index* (AIx).

$$AIx = \frac{(P_s - P_i)}{(P_s - P_d)} \times 100$$

Patients with Type A curves had augmentation indices greater than 12%, while Type B curves had augmentation indexes of 0%-12%. Because the inflection point of Type C curves occurs after systole, there is a negative augmentation index, meaning that the reflected wave is augmenting diastolic pressure, which helps to maintain coronary perfusion pressures (Nichols & O'Rourke, 1998). The older the individual, the greater the shift toward Type B and Type A curves. In addition to the three pulse wave contours

described by Murgo et al. (1980), Nichols and O'Rourke (1998) described a fourth contour they called Type D which only occurs in patients age 65 and older. In a Type D beat, there is no inflection point because the reflected wave occurs early in systole. Almost all human pulse wave contours show a sharp inflection point, Murgo et al. (1980) reported, in contrast with animal models where there is almost never an inflection point.

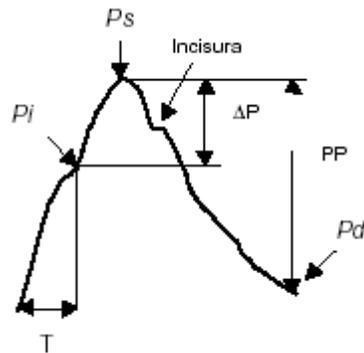


Figure 2-1. Calculation of the augmentation index. The augmentation index is calculated as the difference between P_s and P_i (ΔP), expressed as a percentage of the difference between P_s and P_d (pulse pressure, PP). T is the time between the foot of the wave and the inflection point, which provides a measure of the travel time of the pressure wave to and from the major reflection site.

Arterial Elastance

The conduit arteries and arterioles are characterized by a thick muscular media, while the central arteries, especially the proximal aorta, are characterized by elastic fibers and less muscular media (Nichols & O'Rourke, 1998). The elastic nature of the central arteries is mainly due to elastin protein fibers in the vessel wall. If pressures dilate the artery, the elastic artery is backed by stronger, stiffer collagen fibers. As the collagen fibers are engaged at higher pressures, the slope of the elastance curve increases drastically (i.e., the resulting pressure change is very large for a very small change in vessel diameter). Several terms are used to describe the stiffness of arteries and are often used interchangeably although they represent very different concepts.

The slope of the relationship of the change in pressure for a given change in diameter ($\Delta P/\Delta D$) is called elastance and is a measure of the stiffness of an artery. The term compliance is the inverse of elastance and represents the change in volume of an artery for a given change in pressure. Compliance represents the relative ease of change in diameter for a given pressure, while distensibility is how easily an artery distends. For the purpose of this dissertation, elastance is used because it is directly related to elastic modulus, pulse wave velocity, and augmentation index (Nichols & Edwards, 2001).

As humans age, elastin fibers tend to be stretched to their limit and central artery elastance increases, causing the aorta to be stiffer and less accepting of pulsatile elements of blood flow (Nichols & O'Rourke, 1998). Muscular arteries, on the other hand, are protected by their thick media and do not experience this age related increase in elastance. The same age-related changes of central arterial elastance also are seen in hypertension at younger ages; thus, hypertension can be viewed as an early form of aging (Nichols & O'Rourke, 1998). The increase in aortic elastance causes disruptions in ventricular-vascular coupling directly and by increasing wave reflection and pulse wave velocity.

Vascular-Ventricular Coupling

When the third edition of Sir James Mackenzie's text was published, his editor, James Orr, apparently inserted the following advice: "As regards the relative importance of systolic and diastolic pressures, it may be said that the systolic pressure represents the maximum force of the heart, while the diastolic pressure measures the resistance the heart has to overcome" (Nichols & O'Rourke, 1998, p. 381). Thus, the concept that high diastolic pressure is harmful while high systolic pressure is the sign of a vigorous and fit heart gained widespread popularity and is still taught today (Nichols & Edwards, 2001).

This early hypertensive theory could not possibly have been more wrong. In a normal human being, the proximal aorta is elastic and expands to receive systolic pressure from the heart, storing it in elastic fibers as potential energy. This transfer of energy allows systole to occur in a relatively short amount of time and for maximum ejection to occur with the least amount of myocardial force. After systole, the elastic fibers in the aorta rebound, releasing their energy as kinetic energy and aiding blood flow. With age the aortic elastance increases (Nichols et al., 1995), and the force required for contraction increases and systolic pressure concomitantly increases (Nichols & Edwards, 2001). Because the aorta cannot absorb as much of the heart's energy as potential energy, the pulse wave velocity increases while the diastolic pressure decreases. This has been shown to be true in experiments where the aorta is replaced with a stiff tube and in humans with increased arterial elastance. Because pulse wave velocity increases, the reflected wave returns earlier during systole as described above, further increasing systolic pressure and increasing the systolic duration. This mismatch in vascular-ventricular coupling has far-ranging implications that not only impact blood pressure but also coronary perfusion as it increases the systolic duration and pressure (SPTI), thereby increasing myocardial demand and concomitantly decreasing diastolic pressure and duration (DPTI), decreasing coronary artery perfusion.

Summary

Cardiovascular disease is the largest cause of mortality worldwide, and hypertension is a primary risk factor for both mortality and morbidity (myocardial infarction or cerebrovascular accident). Hypertension is a problem of degree, and traditional office or clinic blood pressure is not a good predictor of target organ damage. Ambulatory blood pressure is an improvement on clinic blood pressures by reflecting changes throughout

the day and by being more reproducible and more highly associated with both mortality and morbidity. Sphygmocardiography improves on traditional blood pressure measurement, and even surpasses ambulatory blood pressure measurement, by allowing the detection and assessment of a variety of hypertension pathologies such as increased arterial elastance, pressure amplification by wave reflection, ventricular-vascular coupling mismatch, and hemodynamic risk for subendocardial ischemia. The current research seeks to study the interaction of all three blood pressure measurement techniques in patients with coronary artery disease and hypertension.

CHAPTER 3 PROCEDURES AND METHODS

Design

This study utilized an observational design within the framework of an ongoing international multi-center clinical trial. The same data were collected on all subjects, regardless of INVEST treatment group between April 2002 and January 2003.

Population and Sample

International Verapamil/Trandolapril Study (INVEST)

INVEST was a large multi-site randomized clinical trial. It had 22,576 with a minimum treatment periods of 2 years at study closeout. The current study was an ancillary study to INVEST. All INVEST subjects were above the age of 50, had essential hypertension, and documented coronary artery disease. Each subject was randomized to one of two treatment strategies: a calcium channel antagonist based strategy comprised of the heart rate slowing calcium antagonist Verapamil, and a noncalcium channel antagonist strategy comprised of the beta blocker atenolol. Each group was also allowed to receive additional medications including an ACE inhibitor or diuretic to attain JNC VI guidelines (Pepine et al., 1998). At the beginning of this research study, every INVEST subject had been on treatment for at least a year.

Sample

Subjects were recruited from three sites of INVEST (Pepine et al., 1998). Approximately 200 INVEST participants were being followed in the Gainesville, FL, area. Many participants lived as far away as West Palm Beach and traveled to

Gainesville for their cardiology care at Shands Teaching Hospital. Additionally, other subjects refer to themselves as “Snow birds” and live in the northern states, returning to Florida for the winter season. Thus, although patients were only recruited from the Gainesville area, the actual sample population is more diverse than might be expected of a localized recruitment effort. INVEST participants in the Gainesville area were asked to participate in this study by their physician or INVEST investigator. This researcher then presented the study to patients who were asked to sign the consent document. More than 64 subjects were recruited, and 41 signed the consent document. Eleven withdrew their consent after trying to wear the ambulatory blood pressure monitor but before obtaining any useful ABP data.

INVEST Participants

The INVEST subjects are (a) either male or female, (b) above the age of 50, (c) have documented hypertension according to JNC VI (1997) criteria and the need for drug therapy, and (d) have documented coronary artery disease (e.g., classic angina pectoris, myocardial infarction 3 months or more ago, abnormal angiography or concordant abnormalities on two different types of stress tests).

INVEST Exclusion Criteria

The following were exclusion criteria for INVEST, but since patients had been under the protocol for more than a year, some criteria were no longer applicable (e.g., some patients were taking atenolol, a beta blocker, under the INVEST protocol).

1. Unstable angina, angioplasty, CABG, or stroke within 1 month. Patients taking beta blockers after myocardial infarction are excluded if study enrollment is planned within 12 months of myocardial infarction. No time limitation if not taking beta blocker.
2. Use of beta blocker within past 2 weeks.

3. Patients without a pacemaker and any of the following: Sinus bradycardia (<50 beats/min), Sick sinus syndrome, AV-block of more than 1st degree.
4. Documented contraindication to verapamil, atenolol, and hydrochlorothiazide.
5. Severe heart failure (NYHA IV).
6. Concomitant severe illnesses that may affect outcome variables where life expectancy is 2 years or less or which are likely to require frequent hospitalizations and/or treatment adjustments.
7. Patients with psychiatric, cognitive, or social conditions that would interfere with giving consent, cooperating or remaining available for up to 2 years.

Specific inclusion criterion (for this study):

1. Patients with documented hypertension, and coronary artery disease who are participating in the INVEST trial.

Specific exclusion criteria (for this study):

1. Unwilling to provide written informed consent.
2. Atrial Fibrillation; traditionally, patients with fibrillation have been excluded from ABP studies because of irregular systole and diastole times.
3. Physically unable to wear blood pressure monitoring device because of previous axillary lymph node resection or upper extremity neuropathy.
4. Severe muscle tremors (e.g. Parkinson's) because these may interfere with automated oscillometric measurement of BP.

Setting

This study was conducted at a human research laboratory in the University of Florida College of Nursing, the 11th floor of Shands Teaching Hospital, University of Florida Cardiology Research Lab, a satellite Shands cardiology clinic, and a private doctor's office who was an INVEST investigator. Institutional Review Board (IRB) for human subjects approval was obtained prior to data collection.

Research Variables and Instruments

Body Mass

Mass was measured either by the clinic nurses or this author using either a calibrated beam balance scale or digital electronic scale and recorded in kilograms.

Body Height

Height was self-reported and recorded in centimeters.

Body Mass Index (BMI)

BMI is a composite measurement incorporating both mass and height. It is calculated by dividing the mass in kilograms by the square of height in meters (kg/m^2).

Ascending Aortic Pulse Wave

Previous published results (Chen et al., 1997; Pauca et al., 2001; Siebenhofer et al., 1999) suggest that accurate contours of the ascending aortic pressure waveform can be obtained from the radial artery pressure waveform using a generalized mathematical transfer function. In the present study, radial artery pressure waveforms were recorded by applanation tonometry and central aortic pressure waveforms calculated using the SphygmoCor (Atcor Medical, Sydney Australia) system. This system averages 10 pressure pulse waves and generates ascending aortic pressures and indices of ventricular/vascular coupling, including ascending aortic pressure wave augmentation index, wave reflection travel time, systolic pressure time index and subendocardial viability ratio.

Using the transfer function to synthesize the central aortic wave from the peripheral wave, agreement between the central aortic and peripheral pressure wave is good; differences between recorded aortic and calculated aortic systolic pressure were 2.4 ± 1.0 mmHg, whereas recorded systolic pressure differed by 20.4 ± 2.6 (mean \pm SEM)

mmHg (Karamanoglu et al., 1993). Linear relationships also have been demonstrated between brachial blood pressures and corresponding central pressures derived by the transfer function method (Karamanoglu et al., 1993). The transfer function has recently been validated by AAMI SP10 standards in patients with coronary artery disease under both baseline and nitroglycerine infusion (Pauca et al., 2001).

The following variables are obtained from the aortic pulse wave:

- Central Systolic BP (CSBP)
- Central Diastolic BP (CDBP)
- Central Pulse Pressure (CPP): (CSBP) – (CDBP)
- Central Mean Arterial Blood Pressure (CMAP): $[2(\text{CDBP}) + \text{CSBP}]/3$
- Heart Rate (HR)

Augmentation Index (AIx)

Kelly, Daley, Avolio, and O'Rourke (1989) defined AIx as the ratio of augmentation pressure and PP expressed as a percentage. Augmentation pressure is defined as the difference in pressure between the early and late systolic shoulders of central aortic pressure waveforms. In this study the central aortic wave was synthesized from a recorded peripheral wave recorded using a radial applanation tonometer (Millar Pressure Tonometer, Millar Instruments) and a pulse wave analysis system with a generalized transfer function (SCOR-Px/P, SphygmoCor™ pulse wave analysis system, PWV Medical, Sydney, Australia). This device automates the assessment of AIx, expressed as a percentage, using the following formula: $\text{AIx} = 100 \times (\text{Ps} - \text{Pi}) / (\text{Ps} - \text{Pd})$, where Pi is the first systolic shoulder (inflection point), Ps is the peak systolic pressure (SBP), and Pd is the minimum DBP (see Figure 3-1).

Several studies (Liang et al., 1998; Seibenhofer, 1999; Wilkinson et al., 1998) previously reported excellent reproducibility for AIx measurements with a between-visit

correlation coefficient of .98, standard deviation of intraobserver measurement difference of 2.70% to 5.37%, and standard deviation of interobserver measurement differences of 3.80%.

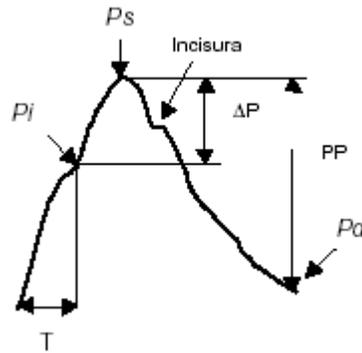


Figure 3-1. Calculation of the augmentation index. The augmentation index is calculated as the difference between P_s and P_i (ΔP), expressed as a percentage of the difference between P_s and P_d (pulse pressure, PP). T is the time between the foot of the wave and the inflection point, which provides a measure of the travel time of the pressure wave to and from the major reflection site.

Subendocardial Viability Ratio (SEVR)

Buckberg et al. (1972a) first described the subendocardial viability ratio as the ratio of diastolic pressure time index to the systolic pressure time index. The integral of systolic portion of the ascending aortic pulse wave is calculated as the systolic pressure time index (SPTI), and a similar calculation is made for the diastolic portion of the wave corresponding to diastolic pressure time index (DPTI). Figure 3-2 depicts the process.

Ambulatory Blood Pressure (ABP) Parameters

An autonomic noninvasive cuff-oscillometric recorder (Model 90207, SpaceLabs™ Inc., Redmond, WA) measured ambulatory blood pressure. This monitor measures BP by detection of oscillations transmitted from the brachial artery to the cuff. The SpaceLabs™ monitor was equipped with four different size adult cuffs. A SpaceLabs™ Model 9029 Data Interface Unit was used for report generation.

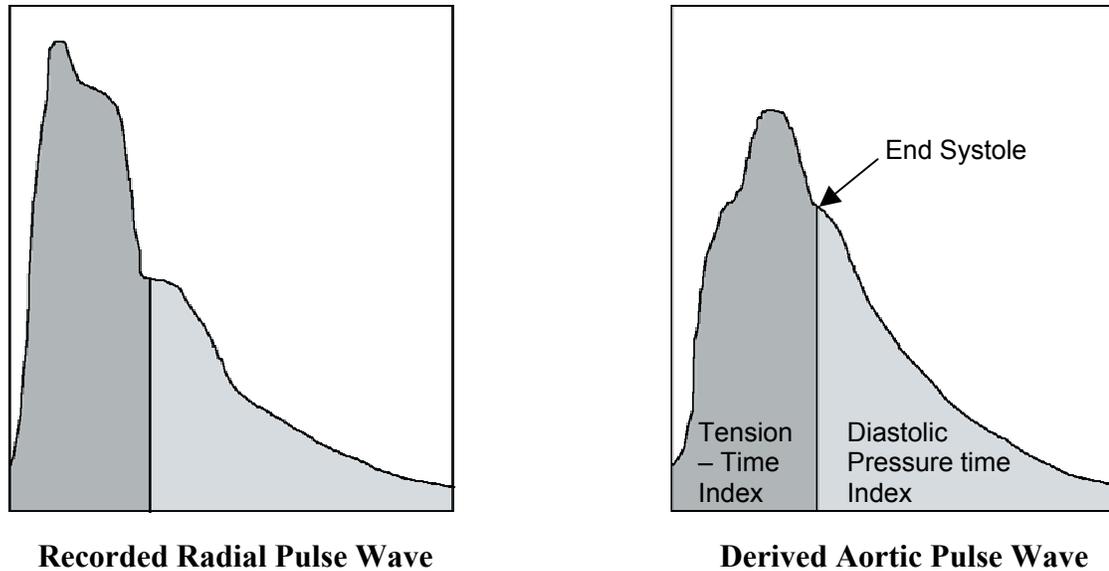


Figure 3-2. Calculation of SEVR from recorded radial pulse wave. The radial pulse wave is transformed via a transfer function to an ascending aortic pulse wave. The aortic wave is divided into systolic (darker shaded) and diastolic (lighter shaded) periods. The integral of the area under the curve for each portion represents the SPTI and DPTI, respectively.

Average pressures and standard deviations were calculated. Two methods may be used to calculate average pressures. One may average all the readings for a given hour and then average the hour averages. Alternatively, one may simply average all the readings in the specified time period. The former method may give undue weight to measures taken during hours that have fewer readings. Furthermore, it makes analysis of variation and error more difficult. The second method was used in this study as it also reflects the author's belief that the true value of ambulatory blood pressure is in averaging 40 to 50 readings of a continuous biological variable rather than taking a single reading. Using this method 24-hour, daytime, and nighttime averages were calculated. Ambulatory BP variability was defined as the standard deviation of the 24-hour APB average. The day-night BP difference, or nocturnal BP reduction, was defined as the difference between the nighttime pressure average (NP) and the daytime pressure average (DP), using

individually defined periods of sleep and wake time parameters. Percentages of nocturnal BP reduction were computed by the following formula: $100 \% \times (DP-NP)/(DP)$.

The validity of the SpaceLabs 90207 ABP monitor has been established. According to the validation protocols of British Hypertension Society and the Advancement of Medical Instrumentation, the SpaceLabs 90207 satisfies the criteria for accuracy (O'Brien, Atkins, & Staessen, 1995).

- 24-hour average Systolic BP (ASBP)
- 24-hour average Diastolic BP (ADBP)
- 24-hour average Pulse Pressure (APP): $[\Sigma(SBP - DBP)]/N_{\text{readings}}$
- 24-hour average Mean Arterial Blood Pressure (AMAP): $[\Sigma(2*DBP + SBP)/3]/N_{\text{readings}}$
- 24-hour average Heart Rate (AHR)
- Blood Pressure Variability ASBPST: Standard Deviation of ASBP
- Daytime average Systolic BP (DSBP)
- Daytime average Diastolic BP (DDBP)
- Daytime average Pulse Pressure (DPP): $DSBP - DDBP$
- Daytime average Mean Arterial Blood Pressure (DMAP): $(2*DDBP + DSBP)/3$
- Daytime average Heart Rate (DHR)
- Nighttime average Systolic BP (NSBP)
- Nighttime average Diastolic BP (NDBP)
- Nighttime average Pulse Pressure (NPP): $(NSBP) - (NDBP)$
- Nighttime average Mean Arterial Blood Pressure (NMAP): $(2*NDBP + NSBP)/3$
- Nighttime average Heart Rate (N-HR)

Clinic Blood Pressure

Clinic brachial BP was measured by the INVEST investigators using a traditional cuff and stethoscope. Two readings were obtained at every visit.

- Clinic Systolic BP (CLSBP)
- Clinic Diastolic BP (CLDBP)
- Clinic Pulse Pressure (CLPP): $CLSBP - CLDBP$
- Clinic Mean Arterial Blood Pressure (CLMAP): $(2*CLDBP + CLSBP)/3$
- Clinic Heart Rate (CLHR)

Study Protocol

History and Clinic Assessment

All subjects signed a consent document before any measurements were made. Health history and demographic data (other than gender and birth date) were obtained from the patient's chart. The nurses running the clinics took blood pressure in accordance with JNC VI guidelines. A second reading was obtained by either an INVEST investigator or the patient's doctor.

Tonometry Protocol

All tonometry measurements were taken at the right radial artery with the patient sitting upright. The internal software calculates a quality index. Measurements were repeated until two readings with quality indices greater than 80 were obtained. If after 10 readings a quality index of 80 was not attainable, then the two highest quality readings were used.

Ambulatory Blood Pressure Monitoring Protocol

The subjects were instructed to keep a regular sleep and wake pattern and to avoid abnormal physical exertion and psychological stress during the ABP recording day. Ambulatory BP was recorded on an ordinary weekday.

Subjects were fitted with an ABP monitor and were familiarized with its operation. The monitor was programmed to measure blood pressure over a 24- hour period at the frequency of every 20 minutes throughout the duration. A cuff of the proper size, determined by upper arm circumference, was placed on the subject's preferred arm and attached by flexible tubing to the monitor. The center of the inflatable bladder of the cuff was placed directly over the brachial artery. The investigator inserted a finger between

the cuff and the arm to ensure the cuff's fit was not too tight. The monitor was then strapped to the patient's hip or held in a sling on the patient's shoulder.

The monitor emitted a series of alarm sounds 5 seconds prior to cuff inflation between the hours of 0900 and 2100. It was silent during the nighttime hours. The investigator instructed the subjects to keep the limb quiet and allow their arm to hang freely at their side during cuff inflation and deflation. To avoid reading errors due to hydrostatic pressure differences, the subjects were instructed to keep the level of the cuff near the heart level. Subjects were given a diary and asked to record their hour of recline and awakening as well as the times they took their medications. On the back of the diary were troubleshooting and frequently asked questions regarding the ABP monitor. Subjects were asked to return the monitor and the diary to the investigator after a minimum elapsed time of 24 hours. (Subjects who lived more than 30 minutes from Gainesville were given a stamped self-addressed mailer to return the monitor.) The 24-hour data for each subject was then downloaded and compared with the subject's diary entries. The individually defined periods of sleep and wake time indicated on the diary was used to compute the subject's nocturnal blood pressure reduction. However, less than half of the subjects returned their diaries, so fixed wake and sleep periods were defined. Daytime was defined from 0900 to 2100. Nighttime was defined from 0000 to 0600. An observer would immediately notice that several hours of the day were missing in these definitions. The reason for these conservative definitions of daytime/nighttime is to ensure that patients are actually awake or asleep during the defined times. More liberal definitions would probably have included measurements on patients who were sleeping during daytime and awake during nighttime.

Data Collection Methods and Data Reduction

Every attempt was made to ensure data integrity during the data collection and reduction process. Wherever possible, data were handled by the computer rather than being entered manually from forms or printouts. All data were collected or entered on a Compaq Presario 2715 Notebook computer. Tonometry data were collected directly onto the computer in real time via a serial connection. ABP monitors were downloaded to the computer upon their receipt via serial cable. Subjects' height, mass, date of birth, gender, medications, and clinic blood pressures were entered into the appropriate fields within the tonometry database.

Tonometry

Tonometry data were exported to an ASCII text file. The file was then imported to an Access (MicroSoft, Redmond, WA) database. All the central blood pressures were calculated by the tonometry software and were exported directly.

Height, Mass, Date of Birth, Gender, Medications and Clinic Blood Pressures

These data were already in the Access database, having been a part of the tonometry database. The BMI was automatically calculated from the mass and height by the tonometry program, as was clinic MAP and PP (CLMAP, CLPP). These data were exported directly to the database. However, the date of birth and date of tonometry reading were recorded in dd/mm/yyyy format (Sphygmocor is an Australian based company), and the US software assumes that dates are formatted mm/dd/yyyy. So dates that contained day values greater than 12 (e.g., June 23rd) were imported correctly; however, dates that contained a day value of 12 or less had the month and day transposed, thus June 12th would become December 6th. Every effort to stop this transposition or

automatically reparse the dates was unsuccessful, and eventually the dates were simply corrected manually.

ABP Data

Management of the ABP data is extremely important, as 72 readings are anticipated per patient (3 readings an hour for 24 hours). For only 30 patients, more than 2,000 readings are anticipated. Thus, manually copying the readings into a database is an effective way to ensure data errors. Ideally, the data simply would be exported in a usable and analyzable format to a database or spreadsheet. There is no way to export either the entire database or any subsets of the database. Individual readings can be exported, but to some unknown proprietary format that is not readable by Excel (spreadsheet software), Access, or a text editor. The raw data tables can, however, be copied to an Excel spreadsheet as shown in Figure 3-3.

Unfortunately, the raw data as copied are not very usable. A series of parsing steps are necessary in order to make the spreadsheet useful for interpretation. Column E contains the reading number; however, it is mixed with two letter codes *M* and *R*, respectively, for *manual* and *repeated* readings. In cases where a code is used, a space is inserted before the reading number. To separate these two codes, extra columns are inserted after column E in the above figure. In the new blank column F is inserted the following formula =Trim(E). Thus, column F consists of column E without the extra spaces. In column G the formula =Right(F,1) which fills column G with the right most character from column F. Next, the data are sorted by column G, so that readings with a letter code appear at the top of the list; the readings with only numbers are deleted, so that column G consists only of reading codes. The formula =Left(F, (Len(F)-2)) is applied to column H. This makes column H consist of only the number part of Column F. At this

point, columns G and H are selected, copied, and then pasted over themselves using the Paste > Special > Values command. This converts the cells from formulas to actual numbers. At this point, columns E and F can be deleted and columns G and H take their place as seen in Figure 3-4.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1						Day & Time	Systolic	Diastolic	MAP	Heart Rate	Event Code	Edit	Status	Diary	Activity
2	1	249	29	6/12/2002	1 R	1-12:58	0	0	0	0	0	13	EE		
3					2 M	1-12:58	0	0	0	0	0	11	EE		
4					3 R	1-13:01	184	79	120	53					
5					4	1-13:18	0	0	0	0	11	EE			
6					5 R	1-13:21	199	88	132	56					
7					6 M	1-13:23	0	0	0	0	0	3	EE		
8					7	1-13:38	0	0	0	0	0	3	EE		
9					8 M	1-13:58	0	0	0	0	0	48	EE		
10					9 R	1-14:01	199	90	129	54					
11					10	1-14:18	175	89	108	54					
12					11	1-14:38	167	104	111	62					

Figure 3-3. ABP Spreadsheet with directly copied ABP data. Highlighted cells are to be copied for all readings in the session.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	
1	Seq	SiteID	PatientID	InitDate	Reading#	Code	DayTime	SBP	DBP	MAP	HR	EventCode	Edit	Status	InBed	Medication
2	1	249	29	6/12/2002	1	R	1-12:58	0	0	0	0	0	13	EE		
3	2	249	29	6/12/2002	2	M	1-12:58	0	0	0	0	0	11	EE		
4	3	249	29	6/12/2002	3	R	1-13:01	184	79	120	53					
5	4	249	29	6/12/2002	4		1-13:18	0	0	0	0	11	EE			
6	5	249	29	6/12/2002	5	R	1-13:21	199	88	132	56					
7	6	249	29	6/12/2002	6	M	1-13:23	0	0	0	0	0	3	EE		
8	7	249	29	6/12/2002	7		1-13:38	0	0	0	0	0	3	EE		
9	8	249	29	6/12/2002	8	M	1-13:58	0	0	0	0	0	48	EE		
10	9	249	29	6/12/2002	9	R	1-14:01	199	90	129	54					
11	10	249	29	6/12/2002	10		1-14:18	175	89	108	54					
12	11	249	29	6/12/2002	11		1-14:38	167	104	111	62					

Figure 3-4. ABP Excel Spreadsheet after parsing.

At this point, the ABP data were imported to the same Access database as the tonometry data. MAP and PP were calculated by using a query with the appropriate formulas. Filtering out readings with a systolic pressure of zero eliminated error readings. Using a *Totals* query, the data were then summarized by grouping on SiteID, PatientID, and Date. Averages and standard deviations were calculated for each variable as well as the number of valid readings for each patient.

Daytime and nighttime averages were also created at this time by filtering on the field DayTime (e.g., 1-18:46). The middle number, 18, is the number of interest, as it denotes the hour in which the reading took place. By filtering based on this number using the function =Mid(DayTime, 3,2), daytime was defined as the hours between 09 and 21. Nighttime was defined as the hours between 00 and 06.

Merging the Data

At this point, the data from the Tonometry and ABP source tables were ready to be merged. A query was created that linked the data together by the SiteID, PatientID, and Date of reading. The data were then exported to an Excel spreadsheet where it could be imported into either SAS or SPSS.

Methods of Statistical Analyses

Data were analyzed using SAS (SAS Institute Inc., Cary, North Carolina) and SPSS. Descriptive statistics and graphs were calculated in SPSS as well as T-tests, and SAS was used to analyze the data with the general linear model for repeated measures, where each subject served as his own control. A difference of 5 mm of mercury was set as the minimum clinically significant difference. Estimates were calculated with a 95% confidence coefficient. An alpha of 0.05 was set for statistical tests.

CHAPTER 4 RESULTS

The primary purpose of this study was to determine the differences in blood pressure readings between clinic blood pressure, ambulatory blood pressure, and tonometry-derived central blood pressure in patients of INVEST. Secondary purposes of the study were to characterize the hemodynamic profiles of INVEST patients using various parameters of ambulatory blood pressure (circadian rhythm) and applanation tonometry (SEVR and Augmentation index). A third purpose of the study was to compare the two treatment groups in INVEST with regard to the above parameters.

This chapter first presents descriptive results, including means, standard deviations, and frequency data for each variable. The three hypotheses posed in Chapter 1 are addressed using repeated measure ANOVA and paired *t*-tests.

Descriptive Results

Subject Demographics

Over 70 INVEST subjects were contacted regarding this substudy in person or by phone. The study was presented in person to 64 subjects. Of those three were not asked to participate due to impaired cognitive function, as the investigators deemed they would be unable to wear the ambulatory blood pressure monitor. Forty-one subjects signed the consent document. Six withdrew after wearing the ambulatory blood pressure monitor but without having any usable readings; another five never wore the monitor, citing schedule or lifestyle conflicts.

Subject demographics expressed in numbers and percentages were gender, race, and age. Table 4-1 shows the subject demographics. The statistics are given for both treatment strategies as well as the total for this study. Table 4-2 shows the medication usage for subjects in the study.

Clinical Measurements

Table 4-3 lists the mean clinical measurements for the entire study. The mean age was 67 ± 9 years. The mean BMI was 28.62 ± 5.82 . The mean clinical SBP and DBP were 134 ± 16 mmHg and 72 ± 10 mmHg, respectively.

Figure 4-1 shows scatter plot matrices of the relationships of the clinical, central, and 24-hour average measurements for systolic, diastolic, mean, and pulse pressure. Note that in every case the central and clinical pressures seem to have very strong linear relationships, with the relationship being strongest for diastolic pressure, and weakest for pulse pressure. It is important to note that a strong linear relationship does not mean that they are the same, but that they seem to change at a similar rate.

Analytic Results

Purpose 1: To Determine the Difference Between the Clinic Measurements, ABPM Measurements, and Calculated Central BPs in Patients Participating in the NVEST.

For each blood pressure parameter—systolic, diastolic, etc.—General linear Model with repeated measures analysis was used. An example follows below:

```
PROC GLM;
  MODEL CLDBP CDBP ADBP = / NOUNI;
  REPEATED TIME 3 / PRINTE;
  REPEATED TIME 3 CONTRAST(1)/ SUMMARY NOU NOM;
  REPEATED TIME 3 PROFILE / SUMMARY NOU NOM;
```

Table 4-1: Demographic Summary by INVEST Group and Total

	Invest Group				Total	
	NCAS*		CAS*		N	%
	N	%	N	%		
Total	19	63.3	11	36.7	30	100
Gender						
Male	13	68.4	6	54.5	19	63.3
Female	6	31.6	5	45.5	11	36.7
Race						
White	15	78.9	8	72.7	23	76.7
Black	2	10.5	1	9.1	3	10.0
Asian	1	5.3	0	0	1	3.3
Hispanic	1	5.3	2	18.2	3	10.0
Age						
50 - 59	4	21.1	3	27.3	7	23.3
60 - 69	7	36.8	3	27.3	10	33.3
70 - 79	7	36.8	4	36.4	11	36.7
80 - 89	1	5.3	1	9.1	2	6.7
Positive Stress Test						
No	18	64.3	10	35.7	19	63.3
Yes	1	50.0	1	50.0	11	36.7
Angina Pectoris						
No	13	68.4	6	37.5	19	63.3
Yes	6	54.5	5	35.7	11	36.7
Abnormal Angiogram						
No	10	62.5	6	37.5	16	53.3
Yes	9	64.3	5	35.7	13	46.7
Myocardial Infarction						
No	15	60.0	10	40.0	19	63.3
Yes	4	80.0	1	20.0	11	36.7
Stroke						
No	18	64.3	10	35.7	19	63.3
Yes	1	50.0	1	50.0	11	36.7
CABG (bypass surgery)						
No	16	61.5	10	38.5	19	63.3
Yes	3	75.0	1	25.0	11	36.7
PTCA (angioplasty)						
No	17	63.0	10	37.0	19	63.3
Yes	2	66.7	1	33.3	11	36.7
Renal Insufficiency						
No	18	62.1	11	37.9	19	63.3
Yes	1	100.0			11	36.7

Table 4-1 (continued).

Past Smoking History						
No	17	68.0	8	32.0	19	63.3
Yes	2	40.0	3	60.0	11	36.7
Recent Smoking History						
No	18	64.3	10	35.7	19	63.3
Yes	1	50.0	1	50.0	11	36.7
Cancer						
No	19	67.9	9	32.1	19	63.3
Yes	0	0	2	100.0	11	36.7
Carotid Bruit						
No	18	62.1	11	37.9	19	63.3
Yes	1	100.0			11	36.7
Peripheral Edema						
No	18	64.3	10	35.7	19	63.3
Yes	1	50.0	1	50.0	11	36.7
Diabetes Mellitus						
No	18	64.3	10	35.7	19	63.3
Yes	1	50.0	1	50.0	11	36.7
Lipid disorder						
No	15	68.2	7	31.8	19	63.3
Yes	4	50.0	4	50.0	11	36.7

*NCAS represents those randomized to the arm initially assigned to atenolol. CAS represents subjects who had been randomized to the verapamil arm of INVEST. No subjects had a history of the following illnesses: Unstable angina, Sick sinus syndrome, Class VI Heart Failure, Sinus Bradycardia, A-V Block < 1, Left ventricular hypertrophy, arrhythmia, Alzheimer's, Gastrointestinal bleed, TIA, jugular venous distension, rales, cardiomegaly, or S3 gallop.

Table 4-2: Medication Usage for INVEST ABP Substudy

	Yes	Yes (%)	No	No (%)
Beta Blocker	14	47%	16	53%
Calcium Channel Blocker	11	37%	19	63%
Diuretic	13	43%	17	57%
ACE Inhibitor	18	60%	12	40%
Angiotensin Receptor Blocker	23	77%	7	23%
Nitrate	3	10%	27	90%
Statin	8	27%	22	73%
Aspirin	18	60%	12	40%
Anti-Platelet (other than aspirin)	15	50%	15	50%
Coumadin	2	7%	28	93%
Psychotropic (including SSRI)	1	3%	29	97%
Antihistamine	4	13%	26	87%
Synthroid	2	7%	28	93%
Narcotics	3	10%	27	90%
Hypoglycemics (including insulin)	1	3%	29	97%
Digoxin	6	20%	24	80%
Other Medications	16	53%	14	47%

Table 4-3: Summary Statistics for Clinical Measurements

	N	Mean	Std. Deviation	Minimum	Maximum
Age	30	66.9	9.1	51.0	83.0
Height (cm)	30	170.8	9.0	149.0	188.0
Mass (kg)	30	83.3	17.1	45.0	120.0
BMI (kg/m ²)	30	28.6	5.8	15.9	41.4
Clinical SBP (mmHg)	30	134.0	16.3	96.0	170.0
Central SBP (mmHg)	30	124.1	15.8	87.5	156.5
24 hour SBP (mmHg)	30	130.3	13.4	108.2	160.2
Daytime SBP (mmHg)	30	132.4	13.8	107.7	162.9
Nighttime SBP (mmHg)	30	124.3	16.0	96.6	158.3
Clinical DBP (mmHg)	30	72.8	10.9	58.0	100.0
Central DBP (mmHg)	30	73.4	11.1	58.5	102.0
24 hour DBP (mmHg)	30	68.7	8.5	52.0	88.3
Daytime DBP (mmHg)	30	70.3	9.0	51.8	91.7
Nighttime DBP (mmHg)	30	64.2	10.0	48.1	85.3
Clinical MAP (mmHg)	30	93.2	11.7	72.0	123.3
Central MAP (mmHg)	30	92.9	13.1	70.5	127.5
24 hour MAP (mmHg)	30	91.5	9.5	77.0	112.2
Daytime MAP (mmHg)	30	93.2	10.1	77.0	114.0
Nighttime MAP (mmHg)	30	86.7	11.5	69.9	113.0
Clinical PP (mmHg)	30	61.3	12.0	33.0	88.0
Central PP (mmHg)	30	50.7	9.0	27.5	72.0
24 hour PP (mmHg)	30	61.6	9.9	42.5	85.2
Daytime PP (mmHg)	30	62.1	10.5	43.6	86.6
Nighttime PP (mmHg)	30	60.1	9.7	38.8	81.4
Heart Rate (bpm)	30	59.6	11.1	37.5	79.0
24 hour HR (bpm)	30	62.2	8.9	47.2	78.3
Daytime HR (bpm)	30	63.0	9.4	47.5	80.2
Nighttime HR (bpm)	30	60.7	9.1	46.4	84.5
24 hour HR SD	30	6.8	2.9	3.0	17.4
Daytime HR SD	30	7.0	3.2	3.0	20.2
Nighttime HR SD	30	3.8	2.0	0.7	10.0
24 hour SBP SD	30	14.3	3.1	9.0	21.2
24 hour DBP SD	30	9.9	2.0	6.6	15.5
24 hour MAP SD	30	11.6	2.3	8.5	16.6
Daytime SBP SD	30	13.8	3.3	9.0	21.2
Daytime DBP SD	30	9.3	2.4	6.7	17.3
Daytime MAP SD	30	11.0	2.8	7.1	18.1
Nighttime SBP SD	30	10.6	4.1	0.7	20.2
Nighttime DBP SD	30	8.1	2.5	4.0	15.1
Nighttime MAP SD	30	8.9	2.8	3.7	16.6
Number of ABP readings	30	63.7	10.7	28.0	77.0
Number of Daytime ABP readings	30	48.4	10.2	25.0	68.0
Number of Nighttime ABP readings	30	15.3	5.6	2.0	22.0

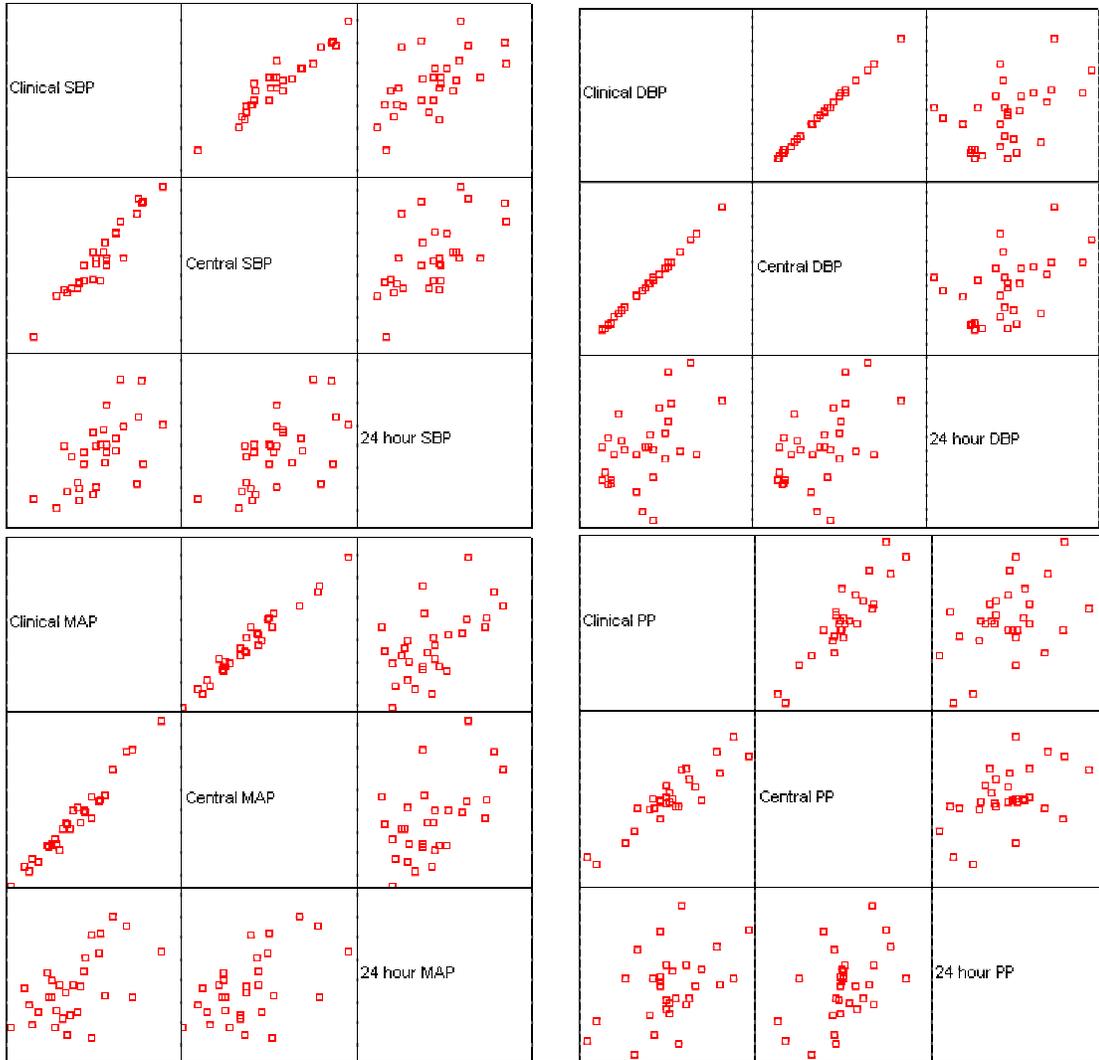


Figure 4-1. Scatter matrices for Systolic, Diastolic, Mean, and Pulse pressures.

If the sphericity Chi-squared test was significant, indicating significant correlation between one or more response variables, then univariate analysis was not appropriate, and the multivariate analysis was used to assess significance. Contrast was used to compare both central and ambulatory measurements to clinical measurements.

Systolic pressure showed a significant correlation ($\chi^2 = 56.29$, $p < 0.0001$) among one or more response variables. MANOVA tests for equality among systolic measurements showed a significant difference ($F = 58.09$, $p < 0.0001$). Diastolic pressure showed a significant correlation ($\chi^2 = 56.29$, $p < 0.0001$) among one or more response variables.

MANOVA tests for equality among diastolic measurements showed a significant difference ($F = 58.09, p < 0.0001$). Mean pressure showed a significant correlation ($\chi^2 = 56.29, p < 0.0001$) among one or more response variables. MANOVA tests for equality among mean measurements showed a significant difference ($F = 58.09, p < 0.0001$). Pulse pressure showed a significant correlation ($\chi^2 = 56.29, p < 0.0001$) among one or more response variables. MANOVA tests for equality among pulse measurements showed a significant difference ($F = 58.09, p < 0.0001$). Table 4-4 summarizes the mean differences for each blood pressure parameter:

Table 4-4: Comparison of Means \pm 2SE for Clinical, Central, and Ambulatory Measurements

	Clinical	Central	ABP
Systolic Pressure (mmHg)	134 \pm 6.0	124 \pm 5.8**	130 \pm 2.8
Diastolic Pressure (mmHg)	73 \pm 4.0	73 \pm 4.0	69 \pm 3*
Mean Arterial Pressure (mmHg)	93 \pm 4.2	93 \pm 4.8	91 \pm 3.4
Pulse Pressure (mmHg)	61 \pm 4.4	51 \pm 3.6**	62 \pm 2.6

** denotes statistical difference with Clinical BP at $p < .0001$. * denotes statistical significance with Clinical BP at $p < 0.05$

The difference between clinical and central SBP was 10 ± 2 mmHg. The difference between clinical PP was 11 ± 2 mmHg. The difference between clinical and ambulatory DBP was 4 ± 3 mmHg. Clinic and central BPs were very highly correlated for both SBP ($r = .952, p < 0.0001$) and DBP ($r = .999, p < 0.0001$). Clinic and ambulatory blood pressures were also correlated, but to a much lesser degree; SBP correlation was $r = .606$ ($p < 0.0001$), and DBP correlation was $r = .484$ ($p < 0.007$).

The null hypothesis for Purpose 1 was that there is no difference between clinic, ambulatory, and central measurements of blood pressure. We must reject the null hypothesis and conclude that there is a significant difference between the three measurements. Central systolic and pulse pressure were significantly different from

clinical pressures ($p < 0.0001$), while central diastolic and mean arterial pressure were not significantly different. Diastolic ABP was the only ambulatory parameter that was significantly different from the clinic BP ($p < 0.05$), however, the point estimate of the difference was 4 ± 3 mmHg is less than the a priori clinically significant value of 5 mmHg.

Purpose 2: To Determine the Circadian Systolic and Diastolic BP Parameters of INVEST Patients

Independent sample paired t-tests were used to assess the null hypothesis that there is no difference between the daytime and nighttime measurements for each BP parameter. Systolic ($t = 4.285$, $df = 29$, $p < 0.0001$), diastolic ($t = 4.414$, $df = 29$, $p < 0.0001$), and mean arterial pressure ($t = 3.984$, $df = 29$, $p < 0.0001$) all showed a significant difference greater than 5 mmHg. Table 4-6 summarizes the findings for circadian characteristics. Pulse pressure ($t = 2.015$, $df = 29$, $p < 0.053$) was not significantly different between daytime and nighttime. Although approaching statistical significance, the mean PP difference of 2 ± 1 mmHg was not clinically significant. Heart rate ($t = 2.212$, $df = 29$, $p < 0.035$) was significantly different with a drop of 2.3 ± 2 bpm. It is not known whether this amount of drop is clinically significant. BP variation as defined by average systolic BP standard deviation was significantly different ($t = 3.576$, $df = 29$, $p < 0.001$) from day to night with an average difference of 3.2 ± 1.8 mmHg. Diastolic variation was not statistically significant ($t = 1.919$, $df = 29$, $p < 0.065$). Heart Rate variation was significantly different ($t = 4.645$, $df = 29$, $p < 0.0001$) with a mean difference of 3.2 ± 1.4 bpm. Finally, there are approximately three times as many readings during daytime as there are during nighttime.

Out of 4309 ABP readings, 1620, fully 38% of all ABP readings were errors. There were 2310 daytime readings, of which 923 (40%) were errors. There were 995 nighttime readings, with 331 errors, an error rate of 33%.

With regard to the null hypothesis for purpose 2, that there is no difference between Daytime and Nighttime values for systolic and daytime blood pressures, we must reject the null hypothesis and conclude that there is a statistically significant drop from daytime to nighttime pressures. The study showed that, on average, subjects had a nocturnal drop in MAP and DBP of approximately 6 ± 3 mmHg. Nocturnal systolic drop was 8 ± 4 mmHg. Table 4-5 shows that although all of these are statistically and clinically significantly, no blood pressure parameter meets the 10% drop criteria to be considered a nocturnal dipper.

Table 4-5: Estimated Difference Between Daytime and Nighttime Measures (Mean \pm 2SE)

	Mean of (Day – Night)	Percentage Drop	C _v (%) (SE/Mean)
Systolic (mmHg)	8.2 \pm 3.8**	6%	23%
Diastolic (mmHg)	6.2 \pm 2.8**	9%	23%
Mean (mmHg)	6.6 \pm 3.2**	7%	25%
Pulse (mmHg)	2.0 \pm 2.0 [†]	3%	50%
Heart Rate (bpm)	2.3 \pm 2.0 [†]	4%	45%
Systolic Variation (mmHg)	3.2 \pm 1.8*	23%	28%
Diastolic Variation	1.2 \pm 1.2	13%	52%
Heart Rate Variation (bpm)	3.2 \pm 1.4**	46%	22%
Number of readings	33.2 \pm 4.6**	68%	7%

Positive differences indicate a drop in the measurement from day to night. **Denotes significant difference at $p < 0.0001$. *Denotes significant difference at $p < 0.05$.

[†]Denotes statistical significance that is not considered clinically significant (i.e. < 5 mmHg). It is important to note that this criterion is not applied to the differences in BP variation, as the clinically significant variation is not known.

Purpose 3: Characterize the Central Hemodynamic Parameters for Patients Participating in INVEST Augmentation Index and of Patients Participating in INVEST

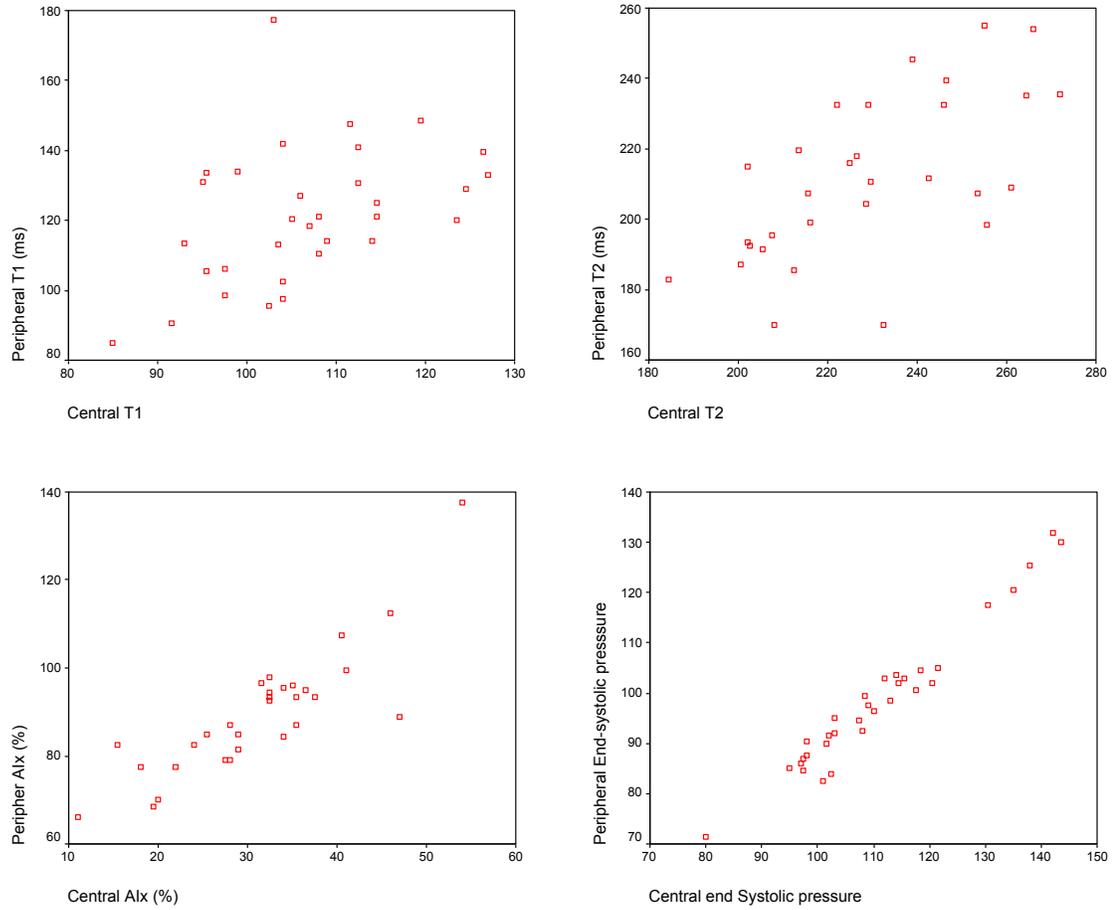
Central hemodynamic blood pressures are listed in Table 4-6. The mean heart rate was 61 ± 4 bpm. Mean SEVR was $172 \pm 14\%$. Mean ejection duration was $32 \pm 2\%$ of the cardiac period. End systolic pressure was 111 ± 3 mmHg. Central SBP was 124 ± 6 mmHg, while systolic mean pressure (average pressure through systole) was 109 ± 4 , a difference of 15 ± 1.2 mmHg ($t = 25.455$, $df = 31$, $p < 0.0001$). However, the two measurements were highly correlated ($r = 0.986$, $p < 0.0001$). Central DBP was 74 ± 4 mmHg, while diastolic mean pressure (average pressure through diastole) was 86 ± 4 , a difference of -12 ± 1.2 mmHg ($t = -18.589$, $df = 31$, $p < 0.0001$). Again, the two measurements were highly correlated ($r = 0.958$, $p < 0.0001$). The mean Augmentation Index was $31 \pm 4\%$. When normalized for a constant heart rate of 75 bpm, the mean fell to $24 \pm 2\%$, a difference of $6 \pm 2\%$ ($t = 6.633$, $df = 30$, $p < 0.0001$). The two measurements of augmentation were highly correlated ($r = 0.827$, $p < 0.0001$).

Purpose 4: To Compare the two Treatment Strategies in INVEST in Terms of Differences Between 24-Hour, Daytime, and Nighttime BP Values and BP Variability

Paired t-tests were used to analyze the differences between treatment strategies. The only differences that were significant at the .05 level were daytime MAP, nighttime HR, and nighttime SBP SD. However, with Bonferroni's ($0.05/42 = 0.001$) adjustments for the number of tests performed in this segment, there were no statistically significant differences. It is important to note that the small sample size limits the usefulness of these tests as shown by the very large coefficient of variation (C_v). Thus regarding the null hypothesis for purpose 4, that there is no difference between the INVEST groups, we cannot reject the null hypothesis and conclude that there is not enough evidence to suggest that the groups are different.

Table 4-6: Mean \pm 2SE for Central Hemodynamic Blood Pressures

	Mean \pm 2SE	Minimum	Maximum	SD	N
Peripheral SBP (mmHg)	135 \pm 6	96	170	17	30
Peripheral DBP (mmHg)	73 \pm 4	58	100	11	30
Peripheral MAP (mmHg)	93 \pm 4	71	128	13	30
Peripheral T1 (ms)	121 \pm 6	85	178	19	30
Peripheral T2 (ms)	212 \pm 8	170	255	23	30
Peripheral Alx (%)	90 \pm 6	66	138	14	30
Peripheral ESP (mmHg)	99 \pm 4	72	132	14	30
Peripheral P1 (mmHg)	134 \pm 6	96	170	17	30
Peripheral P2 (mmHg)	127 \pm 6	90	157	18	30
PT1 duration (%)	38 \pm 2	24	51	6	30
PT2 duration (%)	66 \pm 2	53	74	5	30
SEVR (%)	172 \pm 14	102	263	38	30
HR (BPM)	61 \pm 4	38	84	12	30
Cardiac Period (ms)	1025 \pm 76	711	1610	216	30
Ejection Duration (ms)	319 \pm 12	248	384	32	30
Diastolic Duration (ms)	706 \pm 70	426	1253	196	30
Ejection Duration (%)	32 \pm 2	23	44	5	30
Diastolic Duration (%)	68 \pm 2	57	78	5	30
Central Pulse PP (mmHg)	50 \pm 4	28	72	10	30
Central Augmentation Pressure (mmHg)	15 \pm 2	6	28	6	30
Central Alx (%)	31 \pm 4	11	54	10	30
Central Alx normalize for HR75 (%)	24 \pm 2	14	43	8	30
Central P1 Height (mmHg)	35 \pm 2	14	52	8	30
Central TR (ms)	135 \pm 4	108	161	12	30
Central SBP (mmHg)	124 \pm 6	88	157	16	30
Central Systolic Mean BP (mmHg)	109 \pm 4	80	142	14	30
Central DBP (mmHg)	74 \pm 4	59	102	11	30
Central Diastolic Mean BP (mmHg)	86 \pm 4	66	118	12	30
Central MAP (mmHg)	93 \pm 4	71	128	13	30
Central T1 (ms)	107 \pm 4	85	127	10	30
Central T2 (ms)	226 \pm 8	183	272	25	30
Central AI (P2/P1)	148 \pm 8	112	223	23	30
Central ESP	111 \pm 6	80	144	15	30
Central P1 (mmHg)	109 \pm 4	81	141	14	30
Central P2 (mmHg)	124 \pm 6	88	157	16	30
CT1 duration (%)	34 \pm 2	25	44	4	30
CT2 duration (%)	71 \pm 2	64	78	3	30



Figures 4-2. Relationship of peripheral and central measures. T1 is the time to the first inflection point or shoulder of the pulse wave. T2 is the time to the second inflection point.

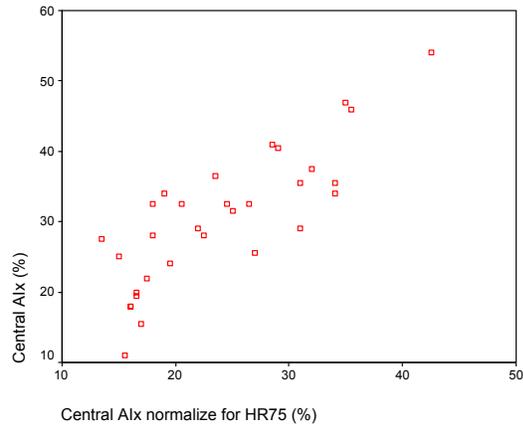


Figure 4-3. Relationship of AI to AI normalized for HR.

Table 4-7: Mean Difference between NCAS and CAS Arms of INVEST

	Mean Diff \pm 2SE*	t	df	Sig. (2-tailed)	C _v
Age	.4 \pm 7.2	.100	19	.921	1000%
Height (cm)	.7 \pm 7.2	.203	18	.841	492%
Mass (kg)	4.0 \pm 12.4	.636	24	.531	157%
BMI (kg/m ²)	.9 \pm 4.6	.404	20	.691	248%
Clinical SBP (mmHg)	-9.4 \pm 11.4	-1.650	24	.112	61%
Central SBP (mmHg)	-6.7 \pm 11.4	-1.172	24	.253	85%
24 hour SBP (mmHg)	-6.2 \pm 9.4	-1.321	25	.198	76%
Daytime SBP (mmHg)	-7.0 \pm 9.6	-1.445	25	.161	69%
Nighttime SBP (mmHg)	-2.7 \pm 11.4	-.470	25	.643	213%
Clinical DBP (mmHg)	-5.2 \pm 8.6	-1.210	17	.242	83%
Central DBP (mmHg)	-5.3 \pm 9	-1.179	17	.255	85%
24 hour DBP (mmHg)	-6.2 \pm 6.0	-2.042	21	.054	49%
Daytime DBP (mmHg)	-6.5 \pm 6.6	-1.973	20	.062	51%
Nighttime DBP (mmHg)	-4.1 \pm 7.4	-1.125	23	.272	89%
Clinical MAP (mmHg)	-6.6 \pm 8.8	-1.497	19	.151	67%
Central MAP (mmHg)	-6.0 \pm 10.4	-1.149	18	.266	87%
24 hour MAP (mmHg)	-6.7 \pm 6.8	-1.981	22	.060	50%
Daytime MAP (mmHg)	-7.5 \pm 6.2*	-2.096	22	.048	48%
Nighttime MAP (mmHg)	-3.6 \pm 8.4	-.846	23	.406	118%
Clinical PP (mmHg)	-4.2 \pm 8.2	-1.023	27	.315	98%
Central PP (mmHg)	-1.5 \pm 6.6	-.446	28	.659	224%
24 hour PP (mmHg)	.0 \pm 7.6	-.003	20	.998	34347%
Daytime PP (mmHg)	-.5 \pm 8.2	-.125	20	.902	798%
Nighttime PP (mmHg)	1.4 \pm 7.4	.382	21	.706	262%
Heart Rate (bpm)	-6.8 \pm 8.0	-1.677	21	.108	60%
24 hour HR (bpm)	-6.2 \pm 6.6	-1.889	20	.073	53%
Daytime HR (bpm)	-6.1 \pm 7.8	-1.781	21	.089	56%
Nighttime HR (bpm)	-7.6 \pm 7*	-2.189	16	.043	46%
24 hour HR SD (bpm)	.6 \pm 1.8	.675	27	.505	148%
Daytime HR SD (bpm)	.6 \pm 2.0	.566	26	.576	177%
Nighttime HR SD (bpm)	.7 \pm 1.4	.940	22	.357	106%
24 hour SBP SD (mmHg)	1.1 \pm 2.0	1.047	28	.304	96%
24 hour DBP SD (mmHg)	1.1 \pm 1.4	1.626	28	.115	61%
24 hour MAP SD (mmHg)	1.0 \pm 1.6	1.323	28	.197	76%
Daytime SBP SD (mmHg)	.8 \pm 2.2	.749	28	.460	134%
Daytime DBP SD (mmHg)	1.2 \pm 1.6	1.627	28	.115	61%
Daytime MAP SD (mmHg)	1.2 \pm 1.8	1.257	27	.219	80%
Nighttime SBP SD (mmHg)	3.2 \pm 2.8*	2.300	23	.031	43%
Nighttime DBP SD (mmHg)	1.1 \pm 2.0	1.165	18	.259	86%
Nighttime MAP SD (mmHg)	1.1 \pm 2.0	1.073	23	.294	93%
Number of ABP readings	.8 \pm 8.0	.207	23	.838	484%
Number of Daytime ABP readings	-.8 \pm 8.6	-.173	16	.865	578%
Number of Nighttime ABP readings	1.6 \pm 4.8	.652	15	.525	153%

*Means are NCAS-CAS. Positive readings indicate that the NCAS has a higher mean than CAS group.

CHAPTER 5 DISCUSSION AND CONCLUSIONS

All descriptive and analytic results that addressed each research hypothesis are discussed in this chapter. Conclusions and implications for clinical practice as well as recommendations for future research also are provided.

Discussion of Results

Demographics

Sixty-four percent of the subjects in the study were men, compared with approximately 48% in the overall INVEST population (Pepine et al., 1998). Seventy-six percent were white, 10% black, 3% Asian, and 10% Hispanic, compared to 48.3% white, 13.4% black, 35.7% Hispanic, 0.7% Asian, and 1.9% other in the overall INVEST population. Seventy percent were above the age of 65, compared with 50.7% for INVEST. Only 7% were diabetic compared with 22.6% reported for INVEST (Pepine, in press). Sixty-four percent were on a lipid-lowering agent, while only 27% had documented dyslipidemia. Thirty percent were on a nitrate other than sublingual nitroglycerine.

Clinical Characteristics

Of the 30 subjects who completed the study protocol and were included in the analysis, 37% were taking a calcium channel blocker at the study visit. Meanwhile, 47% of subjects taking a beta blocker. These numbers do not add up to 100% because INVEST protocol allowed the subjects' physicians to customize hypertensive therapy based on individual patient needs, first using the three drugs provided in each strategy

and then additional hypertensive therapy could be added so long as the strategy was maintained. Thus, if a patient were intolerant to atenolol, trandolapril and/or HCTZ could be used in its stead to maintain the noncalcium antagonist strategy. This explains the missing 16%. The treatment groups for INVEST are based on intention to treat.

The mean BMI was 28.6 ± 5.8 . (Note: All summary statistics are given as mean \pm SD—standard deviation—while all figures used for estimation are given mean \pm 2SE—standard error.) This indicates that the average subject was overweight but not obese by National Institutes of Health obesity guidelines (Obesity Education Initiative, 1998).

Purpose 1: To Determine the Difference Between the Clinic Measurements, ABPM Measurements, and Calculated Central BPs in Patients Participating in the Invest

The null hypothesis for Purpose 1 was that there is no difference between clinic, ambulatory, and central measurements of blood pressure. We must reject the null hypothesis and conclude that there is a significant difference between the three measurements. Central systolic and pulse pressure were significantly different from clinical pressures ($p < 0.0001$), while central diastolic and mean arterial pressures were not significantly different. Diastolic ABP was the only ambulatory parameter that was significantly different from the clinic BP ($p < 0.05$); however, the point estimate of the difference was 4 ± 3 mmHg, so its clinical significance is somewhat dubious.

Central and clinic differences

Despite the large difference between central and clinic SBP (10 ± 2 mmHg), the highly linear relationship between them casts some doubt into the significance of this finding. If this relationship can be generalized to the larger INVEST population, central systolic pressure could simply be estimated by subtracting 10 mmHg from the clinic blood pressure. This finding agrees with the conclusions of Cameron, McGrath, and Dart

(1998), who concluded that the use of a generalized transfer function (GTF) was unnecessary, and simple linear relationships would suffice for the calculation of central blood pressure parameters. It is important to note that in both the current study and the study by Cameron, et al. (1998), the population studied was an average of 60 years or older (66 years for the current study). Nichols and O'Rourke (1998) acknowledged that in patients over the age of 60, brachial clinic BP is a good estimate of central BP.

Figure 4-1 shows that central diastolic pressure was essentially in unity with clinic DBP. Central mean arterial pressure was strongly related to clinic MAP. Of all the parameters, pulse pressure showed the weakest relationship between central and clinic measures, but was still very strong at $r = .908$ ($p < .0001$). Using MAP and PP in analysis instead of SBP and DBP may be useful in helping to tease out the clinically significant relationships, as it is more representative of steady and pulsatile pressure (O'Rourke, 1983, 1999), as opposed to merely recording the minimum and maximum values of the pressure wave. The limited scope of this study does not permit any conclusions about such speculations.

Ambulatory and clinic differences

Figure 4-1 shows that the relationship of clinic to ambulatory blood pressures is far less linear. The correlations for SBP and DPB are $.6$ ($p < .0001$) and $.5$ ($p < .007$), respectively. This agrees with Mancia and Parati (2000) who concluded that the correlation of clinic and ambulatory pressures are rarely greater than $.5$ for either SBP or DBP. Despite the lack of linear relationship, there was no significant difference seen between the clinic and ambulatory pressures, except DBP, where the mean difference was 4 ± 3 mmHg. The point estimate is less than 5, the *a priori* minimum clinically significant difference, although the 95% confidence interval is from 1 to 7 mmHg.

Certainly this cannot be cited as evidence of a large difference in ambulatory and clinic blood pressures. Because this study was cross sectional in design, it cannot evaluate Mancia and Parati's claim that ABP is three times as reproducible as clinic blood pressure. However, the standard error was consistently smaller than that of the other two methodologies, sometimes by as much as half.

Circadian Characteristics

The study showed that on average, subjects had a nocturnal drop in MAP and DBP of approximately 6 ± 3 mmHg. Nocturnal systolic drop was 8 ± 4 mmHg. Table 4-5 shows that although all of these are statistically and clinically significant, no blood pressure parameter meets the 10% drop criteria to be considered a nocturnal dipper. It is important to note that fixed day/night definitions were used (daytime: 0900-2100; nighttime: 0000-0600), and that individually determined definitions show larger dipping differences (May, Arildsen, & Damsgaard, 1998). This limitation was due to a large number of subjects who did not return their activity diaries with the blood pressure monitor. A further limitation was that the fixed definition of day was twice as long as the night. Moreover, the definition of daytime and nighttime excludes the hours of 0600 to 0900, the time of early morning blood pressure rise and coincident increase in cardiovascular events. However, as Mancia and Parati (2000) noted, the early morning rise in blood pressure is not useful either as a diagnostic tool or as a treatment goal. There were three times as many daytime readings as nighttime readings, instead of the anticipated twice as many. However, looking at the rate of failed readings—40% during daytime versus 33% during nighttime—one would assume that there should be a higher than anticipated ratio of nighttime to daytime readings. The answer to this lies in the total number of daytime and nighttime readings—several subjects simply turned off the

monitor sometime during the night. This underscores the importance of Schwan and Pavek's findings (1989) that nocturnal blood pressure is not a reliable measure.

Moreover, Omboni et al. (1998) showed that repeated ABP measurements showed as much as a 40% change in dipping status from night to night. Because of the difficulty in getting subjects in this study to wear the monitor once, much less twice, it is impossible to verify the assertion of Omboni, et al. However, systolic blood pressure variability and heart rate variability dropped by 23% and 46%, respectively. The significance of this reduction has not been established.

The high number of failed readings during both day and night reflects the inherent oxymoron of ambulatory monitoring. In order to take the blood pressure, the patient must remain still. Any movements, whether walking, arm motion, or even talking can cause a failed reading. This reinforces this author's belief that the true value of ABP is in the increased number of measurements rather than any actual diurnal pattern. Thus, ambulatory monitoring is not truly ambulatory. The number of failed readings compromised the data only in one patient at nighttime, and this is primarily because the patient took the monitor off. The monitor reattempts failed readings after a 2-minute delay, so the number of failed readings is not indicative of the total number of readings.

Despite the limitations of this study, it is quite apparent that there was a clinically significant drop in blood pressure for SBP, DBP, and MAP, but that none of these was considered great enough to classify the subjects as dippers. Because this study was conducted after the randomization procedure for INVEST, it is impossible to know how nocturnal reduction changed after beginning treatment.

Central Hemodynamics

This study represents the first use of applanation tonometry and noninvasive measurements of central hemodynamic parameters in a subset of a large randomized hypertension trial. As such, there are no published data with which to compare the data at this time. It is important to note that 35 tonometry-derived parameters are reported, of which 11 are peripheral readings, with the remainder being calculated central measures. Figure 4-2 shows the relationship of various peripheral and derived central measurements. The only measurements showing a strong linear relationship, similar to that of central and clinic SBP (as previously discussed above), was end-systolic pressure ($r = .98$, $p < 0.0001$).

A small but significant inverse correlation between HR and AI has been reported by previous observational studies (Cameron et al, 1998; Yasmin & Brown, 1999). A moderate and inverse linear relationship between HR and AI with incremental pacing has also been reported (Wilkinson et al., 2000). In this study, the level of HR and AI did display a significant, but weak, inverse linear relationship ($r = -.6$, $p < .0001$). Tsai (2001) found that AI seemed to be more closely related to gender and age than to SBP or BMI, indicating that perhaps AI is more a function of age than hypertension. The influence of gender was not evaluated for this study. The Sphygomocor software automatically calculates the AI normalized to an HR of 75 bpm. There was no correlation between HR and AIHR75; furthermore, adjusting AI for HR reduced the 95% confidence interval length by half, from $\pm 4\%$ to $\pm 2\%$. The average AI when adjusted for HR was $24 \pm 2\%$, and the minimum was 14%. Thus, the average INVEST subject would be considered to have a Type A pulse wave contour according the Murgu classification scheme.

The average SEVR was $172 \pm 14\%$, indicating that the subjects are not likely to suffer from coronary ischemia due to a lack of diastolic driving perfusion pressure combined with an elevated tension-time index. The relatively low average heart rate of 60 ± 4 bpm most likely helps to contribute to the high SEVR in this study. The ejection duration took up a mean of $32 \pm 2\%$ of the cardiac cycle, giving an ejection/diastole ratio of 1:2. This has been described as an ideal ratio, with ejection taking up approximately a third of the cardiac cycle (Nichols & O'Rourke, 1998).

The other central hemodynamic parameters such as time to the first and second inflection points (T1, T2) and pressure at those inflections (P1, P2) are also reported. These parameters are used to calculate SEVR, and augmentation index, but are probably not clinically significant in and of themselves.

Comparisons of INVEST Treatment Strategies

This purpose proved impossible to assess in the given study simply due to the small sample size, resulting in very large coefficients of variation for the differences between the groups, as Table 4-7 shows. To determine the differences in these parameters, the sample size would need to be at least four times larger to detect any differences.

Conclusions

In this population of patients with coronary artery disease and hypertension, central and clinic blood pressures had very strong linear relationships across the board, with SBP and PP being significantly different. However, due to the very strong linear relationship, it was unclear as to whether the generalized transfer function was truly necessary or whether a simple linear correction can be used in subjects over the age of 55. With regard to ambulatory pressure, the only parameter that was significantly different from clinic pressure was DBP, but even then the difference was not clinically significant. The

correlation of ambulatory to clinic pressure is similar to that of previously reported studies.

There was a drop in nocturnal BP, but not enough for the subjects to be considered *dippers*. This might reflect the wearing off of blood pressure lowering medications throughout the night, or because of the lack of baseline data, may simply indicate that these patients are, in fact, nondippers. The reduction in blood pressure variability certainly indicates that the study population is most likely highly reactive to stressors throughout the day.

The AI adjusted for HR was 26%, indicating that the INVEST subjects had Type A pulse wave contours and a quarter of their central pulse pressures were due to wave reflection. The SEVR was relatively high at 174% indicating that the augmented systolic pressure was not affecting coronary perfusion. Ejection duration was appropriate at one third of the cardiac cycle.

No conclusion could be made about the differences between groups due to the small sample size.

Implications for Clinical Practice

The main implication for clinical practice is that in patients over the age of 60, central blood pressure can be estimated by simple linear relationship to clinic blood pressures, obviating the need for expensive tonometry equipment. The significance in younger patients cannot be determined from this study. The simple linear relationships found in the current study and by Cameron et al. (1998) may or may not be found in younger populations. With the current trend to treat high blood pressure in younger patients, knowing the impact of central blood pressure on mortality and long-term vascular complications remains an important area of research.

Until more research is done, it will not be known whether the other tonometry derived measures such as SEVR, AIX, and ejection duration will prove to be significant in reducing organ damage associated with high blood pressure. Implementing tonometry into practice should be very simple, although it does take more time to execute than a simple clinic blood pressure. The main obstacle in its widespread adoption is the price and the dubious clinical value of the derived central measures.

When first researching ambulatory blood pressure, it seems to be a panacea for all of the faults of traditional blood pressure readings. It eliminates operator bias, is more reproducible, is not significantly affected by placebo, and eliminates white coat hypertension (Mancia & Parati, 2000). Yet, in the JNC VI guidelines (1997), it is only indicated in a few circumstances and not for general follow-up. The reason for this apparent dichotomy of usefulness and recommended usage becomes very clear when using the ABP monitors. Only one unit can be used on any given day for one subject, and if that subject was seen late in the day, then the unit may be out of commission for 2 days. Furthermore, subjects who live more than 20 minutes away may be unwilling to come back to the office to return the monitor. This happened several times during this study. Two subjects kept a monitor for more than 2 weeks. After 2 weeks one of the monitors was returned with no usable data on it but just a long series of failed readings. (These were not included in the number of failed readings reported in Chapter 4.) To get around this logistic problem, subjects who lived more than 30 minutes away from the clinic were given self-addressed stamped boxes to mail back the monitors. The problem with this approach was that quite often monitor accessories such as the waist strap were missing upon receipt of the mailed box.

Subjects were instructed in the use of the monitor and given an information sheet with frequently asked questions and troubleshooting information, and this researcher's phone number. Yet, there were numerous complaints of not being able to use the monitor correctly. Some subjects complained that they had to wear their clothes the whole time and that the inconvenience of not being able to take a shower was aggravating. Others complained about not being able to roll over due to the monitor being strapped to their waists at night. Such complaints that were clearly contrary to the operating instructions were much more common in subjects above the age of 65, although young age was no guarantee of a low percentage of failed readings. Five subjects felt strongly enough about their experience that they included notes detailing their discontent with the ABP monitors and refused to wear the monitor again. Several other subjects related that they dreaded the thought of having to wear the monitor again.

Based on these experiences, this researcher cannot recommend that ABP be used on a widespread basis and agrees with the JNC VI (1997) recommendations that ABP be used only for selected purposes, such as evaluating white-coat hypertension.

As for the profession of nursing, neither ABP nor applanation tonometry will supplant brachially measured clinic blood pressures for years to come. It is more critical than ever that nurses use proper technique in measuring blood pressure. The seemingly simple things, such as having the subject rest for 5 minutes, having back supported, having arm supported at heart level, and using the right size cuff, can make quite a difference in the measurement of blood pressure. However, nurses must always remember that blood pressure is much more than two numbers recorded on a page, much more than the peak

and trough of a periodic wave. Nurses must be trained to understand the inherent nature of blood pressure's relationship to central and muscular arteries.

Recommendations for Further Research

A limitation of this study is the lack of baseline ABP and tonometry data. INVEST had been running for 4 years at the time data collection for this study began, making the collection of baseline data an impossibility. This study was conducted to provide data regarding the comparability of different blood pressure measurement methods. It is recommended that ABP and tonometry would be a useful tool in future large clinical trials to correlate changes from baseline BP parameters and to evaluate the effect of treatment on BP parameters and how they ultimately effect end organ function.

The question raised by the HOPE trial (Dagenais et al., 2001) is whether some blood pressure medications can have a beneficial effect on coronary artery disease that is greater than can be attributed to the blood pressure alone. Nichols and O'Rourke (2001) contend that perhaps the benefit was from lowered central blood pressure. The linear relationship found in this study lends weight to the HOPE trial's theory. However, due to the lack of baseline data, it cannot be determined whether the change in blood pressure due to treatment also exhibits the same linear relationship. Future studies based on the HOPE hypothesis such as the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (Yusuf, 2002) should implement a substudy comparison of clinic blood pressure to central blood pressure.

The accelerated timeline of this study, combined with a small number of ABP monitors (as described above), accounted for the small sample size. The small study size did not allow for any conclusions regarding comparisons of the two INVEST groups. Another limitation was the geographic bias, reflected in the ethnic make up of the study

participants. Both of these limitations can be avoided in future studies by including ABP and tonometry during the randomization process. The original study protocol called for two ambulatory blood pressure readings, but it quickly became apparent that this would not be possible, as more than half the enrolled subjects either refused outright to wear the monitor again or cited schedule conflicts. The limited timeline combined with the limited number of ambulatory blood pressure monitors did not allow enough repeated measurements to be able to analyze two ABP measurements. Patients had no inducement to continue the study; they were receiving free study medication for participating in INVEST, but their participation in this study was uncompensated. The lack of incentive plus the relatively short interval between ABP sessions are directly responsible for the high dropout rate. It is recommended that future studies compensate patients for the ABP use or make other study benefits contingent on wearing the ABP monitor, allow for a longer time between ABP sessions, so that patients have had time to forget how much they dislike wearing the monitor, and reduce the number of readings to every half hour during the day and every hour at night.

Summary

In this population there is a highly linear relationship between central and clinic blood pressures in regard to SBP, DBP, MAP, and PP. SBP and PP are significantly different using the two methodologies. It is not known whether central blood pressure changes linearly with changes in clinic pressure. There was no difference between ABP and clinic blood pressures, which demonstrated weak but significant linear relationships. A significant drop in nocturnal blood pressure was demonstrated, but the drop was not large enough to classify the subjects as dippers. No conclusions could be made about differences between the INVEST treatment groups due to the small sample size. Systolic

augmentation by wave reflection accounted for more than 30% of systolic pressure. The increased pressure was not likely to cause subendocardial ischemia according to the average SEVR. Recommendations for future studies are offered:

1. Replicate the study on a larger scale with enough time for baseline data.
2. Determine whether the simple linear relationships found here between central and clinic BP are also found in younger hypertensive populations.
3. Include tonometry and ABP at the randomization phase of future studies to allow these additional data to be correlated to changes in clinic BP.
4. Give incentive to participants to continue ABP use, and allow a longer interval between repeated ABP sessions.

Emerging Trends

Blood Pressure by Any Means Necessary

There are two schools of thought among science and medical community concerning blood pressure reduction. The first is that blood pressure reduction by any means is effective in reducing mortality. This belief is supported by predictive models that show no plateau or J-curve in the risk reduction with blood pressure reduction (Glynn, L'Italien, Sesso, Jackson, & Buring, 2002). One pharmaceutical company even has brochures advocating “going the extra millimeter.” This theory has garnered recent support by the results of the ALLHAT study that showed no difference between treatment arms of an ACE inhibitor, calcium channel blocker, and a thiazide diuretic (ALLHAT Collaborative Study Group, 2002). However, it should be noted that this same study also undermines the theory, since a fourth treatment arm with an alpha-receptor blocker was discontinued due to a high incidence of cardiovascular events.

The second school of thought states that not only is blood pressure reduction important, but the method of blood pressure reduction is just as important because the

underlying physiological mechanism is what truly matters. This belief touts the HOPE trial a shining example. Patients treated with a “tissue” ACE inhibitor exhibited huge decreases in incidence of heart attack and other cardiovascular events—decreases much larger than would be expected by the modest blood pressure reductions (Dagenais et al., 2001). However, it must be remembered that the HOPE trial was not a blood pressure trial. Patients enrolled in it were either normotensive or had hypertension *already controlled* by other classes of drugs.

Unfortunately, no clinical trial to date has adequately resolved this dilemma. It is hoped that the tools of ambulatory blood pressure and arterial tonometry will help us reconcile these two schools of thought.

Vive le Difference

Over the years, a growing concern has been coronary artery disease in women. Large advertising campaigns have been launched in the media to raise awareness in the United States that coronary artery disease is the highest killer of women in the United States and that heart attacks are more likely to be fatal in women. It has also become apparent that science does not understand fully the differences in pathophysiology of heart disease between the sexes. However, the WISE study has shown that men tend to suffer from blockages of the large coronary arteries, while women tend to suffer from ischemia in the smaller coronary vessels (Reis et al., 2001). The implications of this are not fully understood, but it is this author’s opinion that it may indicate that the Subendocardial Viability Ratio may be more important in women than in men.

Cost of Entry: A Final Word on Applanation Tonometry and ABP

The cost of these two technologies is prohibitive at this juncture and is truly the largest obstacle to their widespread adoption. A tonometry unit costs between \$12,000 and

\$16,000, while an ambulatory blood pressure monitor costs about \$2,000. However, one tonometry unit can be used on as many subjects or patients who come into the clinic in a given day, thus making its cost per patient less than ABP. In order to collect data on five patients in a day, five ABP monitors are necessary. It is easy to see that this can quite quickly become expensive. It is also unclear as to why the ABP monitors cost so much money. They are simply small automatic BP machines with a programmable memory chip. If they were less expensive, say \$100, it would be possible for patients to buy their own monitors, which they could wear for a few hours or 24 hours and then bring it to their doctor's offices to be read. In fact, the software is able to download the monitor's data over the phone. Economies of scale would certainly make up the difference in lost revenue due to the lower price.

The software of both Sphygmocor and ABP report manager needs to be updated. The Sphygmocor software needs to allow users the option of exporting dates in an MDY format to avoid the manual correction described in Chapter 3. Moreover, when the data are exported, hemodynamic parameters are given cryptic 2-6 letter abbreviations that are sometimes not at all obvious as to what they represent. Some parameters are repeated multiple times. There is no documentation as to what these codes represent. In order to analyze the results, this researcher had to compare the exported data with multiple Sphygmocor reports looking for corresponding fields. The export function needs to use more descriptive fields as well as documenting what each field represents. The ABP Reports Manager software was similarly lacking. The software as it is currently designed is only meant to print reports on an individual ABP session for one patient. Sessions are stored as separate files in a proprietary format. The software needs to be redesigned so

that sessions are stored in a relational database. This will allow multiple sessions from the same patient to be analyzed. It also needs to be able to export selected sessions to an external database. Additionally, there were several combined fields that would have been better if they were separated, such as the reading number and any modifier codes indicating whether the reading was regular, manual, or a retry. These changes will enable future research to go much more smoothly and will help to eliminate errors in data entry and management.

APPENDIX A
CONSENT DOCUMENT

IRB# _____

Informed Consent to Participate in Research

**The University of Florida
Health Science Center
Gainesville, Florida 32610**

You are being asked to take part in a research study. This form provides you with information about the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Your participation is entirely voluntary.

1. Name of Participant ("Study Subject")

2. Title of Research Study

Comparison of Non-Invasive Blood Pressure Methodologies: A Substudy of The International Verapamil SR/Trandolapril Study (INVEST).

3. Principal Investigator and Telephone Number(s)

Eileen Handberg, PhD, ARNP (352-846-0612)

4. Source of Funding or Other Material Support

Abbott Inc.

5. What is the purpose of this research study?

The purpose of this study is to collect additional blood pressure measurements that may provide useful information in order to improve the way health care practitioners treat patients with high blood pressure and heart disease.

6. What will be done if you take part in this research study?

You are being approached to participate in this research study because you have high blood pressure and coronary artery disease and are participating in INVEST. Once the study is explained to you, and if you wish to participate, you will be asked to sign this consent form.

Your participation will require you to take part in the following testing procedures: On two occasions, you will be asked to wear a blood pressure monitor for 24 hours. When you wear the blood pressure monitor, you will be asked to keep a simple journal that tells what kind of activity you were doing when the cuff inflates. Additional measurements of your blood pressure will be taken using a different method. Tonometry readings use a device that looks like a blunt pencil. It will be pressed gently against the arteries in your wrist, neck, and groin for a few seconds to measure the pressures there. These will be taken in clinic on the days you have the blood pressure monitor placed. The procedures takes about 15 minutes.

7. What are the possible discomforts and risks?

The 24 hour blood pressure machine will take readings every 20 minutes. This may cause some discomfort as it inflates. There are no risks above your ordinary daily life risks. There are no risks associated with the tonometry measurements.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, you may ask questions now or call the Principal Investigator or contact person listed on the front page of this form.

8a. What are the possible benefits to you?

You will be given a copy of the blood pressure readings. These may assist your doctor in treating your blood pressure and coronary artery disease.

8b. What are the possible benefits to others?

As we understand high blood pressure and its relationship to coronary artery disease better, we may be able to treat patients with high blood pressure better, causing them to live longer and with fewer complications like heart attacks and strokes.

9. If you choose to take part in this research study, will it cost you anything?

No

10. Will you receive compensation for taking part in this research study?

You will receive a copy of the blood pressure readings.

11. What if you are injured because of the study?

If you experience an injury that is directly caused by this study, only professional medical care that you receive at the University of Florida Health Science Center will be provided without charge. However, hospital expenses will have to be paid by you or your insurance provider. No other compensation is offered.

12. What other options or treatments are available if you do not want to be in this study?

You are free not to participate in this study. Alternative treatment would be to continue with standard medical therapy currently available as decided by your doctor.

13a. Can you withdraw from this research study?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty, and you will not lose any benefits you are entitled to.

If you decide to withdraw your consent to participate in this research study for any reason, you should contact Eileen Handberg, PhD, ARNP at (352) 846-0612.

If you have any questions regarding your rights as a research subject, you may phone the Institutional Review Board (IRB) office at (352) 846-1494.

13b. If you withdraw, can information about you still be used and/or collected?

No further information will be collected on you, but information that has already been collected will still be used in the analysis.

13c. Can the Principal Investigator withdraw you from this research study?

You may be withdrawn from the study without your consent for the following reasons:

If you are unable to tolerate, or there is a contraindication to wearing of the ambulatory blood pressure monitor.

14. How will your privacy and the confidentiality of your research records be protected?

Authorized persons from the University of Florida, the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect the confidentiality of them to the extent permitted by law. Otherwise, your research records will not be released without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

15. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals.

16. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how privacy will be protected:

Signature of Person Obtaining Consent	Date
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You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your privacy will be protected. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting	Date
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APPENDIX B
ABP DIARY

INVEST SUBSTUDY

Ambulatory Blood Pressure Instructions

The blood pressure cuff will inflate every twenty minutes.

If the machine does not get a good blood pressure reading, it will inflate again after two minutes. It will keep repeating until it gets a good reading.

The most common cause of bad readings are moving your arm while the machine is inflated.

When the cuff inflates, hold your arm still and let it hang by your side.

If you cannot let your arm hang still for an extended period of time (if you are driving for example), then the machine will try two more times and then wait for the next scheduled reading.

If you want to exercise or take a shower, wait until it finishes taking reading and then shower before the next reading. Do not forget to put the cuff back on when you finish your shower or exercising.

If you take longer than twenty minutes, the cuff will inflate while not on your arm. If this happens, press START/STOP, then unscrew the cuff from the machine and deflate the cuff. Then reconnect it and press START/STOP again.

Please wear the machine until _____ on _____. Then press the START/STOP button until it beeps and return the machine to the cardiology clinic.

If you have any problems or questions you can reach Pat Heyman at 352-281-3634.

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BIOGRAPHICAL SKETCH

Patrick Heyman was born in Gainesville, Florida. His parents became missionaries when he was six, and he spent the rest of his formative years in Liberia, Costa Rica, and Uruguay. After two years at the United States Air Force Academy, he transferred to Palm Beach Atlantic College where he received a Bachelor of Science in biology. After two years of working in the travel industry, Patrick enrolled at the University of Florida in the College of Nursing. While in school he supported himself by working as a ballroom and Latin dance teacher, donating his talents to charities including Stop Children's Cancer, Children's Miracle Network, and the American Heart Association.

Upon graduating with a Bachelor of Science in Nursing, Patrick was accepted to the newly formed, combined master/Ph.D program at the University of Florida. While in the master's portion, he worked as a research assistant in the College of Nursing's Office for Research Support where he was responsible for poster presentations, website design, database design and management, and electronic form automation. He also served on the Research and Evaluation Committee as a student representative. He completed his Master of Science in Nursing in 2000 and took a leave of absence to hone his clinical skills at the cardiovascular nursing unit at Shands at AGH. Patrick also used this time to obtain his license as an Advanced Registered Nurse Practitioner (ARNP) in the state of Florida and national board certification from the American Nurses Credentialing Center (ANCC). After an eight-month absence, he resumed his doctoral studies.

Upon returning to his studies, Patrick became involved in the International Verapamil/Trandolapril Study (INVEST) as co-investigator of the Ambulatory Blood Pressure Substudy. His involvement included drafting the protocol and Institutional Review Board (IRB) proposal, writing a grant, data collection, and write up of results. Patrick also began working at Gainesville Family Physicians during this time as an Adult Nurse Practitioner.

He will graduate in May 2003 from the University of Florida with his Ph.D. in nursing and minor in exercise physiology. He will continue to practice as a nurse practitioner while teaching as a part time faculty at the College of Nursing.