SYMPATHETIC INFLUENCES ON THE HUMAN HEART

SYMPATHETIC INFLUENCES ON THE HUMAN HEART: MEASUREMENT, CONTROL AND ROLE IN HYPERTENSION

by

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Abstract

The pathological consequences of even mild increases in blood pressure warrant treatment for hypertension in its early stages. However, chronic drug treatment programmes are generally not advantageous during the early stages of hypertension. Augmented sympathetic outflow to the heart plays a role in the early stages of hypertension, and perhaps the development of hypertension. Environmental factors are often responsible for increases in sympathetic outflow to the heart. Therefore, an alternative hypertensive treatment involves behavioural control over increases in sympathetic activity. This treatment includes biofeedback training. The literature indicates that the R-wave to ear pulse wave interval (RPI) is the most appropriate index of sympathetic influences for biofeedback training.

An experiment is reported in which unconstrained normotensive subjects were asked to produce changes in RPI with and without the aid of analog feedback. Five subjects learned to produce bidirectional changes in RPI. These subjects generally showed more RPI shortening than lengthening. The data indicate that moderately heavy levels of exercise were employed to shorten RPI. This is consistent with increased sympathetic activity. Some subjects were consistently able to lengthen RPI. However, this study produced converging evidence indicating that RPI lengthening was often a product of reduced left ventricular preload. Preload influences on RPI appear to have led subjects to adopt behavioural strategies which were inconsistent with

reduced sympathetic activity during attempts to lengthen RPI. Therefore, caution must be employed when using RPI to index and teach control over sympathetic activity. It is suggested that incorporating information about left ventricular ejection time or cardiac interbeat interval will improve RPI as a measure of sympathetic influences on the human heart.

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Abbreviations

DBP	Diastolic blood pressure
dP/dt	Change in pressure over time
EMG	Electromyogram
IBI	The cardiac interbeat interval which begins with the same R-wave that the RPI with which it is paired also begins
IBI+	The cardiac interbeat interval which ends with the R-wave that the RPI with which it is paired begins
ICI	Intercycle interval
MVT	Movement
RPI	Electrocardiogram R-wave to peripheral pulse wave interval
SBP	Systolic blood pressure
SC	Skin conductance
TPR	Total peripheral resistance
Vmax	Maximum cardiac contraction velocity

Chapter One

Introduction and Overview

This thesis examines issues concerning augmented sympathetic outflow to the human heart and issues concerning hypertension, since hypertension is a possible long-term consequence of augmented sympathetic outflow. Methods for assessing changes in sympathetic outflow to the heart are discussed. This thesis also addresses the prospect of teaching subjects to voluntarily control sympathetic activity through biofeedback as a means of reducing the risk of hypertension and diseases associated with this condition. An experiment is reported which explored the feasibility of this approach.

The thesis is organized into separate chapters dealing with (a) hypertension and mechanisms of blood pressure control, (b) the development of hypertension, (c) management of hypertension, and (d) an experiment on the learned control of cardiac sympathetic activity. The purpose of this introductory chapter is to give a brief overview of subsequent chapters dealing with these topics.

A. Hypertension and Mechanisms of Blood Pressure Control

Chapter 2 provides a definition of hypertension, and outlines the prevalence of hypertension, the pathological consequences of hypertension, and problems associated with the prevention of hypertension. In order to better understand hypertension, background information on cardiovascular physiology is provided. Intrinsic and neural control over blood pressure is also discussed.

Although hypertensives are a heterogeneous population, it appears that a large percentage of North Americans display elevations in blood pressure which have been associated with a variety of cardiovascular diseases. Since increases in blood pressure usually occur over protracted periods, two major concerns are the level of blood pressure at which drug treatment should begin, and the delineation of other factors which are predictive of future morbidity. For example, if patients who show larger, sympathetically mediated increases in cardiac output are more likely to develop sustained increases in diastolic blood pressure, then treatment should be directed towards this group of patients, when they show mild elevations in blood pressure.

Chapter 2 goes on to provide some background information on hemodynamics. Blood pressure level is shown to be a consequence of the rate at which blood is pumped into the arterial branches of the vasculature (cardiac output), and the amount of resistance which opposes the departure of blood from the arterial branches of the vasculature (total peripheral resistance). Since a variety of processes can produce changes in blood pressure, transient increases in blood pressure could result from many physiological changes. The kidneys and baroreceptors are responsible for the regulation of blood pressure, and their function must be reset if blood pressure increases are to be sustained for prolonged periods.

Chapter 2 also discusses the role that the autonomic nervous system plays in the control and regulation of blood pressure. The data indicate that the parasympathetic nervous system controls heart rate in resting subjects, and mediates reductions in heart rate that occur when

the baroreceptors sense an increase in blood pressure. Sympathetic outflow to the heart increases with increasingly strenuous exercise. The sympathetic nervous system appears to mediate increases in heart rate that occur when the baroreceptors sense a decrease in blood pressure. The sympathetic nervous system can increase blood pressure by increasing cardiac contractile force, by increasing vascular resistance, and by causing the kidney to retain water. In addition to exercise, a variety of environmental stimuli appear to be able to evoke sympathetically mediated increases in blood pressure, while subjects show minimal somatomotor activity.

B. The development of hypertension

Chapter 3 examines environmental conditions which evoke increased cardiac output. Data are provided which suggest that cardiac output may be a causal factor in sustained as well as transient hypertension. Mechanisms which could mediate the development of hypertension resulting from increased cardiac output are discussed.

In chapter 3 it is argued that the clinics in which blood pressure is assessed contain some of the environmental stimuli which evoke sympathetically mediated increases in blood pressure in resting subjects. The data reveal that borderline cases of hypertension often display excessive increases in sympathetic outflow in threatening environments. Data also suggest that borderline hypertensives have increased sensitivity to adrenergic neurotransmitters, and that they have a vagal dysfunction. These conditions often result in borderline hypertensives showing excessive increases in cardiac output. Data are reviewed which indicate that increased cardiac output is a precursor to

the development of sustained hypertension. Increased cardiac output is shown to precede sustained hypertension. In addition, the offspring of hypertensives also display excessive increases in cardiac output. This may be important, since the data indicate that hypertension may result from the combination of genetic and environmental factors. Finally, there is a discussion of animal studies which examine the effects of reduced cardiac output on blood pressure elevations in spontaneously hypertensive rats. However, the data from these studies are inconclusive. Therefore, excessive cardiac output cannot be directly implicated in the development of hypertension, but it remains a primary suspect.

Chapter 3 also includes a discussion of the mechanisms by which increased cardiac output, and other consequences of increased sympathetic activity, might produce sustained increases in blood pressure. Exercise is not associated with hypertension, but involves increases in cardiac output. Therefore, it is assumed that the mechanisms by which excessive cardiac output, and other consequences of increased sympathetic activity lead to hypertension, are not active during periods of exercise. Increased sympathetic outflow increases the availability of a number of nutrients which are metabolized during exercise. These nutrients may contribute to increased vascular resistance if left unmetabolized. For example, free fatty acids may enter the vascular walls causing a narrowing of the vascular lumen. Environmental stimuli which evoke increased sympathetic activity cause reductions in blood flow to the kidneys. However, these reductions do not occur during exercise. Extended periods of excessive cardiac output

also evoke reductions in blood flow to the skeletal musculature. These reductions in blood flow are the result of increased vascular resistance in these vascular beds. It has been hypothesized that the need to repeatedly increase vascular resistance eventually brings about structural change to permanently reduce blood flow. When this occurs in the renal vasculature, the kidneys are buffered from increased blood pressure. Therefore, their functioning is reset and sustained hypertension results. While these hypotheses are plausable, they still lack direct evidence. A better understanding of cardiovascular functioning is necessary if these hypotheses are to be adequately investigated. Meanwhile, the options for the treatment of hypertension remain limited.

C. The Management of Hypertension

Chapter 4 examines pharmacological and behavioural approaches to blood pressure control. The advantages and disadvantages of drug treatments are discussed. Procedures which are designed to result in learned control over increased sympathetic outflow to the heart are offered as alternative treatments. Measures of sympathetic influences on the heart are discussed. In addition, studies which examined learned control over one such measure are reviewed.

Chapter 4 begins with a discussion of the use of sympathetic beta-adrenergic receptor blocking agents in the treatment of hypertension. Beta-blockers reduce cardiac output. These drugs appear to be most effective in subjects who have mildly elevated blood pressures. There is some evidence that pharmacological reductions in blood pressure can reduce morbidity and mortality in patients with mild

hypertension. However, the percentage of those taking the drugs who are actually helped is quite small, especially in comparison to the percentage of those taking the drugs who experience adverse side effects. In addition, the cost of drug treatment for hypertension is quite high. Therefore, it seems worthwhile to investigate other forms of blood pressure control. At present, one potential form of blood pressure control is learned control over increased sympathetic outflow to the heart.

The first step in the examination of learned control over increased sympathetic outflow to the heart, is obtaining an adequate method of assessing changes in sympathetic activity. A number of invasive, and non-invasive techniques for assessing sympathetic activity are examined in Chapter 4. It is argued that a reliable, easily obtainable index of changes in sympathetic outflow to the heart, is desirable for use in biofeedback settings. The data indicate that the time interval which is initiated by the electrocardiogram R wave, and terminated by the arrival of the associated blood pulse wave at some peripheral site (RPI), might provide such an index.

Chapter 4 goes on to review the literature on the learned control over changes in RPI. Biofeedback training does not appear to aid resting subjects in RPI control, when they are told to keep still, and breathe normally. However, some evidence suggests that biofeedback training does aid in reducing sympathetic outflow to the heart under task conditions which normally evoke increases in sympathetic activity. Another problem is that most biofeedback training studies used an RPI measure that was terminated by the arrival of the pulse wave at the

subject's wrist. This measure appears to be sensitive to changes in vascular resistance, which could confound its relationship with sympathetic influences on the heart. These studies also involved verbal instructions which limited the strategies available to the subjects for producing RPI change. Biofeedback training might be more successful if subjects were given free reign to control the feedback display and if an improved measure of sympathetic as opposed to vascular effects was employed.

D. An Experiment on Learned Control of RPI Change

Chapter 5 begins with a discussion of some strategies subjects would be expected to employ when learning to produce changes in sympathetic outflow to the heart, in an unconstrained situation. An experiment is then described in which subjects were trained to produce bidirectional changes in RPI which is terminated at the ear, rather than at the wrist as in previous research. This modification was thought to favor domination of sympathetic contractile effects on RPI over vascular ones.

The study reported here found that some subjects were able to produce bidirectional changes in RPI. As expected, RPI shortening was often induced by engaging in moderately strenuous forms of exercise and reductions in respiration rate. Subjects were also expected to employ respiratory strategies to lengthen RPI. However, the relationships that were observed were unexpected. RPI was found to lengthen during long, deep inhalations, during which sympathetic outflow is assumed to have increased. In addition, small elevations of heart rate induced by light exercise were also associated with RPI lengthening. These findings seem

to indicate that intrinsic hemodynamic mechanisms were confounding the relationship between RPI and sympathetic activity. This confound led some subjects to increase their overall activity levels during attempts to produce elongations of RPI. Since these intrinsic loading factors have the potential to disrupt the processes of gaining learned control over sympathetic influences on the heart, chapter 5 concludes with some suggested methods for reducing the influences of loading factors on RPI.

The major intrinsic loading factor which disrupted the association between RPI and sympathetic outflow to the heart was preload. Preload refers to the amount of blood in the left ventricle of the heart, just prior to contraction. As preload increases, cardiac contractile force increases, and RPI is shortened. However, increases in preload are also associated with a lengthening of cardiac interbeat interval, and the length of the time period during which blood is pumped from the left ventricle. Both of these time intervals can be derived from the signals employed in the measurement of RPI. Therefore, information provided by changes in these variables could reduce the effects of loading factors on RPI. For example, when RPI is assessed alone, it is difficult to determine if RPI shortening reflects increased sympathetic outflow, or increased preload. However, the source of RPI variance might be determinable if cardiac interbeat interval is examined concurrently. If cardiac interbeat interval was shortened, then increased sympathetic activity was probably the cause of RPI shortening. On the other hand, if cardiac interbeat interval was lengthened, then increased preload was probably the cause of RPI shortening. Feedback training procedures could be devised, where subjects received only

information about RPI change, when cardiac interbeat interval changed in the same direction. This could reduce the disrupting effects of RPI changes caused by changes in preload. This is one example of a situation where the use of multiple measures of hemodynamics might be advantageous.

It appears that advances in hypertension research have been hampered by a preoccupation with blood pressure measurement, and the exclusion of other hemodynamic parameters and behavioural parameters. Only a small percentage of subjects who show increases in blood pressure into the hypertensive range, show subsequent larger increases in blood pressure. The pathological consequences of hypertension make the treatment of high blood pressure a necessity. However, if hypertension is to be prevented, then it must be possible to delineate at risk individuals accurately. Simply monitoring blood pressure is not going to increase predictive power. It is necessary to investigate a variety of physiological and behavioural parameters which may play a role in the development of hypertension. Further research into environmentally induced increases in sympathetic outflow, and the consequences of increased sympathetic outflow, could aid in the prediction, and prevention of hypertension.

Chapter Two

Hypertension and Mechanisms of Blood Pressure Control

Hypertension is defined as increased arterial blood pressure. Hypertension is often considered a condition which can be clearly distinguished from a state of normal arterial blood pressure (e.g. Canada Health Survey, 1981). However, there is no logical basis for making a distinction between normotensives and hypertensives (Kannel, 1977). Any cutoff point used to separate hypertensives from normotensives is arbitrary (Pickering, 1968). Diagnosing hypertension is also complicated by the fact that arterial blood pressure is variable, that is, it is not a static parameter (Pickering & Sleight, 1977). It appears that the risk of adverse consequences increases with increased blood pressure. However, it is generally accepted that in adults, systolic blood pressures above 140 mm Hg, or diastolic blood pressures above 90 mm Hg are in the hypertensive range (Canada Health Survey, 1981).

Studies have been undertaken to estimate the prevalence of hypertension using the 90 mmHg diastolic blood pressure (DBP) cutoff. A screening of one million Americans found DBP to be above 90 mm Hg in 20% of the population between the ages of 30 and 39, 29% of the population between the ages of 40 and 49, and 35% of those over 50 (Stamler, Stamler, Riedlinger, Algera & Roberts, 1976). Subjects were examined in schools, shopping centers or mobile vans. The Hypertension Detection and Follow-up Program Cooperative Group (1977) found that among a sample

of over 150,000 Americans between the ages of 30 and 69, 25.3% had a DBP over 90 mm Hg. Subjects in this study were examined either at home or at work.

Since arterial blood pressure may be increased by the procedures involved in its measurement, a more conservative cutoff for estimating the prevalence of hypertension is sometimes used. Data gathered from 1971 to 1975 revealed that 18% of adults in the U.S. had a DBP above 95 mm Hg (National Center for Health Statistics, 1981). It was estimated that over 1.7 million, or 13% of Canadians, 25 years and older, were hypertensive, based on the 95 mm Hg DBP cutoff (Canada Health Survey, 1981). Although Canadian figures are lower, hypertension is still quite common among North American adults in both countries.

Increased systolic blood pressure (SBP) is also a factor in the diagnosis of hypertension. It appears that approximately 20% of American adults have a resting SBP reading of over 150 mm Hg (Pooling project research group, 1978). It has also been estimated that 18% of Canadian males over the age of 25 have a SBP above 145 mm Hg (Canada Health Survey, 1981). These data suggest that reliance on DBP without considering SBP may result in an underestimation of the prevalence of hypertension.

A. Hypertension and the Risk of Morbidity and Mortality

High blood pressure is thought to be a causal factor in a number of pathological conditions (Weinstein & Stason, 1976). Hypertension may facilitate cerebrovascular aneurysm and thrombosis, leading to stroke. It may play a role in the development of a state of cardiac ischemia, because of the acceleration of coronary artery disease seen under

conditions of high arterial pressure. Cardiac ischemia is responsible for angina and infarction. Hypertension is also associated with an increased incidence of congestive heart failure. High blood pressure may contribute to renal atherosclerosis, and subsequently kidney failure. While ethics prohibit a direct investigation of the clinical effects of increased blood pressure in humans, much converging evidence indicates that hypertension can cause cardiovascular disease.

Studies have been conducted to compare the prevalence rates of various cardiovascular diseases among normotensives and hypertensives. One study found the incidence of coronary heart disease to be 2.43 times higher in hypertensives (Kannel, 1977). The risk of coronary heart disease increases with increased arterial blood pressure (see Short, 1975). Studies in Massachusetts, Hawaii, and Puerto Rico found a correlation between DBP and the prevalence of coronary heart disease (Gordon, Garcia, Palmieri, Kagan, Kannel & Schiffman, 1974). Positive correlations were found for each group, despite the group differences in average blood pressure for age.

Systolic blood pressure has also been associated with cardiac problems. SBP quartile ranking at an initial examination was positively correlated with cardiovascular accident rate over an 8.6 year period (Pooling project research group, 1978). A correlation was found in each of the five population samples, which provided a total of 8300 subjects, 650 of which experienced a cardiac accident during the course of the study. An 18 year follow-up of females who were initially between the ages of 30 and 49, found that those who developed coronary heart disease had an average initial SBP reading of 146 mm Hg, as compared with an

average of 130 mm Hg for those who remained disease free (Kannel, 1977). However, as indicated previously, a logical cutoff blood pressure which could be used to define hypertension was not produced, since blood pressures for some members of the two groups overlapped.

Increased blood pressure has also been examined in relation to the prevalence of cerebrovascular damage. Hypertensives are eight times

more likely to experience a brain infarct than are adults with blood pressures in the normotensive range (Kannel, 1977). Additionally, postmortem examinations revealed that 71% of hypertensives over the age of 65 had cerebrovascular aneurysms, as compared with only 7% of age matched normotensives (Cole & Yates, 1967). Animal studies have shown that the mechanical distention of the vasculature, through increased blood pressure, promotes the development of microaneurysms (Ross Russell, 1975).

It has been estimated that hypertensives are 2.85 times more likely to develop some form of cardiovascular disease as compared with their normotensive counterparts (Kannel, 1977). Ignoring the dichotomy between normotension and hypertension reveals that the risk of cardiovascular disease increases with increasing blood pressure (Keys, 1970). Individuals who have become hypertensive usually experience a gradual increase in their resting blood pressure level. However, hypertension does not have to be severe in order to produce an increased risk of cardiovascular disease. Even patients considered borderline or mild hypertensives are at risk (Julius, 1977; Short, 1975). Part of the risk to these patients is the fact that they are more likely to show a

further elevation of blood pressure. However, a small increase in blood pressure may also produce cardiovascular changes. An extreme example involves a study of children aged 9 to 18. Those children in the highest SBP quintile, which averaged 117 mm Hg, showed an increased left ventricular wall mass (Clarke & Lauer, 1981). Adults are labelled mildly hypertensive if their DBP is between 90 and 104 mm Hg (Lovell, 1981). It has been suggested that mild hypertension can be a causal factor in the development of atherosclerosis (Omae, Takeshita, Veda, Sadoshima, Hirota, Tanaka & Enjoji, 1979). It has been estimated that 70% of all hypertensives can be considered as having a mild form of this condition, and that this group accounts for 60% of the mortality attributed to high blood pressure (Lovell, 1981).

Some researchers feel that even the mild hypertensive subcategory is too broad, and have chosen to make a further distinction by defining a borderline hypertensive group (e.g. Julius & Esler, 1975). Borderline hypertension is defined as a SBP reading below 160 mm Hg, and a DBP reading below 95 mm Hg, but not with both SBP below 140 mm Hg, and DBP below 90 mm Hg (National Center for Health Statistics, 1981). It has been estimated that 17% of Americans between the ages of 25 and 74 are borderline hypertensives. The Canada Health Survey (1981) estimated that 2.9 million or 13% of all Canadians have blood pressure readings in the borderline hypertensive range. It appears that a large number of North American adults have transient or stable elevations in blood pressure which meet the criteria for borderline hypertension.

There appears to be an increased risk of morbidity and mortality in the borderline hypertensive population. Studies have found that

about 26% of borderline hypertensives over the age of 40 showed a further increase in their blood pressure readings (see Julius, 1977). Assuming that increased blood pressure contributes to coronary heart disease, SBP readings between 140 and 159 mm Hg are in part responsible for an estimated 46% of all cases of coronary heart disease in Americans (Kannel, 1977). Normotensive male Americans between the ages of 45 and 74 develop cardiovascular disease at a rate of 1.239% per annum, while borderline hypertensives develop cardiavascular disease at a rate of 2.108% per annum (Kannel, 1977). The annual death rate among borderline hypertensives over the age of 40 is also about twice that of the normotensive population, and this is due at least in part to an excess of cardiovascular related deaths (Julius, 1977). While it is often assumed that DBP is a better predictor of risk (e.g. Hypertension detection and follow-up program cooperative group, 1977), many of the patients in the previously cited studies show only SBP readings in the borderline hypertensive range. These data and other studies (e.g. Pooling project research group, 1978) indicate that both DBP and SBP can be important risk factors.

Drug studies also indicate that reduction of blood pressure is associated with reduced morbidity and mortality, both in severely (see Short, 1975) and mildly hypertensive patients (Lovell, 1981). It also appears that the blood pressure increase shown by borderline hypertensives contributes to cardiovascular disease in these patients (Kannel, 1977; Julius, 1977). Therefore, there is a growing trend toward the treatment of patients with smaller increases in blood pressure (e.g. Lovell, 1981; Perry & Smith, 1978).

Julius (1977) found that only one to two percent of borderline hypertensives develop severe hypertension each year. While borderline hypertensives appear to develop cardiovascular diseases more often than normotensives, the annual rate of disease development is still less than 3% (Kannel, 1977). Since drug treatment does not prevent morbidity or mortality in all cases (Lovell, 1981), the percentage of those expected to be helped by a comprehensive drug treatment programme is reduced even further. Therefore, a comprehensive drug treatment programme for borderline hypertensives would be expensive, and would burden many more patients than it has the potential to help. On the other hand, 40% of patients with the highest quartile ranking for SBP experienced some form of cardiovascular accident over an 8 year period (Pooling project research group, 1978). Therefore, treatment is more clearly indicated in severe cases of hypertension. However, the heterogeneity of the mildly hypertensive population indicates that more work should be devoted to establishing subgroups most likely to become severely hypertensive and develop some form of cardiovascular disease.

B. Physiological Determinants of Blood Pressure

Blood pressure is a variable parameter. This section discusses the multiplicity of blood pressure control.

The total peripheral vascular resistance (TPR) and the cardiac output are the major influences exerting control over arterial blood pressure. In fact TPR is assumed to equal the mean arterial pressure divided by the cardiac output (Julius & Conway, 1968), where mean arterial pressure is equal to the DBP plus one third of the SBP minus the DBP (mean arterial pressure = DBP + 1/3(SBP - DBP)). Since blood

pressure is determined by more than one other physiological variable, SBP and DBP changes are not always correlated. It appears that a number of factors can contribute to a rise in SBP, DBP or both.

The total peripheral vascular resistance (TPR) is a determinant of both SBP and DBP. TPR determines the rate at which blood leaves the arterial system. Increasing TPR reduces this rate, and produces an increase in arterial pressure. TPR is a function of the cross-sectional area of the entire arterial system. Vascular resistance can be changed by a modification of the thickness of the vascular wall. Vascular smooth muscle mass also determines vascular resistance at rest, and phasic changes in resistance can be produced by dilation or contraction of the vascular smooth muscle.

The cardiac output is the amount of blood pumped by the heart per minute, and is also a determinant of both SBP and DBP. Increases in cardiac output produce increases in arterial blood volume, and therefore arterial blood pressure. Cardiac output is a function of heart rate and stroke volume. If heart rate or stroke volume increases while the other is maintained or increased, then cardiac output will also increase. Stroke volume is a function of cardiac left ventricular filling, cardiac left ventricular contractility, and DBP. The mutual influence between DBP and stroke volume represents part of the negative feedback loop designed to dampen increases in blood pressure. DBP is a force which opposes the output of blood from the heart. As DBP increases, cardiac contraction results in reduced outflow on each beat, and therefore, by definition, it reduces stroke volume. Heart rate increases also cause a reduction in stroke volume, since there is less time for cardiac filling

during each beat. However, contractility will usually increase during prolonged periods of heart rate and DBP increase, acting to maintain stroke volume at a constant level. Exercise is an example of a situation where these variables combine to produce an increase in blood pressure and heart rate, while stroke volume remains constant or increases slightly (Berne & Levy, 1972).

Cardiac control over blood pressure has been known for some time. Liljestrand and Stenstrom (1925) found increases in cardiac output in each of five hypertensives studied. Increases were particularly large in the more mildly hypertensive patients. They concluded that blood pressure is not only influenced by vascular factors, but by a cardiac component as well. More recently it has been found that cardiac output can account for nearly 60% of blood pressure variability in borderline hypertensive patients (Inoue, Smulyan, Young, Grierson & Eich, 1973). Therefore, individual cases of hypertension may be the result of an increased cardiac output, TPR, or both.

Blood volume is a secondary variable which exerts control over blood pressure through cardiac output. Increases in blood volume will increase cardiac output and therefore blood pressure (Safar, Weiss, Levenson, London & Milliez, 1973). The kidney is responsible for maintaining a constant level of blood volume, through pressure diuresis. Fluid output will always exceed input if renal arterial pressure is greater than the hypothetical set point (Guyton, 1978). It is possible that given a change in this set point, increased blood volume, cardiac output, and blood pressure could result.

Several elements of the cardiovascular system, including the baroreceptors and the kidney, operate to maintain a stable blood pressure. These elements work to ensure that there is sufficient pressure to provide adequate blood flow, without overburdening the system. For example, reduced TPR evokes a baroreceptor reflexive increase in cardiac output (see McCubbin & Ferrario, 1977). Conversely, increased pressure on the baroreceptors causes an increase in baroreceptor firing rate, and therefore, reduced heart rate and blood pressure. Additionally, blood volume loading invokes an immediate reduction in TPR (Safar et al., 1973), and an eventual increase in fluid excretion (Guyton, 1978). Therefore, sustained hypertension probably involves a change in the functioning of the baroreceptors, and the kidney.

Given the many relationships involved in blood pressure control, it becomes evident that there are many possible scenarios in which an elevation of arterial blood pressure could occur. One such scenario involves an increase in TPR, while other variables are held constant. This would cause an increase in blood pressure by a reduction in the rate at which blood leaves the arterial system. However, this situation appears only to produce a transient increase in blood pressure. Humans who have had all 4 limbs removed show a 60% increase in TPR, yet their blood pressure does not change (Guyton, 1978). Conversely, in cases where TPR is reduced, blood pressure reductions are still only transient.

As previously stated, blood volume loading produces a rise in arterial pressure which is counteracted by a reduction in TPR, and an

increase in fluid excretion. However, kidney functioning can be altered enough to produce a blood pressure rise despite TPR compensation. An example of this is renal artery clipping used in experimental hypertension research. Kidney malfunctioning has been suggested to play a role in all forms of sustained hypertension, since pressure diuresis would normally work to normalize pressure (Guyton, 1978). There is also empirical evidence of this (e.g. Brod, 1973), however, it is impossible to verify every case. Kidney malfunctioning could also play a role in more transient forms of high blood pressure, and increased blood volume should be considered when cardiac output is found to be the primary source of pressure increase.

Finally, the observation of an increased blood pressure may simply be the result of increased cardiac output, causing a redistribution of blood to the arterial side of the vasculature. Theorectically, such an increase should be compensated for by a reduction in TPR and blood volume. Exercise is an empirical example of a state of increased cardiac output. TPR does decrease during exercise, however, not sufficiently to prevent a rise in mean arterial pressure. Exercise is generally phasic, and although diuresis is increased during exercise, this process is too slow to affect blood pressure.

Another method of inducing an increase in cardiac output is through norepinephrine infusion. The infusion of physiological levels of norepinephrine was found to produce an initial increase in cardiac output and mean arterial pressure (Moss, Vittands & Schenk, 1966). TPR was initially lowered under these conditions. However, after the first hour, TPR began to rise, while cardiac output fell off and mean arterial

pressure was normalized. Decreased cardiac output was not the result of a failure of the infused norepinephrine to stimulate the heart, since cardiac contractility remained elevated. These data indicate that the cardiovascular system does not allow a sympathetically induced increase in cardiac output to be maintained. However, repeated bouts of transient hypertension which are mediated by increased cardiac output may still alter long-term blood pressure control mechanisms, causing sustained hypertension.

Increased cardiac output is induced in animals which are actively avoiding shock (e.g. Forsyth, 1971). As was the case with norepinephrine infusion (Moss et al., 1966), shock avoidance produced an initial rise in cardiac output, and reduced TPR, and a subsequent normalization of cardiac output, and increased TPR. However, in the case of shock avoidance, increased blood pressure was maintained throughout the experiment. A similar, but abbreviated experiment involving humans and shock avoidance, found increases in heart rate and presumably cardiac output, although the latter was not measured directly (Obrist, Gaebelein, Teller, Langer, Grignolo, Light & McCubbin, 1978). These increases were accompanied by increased SBP but a decrease in DBP. This decrease in DBP indicates a reduction in TPR, and a faster rate of blood runoff from the arterial branches. Indirect measurements indicated that cardiac contractility increased, which is consistent with the rise in SBP. This represents an empirical demonstration of changes in cardiac output and TPR which result in SBP changing independently of DBP.

In conclusion, it is apparent that blood pressure regulation is a complicated process. Total peripheral resistance and cardiac output are the two variables with the most direct effect on blood pressure maintenance. However, the control of these variables involves complicated processes. The mechanics of the system indicate that the sympathetic nervous system is important in many cases of increased blood pressure. The next section focuses on autonomic nervous system influences on blood pressure control and regulation. These influences are discussed in relation to energy needs during exercise.

C. Autonomic Regulation and Control of Blood Pressure and Energy Reserves

It is generally accepted that the autonomic nervous system is divided into two parts. These two parts are known as the parasympathetic nervous system and the sympathetic nervous system. Both the parasympathetic and sympathetic nervous systems play a role in blood pressure control and regulation, but they work in opposition to one another. Enhancement of parasympathetic outflow tends to reduce blood pressure, while enhancement of sympathetic outflow tends to increase blood pressure. Some forms of borderline hypertension may involve an imbalance of autonomic nervous system activity, where sympathetic outflow is accentuated in relation to parasympathetic outflow.

The parasympathetic nervous system employs acetylcholine as its neurotransmitter. The sympathetic nervous system employs norepinephrine as its neurotransmitter. The parasympathetic nervous system innervates the heart through vagal nerve fibers. The sympathetic nervous system's

cardiac innervations are simply referred to as cardiac sympathetic fibers. Increased vagal activity causes a reduction in heart rate, but has little effect on cardiac contractility. Only when cardiac contractility is elevated does increasing vagal outflow show an effect on this parameter (Berne & Levy, 1972). Increased sympathetic activity causes an increase in heart rate, and cardiac contractility. Sympathetic influences on cardiac contractility are more clear and pronounced than are the influences of the vagus. Both parts of the autonomic nervous system maintain a tonic outflow to the heart. This means that cardiac control over blood pressure can be influenced by increases or decreases in either, and are most pronounced when one part of the autonomic nervous system increases its outflow and the other part simultaneously decreases its outflow.

There appear to be two classes of sympathetic adrenergic receptors, known as alpha and beta receptors. Stimulation of the sympathetic alpha-adrenergic receptors of the vascular smooth muscle produces vasoconstriction. Stimulation of the sympathetic beta-adrenergic receptors of vascular smooth muscle produces vasodilation. Sympathetic alpha-adrenergic receptors are most evident in vascular smooth muscle of arteries which feed the skin, sphlancnic bed, and the kidney. Therefore, these organs receive a smaller portion of the total cardiac output during a generalized increase in sympathetic nervous system outflow. Sympathetic beta-adrenergic receptors are most evident in vascular smooth muscle of arteries which feed the skeletal and heart muscle. Sympathetic beta-adrenergic receptor stimulation acts to increase blood flow to these areas during actual performance, or the

anticipation of exercise. In addition, sympathetic beta-adrenergic outflow causes dilation of the broncial tree, which also increases the availability of oxygenated blood. These relationships indicate that the sympathetic nervous system is designed to provide additional oxygen to organs required for exercise, at the expense of other parts of the viscera. The parasympathetic nervous system does not appear to innervate vascular smooth muscle.

Stimulation of the kidneys' sympathetic beta-adrenergic receptors causes them to secrete renin. Renin is a hormone which is indirectly involved in water and sodium retention. Renin stimulates angiotensin production. Angiotensin is the hormone which actually alters water and sodium reabsorption. Angiotensin also produces vasoconstriction in a number of vascular beds including the arteries which feed the kidneys. Angiotensin induced vasoconstriction can alter TPR (Guyton, 1978), and it acts to maintain blood volume in two ways. First, angiotensin reduces pressure diuresis by buffering the kidney from higher blood pressures, through renal artery constriction. Second, angiotensin increases water and sodium reabsorption. Thus it seems that in addition to the sympathetic nervous system's ability to increase blood pressure through direct influences on the cardiovascular system, it supports that increase by stimulating the production of hormones which maintain blood volume, and increase TPR.

The sympathetic nervous system also innervates the adrenal medulla. Sympathetic stimulation of the adrenal medulla causes it to release the catecholamines norepinephrine and epinephrine, into the blood stream. When released in excess, the action of these hormones

mimics the action of direct sympathetic cardiovascular stimulation. However, catecholamines released by the adrenal medulla serve mainly metabolic functions. These hormones promote lipolysis and glycogenolysis. These processes are also enhanced through the direct stimulation of beta-adrenergic receptors by sympathetic nerve fibers. This has the effect of increasing blood sugar and free fatty acid levels, which provide energy for physicical activity. It appears that activation of the sympathetic nervous system has several consequences which allow an animal to maintain an increased metabolic rate during exercise. On the other hand, the parasympathetic nervous system is involved mainly in energy storage, and conservation.

Although the sympathetic nervous system appears capable of making energy available for light as well as heavier exercise, it seems that the parasympathetic nervous system is responsible for the heart rate changes which occur during light exercise. At rest, neural control of heart rate is dominated by the vagus. Pharmacological blockade of both autonomic nervous system innervations results in an intrinsic heart rate which is higher than that found in the resting intact preparation. (Julius, Esler & Randall, 1975). Heart rate change is very closely connected with changes in somatic activity (see Obrist, 1981, for review). During periods of light exercise, it is the withdrawal of vagal restraint which produces an increase in heart rate (Robinson, 1966). Initiation of a change in somatic activity necessarily initiates a change in vagal tone, whenever heart rate is primarily under vagal control (Obrist, 1981). Where immediate metabolic needs are concerned, sympathetic influences only become evident under conditions of heavier

exercise (Robinson, 1966). However, sympathetic influences can never be entirely ruled out, especially since there are circumstances where heart rate is under sympathetic control, but physical activity is minimal (e.g. Brod, 1963).

The baroreceptors regulate blood pressure through the autonomic nervous system. There is evidence that when using a resting baseline, the two branches of the autonomic nervous system work independently with regard to blood pressure (Glick & Braunwald, 1965). Increasing blood pressure causes a reduction in heart rate which is due almost exclusively to an increase in vagal restraint. Decreasing blood pressure causes an increase in heart rate which is due almost exclusively to an increase in sympathetic excitation. These conclusions are based on the examination of heart rate changes in response to changes in blood pressure during selective blockade of each branch of the autonomic nervous system. While synergistic action of the two branches cannot be ruled out during blood pressure change in the intact organism, these data indicate that this action is modest at best. It appears that sympathetically induced increases in blood pressure do not necessarily invoke a reflexive drop in sympathetic tone.

Changes in the phases of respiration produce cyclic changes in heart rate known as a respiratory sinus arrhythmia. Heart rate accelerates during inspiration, and is slowed during exhalation. This relationship is maintained mainly through decreases and increases in vagal restraint (Eckberg, Kifle & Roberts, 1980). There is also evidence for sympathetic excitation during inspiration, however, this has not been directly verified in human subjects (see Kirchhein, 1976,

for review). Respiratory sinus arrhythmia can be enhanced by increasing respiratory tidal volume, or by reducing respiratory frequency (Hirsch & Bishop, 1981). These relationships also affect blood pressure, although blood pressure changes are out of phase (Eckberg et al., 1980). This represents another example of a voluntary activity which directly affects blood pressure control.

As was previously stated, activation of the sympathetic nervous system makes energy available to exercising muscle. During periods of heavy exercise, sympathetic outflow is enhanced, and blood pressure is increased. This includes both aerobic (Robinson, 1966), and isometric (Martin, Shaver, Leon, Thompson, Reddy & Leonard, 1974) exercise. However, also mentioned was the fact that sympathetic outflow could be enhanced under conditions where only minor physical activity is involved. Sometimes this enhancement is masked by vagal influences (Obrist, Wood & Perez-Reyes, 1965). Presentation of a stimulus which had been previously paired with shock evoked heart rate deceleration in humans. However, when the vagus was blocked, presentation of the stimulus evoked heart rate acceleration. When subjects were given the opportunity to avoid shock, contingent upon rapid reaction time task performance, increases in beta-adrenergic outflow were clearly evident, even in intact subjects (Obrist et al., 1978). This procedure resulted in a large increase in systolic blood pressure, and no change, or a decrease in diastolic blood pressure. Therefore, there appear to be a number of circumstances where an increase in sympathetic beta-adrenergic activity can produce a large increase in blood pressure.

The autonomic nervous system is clearly involved in blood pressure control and regulation. An imbalance in the influence of the two branches of the autonomic nervous system, in favor of the sympathetic nervous system, results in increased blood pressure. This imbalance represents the means by which energy resources are mobilized during heavy exercise. However, sympathetic dominance can also raise blood pressure under conditions where there does not appear to be an increase in required energy. This state of imbalance appears to be responsible for a large percentage of cases of transient borderline hypertension (Julius & Esler, 1975). The next chapter examines the hypothesis that an autonomic nervous system imbalance in favor of the sympathetic nervous system is responsible for many cases of sustained hypertension.

Chapter Three

The Development of Hypertension

Data presented in the previous chapter indicated that an autonomic nervous system imbalance, in favor of the sympathetic nervous system, could result in increased blood pressure. Increased sympathetic outflow produces an increase in cardiac contractility and heart rate, and therefore it produces an increase in cardiac output. Increased sympathetic outflow also produces a decrease in TPR. These changes result in an increased SBP with little or no change in DBP. Thus, cardiac output is the dominant factor in blood pressure change, under conditions of increased sympathetic outflow.

This chapter examines the role of autonomic nervous system imbalance and increased cardiac output in borderline hypertension, and the development of sustained hypertension. The first section deals with the question of whether an increase in sympathetic activity and cardiac output is observed in hypertension. This section includes a discussion of environmental situations that elicit sympathetic effects and the possible role of these situations in elevating the blood pressure. A second section examines whether an increase in cardiac output and sympathetic activity are causal factors in the progression from borderline to sustained hypertension. A third and concluding section discusses possible mechanisms by which elevated cardiac output might lead to chronic hypertension.

A. Increased Cardiac Output and Sustained Hypertension

As previously mentioned, cardiac involvement in blood pressure control has been known for some time (Liljestkand & Stenstrom, 1925). Increased cardiac output was most evident in those with milder hypertension. Increased blood volume could account for this finding. However, an increase in sympathetic drive was later hypothesized as a causal factor in hypertension (Doyle & Smirk, 1955). Patients' blood pressures were recorded while they were standing and then a reduction in blood pressure was induced by having them assume a prone position. Sympathetic nervous system overactivity was suggested by the finding that blood pressure fell more in the hypertensive patients.

There is no good evidence to indicate that the increased cardiac output seen in borderline hypertension is the result of increased blood volume (see Birkenhager & Schalekamp, 1976, for review). It could be indirectly argued that since many hypertensives with increased cardiac output show high levels of plasma renin activity, it is the renin that increases blood volume and thereby increases cardiac output. However, hypertensives with increased cardiac output and renin levels did not show a reduction in blood pressure when infused with an angiotensin blocking agent (DeQuattro, Barbour, Campese, Fink, Miad & Esler, 1977). Therefore, increased cardiac output in these patients was not due to increased fluid retention.

There is good evidence which indicates that some hypertensives show either increased sympathetic nervous system outflow or receptor sensitivity (see Julius & Esler, 1975, for review). In one study, a group of adolescents with moderately increased blood pressure was

examined (Torok, 1979). These subjects showed increased cardiac output in comparison with their normotensive counterparts. Pharmacological sympathetic beta-adrenergic enhancement produced larger cardiovascular changes in the hypertensive group. In addition, pharmacological sympathetic beta-adrenergic receptor blockade (beta-blockade) also produced larger cardiovascular changes in the hypertensive group. These data indicate that there may be a sympathetic beta-adrenergic receptor oversensitivity in young subjects with moderately elevated blood pressures. However, these findings could also be explained by increased sympathetic nervous system outflow, both at rest, and in response to drug infusion.

Data from adult borderline hypertensives also support the role of the autonomic nervous system in the increased cardiac output found in these patients. When borderline hypertensives and normotensives were given both vagal and beta-blocking agents, heart rate, stroke volume and cardiac output were no longer increased in the borderline hypertensive group as compared with the normotensives who were studied (Julius, Esler & Randall, 1975). Therefore, when increased cardiac output is seen in borderline hypertension, it is most likely the result of increased sympathetic nervous system outflow, or receptor sensitivity, and not increased blood volume.

The role of an increased sympathetic nervous system outflow in increased cardiac output induced borderline hypertension is indirectly supported by data on plasma catecholamine levels (DeQuattro, Miura, Lurvey, Cosgrove & Mendez, 1975). Mild hypertensives (Chobanian, Gavras, Gavras, Bresnahan, Sullivan & Melby, 1978), including borderline

hypertensives (DeQuattro et al., 1975), show increased plasma catecholamine levels at rest. Nestel (1969) examined normotensives and borderline hypertensives at rest, and during the performance of a problem solving task. The task produced urinary catecholamine and SBP changes that were correlated. However, borderline hypertensives showed a greater increase in urinary catecholamine levels and SBP than normotensives did. In addition, the infusion of physiological doses of norepinephrine can produce an increase in cardiac output (Moss et al., 1966). Although the evidence is indirect, these data indicate that an increased sympathetic nervous system outflow is at least partly responsible for increased cardiac output in borderline hypertension.

It was previously stated that an autonomic nervous system imbalance favoring sympathetic nervous system outflow results in an increased SBP without much change in DBP. If such a state is a precursor to sustained hypertension, then it should be displayed in the early stages of mean arterial pressure increase. In fact, many studies include borderline hypertensives whose SBP readings, but not DBP readings, are in the hypertensive range (DeQuattro et al., 1975; Julius, Ellis, Pascual, Matice, Hansson, Hunyor & Sandler, 1974; Safar et al., 1973; Sannerstedt, 1966; Schieken et al., 1981). These borderline hypertensives tend to be younger than those who show increases in both SBP and DBP. For example, Schieken et al. (1981) divided a sample of 9 to 18 year olds into 5 groups, based on SBP ranking. DBP was not increased in the highest SBP quintile.

Parallel findings have been obtained by examining the progression of blood pressure increases in spontaneously hypertensive

rats (SHR). SBP increases in SHR precede DBP increases by about six weeks (Smith & Hutchins, 1979). Therefore, human data and animal data which indicate the ages at which SBP and DBP begin to rise, support the hypothesis that sympathetic beta-adrenergic overactivity mediates blood pressure increase in hypertension.

Many studies indicate that borderline hypertensives show sympathetic beta-adrenergic hyperactivity at rest. The various clinical examination procedures provide the resting baseline data reported by these studies. Borderline hypertensives have shown increased heart rate (L. Johnston, 1980, Julius et al., 1975), stroke volume (Julius et al., 1975) cardiac output (Inoue, Smulyan, Young, Grierson & Eich, 1973; Julius et al., 1975; Stead, Warren, Merrill & Brannon, 1945), SBP (DeQuattro et al., 1975; Julius et al., 1974; Safar et al., 1973; Sannerstedt, 1966), and an indirect measure of cardiac contractility (pre-ejection period) (Inoue et al., 1973; Tarazi, Ibrahim, Dustan & Bravo, 1976), while resting in a clinical setting. Although there are no specific demands being placed on these borderline hypertensives, this does not mean that these values are not elevated in relation to their levels in other environments. For example, repeated exposure to the clinical environment has been shown to result in reduced heart rate (Obrist, 1981), and SBP (Benson, Shapiro, Tursky & Schwartz, 1971; Obrist, 1981; Surwit & Shapiro, 1977). Repeated exposure to a clinic combined with a placebo treatment, have also been shown to result in a reduction in SBP (Goldring, Chasis, Schreiner & Smith, 1956). In addition, many patients who had hypertensive SBP readings in the clinic, had normal SBP readings at home (Julius et al.,1974). Finally, six

borderline hypertensives given a long acting beta-blocker displayed reduced heart rate and SBP throughout their waking hours (Millar-Craig, Kenny, Mann, Balasubramanian & Raftery, 1979). However, the drug had no effect during several of the patients' sleeping hours, when heart rate and SBP were normally lowest. Two conclusions can be drawn from these data. First, increases in sympathetic beta-adrenergic activity can be induced by manipulation of the environment. Second, instructions to rest do not necessarily evoke a basal state of sympathetic beta-adrenergic activity.

It has been known for some time that environmental stimuli can evoke sympathetic activation. Cannon (1920) described the consequences of exposing animals to novel or threatening stimuli. Sympathetic activation produced increased heart rate and cardiac contractility, increased blood flow to the skeletal musculature, and decreased blood flow to the viscera. Cannon (1920) compared these responses with those seen after adrenalin infusion. He concluded that these responses prepared an animal to fight, or flee from a threatening stimulus.

Although sympathetic activation of the kind described by Cannon could be evoked in many animals, hypertension prone animals have often shown sympathetic beta-adrenergic hyperactivity. SHR showed exaggerated sympathetic beta-adrenergic responses to various environmental stimuli (Hallback & Folkow, 1974). In addition, SHR showed increased SBP more often than controls, in response to a less noxious stimulus. Dahl hypertension sensitive rats also showed sympathetic beta-adrenergic hyperactivity compared with Dahl hypertension resistant rats (Friedman & Iwai, 1976). These rats were placed in an environment where lever

pressing was paired with the delivery of both food and shock. This conflict produced a greater SBP increase in the hypertension sensitive group.

Early experiments with human subjects were also successful at evoking sympathetic beta-adrenergic activation. Grollman (1929) recorded several physiological parameters from four normotensive medical students. During the recording session, one of the subject's professors entered, and accused the subject of not studying enough. This procedure evoked large increases in heart rate, cardiac output, and blood pressure. Although these findings are consistent with an increase in sympathetic beta-adrenergic activity, Grollman (1929) was unable to attribute the observed changes to sympathetic activation.

Borderline hypertensive humans, like hypertension prone rats, show significantly greater cardiovascular responses which are indicative of sympathetic beta-adrenergic hyperactivity, under a variety of environmental conditions. For example, Nestel (1969) had normotensive and borderline hypertensive subjects perform a multiple choice task involving visual puzzles. SBP rose in both groups, but it rose more in the borderline hypertensive group. In addition, mathematical problem solving tasks have often been used to examine sympathetic activation in borderline hypertension. One study found that this type of task produced increases in cardiac output, blood pressure, and muscle blood flow in all subjects (Brod, 1963). However, these responses were sustained longer in the borderline hypertensive group. A second study found that a math task evoked larger increases in heart rate and SBP in its borderline hyertensive group, and that these responses were again

sustained longer than in the normotensive group (Bauman, Ziprian, Godicke, Hartroot, Naumann & Lauter, 1973). Borderline hypertensives in this study were placed in the hypertensive category because of increased SBP. DBP was not increased in this group. All subjects were males between the ages of 15 and 25, supporting the notion that increased SBP precedes increased DBP. A third study employed adolescents and compared normotensive subjects with those with occasional DBP reading above the 95th percentile (Falkner, Onesti, Angelako, Fernandes & Langman, 1979). The hypertensive group again showed greater increases in heart rate and SBP relative to controls, and increases were sustained longer in the hypertensive group. Post-stress plasma catecholamine levels were also higher in the hypertensive group.

Several studies have demonstrated an autonomic nervous system imbalance in borderline hypertension. Borderline hypertensives showed larger and longer increases in sympathetic nervous system activity when exposed to a variety of environmental stimuli. There are, however, procedures which evoke increased blood pressure, but fail to demonstrate differences in autonomic nervous system activity between groups of borderline hypertensives, and normotensives.

The cold pressor test involves the immersion of a hand or bare foot into iced water. This procedures causes a reliable increase in blood pressure. However, some researchers have found that the cold pressor test increased blood pressure in normotensives to the same extent it increased blood pressure in mild and severe hypertensives (Boyer, Fraser & Doyle, 1960; Brod, 1963; Price, Lott, Fixler & Browne, 1979; Remington, Lambrath, Moser & Hoobler, 1960). Others have found

hypertensives to respond with greater increases in blood pressure during cold water immersion (Chobanian et al., 1978; Hines & Brown, 1936). The data do not support the hypothesis that borderline hypertensives show larger blood pressure increases than normotensives, during the cold pressor task. This lack of consistency has been used to argue that environmental stimuli are not important in hypertension (Julius & Schork 1971). However, procedures like the cold pressor test appear to be qualitatively different from the procedures involved in mathematical problem solving.

There is evidence to support the intuitive notion that there is no generalized physiological reaction produced by all stressors (Mason, Maher, Hartley, Mougley, Perlow & Jones, 1976). However, response profiles are consistenly reproducable for each type of stressor. LeBlanc, Cote, Jobin & Labrie (1979) found that a mathematics test, and the cold pressor test produced equivalent increases in SBP. However, heart rate increased more during the math test, indicating more TPR involvement in the cold pressor test. Additionally, beta-blockade did not alter SBP changes during the cold pressor test (Obrist et al., 1978). These data indicate that environmentally induced increases in blood pressure are not always mediated by increased cardiac output.

Studies have been conducted in an attempt to specify the procedural parameters which allow the observation of increased sympathetic beta-adrenergic activity. The threat of shock has been employed in several of these studies. Obrist et al. (1965) found that the presentation of a tone, which had been paired with shock, produced a decrease in heart rate, mediated by increased vagal restraint. This

increase in vagal restraint was large enough to mask what appeared to be a small increase in sympathetic activity. However, when subjects were given the opportunity to actively avoid shock, increases in cardiac output were clearly evident (Obrist et al., 1978). In addition, cardiac output remained elevated for a longer period when the avoidance response criterion was made difficult, as opposed to easy or impossible. Pharmacological beta-blockade was used to verify that an increase in sympathetic activity was involved. These data indicate that when subjects remain actively engaged in attempts at controlling aversive environmental stimuli, their sympathetic activity is increased.

Other studies have confirmed the importance of belief in the controllability of the environment. When subjects were lead to believe that shock avoidance was contingent upon their responses, heart rate and SBP increases were greater than when this contingency was not mentioned (Light & Obrist, 1980b). In addition, when response criteria were difficult, SBP increases were larger when subjects were lead to believe they could avoid the presentation of a painfully loud noise (Manuck Harvey, Lechleiter & Neal, 1978). However, when response criteria were made easier, SBP increases were similar whether or not subjects were lead to believe they could avoid noise presentation. These data suggest that procedures which involve active subject participation, such as an arithmetic test, will produce larger increases in sympathetic activity, than procedures which involve passive subject participation, such as the cold pressor test.

Another important procedural parameter is the baseline employed for determining cardiovascular reactivity. The law of initial values

may have been operative in studies involving hypertensive subjects. If participation in an experiment and the anticipation of the test procedures are sufficient to increase sympathetic beta-adrenergic activity, then the test procedures may not be able to increase sympathetic beta-adrenergic activity much further. As previously indicated, entering a clinic or laboratory, often evokes increased SBP and an increased sympathetic beta-adrenergic activity level in borderline hypertensives.

Remington et al. (1960) found that the offspring of hypertensives did not show a greater increase in SBP during the cold pressor test. However, these subjects had higher SBP values during all phases of the experiment. Similarly, Price et al. (1979) did not find greater SBP reactivity amoung adolescents with elevated blood pressures. However, these subjects displayed greater increases in heart rate and SBP in anticipation of the test. These data suggest that measures of sympathetic beta-adrenergic activity recorded just prior to the onset of an experimental procedure are not indicative of basal activity level. These data also suggest that various experimental procedures would be more sensitive to changes in sympathetic beta-adrenergic activity, if they employed a more familiar enviroment for assessing basal activity level.

These conclusions are supported by the work of Obrist and his coworkers (see Obrist, 1981). Obrist (1981) divided subjects into quintiles based on the magnitude of their heart rate increases during shock avoidance. Obrist assumed that subjects in the quintile

representing the greatest amount of heart rate change, also represented the greatest amount of sympathetic beta-adrenergic activity change. The validity of this was supported by the fact that SBP reactivity and average SBP during shock avoidance, increased with increasing heart rate reactivity. In addition, heart rate changes during shock avoidance were attenuated by beta-blockade (Obrist et al., 1978). Obrist et al. (1978) originally used the rest period immediately prior to task onset as their baseline for determining reactivity. When this baseline was employed, subjects who showed the largest heart rate increases during shock avoidance, could not be differentiated from the other subjects when data from a cold pressor test was assessed (Obrist, 1981). The results supported the importance of active control in eliciting increases in sympathetic beta-adrenergic activity.

Subsequently, new baseline data were collected from these same subjects. These data were collected one to two weeks after the initial session, and were not followed by any task demands. Subjects were then divided into quartiles based on heart rate differences between shock avoidance and this new "relaxation" baseline (Obrist, 1981). The four quartiles did not have different heart rate relaxation baselines. However, both the cold pressor test, and task anticipation evoked greater heart rate and SBP increases in the highest quartile, when the relaxation baseline was used for comparison. Pharmacological beta-blockade suggested that the cardiovascular changes produced by task anticipation were sympathetically mediated. Therefore, when a basal sympathetic beta-adrenergic activity level was employed for comparison, cardiovascular reactivity was consistent across a number of different

conditions. The importance of the law of initial values was also supported by the fact that some subjects who showed below average increases in heart rate from pretask baseline to shock avoidance, were placed in the highest quartile when the relaxation baseline was used to determine reactivity (Obrist, 1981).

Repeated exposure to an environment leads to the habituation of increased sympathetic beta-adrenergic activity evoked by that environment. However, individual differences in reactivity to a particular task appear to be relatively stable. Parachuting from a mock tower produced increased heart rates in experienced as well as novice jumpers (Stromme, Wikeby, Blix & Ursin, 1978). Experienced jumpers also showed the same increases in SBP, despite training, and a decline in the amount of catecholamines produced by the task. Manuck & Garland (1980) had 19 subjects perform the same cognitive task twice, 13 months apart. Individual subjects' heart rate changes during the second session were highly correlated with changes produced in the first session, although slightly reduced. This was also true for changes in SBP. Similarly, heart rate and SBP reactivity to shock avoidance remained stable over a two year period (Obrist, 1981). It appears that sympathetic beta-adrenergic overreactivity is reproducable.

Although these data were collected using normotensive subjects, the procedures often caused subjects to show SBP readings in the hypertensive range (e.g. Obrist, 1981). Therefore, these data do have some direct implication for research in borderline hypertension. They indicate that where an autonomic nervous system imbalance occurs in borderline hypertension, this imbalance is enhanced by placing the

patient in a threatening situation, where the patient believes that the outcome of the situation depends upon his own behaviour. These data also indicate that caution should be used when selecting a baseline sampling period. Novelty seems to increase sympathetic beta-adrenergic activity more in borderline hypertensives. When baseline data are collected in a novel environment, subsequent changes will be different from those changes observed in relation to baseline data collected in a familiar environment. When these factors are taken into consideration, sympathetic beta-adrenergic reactivity in response to changes in the environment, appears to play a major role in borderline hypertension.

It appears that there may be several situations which can evoke an increase in sympathetic beta-adrenergic activity. The data indicate that hypertension prone rats, and borderline hypertensive humans show exaggerated and prolonged responses in these situations. Indirect evidence suggests that the exaggerated cardiovascular responses displayed by borderline hypertensives, were caused by increased sympathetic beta-adrenergic outflow. In addition, some evidence indicates that increased beta-adrenergic receptor sensitivity is involved (Torok, 1979).

An autonomic nervous system imbalance in favor of the sympathetic nervous system could involve low parasympathetic tone, as well as increased sympathetic nervous system activity. Indirect data are available which indicate that borderline hypertensives can display exaggerated vagal withdrawl. Julius et al. (1975) found that the heart rate, stroke volume, and cardiac output of borderline hypertensives were elevated at rest while autonomic nervous system innervations were

intact, and while sympathetic beta-adrenergic receptors were blocked. Borderline hypertensives and normotensives had equivalent cardiac outputs only when both autonomic nervous system branches were blocked in all subjects. In another study, pharmacological denervation revealed that exaggerated heart rate and sympathetic increases induced in SHR by aversive stimulation involved decreased parasympathetic nervous system outflow as well as increased sympathetic nervous system activity (Hallback & Folkow, 1974).

As the data previously presented indicate, respiratory sinus arrhythmia (RSA) is mediated mainly by the vagus. A study by L. Johnston (1980) examined the magnitude of RSA in borderline hypertensives and normotensives. RSA was exaggerated by increasing tidal volume and reducing respiratory rate. Taking a deep breath was immediately followed by decreased heart rate in normotensives, but not borderline hypertensives. In addition, heart rate increased more during inhalation in normotensives than borderline hypertensives. Increased resting heart rate amoung the borderline hypertensives may explain the latter result, but not the former. The strength of these data is also reduced by the lack of control over, and measurement of respiration volume and frequency. However, these findings are consistent with the hypothesis that the autonomic nervous system imbalance found in borderline hypertension, involves vagal dysfunction.

A study by Glick & Braunwald (1965) indicated that the reduced heart rate invoked by increased blood pressure was due almost exclusively to an increase in vagal restraint. One study found that a group of hypertensives, which included borderline hypertensives, showed

deficient vagal restraint in response to increased blood pressure (Simon, Safar, Weiss, London & Milliez, 1977). Hypertensives required smaller doses of the vagal antagonist, atropine, to abolish reflexive cardiac slowing caused by increased blood pressure.

It was previously noted that when subjects changed the level of their somatic activity, a vagally mediated change in heart rate occured (see Obrist, 1981). Therefore, a note of caution is necessary here. Observations of decreased parasympathetic tone amoung SHR and borderline hypertensives, may have been the result of increased somatic activity. If borderline hypertensives and SHR display more somatic activity than their normotensive counterparts, then their oxygen consumption, and tissue oxygen extraction should also be increased. Studies have shown that borderline hypertensives comsume oxygen at a faster rate than normotensive controls (Gorlin, Brachfield, Turner, Messer & Salazar, 1959; Lund-Johansen, 1967; Stead et al., 1945). However, these same studies revealed that oxygen extraction was reduced in these borderline hypertensives. These data indicate that the reduced vagal restraint observed in borderline hypertensives is due to something other than increased somatomotor activity.

One possibility is that reduced vagal tone was the result of increased respiration rate. Increased respiration rate results in a reduction of heart rate variability (Eckberg, Kifle & Roberts, 1980; Hirsch & Bishop, 1981). This reduction is RSA is caused by a failure of the baroreceptors to increase vagal restraint during expiration (Eckberg et al., 1981). Therefore, increased respiration rate is a plausible

cause of reduced vagal activity in borderline hypertension. However, this hypothesis has not been directly tested.

In conclusion, the data strongly support the hypothesis that in many cases, borderline hypertension involves an autonomic nervous system imbalance. This imbalance is enhanced by environmental stimulus parameters which include novelty and controllability. Failures to demonstrate sympathetic beta-adrenergic overreactivity in borderline hypertension could be explained by the use of uncortrollable stressors and inappropriate baselines. It has not yet been established whether the autonomic nervous system imbalance seen in borderline hypertension represents increased sympathetic nervous system outflow or increased receptor sensitivity, or both. It is also not certain whether or not the autonomic nervous system imbalance involves vagal dysfunction. However, an autonomic nervous system imbalance which produces increased cardiac output is apparent in many cases of borderline hypertension. The next section examines data which implicates environmentally induced increases in cardiac output in the progression from borderline to severe hypertension.

B. Increased Cardiac output as a Causal Factor in Sustained Hypertension

The data reviewed above indicate that borderline hypertension is associated with increased sympathetic beta-adrenergic activity. The data are also consistent with the view that environmental triggers play a role in causing blood pressure to move into the borderline hypertensive range. However, the data do not necessitate that the environment is a factor in the progression of blood pressure from the

borderline to the severely hypertensive range. This section examines the data which implicate increased sympathetic beta-adrenergic activity and increased cardiac output in this progression.

In order for an increase in cardiac output to be a causal factor in the progression of blood pressure from the borderline to severly hypertensive range, this increase must temporally precede severe hypertension. Data from cross-sectional (e.g., Sannerstedt, 1966) and longitudinal (e.g., Lund-Johansen, 1977) studies indicate that increased cardiac output precedes increased TPR. Some studies also suggest that sympathetic beta-adrenergic overreactivity and increased cardiac output increase the risk of developing hypertension (e.g., Levy, White, Stroud & Hillman, 1945).

Cross-sectional studies have divided groups of hypertensives along several different dimensions. These studies consistently demonstrate that younger hypertensives have smaller elevations of blood pressure, but increased cardiac performance parameters indicative of high sympathetic beta-adrenergic tone. The younger hypertensives have little or no elevations of TPR. Studies have found that the mildly hypertensive group had increased cardiac output relative to the severly hypertensive group (Bello, Sevy & Harakal, 1965; Safar et al., 1973; Sannerstedt, 1966), and relative to the normotensive group (Sannerstedt, 1966). Other studies divided their hypertensive sample by age, and found that the younger hypertensives had lower TPR and blood pressure, and increased heart rate and cardiac output relative to older hypertensives (Frolich, Kozul, Tarazi & Dustan, 1970; Lund-Johansen, 1967). Inoue et al. (1973) separated their sample of hypertensives

based on cardiac output. Hypertensives with increased cardiac output were younger, showed signs of increased cardiac contractility, and had lower blood pressure and TPR. Finally, a study which involved only borderline hypertensives, found that only younger borderline hypertensives had increased cardiac output relative to age matched normotensive controls (Julius & Conway, 1968). These data indicate a gradual change from cardiac to vascular control over blood pressure, as hypertension becomes more severe, regardless of age (Safar et al., 1973).

Longitudinal studies have also found that the progression of hypertension involves an increased cardiac output, giving way to an increased TPR. Lund-Johansen (1977) performed a 10 year follow-up examination of borderline hypertensives who were between the ages of 17 and 40 at the start of the study. These borderline hypertensives showed a reduction in heart rate, stroke volume and cardiac output relative to their initial values. Meanwhile TPR had increased in these subjects. There was also a trend toward increased blood pressure at the 10 year follow-up. Eich et al. (1966) followed a group of borderline hypertensives for 4 years. Cardiac output was initially elevated in 16 of these borderline hypertensives. Twelve of the borderline hypertensives with an initially elevated cardiac output later showed a normalization of cardiac output, and an elevated TPR. In addition, DBP had increased in eight of these subjects. Another 4 year follow-up study produced similar results (Weiss, Safar, London, Simon, Leveson & Milliez, 1978). A group of borderline hypertensives showed an initial

increase in cardiac output which was followed by cardiac normalization and increased TPR. SBP and DBP also rose in this study.

These data indirectly suggest that increased cardiac output, resulting from increased sympathetic beta-adrenergic activity, is a causal factor in the progression of hypertension. However, a study by Julius, Quardir & Gajendragadkar (1979) did not support this conclusion. Borderline hypertensives began this study with a mean age of 26 years, and were followed for a period of 15 to 137 months. Heart rate, cardiac output, stroke volume, and blood pressure all showed a trend toward normalization at the follow-up examination. However, this is not a strong arguement against a role of increased sympathetic beta-adrenergic activity in the development of hypertension. Clearly only a minority of borderline hypertensives become severely hypertensive (Julius, 1977). Although most borderline hypertensives display increases in cardiac output, there could be individual differences in the frequency, duration and magnitude of these increases, which dictate subsequent blood pressure changes. Since subjects in the Julius et al. (1979) study were tested while resting, the observed trends could represent a habituation of increased sympathetic nervous system activity produced by the observational setting. Actually, this explanation could hold true for all previously mentioned follow-up studies where cardiac output returned to normal after repeated examination. However, this does not detract from the data which demonstrate the high frequency of increased cardiac output in the early stage of hypertension.

Medical records have also supported the role of increased cardiac output in the development of hypertension. Paffenbarger, Thorne & Wing (1968) contacted middle-aged males for whom they had medical data which was collected during their first year at university. Subjects whose medical records indicated a heart rate of more than 90 beats per minute were 30% more likely to become hypertensive. Those with an elevated SBP also had an increased risk of becoming hypertensive. Similar results were obtained by Levy et al. (1945). Army officers were given yearly physical examinations. Those officers who had a heart rate of 100 beats per minute or more at one examination, followed by a finding of less than 100 beats per minute during a subsequent examination, were 3.5 times more likely to become hypertensive, based on age matched control rates for morbidity. Officers who showed a transient elevation in SBP above 150 mm Hg, or DBP above 90 mm Hg, which was followed by a normalization of blood pressure, were also 3.5 times more likely to become hypertensive. In addition, officers who showed both transient increases in heart rate and blood pressure, were 7.5 times more likely to become hypertensive. While these data are again indirect, they add more support to a role of increased cardiac output in the production of many cases of hypertension.

Genetic factors may be influential in the development of an autonomic nervous system imbalance. Genetic factors are influential in the development of hypertension. Pickering (1968) observed that average blood pressure increased with age. The population variance of blood pressure also increased with age. In addition, the sex of the subject also determined blood pressure. Based on this information,

Pickering (1968) developed a method of standardizing blood pressure values, based on the sex and age of the subject. This method was then used to establish frequency distributions of age and sex adjusted scores for relatives of hypertensives and normotensives. The resulting curves were similar in shape, but the relatives of the hypertensives showed increased blood pressure. Pickering (1968) found that the resemblance between the hypertensive group and each of their first degree relatives was the same, regardless of the sex of the relative. Genetic factors are further implicated by other data which indicate that the offspring of hypertensives are at risk for hypertension (Miall & Oldham, 1955).

Other types of familial studies have also implicated a genetic factor in the development of hypertension (see Pickering, 1968, for review). Subjects with two hypertensive parents became hypertensive more often than subjects with one hypertensive parent. In addition, subjects with one hypertensive parent became hypertensive more often than subjects with no hypertensive parents. A genetic factor is further implicated by data from twin studies. These studies have found that monozygotic twins had blood pressures that were more alike than dizygotic twins. Pickering (1968) concluded that inheritance probably accounted for between 36 and 67 percent of blood pressure variance.

Another group of researchers also came to the conclusion that heredity was a factor in DBP determination (Cruz-coke, Donoso & Barrera, 1973). More than fifty percent of DBP variance could be accounted for genetically, when highland and lowland Chileans were examined separately. However, associations between relatives was reduced when comparisons were made between the two populations. Lowland Chilean

adults showed an increased blood pressure with increasing age, but highland Chilean adults did not show this increase. It appears that people in this culture have the propensity to become hypertensive, but some element or elements in the environment are necessary to produce increased blood pressure. These environmental elements appear to be more prevalent in the lowlands.

Paffenbarger et al. (1968) found that a genetic factor and increased SBP combined to increase the risk of hypertension. More than 23 percent of university students with SBP over 130 mm Hg, and a hypertensive parent became hypertensive. However, less than 10 percent of students with a SBP below 130 mm Hg, and a hypertensive parent became hypertensive. Since DBP was well within normotensive limits amoung all students, increased SBP probably represented increased sympathetic beta-adrenergic activity, and not increased TPR.

Studies which have examined the adolescent offspring of hypertensives have found these offspring to have increased SBP (Miall & Oldham, 1955; Remington et al., 1960). In addition, Light and Obrist (1980a) found parental hypertension to be most prevalent in university students who had above average heart rate and SBP prior to the introduction of any specific task demand.

Studies have also found that the offspring of hypertensives show larger increases in sympathetic beta-adrenergic activity when participating in tasks which require active involvement. Manuck & Proietti (1982) examined subjects with and subjects without at least one hypertensive parent. Heart rate was always higher in the group with hypertensive parents. However, DBP never differentiated the two groups.

Two cognitive tasks produced greater increases in SBP and heart rate amoung the offspring of hypertensives. Similarly, finding a higher heart rate and SBP in subjects while they relaxed in an environment that was no longer novel, was associated with increased prevalence of parental hypertension (Hastrup, Light & Obrist, 1982). The incidence of parental hypertension was also increased amoung those subjects who showed higher than average heart rate and SBP reactivity during a shock avoidance task.

The data indicate that the offspring of hypertensive parents are more likely to become hypertensive. In addition, these offspring show larger increases in cardiac output when participating in tasks which evoke increased sympathetic beta-adrenergic activity. These conditions are also found to exist amoung borderline hypertensives. However, the offspring of hypertensives show increased cardiac output and sympathetic beta-adrenergic reactivity even before they show casual blood pressure readings in the borderline hypertensive range. These data do not directly implicate increased cardiac output as a causal factor in the development of hypertension. However, future work in human hypertension must include an examination of increased cardiac output, because of its role in borderline hypertension, and its association with an increased risk of sustained hypertension.

Although it is clearly unethical to produce experimental hypertension in humans, it is possible to do so with animals. Several studies which involve experimental hypertension in animals, have involved increased cardiac output. Cardiac output was increased by exposing the animals to behaviourally contingent stimuli.

Corley, Shiel, Mauck and Barber (1977) trained squirrel monkeys to avoid shock. Performance of the shock avoidance task was associated with increased heart rate. A 24 hour session of shock avoidance was sufficient to produce cardiac pathology and sustained increases in DBP in these animals.

Forsyth (1971) examined the hemodynamic changes which occured in monkeys during shock avoidance. Initiation of shock avoidance behavior produced an immediate increase in heart rate, cardiac output, and mean arterial pressure. Sympathetic beta-adrenergic receptor blockade attenuated these increases (Forsyth, 1976). Therefore, monkeys performing a shock avoidance task appear hemodynamically similar to borderline hypertensives. Both show stress induced increases in sympathetic beta-adrenergic activity, producing increased cardiac output and blood pressure. However, by the end of 72 hours of task performance, cardiac output had returned to normal in these monkeys (Forsyth, 1971). The monkeys now had an increased TPR, while blood pressure remained elevated. Environmental conditions had been produced which caused hemodynamic changes which have been observed in hypertensives as they progressed from borderline to severe hypertension.

Finally, Lawler, Barker, Hubbard and Allen (1980) examined the effects of the environment on rats which were genetically predisposed to hypertension. SHR and normotensive rats were crossbred, and their offspring were divided into three groups. One group of animals remained in their home cages throughout the experiment, except for weekly blood pressure measurement. The other two groups were transfered to training cages for 2 hours each day, 5 days each week. The training cages were

small, and Lawler et al. (1980) considered placement in a training cage a form of mild restraint. Each of the training cages contained a running wheel. While in the training cages, one group of rats received 3 weeks of shock avoidance training. Wheel running was required for an animal to avoid tail shock. Following the 3 weeks of training, the response-shock contingency changed for these animals. Wheel running was required to avoid five shocks, but was followed by one shock.

At the end of 3 weeks of training, SBP was not different between the three groups. However, after a total of 15 weeks of exposure to the experimental procedures, the SBP of the group which was transfered to training cages, but not shocked, was increased relative to the SBP of the group which remained in home cages. The SBP of the shocked group was increased relative to either of the other two groups. These data support the notion that an environmentally induced increase in sympathetic beta-adrenergic activity can interact with a genetic predispositon to produce a sustained increase in blood pressure.

If increased cardiac output is causal in many cases of sustained, severe hypertension, then prolonged use of sympathetic beta-adrenergic receptor blocking agents by normotensives at risk for hypertension, should prevent increased blood pressure in these subjects. It was mentioned previously that reducing blood pressure in mild hypertensives with drugs, which include beta-blockers, reduced morbidity among these patients (Lovell, 1981). These data also indirectly implicate increased sympathetic beta-adrenergic activity in the progression of hypertension and the morbidity associated with it. More direct evidence on human hypertension are not yet available. However,

with the trend toward the treatment of smaller increases in blood pressure, the prophylactic effects of beta-blockade may soon be testable.

Studies have been conducted to examine the effects of chronic sympathetic beta-adrenergic receptor blockade on the progression of hypertension in SHR. However, the data from these rat studies are inconclusive. SHR display increased cardiac output and contractility during the first weeks of life (Pfeffer & Frolich, 1973). Blood pressure and TPR rise rapidly in these animals during this period. This period is followed by a normalization of cardiac output. Therefore, SHR have been shown to display increased sympathetic beta-adrenergic activity during a period of rising blood pressure, which appears to make SHR good models for testing beta-blockade.

Pfeffer and coworkers have studied the effects of chronic beta-blockade on blood pressure in SHR in two studies (Pfeffer, Frolich, Pfeffer & Weiss, 1974; Pfeffer, Pfeffer, Weiss & Frolich, 1977). In the first study (Pfeffer et al., 1974) beta-blockade was begun at 4 weeks of age, and continued for 4 weeks. Heart rate was lowered by drug treatment throughout those 4 weeks, indicating that drug treatment was successful at blocking beta-adrenergic receptors. However, despite the reduction in sympathetic beta-adrenergic activity, blood pressure increases were not inhibited. These data contradict the notion of the importance of increased cardiac output in the development of hypertension. However, the results of this study did not indicate that there was cardiac contol of the blood pressure in the treated SHR. That is, that in addition to reducing heart rate, beta-blockade should have

also initially reduced SBP, if increased cardiac output was responsible for blood pressure control. However, SBP was never altered by beta-blockade. This suggests that some factor other than increased sympathetic beta-adrenergic activity was responsible for increased SBP in these SHR.

Pfeffer et al. (1977) used two beta-blocking drugs, propranolol and timolol, to examine the effects of chronic beta blockade on blood pressure in SHR. Treatment began at conception, and continued till the SHR were 12 weeks of age. Beta-blockade again reduced heart rate, but as a group, the treated SHR did not show an inhibition of blood pressure increases. However, treated males did show a trend toward lower blood pressure. In fact, timolol treated male SHR showed a reduction in SBP at 12 weeks. These data are difficult to explain, since propranolol had a greater effect on cardiac performance.

Two studies found more clear reductions in blood pressure increases in SHR treated with the beta-blocker propranolol (Conway, Darwin, Hilditch, Loveday & Reeves, 1975; Weiss, Lundgren & Folkow, 1974). Conway et al. (1975) treated SHR with propranolol from birth to 60 days of age. Untreated SHR showed more SBP increase at 70 days of age, than did treated SHR. Weiss et al. (1974) treated SHR with propranolol from 10 weeks to 8 months of age. Untreated SHR showed SBP increase at 8 months, while treated animals showed a SBP which did not differ from normotensive controls. These data are encouraging. However, inconsistencies make it difficult to draw conclusions.

Good direct evidence demonstrating that hypertension can result from the effects of increased sympathetic beta-adrenergic activity is

lacking. A large body of converging evidence is available which indicates that hypertension is often preceded by increased sympathetic beta-adrenergic activity, and cardiac dominance in blood pressure control. Even so, it is difficult to determine how often sustained hypertension has been preceded by increased cardiac output, based on the available data. The use of resting conditions to examine hemodynamics in borderline hypertension, has probably resulted in an underestimation of the percentage of cases which involve increased cardiac output. Especially since many subjects who are considered to be borderline hypertensives, but who no longer have blood pressures in the hypertensive range when examined. However, there is no logical basis for the use of a particular environmental setting to test for a sympathetic beta-adrenergically mediated rise in SBP. Tests done in multiple, naturalistic settings may be informative, but this has not yet been determined. Therefore, it is difficult to estimate the prevalence of an autonomic nervous system imbalance in borderline hypertension.

If mean arterial pressure is raised, and cardiac output is normal, then by definition, TPR must be raised. Borderline hypertensives who are found to have increased TPR, may no longer be in the initial stages of hypertension. It is possible that had these borderline hypertensives been examined at an earlier age, cardiac control over increased blood pressure would have been found. This possibility, combined with problems involved in determining prevalence, make it difficult to validly estimate the incidence of increased cardiac output prior to sustained hypertension.

However, it does seem clear that borderline hypertensives and the offspring of hypertensives are more likely to become hypertensive than the population in general. As a group they often show an autonomic nervous system imbalance in favor of the sympathetic nervous system, which raises SBP into the hypertensive range. The environment appears to evoke this imbalance in many, if not all cases. Entry into a laboratory or clinic for observation can evoke large increases in SBP in subjects who have a normotensive resting blood pressure. In many cases the environment may interact with a genetic factor to produce hypertension. A predisposition towards showing an autonomic nervous system imbalance may be the result of this genetic factor.

From these conclusions, one would predict that given sufficient exposure to environmental stimuli which produce increased cardiac output, any person would become hypertensive. One would also predict that less exposure is necessary for those people who consistently display larger increases in cardiac output. However, a limited number of observations of environmental stimuli producing an increased cardiac output and SBP in the borderline hypertensive range, does not necessitate a progression to sustained hypertension. It is not possible to know when or to what degree an animal is experiencing increased sympathetic beta-adrenergic activity without actually measuring some physiological parameter such as cardiac performance. Therefore, a valid and easily obtained measure of sympathetic beta-adrenergic influences on the human heart would be useful in testing these predictions, as they relate to human hypertension.

C. Possible Mechanisms Mediating Long Term Sympathetic Effects on Blood Pressure Regulation

In the last section it was established that increased sympathetic beta-adrenergic activity often precedes sustained hypertension. Data also indicated that those who reacted to physical examination with increased sympathetic beta-adrenergic activity, were at an increased risk for the development of hypertension. Earlier chapters reviewed the physiological effects of increased sympathetic beta-adrenergic activity. A generalized increase in sympathetic outflow results in an increase in blood oxygen, free fatty acids, cholesterol and angiotensin. Other results are reduced blood flow to the kidney, and mechanical distention of blood vessel walls. This chapter focuses on how these physiological effects could influence blood pressure regulation over an extended period. What mechanisms or pathways are involved?

Exercise was mentioned earlier as an example of a behavioural state which produces increased sympathetic outflow. This results in an increase in cardiac output and SBP, and a concomitant decrease in TPR. DBP increases very little during exercise. These changes are similar to those seen during shock avoidance. Although the data which suggest that exercise can prevent hypertension are not conclusive, it is generally accepted that exercise does not increase the likelihood of the development of hypertension. However, the data presented thus far suggest that increased cardiac output in a resting animal may contribute to blood pressure elevation. Examination of the differences between the effects of increased sympathetic beta-adrenergic activity on an

exercising animal, and the effects of increased sympathetic beta-adrenergic activity on a resting animal, might therefore reveal factors important in the development of sustained hypertension.

Exercise may inhibit blood pressure increases in animals predisposed to hypertension. Although results vary, some studies have reported that exercise may delay the progression of hypertension in rats (see Fregly, 1984, for review). SHR were often used as subjects in these experiments. If the strain of running wheel exercise did not result in an inhibition of blood pressure increase, then it usually had no effect on blood pressure. Only one study reported an acceleration of hypertension with exercise (Suzuki, Oshima & Higuch, 1979, cited in Fregly, 1984). SHR that were forced to exercise on a running wheel displayed increased blood pressure after training, when compared to age matched controls. However, when given the opportunity to exercise on an ad lib basis, this same study reported a delay in blood pressure increase. Therefore, it appears that an animal's physiology responds differently if that animal is forced to exercise, than if that animal is provided with the opportunity to exercise.

Exercise has also been demonstrated to reduce blood pressure in Dahl rats that develop hypertension on a high salt diet. Dahl hypertension sensitive rats have been shown to react to food-shock conflict with a greater increase in SBP, than their hypertension resistant cousins (Friedman & Iwai, 1976). There is evidence that exercise can reduce the rate at which blood pressure rises in Dahl hypertension sensitive rats (see Fregly, 1984, for review). Since rats with other forms of hypertension did not show a reduction in blood

pressure with exercise, it appears that exercise is most beneficial to those hypertension sensitive rats that display increased sympathetic beta-drenergic reactivity.

Exercise appears to normalize the blood pressures of borderline hypertensives. Exercise has been shown to abolish the cardiac output differences observed between borderline hypertensives, and normotensives (Birkenhager & Schalekamp, 1976; Gorlin et al., 1959). Exercising borderline hypertensives and normotensives have also been found to consume oxygen at equivalent rates (Gorlin et al., 1959). Therefore, these data indicate that borderline hypertensives appear normal while exercising. However, they respond differently to environmental demands while engaging in a minimal amount of activity. The most pertinent question here is, why do increased cardiac output and other changes resulting from increased sympathetic beta-adrenergic activity have adverse effects on blood pressure regulation in the resting, but not the exercising animal?

Resting animals experiencing increased sympathetic beta-adrenergic activity show reduced tissue oxygen extraction in relation to the amount of oxygen made available by increased cardiac output. Exercise produces an increase in the amount of oxygen that tissues extract from the blood. This increase in extraction is positively correlated with cardiac output in rats (Sherwood, Brener & Muncor, 1983), dogs (Langer, Obrist, McCubbin, 1979), and humans (Blix, Stromme & Ursin, 1974). This relationship provides the basis for a definition of sympathetic beta-adrenergic overreactivity. Once a regression line has been formulated which defines appropriate cardiac

output in terms of oxygen extraction, then sympathetic overreactivity occurs when cardiac output exceeds the expected cardiac output for the observed level of oxygen extraction.

Certain environmental demands cause a dissociation of oxygen extraction and cardiac output. Rats that were engaged in a shock avoidance task showed excessive cardiac output during periods of low activity (Sherwood et al., 1983). Dogs that were actively avoiding shock showed large increases in cardiac output (Langer et al., 1979). However, oxygen extraction increased very little during these avoidance tasks. Therefore, these animals were in a position where their cardiovascular systems output more oxygenated blood than was needed.

The cardiovascular systems of normotensive humans have also been found to output excessive amounts of oxygenated blood under a variety of conditions. Experienced pilots, as well as novices, showed heart rates in excess of metabolic requirements during takeoffs and landings (Blix et al., 1974). Heart rates which were indirectly shown to be excessive were also observed in ski jumpers, while they waited on the tower in anticipation of their next jump (Imhof, Blatter, Fuccella & Turri, 1969). Beta blockade reduced heart rate by 15% during the period in which the ski jumpers climbed to the top of the tower. Beta blockade reduced heart rate by 34% just prior to jumping, while the subjects were resting. There are also data to indicate that the threat of shock will evoke increased heart rate, despite a normalization of respiration (Harris, Katlick, Lick & Habberfield, 1976; McCaul, Solomon & Holmes, 1979). More innocuous task conditions also appear to be able to evoke excessive cardiac output. Receiving a poor evaluation from a teacher

(Grollman, 1929), speaking in public (Gliner, Bedi & Horvath, 1979), reaction time performance for monetary reward (Light & Obrist, 1983; Tranel, 1983), mental arithmetic (Kahneman, Tursky, Shapiro & Crider, 1969), a visual puzzle task (McCubbin, Richardson, Langer, Kizer & Obrist, 1983), and a space invaders game (Turner, Carroll & Courtney, 1983), have all evoked what appeared to be excessive increases in cardiac output. Finally as was noted previously, simply entering a clinic for examination is sufficient to evoke excessive cardiac output in borderline hypertensives (Gorlin et al., 1959; Lund-Johansen, 1967; Stead et al., 1945).

Studies of the relationship between oxygen extraction and cardiac output provide an operational definition for sympathetic beta-adrenergic overactivity. Excessive cardiac output becomes synonomous with oxygen overperfusion. Oxygen overperfusion is often seen in borderline hypertension. Although Obrist (1981) suggests that oxygen overperfusion could therefore be a causal factor in hypertension, no empirical studies could be found which test this hypothesis.

As already indicated, moderate and heavy exercise are associated with increased metabolic requirements. Increased sympathetic outflow stimulates the release of energy resources, as well as increasing the availability of oxygen to meet the needs of exercising muscles. For example, increased sympathetic outflow promotes lypolysis, thereby increasing the amount of free fatty acid in the blood. This occurs even when the animal is not exercising. Performance of a mathematics problem solving task increased plasma free fatty acid levels in both normotensive, and borderline hypertensive subjects (Baumann et al.,

1973). However, free fatty acid levels were found to be higher in the borderline hypertensive group. There is also some evidence that evoking emotional arousal in hypnotized, immobile subjects can increase their free fatty acid levels (Peterfy & Pinter, 1973). In addition, increased sympathetic outflow caused an increase in free fatty acid levels during a ball-bearing sorting task (Carlson, Levi & Oro, 1968).

If these free fatty acids are not metabolized by exercising muscle, then they may become incorporated into the walls of the vasculature, causing an increase in TPR. High blood pressures cause mechanical distensions of the vascular walls (Ross Russel, 1975). These distentions are believed to promote the influx of fats into the walls (Fry, 1973; Ross Russel, 1975). Therefore, it appears that the effects of increased sympathetic activity can work in coordination to alter one of the two main influences over blood pressure, TPR. Increased SBP caused by excessive cardiac output, and increased free fatty acid levels could in combination be causal factors in the development of hypertension.

Sympathetic outflow also stimulates the release of cholesterol. The ball-bearing sorting task increased the release of cholesterol, as well as free fatty acid (Carlson et al., 1968). Since plasma cholesterol level is associated with the risk of cardiovascular disease (Pooling Project, 1978), increased sympathetic beta-adrenergic activity may play a role in the development of hypertension through its effect on cholesterol release.

It was noted earlier that kidney functions are probably reset in all forms of sustained hypertension, because of the pressure reducing

effects of pressure diuresis (Guyton, 1978). It has been suggested that the renal maintenance of high blood pressure is caused by increased renal vascular resistance (Brod, 1973; Obrist, 1981), probably resulting from vascular stenosis (Mitchell & Schwartz, 1965). Increased sympathetic outflow may contribute to functional changes in the kidney, because, as indicated before, this outflow affects the kidney in a variety of ways.

Environmental conditions which evoke excessive increases in cardiac output, also appear to cause a sympathetically mediated reduction in renal blood flow. For example, hosing down the cages of baboons lead to an 80% reduction in renal blood flow (Vatner, 1978). However, exercising these baboons had no effect on renal blood flow. Task demands have induced similar results in human subjects. An arithmetic task evoked a reduction in renal blood flow, due to increased renal vascular resistance (Brod, 1963). Meanwhile, skeletal muscle blood flow increased eight fold, resulting in a overall reduction in TPR. These demonstrations represent a functional resetting of the kidneys, where pressure diuresis is inhibited, at least in part, by alpha-adrenerically induced vasoconstriction.

Sympathetic control over kidney function also appears to be part mediated by beta-adrenergically induced renin release and the subsequent production of angiotensin. The environment causes the release of renin under conditions where sympathetic activity is increased. For example, inescapable shock caused a rise in plasma renin activity in rats (Leenen & Shapiro, 1974). Beta-blockade abolished the rise in plasma renin. Plasma catecholamine levels are also associated with plasma renin

activity levels in humans (Chobanian et al., 1978). Plasma renin levels increased during mental arithmetic (Bauman et al., 1973). Plasma renin levels may have increased even in anticipation of a physical examination, although basal levels were not available for comparison (Esler, Julius, Zweifler, Randall, Harbourg, Gardiner & DeQuattro, 1977). As mentioned previously, renin stimulates the production of angiotensin, which causes increased renal vascular resistance, and increased salt and water reabsorption. Therefore, a functional adjustment is again made which results in increased blood volume during prolonged sympathetic excitation.

Angiotensin may cause renal vascular constriction by its ability to potentiate the effects of norepinephrine on the cardiovascular system. Long-term infusion of low doses of angiotensin evoked sustained hypertension in dogs that were exposed to a noisy laboratory environment (McCubbin, Soares DeMoura, Page & Olmsted, 1965). However, when these animals received little stimulation, the infusion of angiotensin which was not sufficient to increase blood pressure. Angiotensin infusion also caused larger increases in heart rate and blood pressure during shock avoidance in monkeys (Forsyth, Hoffbrand & Melmon, 1971). Therefore, it seems that the sympathetic nervous system not only increases cardiac output and reduces renal blood flow through direct neural stimulation, these changes are also enhanced through the production of angiotensin. Plasma renin levels are often high in borderline hypertension, and may contribute to increased blood pressure (Esler et al., 1977). However, the functional changes in the kidney which have been described here are only transient. It cannot be

concluded from these data that these changes are related to more permanent structural changes in the renal vasculature.

Folkow (1976) has proposed that transient increases in blood pressure cause functional and structural autoregulation. That is, in order to protect the capillary beds from high blood pressures, the resistance vessels which feed the capillary beds become narrower. This narrowing operates initially through the constriction of vascular smooth muscle, and subsequently through structural changes in the vascular wall. Folkow (1976) argues that this is the cause of increased TPR seen in severe hypertension. In addition, when autoregulation occurs in the renal vasculature, a lower glomeruler filter pressure results, and kidney function is reset.

Two examples of functional autoregulation have already been mentioned. Moss et al. (1966) found that dogs that were infused with physiological levels of norepinephrine exhibited an initial increase in cardiac output and mean arterial pressure. Four hours later, norepinephrine was still stimulating the heart, since cardiac contractility was still raised. However, TPR had risen over the four hours, and cardiac output and mean arterial pressure had returned to normal. Folkow (1976) would argue that the increased cardiac output and mean arterial pressure produced by norepinephrine infusion placed a mechanical burden on the vasculature. The response of the vasculature is to increase resistance to blood flow, in order to reduce this burden. Forsyth (1971) exposed monkeys to 72 hours of a shock avoidance contingency. These monkeys showed an initial rise in cardiac output and mean arterial pressure, and a reduced blood flow to visceral

organs, including the kidney. TPR rose over the 72 hour period, and cardiac output returned to normal. However, unlike norepinephrine infusion, mean arterial pressure remained elevated throughout the 72 hour period of shock avoidance. Increased TPR was closely related to reduced blood flow to the skeletal muscles. Therefore, the most visible occurrence of functional autoregulation was in the vasculature which fed the skeletal muscles.

A generalized increase in sympathetic outflow can be induced through left stellate ganglion stimulation. Functional autoregulation has been demonstrated using left stellate ganglion stimulation to increase cardiac output (Liard, Tarazi & Ferrario, 1976). This was followed by a normalization of cardiac output, and an increase in TPR, while blood pressure remained elevated. It appears that increasing sympathetic activity results in an eventual rise in TPR through the constriction of vascular smooth muscle. This increase may be mediated by increased cardiac output, and a reflexive response to protect against high blood pressure. While this pattern is seen in the development of hypertension, more direct evidence is needed to confirm the role of increased cardiac output in this process.

According to Folkow's (1976) theory, if increased blood pressure persists despite functional autoregulation, then structural changes in the vascular walls will occur. These structural changes will increase vascular resistance in a fully dilated, as well as a constricted vessel. Folkow, Grimbey and Thulesius (1958) studied forearm blood flow in normotensive and hypertensive patients. The vascular smooth muscles in the forearm were relaxed by ischemia, and work. Despite vascular

dilation, peripheral resistance was still elevated in the hypertensive patients, indicating a structural narrowing of the vessels. Others have also postulated that high blood pressure is responsible for the changes which occur in vascular structure (see Fry, 1973, for review). Fry (1973) suggests that high blood pressure places a mechanical stress on the vascular walls. This stress causes the vascular wall cells to increase their permeability to lipoproteins. Lipoprotein influx produces an increase in the population of smooth muscle and connective tissue cells. This increase in cell population is responsible for vessel narrowing.

Mitchell & Schwartz (1965) have also suggested that increased blood pressure can contribute to vascular stenosis. Mechanical stress produces blood flow sheering of the vascular wall. This sheering leads to raised platelet aggregation in the presence of increased blood pressure. Raised platelet aggregation is then responsible for vascular stenosis, and increased peripheral resistance. Augmented intravascular platelet aggregation has been observed in rats exposed to foot shock (Haft & Fani, 1973). Therefore, this is a plausible explanation for increases in TPR, observed after repeated increases in blood pressure caused by increased cardiac output.

There is empirical evidence that sympathetic beta-adrenergic outflow plays a part in structural autoregulation. As was previously indicated, Weiss et al. (1974) were successful at reducing blood pressure increases in SHR, by prolonged treatment with a beta-blocker. In addition to reduced blood pressure, the treated SHR were also found to have less structural change in the vasculature of their hind limbs.

Increased cardiac output may or may not have been responsible for the structural changes seen in untreated SHR. However, some effect of increased sympathetic beta-adrenergic outflow appears to have mediated the structural autoregulation.

Increased sympathetic alpha-adrenergic activity may be involved in autoregulation in normotensive animals. Increased TPR, which resulted from left stellate ganglion stimulation in intact dogs, was not seen when alpha-blockade was employed (Liard et al., 1976). Hypertension prone animals appear to have an increased sensitivity to alpha-adrenergic stimulation, therefore, sympathetic alpha-adrenergic activity may play a more pronounced role in functional autoregulation in this population. Less norepinephrine is required to produce a contractile response from the vascular smooth muscle of SHR, even before these animals become hypertensive, or show signs of vascular stenosis (Bohr & Berecek, 1976). In addition, human hypertensives that were treated with a beta-blocker still showed alpha-adrenergically mediated vasoconstriction, and increased blood pressure, when exposed to various environmental stimuli (Tarazi, 1973). Tarazi (1977) suggested that sympathetic beta-adrenergic outflow is responsible for the alpha-adrenergic response through a feedback loop which is unaffected by beta-adrenergic receptor blockade. This is because left stellate ganglion stimulation did not produce an immediate increase in vascular resistance, even when beta-blockade was employed (Liard et al., 1976). However, the existence of such a feedback loop has not been directly confirmed.

Cardiac output may have a role in resetting baroreceptor sensitivity, to allow sustained increases in blood pressure, without a reflexive reduction in cardiac output and TPR. Baroreceptor firing increases when carotid sinus pressure is increased (McCubbin & Ferrario, 1977). Renal clipping causes a reduction of baroreceptor sensitivity, since larger increases in blood pressure were needed to increase baroreceptor firing in dogs with renal clips (McCubbin, Green & Page, 1956). Maximal firing rate was unsteady and reduced in these hypertensive dogs. In addition, blood pressure and baroreceptor sensitivity are inversely related in humans (Gribbin, Pickering, Sleight & Peto, 1971). Baroreceptor sensitivity was reduced in borderline hypertensives in comparison with normotensive controls, but was greater than the baroreceptor sensitivity exhibited by patients with more severe hypertension (Takeshita, Tanaka, Kuroiwa & Nakamura, 1975). Baroreceptor firing threshold was also increased in hypertensives (Pickering & Sleight, 1977).

Protection of one carotid sinus from increased blood pressure prevents the resetting of baroreceptors in that sinus (McCubbin & Ferrario, 1977). Therefore, it appears that increased blood pressure is responsible for reductions in baroreceptor sensitivity. Since baroreceptor sensitivity changes have been demonstrated in borderline hypertensives, it seems highly likely that increased cardiac output has a role in changing this aspect of blood pressure regulation. However, if the kidneys are still functioning properly, sustained increases in blood pressure will not be tolerated, despite a resetting of the baroreceptors.

A resetting of baroreceptor funtioning is necessary for increased blood pressure to remain elevated, even for short periods. Increased cardiac output appears to be able to cause this resetting, so that baroreceptor firing threshold is increased, and sensitivity is decreased. In addition, structural changes in the renal vasculature, where stenosis causes a shift of blood flow away from the kidneys, may also be responsible for most cases of sustained blood pressure elevation. Functional and structural vascular changes do appear to occur in many cases of borderline and severe hypertension. The role of increased cardiac output in autoregulation has not been adequately established. However, exercising animals, and resting animals that show increased cardiac output without increased tissue oxygen extraction, do appear to differ from one another in several ways. The energy resources which are made available by increased sympathetic beta-adrenergic activity are metabolized faster by the exercising animal. Excessive amounts of free fatty acids and cholesterol could contribute to vascular stenosis. Athough cardiac output is increased in both exercising animals with increased sympathetic beta-adrenergic activity, and resting animals with increased sympathetic beta-adrenergic activity, the distribution of blood flow throughout the body is clearly different. For example, animals that display excessive cardiac output show reduced renal blood flow, while exercising animals show no change in renal blood flow. Therefore, these two type of animals will display different patterns of mechanical distention due to increased cardiac output. The pattern of mechanical distention produced by excessive cardiac output may be responsible for a reflexive increase in TPR.

Chapter Four

The Management of Hypertension

Previous chapters established that high blood pressure is associated with an increase in cardiovascular morbidity, and mortality. This chapter examines the benefits and costs of drug therapies which are designed to reduce blood pressure. Much of this thesis has been devoted to examining the role of sympathetic beta-adrenergic overactivity in hypertension. The importance of this neural factor is supported by the growing use of beta-blockers in the treatment of hypertension. However, extended drug therapy for young, borderline hypertensives, appears undesirable in most cases. Viable alternatives to pharmacological intervention in the treatment of borderline hypertension appear to be needed.

This chapter begins by discussing drug treatments for hypertension in Section A. An alternative method of management is to train subjects to control their sympathetic activity voluntarily, either by avoiding environmental triggers of sympathetic beta-adrenergic activity or through biofeedback. The latter approach requires in vivo measurement of sympathetic activity, which is discussed in Section B. The chapter concludes with a review of biofeedback studies that have tried to teach subjects to control sympathetic beta-adrenergic drive as a prelude to control of this variable in situations that elevate sympathetic activity.

A. Drug Treatments

Drug therapy to reduce blood pressure has been demonstrated to reduce morbidity and mortality amoung severe and mild hypertensives. A five year follow up study compared comprehensive drug therapy, with a control group which received care provided by a community physician (Lovell, 1981). Subjects in this study were chosen on the basis of initial blood pressure readings. All patients had initial DBP readings between 90 and 104 mm Hg. Comprehensive therapy consisted of a series of drug trials, which were terminated when a subject's DBP was below 90 mm Hg. Subjects in the comprehensive therapy group were then given responsibility for taking the prescribed medication as scheduled. However, subjects in the comprehensive therapy group were monitored regularly to ensure that their DBP remained below 90 mm Hg. At the five year follow up examination, subjects who were given comprehensive therapy had an average DBP of 83.4 mm Hg. Those subjects who were referred to a community physician had an average DBP of 87.8 mm Hg. This indicates that standard practice could be improved upon in order to lower DBP amoung the mildly hypertensive population. A 20% lower five year mortality rate among those given comprehensive care, indicates that standard practice could also be improved upon in order to lower mortality amoung the mildly hypertensive population. While this study lacks a no-treatment control group, it still provides good evidence that procedures are now available which would reduce mortality amoung mild hypertensives. Data indicating that drug induced blood pressure reductions in severe hypertensives reduces morbidity and mortality in this population, have been available for some time (see Short, 1975).

However, there is now a growing trend toward the treatment of patients with smaller increases in blood pressure (e.g. Lovell, 1981; Perry & Smith, 1978).

The use of beta-blockers, like propranolol, is increasing in the treatment of hypertension (Lovell, 1981). Beta-blockers have been shown to have the most salient physiological effects on subjects with borderline hypertension (Esler et al., 1977). Beta-blockers appear to normalize cardiac functioning in subjects who demonstrate increased cardiac work. Beta-blockade reduced heart rate by 34% in ski jumpers who were anticipating their next jump (Imhof et al., 1969). Beta-blockade also attenuated heart rate increases evoked by entrance into a novel laboratory setting (Obrist, 1981). In addition, signs of increased cardiac contractility in borderline hypertensives were removed by beta-blockade (Ibrahim, Tarazi, Dustan & Bravo, 1974). Although beta-blockers appear to normalize blood pressure most often in patients with increased cardiac output (Esler et al., 1977), increased cardiac output did not predict the hypotensive response to beta-blockade (Hansson, 1973; Ulrych, Frolich, Dustan & Page, 1968). However, when mean arterial pressure was reduced by beta-blockade, heart rate was reduced as well. These data indicate that increased TPR could be responsible for blood pressure increases in some patients with increased cardiac output. Although these data indicate that beta-blockade normalizes cardiac output, increased cardiac output is not necessarily responsible for increased morbidity in borderline hypertension. For example, the hypotensive response to beta-blockade is often associated

with the attenuation of increased plasma renin activity, which would reduce blood volume (Esler et al., 1977).

When hypertension is not solely the result of increased cardiac output, beta-blockers may still be effective in reducing blood pressure when taken over extended periods. Tarazi (1973) found that propranolol reduced cardiac output in all hypertensives he treated. However, the more severe patients in this study all showed an increase in TPR which was concomitant with the drop in cardiac output. About half of these patients showed a subsequent reduction in TPR to predrug levels with continued treatment with propranolol. Therefore, it appears that beta-blockers may benefit some severely hypertensive patients, but their effects are most clearly seen in milder cases.

It was indicated previously that borderline hypertensives are more likely to develop some form of cardiovascular disease than the general population (Kannel, 1977; Julius, 1977). Given that blood pressure reduction in mild hypertension has been shown to reduce mortality (Lovell, 1981), chronic beta-blockade might be therapeutic in some cases of borderline and mild hypertension. However, the cost of treatment in terms of both monetary expenditures, and adverse side effects, offsets the potential benefits of a comprehensive treatment for these patients. The yearly cost of drug treatment averages around $200 (Weinstein & Stason, 1976). It has been estimated that the cost of treating all Americans with SBP readings above 160 mm Hg, or DBP readings above 95 mm Hg, would be 2 billion dollars annually. If this treatment program included regular observations of those with SBP

reading between 140 and 160 mm Hg, and those with DBP readings between 90 and 95 mm Hg, then this figure jumps to 4.8 billion dollars per year.

The cost of drug side effects is difficult to determine, but may be quite large. Bulpitt, Hoffbrand and Dollery (1979) found that over 40% of hypertensive patients treated with propranolol reported feeling unsteady, and a weakness in their limbs. Over 30% reported having a slowed walking pace, blurred vision, or a blocked nose. Twenty percent reported an overall feeling of tiredness. In all, 78% of the patients examined by Bulpitt et al. (1979) experienced at least one adverse side effect from propranolol treatment. In addition to these side effects, which may hinder regular drug self-administration, complicating conditions often contra-indicate any use of propranolol (Aronow, 1973). For example, hay fever sufferers should not take propranolol during pollen season. These factors reduce the number of patients who can, or are willing to undergo drug therapy over extended periods.

The potential benefits of a comprehensive drug treatment program for all hypertensives are further reduced by the small percentages of mild hypertensives who would develop some disease, or die from having an increased blood pressure. Although approximately 25% of all borderline hypertensives were found to progress to higher blood pressures (Julius, 1977), less than 3% of borderline hypertensives between the ages of 45 and 54 will become more severely hypertensive in any given year (Miall & Brennan, 1979). In addition, as indicated earlier, less than 3% of borderline hypertensives develop a cardiovascular disease in any given year (Kannel, 1977). It appears that if all mildly hypertensive patients were placed in a drug therapy programme, the large majority

would have to pay for drugs, and endure adverse side effects, without receiving any benefit. Since drug treatment does not appear to prevent mortality in all cases (Lovell, 1981), the potential benefits of widespread drug use are quite small, in comparison to the cost of treatment.

The data reviewed in previous chapters indicate that environmental stimuli can potentiate blood pressure increases in animals and perhaps humans who are prone to becoming hypertensive. The data also indicate that stimuli which evoke increased sympathetic activity appears to be responsible for many cases of transient borderline hypertension. It has been known for some time, that reassurance, and placebo therapies can reduce blood pressure (Goldring et al., 1956). In addition, repeated exposure to a novel environment will lead to an habituation of increased sympathetic activity (Benson et al., 1971; Obrist, 1981). Since reduced sympathetic beta-adrenergic activity is one method of achieving normalized blood pressure in many mild hypertensives, it may be possible to treat these patients by manipulating their external environment. Manipulation could be geared toward reducing the frequency and duration of exposure to situations that increase sympathetic drive. Alternatively, borderline hypertensives might be taught to reduce the magnitude of increases in sympathetic beta-adrenergic activity elicited by these situations.

The latter approach is illustrated by a study by DeGood and Adams (1976). These investigators used heart rate feedback to train subjects to reduce the magnitude of heart rate increases evoked by an aversive stimulus. Subjects were exposed to a series of tone-shock

pairings. Subjects that were given heart-rate feedback and told to reduce their heart rates were better at attenuating heart rate increases during the CS exposure, than subjects who were given instructions to relax or who simply listened to music throughout the session. While these findings are encouraging, heart rate may not be a reliable measure of sympathetic beta-adrenergic activity, because of vagal influences. If learned effects are to be exploited in blood pressure control, then a reliable, easily measurable index of sympathetic beta-adrenergic influences on the heart is needed. Such an index would also be valuable for studying the effects of the environment on the cardiovascular system, and examining the role of increased cardiac output in the development of severe hypertension. Research which examines biofeedback training and learned control over an index of sympathetic beta-adrenergic activity could have implications for therapeutic uses for this index. This research could also help to validate the reliability of this index for assessing sympathetic activity. If this index could be used to aid the patient in avoiding or changing environmental conditions which would be likely to increase beta-adrenergic activity, then this knowledge could circumvent the use of pharmacological beta-blockade for treating mild elevations in blood pressure.

B. Measuring Sympathetic Beta-Adrenergic Influences on the Heart

The data reviewed thus far indicate that sympathetic beta-adrenergic overactivity often plays a role in increased blood pressure. The most salient short-term effects of the sympathetic nervous system on blood pressure are mediated by increased cardiac output. Increased

cardiac output results from increased contractile rate and force. Since TPR is usually reduced during a generalized increase in sympathetic activity, increased cardiac output causes a rise in SBP, but acts only to prevent DBP from dropping. These relationships could be employed to establish a measure of sympathetic beta-adrenergic influences on the heart. This section examines possible methods for deriving a measure that could be used for biofeedback training and/or for study of the effects of environmental manipulation on the cardiovascular system.

Since sympathetic beta-adrenergic activity cannot be measured directly, the physiological effects of sympathetic stimulation must be the objects of measurement. Also, the procedures used to measure these effects should not themselves alter sympathetic activity. Although this goal may not be fully achievable in practice, it is preferable that the subject not know what is being measured. It is also preferable that the subject not know when this measurement occurs. For example, city driving was found to produce fluctuations in blood pressure and heart rate when these parameters were recorded by an experimenter who sat in the back seat of the car (Taggart, Gibbons & Somerville, 1969). However, these changes were not observed when the driver rode alone (Littler, Honour & Sleight, 1973). Finally, non-invasive measures are usually prefered over invasive measures.

Increased sympathetic outflow to the heart causes a rise in SBP. Therefore, SBP could be used to index sympathetic influences on the heart. However, SBP is also a function of TPR. Changes in SBP could be indicative of changes in cardiac output, or TPR. In addition, as Obrist (1981) suggested, the blood pressure cuff used to determine SBP, is one

of the most obvious physiological measurement techniques available. While SBP measures are clearly useful for verifying blood pressure change, it is not a good measure of the cardiovascular effects of sympathetic activity.

The sympathetic nervous system provides the only direct neural control over skin conductance. Therefore, skin conductance could be used to index sympathetic activity, provided that skin-conductance changes covary with changes in cardiovascular activity. However, this does not appear to be the case. Skin-conductance changes were not associated with heart-rate changes during shock avoidance (Lawler & Obrist, 1980), or passive exposure to shock (McCaul, Solomon & Holmes, 1979). When differing monetary rewards were used to vary the incentive for reaction time performance rate, some subjects displayed large increases in heart rate, and little change in skin conductance (Tranel, 1983). Conversely, skin-conductance alterations were not reflected in heart-rate change. In addition, heart-rate changes produced by a mental arithmetic task were not correlated with skin-conductance changes (Steptoe & Ross, 1981). These data indicate that individual differences in heart-rate reactivity are not reflected in skin-conductance change. Therefore, skin conductance does not appear to be a good index of sympathetic influences on the heart.

The data presented in previous chapters indicate that changes in sympathetic beta-adrenergic influences on the heart are reflected in heart-rate change. However, these data also indicate that heart-rate change could result from changes in vagal restraint. Pharmacological studies have found that the vagus is the dominant neural influence on

heart rate under normal resting conditions (Berne & Levy, 1972; Julius et al., 1975). When under vagal control, heart-rate changes are closely associated with changes in somatomotor activity (see Obrist, 1981). Therefore, heart-rate changes reflect both sympathetic and parasympathetic influences on the heart. Changes in somatomotor activity disrupt the relationship between sympathetic activity and heart rate. In addition, sympathetic influences on heart rate can be masked by changes in vagal restraint (Obrist et al., 1965). Heart rate, like SBP, can provide useful information about sympathetic control over cardiac output. However, since it is often undesirable, and perhaps impossible to satisfactorally restrict somatomotor activity, heart rate alone is not a good index of sympathetic beta-adrenergic influences on the heart.

As stated earlier, the sympathetic nervous system provides the dominant neural influence on cardiac contractility. The vagus has very little control over cardiac contractility (Berne & Levy, 1972). Vagal influences are seen only at higher levels of sympathetic activity. Therefore, cardiac contractility could be a useful measure of sympathetic beta-adrenergic influences on the heart.

Cardiac contractility refers to the contractile force exerted by the left ventricle of the heart, when pumping oxygenated blood. Although it appears to be a good measure of sympathetic influences on the heart, cardiac contractility cannot be directly measured non-invasively. In addition, no one universally accepted measure of cardiac contractility exists. However, the available invasive procedures currently used to assess cardiac contractility are all based on the same

assumption. These procedures assume that the rate at which cardiac contraction occurs best reflects cardiac contractility during any given contraction (Falsetti, Mates, Greene & Bunnell, 1973; Talley, Meyer & McNay, 1971). One measure of cardiac contractility involves the estimation of the maximum contraction velocity of the heart muscle (Falsetti et al., 1973). This is known as Vmax. Another measure of cardiac contractility examines the rate of change in left intraventricular pressure over time (dP/dt) (Talley et al., 1971). In order to remove the effects of intrinsic changes on left ventricular dP/dt, this parameter has been examined in relation to the amount of pressure in the aorta against which the left ventricle is working, and in relation to the circumference of the left ventricle (Ahmed, Levinson, Schwartz & Ettinger, 1972). The result is the Frank-Levinson index of cardiac contractility. Vmax and the Frank-Levinson index are invasive measures which have been used to validate non-invasive measures of cardiac contractility. Pharmacological beta-blockade and enhancement have also been employed in this validation process. However, it must be remembered, that the invasive measures of contractility are only estimates of sympathetic beta-adrenergic influences on the heart. In addition, it is impossible to rule out a compensatory cardiovascular response, designed to maintain blood flow, when pharmacological methods are employed.

Recent attempts to obtain a non-invasive index of cardiac contractility have usually employed techniques for measuring blood pressure changes at some peripheral point in the arterial system. Since left ventricular dP/dt has been used as an invasive index of

contractility, it appeared logical to assess the validity of dP/dt in a peripheral artery as a non-invasive index (Obrist, Lawler, Howard, Smithson, Martin & Manning, 1974). Obrist et al. (1974) used a low frequency microphone, placed at the base of the neck, to transduce the pulse wave signal from the carotid artery. The maximum positive slope of the pulse wave, like Vmax, was tested for its reliablility as an index of cardiac contractility. Subjects were infused with isoproterenol, a sympathetic beta-adrenergic agonist. This resulted in a rise in the maximum slope of the carotid pulse wave. However, this change was completely attenuated when isoproterenol infusion was preceded by beta-blockade.

Obrist et al. (1978) found that beta-blockade consistently attenuated the carotid dP/dt increases which were evoked by a shock avoidance task. Carotid dP/dt, like heart rate and SBP, was increased for the longest duration when subjects were kept actively involved in shock avoidance. However, carotid dP/dt was less affected by involvement in more passive tasks, such as the cold pressor (Obrist, 1981). Therefore, carotid dP/dt appears to be less sensitive to vascular changes than is heart rate. Subjects for whom shock avoidance was contingent upon reaction-time performance showed larger increases in heart rate, but not carotid dP/dt. Therefore, carotid dP/dt may also be less sensitive than heart rate to changes in sympathetic activity.

Although these data indicate that carotid dP/dt is influenced by sympathetic influences on left ventricular contractility, there are several disadvantages to the use of this measure. For example, TPR seems to affect carotid dP/dt (Lawler & Obrist, 1974). Increased TPR

caused a reduction in arterial dP/dt. In addition, this measure is uncalibrated. That is, there is no value of dP/dt that necessarily corresponds to a particular contractile force across subjects or sessions. Movement artifact was also a common problem with the technique used by Obrist and his coworkers. While recordings from the radial artery in the wrist eliminated this problem, radial dP/dt was not correlated with carotid dP/dt (Obrist et al., 1974). Therefore, technical difficulties have prevented a more complete assessment of the validity of carotid dP/dt as a measure of cardiac contractility, and make it difficult to use as a part of a biofeedback training procedure.

Left ventricular pre-ejection period, which is described in Appendix A, has been widely used as a non-invasive index of cardiac contractility. The pre-ejection period is the time interval which begins with the electrical impulse initiating left ventricular contraction, and which is terminated by the opening of the aortic valve of the left ventricle. Sympathetic outflow to the heart causes the conduction of the electrical impulse to occur more quickly, hastening the onset of mechanical contraction (Abel & McCutcheon, 1979). In addition, as the maximum velocity of cardiac contraction increases, the pressure inside the left ventricle exceeds aortic pressure, and opens the aortic valve sooner. Therefore, as sympathetic outflow, and cardiac contractility increase, pre-ejection period is shortened.

The available data support the close relationship between cardiac contractility, and pre-ejection period. Drugs were used to vary cardiac contractility in dogs (Talley et al., 1971). Left ventricular dP/dt was found to be significantly correlated with left ventricular

pre-ejection period (r=-.70). In humans, pre-ejection period has been found to be significantly correlated with Vmax (r=-.79), the Frank-Levinson index of contractility (r=-.82) (Ahmed, Levinson, Schwartz, Ettinger, 1972), and plasma catecholamine levels (r=-.83) (Cousineau, Lapointe & De Champlain, 1978). In addition, epinephrine and norepinephrine infusion shorten pre-ejection period (Cousineau et al., 1978), and beta-blockade infusion lengthens pre-ejection period (Harris, Schoenfeld, Weissler, 1967). The reliability of pre-ejection period as an index of cardiac contractility is supported by studies which have found that changes in heart rate which were not mediated by changes in sympathetic activity had no effect on pre-ejection period (Harris et al., 1967; Talley et al., 1971).

Pre-ejection period appears to be altered by processes involved in the development of hypertension. Borderline hypertensives often have shortened pre-ejection periods, indicative of increased sympathetic beta-adrenergic activity (Ibramhim et al., 1974; Tarazi et al., 1976). In addition, pre-ejection period and cardiac output together accounted for nearly 60% of blood pressure variability in one group of borderline hypertensives with increased cardiac output (Inoue et al., 1973). Therefore, pre-ejection period could provide good information about sympathetic influences on the heart, which is relevant to research on the development of hypertension.

Non-invasive measurement of pre-ejection period requires the use of a microphone to detect the sound of aortic valve closure (Newlin & Levenson, 1979). As was the case with the carotid dP/dt measurement technique described earlier, measurements made with the microphone are

subject to movement artifact. The procedure employed by Newlin and Levenson (1979) involved the collection of data over the period of 60 heart beats before an average pre-ejection period was calculated. Less data might be required if procedures such as subject immobilization were employed to allow a better signal to noise ratio. However, this procedure still does not allow the calculation of pre-ejection period on every heart beat. In addition, subject immobilization is undesirable anyway, since it may affect the processes being measured. For these reasons, feedback training to control changes in pre-ejection period does not yet appear to be practical.

The time period which begins with the electrocardiogram event called the R wave, and is terminated by the arrival of the pulse wave of blood at a peripheral site, is referred to as the R-wave to pulse wave interval, or RPI (Obrist, 1981). The RPI has been hypothesized to be a good measure of sympathetic beta-adrenergic influences on the heart (Newlin & Levenson, 1979; Obrist, 1981). The RPI contains much of the pre-ejection period and has the advantage of being measureable on every heart beat. However, the time period which is initiated by the electrical impulse responsible for stimulating left ventricular contraction, and which is terminated by the start of muscle contraction is not included in the RPI, since the R wave is coincident with the start of muscle contraction. The reason for employing the R wave is that it is more easily detected. In addition, the excluded portion of the pre-ejection period has not been found to vary significantly in the biofeedback setting (Newlin & Levenson, 1979; Steptoe, Godaert, Ross & Schreurs, 1983). The RPI also covers the time period which is initiated

by the opening of the aortic valve, and terminated by the arrival of the pulse wave of blood at some peripheral point in the arterial system. This is known as transit time. The arrival of the pulse wave is indicated by a rapid rise in blood density and pressure, and the RPI will vary depending upon how much of a rise in blood density is needed to meet the criterion for its termination.

Since the RPI is a composite measure which includes both the pre-ejection period and the transit time, its ability to index sympathetic beta-adrenergic influences on the heart depends upon when and how it varies with each of its component parts. The velocity with which the pulse wave moves through the vasculature is affected by cardiac contractility (Matsuura & Goodyer, 1973). That is, increased cardiac contractility will shorten the transit time portion of the RPI. However, Steptoe, Smulyan & Gribbin (1976) have suggested that transit time reflects mainly vascular influences on blood pressure. Therefore, it is preferable to have RPI covary more with pre-ejection period than with transit time.

There is empirical evidence that this is in fact the case. For example, RPI recordings which were terminated at the radial artery were not correlated with the time it took the pulse wave to travel from the brachial to the radial artery (Lane, Greenstadt, Shapiro & Rubinstein, 1983). Light and Obrist (1983) used a reaction time task with monetary reward for fast performance to evoke increased sympathetic beta-adrenergic activity. RPI and pre-ejection period differentiated subjects who showed large heart-rate changes from those who showed smaller heart-rate changes during the task. However, transit time did

not differentiate these subjects. RPI and pre-ejection period were differentially affected by task difficulty, but transit time was not. In addition, RPI and pre- ejection period abbreviations diminished over time, but transit time remained unchanged over the course of the task. Steptoe et al. (1983) also found that RPI change reflected more of a change in pre-ejection period than transit time during a variety of tasks including a mathematics test, bicycling, and the act of standing up. In addition, Newlin (1981) observed the hemodynamic changes which occurred in subjects involved in a reaction-time task, a stroop test and an isometric handgrip exercise. A median within-subject correlation of .86 was found between RPI to the ear, and pre-ejection period.

RPI also seems to covary with blood pressure in a manner which suggests that it is influenced more by cardiac contractility than vascular resistance. RPI has been found to be correlated with SBP, but not DBP in both normotensive (Lane et al., 1983; Newlin, 1981; Obrist et al., 1979) and hypertensive subjects (Allen, Schneider, Davidson, Winchester & Taylor, 1981).

It does appear that transit time plays more of a role in RPI determination as RPI is terminated further away from the heart. RPI was correlated with transit time more often when it was terminated at the wrist, than when it was terminated at the ear (Steptoe et al., 1983). In addition, there was a non-significant trend toward a covariance between RPI and DBP when the site of RPI termination was moved from the carotid artery to the wrist (Obrist et al., 1979). However, even when RPI was terminated at the wrist, pre-ejection period still contributed more than transit time to RPI variance (Pollack & Obrist, 1983).

RPI appears to be sensitive to increased sympathetic beta-adrenergic activity evoked by external stimuli. Shock avoidance caused a shortening of RPI (which was correlated with heart-rate increase) (Light & Obrist, 1980b; Obrist et al., 1979). RPI was also shortened when fast reaction-time performance resulted in monetary reward (Light & Obrist, 1983). In addition, a mathematics test, an analogies test, and a digit- symbol substitution test all produced significant reductions in RPI that were correlated with increases in heart rate (Steptoe & Ross, 1981).

In my review of the literature, RPI has never been examined in relation to any invasive measure of cardiac contractility. However, Obrist et al. (1979) found a good within-subject correlation between the RPI terminated at the carotid artery, and carotid dP/dt ($r=-.66$). In addition, pharmacological sympathetic beta-adrenergic enhancement significantly shortened the RPI in resting subjects (Weiss, Del Bo, Reichek & Engelman, 1980). Meanwhile, beta-blockade significantly lengthened the RPI in both resting subjects (Weiss et al., 1980), and subjects who showed reduced RPI recordings due to participation in a shock avoidance task (Obrist et al., 1979). Therefore, there is good evidence that changes in sympathetic outflow to the heart are reflected in RPI change.

Although pre-ejection period and RPI are sensitive to changes in cardiac contractility produced by changes in sympathetic activation, at least two factors have been shown to confound these relationships. These factors are referred to separately as preload and afterload, and they are referred to collectively as loading factors. Preload refers to

the amount of blood in the left ventricle at the start of cardiac contraction. Afterload refers to the amount of blood pressure resisting the expulsion of blood from the left ventricle. As preload increases, the resting fiber length of the left ventricle is increased. When this occurs, the Frank-Starling mechanism is invoked. The Frank-Starling mechanism refers to the intrinsic increase in contractile force which occurs when contractile elements are stretched more during ventricular filling. For example, as the amount of left ventricular filling increases, contractility will also increase, and this will be reflected in an increase in pre-ejection period. This logic has been confirmed in dogs (Talley et al., 1971), and humans (Stafford, Harris & Weissler, 1970). Preload appears to affect cardiac contractility to the greatest extent during rest (Lawler, Obrist, Lawler, 1975; Rushmer, 1970), and during postural change (Rushmer, 1970). Since pre-ejection period is the major source of RPI variability, preload is expected to affect RPI as well as pre-ejection period. However, the available data do not give a clear indication that preload is a potent source of RPI variance in the biofeedback setting.

Preload may also have an effect on transit time and pulse-wave rise time. Since increased contractility causes blood to be pumped into the vasculature at a faster rate, the Frank-Starling mechanism should reduce transit time as preload increases (Matsuura & Goodyer, 1973). Increased contractility also causes the pulse wave to rise more rapidly (Lawler & Obrist, 1974). Therefore, intrinsic changes in contractility should produce changes in pulse-wave rise time, just as sympathetically

mediated changes in contractility produce changes in pulse-wave rise time.

Rise time also appears to be affected by changes in afterload. Lawler & Obrist (1974) found that pulse wave rise time was often positively correlated with DBP in resting dogs. Therefore, it seems that increases in afterload may lenghten the pulse wave rise time component of the RPI.

Afterload may also act to produce a change in pre-ejection period which is independent of a change in sympathetic stimulation of cardiac contractility. Afterload increases with increased TPR. As afterload increases, the amount of force resisting the opening of the aortic valve is increased. When this occurs, more intraventricular pressure is necessary to push the valve open. Since it takes longer for the contracting ventricle to reach this higher pressure, the pre-ejection period is lengthened with increasing afterload. This logic has also been confirmed in dogs (Wallace, Mitchell, Skinner & Sarnoff, 1963), and in humans (Steptoe et al., 1983). It appears that an increase in afterload will lengthen the pre-ejection period segment of the RPI. However, as afterload is increased, transit time is expected to be reduced (Lane et al., 1983). Since these two components of the RPI are inversely affected by afterload, it is difficult to determine the effect afterload will have on RPI. It was mentioned previously, that the RPI has not been found to be well correlated with DBP, indicating that afterload may not be a potent source of RPI variance. On the other hand, Weiss et al. (1980) found that drug induced vasodilation, which is assumed to have reduced afterload, caused a

lengthening of RPI in human subjects. If these data are relevant to the intact subject, then it appears that afterload will affect RPI mainly through its effects on transit time and pulse wave rise time. RPI should be inversely related to afterload. However, the actual extent to which afterload affects the RPI in the biofeedback setting is not known.

Since available techniques allow the immediate determination of the RPI during each cardiac cycle, it is a good target measure for biofeedback training. RPI appears to be sensitive to both pharmacologically and behaviorally induced changes in the level of sympathetic beta-adrenergic stimulation of the heart. In addition, one study found that RPI did not covary with somatomotor activity, or respiratory frequency (Newlin & Levenson, 1980). However, subjects in that study were told to breath normally, and avoid excessive movement during recording sessions. Moderate to heavy exercise has been shown to result in increased sympathetic activity (Robinson et al., 1966), and reduced RPI (Steptoe et al., 1983). There may be behaviors which do not evoke changes in sympathetic activation, but which evoke changes in RPI. However, these behaviors have not been discussed in the literature. The next section discusses previous attempts to train subjects to produce changes in RPI. Subjects in these studies were constrained in the amount of somatomotor activity they could employ to produce changes in RPI. Therefore, the ability of subjects to change RPI by the use of behaviors which alter preload or afterload may have been reduced in these studies.

C. Biofeedback Training for RPI Control

A number of attempts to train subjects to control changes in RPI have been reported in the literature. Although comparisons between studies are difficult due to the lack of standard training and assessment procedures, there is agreement that resting, constrained subjects have not been able to produce RPI changes of more than a few milliseconds. However, the procedures used in these studies have not allowed the assessment of a subject's ability to alter ongoing RPI change in an unconstrained manner. This section includes a discussion of procedural variations that might make training more successful.

Cinciripini & Epstein (1981) trained three subjects to produce bidirectional changes in RPI. Each RPI was terminated when the pulse wave reached the left index finger. The first three to four sessions were used for baseline recordings. These sessions began with a 20 minute habituation period. The habituation period was followed by a 40 minute baseline period. The baseline period was used to establish the expected change in RPI for comparisons with changes seen during training. The next eight to ten sessions were used for training. These sessions also began with a 20 minute habituation period. The habituation period was followed by a 20 minute period in which subjects were asked to increase or decrease RPI without feedback. The final 20 minutes of each training session was used for the actual feedback training. Two subjects were given four to five sessions of RPI shortening training, followed by four to five sessions of RPI lengthening training. The third subject received lengthening training

first. Feedback consisted of a red light which was illuminated to indicate appropriate RPI change on each heart beat.

Cinciripini & Epstein (1981) found that RPI lengthened an average of 2.29 msec during the baseline sessions. RPI was lengthened an average of 3.55 msec during lenghten training sessions. RPI was shortened an average of 8.21 msec during shorten training sessions. The changes produced during training indicate that the subjects learned bidirectional control over RPI change. However, RPI was not lengthened significantly more during training than during baseline. It was suggested that RPI shortening represented a change in pre-ejection period since it was associated with SBP increase, but not DBP increase.

D. Johnston (1980) examined RPI control and its relationship to cardiac interbeat interval change. During the first phase of the experiment, 16 subjects were given feedback training to produce bidirectional changes in RPI. RPI was terminated when the pulse wave reached the subjects left wrist. Each subject received five training sessions, each of which consisted of 12, 90 sec trials. Subjects were reinforced for RPI shortening on six trials, and RPI lengthening on six trials. However, subjects were told not to tense their muscles, or alter their breathing pattern during training. Those subjects who were able to produce bidirectional changes in RPI, were studied for 5 additional sessions. During the second phase of the experiment subjects were asked to make changes in RPI, without significantly altering cardiac interbeat interval. Subjects were immediately notified if cardiac interbeat interval varied from the pretrial average.

D. Johnston (1980) found that eight of the original 16 subjects were able to produce bidirectional changes in RPI by the end of the first phase of training. However, it is not possible to discern the magnitude or direction of RPI changes from D. Johnston's (1980) article. During this first phase, RPI change was always accompanied by a cardiac interbeat interval change in the same direction. During the second phase, similar results were obtained. RPI changed only when cardiac interbeat interval also changed. In addition, one subject was unable to keep cardiac interbeat interval from changing, but did not show a concomitant change in RPI. These data strongly suggest that RPI change is mediated sympathetically. The subject who displayed cardiac interbeat interval change without RPI change may have done so by a change in parasympathetic nervous system tone. Since RPI change was always accompanied by a change in cardiac interbeat interval in the same direction, loading factors seemed to have been absent, or at least masked by changes in sympathetic nervous system activity.

Newlin & Levenson (1979) gave eight subjects three days of training to produce bidirectional changes in RPI. RPI was terminated when the pulse wave reached the subjects right index finger. Each session of training consisted of 8 feedback trials, 4 during which subjects were reinforced for RPI shortening, and 4 during which subjects were reinforced for RPI lengthening. Shorten and lengthen trials were presented in a random order. Each trial lasted for 180 cardiac cycles, and was preceded by a pretrial baseline period of 60 cardiac cycles in length. Subjects were asked to breath normally, and avoid physical movement during the experiment.

Newlin & Levenson (1979) found that subjects were able to shorten RPI by the third session of training. RPI was shortened an average of 2.8 msec during shorten training trials. Subjects were unable to lengthen RPI in this experiment. Changes in pre-ejection period and transit time were examined in the 4 subjects who showed the greatest amount of RPI shortening. These 4 subjects shortened RPI an average of 5.5 msec during RPI shorten trials. Pre-ejection period shortened an average of 2.4 msec during these trials, while transit time shortened an average of 3.3 msec. Discrepancies between the amount of RPI change and the amount of change in its two component parts resulted from the use of only a portion of feedback trial cardiac interbeat intervals to determine the durations of component parts. In contrast to the experiments reported above, RPI changes reported here appear to be the result of vascular changes, as well as changes in cardiac sympathetic tone. However, this is not unexpected, since stronger correlations between RPI and DBP have been reported when RPI was terminated at this distance from the heart (Obrist et al., 1979).

Newlin & Levenson (1980) conducted two follow-up experiments to further examine RPI control, and its relationship to pre-ejection period. In the first experiment, 12 subjects were given three sessions of RPI training which consisted of the procedures used earlier (Newlin & Levenson, 1979). However, in this experiment, RPI was terminated when the pulse wave reached the subjects right ear. Subjects were told to breath normally, and to avoid excessive physical movement while attempting to control the strength of their heartbeats. Respiratory frequency and general activity level were recorded during each session.

As a group, subjects were able to produce bidirectional changes in RPI, which were accompanied by changes in pre-ejection period. Subjects shortened RPI an average of 4.8 msec from pretrial values, during shorten training trials of the first session. Subjects lengthened RPI an average of 2.9 msec during lengthen training trials of this session. However, the magnitude of RPI change was reduced over sessions, for both shorten and lengthen trials. This reduction was accompanied by a reduction in the magnitude of pre-ejection period change. Therefore, it appears that when the RPI is terminated when the pulse wave reaches the subject's ear, RPI change is dependent on changes in pre-ejection period.

Comparison of the 6 best and 6 poorest RPI controllers revealed no differences in respiratory frequency, or general activity level. This does not preclude the existence of other, unrecorded somatic or respiratory parameters concomitant with the RPI. However, it does support the notion that changes in the RPI, which is terminated at the ear, are due mainly to sympathetic beta-adrenergic influences on the heart.

The second experiment in the Newlin and Levenson (1980) study employed procedures that were similar to those used in the first experiment. However, subjects in the second experiment were placed in one of three groups. One group received 3 sessions of eight feedback trials during which RPI shortening was reinforced. The second group received three session of eight feedback trials during which RPI lengthening was reinforced. The third group received three sessions of eight trials without feedback information. Subjects in this third group

were asked to increase the strength of their heart beats on four trials during each session, and to decrease the strength of their heart beats on four trials during each session, without feedback to guide their performance.

Newlin & Levenson (1980) found that only subjects who were asked to shorten RPI were able to do so, and only when given feedback. These subjects shortened RPI an average of 3.9 msec during each trial. Subjects who were asked to make changes in the RPI without feedback were unable to do so. RPI shortening was again accompanied by pre-ejection period shortening. However, unlike the first experiment, subjects' ability to shorten RPI did not diminish over sessions. RPI shortening was associated with a shortened cardiac interbeat interval, and a trend toward increased respiratory frequency.

Newlin & Levenson (1980) concluded that the changes they observed in RPI terminated at the ear are largely affected by changes in sympathetic beta-adrenergic activity. However, they did not feel that their findings supported the use of RPI training with clinical populations. Perhaps attempts to train RPI lengthening might be more successful if subjects are first placed in a situation which evokes a rise in sympathetic beta-adrenergic activity.

In a series of experiments, Steptoe examined RPI control in both resting subjects, and subjects who were engaged in some task which resulted in a shortening of RPI (Steptoe 1976, 1977, 1978; Steptoe & Ross, 1981b). Steptoe (1976) examined the effects of feedback presentation on RPI control. RPI was terminated by the arrival of the pulse wave at the wrist. Subjects were placed in one of 4 groups. One

group was instructed to increase blood pressure (shorten RPI) without feedback. The second group was instructed to decrease blood pressure (lengthen RPI) without feedback. The third group was instructed to increase blood pressure with RPI feedback. The fourth group was instructed to decrease blood pressure with RPI feedback. Subjects received four sessions of training. Each session began with an 8 minute baseline data collection period. This period was followed by nine 4 minute trials, separated by 2 minute intertrial intervals. No group received feedback on trials 5 and 9, although the task demands remained the same on these trials. Subjects were told to keep still, and not to make changes in their breathing pattern.

Steptoe (1976) found that the addition of feedback information to instructions to change RPI enhanced control in the increase group, when change scores were derived from the initial baseline. However, feedback control was superior in both directions, when change scores were derived from the pretrial periods. These findings were due to a change in the running baseline over the course of each session. As each session progressed, the average intertrial interval RPI became longer. This accentuated the ability of subjects to lengthen RPI when change scores were derived from the initial baseline. This change in the running baseline also attenuated the ability of subjects to shorten RPI when change scores were derived from the initial baseline. It appears that feedback can enhance specific control over RPI change.

Steptoe (1976) found that subjects who were instructed to increase blood pressure (shorten RPI) exhibited a faster respiration rate and larger respiration amplitude than subjects in the decrease

condition. Increase subjects also showed greater amounts of movement during the last two sessions. These changes were observed despite instructions to refrain from making changes in these parameters. However, changes in activity level and respiratory parameters were not clearly related to the magnitude of RPI change. Therefore, Steptoe (1976) did not conclude that RPI change was mediated by changes in respiration or activity level.

Steptoe (1977) attempted to replicate the effects of feedback training on the learned control of RPI lengthening. In this study, Steptoe presented the feedback display to two groups of subjects who were asked to keep still and breath normally. While both groups were told to reduce blood pressure in the presence of the display, only one group was told that changes in the display represented changes in blood pressure (RPI). The other group was falsely informed that blood pressure changes had no bearing on the display. Except for this difference in instructions, environmental stimuli were equated for the two groups. Following attempts to lengthen RPI under quiet conditions, subjects performed a auditory choice reaction time task, and were asked to continue reducing blood pressure without feedback.

Steptoe (1977) found that subjects who were provided with accurate feedback information for changes in RPI produced greater RPI lengthening from the initial baseline. However, unlike the previous study (Steptoe, 1976), feedback did not improve learned RPI control based on changes from the running baseline. Subjects in both groups showed reduced respiration rate and general activity level during attempts at control. In addition, subjects in both groups continued to

lengthen RPI during the identification task. However, RPI control was maintained longer in the group which was given correct instructions about the feedback display. These results indicate that providing subjects with feedback in a quiet environment may not aid in attempts to lengthen RPI. RPI lengthening was evident when just instructions to reduce blood pressure were given. However, feedback training may aid subjects in lengthening RPI during tests which produce RPI shortening, perhaps through increases in sympathetic beta-adrenergic activity.

Steptoe (1978) further examined the effects of feedback training for RPI control on RPI lengthening during cognitive tasks. In this experiment, one group of subjects was again given feedback for changes in RPI length, and instructed to reduce blood pressure (i.e., lengthen RPI). RPI was again terminated when the pulse wave reached the wrist. However, unlike previous experiments, the control group in this study was given instructions in relaxation. During the experimental sessions, trial periods where subjects were told to reduce blood pressure using feedback or relaxation were alternated with trial periods in which blood pressure reductions were requested while subjects engaged in the auditory choice reaction time task mentioned previously (Steptoe, 1977).

Steptoe (1978) found that subjects were able to lengthen RPI to the same extent, whether they were provided with feedback or instructions to relax. Relaxation subjects and feedback subjects produced similar changes in RPI from both the initial baseline, and the running baseline. RPI was lengthened an average of about 2 msec from the running baseline in both groups, on trials in which subjects were only requested to reduce blood pressure. However, feedback subjects

were again better able to maintain RPI control during the performance of an additional task. The distracting task conditions disrupted RPI control in the group given instructions in relaxation. Therefore, it again appears that feedback training aids in the transfer of RPI control to more distracting settings.

It is interesting to note that while subjects in both the feedback and relaxation groups produced similar changes in RPI under quiet conditions, heart rate was reduced more in the relaxation group. In addition, the relaxation group reduced respiration rate and general activity level more during conditions of quiet control. It is not clear if RPI lenghtening was achieved by different means in these two groups, or if the relaxation group simply engaged in additional, and unnecessary activity during attempts to lower blood pressure.

This study by Steptoe (1978) included a second experiment. In this second experiment, a feedback group and a relaxation group were again used. Three experimental sessions were employed, and each session began with a 10 minute period during which subjects were asked to lengthen RPI under quiet conditions. Subjects in both groups were then asked to lengthen RPI during a series of auditory choice reaction time tasks, and mental arithmetic tasks. Each session ended with instructions to lengthen RPI under quiet conditions, but no feedback was provided to subjects in the feedback group during this final trial period.

Feedback was again unable to aid subjects at increasing the magnitude of RPI lengthening under quiet conditions. However, unlike the first experiment, feedback subjects did not produce more RPI

lengthening during the reaction time task. On the other hand, feedback subjects did show more RPI lengthening during the second session of mental arithmetic. Relaxation and feedback subjects were equally successful at lenghtening RPI during the mental arithmetic task by the third experimental session. Therefore, it appears that feedback training may aid the subject in lengthening RPI during periods of cardiovascular arousal, but this effect does not appear to be robust, based on Steptoe's (1978) results.

The effects of feedback training on RPI control were further examined by Steptoe & Ross (1981b). This study included three groups. One group received RPI feedback, and another received instructions in relaxation. The third group read "neutral" magazines during periods in which feedback and relaxation treatments were administered. Session 1 was used to familiarize the subjects with the experimental setting, and test subject reactivity to three cognitive tasks. Sessions 2 through 5 included periods of quiet RPI control, and exposure to the three cognitive tasks, with and without simultaneous feedback presentation.

Steptoe and Ross (1981b) found that the group given relaxation instructions lengthened RPI an average of 2.6 msec from the running baseline under conditions of quiet control. Relaxation subjects actually showed greater RPI lengthening than feedback subjects. In fact, feedback subjects were no better at lengthening RPI than subjects who read magazines under quiet conditions. This suggests that feedback does not enhance RPI control, when subjects are also given instructions to reduce blood pressure. On the contrary, it has been suggested that

under resting conditions, the feedback display actually handicaps attempts to lengthen RPI (Steptoe & Ross, 1981b).

The results from task trials, on the other hand, tend to favor feedback training. The group given RPI feedback produced more RPI lengthening than the group which read magazines. However, the relaxation group did not produce more RPI lengthening than the group which read magazines. In addition, there was a trend toward more RPI lengthening in the feedback group than in the relaxation group during the first session when the cognitive tasks were combined with instructions to reduce blood pressure. While these results are not overwhelming, they are consistent with earlier studies which indicate that RPI feedback training can lead to more RPI lengthening under conditions where increased sympathetic activity has been evoked.

These conclusions are also supported by the results of a study done by Benthem and Glaros (1982). Subjects in this experiment were placed in one of four groups. During Session 1, all subjects were given a mental arithmetic test, followed by a rest period. During Sessions 2 and 3, however, groups were treated differently. One group was given an arithmetic test, followed by an RPI feedback training period, with instructions to lower blood pressure. RPI was terminated when the pulse wave reached the subject's left ring finger. The second and third experimental sessions for the second group began with a rest period, and was followed by a period of RPI feedback training, as in the first group. The third group was given the mental arithmetic test, followed by a period of false RPI feedback, and instructions to lower blood pressure. The fourth group was given the arithmetic test,

followed by a rest period. The four groups were again treated identically during Session 4. The fourth session began with the arithmetic test, and was followed by a rest period during which subjects were requested to lower blood pressure, without any feedback.

Benthem and Glaros (1982) found that the arithmetic test evoked a similar shortening of RPI in all four groups. RPI shortened an average of 15 msec during the first session's test. The second, third, and fourth groups, as described above, showed similar RPI shortening during the arithmetic test in Session 4. However, the first group, which had been given RPI feedback following the arithmetic test on Sessions 2 and 3, actually showed a slight lengthening of RPI during arithmetic test in session 4. Therefore, these data represent the largest RPI training effects observed to date. Benthem and Glaros (1982) concluded that feedback training can reduce RPI shortening under task conditions, but only when training is preceded by conditions which evoke a shortening of RPI.

It would appear from these studies that RPI feedback training is not the most efficient method of getting resting subjects to lengthen RPI. Instructions to relax appear to be as good or better than feedback training at inducing resting subjects to lengthen RPI. The data suggest, however, that feedback training can be carried over to conditions which tend to evoke RPI shortening. Instructions to relax do not appear to bring about habituation of RPI shortening to task demands as quickly as feedback training does. However, this effect has not been very robust, and guidelines for the most efficient use of feedback training are by no means clearly laid out by these studies. The

procedures employed in the studies reviewed here leave many questions about the control of RPI change unanswered.

Instructions to sit still, and breath normally appear to have restricted subjects abilities to change RPI. Of all the studies reviewed here, only one (Cinciripini & Epstein, 1981) did not give subjects these kinds of instructions. Cinciripini and Epstein (1981) found that unconstrained subjects could produce more RPI shortening than had been previously reported for constrained subjects (Newlin & Levenson, 1979, 1980). Although subjects in that study (Cinciripini & Epstein, 1981) produced only small elongations of RPI, it may still be possible that subjects who are directly told that they are allowed to use any methods they choose to produce feedback changes can produce significant RPI lengthening. Since it is not practical, and perhaps not possible to completely stabilize a subject's activity level and respiratory pattern, verbal instructions which attempt to accomplish this have little chance of being successfully carried out. Therefore, it would be interesting to establish to what extent somatomotor and respiratory changes will affect RPI.

Information about the target response given to subjects in most of the RPI feedback training experiments may also have limited the magnitude of RPI change, and the methods that subjects used to achieve RPI change. Several researchers asked their subjects to produce changes in the feedback by raising or lowering blood pressure (Benthem & Glaros, 1982; Steptoe, 1976, 1977, 1978; Steptoe & Ross, 1981). At least two objections can be made against this practice. First, instructions to change blood pressure may cause subjects to adopt inappropriate

strategies. This is because changes in RPI result from changes in cardiac contractility more often than changes in vascular resistance (Newlin, 1981; Pollack & Obrist, 1983; Steptoe et al., 1983). The goal of training is to train subjects to produce the maximum possible change in the target measure. Biofeedback training is the type of training being examined, and subjects receive information about success and failure from the feedback display. Since the RPI is the result of many complicated processes, verbal instructions to change some visceral parameter cannot provide completely accurate information about task demands. Only the feedback can do that. This leads to the second objection regarding the use of verbal instructions. Since these instructions do not convey precise information about task demands, it is likely that each subject will interpret them differently. This could have the effect of adding another unwanted within group variable. Subjects may tend to use false, preconceived notions about the demands of the task and plan their response strategies accordingly. This problem can be circumvented through procedures which convey minimal information about task demands except the information subjects receive from the feedback display.

Biofeedback training procedures which attempt to restrict information about task demands to changes in the feedback display have been successful at training subjects to produce bidirectional changes in visceral target measures (Roberts, Marlin, Keleher & Williams, 1980). These procedures were viewed as providing the subject with a problem solving task. Based on previous attempts to train RPI control, it appears that the production of changes in RPI within a limited time

frame is a difficult task. Since sympathetic activity level seems to vary with mental task difficulty (e.g. Kahneman, Tursky, Shapiro & Crider, 1969), subjects are expected to experience some increase in sympathetic activity when asked to produce changes in some unspecified physiological parameter based on information gained solely through the feedback display. Although the results of the study by Benthem and Glaros (1982) indicate that a specific task demand such as a mental arithmetic test is necessary for training RPI control, it has also been shown that simply entering a laboratory in order to participate in an experiment can produce increased sympathetic outflow (Obrist, 1981). Therefore, it is possible that presenting the feedback training procedure as if it were a problem solving task, would raise sympathetic beta-adrenergic activity level above baseline. Once a parameter has been raised from baseline, then attempts to move the level of that parameter in the direction of that baseline become practical.

There is evidence that subjects experience increases in sympathetic activity, as measured by shortened RPI, when they enter the laboratory for a training experiment. Cinciripini and Epstein (1981) used baseline and training periods that lasted for 20 minutes each. They found that RPI lengthened an average of 2.29 msec during the 20 minute baseline periods. The purpose for taking baseline measures is to establish a stable response level (Yates, 1980). Once a stable response level has been established, then experimental manipulations can be conducted, and response level changes can be assessed. Baseline measures which are gathered at the begining of an experimental session, do not provide a stable baseline for feedback training. Response

drifting over the course of the session can alter results. For example, Steptoe (1976) found that feedback subjects produced RPI lengthening and shortening of about equal magnitude when the session's initial baseline was used for comparison. However, subjects were found to have produced much more RPI shortening than lengthening when the running baseline was used for comparison. Therefore, this drift effect exaggerates control in the direction of the drift, while underestimating changes in the opposing response (Yates, 1980). The drift effect is reduced by the use of pretrial baselines. Pretrial baselines also allow the use of within subject analyses. Therefore, it is not necessary to attempt to establish appropriate non-contingent feedback control groups when pretrial baselines are employed. It has been suggested that experimenter initiated feedback trials may disrupt learning (Yates, 1980). Therefore, subjects must be given sufficiently long training trials and extended periods of training to fairly assess control. However, the pretrial baseline still appears to be the best measure of response level for examining learned control of RPI.

The goal of RPI feedback training to be reported in this thesis was to attempt to provide subjects with a good measure of sympathetic beta-adrenergic influences on the heart. All of the previous examinations of learned RPI control, with the exception of one (Newlin & Levenson, 1980), employed an RPI which was terminated when the pulse wave reached the subject's wrist or finger. RPI varies more closely with vascular resistance as the pulse wave used to terminate each RPI is detected further away from the heart (Obrist et al., 1979). Therefore, RPI should index sympathetic influences on the heart better when it is

terminated at the ear, than when it is terminated at the wrist. Since the microphone used to transduce blood density in the carotid artery was unreliable (Obrist et al., 1974), the ear densitogram appears to be a better source of the pulse wave signal (Newlin, 1981). The ear provides a stable resting place for a plethysmographic instrument. Therefore, this site is a good candidate for reliably detecting pulse waves that will terminate each RPI, and reflect changes in cardiac pre-ejection period.

In conclusion, it appears that subjects can gain control over RPI. However, the changes they have been observed to produce are not very large. Feedback seems to aid the subject in lengthening RPI during the performance of other tasks. However, feedback may disrupt RPI lengthening in resting subjects. Previous studies which have examined learned RPI control have often involved instructions to keep still and maintain normal breathing. They have also used verbal instructions to guide subject performance in addition to the information provided by the feedback display. These practices may have limited the magnitude and possible sources of RPI change. An argument was made for training procedures which provide subjects with a minimum of information from sources other than the feedback display. This setting may be sufficient to move the tonic level of RPI into a range where both shortening and lengthening are possible. The ear densitogram appears to be the best available source for measuring the pulse wave signal used to terminate the RPI, when the goal is to train subjects to produce changes in sympathetic activity level. In addition, it was argued that a pretrial baseline is the most appropriate standard for assessing RPI change.

Chapter Five

An Experiment on Learned Control of RPI Change

The previous chapter examined attempts by other researchers to train subjects to produce changes in RPI. Most of the changes observed in these experiments were minimal. However, when subjects were not given explicit instructions to refrain from movement, larger reductions in RPI were observed (Cinciripini & Epstein, 1981). In addition, there appeared to be some improvement in RPI lengthening when baseline RPI was shortened (Benthem & Glaros, 1982; Steptoe & Ross, 1981). It was suggested that additional information about RPI control might be gained by allowing subjects to attempt to control RPI in a less constrained environment, where information about the target response is minimal, except for changes in the feedback display. This chapter reports an experiment of this type. As suggested earlier, subjects were trained in an ambiguous task environment that favored dependence on feedback as a guide to success. A running baseline was used to evaluate RPI changes. RPI was terminated at the ear.

There are several response strategies that subjects might use under these conditions to gain control of RPI. One of these is respiratory manipulation, since respiratory parameters affect autonomic nervous system control over cardiac performance. For example, Lum (1981) found that hyperventilation produces physiological signs of sympathetic dominance. These signs included tachychardia, dilated pupils, cold extremities and palmar sweating. Therefore, subjects may

attempt to shorten RPI by increasing respiratory frequency, and subjects may attempt to lengthen RPI by reducing respiratory frequency. The usefulness of this strategy is further supported by studies which examined the learned control of heart-rate change. Levenson (1976) found that subjects who learned to produce bidirectional changes in heart rate always showed changes in respiration rate, which occurred in the same direction as heart-rate change. Similar results were obtained by VanDercar, Feldstein & Solomon (1977). In addition, they found that heart-rate control was lost when subjects were passively respirated, except in those subjects who produced measurable changes in somatomotor activity.

Some caution must be employed when hypothesizing about the usefulness of respiratory strategies for changing cardiavascular parameters. McCaul, Solomon & Holmes (1979) and Harris et al. (1976) found that heart-rate increases produced by the threat of shock were unaffected by the active manipulation of respiratory rate. However, they found that skin conductance was reduced by slowing respiratory frequency. Steptoe (1976) found that subjects who were being trained to shorten RPI initially increased their respiration rate. Respiration rate normalized with continued training, but RPI control continued to increase. In addition, deep breathing reduced heart rate less in borderline hypertensive subjects, despite increased basal heart rate in this group (L. Johnston, 1980). Therefore, it appears that more data are needed to establish whether changes in respiration rate can be useful in RPI control.

In addition to manipulating respiration rate, subjects may also attempt to alter phases of the respiratory cycle. Since inspiration appears to cause an abrupt onset of spinal cardiac sympathetic discharge (see Kirchhein, 1976, for review), subjects may spend more time inhaling during trials where RPI shortening is reinforced, and more time exhaling during trials where RPI lengthening is reinforced. This notion is supported by L. Johnston's (1980) examination of respiratory sinus arrhythmia. Heart rate was found to increase during inhalation, and decrease drastically at the onset of exhalation.

Some subjects are also expected to engage in moderate to heavy levels of exercise during attempts to shorten RPI. Resting subjects engaged in light exercise show heart-rate changes which are mediated by changes in parasympathetic tone (see Obrist, 1981, for review). Therefore, heavier levels of exercise are expected to be required to increase sympathetic activity (Robinson et al., 1966) and shorten RPI. Steptoe (1976) found that some subjects who were being trained to shorten RPI showed an increase in general activity level. However, the magnitude of general activity-level change was not associated with the magnitude of RPI change. Since subjects were told to keep still in Steptoe's (1976) study, changes in general activity level were probably modest. If RPI is a good index of sympathetic activity, then somatomotor strategies should only be successful if subjects show large increases in activity. Information about the effects of general activity level on RPI should be gained by examining learned control in relatively unconstrained subjects. Although not all subjects are expected to discover respiratory or somatomotor responses which might be

useful in RPI control, the simplicity of these strategies should lead one to expect that unconstrained subjects will demonstrate some degree of control over RPI.

A. Method

Subjects. The subjects were 27 male volunteers who received introductory psychology course credit for their participation. Subjects who reported a history of any respiratory disorders (one subject), or cardiovascular disorders (two subjects) were excluded. Subjects with DBP readings above 90 mm Hg, or SBP readings above 130 mm Hg (three subjects) were also excluded. One subject passed the initial screening phase, but was later rejected due to a cardiac electrical abnormality. Two subjects' sessions were terminated early due to equipment malfunction. Data from four subjects were uninterpretable due to noisy signals. One subject did not return for the second experimental session. This left a pool of 12 subjects aged 19 to 27 years. No a priori subject groupings were employed. Subjects participated in the experiment for two sessions of two hours each, conducted on consecutive days.

Apparatus. Electrophysiological recordings were made with Beckman Ag/AgCl electrodes. Electrodes used for skin conductance measurements were filled with a mixture of Unibase and .1M NaCl. All other electrodes were filled with Beckman electrode paste. A mercury strain gauge was used to measure chest circumference. An inflatable cushion in the seat of the subject's chair was coupled with a pressure transducer for measuring general movement. A Hewlett-Packard #780-16 ear plethysmograph was used to transduce ear blood density.

The laboratory configuration allowed continuous polygraph recordings of skin conductance (SC) from one hand, forearm muscle tension (EMG) from one arm, general activity level (MVT), electrocardiographic changes, blood density in the pinna of the left ear, and chest circumference. A BRS digital circuit discriminated the electrocardiogram R-wave, and triggered a cardiotachometer. This produced an analog representation of heart rate for polygraph recording. In addition, during trial periods, RPI changes were recorded relative to the pretrial average based on information provided by a PDP-11 computer.

The BRS digital circuit also discriminated the rise in ear blood density produced by the arrival of the pulse wave. The amount of rise in the blood density signal required for discrimination varied slightly over time due to tonic changes in ear blood flow. Discrimination of the R-wave and pulse wave, set off the Schmidt trigger on the computer's programmable clock. The computer discriminated R-waves from pulse waves based on contiguous signals from the BRS routed to two of the computers digital input channels. Cardiac interbeat interval (IBI) and RPI were determined on-line by the computer. Each IBI must have been between 300 and 1500 milliseconds to have been accepted. Each RPI must have been between 100 and 300 milliseconds to have been accepted. The computer made on-line RPI data available for polygraph recording and feedback.

All other data were routed through the computer's analog-to-digital conversion channels. The computer collected EMG, MVT, heart-rate, and chest-circumference data at a rate of 8 times per second. SC

data was collected at a rate of 4 times per second. Data were collected for 30 seconds prior to, as well as during each trial. This provided a response baseline for feedback, and a running baseline of each measure for comparison with trial data.

At the end of each trial, pretrial and trial means and standard deviations were calculated for each measure, and stored on floppy disk. Pretrial and trial means, standard deviations, and mean changes from pretrial to trial periods were also printed on hard copy at this time. An additional floppy disk was used to store raw data. Chest-circumference data were analyzed to derive average pretrial and trial respiration intercycle interval (ICI), amplitude, and volume (the area under the respiratory envelope). With the exception of respiration amplitude and volume, trial change scores were arithmetic differences between trial and pretrial averages. Change scores for respiration amplitude and volume were the ratios of trial to pretrial values.

During feedback training, subjects were seated in a sound-attenuated, electrically shielded room. The subjects sat in a padded chair, which had been fixed in the upright position. The room was carpeted, and subjects were surrounded by curtains which were suspended from the ceiling, forming a 2 x 3 meter enclosure. A rectangular hole was cut in one curtain to expose the television screen situated in front of the subject's chair. All control equipment was located in other rooms.

The feedback display was drawn on the television screen using Apple computer graphics. The Apple computer made changes in the feedback display based on information from the PDP-11. The feedback

display included of a trial cue, the letter "A" or "B", situated in the upper right-hand quadrant of the television screen. During "training" trials, a short horizontal line appeared towards the bottom of the screen to indicate the response baseline. In addition, a feedback dash was presented and moved up or down with respect to the horizontal line, depending upon the subject's RPI changes. For each type of trial, the feedback was adjusted so that desired changes in RPI produced upward movements of the feedback dash. Feedback sensitivity was adjusted so that each msec lengthening of RPI, relative to baseline, moved the feedback dash one and one half times the distance of the movement produced by each msec shortening of RPI. This was done to produce subjectively similar excursions of the dash on lengthen and shorten trials. A sample feedback display is shown in Appendix B.

Trial cues (the letters A or B) were presented during "test" trials, but no feedback was provided. The television screen remained blank during "blank" trials.

Procedure. The experimental procedures were designed to keep subjects unaware of the nature of the target response (RPI). Information about the response was provided by analog feedback only. Upon arrival, subjects were seated in the reception room. They were given general information about the procedures and were required to sign an informed consent form. The informed consent form insured that subjects were aware that they could withdraw from the experiment at any time. In addition, when signing the form, subjects indicated that they would maintain the integrity of the experiment by not discussing the procedures with their classmates. A copy of the informed consent form

appears in Appendix C. A medical interview was then conducted and blood pressure recorded. A copy of the recording form used for the medical interview appears in Appendix D. If subjects passed this screening procedure, recording electrodes were attached.

Electrodes were attached to several sites, both for recording purposes, and to keep subjects unaware of task demands. An electrode was attached to the hypothenar eminence of each palm for measuring SC. SC reference electrodes were attached to the ventral surface of each wrist, after the area was lightly abraded with sandpaper. One pair of electrodes was attached to each forearm to measure EMG. Cardiac electrical activity was measured by an electrode placed over the sternum, and one placed over a rib on the subject's left side. Two electrodes were placed on the subject's forehead, but no measurements were taken from these electrodes. The subject was then lead into the training room and seated. A strain guage was wrapped around the subject's upper torso for measuring respiratory activity. A plethysmograph was clamped to the pinna of the left ear for measuring blood density.

Subjects were left alone in the room with the lights dimmed, and the door closed. White noise was employed to mask distracting sounds from outside the experimental chamber. An intercommunication system allowed verbal communication between subject and experimenter. Baseline recordings were taken for two minutes to ensure the data were good. Subjects then heard a set of taped instructions which explained the subject's task and the feedback display. For the purposes of training, increases and decreases in RPI were treated as two distinct responses,

which were randomly labelled "A" or "B". Subjects were provided with sample training displays during the instructions. For each type of trial, the subject was told to move the feedback dash upwards. Subjects were also informed that they would be required to perform these tasks without feedback. On these test trials, only the letter cues were provided. Sample displays for these test trials were also provided.

The taped instructions also indicated that bonus money would be paid for good performance. Subjects were told that they were free to use any methods they wanted to produce changes in the target measures, but that they should not touch or put pressure on the electrodes. They were also asked to rest and sit quietly when the display was blank. A transcript of the taped instructions appear in Appendix E.

The session involved a total of 28, 60 second trials. Inter-trial intervals were varied, and averaged about 60 seconds in length. Data were recorded during the last 30 sec of each intertrial interval to provide a baseline for the subsequent 60 sec trial period. The session began and ended with four randomly ordered test trials, two of each type. Two 60 second trial periods also occurred before and after training, while the screen remained blank. Training consisted of 16 feedback trials, eight of each type, presented randomly. However, no more than two of either trial type occurred consecutively. The set of possible trial sequences is presented in Appendix F.

The procedures on the second day of training were similar to those of the first day. However, the consent form was not used, and no medical interview was conducted. An abbreviated version of the taped

instructions were played. This session also consisted of a total of 28 trials.

An unexpected verbal report was taken from subjects, during this second session. The verbal report questionnaire was answered at the end of training, but before the final block of test and blank trials was presented. The first section of the questionnaire asked subjects to report what they did to produce feedback events during each of the two types of training trials. The second section of the questionnaire consisted of a list of cognitive, respiratory and somatomotor activities. Subjects were asked to indicate the extent to which each of these activities were employed during each type of trial. Subjects were also asked to rate their success at producing increases in each of the two responses. A copy of the verbal report questionnaire appears in Appendix G.

B. Results and Discussion

The subject sample was divided into a group of five subjects who produced bidirectional changes in RPI during training trials on Day 2, and a group of seven subjects who did not produce bidirectional changes in RPI during training trials on Day 2. Independent two-sample one-tailed t-tests, which assume equal variance, were employed to establish the existence of within-subject bidirectional changes in RPI.[1]

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[1] Two-sample t-tests without the assumption of equal variance produced an identical breakdown. The tests of Table 1 are preferred here to maintain consistency with earlier practice (Roberts et al., 1980). Both sets of results are tabled in Appendix H.

The results for each subject are given in Table 1. Inspection of these data shows that Subjects D, F, J, L, and R produced bidirectionally significant RPI changes on Day 2 whereas the remaining subjects did not. Henceforth, the five subjects who produced significant bidirectional changes in RPI will be referred to as differentiators, and the seven subjects who did not produce significant bidirectional changes in RPI will be referred to as non-differentiators. Graphical representations of performance by the two groups support this distinction and are given in Figure 1. The data indicate that subjects who are provided only with feedback information about RPI change can produce significant bidirectional changes in RPI. In addition, bidirectional changes appear to be larger (approximately 5.8 msec for all subjects on Day 2) when subjects are told to use any methods they choose to produce these changes, than when subjects were asked to sit still and breath normally (approximately 3.3 msec for all subjects on Day 2, Newlin & Levenson, 1980). Although subjects in the Newlin and Levenson (1980) study received fewer training trials, they received at least as much total exposure time to the feedback as subjects received here.

Differentiators and non-differentiators were compared for between group differences during Day 2 RPI lengthen and shorten training trials. During lengthen training trials, differentiators' RPI change was not different from non-differentiators' RPI change ($t(10)= -0.98$, $p>.05$). Differentiators and non-differentiators were also no different when average lengthen trial changes in heart rate ($t(10)= -0.02$, $p>.05$), respiration ICI ($t(10)= -0.50$, $p>.05$), MVT ($t(10)= 0.07$, $p>.05$), and EMG ($t(10)= 0.46$, $p>.05$) were compared. During shorten training trials,

Table 1

Bidirectional changes in RPI

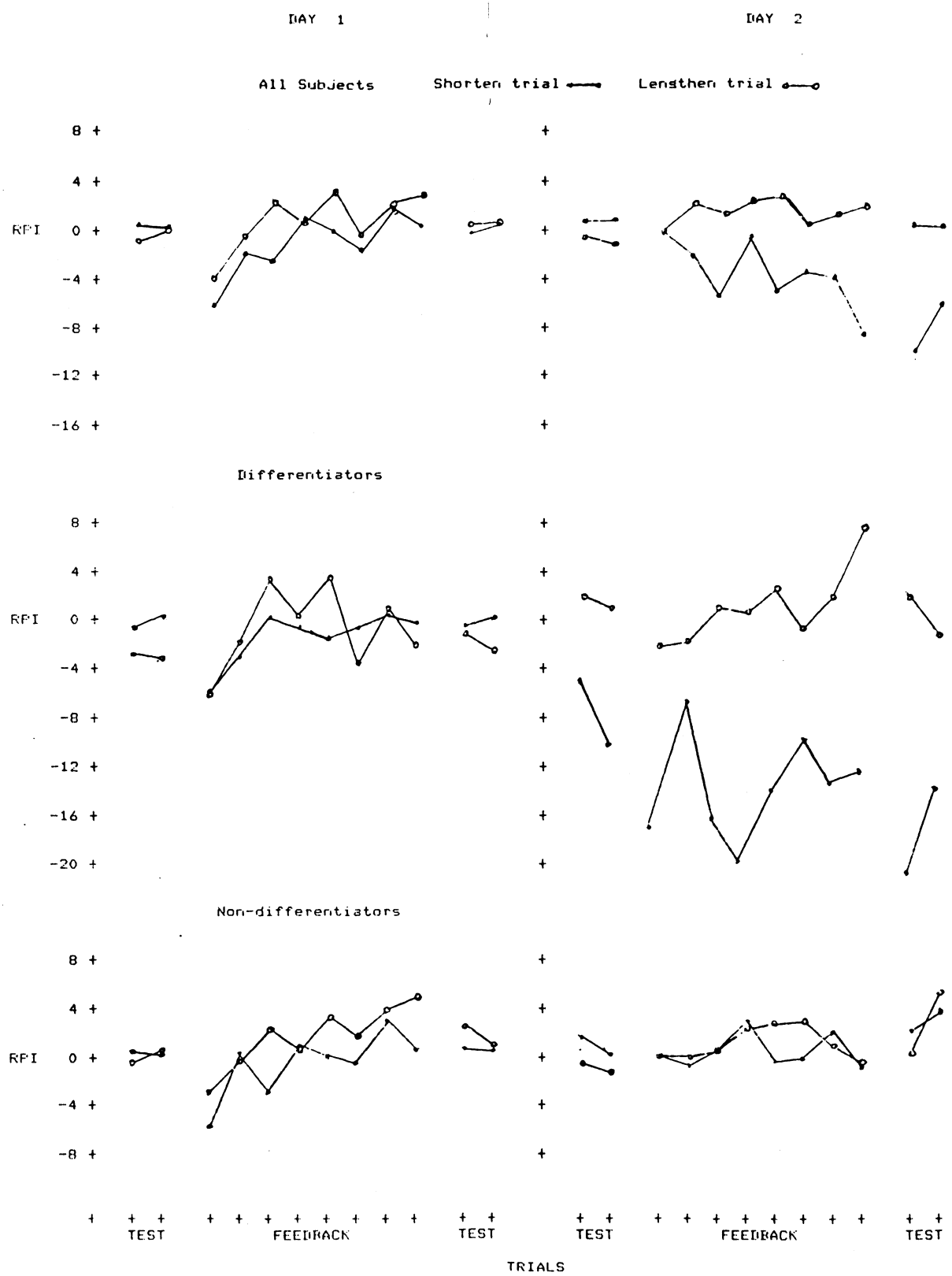
Ss#	t-value[a]	Day 1[b] shorten	Day 1[b] lengthen	Day 2[b] shorten	Day 2[b] lengthen
B	t(14)= 1.367	2.51	2.03	-.13	1.66
C	t(12)=-0.006	-1.43	3.92	-1.60	-1.63
D	t(14)= 3.348**	.56	3.82	-8.70	1.18
F	t(14)= 2.424*	-13.02	-9.57	-16.84	-7.27
G	t(14)= 1.038	-4.13	-4.26	-.59	1.13
I	t(14)= 0.305	.55	2.23	2.24	2.70
J	t(14)= 2.687**	-5.18	-5.49	-12.89	-5.74
L	t(14)= 4.625**	.75	-3.69	-19.08	4.88
P	t(13)=-0.326	-1.29	1.43	3.00	2.22
Q	t(14)= 0.361	1.05	.70	-2.42	-1.16
R	t(14)= 5.368**	.34	-.19	-15.14	2.86
S	t(14)= 0.249	1.93	1.93	.54	.51

[a]Two sample independent t-tests from day 2 training trial data. Alpha levels are for a one-tailed test.

[b]Entries are RPI changes in milliseconds.

*p<.05
**p<.01

Figure 1. RPI changes from pretrial values across two days of training and testing. RPI is in milliseconds.


DAY 1
DAY 2
All Subjects
Shorten trial
Lengthen trial
RPI
8
4
0
-4
-8
-12
-16
Differentiators
-20
Non-differentiators
TEST
FEEDBACK
TEST
TEST
FEEDBACK
TEST
TRIALS

RPI change was greater among differentiators than among non-differentiators ($t(10)= 8.81$, $p<.005$), indicating that differentiators were better able to shorten RPI. Differentiators also showed more heart-rate change on these trials ($t(10)= 3.74$, $p<.005$), indicating that shortened RPI was associated with increased heart rate. Differentiators also shortened their respiration ICI significantly more than non-differentiators during RPI shorten training trials ($t(10)= 3.37$, $p<.005$). EMG ($t(10)= 0.58$, $p>.05$) and MVT ($t(10)= 1.58$, $p>.05$) changes were not different between groups. However, in all cases differentiators' average changes in general activity were greater than those of non-differentiators during shorten trials.

It appears that differentiators distinguished themselves by their ability to shorten RPI. They seem to do so by increasing respiration rate and perhaps general activity level. Data that were reviewed earlier suggested that increased respiration rate reduced vagal control over the heart (Eckberg et al., 1980; Hirsch & Bishop, 1981), and produced a condition of sympathetic dominance (Lum, 1981, Tenney & Lamb, 1965). Therefore, differentiators may have produced sympathetically mediated RPI shortening by increasing respiration rate. A sympathetic mediation of RPI shortening amoung four of the five differentiators is further supported by the magnitude of heart-rate changes produced by these subjects. Heart rates rose above 100 beats per minute in these four cases. These heart rates were consistently associated with increased sympathetic activity in a previous study (Robinson et al., 1966). Therefore, the concomitant data indicate that

RPI shortening produced by differentiators was at least partially mediated by increased sympathetic outflow to the heart.

A different approach to the analysis of response patterns is given in Figures 2, 3, and 4, where the performance of differentiators on each concomitant is portrayed. Application of t-tests to bidirectional performance on Day 2 training trials revealed significant differences in cardiac interbeat interval ($t(8)= 2.64$, $p<.05$), and respiratory ICI ($t(8)= 2.08$, $p<.05$). No significant differences were found for EMG ($t(8)= 1.64$, $p>.05$), MVT ($t(8)= 1.29$, $p>.05$), SC ($t(8)= 1.26$, $p>.05$), respiratory amplitude ($t(8)= 0.43$, $p>.05$), or volume ($t(8)= 0.33$, $p>.05$). Differences in concomitant parameter changes between shorten and lengthen training trials appears to be due only to changes during shorten training trials. Changes were not apparent during lengthen training trials.

Lack of RPI lengthening may have been due to a ceiling effect on Day 2, but not Day 1. If sympathetic activity is increased by initial exposure to the laboratory (e.g., Obrist, 1981), then it would be expected to drift back towards baseline as the session progressed (Cinciripini & Epstein, 1981; Steptoe, 1977). RPI was longer during pre-training blank trials on Day 1 than on post-training blank trials on Day 1 ($t(11)= 2.77$, $p<.01$) when all 12 subjects were tested as a group. However, this drifting was not seen on Day 2 ($t(11)= 0.98$, $p>.05$). On the other hand, heart rate was higher during pre-training blank trials on both Day 1 ($t(11)= 5.07$, $p<.005$), and Day 2 ($t(11)= 2.63$, $p<.05$). This inconsistency is not readily explainable, but it indicates that the

Figure 2. Differentiators EMG, MVT and SC changes from pretrial values across two days of training and testing. EMG and MVT are in arbitrary units. Skin conductance is in micromhos.

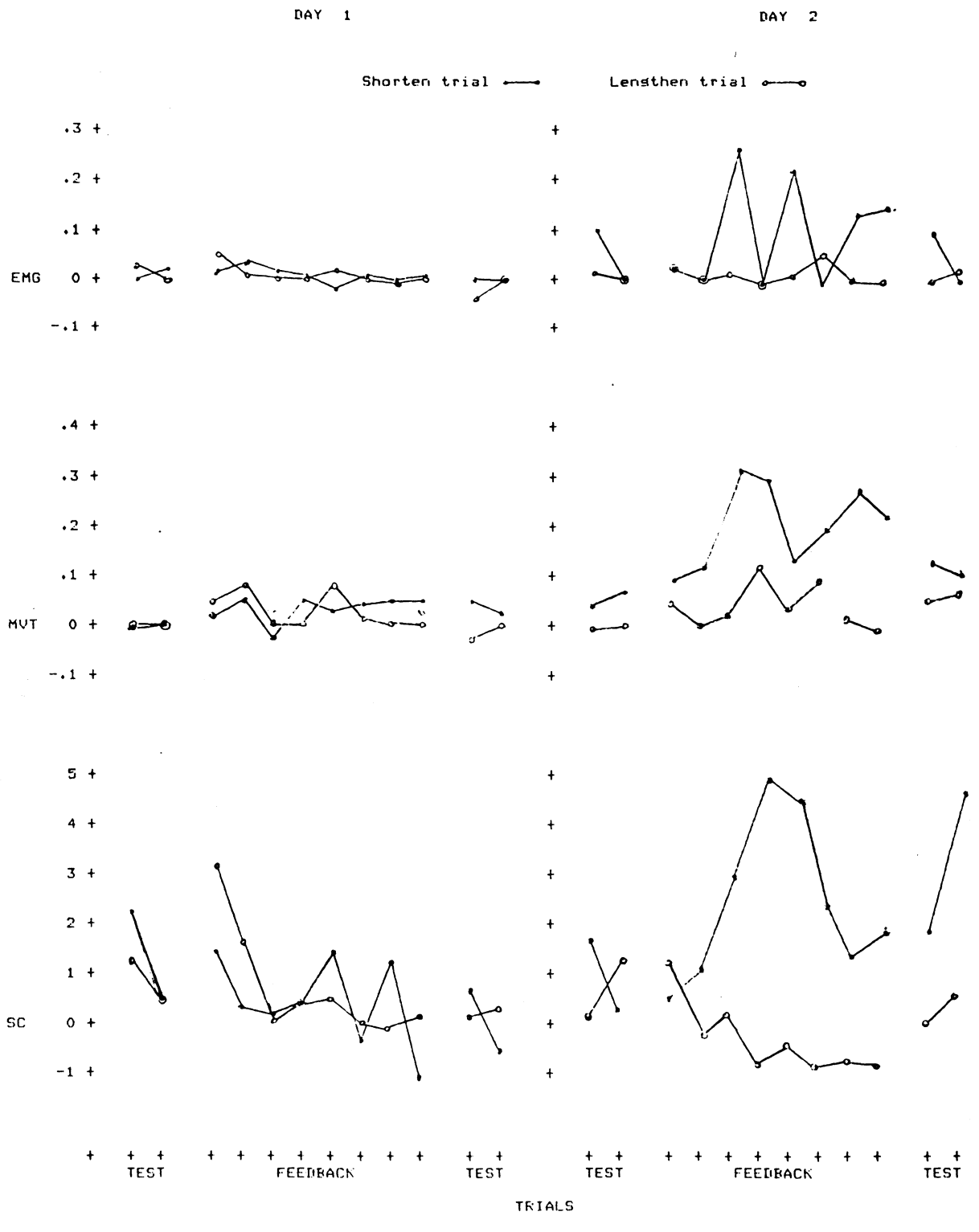

DAY 1
DAY 2
Shorten trial
Lengthen trial
.3
.2
.1
EMG 0
-.1
.4
.3
.2
.1
MVT 0
-.1
5
4
3
2
1
SC 0
-1
TEST
FEEDBACK
TEST
TEST
FEEDBACK
TEST
TRIALS

Figure 3. Differentiators respiratory-ICI, respiratory-amplitude and respiratory-volume changes from pretrial values across two days of training and testing. ICI is in seconds. Amplitude and volume are in arbitrary units.

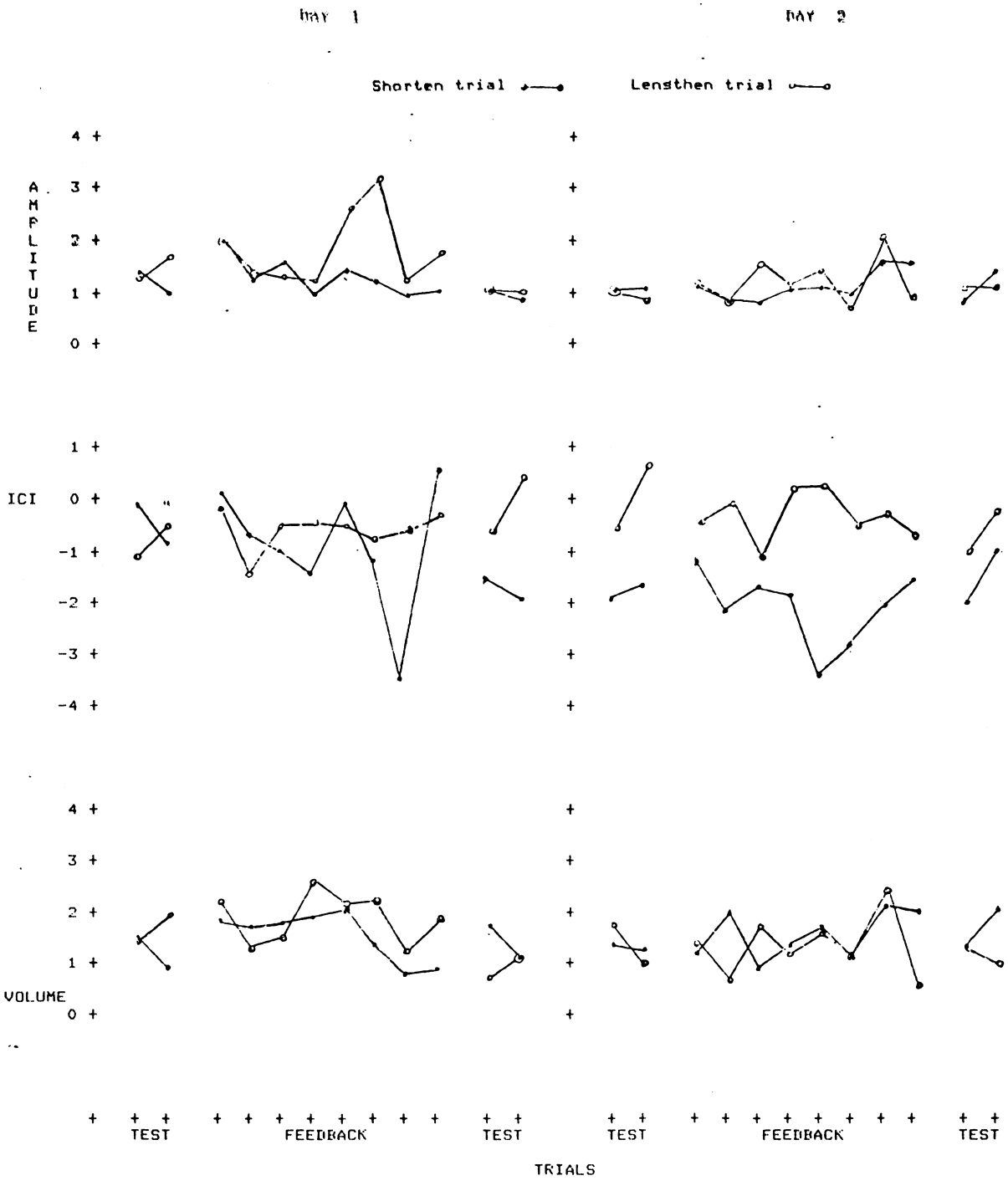
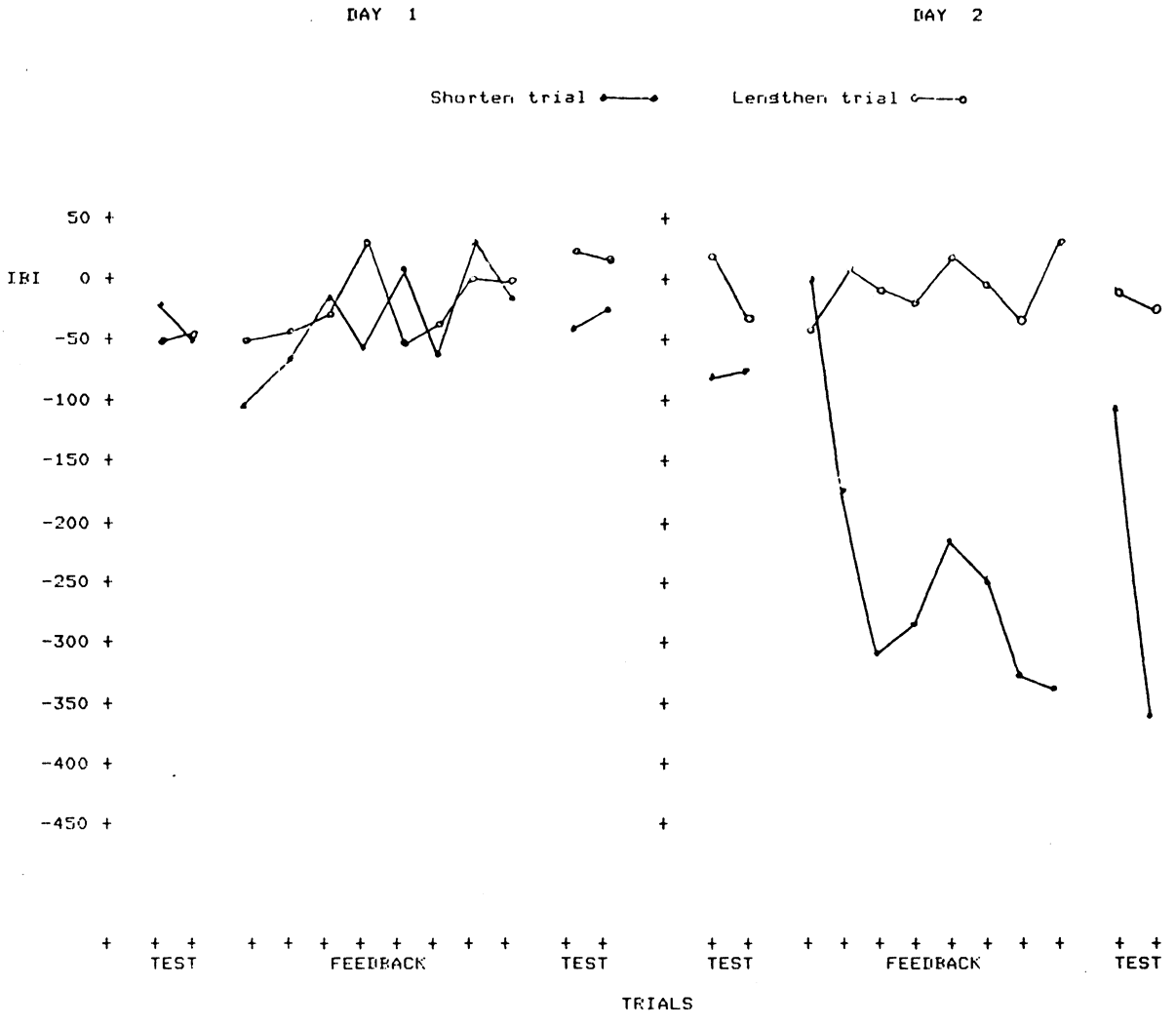

DAY 1
DAY 2
Shorten trial
Lengthen trial
AMPLITUDE
4 +
3 +
2 +
1 +
0 +
ICI
1 +
0 +
-1 +
-2 +
-3 +
-4 +
VOLUME
4 +
3 +
2 +
1 +
0 +
TEST
FEEDBACK
TEST
TEST
FEEDBACK
TEST
TRIALS

Figure 4. Differentiators cardiac interbeat-interval changes from pretrial values across two days of training and testing. IBI changes are in milliseconds.


DAY 1
DAY 2
Shorten trial
Lengthen trial
IBI
50
0
-50
-100
-150
-200
-250
-300
-350
-400
-450
TEST
FEEDBACK
TEST
TEST
FEEDBACK
TEST
TRIALS

feedback task may not have maintained increased sympathetic activity throughout the two days of training.

Within-subject t-tests (with and without the assumption of equal variance) were used to determine if bidirectional differences in RPI were present on training trials of Day 1. Two subjects fell into the category of differentiator, based on Day 1 RPI data (Subject C: $t(14)= 1.89$, $p<.05$); Subject F: $t(12)= 2.21$, $p<.05$); assuming equal variance). Subject F was categorized as a differentiator on Day 2, but Subject C was not. A likely explanation for this finding is that pretrial RPI values consistently differed between shorten and lengthen training trials on Day 1, for Subject C. This would give the appearance of differentiation, due to regression toward the mean. Shorten pretrial values were consistently longer than lengthen pretrial values for this subject on Day 1 ($t(7)= 2.47$, $p<.05$). The average pretrial RPI for all Day 1 training trials was shorter than the average pretrial RPI for Day 1 shorten training trials, and longer than the average pretrial RPI for Day 1 lengthen training trials. It is not unreasonable to assume that RPI would drift toward the average pretrial RPI for all training trials. If this was the case here, then RPI would consistently have drifted in the appropriate direction during training trials, because of random variance, not active subject control. Subject C did not have this advantage on Day 2, and did not produce significant bidirectional RPI changes on Day 2.

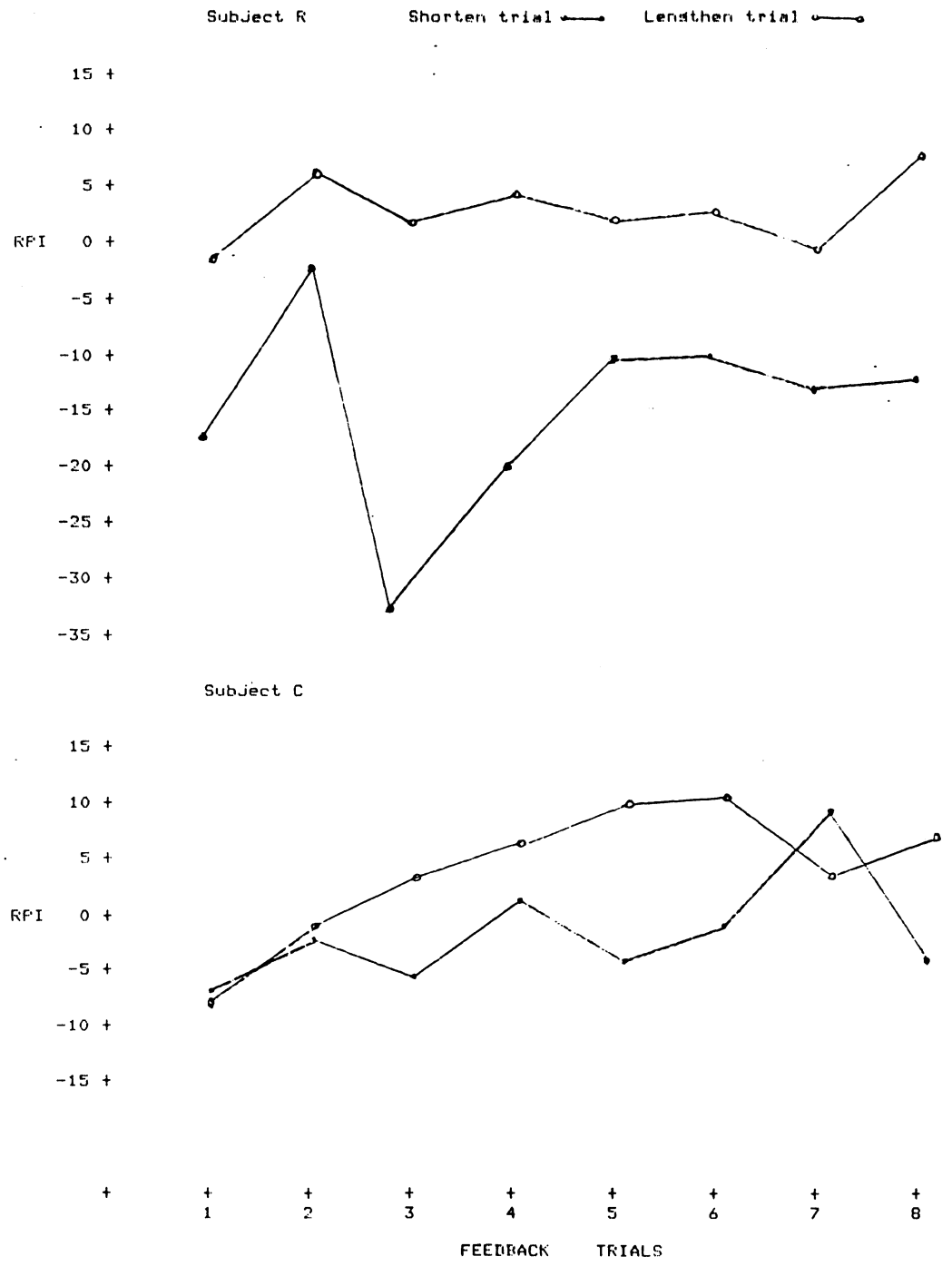
Examination of the Day 2 pretrial values of differentiators, revealed that Subject R had shorten pretrial values that were also significantly longer than his lengthen pretrial values ($t(7)= 2.48$,

$p<.05$). However, Subject R continues to be considered a differentiator due to the magnitude of his bidirectional RPI change in comparison with that of Subject C on Day 1. Subject R produced bidirectional RPI changes on Day 2 that appear to be much larger than the bidirectional changes produced by Subject C on Day 1. The performance of these two subjects is compared in Figure 5.

Within-subject t-tests which assumed equal variance were also used to evaluate bidirectional changes in RPI during test trials given at the end of Day 2, during which subjects performed the responses without feedback. This analysis indicated that significant RPI changes were made by two subjects (Subject R: $t(2)= 22.489$, $p<.005$; Subject C: $t(2)=3.786$, $p<.05$). The results for Subject C may have been a fluke, since this subject did not differentiate successfully during training trials on Day 2. Application of a 1-sample t-test to the concluding test performance of differentiators as a group was significant, $t(4)= 2.31$, $p<.05$. This corroborates the impression given in Figure 1, which indicates that differentiators were able to produce significant bidirectional changes in RPI without feedback to guide their performance.

One-sample t-tests were used to examine unidirectional RPI changes for each subject during training trials. Day 1 and Day 2 data, and lengthen and shorten training trial data were examined separately. Subject C consistently lengthened RPI during Day 1 RPI lengthen training trials ($t(7)= 1.94$, $p<.05$). However, Subject C did not consistently shorten RPI during Day 1 RPI shorten training trials ($t(7)= -.07$, $p>.05$). On Day 1, Subject F consistently shortened RPI during both

Figure 5. RPI changes from pretrial values for Subjects R and C. Day 2 training trial data is present for Subject R and Day 1 training trial data is presented for Subject C. RPI is in milliseconds.


Subject R
Shorten trial
Lengthen trial
15 +
10 +
5 +
RPI 0 +
-5 +
-10 +
-15 +
-20 +
-25 +
-30 +
-35 +
Subject C
15 +
10 +
5 +
RPI 0 +
-5 +
-10 +
-15 +
1
2
3
4
5
6
7
8
FEEDBACK TRIALS

lengthen ($t(5)= 5.29$, $p<.005$), and shorten ($t(7)= 17.82$, $p<.001$) training trials. Although Subjects C and F could both be categorized as differentiators based on their Day 1 RPI data, neither Subject could produce the requested RPI changes in both directions.

Subject C was unable to consistently lengthen ($t(6)= -0.87$, $p>.05$) or shorten ($t(6)= 0.59$, $p>.05$) RPI on Day 2. However, Subject F displayed RPI changes on Day 2 similar to those found on Day 1. Subject F again shortened RPI on lengthen ($t(7)= 1.93$, $p<.05$) and shorten ($t(7)= 14.53$, $p<.005$) training trials. Subject F was categorized as a differentiator on Day 2, as was Subject J. Subject J also shortened RPI on lengthen ($t(7)= 2.88$, $p<.05$) and shorten ($t(7)= 7.30$, $p<.005$) training trials. These subjects produced what were considered to be bidirectional changes by shortening RPI more on shorten trials, than on lengthen trials. They were unable to produce consistent RPI lengthening.

The other 3 differentiators, Subjects D ($t(7)= 3.30$, $p<.01$), L ($t(7)= 3.91$, $p<.005$), and R ($t(7)= 4.79$, $p<.005$), also consistently shortened RPI during Day 2 RPI shorten training trials. No other subjects consistently shortened RPI on Day 2. Subject D did not produce a consistent change in RPI during Day 2 lengthen trials ($t(7)= 0.89$, $p>.05$). However, Subject L ($t(7)= 2.78$, $p<.05$) and Subject R ($t(7)= 2.56$, $p<.05$) both consistently lengthened RPI during Day 2 lengthen training trials. Therefore, not all differentiators showed similar changes in RPI. RPI lengthening again appears to be the more difficult task, since only 2 of the 5 differentiators produced consistent changes

of this kind. However, all 5 differentiators were able to consistently shorten RPI.

Consistent unidirectional RPI changes were also made by some non-differentiators on Day 2 training trials. Subjects G ($t(7)= 2.01$, $p<.05$) and Subject I ($t(7)= 2.11$, $p<.05$) consistently lengthened RPI during Day 2 lengthen training trials. Subject I also consistently lengthened RPI during Day 2 shorten training trials ($t(7)= 2.75$, $p<.05$). Therefore, two subjects found RPI lengthening to be the easier task under these conditions. During lengthen training trials Subjects L and R consistently lengthened RPI while showing a reduction in heart rate. However, RPI lengthening was associated with heart rate increases for Subjects G and I. This is inconsistent with the findings of at least one previous biofeedback study (D. Johnston, 1980). In that study, RPI changed only when cardiac IBI was changed in the same direction, indicating that sympathetic influences on the heart were the dominant source of RPI variance. Any effects of loading factors on RPI change were masked. For example, a lengthening of cardiac IBI produces an increase in preload and a reduction of afterload. These changes would then act to reduce pre-ejection period and therefore shorten RPI. Since RPI was actually seen to lengthen with cordiac interbeat interval, loading factor effects are ruled out in D. Johnston's (1980) study. However, the data from Subjects G and I suggest that loading factors can also be dominant sources of RPI variance. That is, subjects can produce consistent changes in RPI where sympathetic factors are overshadowed.

Data from the verbal report questionnaires indicated that some subjects employed behaviours that are consistent with a sympathetic

mediation of RPI change, but others did not. Differentiators usually reported that some form of exercise was effective on shorten trials, and that they relaxed during lengthen trials. Breathing was said to be more rapid on shorten trials, while slowed and deepened on lengthen trials. Non-differentiators did not usually report gross changes in behaviour from pretrial resting values, and with few exceptions, made no distinctions between strategies used for the two tasks. Subjects who produced significant bidirectional changes in RPI usually reported behaviours that the literature indicates should lead to increased sympathetic activity on RPI shorten training trials, and decreased sympathetic activity on RPI lengthen trials. However, three subjects, including one differentiator (Subject F), reported the use of muscle tension on lengthen trials. This indicates that confounding variables, perhaps the loading factors, disrupted the learning of strategies consistent with reductions in sympathetic activity during RPI lengthening training trials.

Loading factors appear to have affected RPI during shorten training trials, too. Differentiators produced consistent lengthening of RPI during the early stages of exercise. This phenomenon, while small, was consistently observed across training trials and differentiating subjects and is shown as the shaded area in Figure 6. It appears that at the start of shorten trials, subjects took a long deep breath and increased their forearm muscle tension, and general activity level. This maneuver, which can be discerned in the within-trial response patterns given in Figures 7 and 8, produced an increase in heart rate and SC which is consistent with increased

Figure 6. Differentiators' RPI and IBI data from shorten training trials. Median changes from pretrial values over 3 second blocks. RPI and IBI are in milliseconds.

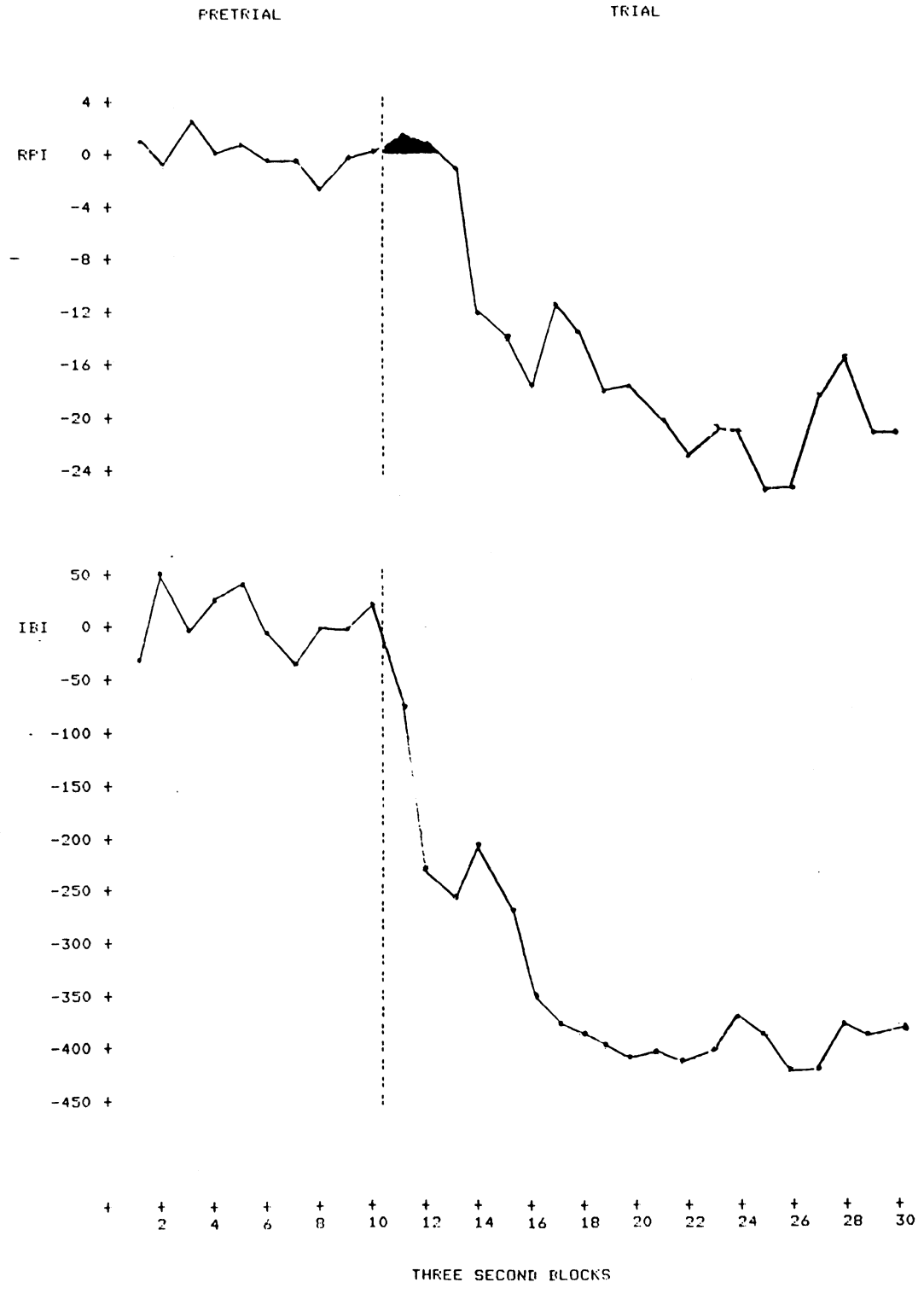

PRETRIAL
TRIAL
RPI
4 +
0 +
-4 +
-8 +
-12 +
-16 +
-20 +
-24 +
IBI
50 +
0 +
-50 +
-100 +
-150 +
-200 +
-250 +
-300 +
-350 +
-400 +
-450 +
+ + + + + + + + + + + + + + + +
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
THREE SECOND BLOCKS

Figure 7. Differentiators' EMG, MVT, heart-rate and SC data from shorten training trials. Median changes from pretrial values over 3 second blocks. EMG and MVT are in arbitrary units. Heart rate is in beats per minute, and SC is in micromhos.

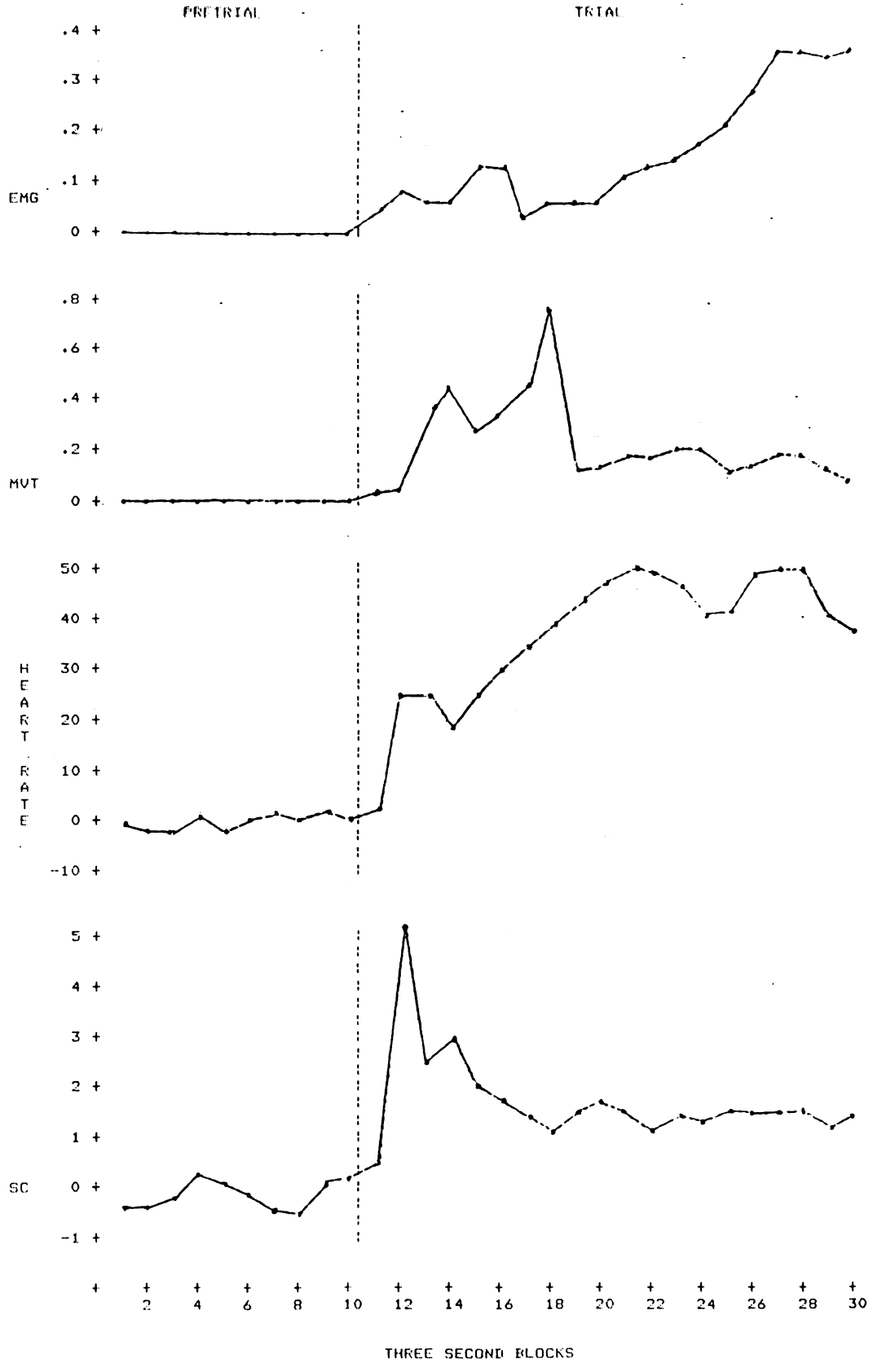
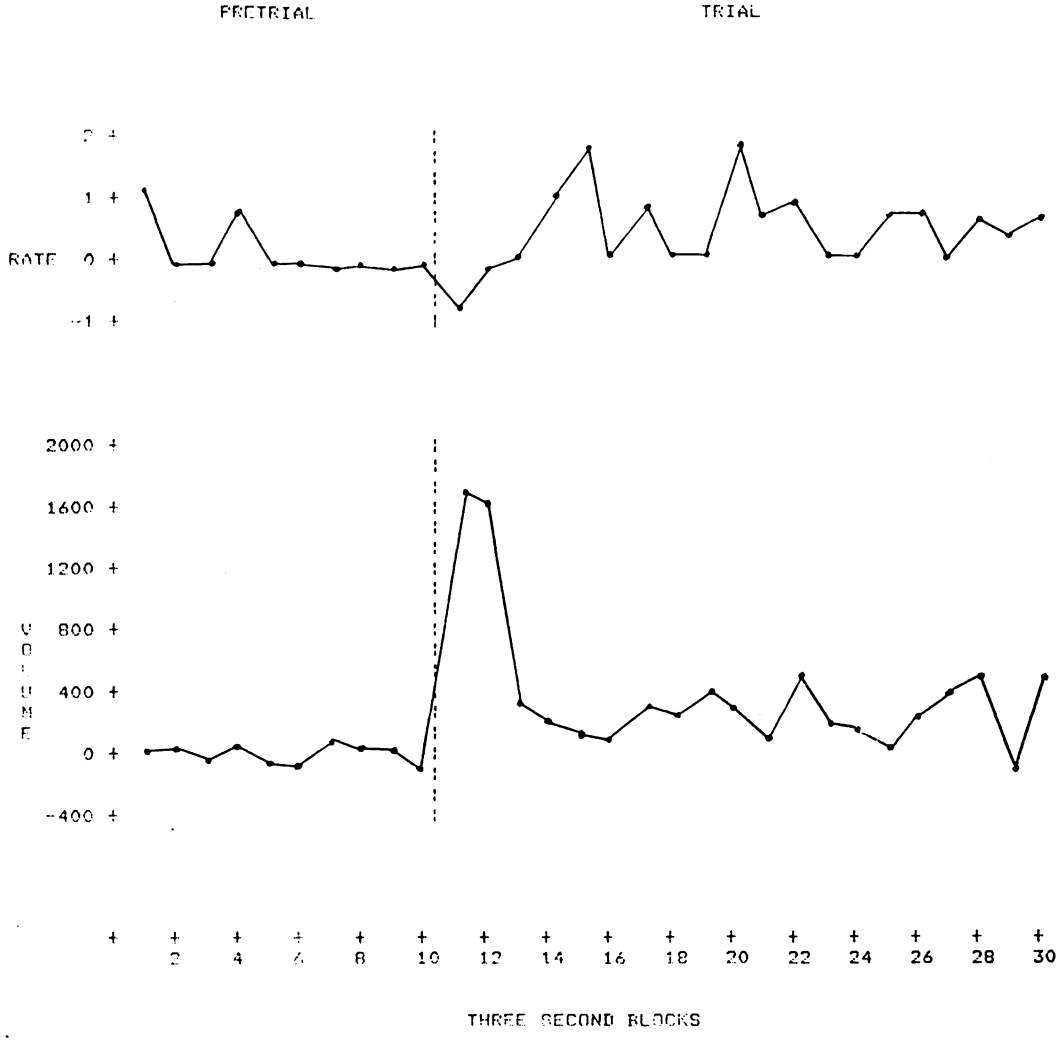

PRETRIAL
TRIAL
EMG
.4 +
.3 +
.2 +
.1 +
0 +
MVT
.8 +
.6 +
.4 +
.2 +
0 +
HEART RATE
50 +
40 +
30 +
20 +
10 +
0 +
-10 +
SC
5 +
4 +
3 +
2 +
1 +
0 +
-1 +
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
THREE SECOND BLOCKS

Figure 8. Differentiators' respiratory rate and volume data from shorten training trials. Median changes from pretrial values over 3 second blocks. Respiratory rate and volume are in arbitrary units.


PRETRIAL
TRIAL
RATE
2
1
0
-1
VOLUME
2000
1600
1200
800
400
0
-400
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
THREE SECOND BLOCKS

sympathetic beta-adrenergic activity. However, this maneuver initially lengthened RPI. Subsequently, respiratory ICI decreased, respiratory volume returned to baseline, and RPI began to shorten. The net result of exercise was RPI shortening. However, finding that the initiation of exercise, produces a phasic lengthening of RPI again inplicated the loading factors as a source of RPI change. There is precedence for such a finding in the literature. Obrist et al. (1974) tested the relationship between sympathetic influences on the heart, and pressure changes in the carotid artery. They too found an inverse covariation between heart rate and carotid dP/dt when small changes in general activity were observed in resting subjects. This finding was probably the result of the Frank-Starling mechanism causing reductions in preload, producing reductions in cardiac contractile force and therefore a lengthening of RPI (Rushmer, 1970).

In order to further investigate the relationships between RPI and the concomitants for which data were gathered, correlation coefficients were calculated. Separate coefficients were calculated for data from three different types of trials: blank trials, shorten training trials during which shortening of the RPI was observed, and lengthen training trials during which lengthening of the RPI was observed. For purposes of trial selection it was not necessary that these RPI changes be statistically significant. Day 2 data from two or three of each trial type were used where good data were available. Trial sampling to find good data began from the final trial of each type and continued backwards. In some cases Day 1 data had to be used due to a lack of good data on Day 2. In other cases, good data were only

available for one trial of a particular type. Occasionally, one concomitant had to be excluded for an individual subject, due to noise or equipment failure during data collection. No good RPI data were available for blank trial analyses for Subject S. In addition, Subject I did not provide any good RPI data during the few training trials in which he was successful at shortening RPI.

Five concomitant variables were used in the calculation of correlation coefficients. Two of these variables were derived from cardiac interbeat interval data. One variable was the cardiac IBI which began with R-wave that also began the RPI with which it was paired. This variable is referred to here as IBI. If sympathetic influences were the major factor in RPI variability, then a correlation analysis might reveal a positive relationship between RPI and IBI. The other cardiac interbeat interval variable ended with the R-wave which began the RPI with which it was paired. This covariant is referred to here as IBI+. If preload was a factor in RPI variability, then a correlation analysis might reveal an inverse relationship between RPI and the cardiac interbeat interval that precedes it (IBI+). This is due to the fact that changes in cardiac interbeat interval alter left ventricular filling time, and preload. Correlation coefficients were also calculated to determine the strength of the relationship between RPI and EMG, MVT and SC. EMG, MVT, and SC data collected between the end of the previous RPI and the end of the current RPI were individually averaged. The averaged data points for each concomtant were paired with the current RPI for the correlation analysis. The within-subject correlations (r) between RPI and IBI, IBI+, SC, EMG, and MVT are

presented in Tables 2, 3 and 4. Significance levels for correlations were based on two-tailed t-tests.

The relationships between RPI and the other variables were complex. For IBI, both significant positive and negative correlations were found. For blank trials, all of the four negative correlations were significant, and three of the seven positive correlations were significant. For shorten training trials, four of the six negative correlations were significant, and four of the five positive correlations were significant. For lengthen training trials, six of the eight negative correlations were significant, while three of the four positive correlations were significant. Subjects' correlations were generally not consistent across trial type. The overall median correlations for blank, lengthen and shorten trials were .02, -.17, and -.05 respectively. Therefore, RPI was not consistently correlated with IBI for this group as a whole.

Correlations between IBI+ and RPI were similar to those found between IBI and RPI. For blank trials, all of the four negative correlations were significant, and four of the seven positive correlations were significant. For shorten training trials, three of the six negative correlations were significant, and all of the five positive correlations were significant. For lengthen training trials, two of the six negative correlations were significant, while three of the six positive correlations were significant. Data from two of the twelve subjects were consistently positive, the remaining subjects were relatively inconsistent. Median correlations for blank, shorten and lengthen trials were .12, .05, and -.10 respectively. These data

Table 2

Blank trial correlations between RPI and 5 concomitants

RPI	change in msec[a]	IBI	IBI+	SC	EMG	MVT
Differentiators						
D	-.75 (192)	.29**	.28**	-.43**	.67**	.67**
F	5.80 (107)	-.76**	-.49**	-.13	-.16	.09
J	1.28 (182)	.15*	.33**	-.09	.15*	-.01
L	2.49 (211)	.41**	.46**	-.20**	.25**	-.03
R	1.52 (231)	.02	.12	-.42**	-.11	-.06
	Median	.15	.28	-.20	.15	-.01
	Number of correlations[b]					
	Negative	1(1)	1(1)	5(3)	2(0)	3(0)
	Positive	4(3)	4(3)	0(0)	3(3)	2(1)
Non-differentiators						
B	-1.03 (191)	.00	.15*	.13	-.13	.03
C	-.13 (135)	.04	.13	.51**	-.16	-.44**
G	.37 (157)	-.18*	-.22**	-.01	-.17*	.05
I	1.82 (221)	-.36**	-.42**	.08	-.04	.02
P	-1.97 (133)	-.18*	.02	-.15	-.06	.22*
Q	-1.16 (106)	.05	-.31**	.51**	.49**	-.22*
S	----------					
	Median	-.09	-.10	.11	-.10	.03
	Number of correlations					
	Negative	3(3)	3(3)	2(0)	5(1)	2(2)
	Positive	3(0)	3(1)	4(2)	1(1)	4(1)

[a]Mean changes from pretrial. Numbers in parentheses indicate of beats used for calculations.

[b]Numbers in parentheses indicate the number of significant r's.

*$p<.05$

**$p<.01$ (two-tailed t test)

Table 3
Shorten trial correlations between RPI and 5 concomitants

RPI change in msec[a]		IBI	IBI+	SC	EMG	MVT
Differentiators						
D	-9.57 (210)	-.06	-.10	.71**	.28**	-.06
F	-14.19 (235)	.51**	.34**	-.27**	-.49**	.13*
J	-15.41 (178)	-.17*	-.13	.01	.09	-.05
L	-25.84 (297)	.85**	.79**	-.00	-.22**	.30**
R	-11.30 (313)	.22**	.17**	-.02	-.13*	.01
	Median	.22	.17	-.00	-.13	.01
	Number of correlations[b]					
	Negative	2(1)	2(0)	3(1)	3(3)	2(0)
	Positive	3(3)	3(3)	2(1)	2(1)	3(2)
Non-differentiators						
B	-1.21 (200)	-.26**	-.28**	-.56**	-.04	-.03
C	-1.21 (230)	.55**	.51**	-.56**	.26**	.17*
G	-1.44 (266)	.00	.17*	-.23*	.08	-.02
I	----------					
P	-4.20 (127)	-.77**	-.48**	-.17	-.01	-.05
Q	-1.27 (51)	-.05	-.14	.10	-.01	.12
S	-1.91 (51)	-.50**	-.33**	.20	.11	.22
	Median	-.15	-.21	-.20	.04	.05
	Number of correlations					
	Negative	4(3)	4(3)	4(3)	3(0)	3(0)
	Positive	2(1)	2(2)	2(0)	3(1)	3(1)

[a]Mean changes from pretrial. Numbers in parentheses indicate of beats used for calculations.
[b]Numbers in parentheses indicate the number of significant r's.
*$p<.05$
**$p<.01$ (two-tailed t test)

Table 4
Lengthen trial correlations between RPI and 5 concomitants

RPI	change in msec[a]	IBI	IBI+	SC	EMG	MVT
Differentiators						
D	2.54 (112)	.46**	.51**	-.82**	.53**	.26**
F	7.10 (175)	.35**	.34**	-.31**	-.27**	-.09
J	3.65 (125)	-.22**	-.06	-.19*	-.15	-.14
L	2.69 (199)	.06	.32**	.60**	-.36**	.30**
R	4.25 (214)	-.22**	-.01	-.38**	.15*	-.13
	Median	.06	.32	-.31	-.15	-.09
	Number of correlations[b]					
	Negative	2(2)	2(0)	4(4)	3(2)	3(0)
	Positive	3(2)	3(3)	1(1)	2(2)	2(2)
Non-differentiators						
B	3.45 (197)	-.45**	-.31**	.12	.16*	-.05
C	6.73 (195)	-.14	.14	-.09	-.07	-.07
G	4.65 (262)	.26**	.11	-.01	.00	-.02
I	5.27 (181)	-.02	-.01	----	-.02	-.13
P	3.82 (168)	-.50**	-.45**	-.07	-.11	.27**
Q	2.41 (99)	-.72**	.18	-.35**	-.54**	-.03
S	4.94 (133)	-.19*	-.07	.06	.16	.13
	Median	-.19	-.01	-.04	-.02	-.02
	Number of correlations					
	Negative	6(4)	4(2)	4(1)	4(1)	5(0)
	Positive	1(1)	3(0)	2(0)	3(1)	2(1)

[a]Mean changes from pretrial. Numbers in parentheses indicate of beats used for calculations.

[b]Numbers in parentheses indicate the number of significant r's.
*p<.05
**p<.01 (two-tailed t test)

indicate that cardiac interbeat interval may have altered RPI by changes in preload. However, this effect was not consistently observed across subjects.

Correlations between SC and RPI were usually negative, as might be expected. However, some variability was present. For blank trials, three of the seven negative correlations were significant, and two of the four positive correlations were significant. For shorten training trials, four of the seven negative correlations were significant, and one of the four positive correlations was significant. For lengthen training trials, five of the eight negative correlations were significant, while one of the three positive correlations was significant. The overall medians for blank, shorten and lengthen trials were -.09, -.09, and -.02 respectively. Therefore, RPI was not consistently correlated with SC across the 12 subjects.

Correlations between EMG and RPI were also quite wide ranging. For blank trials, one of the seven negative correlations was significant, and all of the four positive correlations were significant. For shorten training trials, three of the six negative correlations were significant, and two of the five positive correlations were significant. For lengthen training trials, three of the seven negative correlations were significant, while three of the five positive correlations were significant. The overall median correlations between EMG and RPI for blank, lengthen, and shorten trials were -.06, -.05, and -.01 respectively. These data also suggest that light exercise can lengthen RPI, although once again the effect varies across subjects.

Correlations between MVT and RPI were also variable, but most of the stronger correlations were positive. For blank trials, two of the five negative correlations were significant, while two of the six positive correlations were significant. For shorten trials, none of the five negative correlations were significant, while three of the six positive correlations were significant. For lengthen trials, none of the five negative correlations were significant, while two of the four positive correlations were significant. Overall median correlations for blank, shorten and lengthen trials were .02, -.04, and .01 respectively. Although the correlations between RPI and MVT were inconsistent, these data also support the anomalous finding that increases in activity are associated with lengthening of RPI.

None of the overall median correlations were strong, reflecting the wide range of coefficients. While these data do not link RPI to any one concomitant for all subjects, individual subjects did show strong correlations in both directions for all concomitants. This was demonstrated even in light of the restricted variability of data from blank and lengthen trials. When dealing with individuals, it cannot be assumed that phasic RPI changes will be independent of these concomitants. Nor can it be assumed that phasic RPI changes will necessarily follow any of these concomitants in a particular manner. This is consistent with Schwartz (1974) who reported that phasic IBI and SBP changes were uncorrelated, because heart rate and SBP often moved in different directions. The interaction of preload and sympathetic influences appear to be responsible for this effect.

Data from individual subjects often proved interesting. Observations of the polygraph recordings indicated a link between respiration, heart rate and RPI in resting subjects. Although this relationship has not been statistically evaluated, the pattern reproduced in Figure 9 is typical. The relationships between chest circumference, heart rate and RPI are somewhat distorted, because the chest circumference channel was capacity coupled. However, a strong relationship during the trial is apparent. A number of subjects reported that slowed and/or deepened breathing was effective in causing lengthening of the RPI. Long inhalations seemed to phasically lengthen RPI and increase heart rate. This finding was probably produced by preload changes, caused by the respiratory sinus arrhythmia induced by slowed, deepened breathing (Hirsch & Bishop, 1981). These mechanisms cause RPI to provide a false indication of changes in sympathetic outflow to the heart. RPI should have shortened to reflect the increased sympathetic outflow to the heart which occurs during inhalation (see Kirchheim, 1976, for review). However, RPI actually lengthened during inhalation.

A number of subjects showed consistent RPI elongation on lengthen trials. Heart rate changes during these trials were inconsistent between subjects, and sometimes inconsistent within-subjects. Preload effects are suspected to have been influential when RPI elongation occurred while heart rate was increasing. A sample polygraph record is informative here, too, and is given in Figure 10. In Figure 10 Subject I is found to alternate between short periods of forearm muscle tension and relaxation during the trial. He reported

Figure 9. Sample lengthen RPI training trial data from Subject R. Data are from Day 1, Trial 9. Upward excursions of the display signal indicate success at lengthening RPI. The marker indicates pretrial and trial period. The bar denotes feedback presentation. ECG= Electrocardiogram; DEDS= Differentiated Ear Densitogram Signal; HR= Heart Rate; RESP= Respiration Signal.

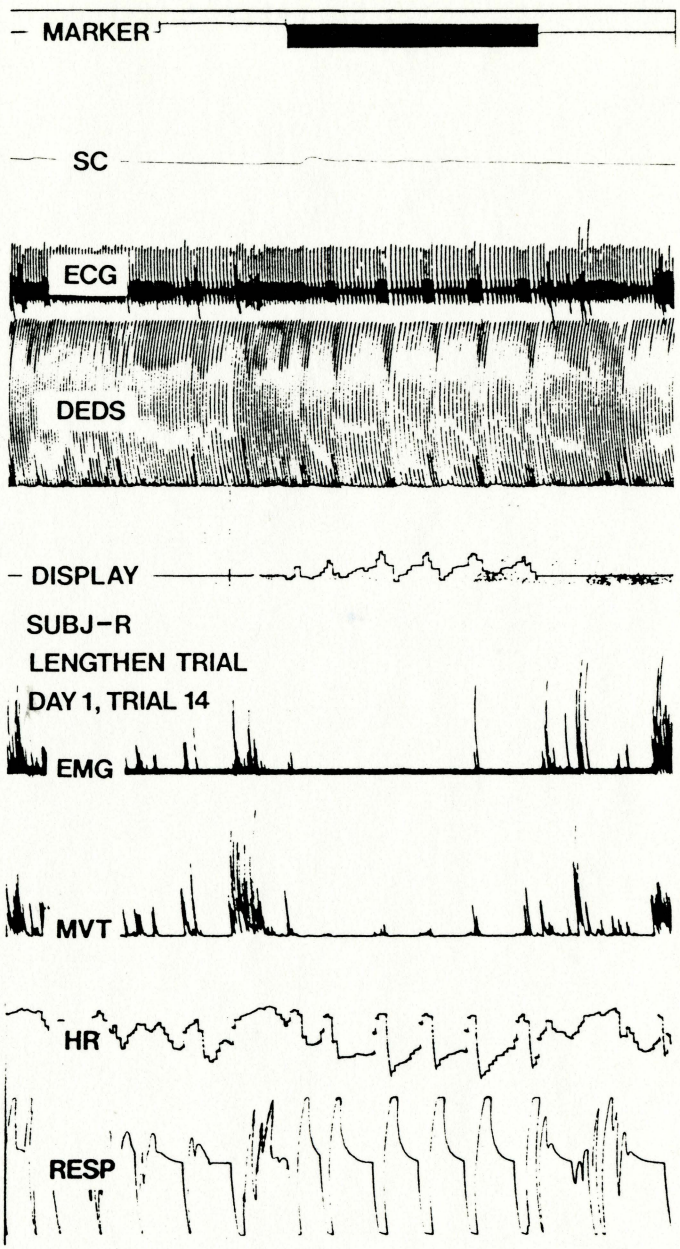
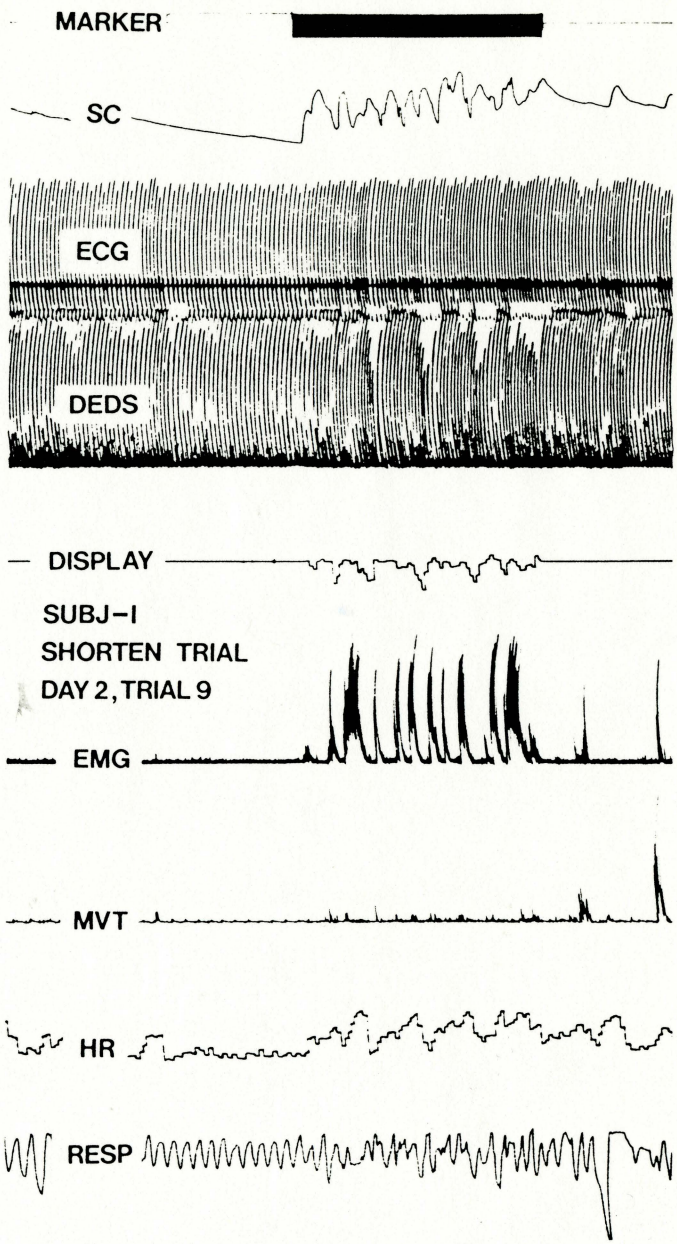

MARKER
SC
ECG
DEDS
DISPLAY
SUBJ-R
LENGTHEN TRIAL
DAY 1, TRIAL 14
EMG
MVT
HR
RESP

Figure 10. Sample shorten RPI training trial data from Subject I. Data are from Day 2, Trial 14. Upward excursions of the display signal indicate success at shortening RPI. The marker indicates pretrial and trial period. The bar denotes feedback presentation. ECG= Electrocardiogram; DEDS= Differentiated Ear Densitogram Signal; HR= Heart Rate; RESP= Respiration Signal.


MARKER
SC
ECG
DEDS
DISPLAY
SUBJ-I
SHORTEN TRIAL
DAY 2, TRIAL 9
EMG
MVT
HR
RESP

these behaviours on the verbal report questionnaire as well. Increased tension lead to phasic increases in heart rate and elongation of RPI. In addition, Subject G consistently lengthened RPI on Day 2 lengthen training trials, and RPI lengthening was accompanied by heart rate increase. Subject G also reported that the use of light physical activity was effective during these trials. Subject I lengthened RPI an average of 2.7 msec on Day 2 training trials. This compares with 2.4 msec bidirectional changes produced by some differentiators in D. Johnston's (1980) study. Also of importance here is the relationship between the recordings of RPI length and pulse wave amplitude, which is indicated by the height of the densitogram signal. As amplitude decreased, RPI lengthened, supporting a preload effect, since decreases in preload reduce pulse wave amplitude (a measure of stroke volume).

The positive relationship between the initiation of exercise, and RPI elongation was what probably lead two subjects to adopt strategies which were contradictory to those of most differentiators. These two subjects reported exercise related activities on lengthen trials and relative relaxation on shorten trials. One of these subjects (F) was able to produce bidirectional changes that placed him in the category with the other differentiators. The other subject (S), a non-differentiator, showed an average RPI elongation of .51 and .54 msecs on shorten and lenghten trials respectively, on Day 2. These changes are relatively small and almost identical. Early training correlations for Subject S showed strong negative correlations between RPI and IBI. The correlation between RPI and IBI was -.49 when data from the second Day 1 shorten training trial were examined. The

correlation between RPI and IBI was -.55 when data from the first Day 1 lengthen training trial were examined. Although Subject S's Day 2 average RPI change scores did not differ, average changes in heart rate were different for the two types of trial. Subject S increased his heart rate an average of over 10 beats per minute on lengthen trials, as compared with an average increase of less than 3 beats per minute on shorten trials. Therefore, preload effects may have masked changes in sympathetic outflow to the heart that would have otherwise affected RPI during RPI feedback training. This lead to the adoption of a behavioural strategy (exercise) which is assumed to be inappropriate during attempts to deduce sympathetic drive.

In conclusion, it appears that unconstrained subjects can produce changes in RPI of greater magnitude than have been previously reported for more constrained subjects (c.f. Newlin & Levenson, 1980). Subjects who learned to produce larger bidirectional changes in RPI did so by shortening RPI when the task demanded it. Although causal relationships cannot be assumed from the data presented here, rapid breathing and moderately heavy exercise seem to lead to tonic RPI shortening. It seems likely that RPI shortening was beta-adrenergically mediated under these conditions. Long, deep inhalations and light activity are linked to phasic RPI lengthening. The data indicate that this effect was due to preload influences. RPI was often significantly, but not consistently correlated with IBI, IBI+, SC, EMG, and MVT. This also suggests that more than one factor can contribute to RPI change.

These data indicate that caution must be used when employing RPI as an index of sympathetic beta-adrenergic activity level. Occasionally subjects did produce RPI elongation while reducing heart rate concurrently. The levels of physical activity shown in some subjects may have been enough to induce an increase in sympathetic drive. Environmental demands have already been reported to cause tonic shortening of RPI (e.g. Newlin, 1981). Therefore, RPI may still be a useful index of cardiac contractility, provided that phasic changes caused by somatomotor activity can be filtered out. However, RPI should not be employed as the sole measure of beta-adrenergic influences on the heart. A major question that remains is whether procedures can be found that will assist interpretation of the RPI measure. This chapter concludes with a discussion of this topic.

C. Improving RPI as a Measure of Sympathetic Beta-Adrenergic Influences on the Heart

RPI would be a better measure of sympathetic beta-adrenergic influences on the heart if it were less affected by changes in loading factors. Previous research has indicated that cardiac contractility can vary widely in animals with low heart rate and a large respiratory sinus arrhythmia (Rushmer, 1970). Preload effects have also been found in other feedback training settings. Schwartz (1977) found that phasic increases and decreases in heart rate were equally likely during a phasic increase in SBP, and that the same was true during a phasic decrease in SBP. It is conceivable that changes in the loading factors could disrupt learned control over sympathetic activity during RPI

feedback training. This section examines possible methods for reducing the amount of RPI variability produced by loading factors.

The data reviewed earlier made it clear that the cardiac systolic time interval, known as cardiac pre-ejection period, can be used as a measure of cardiac contractility (c.f. Talley et al., 1971). Another cardiac systolic time interval, known as left ventricular ejection time, can also be used to index cardiac contractility (Wallace, Mitchell, Skinner & Sarnoff, 1963). Left ventricular ejection time refers to the time period during which blood leaves the left ventricle through the aortic valve. Borderline hypertensives who displayed increases in cardiac output also showed a shortening of left ventricular ejection time, relative to normotensive controls (Frolich et al., 1970). In addition, Wallace et al. (1963) found that increased sympathetic activity reduced left ventricular ejection time, as well as pre-ejection period. However, increased preload produced a lengthening of left ventricular ejection time while shortening pre-ejection period. In addition, increased afterload produced a shortening of left ventricular ejection time while lengthening pre-ejection period. Although Wallace et al. (1963) found these relationships to occur in dogs, they have been confirmed in human subjects (Harris, Schoenfeld & Weissler, 1967; Stafford, Harris & Weissler, 1970). Therefore, it may be possible to reduce the effects of loading factors on RPI, which contains most of the pre-ejection period, by concurrently examining changes in left ventricular ejection time. These data show that during changes in the loading factors, pre-ejection period and RPI are altered in one direction, and left ventricular ejection time is altered in the opposite

direction. That is, when the influences of loading factors dominate, RPI and left ventricular ejection time are negatively correlated.

If the correlation between RPI and left ventricular ejection time is strong, then a meaningful regression equation could be established which relates RPI to left ventricular ejection time. This regression equation could be used to reduce the effects of loading factors on RPI. For example, increased preload will increase left ventricular ejection time. Based on the regression equation, a shorter RPI should be expected given a longer left ventricular ejection time, and no change in sympathetic activity. Since the increase in preload will shorten the observed RPI, as expected, because of a lengthening of left ventricular ejection time, no change in sympathetic activity is assumed. Therefore, the effects of the increase in preload would not result in a change in the deviation between the observed RPI and the expected RPI. On the other hand, increased sympathetic activity will decrease left ventricular ejection time. Based on the regression equation, a longer RPI should be expected given a shorter left ventricular ejection time, and no change in sympathetic activity. Since the increase in sympathetic activity will shorten the observed RPI, the observed RPI will be shorter than expected, indicating an increase in sympathetic activity. Therefore, the effects of the increase in sympathetic activity would result in a change in the deviation between the observed RPI and the expected RPI. Reliable measures of left ventricular ejection time can be derived from the ear densitogram signal (Chirife & Spodick, 1972). Therefore, it may be possible to reduce the

effects of loading factors by simultaneously determining RPI and left ventricular ejection time with the ear densitogram.

The usefulness of this exercise is complicated by the relationship between left ventricular ejection time and heart rate. Increased heart rate produces a shortening of left ventricular ejection time (Weissler, 1974), but appears to have no effect on pre-ejection period (Talley et al., 1971). The extent to which heart rate confounds the effects of the loading factors on the systolic time intervals is an empirical question. Even if there is a high probability that changes in heart rate will adversely affect the type of analyses outlined above, the ease with which left ventricular ejection time data can be gathered from the ear densitogram signal, makes these analyses appear worthwhile for future work with the RPI.

Light & Obrist (1983) have suggested that sympathetic beta-adrenergic reactions to environmental stimuli may be more accurately assessed using both heart rate and RPI. This approach may also be useful in the feedback setting. For example, Schwartz (1977) found that subjects in one experiment produced larger decreases in SBP, when only those decreases in SBP which were accompanied by decreases in heart rate were reinforced. Subjects in a similar experiment produced smaller decreases in SBP when simply given feedback for any change in SBP. Similar results were found for feedback training where subjects were reinforced for decreases in DBP. While the need to make comparisons across studies detracts from the conclusiveness of these data, they are encouraging. Feedback training conditions could be set up where only those elongations of RPI which are accompanied by an elongation of

cardiac interbeat interval are reinforced. In addition, RPI shortening would only be punished if it was accompanied by a shortening of cardiac interbeat interval. Other changes would have no effect on the feedback display. This type of RPI feedback training should have the effect of eliminating light exercise strategies during attempts to lengthen RPI. However, this procedure would probably reduce the feedback density by 50% (Schwartz, 1977). Since Schwartz (1977) reported good training effects despite this reduction, this type of procedure seems worth investigating.

In conclusion, it appears that loading factors have the potential to disrupt learned control over sympathetic activity during RPI feedback training. Additional information about these loading factors and about sympathetic activity could be gained from examination of left ventricular ejection time and cardiac interbeat interval. This information might be useful in improving RPI as an index of sympathetic beta-adrenergic influences on the heart. This information might also be useful in improving procedures designed to examine learned control over sympathetic activity through feedback training.

Chapter Six

Summary and Conclusions

A large portion of the North American population has been found to have elevated blood pressure, which has been associated with increased morbidity and mortality. It appears that even mild elevations of blood pressure can lead to pathological consequences. The data clearly demonstrate that an autonomic nervous system imbalance in favor of increased sympathetic outflow is often responsible for systolic blood pressure elevations into the borderline hypertensive range. Therefore, this imbalance may be indirectly responsible for some cases of cardiovascular disease. The SBP elevations associated with increased sympathetic outflow are mediated by increased cardiac output. There is evidence which implicates increased sympathetic beta-adrenergic activity, and increased cardiac output in the development of sustained increases in diastolic blood pressure. However, these data are usually only based on correlations. More direct confirmational data are lacking.

Both genetic and environmental factors appear to be responsible for blood pressure variance amoung the general population. The offspring of individuals with higher blood pressures are more likely to develop high blood pressure. However, the environment can affect resting blood pressure levels. The most salient effect of the environment on the cardiovascular system, is increased cardiac output. The offspring of hypertensives, like many borderline hypertensives,

display excessive increases in cardiac output in a variety of settings. Theories have been offered in an attempt to explain how increased cardiac output, and other consequences of increased sympathetic outflow, might increase TPR, and alter kidney function. Again, direct confirmational data are lacking.

In order to prevent the increased morbidity and mortality rates associated with increased blood pressure, there is a trend toward treating individuals with smaller increases in blood pressure. Blood pressure is still mainly under cardiac control in many of these individuals. Drug treatments are costly. In addition, adverse effects of these drug treatments may offset the benefits they provide, particularly among mild hypertensives. Since sympathetic influences on the heart play a major role in elevating blood pressure in these individuals, research to gain a better understanding of how the environment affects sympathetic influences on the heart seems warranted. Much of the data in this area have come from examinations of behavioural factors in the control of cardiovascular parameters.

One such behavioural approach concerns exercise programmes and their effects on blood pressure. Although the data are not consistent, there is some evidence that indicates that exercise can delay the development of high blood pressure. Some studies have been unsuccessful in their attempts to reduce blood pressure in SHR through exercise, while others have reported positive results (see Fregly, 1984, for review). Inconsistencies in the data may be due to an interaction of the blood pressure reducing effects of exercise and the blood pressure increasing effects of aversive environmental stimulation resulting from

forced exercise (Suzuki et al., 1979, cited in Fregly, 1984). Many of the studies cited by Fregly (1984) employed a fixed schedule for their exercise regimen. Therefore, studies which have reported a lack of effect of exercise on blood pressure in SHR might have been successful, had these methodological confounds not been present. Human borderline hypertensives often show excessive cardiac output while resting, but not during exercise (Birkenhager & Schalekemp, 1976). Exercise has been found to reduce resting heart rate (Blackburn, 1978). Since borderline hypertension is often the result of increased heart rate, exercise may reduce or eliminate excessive cardiac output, and therefore, reduce blood pressure. There is some data to support this notion. However, these data are confounded by changes in weight during exercise, which has also been associated with a change in blood pressure (Blackburn, 1978). While these data are not conclusive, they warrant further investigation.

Another form of behavioural intervention is concerned with better management of those situations that elevate sympathetic beta-adrenergic drive and blood pressure. When predisposing circumstances cannot be avoided, one plausible approach is to teach subjects, through biofeedback, to reduce the frequency, magnitude, and duration of increases in sympathetic activity which result from various environmental stimuli. Steptoe (1977) has suggested that biofeedback training may be more appropriate under distracting conditions which normally evoke increased sympathetic outflow than in other circumstances. In a similar vein, Obrist (1981) suggested that learned sympathetic control under conditions of environmental stress may be

better suited for the prevention of high blood pressure. It does not seem worthwhile to attempt to train patients to reduce sympathetic activity once they no longer respond to the conditioning environment with increased sympathetic activity. Data provided by Steptoe and Ross (1981b) indicate that biofeedback training may be more successful under stressful conditions. These investigators found that biofeedback for a systolic time interval (R-wave to the radial pulse wave interval) produced the greatest amount of cardiac interbeat interval and RPI elongation in those subjects who initially showed the greatest amount of cardiac interbeat interval shortening. If learned control over increases in sympathetic activity is to be beneficial to those at risk for the development of hypertension, then conditions which evoke increased sympathetic activity appear most suitable for training (DeGood & Adams, 1976).

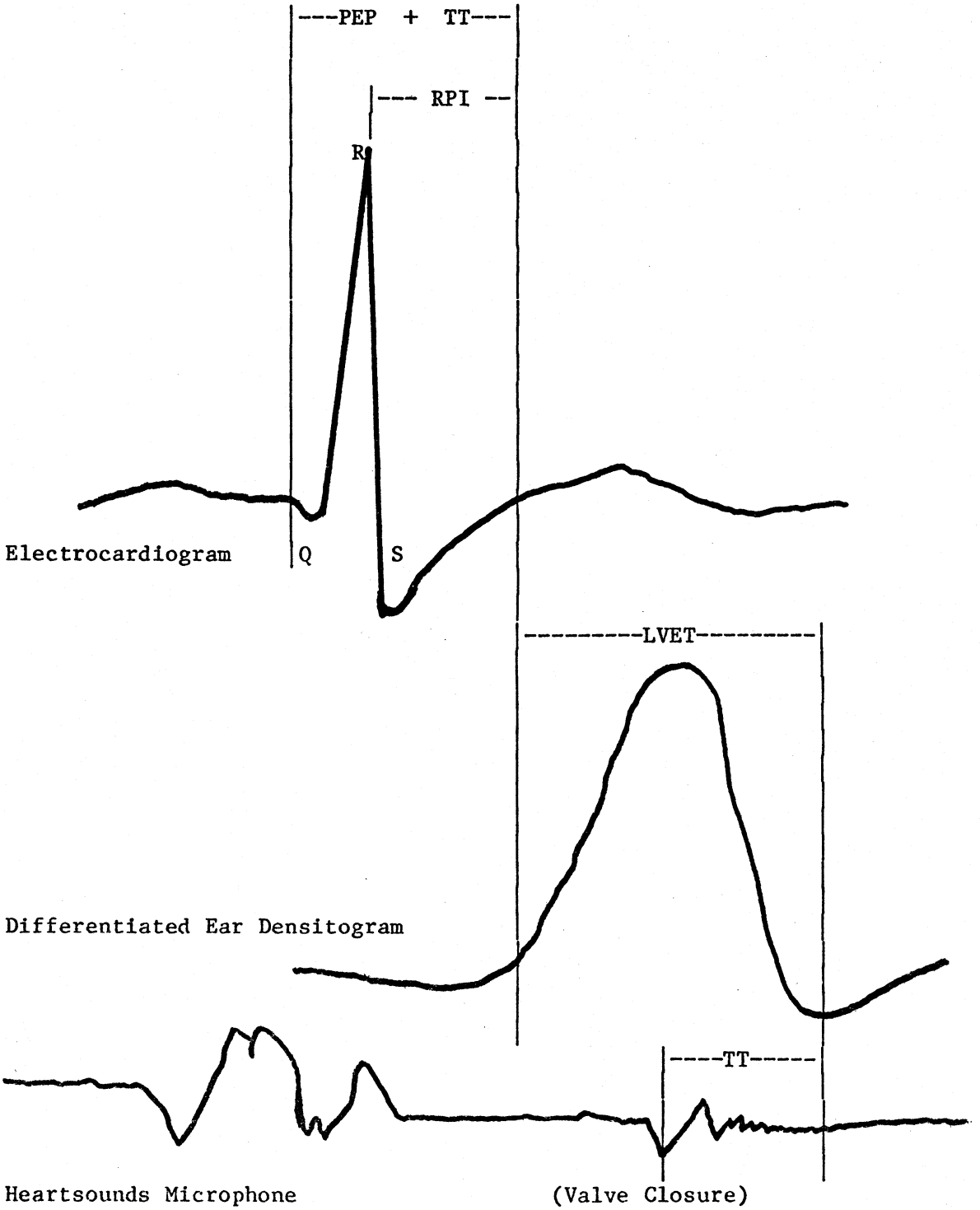
Research into learned control over increases in sympathetic activity requires the availability of a reliable, non-invasive measure of changes in sympathetic outflow to the heart. The data indicate that the time interval elapsing between the R-wave of the electrocardiogram and the arrival of the conducted peripheral pulse wave at the ear (RPI) may provide a good index of these changes. Data reported in this thesis indicate that unconstrained subjects can learn to produce bidirectional changes in RPI. RPI shortening seen during exercise may have resulted from increased sympathetic activity. However, RPI lengthening often appeared to be the result of phasic reductions in preload. Therefore, preload confounded the relationship between RPI and changes in sympathetic outflow to the heart. In some cases, preload also disrupted

learned decreases in sympathetic activity. Concurrent examination of left ventricular ejection time and cardiac interbeat interval may help to improve the reliability of RPI as an index of sympathetic influences on the heart.

Since it is not possible to directly assess sympathetic influences on the heart, it seems prudent to examine as many indirect measures of sympathetic influences on the heart as one possibly can. Even if subjects cannot be taught to inhibit increases in sympathetic activity, examination of learned control over RPI and other measures of sympathetic activity will increase our understanding of somatomotor and respiratory effects on these measures. These examinations could also provide new information about how the autonomic nervous system interacts with the environment. This type of information could be useful in delineating subgroups of the general population who are most likely to become severely hypertensive.

Appendix A

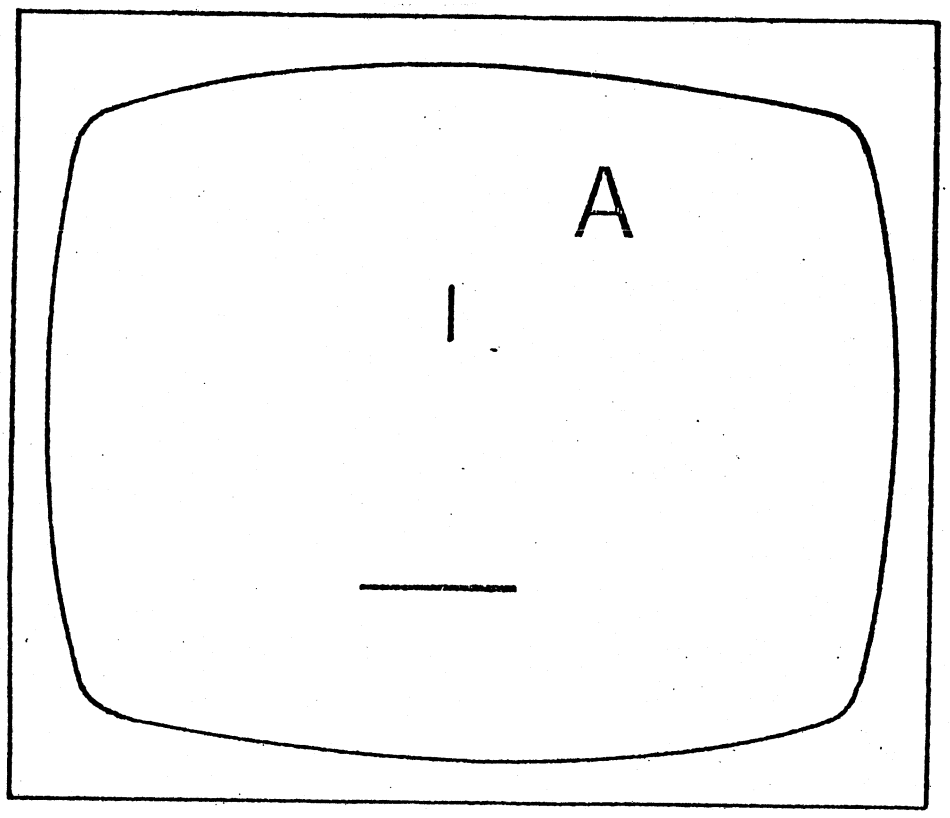
Determination of Systolic Time Intervals



PEP = Pre-ejection Period; LVET = Left Ventricular Ejection Time; TT = Pulse Transit Time.

Appendix B

The Feedback Display



The horizontal line remained fixed in place and depicted the level of the response at the beginning of the trial (pretrial mean). The dash moved in a vertical plane and depicted the current value of the response. Trial type was designated by the alphabetic character (A or B) displayed in the upper right-hand quardrant of the screen.

Appendix C

Informed Consent

I understand that this experiment involves two physiological responses, not normally thought of as being voluntarily controllable. While the procedures used here are not harmful, I understand that I am free to withdraw at any time. I agree to refrain from discussing this experiment with my classmates, in case they should be recruited as subjects.

_____

Appendix D
Standard Interview
(confidential)

NAME: SEX:
TELEPHONE NUMBER: AGE:
OCCUPATION: WEIGHT:
WITH WHICH HAND DO YOU WRITE? HEIGHT:

Have you ever taken part in an experiment in which physiological recordings were made? If so, give details.

Have you read any hand-outs describing this research or talked with previous participants? If so, give details.

Have you smoked or consumed coffee or an alcoholic beverage in the last 1/2 hour?

Are you presently taking any medications?

MEDICAL HISTORY

Have you had any respiratory disorders (asthma, bronchitis)?

Have you had any skin conditions (eczema, blistering)?

Are you diabetic?

Have you ever had any heart or cardiovascular problems?

ever had ECG? why?
high blood pressure?
rheumatic fever?
heart murmur?
other problem (angina, arrhythmia, heart attack)

Blood Pressure:____/____
Family History:

Reflexes:

Balance
finger to tongue
fainting spells of dizziness?
Are you epileptic?

Do you smoke?

Date_____

Appendix E

Taped Instructions

Day 1

In this experiment we are going to teach you to control two physiological responses that are not usually thought of as being controlled voluntarily. For convenience we will call one response Response A, and the other response Response B. The training procedure will be as follows.

From time to time a horizontal line and a small vertical dash will appear in the center of the television screen in front of you. Above the line and dash will appear the letter A or the letter B. These letters indicate to you which physiological response, Response A or Response B, you are to control. A typical display will look like this on A trials (sample) or like this on B trials (sample). The horizontal line represents your average level of physiological responding before the start of each trial. Movements of the dash away from this horizontal line, on the other hand, will be produced by changes in the physiological response, Response A on A trials, or Response B on B trials. Your task is to move the dash as far as possible in the direction of the letter A on A trials and to move the dash as far as possible in the direction of the letter B on B trials. If possible, do not allow the dash to fall below the horizontal line after the trial had begun. Instead, move it as far as you can in the direction of the

letter A or the letter B. When there is no visual display on the screen, you should rest and wait for the next trial.

We are going to begin by giving you 8 trials on which you are to move the dash toward the A and 8 trials on which you are to move the dash toward the B. These trials will be given in an irregular order. However, in addition to these trials we are going to give you some test trials on which the letter A or B will appear, but the dash and horizontal line will not be presented. On test trials the display will look like this when Response A is to be produced (sample) or like this when Response B is to be produced (sample). You should attempt to produce the required response as best you can on test trials, even though the dash will not be available to tell you how successful you have been. Test trials will be given at the beginning of the session and again when the session is finished. You will of course be puzzled as to what you should do on test trials given at the beginning of the session since at this time you will not have had an opportunity to learn about Response A or Response B from the feedback dash. We ask that you simply do the best you can. Our purpose in giving you test trials at the outset is to illustrate what will be required when the session is finished.

Feel free to use any method you wish to produce Response A or Response B, but please do not touch or put pressure on the electrodes we have attached to your body. This will create artifact in our recordings.

To provide extra incentive we are going to pay you bonus money for performing successfully. You could earn up to $2.00 in bonus money

for today's session if you do well. You will be told how much bonus money you have earned when the session is finished.

If you would like to have these instructions repeated, please tell us now. Otherwise, the experiment will begin in two or three minutes.

Day 2

The procedure for today will be the same as in the pervious session. Remember that your task is to move the feedback dash as far as possible in the direction of the letter A on A trials, and, to move the dash as far as possible in the direction of the letter B on B trials. As before, the session will begin and end with a series of test trials on which we ask that you produce Response A or B without feedback to guide your performance.

We will again pay bonus money for performing successfully. You could earn up to $2.00 in bonus money for today's session. Remember that you may use any method you wish to produce Response A or Response B, but please do not touch or put pressure on the electrodes we have attached to your body. This will create artifact in our recordings.

If you would like to have these instructions repeated, please say so now. Otherwise, the experiment will begin shortly.

Verbal Report

The training session is now finished. We are going to bring in a short questionnaire we would like to have you fill out. Please do not get out of the chair or remove the electrodes.

Appendix F

Trial Sequences

Testing Block

4,2,6,4,6,2

6,4,2,6,4,2

6,2,4,4,6,2

4,6,2,6,4,2

Training Block

3,3,5,3,5,5,3,3,5,3,3,5,5,3,5,5

3,5,3,3,5,3,5,3,3,5,5,3,5,5,3,5

5,5,3,5,3,3,5,5,3,5,5,3,3,5,3,3

5,3,5,5,3,5,3,5,5,3,3,5,3,3,5,3

2 - blank trial

3 - train shorten trial

4 - test shorten trial

5 - train lengthen trial

6 - test lengthen trial

Appendix G

Verbal Report Questionnaire

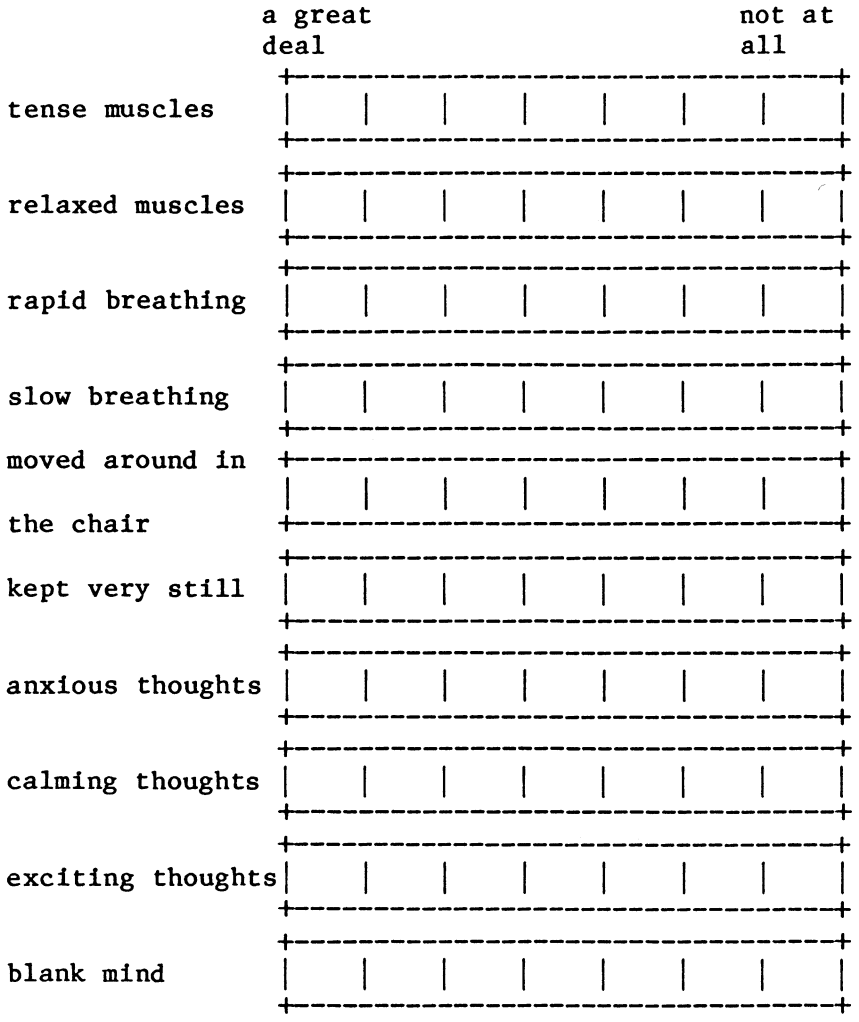
Questionnaire #1

Your Name_____ Date_____

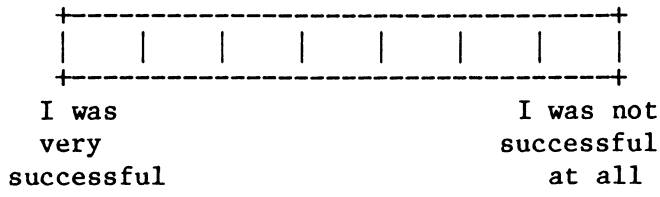
1. Describe what you did to make the dash move in the direction of the A on A-trials:

2. Describe what you did to make the dash move in the direction of the B on B-trials:

3. We would like to have you describe what you did on A and B trials using the scales given below. On each scale place an "A" in the box that best describes what you did on A trials, and, on the same scale place a "B" in the box that best describes what you did on B trials. You may place these letters in the same or different boxes on each scale, as you see fit. Please place an "A" and a "B" on every scale, even if you find this difficult.



Please rate the degree of success you experienced in moving the dash in the direction of the letter A on A trials, and the letter B on B trials. As before, you may place the letters "A" and "B" in the same box or in different boxes, as you see fit.



Appendix H

t-test Comparisons

t-values for bidirectional changes in RPI

Subject	With the assumption of equal variance	Without the assumption of equal variance
B	t(14)= 1.37	t(16)= 1.37
C	t(12)= -0.01	t(12)=-0.01
D	t(14)= 3.35**	t(11)= 3.38**
F	t(14)= 2.42*	t(8)= 2.42*
G	t(14)= 1.04	t(10)= 1.04
I	t(14)= 0.31	t(13)= 0.30
J	t(14)= 2.69**	t(15)= 2.69**
L	t(14)= 4.63**	t(9)= 4.62**
P	t(13)= -0.33	t(14)=-0.33
Q	t(14)= 0.36	t(15)= 0.36
R	t(14)= 5.37**	t(9)= 5.37**
S	t(14)= 0.25	t(11)= 0.25

*p<.05
**p<.01

REFERENCES

Abel, F. L. & McCutcheon, E. P. Cardiovascular Function: Principles and Applications. Boston: Little, Brown & Co., 1979.

Ahmed, S. S., Levenson, G. E., Schwartz, C. J. & Ettinger, P. O. Systolic time intervals as measures of the contractile state of the left venticular myocardium in man. Circulation, 1972, 46, 559-571.

Allen, R. A., Schneider, J. A., Davidson, D. M., Winchester, M. A. & Taylor, C. B. The covariation of blood pressure and pulse transit time in hypertensive patients. Psychophysiology, 1981, 18, 301-306.

Baumann, R., Ziprian, H., Godicke, W., Hartrodt, W., Naumann, E. & Lauter, J. The influence of acute psychic stress situations on biochemical and vegetative parameters of essential hypertensives at the early stages of the disease. Psychotherapy and Psychosomatics, 1973, 22, 131-140.

Bello, C. T., Sevy, R. W. & Harakal, C. Varying hemodynamic patterns in essential hypertension. American Journal of the Medical Sciences, 1965, 250, 58-69.

Benson, H., Shapiro, D., Tursky, B. & Schwartz, G. E. Decreased systolic blood pressure through operant conditioning techniques in patients with essential hypertension. Science, 1971, 173, 740-742.

Benthem, J. A. & Glaros, A. G. Self control of stress-induced cardiovascular change using transit time feedback. Psychophysiology, 1982, 19, 502-505.

Birkenhager, W. H. & Schalekamp, M. A. D. H. Control Mechanisms in Essential Hypertension. Amsterdam: Elsevier, 1976.

Blackburn, H. Non-pharmacological treatment of hypertension. In H. M. Perry & W. M. Smith (Eds.), Mild hypertension: to treat or not to treat. Annals of the New York Academy of Science, 1978, 304, 236-242.

Blix, A. S., Stromme, S. B. & Ursin, H. Additional heart rate - an indicator of psychological activation. Aerospace Medicine, 1974, 45, 1219-1222.

Bohr, D. F. & Berecek, K. H. Relevance of vascular structural and smooth muscle sensitivity changes in hypertension. Australian and New Zealand Journal of Medicine, 1976, 6 (Supplement 2), 26-34.

Boyer, J. T., Fraser, J. R. E. & Doyle, A. E. The hemodynamic effects of cold immersion. Clinical Sciences, 1960, 19, 539-550.

Brod, J. Hemodynamic basis of acute pressor reactions and hypertension. British Heart Journal, 1963, 25, 227-245.

Brod, J. Regional blood flow in essential hypertension. In G. Onesti, K. E. Kim & J. H. Moyer (Eds.), Hypertension: Mechanisms and Management. New York: Grune & Stratton, 1973.

Bulpitt, C. J., Hoffbrand, B. I. & Dollery, C. T. Contribution of drug treatment to symptoms of hypertensive patients. In F. Gross & T. Strasser (Eds.), Mild Hypertension: Natural History and Management. Toronto: Copp Clark Pitman, 1979.

Canada Health Survey, Canada Health Survey: The Health of Canadians. 1981.

Cannon, W. B. Bodily Changes in Pain, Hunger, Fear and Rage. New York: D. Appleton, 1920.

Conway, J., Darwin, K., Hilditch, A., Loveday, B. & Reeves, M. Effect of propranolol on blood pressure in normal and hypertensive rats. Clinical Sciences and Molecular Medicine, 1975, 48 (Supplement 2), 101s - 103s.

Carlson, L. A., Levi, L. & Oro, L. Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid. Journal of Clinical Investigation, 1968, 47, 1795-1805.

Chirife, R. & Spodick, D. H. Densitography: A new method for evaluation of cardiac performance at rest and during exercise. American Heart Journal, 1972, 83, 493 - 503.

Cinciripini, P. M. & Epstein, L. H. Pulse transit time feedback and bidirectional blood pressure change. Psychophysiology, 1981, 18, 630 - 634.

Chobanian, A. V., Gavras, H., Gavras, I., Bresnahan, M., Sullivan, P. & Melby, J. C. Studies on the activity of the sympathetic nervous system in essential hypertension. Journal of Human Stress, 1978, 4, 22-28.

Cole, F. M. & Yates, P. O. The occurrence and significance of intracerebral microaneurysms. Journal of Pathology and Bacteriology, 1967, 93, 393-411.

Corley, K. C., Shiel, F. O'm., Mauck, H. P. & Barber, J. H. Myocardial degeneration and cardiac arrest in the squirrel monkey: Physiological and psychological correlates. Psychophysiology, 1977, 14, 322-328.

Cruz-Coke, R., Donoso, H. & Barrera, R. Genetic ecology of hypertension. Clinical Sciences, 1973, 45 (Supplement 1), 55-65.

Davignon, A., Rey, C., Payot, M., Biron, P. & Moneau, J. G. Hemodynamic studies of labile essential hypertension in adolescents. In M. I. New & L. S. Levine (Eds.), Juvenile Hypertension. New York: Raven Press, 1977.

DeGood, D. E. & Adams, A. S. Control of cardiac response under aversive stimulation. Biofeedback and Self-Regulation, 1976, 1, 373-385.

DeQuattro, V., Barbour, B. H., Campese, V., Fink, E. J., Miand, L. & Esler, M. Sympathetic nervous hyperactivity in high-renin hypertension. Mayo Clinic Proceedings, 1977, 52, 369-373.

DeQuattro, V., Miura, Y., Lurvey, A., Cosgrove, M. & Mendez, R. Increased plasma catecholamine concentrations and vas deferens norepinephrine biosynthesis in men with elevated blood pressure. Circulation Research, 1975, 36, 118-126.

Doyle, A. E. & Smirk, F. H. The neurogenic component in hypertension. Circulation, 1955, 12, 543-552.

Eckberg, D. L., Kifle, Y. T. & Roberts, V. L. Phase relationship between human respiration and baroreflex responsiveness. Journal of Physiology, 1980, 304, 489-502.

Eich, R. H., Cuddy, R. P., Smulyan, H. & Lyons, R. H. Hemodynamics in labile hypertension: A follow up study. Circulation, 1966, 34, 299-307.

Esler, M. D., Julius, S., Zweifler, A., Randall, O., Harbourg, E., Gardiner, H. & DeQuattro, V. Mild high-renin essential hypertension: A neurogenic human hypertension? New England Journal of Medicine, 1977, 296, 405-411.

Falkner, B., Onesti, G., Angelako, E. T., Fernandes, M. & Langman, C. Cardiovascular response to mental stress in normal adolescents with hypertensive parents. Hypertension, 1979, 1, 23-30.

Folkow, B. Structural changes in heart and vessels during hypertension with aspects of their reversibility. Australian and New Zealand Journal of Medicine, 1976, 6 (Supplement 2), 35-39.

Folkow, B., Grimby, G. & Thulesius, O. Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance. Acta Physiologica Scandinavica, 1958, 44, 255-272.

Folkow, B., Hallback, M., Lungren, H. & Weiss, L. Background of increased flow resistance and vascular activity in spontaneously hypertensive rats. Acta Physiologica Scandinavica, 1970, 80, 93-106.

Forsyth, R. P. Regional blood flow changes during 72 hour avoidance. Science, 1971, 173, 546-548.

Forsyth, R. P. Effect of propranolol on stress-induced hemodynamic changes in monkeys. In P. R. Saxena & R. P. Forsyth (Eds.), Beta-adrenergic Blocking Agents. Amsterdam: North-Holland, 1976.

Forsyth, R. P., Hoffbrand, B. I. & Melmon, K. L. Hemodynamic effects of angiotensin in normal and environmentally stressed monkeys. Circulation, 1971, 44, 119 - 129.

Fouad, F. M., Tarazi, R. C., Dustan, H. P. & Bravo, E. L. Hemodynamics of essential hypertension in young students. American Heart Journal, 1978, 96, 646 - 654.

Fregly, M. J. Effect of an exercise regimen on development of hypertension in rats. Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 1984, 56, 381-387.

Friedman, R. & Iwai, T. Genetic predisposition and stress-induced hypertension. Science, 1976, 193, 161-162.

Frolich, E. D., Kozul, V. J., Tarazi, R. C. & Dustan, H. P. Physiological comparison of labile and essential hypertension. Circulation Research, 1970, 27 (Supplement 1), 55-63.

Fry, D. L. Responses of the arterial wall to certain physical factors. In Ciba Foundation Symposium, Atherogenesis: Initiating Factors. Amsterdam: Elsevier, 1973.

Gittleman, B., Shatin, L., Bierenbaum, M. C., Fleishman, A. & Hayton, T. Effects of Quantified stressful stimulation on blood lipids in man. Journal of Nervous and Mental Disease, 1968, 147, 196-201.

Glick G. & Braunwald, E. Relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of heart rate. Circulation Research, 1965, 16, 363-375.

Gliner, J. A., Bedi, J. F. & Horvath, S. M. Somatic and non-somatic influences on the heart: Hemodynamic changes. Psychophysiology, 1979, 16, 358-362.

Goldring, W., Chasis, H., Schreiner, G. E. & Smith, H. W. Reassurance in the management of benign hypertensive disease. Circulation, 1956, 14, 260 - 264.

Gordon, T., Garcia-Palmieri, M. R. Kagan, A., Kannel W. B. & Schiffman, J. Differences in coronary heart disease in Framingham, Honolulu, and Puerto Rico. Journal of Chronic Diseases, 1974, 27, 329-344.

Gorlin, R., Brachfield, N., Turner, J. D., Messer, J. V. & Salazar, E. The idiopathic high cardiac output state. Journal of Clinical Investigation, 1959, 38, 2144-2153.

Gribbin, B., Pickering, T. G., Sleight, P. & Peto, R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circulation Research, 1971, 29, 424-431.

Grim, C. E., Luft, F. C., Miller, J. Z., Rose, R. J., Christian, J. C. & Weinberger, M H. An approach to the evaluation of genetic influences on factors that regulate arterial blood pressure in man. Hypertension, 1980, 2, I34-I42.

Grollman, A. Physiological variation in the cardiac output of man. The effect of psychic disturbances on the cardiac output, pulse, blood pressure and oxygen consumption of man. American Journal of Physiology, 1929, 89, 584-588.

Guyton, A. C. Essential cardiovascular regulation - the control linkages between bodily needs and circulatory function. In C. J. Dickinson & J. Marks (Eds.), Developments in Cardiovascular Medicine. Lancaster: MTP, 1978.

Haft, J. I. & Arkel, Y. S. Effect of emotional stress on platelet aggregation in humans. Chest, 1976, 70, 501-505.

Hallback, M. & Folkow, B. Cardiovascular responses to acute mental stress in spontaneously hypertensive rats. Acta Physiologica Scandinavica, 1974, 90, 684-698.

Hansson, L. Beta-adrenergic blockade in essential hypertension. Effects of propranolol on hemodynamic parameters and plasma renin activity. Acta Medica Scandinavica, 1973, (Supplement 550), 1-40.

Harlan, W. R., Osbourne, R. K. & Graybiel, A. Prognostic value of the cold pressor test. American Journal of Cardiology, 1964, 13, 683-687.

Harris, V., Katlick, E., Lick, J. & Habberfield, T. Paced respiration as a technique for modification of autonomic response to stress. Psychophysiology, 1976, 13, 386-391.

Hastrup, J. L., Light, K. C. & Obrist, P. A. Parental hypertension and cardiovascular response to stress in healthy young adults. Psychophysiology, 1982, 19, 615-622.

Hines, E. A., Jr. & Brown, G. E. The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. American Heart Journal, 1936, 11, 1-9.

Hirsch, J. A. & Bishop, B. Respiratory sinus arrhythmia in humans: How breathing pattern modulates heart rate. American Journal of Physiology, 1981, 241, H620-H629.

Hypertension Detection and Follow-up Program Cooperative Group. A progress report. Circulation Research, 1977, 40 (Supplement 1), I106-I109.

Ibrahim, M. M., Tarazi, R. C., Dustan, H. P. & Bravo, E. L. Cardioadrenergic factor in essential hypertension. American Heart Journal, 1974, 88, 724-732.

Imhof, P. R., Blatter, K., Fuccella, L. M. & Turri, M. Beta-blockade and emotional tachycardia: Radiotelemetric investigations in ski-jumpers. Journal of Applied Physiology, 1969, 27, 366-369.

Inoue, K., Smulyan, H., Young, G. M. Grierson, L. C. & Eich, R. H. Left ventricular function in essential hypertension. American Journal of Cardiology, 1973, 32, 264-270.

Johnston, D. The control of pulse transit time independently of interbeat interval by providing feedback for both. Biofeedback and Self-Regulation, 1980, 5, 105-118.

Johnston, L. C. The abnormal heart rate response to a deep breath in borderline labile hypertension: A sign of autonomic nervous system dysfunction. American Heart Journal, 1980, 99, 487-493.

Julius, S. Borderline hypertension: Epidemiological and clinical implications. In J. Genest, E. Koiw, O. Kuchel, (Eds.), Hypertension: Physiopathology and Treatment. New York: McGraw-Hill, 1977.

Julius, S. & Conway, J. Hemodynamic studies in patients with borderline blood pressure elevation. Circulation, 1968, 38, 282-288.

Julius, S., Ellis, C. N., Pascual, A. V., Matice, M., Hansson, L., Hunyor, S. N. & Sandler, L. N. Home blood pressure determination. Journal of the American Medical Association, 1974, 229, 663-666.

Julius, S. & Esler, M. D. Autonomic nervous cardiovascular regulation in borderline hypertension. American Journal of Cardiology, 1975, 36, 685-696.

Julius, S., Esler, M. D. & Randall, D. S. Role of the autonomic nervous system in mild human hypertension. Clinical Science, 1975, 48, 243s-252s.

Julius, S. & Schork, M. A. Borderline hypertension - a critical review. Journal of Chronic Diseases, 1971, 23, 723-754.

Julius, S., Quardir, H. & Gajendragadkar, S. Hyperkinetic state: A precursor of hypertension? A longitudinal study of borderline hypertension. In F. Gross & T. Strasser (Eds.), Mild Hypertension: Natural History and Management. Toronto: Copp Clark Pitman, 1979.

Kahneman, D., Tursky, B., Shapiro, D. & Crider, A. Pupillary, heart rate and skin resistance changes during a mental task. Journal of Experimental Psychology, 1969, 79, 164-167.

Kannel, W. B. Importance of hypertension as a major factor in cardiovascular disease. In J. Genest, E. Koiw & O. Kuchel (Eds.), Hypertension: Physiopathology and Treatment. New York: McGraw-Hill, 1977.

Keys, A. Coronary Heart Disease in Seven Countries. Circulation, 1970, 41 (Supplement I), I1-I211.

Kirchhein, H. R. Systemic arterial baroreceptor relexes. Physiological Reviews, 1976, 56, 100-176.

Kuller, L. H., Crook. M., Almes, M. J., Detre, K., Reese, G. & Rutan, R. Dormont High School blood pressure study. Hypertension, 1980, 2, I109-I116.

Lane, J. D. The effects of self-control of respiration upon experimental pain. Psychophysiology, 1981, 18, 162-163. (Abstract)

Lane, J. D., Greenstadt, L., Shapiro, D. & Rubinstein, E. Pulse transit time and blood pressure: An intensive analysis. Psychophysiology, 1983, 20, 45-49.

Langer, A. W., Obrist, P. A. & McCubbin, J. A. Hemodynamic and metabolic adjustments during exercise and shock avoidance in dogs. American Journal of Physiology, 1979, 236, H225-H230.

Langos, J., Kvetnansky, R., Blazicek, P., Novotny, J., Vencel, P., Burdiga, A. & Mikulaj, L. Plasma renin activity and dopamine-beta-hydroxilase activity and catecholamine excretion in man during stress. In E. Usdin, R. Kvetnansky & I. J. Kopin (Eds.), Catecholamines and Stress. Don Mills: Pergamon of Canada, 1976.

Lawler, J. E., Barker, G. F., Hubbard, J. N. & Allen, M. T. The effects of conflict on tonic levels of blood pressure in the genetically borderline hypertensive rat. Psychophysiology, 1980, 17, 363-370.

Lawler, J. E., Obrist, P. A. & Lawler, K. A. Cardiovascular function during pre-avoidance, avoidance and post-avoidance in dogs. Psychophysiology, 1975, 12, 4-11.

Leblanc, J., Cote, J., Jobin, M. & Labrie, A. Plasma catechoamines and cardiovascular responses to cold and mental activity. Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 1979, 47, 1207-1211.

Leenen, F. H. & Shapiro, A. P. Effect of intermittent electric shock on plasma renin activity in rats. Proceedings of the Society of Experimental Biology and Medicine, 1974, 146, 534-538.

Levenson, R. W. Feedback effects and respiratory involvement in voluntary control of heart rate. Psychophysiology, 1976, 13, 108-114.

Levy, R. L., White, P. D., Stroud, W. D. & Hillman, C. C. Transient tachycardia. Journal of the American Medical Association, 1945, 129, 585-588.

Liard, J. F., Tarazi, R. C. & Ferrario, C. Hemodynamic effects of stellate ganglion stimulation in conscious dogs. In S. Julius & M. D. Esler (Eds.), The Nervous System in Arterial Hypertension. Springfield, Illinois: Charles Thomas, 1976.

Light, K. C. & Obrist, P. A. Cardiovascular reactivity to behavioral stress in young males with and without marginally elevated casual systolic pressures. Hypertension, 1980a, 2, 802-808.

Light, K. C. & Obrist, P. A. Cardiovascular response to stress: Effects of opportunity to avoid, shock experience, and performance feedback. Psychophysiology, 1980b, 17, 243-252.

Light, K. C. & Obrist, P. A. Task difficulty, heart rate reactivity, and cardiovascular responses to an appetitive reaction time task. Psychophysiology, 1983, 20, 301-312.

Liljestkand, G. & Stenstrom, M. Clinical studies on the work of the heart during rest. III. Blood flow in cases of increased arterial blood pressure with observation on the influence of preganacy on the blood flow. Acta Medica Scandinavica, 1925, 63, 142-152.

Littler, W. A., Honour, A. J. & Sleight, P. Direct arterial pressure and ECG recording during motor car driving. British Medical Journal, 1973, II, 273-277.

Lovell, R. R. H. Mild Hypertension: The Pressure to Treat. Proceedings of a Symposium by Satellite. Australia: Merck, Sharp and Dohme, 1981.

Lum, L. C. Hyperventilation and anxiety state. Journal of the Royal Society of Medicine, 1981, 74, 1-4.

Lund-Johansen, P. Hemodynamics in early essential hypertension. Acta Medica Scandinavica, 1967, Supplement 482, 1-105.

Lund-Johansen, P. Central Hemodynamics in essential hypertension. Acta Medica Scandinavica, 1977, Supplement 606, 35-42.

Manuck, S. B. & Garland, F. N. Stability of individual differences in cardiovascular reactivity: A thirteen month follow up. Physiology and Behavior, 1980, 24, 621-624.

Manuck, S. B. & Harvey, A. H., Lechleiter, S. C. & Neal K. S. Effects of coping on blood pressure responses to threat of aversive stimulation. Psychophysiology, 1978, 15, 544-549.

Manuck, S. B. & Proietti, J. M. Parental hypertension and cardiovascular response to cognitive and isometric challenge. Psychophysiology, 1982, 19, 481-489.

Mason, J. W., Maher, J. T., Hartley, L. H., Mougey, E. H., Perlow, M. J. & Jones, C. G. Selectivity of corticosteroid and catecholamine responses to various natural stimuli. In G. Serban (Ed.), Psychopathology of human adaptation. New York, Plenum Press, 1976.

Matsuura, T. & Goodyer, A. V. N. Effect of a pressure load on left ventricular systolic time intervals. American Journal of Physiology, 1973, 224, 80-85.

McCaul, K. D., Solomon, S. & Holmes, D. S. Effects of paced respiration on physiological responses to threat. Journal of Personality and Social Psychology, 1979, 37, 564-571.

McCubbin, J. A., Richardson, J. E., Langer, A. W., Kizer, J. S. & Obrist, P. A. Sympathetic neural function and left ventricular performance during behavioral stress in humans: The relationship between plasma catecholamines and systolic time intervals. Psychophysiology, 1983, 20, 102-110.

McCubbin, J. W. & Ferrario, C. M. Baroreceptor reflexes and hypertension. In J. Genest, E. Koiw & O. Kuchel (Eds.), Hypertension: Physiopathology and Treatment. New York: McGraw-Hill, 1977.

McCubbin, J. W., Green, J. H. & Page, I. H. Baroreceptor function in chronic renal hypertension. Circulation Research, 1956, 4, 205-210.

McCubbin, J. W., Soares DeMoura, R., Page, I. H. & Olmsted, F. Arterial hypertension elicited by subpressor amount of angiotensin. Science, 1965, 149, 1394-1395.

Miall, W. E. & Brennan, P. J. Observations on the natural history of mild hypertension in the control groups of therapeutic trials. In F. Gross & T. Strasser (Eds.), Mild Hypertension: Natural History and Management. Toronto: Copp Clark Pitman, 1979.

Miall, W. E. & Oldham, P. D. A study of arterial blood pressure and its inheritance in a sample of the general population. Clinical Science, 1955, 14, 459-488.

Millar-Craig, M. W., Kenny, D., Mann, S., Balasubramanian, V. & Raftery, E. B. Effect of once-daily atenolol on ambulatory blood pressure. British Medical Journal, 1979, I, 237-238.

Mitchell, J. R. A. & Schwartz, C. J. Arterial Disease. Oxford: Blackwell, 1965.

Moss, A. J. Vittands, I. & Schenk, E. A. Cardiovascular effects of sustained norepinephrine infusions. I. Hemodynamics. Circulation Research, 1966, 18, 596-604.

National Center for Health Statistics. Hypertension in adults 25 - 74 years of age; United States, 1971 - 1975. Vital and Health Statistics, 1981, 11(221).

Nestel, P. J. Blood pressure and catecholamine excretion after mental stress in labile hypertension. Lancet, 1969, I, 692-694.

Newlin, D. B. & Levenson, R. W. Pre-ejection period: Measuring beta-adrenergic influences on the heart. Psychophysiology, 1979, 16, 546-553.

Newlin, D. B. & Levenson, R. W. Voluntary control of pulse transmission time to the ear. Psychophysiology, 1980, 17, 581-585.

Obrist, P. A. Cardiovascular Psychophysiology: A Perspective. New York: Plenum Press, 1981.

Obrist, P. A., Gaebelein, C. J., Teller, E. S., Langer A. W., Grignolo, A., Light, K. C. & McCubbin, J. A. The relationship amoung heart rate, carotid dP/dt, and blood pressure in humans as a function of the type of stress. Psychophysiology, 1978, 15, 102-115.

Obrist, P. A., Howard, J. L., Lawler, J. E., Sutterer, J. R. Smithson, K. W. & Martin, P. L. Alteration in cardiac contractility during classical aversive conditioning in dogs: Methodological and theoretical implication. Psychophysiology, 1972, 9, 246-261.

Obrist, P. A., Light, K. C., McCubbin, J. A., Hutcheson, J. S. & Hoffer, J. L. Pulse transit time: Relationship to blood pressure and myocardical performance. Psychophysiology, 1979, 16, 292-301.

Obrist, P. A., Wood, D. M. & Perez-Reyes, M. Heart rate during conditioning in humans: Effects of UCS intensity, vagal blockade and adrenergic block of vasomotor activity. Journal of Experimental Psychology, 1965, 70, 32-42.

Omae, T., Takeshita, M., Veda, K., Sadoshima, S., Hirota, Y., Tanaka, K. & Enjoji, M. Necropsy-based population survey in Hisayama. In F. Gross & T. Strasser (Eds.), Mild Hypertension: Natural History and Management. Toronto: Copp Clark Pitman, 1979.

Paffenbarger, R. D., Thorne, M. C. & Wing, A. C. Chronic disease in former college students, VIII: Characteristics in youth predisposing to hypertension in later years. American Journal of Epidemiology, 1968, 88, 25-32.

Perry, H. M. & Smith, W. M. (Eds.) Mild Hypertension: To Treat or not to Treat. Annals of the New York Academy of Science, 1978, 304, 236-242.

Peterfy, G. & Pinter, E. J. Some physiological aspects of emotional stress. In K. Lissak (Ed.), Hormones and Brain Function. New York, N.Y.: Plenum Press, 1973.

Pfeffer, M. A. & Frolich E. D. Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. Circulation Research, 1973, 32 (Supplement I), I-28-I-38.

Pfeffer, M. A., Frolich, E. D., Pfeffer, J. M. & Weiss, A. K. Pathophysiological implication of the increased cardiac output of young spontaeously hypertensive rats. Circulation Research, 1974, 34 (Supplement I), I-235-I-242.

Pfeffer, M. A., Pfeffer, J. M., Weiss, A. K. & Frolich, E. D. Development of SHR hypertension and cardiac hypertrophy during prolonged beta blockade. American Journal of Physiology, 1977, 232, H639-H644.

Pickering, G. W. High Blood Pressure, 2nd Edition. New York: Grune & Straton, 1968.

Pickering, T. G. & Sleight, P. Baroreceptors and hypertension. Progress in Brain Research, 1977, 47, 43-60.

Pollack, M. H. & Obrist, P. A. Aortic-radial pulse transit time and ECG Q wave to radial pulse wave interval as indices of beat-by-beat blood pressure change. Psychophysiology, 1983, 20, 21-28.

Pooling Project Research Group. Relation of blood pressure serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. Journal of Chronic Diseases, 1978, 31, 201-306.

Price, K. P., Lott, G., Fixler, D. E. & Browne, R. H. Cardiovascular responses to stress in adolescents with elevated blood pressures. Psychosomatic Medicine, 1979, 41, 74. (Abstract)

Provoost, A. P., Bohus, B. & De Jong, W. Differential influence of neonatal sympathectomy on the development of DOCA-salt and spontaneous hypertension in the rat. Progress in Brain Research, 1977, 47, 417-424.

Randall, D. C., Cattrill, C. M., Todd, E. P., Price, M. A. & Wachtel, C. C. Cardiac output and blood flow distribution during rest and classical aversive condition in monkeys. Psychophysiology, 1982, 19, 490-497.

Randall, D. C., Kaye, M. P., Randall, W. C., Brady, J. V. & Martin, K. H. Response of primate heart to emotional stress before and after cardiac denervation. American Journal of Physiology, 1976, 230, 988-995.

Remington, R. D., Lambrath, B., Moser, M. & Hoobler, S.W. Circulatory reactions of normal and hypertensive subjects and the children of normal and hypertensive parents. American Heart Journal, 1960, 59, 58-70.

Robinson, B. F., Epstein, S. E., Beiser, G. D. & Braunwald, E. Control of heart rate by the autonomic nervous system: Studies in man on the interrelation between baroreceptor mechanisms and exercise. Circulation Research, 1966, 19, 400-411.

Ross Russell, R. W. How does blood-pressure cause stroke? Lancet, 1975, 2, 1283-1285.

Rushmer, R. F. Cardiovascular Dynamics, 3rd edition. Philadelphia: W. B. Saunders, 1970.

Safar, M. E., Weiss, Y. A., Levenson, J. A., London, G. M. & Milliez, P. L. Hemodynamic study of 85 patients with borderline hypertension. American Journal of Cardiology, 1973, 31, 315-319.

Sannerstedt, R. Hemodynamic response to exercise in patients with arterial hypertension. Acta Medica Scandinavica, 1966, Supplement 458.

Schieken, R. M., Clarke, W. R. & Lauer, R. M. Left ventricular hypertrophy in children with blood pressures in the upper quintile of the distribution. The muscatine study. Hypertension, 1981, 3, 669-675.

Schwartz, G. E. Toward a theory of voluntary control of response patterns in the cardiovascular system. In P. A. Obrist, A. H. Black, J. Brener & L. V. Dicara (Eds.), Cardiovascular Psychophysiology: Current Issues in Response Mechanisms, Biofeedback and Methodology. Chicago: Aldine, 1977.

Shapiro, A. P. & Melhado, J. Factors affecting development of hypertensive vascular disease after renal injury in rats. Proceeding of the Society of Experimental Biology and Medicine, 1957, 96, 619-623.

Sheperd, J. T. & Vanhoutte, P. M. The Human Cardiovascular System. New York: Raven, 1979.

Sherwood, A., Brener, J. & Moncur, D. Information and states of motor readiness: Their effects on the covariation of heart rate and energy expenditure. Psychophysiology, 1983, 20, 513-529.

Short, D. A policy for hypertension. British Heart Journal, 1975, 37, 893-896.

Simon, A. C., Safar, M. E., Weiss, Y. A., London, G. M. & Milliez, P. L. Baroreflex sensitivity and cardiopulmunary blood volume in normotensive and hypertensive patients. British Heart Journal, 1977, 39, 799-805.

Smith, T. L., Hutchins, P. N. Central hemodynamics in the developmental stage of spontaneous hypertension in the unanesthetized rat. Hypertension, 1979, 1, 508-517.

Stamler, J., Stamler, B., Riedlinger, W., Algera, G. & Roberts, R. Hypertension screening of 1 million Americans. Journal of the American Medical Association, 1976, 235, 2299-2306.

Stead, E. A., Warren J. V., Merrill, A. J. & Brannon, E. S. The cardiac output in male subjects as measured by the technique of right atrial catherization. Normal values with observations on the effect of anxiety and tilting. Journal of Clinial Investigation, 1945, 24, 326-331.

Steptoe, A. Blood pressure control: A comparison of feedback and instructions using pulse wave velocity measures. Psychophysiology, 1976, 13, 528-535.

Steptoe, A. Blood pressure control with pulse wave velocity feedback: Methods of analysis and training. In J. Beatty & H. Legewie (Eds.), Biofeedback and Behavior. New York: Plenum Press, 1977.

Steptoe, A. Voluntary blood pressure reductions measured with pulse transit time: Training condition and reactions to mental work. Psychophysiology, 1977, 14, 492-498.

Steptoe, A. The regulation of blood pressure reactions to taxing conditions using pulse transit time feedback and relaxation. Psychophysiology, 1978, 15, 429-438.

Steptoe, A., Godaert, G., Ross, A. & Schreurs, P. The cardiac and vascular components of pulse transit time: A computer analysis of systolic time intervals. Psychophysiology, 1983, 20, 251-259.

Steptoe, A. & Ross, A. Psychophysiological reactivity and the prediction of cardiovascular disorders. Journal of Psychosomatic Research, 1981a, 25, 23-31.

Steptoe, A. & Ross, A. The analysis of behavioral control over cardiovascular activity using pulse transit time methodology. Physiology and Behavior, 1981, 26, 927-933.

Stromme, S. B., Wikeby, P. C., Blix, A. S. & Ursin H. Additional heart rate. In H. Ursin, H. Baade & S. Levine (Eds.), The Psychobiology of Stress. New York: Academic Press, 1978.

Surwit, R. S. & Shapiro, D. Biofeedback and meditation in the treatment of borderline hypertension. In J. Beatty & H. Legewie (Eds.), Biofeedback and Behavior. New York: Plenum Press, 1977.

Taggart, P, Gibbons, P. & Somerville, W. Some effects of motor car driving on the normal and abnormal heart. British Medical Journal, 1969, IV, 130-134.

Takeshita, A., Tanaka, S., Kuroiwa, A. & Nadamura, M. Reduced baroreceptor sensitivity in borderline hypertension in man. Circulation, 1975, 51, 738-742.

Talley, R. C., Meyer, J. F. & McNay, J. L. Evaluation of the pre-ejection period an an estimate of myocardial contractility in dogs. American Journal of Cardiology, 1971, 27, 384-391.

Tarazi, R. C. Long-term hemodynamic effects of beta-adrenergic blockade. In G. Onesti, K. E. Kim & J. H. Moyer (Eds.), Hypertension, Mechanisms and Management. New York: Grune & Stratton, 1973.

Tarazi, R. C. The heart in hypertension: Its load and its role. In J. O. Davis, J. H. Laragh & A Selwyn (Eds.), Hypertension: Mechanisms, Diagnosis & Management. New York: H.P. Publishing Co., 1977.

Tarazi, R. C., Ibrahim, M. M., Dustan, H. P. & Bravo, E. L. Use of systolic time intervals in studying hypertension. Australian and New Zealand Journal of Medicine, 1976, 6 (Supplement I), 8-14.

Tenney, S. M. & Lamb, T. W. Physiological consequences of hypoventilation and hyperventilation. In W. O. Fenn & H. Rahn (Eds.), Handbook of Physiology, Section 3, Respiration (2). Washington, D. C.: American Physiological Society, 1965.

Thomas, G. W., Ledingham, J., Beilin, L. J. & Stott, A. N. Reduced plasma renin activity in essential hypertension: Effects of blood pressure, age and sodium. Clinical Science and Molecular Medicine, 1976, 51, 185S-188S.

Torok, E. The beginnings of hypertension: Studies in childhood and adolescence. In F. Gross & T. Strasser (Eds.), Mild Hypertension: Natural History & Management. Toronto: Copp Clark Pitman, 1979.

Tranel, D. T. The effects of monetary incentive and frustrative nonreward on heart rate and electrodermal activity. Psychophysiology, 1983, 20, 652-657.

Turner, J. R., Carroll, D. & Courtney, H. Cardiac and metabolic responses to "Space Invaders": An instance of metabolically-exaggerated cardiac adjustment? Psychophysiology, 1983, 20, 544-549.

Ulrych, M., Frolich, E., Dustan, H. & Page, I. Immediate hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation, 1968, 37, 411-416.

VanDercar, D. H., Feldstein, M. A. & Solomon, H. Instrumental conditioning of human heart rate during free and controlled respiration. Biological Psychology, 1977, 5, 221-232.

Vatner, S. F. Effects of exercise and excitement on mesenteric and renal dynamics in conscious, unrestrained baboons. American Journal of Physiology, 1978, 234, H210-H214.

Weinstein, M. C. & Stason, W. B. Hypertension: A Policy Perspective. Cambridge, Mass.: Harvard University Press, 1976.

Weiss, L., Lundgren, Y. & Folkow, B. Effects of prolonged treatment with adrenergic beta-receptor antagonists on blood pressure, cardio-vascular design and reactivity in spontaneously hypertensive rats. Acta Physiologica Scandinavica, 1974, 91, 447-457.

Weiss, Y. A., Safar, M. E., London, G. M., Simon, A. C., Levenson, J. A. & Milliez, P. M. Repeated hemodynamic determinations in borderline hypertension. American Journal of Medicine, 1978, 64, 382-387.

Yates, A. Biofeedback and the Modification of Behavior. New York: Plenum Press, 1980.