

ECHOCARDIOGRAPHIC ASSESSMENT OF CARDIAC ABNORMALITIES
AND THEIR RELATIONSHIP TO EXERCISE SYSTOLIC BLOOD PRESSURE
IN ICELANDERS AND IN CANADIANS OF ICELANDIC DESCENT:
IMPLICATIONS FOR EARLY DETECTION OF ESSENTIAL HYPERTENSION

by Barbara J. Naimark

A Thesis
submitted to the Faculty of Graduate Studies
as a partial requirement for the degree Doctor of Philosophy
Department of Physiology
Faculty of Medicine
The University of Manitoba, Winnipeg, Manitoba



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BARBARA J. NAIMARK

A thesis submitted to the Faculty of Graduate Studies of
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ABSTRACT

The relationship between the systolic blood pressure response to exercise (ESBP) and the dimensions of the left atrium and ventricle was studied in two geographically separate, but genetically comparable, populations consisting of males and females, aged 25-63 years, who were either normotensive (<140/90, mmHg) or borderline hypertensive (<140-159 and/or 90-95mmHg) at rest. Group IA (Canadians of Icelandic descent from the Interlake region of Manitoba) had a significantly higher prevalence of an exaggerated ESBP (≥ 200 mmHg), and of left atrial enlargement (LAE), than Group IIA (native Icelanders from Selfoss in Iceland). There was a higher prevalence of left ventricular hypertrophy (LVH) in Group IA males than in Group IIA males but no difference between the females in the two groups. Given their genetic similarity it is suggested that the difference between the two groups is due to environmental factors. Within each group, subjects with an exaggerated ESBP had a higher prevalence of LAE and LVH than subjects without an exaggerated ESBP. In a preliminary study, plasma norepinephrine levels were higher both at rest and during exercise in subjects with an exaggerated ESBP than in those without. The relationship of ESBP to LAE and LVH was independent of age, body mass and resting SBP. Whereas LVH was absent in the majority of cases with LAE, LAE was present in nearly all cases with LVH. These findings indicated that LAE is commonly a precursor of LVH in early hypertension and it is suggested that the presence of LAE may add to the value of an exaggerated ESBP in identifying individuals at increased risk of the development of sustained hypertension.

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LIST OF ABBREVIATIONSUnits of Measure

b	beat
cc	cubic centimeter
cm	centimeter
gm	gram
hr	hour
kg	kilogram
km	kilometer
L	liters
m	meter
min	minute
ml	milliliter
mm	millimeter
sec	seconds
ul	microliter

Miscellaneous

BMI	body mass index
BSA	body surface area
BP	blood pressure
DBP	diastolic blood pressure
EHT	essential hypertension
ESBP	exercise systolic blood pressure
FH-HT	family history of hypertension
FS	fractional shortening
HDL	high density lipoprotein
IHD	ischemic heart disease
LADI	left atrial dimension index
LAE	left atrial enlargement
LVEDDI	left ventricular end diastolic dimension index
LVESD	left ventricular end systolic dimension
LVIVS	left ventricular inter-ventricular septum
LVH	left ventricular hypertrophy
LVMi	left ventricular mass index
LVPW	left ventricular posterior wall
NE	norepinephrine
Per. Res.	peripheral resistance
SV	stroke volume

1. INTRODUCTION

The prevalence of cardiovascular diseases, including essential hypertension, varies with geographic location and it has been a matter of considerable ongoing interest to determine the respective roles of heredity and environment in their etiology and pathogenesis. The comparative study of Icelanders and their codescendants in Manitoba, being undertaken jointly by the University of Iceland and the University of Manitoba, has afforded investigators the opportunity to evaluate the aforementioned variables in two genetically similar populations. Any differences found between Canadians of Icelandic descent and native Icelanders can thus be attributed to environmental influences.

1.1 The Study Population

Iceland is a volcanic island in the North Atlantic Ocean, bordering on the Arctic Circle, some 300 km south of the east coast of Greenland and 800 km north of Scotland. Immigration has been negligible over the centuries and therefore the population remains unusually genetically homogeneous. The country is sparsely populated with a total population of close to 250,000 inhabitants, two-thirds of whom live in the capital city Reykjavik and the surrounding area on the southwestern corner of the island. The rest of the country has less than one inhabitant per square kilometer (Petursdottir, 1984).

Icelanders have always been avid collectors of personal data and a great deal of information is available on the people of Iceland from the time the

country was settled 1,100 years ago. In more recent times, the collection and publication of demographic information became centralized with the establishment of the Statistical Bureau in 1916. In 1952, a National Registry was established and citizens were assigned identification numbers in order to prevent confusion of individuals who bore the same name. In 1965 a special committee was established whose main purpose was to begin studying population genetics. The so-called Genetic Committee has computerized the general census from 1910 and traced the ancestors of those alive in 1910 back to 1840. These records were useful in identifying the ancestors of the Canadians of Icelandic descent living in the Interlake region of Manitoba.

In 1967, a large-scale follow-up health survey was initiated by the Icelandic Heart Association. Its primary goal was to to detect cardiovascular diseases in their early stages, to determine their prevalence and incidence, and to study their etiology in the search for preventive measures. Forty-five thousand Icelanders were screened by the Heart Association and, in cooperation with the Genetic Committee, studies of many diseases have been undertaken, including cardiovascular and cerebrovascular diseases (Thordarson and Fridriksson, 1980; Thordarson and Fridriksson, 1977; Gudmundson *et al.*, 1980; Gudmundson and Jensson, 1980).

One of the important undertakings to emerge from these cooperative studies was the Icelandic-Canadian Collaborative Project. The project was initiated following a 1975 report of statistics from the Manitoba Department of Health and Social Development showing a significant difference in ischemic heart disease (IHD) mortality between two populations with a common ancestry but residing in different environments; the two populations concerned were Canadians of Icelandic descent residing in the province of

Manitoba and native Icelanders (Axelsson *et al.*, 1981). An epidemiological study was initiated to investigate the underlying elements contributing to the difference in the reported mortality rate. A record was compiled for each of the 20,000 persons who left Iceland in the great emigration which took place between 1870 and 1914. The record lists age and occupation, which part of the country they came from, when and where they left Iceland, and their destination (Kristjansson, 1983). Many of the migrants settled in "New Iceland", an area north of Winnipeg between Lake Winnipeg and Lake Manitoba, known as the Interlake region of the Province of Manitoba.

An assessment was undertaken of the prevalence of risk factors for cardiovascular disease in children and adults in the two populations (Axelsson, Palsson *et al.*, 1981; Axelsson, Sigfusson *et al.*, 1981; Axelsson, Jonsson *et al.*, 1981; Petursdottir *et al.*, 1982; Way *et al.*, 1988; Sigurdsson *et al.*, 1990; Axelsson *et al.*, 1990).¹ Because of their genetic similarity and the availability of detailed genealogical information concerning them, the two populations provided a unique opportunity for the use of epidemiological research to evaluate the role of the environment in the pathogenesis of essential hypertension (EHT).

A number of papers arising from the Icelandic-Canadian Study have been published describing such characteristics of the native Icelanders as: serum lipids in children and adults, comparisons of total serum cholesterol and triglycerides between town and farm dwelling youths, blood pressure in adult females (Petursdottir *et al.*, 1981; Axelsson *et al.*, 1981). Other studies compared Icelanders and Canadians of Icelandic descent with respect to such

¹Prevalence refers to a static picture or "snapshot" of the number of persons who have a disease or a characteristic under study in a population at one point in time. (Freidman 1976)

characteristics as blood lipids and prevalence of obesity in youngsters (6-20 years) and total serum cholesterol, HDL and LDL cholesterol and triglycerides in the adult populations (Way *et al.*, 1988; Axelsson *et al.*, 1990). In the adult populations (aged 20-69), Icelanders had a more favorable "atherogenic index" (ratio of HDL cholesterol to total cholesterol) than their Canadian counterparts, 0.248 and 0.196 respectively.

Recently the fatty acid composition of 114 men, aged 55-66 years, from the Interlake was reported by Skuldottir *et al.*, (1990). Preliminary results indicate that the percentage fatty acid composition of plasma phospholipids in males of Canadians of Icelandic descent differed significantly from that of Icelandic males aged 50-67. The omega-3/omega-6 ratio was 0.44 in Icelandic males versus 0.14 in the Interlake males. The fatty acid profile of plasma phospholipids has been of particular interest in recent years since there is evidence of a correlation between atherosclerosis, and its clinical manifestations, and the fatty acid composition of phospholipids. Special attention has focused on the omega-3/omega-6 polyunsaturated fatty acid ratio. It has been suggested that a low omega-3/omega-6 fatty acid ratio may be an independent risk factor for ischemic heart disease.

Among the risk factors evaluated, particular attention was paid to EHT - one of the most important precursors of cardiovascular disease. There is good evidence to suggest that EHT should be thought of not only as a cardiovascular risk factor but also as a clinical disease *per se* with a prevalence sufficiently high in acculturated societies to warrant it being referred to as a serious public health problem (Horan and Lenfant, 1990). Epidemiological and actuarial statistics have revealed that premature cardiovascular morbidity and mortality are directly related to the level of

blood pressure (Kannel, 1974; Society of the Association of Life Insurance Medical Directors and the Society of Actuaries, 1980).

1.2 The Detection of Early Essential Hypertension

Defining a blood pressure level at which an individual is labelled hypertensive is somewhat arbitrary. If the systolic and diastolic pressures are above 160 mmHg and 95 mmHg respectively the blood pressure is considered to be clearly abnormal; pressures below 140 mmHg systolic and 90mmHg diastolic are considered to be clearly normal (World Health Organization 1978). The significance attributed to pressures between these limits has varied from study to study. However systolic blood pressure (SBP) between 140 and 159 mmHg and diastolic blood pressure (DBP) between 90 and 95 mmHg are regarded as borderline abnormal and are referred to as "borderline hypertensive" in several studies reviewed by Julius and Schork (1971). Accordingly for the purpose of the studies reported in this thesis, normotension will be defined as blood pressure <140/90 mmHg, and borderline HT as blood pressures of 140-159/ 90-95 mmHg.

The incipient stages of a disease process are of particular research interest, and the challenge is particularly great in diseases such as essential hypertension which may remain clinically "silent" for many years before cardiovascular abnormalities become obvious. Accordingly the focus of the studies reported in this thesis was the detection of the incipient stages of EHT. There were two reasons for this approach: first, it is well recognized that detection and intervention in the early stages of hypertensive disease enhances the possibility of preventing or ameliorating cardiovascular complications (Kannel and Thom, 1984); second, the study of its earliest

stages is more likely to enhance the elucidation of the pathogenesis of this complex disease than would the study of established disease. It has been suggested that if it were possible to identify individuals who are normotensive but at increased risk for the development of EHT, measures might be applied which could prevent or delay its onset. Of particular importance has been the observation that the risk of complications in individuals with any given level of blood pressure was higher for those with evidence of left ventricular hypertrophy (LVH) than in those without this abnormality (Sokolow and Perloff 1961; Breslin *et al.*, 1966; Kannel *et al.*, 1972). This finding led the World Health Organization (1978) to recommend that evidence of LVH be used in addition to level of blood pressure to classify the severity of hypertension.

The suggestion that the systolic blood pressure response to exercise may be an important means to identify normotensive individuals at risk of developing hypertension has been made by a number of authors (Naughton, 1982; Wilson and Meyer, 1981; Dlin *et al.*, 1983). It has also been proposed that, in established EHT, cardiac abnormalities are more closely correlated with blood pressure during activity or stress than with casual resting blood pressure measured in the physician's office (Ren *et al.*, 1985; De Gaudemaris *et al.*, 1985; Rowlands *et al.*, 1981; Devereux *et al.*, 1983; Drayer *et al.*, 1983; Ferrara *et al.*, 1987).

Naimark *et al.*, (1990) first demonstrated an association in normotensive and borderline hypertensive subjects between exercise systolic blood pressure (ESBP) and electrocardiographic abnormalities evidence suggestive of left atrial enlargement (LAE) and LVH; features normally associated with established EHT and as noted above, predictive of future

cardiovascular sequelae (Dunn *et al.*, 1977; Dreslinski *et al.*, 1981; Levy *et al.*, 1990). Whether high ESBP with associated atrial and ventricular abnormalities is a precursor of EHT is not known.. Although electrocardiography permits the indirect assessment of left ventricular structure and function, this method has been shown to be relatively inaccurate (Sokolow and Perloff 1961; Breslin *et al.* 1966; Kannel *et al.*, 1972; Dunn FG *et al.*, 1977; Alderman, 1980) and it was therefore of interest to determine in these predominantly normotensive study populations whether there was an association between high levels of ESBP and LAE and LVH as detected by echocardiography . Echocardiography, a non-invasive tool for determination of left ventricular and left atrial dimensions, has been shown to be more sensitive and specific than the electrocardiogram for detecting LVH and LAE (see below, pages 43-46).

It is known that a subset of individuals with early EHT exhibit a hyperkinetic circulation characterized by an increased cardiac output involving an increase in both stroke volume and heart rate. These hemodynamic changes are abolished with pharmacological blockade (propranolol and atropine). Thus derangement of autonomic nervous system function has been suggested as a mechanism to explain both the hyperkinetic circulation and the association between ESBP and cardiac abnormalities in hypertension. The presence of elevated plasma concentrations of the adrenergic neurotransmitters norepinephrine (NE) and/or epinephrine (E) in early EHT supports the suggestion that sympathetic activation may be involved in its pathophysiology via stimulation of the heart and/or vasoconstriction. Accordingly it was also of interest to

determine if the plasma concentration of NE and E were correlated with ESBP and with LAE and LVH.

To test the foregoing hypotheses echocardiographic measurements of left atrial and left ventricular dimensions were carried out in native Icelanders and in Canadians of Icelandic descent, and the results related to ESBP and other variables. The results of the investigations reported in this thesis contribute to the elucidation of the pathophysiology of EHT and the underlying cause(s) for the difference in mortality from IHD between the two populations noted in earlier studies.

2. LITERATURE REVIEW

In this section the literature concerning the etiology and pathogenesis of EHT, EHT and cardiovascular morbidity and mortality, heredity and EHT, detection of early EHT and hemodynamic changes in early EHT will be reviewed. This review will be concerned principally with studies of humans since, despite the obvious benefits of control over various genetic and environmental influences which their use confers, animal models are not entirely satisfactory alternatives to the study of humans.

2.1 Etiology and Pathophysiology of Essential Hypertension

The multifactorial nature of EHT has become widely accepted, but the etiology of the disease has defied complete understanding. The factors believed to contribute to the etiology and pathogenesis of EHT in humans fall into two main categories: genetic and environmental; with environmental influences interacting with what is thought to be a random polygenic predisposition.

The etiologic factors involved in EHT ultimately result in abnormalities in the regulation of one or more of the control mechanisms by which blood pressure is regulated, resulting in a transient or sustained increase in blood pressures. Several lines of investigation related to the pathogenesis of EHT have been pursued, including studies of the role of abnormalities in the intake, metabolism, and cellular transport of cations, and in neuro-regulatory mechanisms.

2.1.1 The Role of Sodium in Essential Hypertension

a. Sensitivity to Salt Loading

Most workers agree that certain sub-populations (normotensive blacks, caucasians over the age of forty, and off-spring of hypertensive parents) are at greater risk for the development of hypertension. These particular groups are more apt to be salt-sensitive than salt-resistant (Luft *et al.*, 1977, 1979; Grim *et al.*, 1979; Falkner *et al.*, 1982). The phenomenon of salt-sensitivity and resistance is demonstrable in both normotensive and hypertensive individuals and can be identified by rapid sodium and volume loading and depletion. In two studies using the National Institutes of Health (NIH) salt-loading protocol it was shown that hypertensive patients whose pressures were normalized by salt depletion retained more sodium when salt loaded and pressure rose more than did patients whose pressures were unaffected, or little affected by the changes in salt intake (Kawasaki *et al.*, 1978; Fujita *et al.*, 1980). However Campese *et al.*, using the same salt loading protocol, demonstrated that not all patients with salt-sensitive hypertension respond similarly (Campese *et al.*, 1982).

Dustan and Kirk (1989) used the NIH protocol (salt depletion followed by salt loading) and a second protocol in which salt loading preceded salt depletion. The second manouever was used to determine if the greater sodium retention found in salt-sensitive hypertensive subjects of the NIH group only reflected the highly artificial condition in which salt loading followed a period of rigid salt restriction, a situation irrelevant in free-living individuals. Since they found no statistically significant relation between blood pressure change and the amount of sodium lost during depletion or retained during loading, the authors concluded that other factors were

responsible for the pressure increases and decreases during manipulations of sodium intake.

b. Abnormalities of Sodium Metabolism

A more direct assessment of the role of sodium in the etiology of hypertension involves the study of sodium transport mechanisms. Unfortunately study of sodium transport in hypertension in humans is problematic in that samples of vascular smooth muscle, the tissue most immediately involved in the development of hypertension, can rarely be obtained. In most cases sodium transport in humans is studied using erythrocytes and leukocytes because of their accessibility. It is assumed that the transport processes of these cells are representative of those that take place in other body tissues. The key questions of interest are: Is there an abnormality in intracellular sodium content and sodium transport in persons with hypertension? If so, is that abnormality associated with the genetic tendency to develop hypertension or is the abnormality present only in the developed disease (Hilton 1986).

In human red and white cells, sodium flux involves passive entry of sodium and three sodium transport systems: (i) the furosemide (bumetanide) - sensitive Na^+ , $-\text{K}^+$ cotransport system which catalyzes inward and outward fluxes of Na^+ and K^+ depending on intracellular concentrations of the two ions; (ii) a Na^+ - Na^+ countertransport system which catalyzes a one-to-one exchange of internal for external Na^+ (Li^+ and perhaps H^+ may replace sodium in this system); (iii) a ouabain-sensitive Na^+ - K^+ pump, which catalyzes the exchange of internal sodium for external potassium coupled to the hydrolysis of ATP, generating electrochemical gradients of Na^+

and K^+ across the cell membrane. Other Na^+ transport systems such as that involving Na^+-Ca^{++} exchange are lacking in human red blood cell membranes (Garay *et al.*, 1986). (Discussion of this system is found in the section describing natriuretic hormones).

Increased passive entry of sodium (sodium leak) in erythrocytes and leukocytes from essential hypertensives has been demonstrated through measurement of unidirectional Na^+ influx. Approximately 50% of the studies found no statistically significant increases in the sodium content of red cells in the hypertensive group compared with controls. In studies with larger series significant increases in sodium content of red cells were observed in hypertensive subjects. Even in studies where statistically significant increases were not demonstrated, the mean level of intracellular sodium in the hypertensive group tended to exceed that in controls. In human white blood cells, increased permeability of the cell membrane to sodium has been more consistently demonstrated. It is believed that the sodium leak may be compensated for by an increase in the maximal rate of the Na^+-K^+ pump and the Na^+-K^+ cotransport system (Williams *et al.*, 1988). In several studies a fall in the sodium efflux in erythrocytes of hypertensive patients was attributed to a decreased affinity of the Na^+-K^+ cotransport system for internal sodium (Garay *et al.*, 1979,1980, 1986). In other laboratories using the same methodology the results were variable (Davidson *et al.*, 1982; Wiley *et al.*, 1984). It has been suggested that even if there is maximal activity of the cotransport system in control cells and no activity in cells from hypertensive patients, the observed differences are too great to have resulted solely from variation in the cotransport mechanism (Hilton, 1986).

Moreover, any abnormality in this flux would not necessarily lead to significant changes in intracellular sodium content (Poston, 1987).

Abnormally high maximal rates of $\text{Na}^+\text{-Li}^+$ countertransport in red cells of hypertensive patients were first described by Canessa *et al.* (1980). Most of the numerous reports on this subject have confirmed these findings. It is assumed that lithium is reabsorbed in the proximal tubules in parallel with sodium and water and that lithium is neither reabsorbed or excreted beyond the proximal tubules. It has been hypothesized that the high $\text{Na}^+\text{-Li}^+$ countertransport in the proximal tubule could represent the primary kidney defect resulting in increased sodium reabsorption. The abnormal countertransport has been frequently associated with an increased maximal rate of $\text{Na}^+\text{-K}^+$ cotransport. The correlation coefficient of 0.8 suggests a significant association between these two abnormalities.

Physiologically, the $\text{Na}^+\text{-K}^+$ pump seems to be the primary mechanism, in various cell types, for the extrusion of sodium. The volume of sodium movement attributed to the pump exceeds considerably the amount that could be moved by cotransport or Na^+ exchange (Williams *et al.*, 1988). Elevated intracellular sodium content coupled with a reduced rate-constant for sodium efflux by the sodium pump in leukocytes from patients with EHT has been demonstrated in a number of laboratories (Araoye *et al.*, 1978; Poston *et al.*, 1981; Boon *et al.*, 1985). The results have not always been as consistent in studies of sodium transport in erythrocytes. There are also conflicting results as to whether the sodium pump in red cells is abnormal in patients with EHT. There are reports of reduced rate-constant efflux of sodium in physiologic mediums and of a decrease in the maximal activity of the pump, while in other papers normal values are reported (Hilton, 1986).

More than one kind of transport abnormality was found in some hypertensive patients (Garay *et al.*, 1986).

c. Genetic or Acquired Changes in Sodium Transport

The evidence for genetic transmission of abnormalities in sodium transport is conflicting. In many cases normotensive offspring of hypertensive parents are used for the study of genetic influences, however it should be noted that this population is heterogeneous in that it contains persons with and without the postulated marker for hypertension (Hilton, 1986). Abnormal $\text{Na}^+\text{-K}^+$ cotransport was originally reported in both patients with established hypertension, and in the normotensive offspring of hypertensive parents. This result however was later shown to be different in black and white populations. In white populations with hypertension the cotransport levels are high. Black populations have consistently lower levels of cotransport even among normotensives. Currently available data suggest that low levels of cotransport in blacks may reflect a susceptibility to sodium induced hypertension and may be a genetic trait. In white hypertensive individuals the high cotransport may reflect compensatory changes in cotransport in response to other primary factors.

Several laboratories have demonstrated familial aggregation and high heritability of abnormal $\text{Na}^+\text{-Li}^+$ countertransport and its relationship to hypertension in human populations (Williams *et al.*, 1983; Lewitter and Canessa, 1985; Kagamimore *et al.*, 1985). Recently Redgrave *et al.* (1989) confirmed the increase in $\text{Na}^+\text{-Li}^+$ countertransport in hypertensives and in addition described the aggregation of elevated $\text{Na}^+\text{-Li}^+$ countertransport in a subset of normal to high renin hypertensive subjects with a strong family

history for hypertension. Other studies, however, have demonstrated a number of non-genetic factors (e.g. oral contraceptive use, physical training) may alter the rate of $\text{Na}^+\text{-Li}^+$ countertransport in hypertensives (Beuckelmann *et al.*, 1984; Adragna *et al.*, 1985). Despite the evidence of genetic influences, the activity of the countertransport system should not be regarded as solely genetically determined.

It has been postulated that the activity of the $\text{Na}^+\text{-K}^+$ ATPase pump is less genetically determined and more responsive to environmental factors than the cotransport or countertransport systems discussed above. Two laboratories have failed to identify any difference in the content or transport of sodium in cells of the normotensive offspring of hypertensive parents and the offspring of normotensive parents (Gray *et al.*, 1984; Chien and Zhao, 1984). Other studies have demonstrated correlations of sodium transport in the cells of spouses and between people living in the same household to be better than correlations between related individuals living in different households (Hunt *et al.*, 1987). However, evidence of some genetic influence on the function of the $\text{Na}^+\text{-K}^+$ pump has been shown in other studies (see natriuretic hormone section below).

d. Natriuretic Hormones

In addition to studies of erythrocytes and leukocytes, other experiments concerned with sodium transport have focused on a factor(s) found in the urine and plasma of humans that appears to inhibit the sodium pump in low-renin forms of hypertension (Hilton, 1986). In the case where sodium intake exceeds the capacity of the kidneys to excrete it, there is a net retention of sodium and water resulting in volume expansion. The initial effect may

be an increase in cardiac output and blood pressure. These events may be rapidly compensated for by the transient secretion of at least two natriuretic hormones, the atrial natriuretic factor (ANF) which is a peptide present in atrial cardiocytes and the endogenous "ouabain-like" factor (OLF), present in human plasma and influenced by the hypothalamus (Bohr and Webb, 1988). (Very recently Hamlyn *et al.* (1989) have isolated and characterized an endogenous pump inhibitor from human plasma.)

The site of action of ANF is the renal glomeruli, where it increases the glomerulii filtration rate. The ANF also interacts with smooth muscle receptors resulting in vasorelaxation (Gray *et al.*, 1986). Initially it was suggested that the ANF might be the "natriuretic hormone" and also the sodium transport inhibitor of EHT, however, it has been demonstrated that ANF has no effect on Na^+ , K^+ -ATPase and could not therefore explain the sodium pump inhibitory effects of extracts from plasma or urine in the volume expanded state (Poston, 1987).

OLF seems to inhibit the Na^+ - K^+ pump and, at the renal tubular level, results in a natriuretic effect. Blaustein *et al.* (1987) have proposed that if the sodium pumps in other cells, including smooth muscle cells (SMC), are also influenced by OLF, the reduced sodium extrusion would raise intracellular sodium, decrease the sodium gradient and consequently result in accumulation of intracellular calcium, perhaps by the Na^+ - Ca^{++} exchange process. In this manner volume depletion would be achieved at the expense of increased contraction in smooth muscle cells. Droogmans *et al.* (1985) argue that a critical role for the Na^+ - Ca^{++} exchange in the regulation of calcium is not certain, since there is as yet no demonstration of a direct causal relation between the reduction of the Na^+ gradient resulting in contraction

and restoration of the gradient resulting in relaxation. They point out that contraction and relaxation can be induced by various procedures in the absence of a Na^+ gradient. In addition after complete dissipation of the Na^+ gradient by prolonged exposure to K^+ -free solutions smooth muscle may be completely relaxed.

de Wardener and MacGregor (1981) have suggested that pump inhibition leading to the natriuretic effect is a compensatory mechanism in individuals with an inherited defect in renal sodium excretion. In support of this hypothesis studies have demonstrated inhibition of the sodium pump in lymphocytes by plasma extracts from not only hypertensives but from young subjects with a history of familial hypertension (Ambrosioni *et al.*, 1981; Costa *et al.*, 1982). In four groups, studied by Boschi *et al.* (1985), normotensives with family history of hypertension (F+); normotensives without family history of hypertension (F-); borderline hypertensives (BL); and established hypertensives (EH); inhibition of the pump was directly related to the intralymphocytic Na^+ content and blood pressure, and was inversely related to intralymphocytic K^+ content, but not to plasma renin or aldosterone in the F+, BL, and EH groups. Aldosterone is known to act upon the sodium-potassium ATPase in the tubular cells of the kidney as well as on other epithelial cells, but has not been shown to have receptors in muscle cells. If there were receptors in muscle cells one might expect there to be an increase in ATPase activity and optimization of intracellular potassium.

Results from other laboratories, however, show increases rather than decreases in pump activity. Garay and Meyer (1979) suggested that the high Na^+ - K^+ pump activity seen in offspring of hypertensive parents and in mild hypertensives represent a compensatory mechanism for extruding a cell Na^+

load and thus preventing severe hypertension. Overbeck's group, using arterial tissue extracted from rats with chronic hypertension, suggested the increased pump activity they found could be explained by the induction of additional $\text{Na}^+\text{-K}^+\text{ATPase}$ molecules in response to the OLF (Overbeck, 1987). This suggestion has been confirmed in another study where an up-regulation of pump abundance was observed as a result of exposure to sublethal concentrations of digitalis glycosides Wolitzky *et al.*, 1986). The link between detected circulating OLF and essential hypertension is at present unresolved.

As the foregoing observations indicate, hypertensives exhibit abnormalities in the cellular transport of sodium but the results are not entirely consistent. There is frank disagreement about whether or not abnormal sodium transport is genetically determined. In any case it is not possible, given the present state of knowledge, to decide whether these abnormalities are primary etiologic factors or are a consequence of the hypertensive state.

2.1.2 The Role of Potassium in Essential Hypertension

a. Sensitivity to Potassium Loading

In some but not all clinical studies of human subjects there was a decrease in blood pressure with potassium supplementation in both normotensive and hypertensive subjects. One study described increased blood pressure during potassium depletion in normotensive men. In most of these studies the numbers of subjects was small and potassium supplementation was of short duration Weinberger, 1988; Khaw and Thom, 1982; McGregor *et al.*, 1982; Iimura *et al.*, 1981; Morgan, 1982; Krishna *et al.*, 1989).

Weinberger (1988) showed that sodium loading increased pressure and at levels above ≥ 300 mEq/day in 8 young normotensive male subjects resulted in a potassium deficit (measured by potassium excretion). He then showed that when potassium losses were replaced, as they occurred, by oral potassium supplementation there was a significant blunting of the blood pressure-raising effects of sodium loading. In a randomized double-blind cross-over study Khaw and Thom reported a small but significant decrease in blood pressure in 20 young healthy normotensive males during potassium supplementation of 64 mmols per day versus controls given a placebo and whose sodium intake was unrestricted. MacGregor *et al.* (1982) studied twenty-three unselected and untreated patients with mild to moderate hypertension. The addition of 60mEq per day of potassium versus placebo caused a small, but significant decrease in mean blood pressure. There was a heterogeneity of response in this study, and some subjects did not respond at all. In other studies there was no antihypertensive effect with potassium supplementation, however the supplement was relatively small (Grim *et al.*, 1980; Gross *et al.*, 1976). There is no data on compliance, risks or side effects of potassium supplementation in any of the studies listed.

b. Abnormalities of Potassium Metabolism

Elevated intracellular sodium content, coupled with a reduced rate-constant for sodium efflux by the sodium pump in blood cells is seen in some patients with essential hypertension and their normotensive relatives (see pages 11-15). Potassium levels should be altered concomitantly, since the intracellular contents of sodium and potassium are closely related by the

active cation transport system and diffusion along the ion gradient (Ericsson *et al.*, 1981).

Studies of the effect of potassium on the sodium -potassium pump primarily involve the use of animal models. The activity of the pump has been shown to be increased, unchanged or decreased in these models. The few studies undertaken in human subjects are also inconsistent.

Nelson and Henningsen measured erythrocyte sodium and potassium in 56 male offspring of hypertensive patients and compared the findings with those in matched controls (Nelson and Henningsen, 1983). Re-measurement in 4-6 months in a sample of the original group was carried out. There was a significant correlation between the two intra-individual measurements of intracellular sodium and potassium. The authors propose that the negative correlations found between sodium and potassium in erythrocytes in offspring seem to support the idea of abnormal pump function.

Total body potassium, measured by whole body counting is a good measure of total intracellular potassium provided correction is made for differences in body composition. Ericsson *et al.* (1981) in a study of total body and erythrocyte potassium in mild hypertensives found decreased intracellular potassium concentration in hypertensives compared to age and sex matched controls. There was no correlation between intracellular potassium measured by whole body counting and erythrocyte potassium. In the hypertensives a negative correlation existed between serum potassium and erythrocyte potassium. No correlation was found between potassium decrease and urinary aldosterone or plasma renin level. An inhibition of the active sodium-potassium exchange is proposed as the mechanism.

Similar findings were reported by Beretta-Piccoli *et al.* (1982). Plasma potassium concentration, exchangeable potassium and total body potassium correlated inversely and significantly with arterial pressure in hypertensive patients. These correlations were greater in young hypertensives than in older patients. Mean values for the plasma concentrations of active and total renin and for angiotensin II and aldosterone were within normal ranges in hypertensive patients. The inverse relation of arterial pressure with plasma potassium is compatible with the cell-sodium hypothesis since decreasing extracellular potassium concentration produces vasoconstriction by inhibiting sodium transport and increasing cellular sodium. On the other hand, the authors argue, the renal abnormality and resetting of pressure-natriuresis could develop as a consequence of the sympathetic nervous system. The authors suggest that since plasma and whole body potassium are related to arterial pressure primarily in the young patients and since the sympathetic nervous system is most overactive in the young hypertensive, the sympathetic nerve activity could be the primary mechanism in development of hypertension. The decreased extracellular potassium and resulting vasoconstriction could in part be caused by an overactive sympathetic nervous system.

Anderson *et al.*, (1971) and Dargie *et al.*, (1974) report normal total body potassium measured by whole body counting in hypertensives. However Anderson *et al.* related total body potassium to body weight, with no correction for differences in body composition. Dargie *et al.*, related total body potassium to corresponding values derived from anthropometric data. However they investigated only a small number of subjects so that conclusive statements about their results can not be made .

In summary, potassium supplementation blunts the blood pressure effect of salt-loading but does not consistently lower pressure in hypertensive humans. The effects of potassium have been attributed to abnormalities in cellular transport affecting vascular smooth muscle tone, in endothelial cell function and in sympathetic activity; however, none of the studies supporting these suggestions are conclusive.

2.1.3 The Role of Calcium in Essential Hypertension

a. Sensitivity to Calcium Loading

A number of studies investigating the effect of calcium supplementation on blood pressure have been carried out in normotensive and hypertensive subjects. The results have not been consistent. In normotensives, Belizan *et al.*, (1983), in a non-blinded study, showed that when large amounts of calcium (1000 mg/day) are given for a 22 week period to young normotensive subjects, there is a small but significant fall in the supine diastolic pressure. Lyle *et al.*, (1987) reported small (2-3mmHg) but consistent reductions of mean arterial pressure in a group of normotensive men supplemented by 1500mg/day of calcium compared with a control group. These results are not consistent with McCarron and Morris, (1985). In a double-blind study their group reported no effect of calcium supplementation of 1 g/day over an 8 week period on the blood pressure in 32 normotensive persons. This outcome was also shown in a blinded parallel study by Nowson and Morgan, (1989). They reported no significant effect of calcium supplementation versus placebo on blood pressure in 48 normotensive individuals receiving either 10 or 20 mmoles of calcium carbonate/day.

Among hypertensive patients McCarron and Morris, (1985) and Resnick *et al.*, (1984) have reported an antihypertensive effect in one third to one half of the patients given supplemental calcium. Grobee and Hofman (1986), in a double-blind parallel with placebo study, reported that mild hypertensives given 1 g/day of calcium experienced a decrease in diastolic blood pressure at 6 and 12 weeks of 3 and 2 mmHg respectively. Nowson and Morgan, (1989) showed no significant blood pressure change in blood pressure of all hypertensives following calcium supplementation. A small group of patients responded to calcium supplementation with a fall in SBP that was significantly different than with placebo. These patients were re-randomized to either calcium supplementation or placebo and in the rechallenge the response was not verified, i.e. calcium did not reduce blood pressure more than the placebo in the initially responding sub-group. Abstracts by Strazzullo *et al.*, (1985), and Singer *et al.*, (1985), reported little or no effect of calcium supplementation in small groups of hypertensive patients.

b. Abnormalities of Calcium Metabolism

Individuals with EHT have an increase in urinary calcium excretion (Kesteloot, 1984; Staessen *et al.*, 1983; Strazzullo *et al.*, 1983). One explanation for this finding is increased intake and excretion of sodium, since excretion levels of the two ions are closely correlated. Several studies indicate that alterations in sodium balance plays an important part in determining urinary calcium excretion (Ackerman, 1971; Muldowney *et al.*, 1982; Breslau *et al.*, 1982). An alternate explanation would be the presence of a primary renal defect in calcium control (Strazzullo *et al.*, 1983; McCarron *et al.*, 1980). It has been proposed that a defect exists in the proximal tubule,

and that an overactive parathyroid hormone (PTH) secretion compensates to some degree for calcium loss by increasing calcium reabsorption in the distal part of the nephron thereby maintaining extracellular calcium concentrations (Angus *et al.*, 1973).

Strazzulo *et al.* (1983) studied 55 hypertensives with normal renal function. Twenty-four hour urinary calcium was significantly higher in the hypertensive group and showed little overlap with the normotensive group. The effect of sodium intake and excretion was controlled for by determining the calcium/sodium ratio in 24hr urine. Sodium excretion in hypertensives was not significantly different than the normotensive group. There was an enhanced secretion of PTH in the hypertensive group and no difference in total or ionized calcium compared with normotensives. These findings support the concept of a renal calcium defect.

In another study, increased urinary calcium secretion and increased PTH secretion was found in the group of hypertensive subjects, but unlike Strazzulo *et al.* the authors found no reduction in total and ionized calcium (McCarron *et al.*, 1980). This difference could reflect patient selection, since more severely hypertensive individuals were included in the hypertensive group of the latter study. The conflicting results in these studies with regard to serum total and ionized calcium levels and blood pressure are mirrored in other studies. A significant increase in total serum calcium concentration in hypertensive individuals has been reported (Bulpitt *et al.*, 1976; Robinson *et al.*, 1982) Reports of lower ionized calcium levels in hypertensives versus normotensives in the study by McCarron *et al.*, (1980) was also reported by Resnick *et al.*, (1983) in low-renin hypertensives. But other studies show either no difference in calcium levels (Kestelhoot *et al.*, 1983;) or a positive

relation between blood pressure and ionized calcium levels (Hunt *et al.*, 1984). Kaplan and Meese, (1986) caution that the relatively small differences seen in several studies could reflect nonspecific alterations since levels of total and ionized calcium in the blood may be altered by various factors, such as recent alcohol intake, diuretic therapy, change in blood pH, or recent physical activity.

c. Calcium influx and efflux from cells

It has been proposed that the primary defect in HT may be the calcium (Ca^{++}) handling at cellular levels. Free Ca^{++} concentration in the cells is the rate-limiting determinant for many physiological responses. There is evidence in hypertensive human subjects of increased permeability of the erythrocyte membrane to calcium ions. Studies have demonstrated a reduced red cell membrane calcium binding capacity in hypertensive subjects compared to normotensive controls (Postnov and Podukin, 1979; Cirillo *et al.*, 1989). An increase of intracellular exchangeable calcium has also been demonstrated in adipose tissue of patients with EHT. It is proposed that membrane calcium binding could be involved in the regulation of membrane permeability and of transmembrane calcium fluxes. Studies of calcium handling by cell membranes in erythrocytes, lymphocytes and vascular smooth muscle (VSM) from hypertensive rats also show a decrease in cell binding capacity and increased calcium permeability suggesting a membrane abnormality that is generalizable to several cell lines (Noon *et al.*, 1978; Suzuki *et al.*, 1979; Winqvist and Bohr, 1983). For example, VSM from hypertensive animals maintains a tonic contraction in a solution containing physiological concentration of calcium. VSM from normotensive rats

remains relaxed under the same conditions. If calcium is removed from the solution VSM from the hypertensive animals relaxes, but that from normotensive animals does not respond. When calcium is reintroduced hypertensive VSM contracts again. This phenomenon has been interpreted to indicate there is a leak in the membrane of the hypertensive animal through which calcium can enter to stimulate the observed contraction.

Bohr and Webb, (1988), Furspan and Bohr, (1988) and Bohr, (1989) support the hypothesis that there is a generalized membrane abnormality in hypertension and they suggest its primary cause is the deficit in the amount of calcium bound to the membrane. Observations supporting this hypothesis are based on monovalent ion flux measurements. Potassium flux in lymphocytes in physiological salt solution containing calcium in concentrations from 0 to 3 mM. showed that as calcium concentration increased potassium flux decreased (at any calcium concentration potassium flux was greater in spontaneously hypertensive rats (SHR) than in the normotensive control suggesting that less calcium is bound to the membrane in the hypertensive rat). The authors have described the phenomenon of increasing calcium concentration and associated decreasing potassium flux as "membrane stabilization" (relaxation). It is proposed that calcium binds to a "calcium binding protein" on the channel, structural changes occur in the protein resulting in channel blockade or inactivation and hence relaxation. In support of this proposal Kowarski *et al.*, found significant reductions of an "integral membrane calcium-binding protein" in various tissues of the SHR compared to those from WKY rats. Studies from Bohr's laboratory also employed genetic procedures to test the possible causal relationship between membrane changes and elevated arterial blood pressure. It was observed that

the degree of abnormality in potassium flux is significantly correlated with the blood pressure elevation in the F₂ generation, indicating a genetic association between these two traits (Furspan *et al.*, 1987). Critics suggest that the critical words describing all the findings associated with concept of membrane stabilization are the words "above physiological levels". Stabilization was only seen with concentrations of calcium many times higher than the physiologic concentration of 1.0 to 1.4 mM. and therefore it is argued, extrapolation to an *in vivo* milieu is not warranted (Kaplan and Meese, 1987).

Two known systems are responsible for Ca⁺⁺ extrusion from cells against its concentration gradient: the Na⁺-Ca⁺⁺ exchange and the Ca⁺⁺ pump (Postnov and Orlov, 1985). The former mechanism has been described earlier. The calcium extrusion pump, studied in red blood cell membranes, is a calcium and magnesium requiring ATPase. It is stimulated by calmodulin and inhibited by vandate and its characteristics are different than the pump that sequesters calcium in the sarcoplasmic reticulum (SR) (Costa *et al.*, 1982). It has been shown that Ca⁺⁺ efflux from erythrocytes of hypertensive patients is 30-40% less than in normotensive patients (Postnov and Orlov, 1984). Most investigations of the calcium extrusion pump have involved animal models. Orlov *et al.*, (1983) evaluated the activity of the pump by the ⁴⁵Ca accumulation rate in inside-out vesicles. In preparation of inside-out vesicles, membranes were treated with EGTA resulting in removal of calmodulin. In the absence of calmodulin, pump activity in normotensive and hypertensive rats was the same. Addition of calmodulin led to a significantly smaller increase in the activity of the pump in the hypertensive rats. The defect in the pump of red blood cell membranes has been shown to

exist in calcium pumps of other membranes. Kwan *et al.*, compared the ATP-dependent calcium accumulation into inside-out sarcolemmal vesicles from mesenteric arteries of normotensive and hypertensive rats (Kwan *et al.*, 1979). This measure of active calcium extrusion was reduced in both SHR and mineralocorticoid-induced hypertension. Postnov and Orlov, (1984) presented evidence that calcium uptake by plasma membrane vesicles from rat brain is 40% less in SHR than in WKY rats.

There has been no consistent results in studies of the effects of calcium loading on blood pressure. Although renal handling of calcium may be abnormal in hypertensives there is no clear pattern of abnormality in plasma levels. In contrast to the variability of these results, several groups have found abnormalities of cellular transport of calcium in hypertensives. Increased cellular permeability is associated with a decrease in cell membrane binding capacity and there is evidence in hypertensive animals of impairment of the calcium pump. It is however not known whether these abnormalities are primary etiologic factors in hypertension. In an early study by Douglas, (1968) it was proposed that Ca^{++} is essential in the regulation of neurotransmitter release from neural tissues.

2.1.4 The Role of Magnesium in Essential Hypertension

a. Sensitivity to magnesium loading

It has long been known that pharmacologic doses of magnesium salts can produce hypotension and attenuate high blood pressure in hypertensive patients (Blackfan and Hamilton, 1925). Dyckner and Wester, (1983) conducted a study on 20 patients receiving long term diuretic treatment for arterial hypertension or congestive heart failure. Both groups received

magnesium supplements for six months. There was a significant decrease in both systolic and diastolic blood pressure (12/8 mmHg) in both groups. Motoyama *et al.*, (1989), in a four week study of oral magnesium supplementation of 21 mild to moderate male hypertensives demonstrated a significant decrease in mean blood pressure. However, Cappuccio *et al.*, (1985) found no change in blood pressure in a randomized, cross-over study in 17 mild to moderate hypertensive patients ($\leq 154/100$ mmHg) following one month of magnesium supplementation. Cappuccio argued that no definite conclusions could be drawn from the hypotensive effect of magnesium in the Dyckner/ Wester study since the control group did not receive placebo. The authors acknowledged that in their study magnesium supplementation lasted for only one month and they too could not draw definite conclusions on the effect of magnesium supplementation on blood pressure. Motoyama *et al.*, can also be criticized for the short duration of their study.

b. Abnormalities of magnesium metabolism

It has been suggested that intracellular magnesium deficiency exists in essential hypertension (Resnick *et al.*, 1984). Magnesium controls cell membrane sodium pump activity, which in turn plays a major role in sodium-potassium transport across cell membranes, thereby affecting vascular tone and reactivity and blood pressure (Altura and Altura, 1984). Consistently lower levels of free intracellular magnesium in human erythrocytes has been demonstrated in untreated hypertensive individuals than in normotensive controls (Resnick *et al.*, 1984). In hypertensive patients on long-term thiazide, oral magnesium supplementation produced a hypotensive effect compared with untreated patients. The investigators

suggested that the hypotensive effect was mediated by magnesium activation of the cell membrane pump leading to attenuation of the vasoconstriction induced by magnesium deficiency in the patients on long term diuretic therapy . Motoyama *et al.*, (1989) showed that the Na^+ efflux constant increased in untreated hypertensive patients following supplementation with magnesium. There was also a significant positive correlation between prestudy sodium efflux and the decrease in mean blood pressure.

Apart from being a necessary activator of $\text{Na}^+\text{-K}^+\text{ATPase}$, magnesium is also a calcium antagonist. Magnesium inhibits release of calcium from the sarcoplasmic reticulum by competition for a calcium receptor on a calcium-regulated efflux channel and drives calcium into the SR through stimulation of $\text{Ca}^{++}\text{ATPase}$ (Stephenson and Podolsky, 1977). Magnesium also directly blocks the slow-calcium channel. Magnesium depletion in cell membranes could result in reduced antagonism of calcium transport and increased cytosolic calcium (Altura *et al.*, 1982).

Studies of extracellular magnesium metabolic abnormalities in human hypertension are conflicting. In early studies it had been demonstrated that hypertension, in the absence of overt renal disease, was associated with elevations of serum magnesium levels (Walker and Walker, 1936). Other workers found lower levels of serum magnesium in hypertensive patients (Albert *et al.*, 1958). Resnick *et al.*, (1983) suggest that a reason for conflicting results could be that hypertensives in earlier studies were considered together as a single homogeneous group, and as such would appear to have no deviations in magnesium metabolism, and be indistinguishable from normal controls. In their study, Resnick and associates divided the untreated

hypertensive subjects according to plasma renin activity (low, normal and high). There was a negative correlation between plasma renin activity and serum magnesium levels in the hypertensive patients. The authors speculate that since each renin sub-group has a distinctive magnesium profile it raises the possibility that the pathophysiologic mechanism that causes either suppression or stimulation of renin is also involved in the companion deviation of magnesium levels. Other investigators were unable to replicate the findings of Resnick *et al.* Cappuccio *et al.*, found no difference in plasma magnesium concentrations between patients with low plasma renin activity and those with normal renin activity, and two other studies showed no correlation between serum magnesium concentration and plasma renin activity (Tillman and Semple, 1988; Motoyama *et al.*, 1989; Cappuccio *et al.*, 1985).

Animal studies are more consistent and point to a causal relation between decreased concentration of magnesium ion in blood or other tissues and hypertension. Hypomagnesaemia has been shown to induce sharp increases in tension development in a variety of mammalian blood vessels (Altura and Altura, 1974). In a study of dietary magnesium deficiency in rats examination of mesenteric microcirculation in the magnesium-deficient rats revealed vasoconstriction or enhanced vascular tone. The vessel measurements also showed a progressive, quantitative reduction in lumen size (Altura *et al.*, 1984).

d. Role of magnesium in hypertension.

Although the evidence is not conclusive, the findings from clinical studies suggest an inverse relationship between magnesium intake and blood

pressure. Low levels of intracellular magnesium may be responsible for inhibition of sodium-potassium transport and thus result in increased vascular tone. Extracellular magnesium levels do not show a consistent pattern in hypertensive subjects; but induction of low magnesium levels in experimental animals results in vasoconstriction and hypertension. On balance it may be concluded that magnesium may play a role in EHT but it has not been established that abnormalities in magnesium levels or transport are essential etiologic factors.

2.1.5 Role of Endothelium in Essential Hypertension

The importance of the endothelium in modulating the activity of the vascular smooth muscle and therefore regulating vascular tone was first suggested by Furchgott and Zawadzki, (1980). These investigators reported that in isolated rabbit arteries, damage or absence of endothelial cells inhibited the vasodilator action of acetylcholine and other substances. It appears that the endothelium "message" to blood vessels consists of a potent, but short-lived substance, the endothelium relaxing factor (EDRF) (Vanhoutte, 1989). EDRF diffuses to the vascular smooth muscle where the factor activates soluble guanylate cyclase (Holzmann, 1982; Rapoport RM and Murad F, 1983). Relaxation by EDRF is accompanied by an accumulation of intracellular cyclic guanosine 5' monophosphate (cGMP) in the vascular smooth muscle. This action was similar to that exerted by nitric oxide, the final modulator of relaxation of the nitrovasodilators and it has been proposed that EDRF is nothing more than nitric oxide. This interpretation has been confirmed through chemical analysis in which EDRF and nitric oxide biologic and physiochemical properties were indistinguishable

(Palmer *et al.*, 1987). Despite these findings, no unanimity of opinion has resulted on the question of whether or not nitric oxide and EDRF are identical (Marshall and Kontos, 1990). It now appears, that in addition to nitric oxide which has no effect on membrane potential, certain cells can release another relaxing factor which acts through hyperpolarization of the membrane (Feletou and Vanhoutte, 1988).

Endothelium-dependent relaxation has subsequently been shown to occur in humans by *in vitro* studies using arterial preparations and studies in normal humans have confirmed the regulatory action of endothelium (Luscher *et al.*, 1987; Greenberg *et al.*, 1987). Recently Panza *et al.*, (1990) have demonstrated that endothelium-mediated vasodilation is impaired in patients with EHT.

In addition to production of vasorelaxant EDRF, it has been demonstrated that endothelial cells synthesize a contracting factor. In 1988 Yanigasawa and colleagues isolated and characterized a potent vasoconstrictor peptide from the supernatant of porcine endothelial cells (endothelin). Using rat mesangial cultured cells as a model, Simonson and Dunn, (1989) suggested that endothelin stimulates the phosphoinositide metabolic pathway, and therefore mobilizes calcium from intracellular stores and activates the influx of extracellular calcium. It has been suggested that the pathogenesis of EHT is associated with two interrelated phenomenon, the blunting of the release of EDRF from endothelial cells and at the same time, no change in the release of endothelin from the endothelial cells (Vanhoutte, 1988; 1989).

2.1.6 The Role of the Phosphoinositide System in Essential Hypertension

The discovery and elucidation of the roles (including the "endothelin" factor discussed above) played by phosphoinositide (PI) metabolism and protein kinase C related biochemical events in cell membrane function may also shed light on the possible primary underlying hypertensive mechanism (Marche, 1989). Protein kinase C is an enzyme which depends on calcium, phospholipids and diacylglycerol (DAG) for its full activity (Nishizuka, 1984; Nishizuka, 1986). Protein kinase C is activated by DAG, which is formed from inositol phospholipids in the plasma membrane by phospholipase C and Ca^{++} , and is regarded as an intermediate between extracellular signals and physiological responses. It has been reported that the activity of phospholipase C was increased in the aorta of SHR, which may indicate an abnormality in the protein kinase C-mediated signal transduction in EHT (Uehara *et al.*, 1988).

Postnov *et al.*, (1987) in studies of plasma membrane abnormalities in red blood cells demonstrated abnormalities of the membrane skeleton and of protein kinase C. The authors suggested that the appearance of unusual cup-shaped erythrocytes was due to cell shrinking, caused by alteration of the cytoskeleton. In an earlier study (Chien, 1977) demonstrated indirect indications of an involvement of the cytoskeleton in EHT patients. There was a decreased deformability of red blood cells, indicating an enhanced rigidity of the cytoskeleton.

Analyzing the changes in erythrocyte volume and shape led to the proposal that the cytoskeleton-dependent performances might indicate the involvement of the phosphatidylinositol transmembrane signaling system in

membrane alteration, particularly the part that mediates signal transduction via DAG, resulting in protein kinase C activation (Berridge, 1984; Berridge, 1987; Nishizuka, 1984). It is known that substrates for protein kinase C are membrane skeletal proteins, phosphorylated by this kinase, initiating, along with other protein kinases, certain cytoskeleton-dependent reactions (e.g. cell shrinkage) and activating $\text{Na}^+\text{-H}^+$ exchange, thus inducing increased concentration of cytoplasmic calcium (Postnov, 1990).

Using a phorbol ester which imitates the natural activation of protein kinase C by DAG, a series of studies were carried out by Postnov *et al.*, to determine the action of protein kinase C on the cytoskeleton and on the ion transport characteristics of these cells discussed above. It was shown that activation of protein kinase C reproduces the change in the erythrocyte shape and volume as well as cytoskeleton phosphorylation, and these changes were similar to those seen in EHT. Further, increased rates of $\text{Na}^+\text{-Na}^+$ and $\text{Na}^+\text{-H}^+$ exchange and an increase in calcium influx were also seen. It was then demonstrated that protein kinase C activity was twofold greater in the erythrocytes of EHT patients compared to normotensive controls. Based on these and other animal model studies Postnov suggests that the PI transmembrane signalling system is at the center of the search for the cause of membrane alterations as well as for the etiologic basis of EHT.

2.1.6 The Role of Neural Factors in Essential Hypertension

It has also been suggested that there may be a neural-renal interrelationship in the pathogenesis of EHT. Impaired sodium excretion is probably the initiating factor in salt-sensitive hypertension, and it has been

suggested that there may be a role for the renal sympathetic nerves (Dustan, 1987; Dustan *et al.*, 1986).

As discussed earlier abnormal protein kinase C activity may play a pivotal role in the pathophysiology of essential hypertension. In a recent study by Tsuda and Masuyama, (1990) it was suggested that since there are high concentrations of protein kinase C in the nervous system compared to other tissues, this enzyme could play an important role in regulation of neural activity. To investigate the concept, the effect of a specific protein kinase C inhibitor (H-7) on vascular adrenergic transmission was studied. In isolated mesenteric vasculature of SHR and WKY rats, it was demonstrated that NE release was inhibited by H-7 in a dose-dependent manner, with concomitant reduction of pressor responses of the preparation. Further it was demonstrated that the suppressive magnitude of stimulation-evoked NE release was more pronounced in the SHR rats.

There is evidence to show that in a fraction of EHT subjects there is a large neurogenic component and the question is whether this operates in the pathogenesis of EHT (see section 2.5 Hemodynamic Changes in EHT). In humans, studies are necessarily indirect. In one investigation tests involving mental stress showed that normotensive subjects with a positive family history of HT had increases in BP and HR and that these increases were significantly greater than the increases seen in normotensive controls with a negative family history of hypertension. These findings suggest that there may be abnormal neural mechanisms involved even before EHT develops (Falkner *et al.*, 1979).

2.1.7 Role of the Structural Factor in Essential Hypertension

According to another theory, a "structural factor" is believed to be the primary cause of EHT. It has been shown that tonic activity in vascular smooth muscle is consistently greater in hypertensive than in normotensive human subjects. There would appear to be an upward resetting of the baseline conditions in smooth muscle of hypertensives resulting in increased vascular hyperreactivity. This phenomenon leads to what has been called "structural amplification" of changes in vascular resistance. It is postulated that functionally determined "pressor stimuli" lead to a positive feedback interaction with the structural amplifier, so that even minor pressor stimuli would lead to increased resistance and hence pressure increases (Folkow, 1990).

2.2 Essential Hypertension and Cardiovascular Morbidity and Mortality

Among the identified precursors of cardiovascular morbidity and mortality EHT plays a dominant role. Indeed of all the risk factors, which include elevated serum cholesterol, diabetes and cigarette smoking, EHT emerges as an independent contributor to coronary heart disease, stroke, aortic aneurysm and peripheral vascular disease (Kannel, 1974; Kannel and Thom, 1984). Since EHT contributes to the premature development of atherosclerosis, the detection and assessment of early stages of EHT are important in the study of genetic and environmental factors in the pathogenesis of EHT and its cardiovascular complications.

In the twenty years between 1963 and 1983, the overall death rate for all cardiovascular diseases declined by 36% in the United States (Kannel and

Thom, 1984). In Canada, between 1952 and 1986 "cardiovascular mortality (ages 35-90) showed a relatively stable decrease which was modelled best with age (at each 5 year level) and cohort (year of birth) for both sexes" (Semenciw *et al.*, 1989). Over the decade of the 1990's the cardiovascular mortality rate for ages 35-90 is predicted to decrease from the current 780 per 100,000 among men and 415 per 100,000 among women to 655 and 310 per 100,000, respectively. Between 1980 and 1985 total cardiovascular disease mortality rate for ages 25-85+ in the Interlake region was 534 per 100,000 (both sexes combined), and IHD mortality rate (both sexes combined) was 394 per 100,000. In Iceland between 1984 and 1988 cardiovascular disease mortality for ages 25-74 was 135 per 100,000 (both sexes combined), and IHD crude mortality rate was 122 per 100,000 (both sexes combined), (Dept. of Public Health, Iceland). It is of interest to note that the higher IHD mortality rates in the Interlake population compared to the Icelandic population, observed in the 1970's, persisted in the 1980's. An age standardized mortality rate is needed in order to confirm the higher IHD mortality rates in the Interlake given the limitations of the crude mortality rate used in the case of the 1980's Icelandic data.

2.3 Heredity and Essential Hypertension

The genetic contribution to the pathogenesis of EHT has long been recognized. However, determining how much of observed BP variability is due to genetic segregating factors and how much is due to environmental or cultural stimuli is problematic (Camussi and Bianchi, 1988). Several studies have revealed familial aggregation of EHT; however, since these families shared both common genes and a common environment, it was difficult to determine the extent of genetic influences (Beresford and

Holland, 1973; Schweitzer *et al.*, 1967). Twin studies, and studies of families in which adoptive children and natural children of hypertensive parents have been compared, lend support to the importance of heredity (Havlik *et al.*, 1979; Zinner *et al.*, 1971). The influence of environment has also been revealed in population studies. First degree relatives of normotensive preindustrialized people who have migrated to an industrialized region develop increased BP levels following adoption of the diet and other characteristics of the new environment (Sever *et al.*, 1980; Page *et al.*, 1974).

2.4 Detection of Early or Incipient Essential Hypertension

2.4.1 Resting versus Exercise Blood Pressure

In the study of EHT it has been observed that BP measured at rest, even when strict protocols involving repeat determinations are used, may not be a reliable indicator of the presence or absence of EHT (Medical Research Council Working Party 1985; Report by the Management Committee: the Australian Therapeutic Trial in Mild Hypertension, 1980). In one longitudinal study a diagnosis of EHT based on measurements of resting BP levels it was found that, at the end of three years, approximately 40% of subjects categorized as hypertensive were in fact found to be normotensive (Weber, 1988).

It has been suggested that ambulatory BP and exercise BP are more reproducible and more reliable in the assessment of BP than casual resting BP measurements; in part at least, because BP measured during physical activity is not subject to the variability associated with the stress of clinic visits (Floras *et al.*, 1981; Pickering *et al.*, 1985; Weber, 1988; Millar-Craig *et al.*,

1980; Leibel *et al.*, 1982). ESBP variability in 156 middle-aged subjects was studied via treadmill exercise tests, performed on two occasions with an average of 9 months between the tests (range: 1 to 30 months). It was found that ESBP values were within 10% of the first determination in two-thirds of the subjects. The overall mean pressure difference of 8.6mmHg at the second test was not significantly different from baseline ESBP (Irving *et al.*, 1977). Data obtained during exercise on a bicycle ergometer in 19 young male subjects on two occasions, separated by a mean interval of 9.8 days, showed that ESBP and HR were not only reproducible but were even more so as exercise progressed (Caen *et al.*, quoted by Comess and Fenster, 1981).

In addition to its reliability, it has been suggested that measurement of BP during exercise might be a better means of identifying individuals who are at increased risk for development of EHT (Wilson and Meyer, 1981; Davidoff *et al.*, 1982; Dlin *et al.*, 1983; Jackson *et al.*, 1983). All of these studies defined normotension as BP \leq 140/90 mmHg. Specifically, Wilson and Meyer, and Dlin *et al.*, stated that individuals with resting BP \leq 140/90 mmHg but with ESBP in excess of 225 mmHg (the method of exercise testing was treadmill and bicycle ergometry respectively) were at increased relative risk (2.28 and 2.30 fold respectively) for developing EHT. Wilson and Meyer contended that, even with statistical control in the analysis of factors such as family history of cardiovascular disease, weight on first visit, weight change, hypercholesteremia, alcohol consumption and smoking, the "hyper-responders" had a "point estimate of relative risk for the development of resting EHT well over unity when compared with controls". Davidoff *et al.*, tested normotensives using bicycle ergometry. Those individuals with an ESBP \geq 200mmHg showed a relative risk of 2.06 for developing EHT

compared to normotensives with an ESBP < 200mmHg. Jackson *et al.*, also tested normotensives using bicycle ergometry. In that study, individuals with an ESBP \geq 230mmHg were 3.39 times more likely to develop EHT on follow-up than were control subjects.

The variability in the reported "hypertensive response" of blood pressure to exercise was probably due to the heterogeneity of the populations tested. There is no consensus on the definition of an exaggerated ESBP in either normotensive or hypertensive individuals. In a study of normal men and women 48-63 years of age, during bicycle exercise at various workloads, it was found that average ESBP in the normotensive subjects (resting BP <170mmHg systolic and <100mmHg diastolic) was 196 ± 22 mmHg (mean \pm standard deviation) in women and 212 ± 23 mmHg in men, at a heart rate (HR) of approximately 150 beats per minute (Astrand 1965). In another study using treadmill exercise, it was found that, in normotensive (<140/90mmHg) middle-aged males, the mean increase in systolic pressure from rest to near maximal exercise was 60 ± 20 mmHg (Bruce *et al.*, 1973). In a later study Bruce *et al.*, (1974) found that the mean value of systolic pressure during maximal exercise in 1275 healthy men with a mean age of 44.5 years was 185 ± 22 mmHg. In an attempt to establish the normal BP response during near maximal bicycle exercise, 1678 males with a mean age of 48.1 years were studied (Erikssen *et al.*, 1980). The mean BP at rest was found to be 130mmHg systolic and 91 mmHg diastolic and mean ESBP was found to be 213mmHg. An earlier study by Walthius *et al.*, (1977) also attempted to establish a complete set of reference values for ESBP in men at maximal exercise. Seven hundred and four men, with a median age of 37 years and a

median resting BP of 130mmHg were treadmill tested. The median ESBP at maximal exercise was 200mmHg.

Studies of ESBP in hypertensive subjects (>140/90 mmHg and > 170/100 mmHg) have also yielded variable results, with the range of ESBP being 197-242 mmHg (Astrand, 1965; Bruce *et al.*, 1974; Franz, 1982). One study evaluated normotensive (Group I), borderline hypertensive (Group II) and hypertensive subjects (Group III). Mean resting BP was 134/85 mmHg, 150/92, and 164/105 mmHg respectively. Two distinct exercise profiles were identified in Group II: 57.7% of the subjects in Group II had mean ESBP which was not significantly different than Group III (211mmHg), while the remaining 42.3% of subjects in group II had mean ESBP which did not differ significantly from Group I (183 mmHg).

The preponderance of studies involved systolic BP during exercise since most investigations show that diastolic BP is not a reliable measurement during exercise due to background noise interfering with auscultation of the 4th and/or 5th Korotkoff sounds (Erikssen, 1980; Comess and Fenster, 1981).

2.4.2 Clinical Significance of Blood Pressure Measured During Activity

Clarification of the clinical significance of 24 hour ambulatory monitoring and exaggerated ESBP in hypertensive individuals has been provided in studies using electrocardiography and echocardiography. Sokolow *et al.* (1966) compared BP in hypertensive patients measured during daily activity (using a portable monitor which recorded BP every 1/2 hour) with clinic BP measured at rest once during three successive clinic visits.

They found that electrocardiographic left ventricular hypertrophy (EKG-LVH) related more closely to the average BP during daily activity than to the casual clinic BP. Ren *et al.*, (1985) observed that hypertensive patients with an ESBP of 190 mmHg or greater tended to have an increased left ventricular mass. De Gaudemaris *et al.*, (1985) demonstrated that, in hypertensive subjects, LVH is more strongly related to both exercise BP and to BP during daily activity (ambulatory BP) than to a single casual measurement of BP at rest. These findings have been supported in other echocardiographic studies which showed that LVH in patients with EHT was more closely related to BP during activity or stress than to casual BP (Rowlands *et al.*, 1981; Devereux *et al.*, 1983; Drayer *et al.*, 1983; Ferrara *et al.*, 1987).

In a recent study, Naimark *et al.* (1990) extended the investigation of the relationship between exercise BP and electrocardiographic abnormalities to include normotensive subjects and an assessment of electrocardiographic atrial abnormalities. The study had several characteristics which distinguished it from previous studies in the field. First of all, it was the largest study in terms of number of subjects investigated. Second, it was the most comprehensive study in terms of of the range of subject age investigated. Third, it was the only study in which cardiologic abnormalities were related to ESBP in normotensive individuals. In both normotensive and borderline hypertensive subjects, an association between ESBP and EKG-LVH and LAE was demonstrated. In that study it was postulated that the abnormalities were related to dimensional changes in the atria and ventricles. Echocardiographic measurements needed to test that hypothesis were not available. The present study was directed at studying this hypothesis.

2.4.3 The Role of Echocardiography

Despite useful hemodynamic information provided by angiography, direct assessment of left ventricular function in patients with hypertensive heart disease has always been impeded by difficulty in justifying invasive study of the left ventricle. Electrocardiography, although a noninvasive technique, as noted above, has been shown to be a relatively insensitive tool in the diagnosis of early hypertensive heart disease.

Echocardiography, a non-invasive indicator of anatomic features of the heart, has become a particularly popular means for assessing cardiac structure and function. It has provided an accurate method for measuring ventricular wall thickness, end-diastolic and end-systolic dimensions (Feigenbaum, 1986). These measurements are used to calculate left ventricular mass LVM. The LVM is estimated by determining the volume of the epicardial surface of the ventricle and subtracting the volume of the cavity of the ventricle. The difference represents the volume of the left ventricular wall. Determination of volume is calculated by cubing the echocardiographic dimensions using the cube function formula, and the specific gravity of cardiac muscle is used to convert the ventricular wall volume into left ventricular mass (Pombo *et al.*, 1971; Troy *et al.*, 1972).

Several studies have indicated a close statistical relationship between echocardiographic and angiographic estimates of (LVM) (Troy *et al.*, 1972; Murray *et al.*, 1972). Devereux and Reichek (1977) determined the accuracy of echocardiography for determining LVM through analysis of the relationship between the antemortem left ventricular echogram and postmortem anatomic LVM. Both autopsy and echocardiographic LVM were obtained on 34 patients. The mean interval between echocardiographic study

and autopsy was 23 days (range 1-120 days). Echocardiographic methods examined correlated significantly with anatomic LVM [$r=0.86$ ($p<0.0001$) to $r=0.96$ ($p<0.0001$)] .

To improve standardization of echocardiographic left ventricular anatomic measurements, echographic left ventricular dimensions and mass were related to body size indexes [height, weight, body surface area, Quetelet Index (sometimes referred to as weight- height index or body mass index (kg/m^2), ponderal index ($^3/\text{kg}/\text{m}$)] and to sex, age, and blood pressure. All measurements of chamber size, wall thickness and mass differed between men and women. LVM was related most closely to body surface area among the measurements of body size. Indexation by body surface area eliminated sex differences in wall thickness and internal dimension, but a significant sex difference in left ventricular mass index (LVMI) persisted (Devereux *et al.*, 1984).

Echocardiography also provides a simple noninvasive means of assessing left atrial dimension. The diastolic dimension of the left atrium (LA) expressed in relation to body surface area has been found to be a sensitive method of assessing the presence of left atrial enlargement (Dreslinski *et al.*, 1981). It has been proposed by Frolich *et al.* (1971) that the finding of an enlarged atrium does not necessarily indicate atrial disease but rather may reflect atrial manifestations of diminished compliance of the "hypertrophying" left ventricular myocardium. Dreslinski *et al.* also contend that the enlarged atrium is an important clue to abnormalities in the left ventricle, such as reduced compliance, even in the absence of left ventricular enlargement.

The initial echocardiographic technique for evaluating cardiac function utilized M-mode measurements. These measurements have withstood the test of time and, when used with the two-dimensional measurement technique, added reliability and accuracy in the assessment of cardiac structure and function (Feigenbaum, 1986). In both echocardiographic methods, sound is transmitted to and through the heart. Some of the sound energy is reflected back by each acoustic interface encountered and is received by the transducer. The elapsed time from transmission of the sound to reception of the echo is converted to a display of the distance between each reflector and the transducer. A number of depth samples taken in sequence create an imaging plane and make up a two-dimensional echocardiogram (Popp and Macovski, 1980). Any one of the directions of the sound beam may be sampled repeatedly to print out the pattern of distance to the reflector over time in order to record the motion of individual structures (M-mode) (Popp, 1990).

2.5 Hemodynamic Changes in Early Essential Hypertension

In a subset of individuals with early EHT, hemodynamic function is often characterized by a rapid heart rate, enhanced stroke volume and elevated cardiac output (Messerli *et al.*, 1978). Because of the increment of cardiac output and stroke volume, left ventricular stroke work is augmented. Left ventricular end-diastolic pressure may become elevated as a result of an increase in end-diastolic volume or as a result of reduced ventricular compliance. As noted earlier it has been shown that early changes include impaired diastolic filling of the left ventricle. This was attributed to reduced compliance of the left ventricle since there was no evidence of increased left

ventricular end-diastolic volume, left ventricular hypertrophy or increased vascular impedance (Dreslinski *et al.*, 1981).

It was suggested that the increased cardiac output reflected a redistribution of blood resulting in a higher ratio of cardiopulmonary blood volume to total blood volume (TBV). This redistribution was attributed to a neurogenically mediated decrease in the capacity of venous reservoirs below heart level (Ulyrch *et al.*, 1969). This finding was supported by another study demonstrating that in two-thirds of borderline hypertensive subjects there was an increased cardiac output, and an increase in the cardiopulmonary/total blood volume (CPBV/TBV) ratio, associated with a decreased venous compliance and increased venous return (Safar *et al.*, 1977). In an earlier study by Safar *et al.*, (1973) it was shown that the increased venous return was not due to an expansion of the total blood TBV since TBV in early HT was normal or low and therefore the increased return was due to a decrease in venous compliance in the peripheral circulatory system. The CPBV/TBV ratio was found to be directly correlated to vascular reactivity, and to NE and dopamine-hydroxylase activity (Safar *et al.*, 1977). Given these findings, and the fact that constriction of capacitance vessels is related to sympathetic hyperactivity, the CPBV/TBV ratio was used as an index of neural activity.

Further evidence that the hyperdynamic circulation of early EHT is of neurogenic origin was provided by the demonstration that the enhanced cardiac output, heart rate and stroke volume could be abolished with pharmacological blockade (Julius, 1976).

Investigation of plasma catecholamines as a measure of autonomic activity has been carried out by a number of investigators (Goldstein, 1981;

Bertel *et al.*, 1980; Philipp *et al.*, 1978). Plasma norepinephrine (PNE) concentrations are considered sensitive to changes in sympathetic tone (Goldstein *et al.*, (1983), and increased PNE concentrations have been found in both early and established hypertensives (Louis *et al.*, 1974; Nestel, 1969). Several studies have shown that physical and emotional stimuli that increase BP and heart rate (HR) also increase PNE (Lake *et al.*, 1976; Watson *et al.*, 1979; Robertson *et al.*, 1979). PNE levels have also been significantly correlated with diastolic blood pressure and it has been shown that both blood pressure and norepinephrine levels fall after ganglionic blockade or suppression with clonidine (Goldstein *et al.*, 1985; Sullivan *et al.*, 1986).

de Champlain *et al.* (1976) reported that circulating catecholamine (CA) levels were increased only in some hypertensive patients. Hypertensive patients were subdivided into either a hyperadrenergic (HADR) or a normoadrenergic (NADR) group according to their basal CA levels. Clinically these two groups of patients were found to have the same average BP, but HADR patients were found to have a higher heart rate and increased myocardial contractility compared to NADR patients, suggesting hyperkinetic cardiac functions in the HADR subgroup (de Champlain *et al.*, 1980). HADR patients were also shown to have a potentiated CA and PNE responses to standing for 10 minutes, whereas NADR patients had normal responses (de Champlain *et al.*, (1976)) . More recent studies from the same laboratory established that only PNE responses were enhanced during postural change while plasma epinephrine (PE) responses were normal in HADR suggesting the existence of a specific hyperreactivity of sympathetic fibers and a normal reactivity of the adrenal medulla in the HADR patients (de Champlain *et al.*, 1987). In response to dynamic exercise, the PNE and PE responses were found

to be enhanced and longer lasting after the end of exercise in the HADR group. In response to cold pressor test and to isometric exercise, the PNE and PE responses were found to be identical in HADR and NADR patients and similar to the responses observed in normotensive subjects (de Champlain *et al.*, 1987). The basis for increased sympathetic reactivity may reside in an increased content of neurotransmitters in sympathetic nerve terminals (Folkow, 1982), or in a proliferation of sympathetic nerve terminals supplying the arterial bed (Scott and Pang, 1983) or both.

Floras *et al.*, (1986) demonstrated that bicycle exercise significantly increased mean arterial pressure, HR and PNE. Both the maximum mean arterial pressure and the peak HR attained during bicycle exercise were related to the exercise PNE. Increases in PNE were not greater in older or more hypertensive subjects. Unlike earlier studies, PNE was unrelated to BP at rest. In addition, mental arithmetic tests and isometric exercise raised BP but not PNE. It appeared that isotonic exercise reflected variations in sympathetic activity of the hypertensive subjects and it was noteworthy that both the absolute increase in PNE during bicycle exercise and the relative increase in mean arterial pressure were greater in subjects with lower resting pressures. This observation supported the concept that it was the borderline or mild hypertensive who displayed an exaggerated sympathetic response.

Although an increased sympathetic activity could be responsible for the pressor response observed in hypertensive subjects during isotonic exercise, conflicting results have been obtained with regard to plasma CA concentrations. In studies which have compared plasma CA levels in hypertensive and normotensive subjects during isotonic exercise it has been reported that plasma CA concentrations in the hypertensive group were

higher (Planz *et al.* 1976; Robertson *et al.*, 1979; Phillip *et al.*, 1978; Watson *et al.*, 1980) similar (Hanquet *et al.*, 1981; Bertel *et al.*, 1980; or even lower (Rysanek *et al.*, 1982) than in the normotensive group. However, in two of the foregoing studies, reporting greater (Planz *et al.*, 1976) or smaller (Rysanek *et al.*, 1982) increases in plasma CA concentrations in hypertensive subjects than in the corresponding normal subjects, mean heart rates reached during exercise were also higher and lower, respectively, in hypertensives than in normotensives. Furthermore the greater increases in plasma CA reported by Phillip *et al.*, (1976) and by Watson *et al.*, (1980) may not necessarily be linked with hypertension since the mean age was significantly higher in the hypertensive group of subjects than in the normotensive control groups.

3. RATIONALE

The rationale which underlies the postulated association between the ESBP and echocardiographic abnormalities may be formulated as follows:

If an exaggerated ESBP is an indicator of increased risk of hypertensive disease, and if echocardiographic abnormalities (LAE and LVH) are indicators of hypertensive disease, then one may postulate that subjects with an exaggerated ESBP will exhibit increased prevalence of LAE and /or LVH. The relationship between ESBP in normotensives and borderline hypertensives and echocardiographic abnormalities has not been investigated. Such an investigation would seem to be a logical step in the search for prognostic indicators of early impairment of cardiac function.

It has been demonstrated that ambulatory BP is a better predictor of cardiovascular complications than is casual resting BP (Sokolow *et al.*, 1966). However, the technique of ambulatory BP monitoring is cumbersome and expensive. Since it has also been demonstrated that ESBP correlates more strongly with ambulatory BP than with casual clinical measurements, it would suggest that the ESBP is a better tool for assessing the risk of EHT, and its associated cardiovascular abnormalities, than is casual resting BP (Millar-Craig *et al.*, 1980). Among these associated abnormalities are changes in the echocardiogram; in particular left atrial dimension and left ventricular mass.

The abnormalities in the ESBP and in the echocardiogram in EHT may have a common pathophysiological basis. The hemodynamic abnormalities present in approximately 30% of those with early stages of EHT include increased cardiac output, rapid heart rate and increased stroke volume. It has been postulated that the abnormal blood pressure represents a response to

increased cardiac output due to excessive adrenergic activity. In functional terms the result of the increased adrenergic input to the heart is a shift in the Frank-Starling curve upward and to the left (Frolich *et al.*, 1970). This in turn results in both hypertensive man and spontaneously hypertensive rats, in a hyperkinetic circulation manifested by tachycardia, increased cardiac output and increased myocardial contractility (Frolich and Pfeffer, 1970). At the same time it is proposed that increased adrenergic activity results in venoconstriction which shifts the blood to the central circulation and adds to the "hyperfunction" of the heart (Freis, 1960). Such "hyperfunction" may effect the left atrium before signs of LVH appear (Frolich *et al.*, 1971). It has also been indicated that in early HT impaired diastolic filling of the left ventricle due to reduced compliance leads to impaired atrial emptying, LAE and associated echocardiographic abnormalities (Dreslinski *et al.*, 1981).

On the basis of the foregoing considerations it is plausible to suggest that a propensity to high cardiac output and excessive adrenergic activity could, on the one hand lead to excessive increases in ESBP and on the other could lead to echocardiographic abnormalities. It is therefore reasonable to propose that there is an association between excessive ESBP and the presence of LAE and LVH despite a normal blood pressure level at rest. It is also plausible to suggest that genetically similar populations living in different environments, which have previously been shown to have differences in the pattern of cardiovascular morbidity and mortality, may also demonstrate differences in either the blood pressure response to exercise, or the relationship between an exaggerated ESBP and LAE and LVH, or both.

4. OBJECTIVES

There were three general objectives for the work described in this dissertation. The first was to compare the prevalences of an exaggerated ESBP and cardiac abnormalities in normotensive and borderline hypertensive Canadians of Icelandic descent with the corresponding prevalences in Icelanders; in order to determine if these genetically similar populations exhibit differences in these cardiovascular characteristics in association with their different environmental circumstances. The second general objective was to relate certain cardiac dimensions with the attained level of ESBP in order to determine if the relationship between ESBP and cardiac abnormalities, noted in a previous study using electrocardiography, could be corroborated using the more direct measure of cardiac dimensions afforded by echocardiography. The third general objective was to begin an examination of the possible role of catecholamines in the association between cardiac abnormalities and ESBP by conducting a pilot study in which plasma levels of NE and E at rest and during exercise are measured and related to ESBP levels and cardiac dimensions.

In connection with the general objectives the following specific objectives were pursued:

- i. comparison of the prevalence of echocardiographic LAE and LVH in subjects whose resting BP did not exceed 139/89 mmHg and whose ESBP was equal to or exceeded 200mmHg, with those subjects who had normal resting blood pressure but whose ESBP was less than 200mmHg.

ii. comparison of the prevalence of LAE and LVH in subjects with resting BP in the range of 140-159 mmHg systolic and/or 90-95 mmHg diastolic (who had never been on antihypertensive medication) and whose ESBP was ≥ 200 mmHg; and to compare them to untreated subjects with resting BP in the same range whose ESBP was < 200 mmHg..

iii. determination of the relationship between age, resting BP, body mass index, cardiac index, peripheral resistance, resting and exercise heart rate, workload and echocardiographic indices of LAE and LVH both in terms of independent effects of these factors as well as their joint relationship

iv. comparison of the results obtained in i, ii, and iii above in Canadians of Icelandic descent with those obtained in Icelanders

v. determination of the relationship of plasma NE and E to ESBP and to the prevalence of LAE and LVH in a sample of Canadians of Icelandic descent.

5. HYPOTHESES

The hypotheses to be tested were as follows:

i. There is a difference in prevalence of exaggerated ESBP, and associated echocardiographic abnormalities, between native Icelanders and Canadians of Icelandic descent.

ii. Subjects who are normotensive at rest and who have an exaggerated ESBP also have a higher prevalence of echocardiographic LAE than normotensive subjects without an exaggerated ESBP.

iii. Subjects who are normotensive at rest and who have an exaggerated ESBP also have a higher prevalence of echocardiographic LVH than normotensive subjects without an exaggerated ESBP.

iv. Subjects who are borderline hypertensive at rest and who have an exaggerated ESBP also have a higher prevalence of echocardiographic LAE than normotensive subjects without an exaggerated ESBP.

v. Subjects who are borderline hypertensive at rest and who have an exaggerated ESBP also have a higher prevalence of echocardiographic LVH than borderline hypertensive subjects without an exaggerated ESBP.

vi. There is an effect of ESBP which is independent of the effects of age, sex, body mass index family history of EHT, smoking and resting SBP, on the echocardiographic indices of LAE and LVH.

vii. There is an association between the plasma levels of NE and E at rest and during exercise and the levels of ESBP and cardiac dimensions.

6. METHODS AND MATERIALS

6.1 Background Information

The study employed a cross-sectional design, that is an examination of the relationship between diseases or other characteristics or variables of interest as they exist in a defined population at one particular time (Friedman, 1974). The subjects were drawn from two populations; Canadians of Icelandic descent and native Icelanders.

Iceland was settled about 900 AD by Nordic and Celtic peoples. Immigration since that time has been negligible, and the country has remained isolated for many centuries. As a result of the isolation Icelanders are a genetically homogeneous population (Axelsson *et al.*, 1981). One of the groups studied for the collaborative project were native Icelanders of the town of Selfoss, part of the semi-rural district of Arnessysla located in southwest Iceland.

Between 1870 and 1914 some 18,000 Icelanders (approximately 20% of the Icelandic population during that period) migrated to North America. A significant number settled in the Interlake District of Manitoba. Intermarriage of Icelanders with other groups of non-Icelandic Interlakars was rare until World War II (Way *et al.*, 1988). After the war intermarriage became more common, but nevertheless hundreds of families of pure-Icelandic descent remained, and it was from these families that the second group of subjects were selected.

Since the two study populations were separated geographically for three to four generations, it was an assumption of the investigators that

genetically attributable patterns of health and disease should be similar in these populations and differences in these patterns would indicate an environmental influence (Axelsson *et al.*, 1981). As noted in the introduction statistics from the Manitoba Department of Health and Welfare (1977) showed that the ischemic heart disease (IHD) mortality rate was higher in Canadians of Icelandic descent than in Icelanders (343 per 100,000 versus 173 per 100,000 respectively). Since IHD is a multifactorial disease and both heredity and the environment influence its development, it was decided to compare cardiovascular risk factors in adults of the two populations.

Potential adult subjects were contacted by telephone and invited to participate in the study (see Figures 1 and 2 for sampling frame and procedures flow chart respectively). In the majority of cases, those who chose not to participate stated work commitments prevented them from taking part. The final study population included 314 men and women from Gimli, Arborg and Riverton (towns in the Interlake district of Manitoba) (**Group I**), and 252 men and women from Selfoss (a town in the district of Arnessysla in Iceland) (**Group II**).

Subjects received a letter describing procedures and aims of the study a few weeks before measurements began. Informed written consent was obtained from all subjects. The subjects were all volunteers who gave informed written consent after being verbally apprised of the nature, and potential risks of the study. The protocol was reviewed and accepted by the Ethical Review Committees, of the Faculty of Medicine, University of Manitoba and the University of Iceland. In all subjects, personal and family cardiovascular histories were obtained, along with information on height and weight, and the use of medications and tobacco. Fasting venous blood was

drawn for lipid analysis, lung function was assessed and subjects were exercised using bicycle ergometry.

6.2 Subjects.

A subgroup of Group I subjects (Subgroup IA) and a subgroup of Group II subjects (Subgroup IIA) were selected out of the total population (see Figures 1 and 2) for the purpose of echocardiography using specific criteria (see section 6.2.1). Later a sample of 20 males from the Interlake region, (Subgroup I B), were selected for treadmill exercise testing and plasma catecholamine analyses in a smaller pilot study. Data for men and women in Subgroups IA and IIA were analyzed separately. Clinical data, resting blood pressure measurements and responses to the questionnaire were obtained in all the subjects in the subgroups.

6.2.1 Criteria for inclusion in the Subgroups IA and IIA

The criteria for inclusion in the Subgroups IA and IIA were:

- a) On clinical examination subjects were free of evidence of coronary artery, peripheral vascular, renovascular and cerebrovascular disease.
- b) The subjects had never been on antihypertensive therapy.
- c) The subjects did not have a resting systolic or diastolic pressure in excess of 160mmHg and 95 mmHg respectively.
- d) During exercise testing the subjects did not have signs or symptoms of ischemia (defined as chest tightness, or pain on exertion accompanied by 1mm or more horizontal ST segment depression of greater than 2 mm in the absence of symptoms).

- e) The subjects achieved an exercise heart rate of at least 80% of their age-predicted maximum.

These criteria were used in order to exclude subjects whose blood pressure response to exercise, ability to exercise and electrocardiogram characteristics were impaired by overt disease or medication use.

6.3 Study Protocols

6.3.1 Questionnaire

The questionnaire was designed to be administered by a trained nurse-interviewer. The information elicited and its categorization are described below.

- a) The sex of each subject was recorded.
- b) Occupations were recorded and later coded in 9 categories using the Standard Occupation Classification (Statistics Canada, 1980).
- c) Marital status was recorded according to the categories: married, single, widowed or divorced.
- d) Current cigarette smoking habits were recorded according to the following categorization: current smokers with level of cigarette consumption per day noted; those who had never smoked; those who were no longer smokers with duration since cessation noted.
- e) Family history of myocardial infarction, diabetes, stroke, or hypertension in a parent or sibling, who was under the age of 55 years at the time of diagnosis, was recorded.
- f) Current medications were listed and any known disease or disability recorded.

6.3.2 Clinical data

Clinical data obtained included age (years), height (cm), weight (kg), cardiac index and peripheral resistance at rest, and workload during exercise (watts).

6.3.3 Resting blood pressure

Supine and seated BP were recorded using a mercury sphygmomanometer. The measurement protocol used was similar to that recommended by the Canadian Hypertension Society (1984). The subject rested for ten minutes in the supine position. BP was then recorded with arm bared and well supported. A cuff of appropriate size for the mid-upper arm circumference, namely 15 x 23 cm for adult arm size less than 33cm, and 15cm x 33cm for adult arm size 33 to 41 cm, was applied snugly with the lower edge approximately 3cm above the crease of the elbow and the bladder centered over the brachial artery. The radial pulse was palpated while the cuff was inflated to 30mmHg above the level at which the radial pulse disappeared. The systolic and diastolic pressures were identified as the first and fifth Korotkoff sounds, respectively. Three successive BP readings with at least one minute intervals between readings were taken in the right arm, and the mean of the second and third readings were used to determine the final supine BP for recording and statistical purposes. The above procedure was repeated in the seated position prior to exercise.

6.3.4 Bicycle ergometry - Subgroup IA and IIA

Standardized bicycle ergometry was performed in the sitting position on a mechanically braked Monark bicycle.

a) The subject was "warmed up" for 3 minutes with a starting load of 25-50 watts. [watt is a unit of power (work/time); 1 watt = 6.12 kpm.min⁻¹]

b) The load was increased stepwise every 6 minutes, by 50 watts and exercise was continued until 80% of the age predicted maximum HR was achieved or the subject was fatigued.

c) During recovery the load was decreased to 50 watts and cycling speed was reduced to approximately 30 revolutions for two minutes.

d) The subject then remained seated at rest for an additional 6 minutes. It has been our experience and the experience of others (Committee on Exercise, American Heart Assoc. 1972), that after a 6 minute post-exercise rest period BP and HR have returned to near pre-exercise levels and the EKG has reverted to a pre-exercise pattern.

e) Exercise was preceded by a recording of a 12-lead electrocardiogram (25mm/sec chart speed and at a sensitivity of 1mV/cm). Electrocardiograph lead V₃, and heart rate (HR) were monitored throughout the exercise test. BP was recorded every 2 minutes during exercise and during the 6 minute post exercise period.

6.3.5 Echocardiography - Subgroup IA and IIA

Echocardiographic measurements were made from two-dimensional directed M-mode echocardiograms. Each subject was studied in the supine and left lateral decubitus position. Studies were performed using a Dasonics 9

CV 400 transceiver interfaced with a Honeywell 1856 strip-chart recorder, and an A 2.25 MHz 1.25 cm. diameter unfocused Aerotech transducer.

Measurements were obtained according to the criteria of the American Society of Echocardiography using the leading edge to leading edge convention (Sahn *et al.*, 1978). At least three determinations were obtained and averaged in each subject. All of the echocardiograms were obtained by a single ultrasonographer using the identical protocol. The echocardiograms were evaluated by the same cardiologist, an experienced echocardiographer, who had no knowledge of the clinical status of the subjects.

6.3.5.1 Left ventricle measurements

Left ventricular (LV) measurements were obtained when the M-Mode ultrasonic beam was positioned between the papillary muscle and the tips of the mitral valve. The diastolic dimension was taken at the onset of the QRS complex and the end-systolic dimension was taken at the point of the peak downward (posterior) motion of the interventricular septum. Interventricular septal thickness and posterior wall thickness were measured at end diastole as defined by the onset of the QRS complex.

Measurements made of LV wall thickness and cavity dimensions were used to calculate LVM using the formula of Troy *et al.*, (1972) :

$$\text{LVM (g)} = 1.05 \left[(\text{LV internal diastolic diameter} + \text{LV septal thickness} + \text{posterior wall thickness})^3 - (\text{LV diastolic internal diameter})^3 \right]$$

(Mass is estimated from the specific gravity of ventricular muscle, which is assumed to be 1.05 g/cm³)

Left ventricular mass index (LVMI) (gm/m^2) was computed by dividing LVM by body surface area to correct for the effect of body size.

Body surface area (m^2) was defined as:

$(0.0001) (71.84) (\text{wt to the } 0.425 \text{ power} \times \text{ht to the } 0.725 \text{ power})$

where wt = weight in kilograms and height = height in centimeters (Savage *et al.*, (1987).

LVH was defined as left ventricular mass index (LVMI) $\geq 125 \text{g}/\text{m}^2$ for men and $\geq 101 \text{g}/\text{m}^2$ for women (Casale *et al.*, 1986; Savage *et al.*, 1987).

The following criteria, developed by Savage *et al.*, (1987) for use in the Framingham Study, were used to define the type of LVH in the population: in the present study:

- a) disproportionate septal LVH: $\text{IVS}/\text{LVPW} \geq 1.3$ (where IVS= interventricular septum and LVPW= left ventricular posterior wall)
- b) concentric LVH: echo LVH with $\text{RWT} \geq 45\%$ without disproportionate septal LVH. [where RWT = relative wall thickness defined as $2 \times \text{LVPW}/\text{LVIDD}$ (left ventricular internal diastolic dimension)]
- c) eccentric-dilated LVH: echo LVH with $\text{RWT} < 45\%$ with LVIDDI (left ventricular internal diastolic dimension index) exceeding normative reference value defined as $3.2 \text{ cm}/\text{m}^2$ for women and $3.1 \text{ cm}/\text{m}^2$ for men.
- d) eccentric non-dilated LVH: echo LVH with $\text{RWT} < 45\%$ with LVIDDI $< 3.2 \text{ cm}/\text{m}^2$ for women and $3.1 \text{ cm}/\text{m}^2$ for men.

Percent fractional shortening of the left ventricle was calculated using the formula of Quinones *et al.*, (1978):

$$(\text{LVIDD} - \text{LVIDS}) / \text{LVIDD} \times 100$$

Stroke volume was calculated using the formula of Popp and Harrison, (1970):

$$\text{Stroke volume (SV)} = 1.05 (\text{LV diastolic diameter}^3 - \text{LV systolic diameter}^3)$$

Cardiac output (L) was then calculated as $\text{SV} \times \text{HR}$ (resting), cardiac index as L/m^2 and peripheral resistance (mmHg/L) as mean arterial pressure/cardiac output.

6.3.5.2 Left atrium measurements

Left atrial dimension (LAD) was recorded at end systole, (its maximal dimension). The measurement was made from the leading edge of the posterior aortic wall to the leading edge of the posterior atrial wall. The left atrial dimension index was defined as the ratio of LAD/ body surface area (cm/m^2). LAE was defined as left atrial dimension index (LADI) $\geq 2.0 \text{ cm}/\text{m}^2$ (Hirata *et al.*, 1969).

6.3.6 Modified Balke Treadmill test - Subgroup IB

Exercise testing was performed on a treadmill using a modification of the Balke procedure (Balke and Ware 1959).

- a) The subject was "warmed-up" on the treadmill by walking for 2 minutes at 2.4 km/hr and 0° elevation, then 3.2 km/hr at 0° elevation for 1 minute.
- b) The speed was then increased to 4.2 km/hr and elevation remained at 0° during exercise.
- c) Exercise was continued for 10 minutes.
- d) During recovery the speed was reduced to 2.4 km/hr for 30 seconds to 1 minute.
- e) The subject remained seated at rest for an additional 6 minutes at the end of exercise.
- f) The Marquette Electronics Inc. Computer-Assisted System for Exercise-Series 3510, number IF 360120, 2.5 amp, 60 Hz, 115 volts, was used to monitor the EKG and HR at rest, during exercise and recovery. Leads V₃, V₅ and AVF were monitored during exercise, and just prior to exercise, BP, HR and a 12 lead EKG at a paper speed of 25mm/sec and at a sensitivity of 1mV/cm was recorded.
- g) HR was measured every minute throughout exercise and during the six minutes after exercise had ceased.

6.3.7 Collection of Blood for Plasma Catecholamine

Estimation- Subgroup IB

- a) subjects were asked to abstain from tobacco and caffeine for at least 12 hours before laboratory testing
- b) blood samples were obtained between 7 AM and 4 PM after an overnight fast of at least 12 hours
- c) peripheral venous samples (5 mls) to measure levels of plasma norepinephrine and plasma epinephrine were obtained from each subject by means of a small catheter (Cathlon 18 gauge) positioned in an antecubital vein just before the rest period. The catheter was kept patent by the establishment of a 250cc normal saline intravenous infusion that ran over the testing period
- d) the first blood sample was withdrawn after 15 minutes of supine rest in a quiet room without environmental distractions
- e) subsequent blood samples were withdrawn at seated rest before exercise testing began, after 9 minutes of treadmill exercise, and after 6 minutes of recovery

6.3.8 Plasma Catecholamine Determination Using Liquid

Chromatography With Electrochemical Detection (Hallman *et al.*, 1978)

- a) blood was drawn into cold heparinized tubes (Vacutainer^(R))
- b) the tubes were placed on ice
- c) the blood was centrifuged promptly at 1000 g for 10 minutes.
- d) the plasma was removed, frozen and stored at -70°
- e) for each determination 0.75 ml plasma was used

- f) an internal standard, 6 pmol α -methyl-dopamine (Merck, Sharpe & Dome) was added in 10 μ l 10.1 M perchloric acid (Merck)
- g) the sample was diluted with 0.75 ml H₂O (pH 7.4)
- h) an antioxidant, 40 μ l freshly prepared 5mM sodium bisulphate (NaHSO₃, Fisher) was added.
- i) pH was adjusted to 8.6 by addition of 1M Tris (Sigma) buffer pH 8.6 with 2 g Na₂ EDTA
- j) 15 mg of acid-washed alumina was added and the tube vigorously shaken
- k) the alumina was washed three times with water and after the last washing the supernatant was removed as completely as possible
- l) the catecholamines were desorbed with 50 μ l 0.1 perchloric acid
- m) after swirling the tubes to ensure complete elution of catecholamines from the alumina, the supernatant was pipetted into microcentrifuge tubes and centrifuged at 15,000 g. Twenty μ l of the supernatant was injected into the column.

The potential applied was +0.6 volts. The potential was kept constant and the current flow was measured using an electric controller. The chromatographic apparatus included a Spectra-Physics SP8700 solvent delivery system with an LC-4A amperometric detector (Bioanalytical Systems) in an oxidation mode. The column was a NOVAPACTM C18 (part number 086344) reverse phase (Water Associates). The results were recorded on a Hewlett-Packard integrator 3390A. High performance liquid chromatography coupled with electrochemical detection offers a high degree (picogram) of sensitivity and specificity in determination of catecholamines.

6.4 Statistical Analyses

All data were analyzed using the Statistical Analysis System SAS Institute software (1985) on an Amdahl computer located at the University of Manitoba. Descriptive data was reported separately for males and females in each community. Summary statistics for continuous variables were expressed as the mean and standard deviation. Categorical variables are presented as proportions. Differences in characteristics between men from Iceland and the Interlake, and women from Iceland and the Interlake were assessed using a two sample t test for continuous variables and chi square test of equality of proportions for categorical variables (Armitage, 1971). Univariate interrelationships between echocardiographic characteristics were expressed using Pearson correlation coefficients. One-way Analysis of Variance (ANOVA) was used to compare mean LADI and LVMI within categories of ESBP. The Bonferroni Correction was used to adjust for multiple comparisons of means of significant effects (Miller 1981). The joint relationship of characteristics for prediction of LADI and LVMI were tested using backward stepwise fitting of the multiple linear regression model. A probability level (p-value) of less than 0.05 was considered significant for hypothesis testing.

7. RESULTS

There were 283 subjects who met the criteria for inclusion in Subgroup IA and Subgroup IIA. They represent 65% of the total number of subjects from the Interlake district of Manitoba and from the town of Selfoss in the Arnessysla region of Iceland who participated in the collaborative study. Data for males and females were analyzed separately. There were 77 males and 71 females from the Interlake region (Group IA); and 68 males and 67 females from Selfoss (Group IIA). Ten females aged 60-64 years were deleted from the Interlake population since there were no females in the Selfoss population over the age of 59 years. The age range of the Interlake population was 28-64. The mean ages \pm 1sd were: 46 ± 11 for the males and, following deletion of the older females, 44 ± 11 for the females. The age range of the Selfoss population was 26-63 with a mean age of 43 ± 10 for the males and 40 ± 10 for the females (Tables 1 and 21).

7.1 Male Subjects

7.1.1 Social, Economic, Family and Health History

As shown in Table 2, 99% and 97% of males in the Interlake and in Selfoss respectively were employed. Over 60% of the subjects in each population was employed in the farming, fishing, processing or transportation industries. Ninety percent and 81% of Interlake and Selfoss subjects respectively were married. (Table 3). Thirty percent of Interlake males were smokers, and 34% of Selfoss males were smokers (Table 4).

7.1.2 Clinical Data

As shown in Table 5, mean body mass index (BMI), ESBP, and heart rate (HR) exercise of the Interlake males were significantly different from the mean values of those variables in the males of Selfoss. Using the weight-height index for the Canadian population as the criterion of overweightedness ($\text{weight}/\text{height}^2 >30$) (Chronic Diseases in Canada 1985) 22% (17/77) and 15% (10/68) of the Interlake and Selfoss study subjects respectively were overweight. A family history of hypertension was reported by 45% of Selfoss subjects, significantly higher than the 25% reported by the Interlake subjects. There were no significant differences between the two groups in: mean age, weight, height, exercise workload, resting systolic and diastolic BP, resting HR, resting cardiac index, stroke volume and peripheral resistance.

As shown in Table 6 there was a significant difference between mean values of LADI for Interlake and Selfoss females, otherwise there was no significant difference in the means of the echocardiographic variables LVMI, LVEDD, LVEDDI, LVESD, LVIVS, LVPW, LVIVS/LVPW and FS.

The mean values of M-mode echocardiographic measurements for the male populations were compared to the normal values reported by Feigenbaum (1986) and Devereux et al. (1983-b). The values for the Interlake subjects and Selfoss subjects respectively together with the corresponding normal values are: mean left ventricular end-diastolic internal dimension (LVEDD) = 54 ± 4 mm and 54 ± 4 mm (normal range 37-56mm); LVEDD corrected for body surface area = 27 ± 3 and 27 ± 2 (normal range 19-32mm); mean left ventricular end-systolic dimension ((LVESD) = 35 ± 5 and 34 ± 4

(normal range 23-39 mm); mean left ventricular interventricular septal thickness (LVIVS) = 7 ± 1 mm and 8 ± 2 mm normal range (6-11mm); mean left ventricular posterior wall thickness (LVPW) = $8 \text{ mm} \pm 1$ and $8 \text{ mm} \pm 2$ (normal range 6-11 mm); mean LAD corrected for body surface area (LADI) = $1.9 \pm .2$ and $1.8 \pm .2$ (normal range 1.2 to 2.2); mean LVMI = 91 ± 22 and 95 ± 34 (normal range 45-125 g/m²); mean fractional shortening (FS) = 36.0 ± 5.6 and 37.6 ± 5.7 (normal range 18 - 42 percent) As indicated all of the mean values in both populations were within normal limits.

LVMI ranged from 52 to 146 g/m², and 49 to 268 g/m² in the Interlake and Selfoss respectively. The prevalence of LVH in the Interlake was (LVMI ≥ 125 g/m²) was 11 % (7/65) and in Selfoss was also 6% (4/68). The range of LADI was 1.3 to 2.3 cm/m² and prevalence of LAE (LADI ≥ 2.0 cm/m²) was 23%(17/76) in Interlake males. In Selfoss the range of LADI was 1.25 to 2.29 cm/m² and the prevalence of LAE was 17% (12/68). LAE occurred in the absence of LVH in 24 of the subjects while LVH occurred in only 3 subjects in the absence of LAE. The criteria of Savage *et al.*, indicate that the hypertrophy was of the preload, volume-induced, eccentric type in all male subjects but one - where the LVH was of the concentric type.

Frequency histograms of LVMI and LADI are shown in Figures 4 and 5. For males in both populations, distribution of LADI and LVMI was tested using the chi-square goodness of fit test and was seen to be normally distributed.

7.1.3 Distribution of Subjects According to Resting SBP, DBP and Exercise SBP

Subjects were divided into two categories of resting SBP (< 140 and 140-159 mmHg) and two categories of resting DBP (<90 and 90-95 mmHg). Four categories of ESBP were defined (<190, 190-199, 200-209 and \geq 210 mmHg). The frequency distribution of ESBP according to site and combinations of resting and exercise blood pressures are depicted in Tables 7 to 11.

Twenty-three percent (18/77) of the Interlakers and 25% (17/68) of the Selfoss participants had blood pressures above the normal resting range. Fifty-seven percent (45/77) and 38% (26/68) of Interlake and Selfoss males had ESBP in excess of 200mmHg.

Fifty-one percent (30/59) of Interlake subjects with normal resting blood pressure had ESBP in excess of 200mmHg. In Selfoss 26% (14/53) of subjects with normal resting blood pressure had ESBP higher than 200mmHg. Eighty-three percent (15/18) and 81% (12/15) of borderline hypertensives in the Interlake and Selfoss respectively had ESBP \geq 200 mmHg.

When ESBP response values of normotensive and borderline hypertensive subjects were combined it was found that Interlake male subjects had significantly higher ESBP than did Selfoss male subjects ($p < 0.05$).

7.1.4 LADI According to Exercise SBP

The relationship of ESBP to the echocardiographic variable LADI is shown in Tables 12 and 13. The relationship was examined by determining the contribution to ANOVA models provided by ESBP when ESBP was categorized as <190mmHg, 190-199 mmHg and \geq 200mmHg. The relationship

of resting SBP to LADI was not determined. Small numbers in resting SBP category 140-159mmHg in two of the three categories of ESBP precluded meaningful analysis.

In the Interlake males (Table 12) there was an increase in mean values across ESBP categories but the difference in means between exercise levels was not significant. In the case of the Selfoss males (Table 13) there was also linear increase of mean LADI across ESBP categories; but here too the difference in mean values between exercise levels was not significant. It was determined by two-way ANOVA with replication that there was no site interaction, and therefore values of the two populations were combined. With combination of the two groups the increase of mean LADI between exercise levels was significant ($p < 0.0015$).

7.1.5 LVMI According to Exercise SBP

The relationship of ESBP to the echocardiographic variable LVMI is shown in Tables 14 and 15. The relationship was examined by determining the contribution to ANOVA models provided by ESBP when ESBP was categorized as < 190 mmHg, 190-199 mmHg and ≥ 200 mmHg. The relationship of resting SBP to LVMI was not determined. Small numbers in resting SBP category 140-159mmHg in two of the three categories of ESBP precluded meaningful analysis.

In the Interlake males (Table 14) there was an increase of mean values of LVMI across ESBP categories. The difference between mean values was, however not significant. In the case of the Selfoss males (Table 15) the difference in mean values of LVMI between exercise levels was significant ($p < 0.05$). It was determined by two-way ANOVA with replication that there

was no site interaction, and therefore values of the two populations were combined. When the two populations were combined the increase of mean LADI between exercise levels was significant ($p < 0.0025$)

7.1.6 Correlation Between Subject Characteristics for Dependent Variables LADI and LVMI.

For the purpose of univariate and multivariate analyses, LADI and LVMI were treated as dependent variables. Other variables in Tables 16-20 were treated as independent variables.

The relation of clinical variables to LADI and LVMI are shown in Table 16. In the Interlake males there was a correlation of LADI with the independent variables ESBP ($r = .23$, $p < 0.05$), cardiac index ($r = .43$, $p < 0.001$), and exercise workload ($r = -.23$, $p < 0.05$). There were no significant correlations between LADI and the independent variables age, supine SBP, HR exercise.

In the Selfoss males LADI correlated significantly with age ($r = .31$, $p < 0.01$), ESBP ($r = .27$, $p < 0.05$) and cardiac index ($r = .34$, $p < 0.01$), exercise workload ($r = -.23$, $p < 0.05$); there were no significant correlations between LADI and the independent variables supine SBP, HR exercise.

In the Interlake males, age ($r = .30$, $p < 0.01$), ESBP ($r = .33$, $p < 0.01$), HR exercise ($r = .32$, $p < 0.01$), and cardiac index ($r = .57$, $p < 0.00001$) were significantly correlated with LVMI; there were no significant correlation between LVMI and the independent variables supine SBP and exercise workload.

In Selfoss males, age ($r = .38$, $p < 0.01$), supine SBP ($r = .31$, $p < 0.01$), ESBP ($r = .31$, $p < 0.01$), cardiac index ($r = .50$, $p < 0.01$), were significantly correlated with LVMI.

There was no significant correlation between the independent variables BMI, supine DBP and HR rest, peripheral resistance, FS , smoking or occupation 6-8 and the dependent variables LADI and LVMI in either population.

7.1.7 Multiple Linear Regression Models for the Prediction of LADI and LVMI

The significant parameters of the linear multiple regression models for LADI and LVMI and the independent variables for males of the Interlake and Selfoss are listed in Tables 17 to 20. Standardized regression coefficients were used to provide a unitless scale so that there could be a comparison of effects. As shown in Table 17, for the Interlake males, in the final multivariate model the variables ESBP, cardiac index and workload exhibit an independent effect in the prediction of LADI. ESBP and cardiac index are associated with higher LADI, whereas exercise workload is associated with lower LADI. The R^2 for the model was 0.38 ($p < 0.0001$). As shown in Table 18 in the Selfoss males ESBP cardiac index and occupation (categories 6-8) exhibited an independent effect in the prediction of LADI. As was the case with the Interlake males ESBP and cardiac index are associated with higher LADI. Blue-collar occupations (6-8) were associated with lower LADI. Age correlated with LADI in the univariate model, but dropped out in the final multivariate model. R^2 for the model was 0.21 ($p < 0.0056$)

Table 19 indicates that ESBP, HR exercise and cardiac index exhibited an independent effect in the prediction of LVMI in the Interlake subjects. Age,

which was significant in the univariate analysis did not exert an independent effect in the final model. R^2 for the model was 0.47 ($p < 0.0001$)

Table 20 shows that age, ESBP and cardiac index exhibited an independent effect in the prediction of LVMI in the Selfoss subjects, Supine SBP was significant in the univariate model, but failed to exert an independent effect in the final model. R^2 for the model was 0.51 ($p < 0.0001$).

7.2 Female Subjects

7.2.1 Social, Economic, Family and Health History

As depicted in Table 22 82% and 83% of female subjects in the Interlake and Selfoss were employed outside the home. Of those females who were employed approximately 20% in each population were employed in clerical and sales related occupations. Twenty-eight percent of the subjects in Selfoss and 14% of the subjects in the Interlake were employed in the farming, fishing, processing or transportation industries. Ninety-two percent and 93% of Interlake and Selfoss subjects respectively were married (Table 23). Thirty-seven percent of Interlake females and 43% of Selfoss females were smokers (Table 24). A family history of hypertension was reported by 45% of Interlake subjects, not significantly higher than the 37% reported by the Selfoss subjects.

7.2.2 Clinical Data

As shown in Table 25 mean HR exercise of the Interlake females were significantly different from the mean HR exercise of the females of Selfoss. Other clinical variables : age, height, weight, BMI, BSA, resting SBP and DBP, ESBP, HR resting, stroke volume, cardiac index, peripheral resistance and

exercise workload were not significantly different in the two groups. The weight-height index for the Canadian population as the criterion for overweightedness (weight/ height ² >35 respectively) (Chronic Diseases of Canada, 1985) were used to assess overweightedness in female subjects. Ten percent and 7% at 95th percentile cut-off point respectively were overweight in the Interlake and the Selfoss populations.

As shown in Table 26 there was no significant difference in mean values of the echocardiographic variables LVMI, LVEDD, LVEDDI, LVESD, LVIVS, LVPW and LVIVS/LVPW between Interlake females and Selfoss females. However there was a small but significantly higher LADI in the Interlake females.

The mean values of M-mode echocardiographic measurements for the female populations were compared to the normal values reported by Feigenbaum (1986) and Devereux et al. (1983). The values for the Interlake subjects and Selfoss subjects respectively together with the corresponding normal values are: mean left ventricular end -diastolic internal dimension (LVEDD) - 49 ± 4 mm and 49 ± 3 mm (normal range 37-56mm); LVEDD corrected for body surface area - 28 ± 2 and 27 ± 2 (normal range 19-32mm); mean left ventricular end-systolic dimension (LVESD) - 31 ± 4 and 30 ± 3 (normal range 23-39 mm); mean left ventricular interventricular septal thickness (LVIVS) - 6 ± 1 mm and 6 ± 2 mm (normal range 6-11mm); mean left ventricular posterior wall thickness (LVPW) - $7 \text{mm} \pm 1$ and $6 \text{mm} \pm 2$ (normal range 6-11 mm); mean LAD corrected for body surface area - left atrial index (LADI) $1.9 \pm .2$ and $1.8 \pm .2$ (normal range 1.2 to 2.2); mean LVMI - 74 ± 15 and 69 ± 16 (normal range 45-100 gm/m²). As indicated all of the mean values in both populations were within normal limits.

LVMI ranged from 46 to 111 g/m², and 44 to 117 g/m² in the Interlake and Selfoss respectively. The prevalence of LVH in the Interlake was (LVMI \geq 100 gm/m²) was 6 % (4/61) and in Selfoss was also 6% (4/67). The range of LADI was 1.3 to 2.26 cm/m² and prevalence of LAE (LADI \geq 2.0 cm/m²) was 25%(16/61) in Interlake females. In Selfoss the range of LADI was 1.19 to 2.19 cm/m² and the prevalence of LAE was 12% (9/67). LAE occurred in the absence of LVH in 22 of the subjects while LVH occurred in only 2 subjects in the absence of LAE. The criteria of Savage *et al.*, indicate that the hypertrophy was of the preload, volume-induced, eccentric type in all female subjects.

Frequency histograms of LVMI and LADI are shown in Figures 6 and 7. For females in both populations, distribution of LADI and LVMI was tested using a chi-square goodness of fit test and was seen to be normally distributed.

7.2.3 Distribution of Subjects According to Resting SBP, DBP and Exercise SBP

The female subjects were divided into two categories of resting SBP (< 140 and 140-159 mmHg) and two categories of resting DBP (<90 and 90-95 mmHg). Four categories of ESBP were defined (<190, 190-199, 200-219 and \geq 220 mmHg). The frequency distribution of ESBP according to site and combinations of resting and exercise blood pressures are depicted in Tables 27 to 31.

Ten percent (6/61) of the Interlakers and 18% (12/67) of the Selfoss participants had blood pressures above the normal resting range. Thirty-two

percent (20/61) and 19% (13/67) of Interlake and Selfoss females had ESBP in excess of 200mmHg (Table 27).

Twenty-nine percent (16/55) of Interlake subjects with normal resting blood pressure had ESBP in excess of 200mmHg (Table 28). In Selfoss 11% (6/55) of subjects with normal resting blood pressure had ESBP that exceeded 200mmHg (Table 29). Sixty-six percent (4/6) and 58% (7/12) of borderline hypertensives in the Interlake and Selfoss respectively had ESBP \geq 200 mmHg.

When ESBP values were combined for normotensive and borderline hypertensive subjects (Tables 30 and 31), it was found that although there were more hyperresponders in the Interlake it did not reach the level of significance ($p < 0.09$).

7.2.4 LADI According to Exercise SBP

The relationship of ESBP to the echocardiographic variable LADI is shown in Tables 32 and 33. The relationship was examined by determining the contribution to ANOVA models provided by ESBP when ESBP was categorized as < 190 mmHg, 190-199 mmHg and ≥ 200 mmHg. Resting SBP categories < 140 mmHg and 140-159mmHg were combined due to small numbers in the latter category.

In the Interlake females (Table 32) there was not a linear increase of mean LADI across exercise blood pressure categories and the mean difference between exercise levels was not significant ($p < 0.41$). In the case of the Selfoss females (Table 33) there was a linear increase of mean LADI across exercise blood pressure categories and the mean difference between exercise levels was significant ($p < 0.0097$).

7.2.5 LVMI According to ESBP

The relationship of ESBP to the echocardiographic variable LVMI is shown in Tables 34 and 35. The relationship was examined by determining the contribution to ANOVA models provided by ESBP when ESBP was categorized as <190mmHg, 190-199 mmHg and \geq 200mmHg. Resting SBP categories <140mmHg and 140-159mmHg were combined due to small numbers in the latter category.

In the Interlake females and the Selfoss females (Table 34 and 35) there was a linear increase of mean LVMI across exercise blood pressure categories and the mean difference between exercise levels was significant, ($p < 0.0039$ and $p < 0.0001$).

7.2.6 Correlation Between Subject Characteristics for Dependent Variables LADI and LVMI.

Univariate analyses were undertaken to select the relevant variables for multivariate analysis. For both univariate and multivariate analyses, LADI and LVMI were treated as dependent variables. Other variables in Tables 36-40 were treated as independent variables.

The relationships of clinical variables to LADI and LVH are shown in Table 36. In the Interlake females there was a modest LADI correlation with the independent variable cardiac index ($r = .22$, $p < .05$). FH-HT and occupation (6-8) were significantly related to LADI (chi-square $p < 0.03$, $p < 0.05$ respectively- not shown). There were no significant correlations between LADI and the independent variables age, BMI, supine SBP, ESBP, HR exercise, and exercise workload.

In the Selfoss females LADI correlated significantly with age ($r=.29$, $p<0.05$), supine SBP ($r=.25$, $p<0.05$), ESBP ($r=.36$, $p<0.01$) and cardiac index ($r=.26$, $p<0.05$). There was no significant correlation between LADI and the independent variables BMI, HR exercise and exercise workload.

In the Interlake females, age ($r=.37$, $p<0.01$), BMI ($r=.46$, $p<0.001$), resting SBP ($r=.50$, $p<0.0001$), ESBP ($r=.52$, $p<0.0001$), HR exercise ($r=.35$, $p<0.01$), and cardiac index ($r=.26$, $p<0.05$) were significantly correlated with LVMI. FH-HT was significantly related to LVMI (chi-square $p<0.04$) and occupation (6-8) was not correlated with LVMI (not shown).

In Selfoss females, age ($r=.39$, $p<0.01$), BMI ($r=.29$, $p<0.05$), supine SBP ($r=.36$, $p<0.01$), ESBP ($r=.40$, $p<0.001$), HR exercise ($r=.43$, $p<0.001$) cardiac index ($r=.35$, $p<0.01$) exercise workload ($r=-.29$, $p<0.05$) were significantly correlated with LVMI.

There was no significant correlation between the independent variables supine DBP, HR rest, peripheral resistance, FS, or smoking and the dependent variables LADI and LVMI in either population.

7.2.7 Multiple Linear Regression Models for the Prediction of LADI and LVMI.

The significant parameters of the linear multiple regression models for LADI and LVMI and the independent variables for females of the Interlake and Selfoss are listed in Tables 37 to 40. Standardized regression coefficients were used to provide a unitless scale so that there could be a comparison of effects. As shown in Table 37, for the Interlake females, in the final multivariate model the variables FH-HT, blue collar occupations (6-8 see Table 22), exercise workload and cardiac index exhibit an independent effect

in the prediction of LADI. FH-HT and cardiac index are associated with higher LADI, whereas occupations 6-8 and exercise workload is associated with lower LADI. The R^2 for the model was 0.29 ($p < 0.0008$).

Table 38 indicates that cardiac index and ESBP exhibited an independent effect in the prediction of LADI in the Selfoss subjects. Age, supine SBP which were significant in the univariate analysis did not exert an independent effect in the final model. R^2 for the model was 0.27 ($p < 0.0053$)

As shown in Table 39 in the Interlake females the variables ESBP, FH-HT, workload and cardiac index exhibit an independent effect in the prediction of LVMI. ESBP, FH-HT and cardiac index are associated with higher LVMI, whereas workload is associated with lower LVMI. Age, BMI, supine SBP and exercise HR were correlated with LVMI in the univariate model, but dropped out in the final multivariate model. R^2 for the model was 0.53 ($p < 0.0001$)

Table 40 shows that ESBP, HR exercise and cardiac index exhibited an independent effect in the prediction of LVMI in the Selfoss subjects. Age, BMI, supine SBP and workload were significant in the univariate model, but failed to exert an independent effect in the final model. R^2 for the model was 0.38 ($p < 0.0001$).

7.3 Plasma Norepinephrine at Rest and During Exercise

Based on resting SBP and ESBP measured in 1988 twenty age-matched (range 30-60 years) male subjects from the Interlake were selected for a pilot study of plasma catecholamine levels in relation to blood pressure status at rest and during exercise. In 1988, 10 of the subjects were normotensive at rest ($< 140/90$ mmHg) with ESBP < 200 mmHg, 8 were normotensive at rest with

ESBP \geq 200 mmHg, and 2 were borderline hypertensive at rest(140-159 mmHg systolic and/or 90-95mmHg diastolic) with ESBP \geq 200mmHg.

It had been intended to analyze the plasma samples for NE and E, but for technical reasons only values for NE could be determined. However Cleroux *et al.*, (1985) demonstrated that the pattern of changes for NE and E with exercise were similar. At rest NE values in subjects who were normotensive at rest and during exercise had a mean of 234.5 pg/ml \pm sd 32.1 whereas the values in subjects with ESBP \geq 200 mmHg had a mean of 257.8 \pm sd 10.6. The difference was significant at $p < 0.025$. During exercise the corresponding means were: ESBP $<$ 200mmHg = 239.4 \pm sd 23.3; and ESBP \geq 200 mmHg =256.1 \pm sd 16.4. The difference was significant at $p < 0.05$. No significant difference was seen in mean NE levels between rest and exercise in either group, and there was no significant correlation between mean NE and LADI or LVMI.

8. DISCUSSION

8.1 The Study Populations

As noted in the Introduction (p.2) it was in the 1970's that the difference in ischemic heart disease mortality between residents of Iceland and the descendants of the "New Icelanders" was reported. The higher mortality rates noted in Interlake residents have persisted to the present time. In fact the ischemic heart disease crude mortality rate has increased somewhat in the Interlake between the mid-seventies and the present, while in Iceland the mortality rate over the same time period has remained stationary in the male population, and has declined in the female population (Olafsson *et al.*, 1988). The cause of this difference between males and females is unknown. The trend in the prevalence of the conventional risk factors does not yield an explanation. Olafsson has suggested that the difference may lie in differences in activity and stress levels.

The fact that there is a higher ischemic heart disease mortality in the Interlake can be attributed to the influence of the higher cardiovascular risk profile in Canadians of Icelandic descent compared to native Icelanders. In the male population in the Interlake there is a less favorable atherogenic index (ratio of HDL cholesterol to total cholesterol), a low omega-3/omega-6 fatty-acid ratio (Skuldottir *et al.*, 1990), and more overweightedness than in the males from Iceland (Sigurdsson *et al.*, 1990). In the sub-population investigated in the present study there was a significantly greater frequency of a family history of hypertension in Selfoss males compared to Interlake males. It is possible that the reporting of a family history of hypertension may

not be equally reliable in the two populations. The prevalence of borderline hypertension was similar in the male populations, but there was a higher prevalence of borderline hypertension in females from Selfoss than in females from the Interlake. Smoking behavior was not significantly different between the two populations, and, one-third of all subjects reported they are current smokers.

Cerebrovascular mortality in the two communities, determined in the mid 1980's was virtually the same at about 60 per 100,000 of population.² According to Olafsson, (1988), although the death rate from cerebrovascular diseases in Iceland has declined significantly between 1970 and 1986, "most likely because of more intensive awareness and treatment of hypertension, the prevalence of cerebrovascular disease remains unchanged".

Apart from demonstrating that the two populations differ in certain significant respects these earlier studies also demonstrated that native Icelanders and Interlake residents of Icelandic descent are excellent subjects for clinical and epidemiological study. They have a profound interest in their origins and in their common heritage and community characteristics. As a result they are willing, co-operative, compliant and reliable so that sequential studies are marked by very high follow-up rates - usually over 95 per cent.

The two sub-populations studied for the purpose of this dissertation had similar demographic characteristics. The total numbers of subjects and the sex distribution were similar. Both groups of subjects were required to meet the same selection criteria with respect to blood pressure status, freedom

² Interlake cerebrovascular mortality between 1980 and 1985 for persons aged 25 to 85 years or older was 59/100,000 (Department of Vital Statistics, Manitoba). Iceland cerebrovascular mortality between 1982 and 1986 for persons aged 0 to 85 years or older was 61/100,000 (Statistical Bureau of Iceland).

from clinical cardiovascular disease, absence of use of anti-hypertensive medication, lack of evidence of ischemia during exercise and the ability to exercise at an intensity sufficient to raise the heart rate to 80 per cent of the age-predicted maximum. The subjects were also selected so that the two groups had a similar age range, although as noted in the description of the results, to achieve this a small number of the oldest females in the Interlake group were excluded. The inclusion or exclusion of these subjects did not alter the statistical findings.

Values for the weight-height index of overweightedness (Body Mass Index $\geq 35 \text{ kg/m}^2$) for females from the Interlake and from Selfoss were 10 and 7 per cent respectively. These values were somewhat lower than for females in the the Canadian population as a whole for whom the corresponding figure was 15 per cent. The findings in the male subjects differed from those in the females in two respects. First, Interlake males had a higher weight-height index than Selfoss males (22 per cent vs 15 per cent) (Body Mass Index $\geq 30 \text{ kg/m}^2$). Second, the index in both groups was higher than that for males in the Canadian population as a whole, in which the value was 9 per cent. There are recognized limitations in the use of indirect measures of "overweightedness" or adiposity, such as weight-height indices, for epidemiological purposes; in that the use of such indices is likely to result in individuals being categorized as obese when they merely have a large lean body mass in relation to their height (Revicki and Israel, 1986). The characteristics of the two population samples indicate that they are comparable demographically and with respect to most physical characteristics except for the differences in overweightedness noted in male subjects. Since body habitus may influence certain hemodynamic and cardiovascular

variables such as exercise systolic blood pressure and left ventricular mass, body size was taken into account in the analyses of the cardiovascular data.

8.2 Resting Blood Pressure

A comparison of the prevalence of borderline hypertension (140-159/90-95 mmHg) with the values for the sexes combined, revealed similar total prevalences of 17% and 21% in the Interlake and Selfoss respectively. Two blood pressure surveys have recently been reported: one for the Province of Manitoba (Heart Health Survey, unpublished data) and one for Canada (Canadian Blood Pressure Survey 1989). In both surveys, (age range 18 to 64 years or older) hypertension was defined as a diastolic blood pressure ≥ 90 mmHg, and/or the use of anti-hypertensive medication, salt restriction and /or weight reduction, specifically prescribed for blood pressure control. The prevalence of hypertension (both sexes combined) was estimated to be 22% and 18% in Manitoba and Canada respectively. In the Canadian Blood Pressure Survey, when hypertension is defined using a diastolic blood pressure ≥ 90 mmHg (mean of the two measurements made at the time of the interview) as the sole criterion, the prevalence of hypertension was estimated to be 10 percent.

It is difficult to compare the prevalence rate of "borderline essential hypertension" among the subjects who had echocardiographic measurements with the prevalence in the general populations of the Province of Manitoba, or of Canada, since the criteria for the definition of hypertension were different. The definition of borderline hypertension in the present study included an elevated systolic blood pressure and/or an elevated diastolic blood pressure. In addition, no subject was on medication

for essential hypertension and no diastolic blood pressure was greater than 95 mmHg. Using the second definition of the Canadian Blood Pressure Survey (diastolic blood pressure ≥ 90 mmHg), the prevalence of hypertension in the Interlake and Selfoss was 12% and 15% respectively (values for both sexes combined). According to Icelandic statistics, during the period 1970-1983 the prevalence rate of hypertension in Iceland (for subjects aged 25-70 years or older was 25% when hypertension was defined as blood pressure $\geq 160/95$ mmHg, or the use of anti-hypertensive therapy). This prevalence rate is not only higher than that seen in the Canadian population but also higher than in most surrounding European countries (Olafsson *et al.*, 1988). Again comparison with the two Canadian surveys was difficult since the systolic pressure as well as the diastolic pressure was used to define the prevalence of hypertension in Iceland.

It is of interest to note that recent prospective studies have directed attention to systolic pressure as a better guide to all-cause mortality (Rutan *et al.*, 1988), cardiac failure (Kannel *et al.*, 1972; Garland *et al.* 1983), and stroke (Kannel *et al.*, 1981), rather than diastolic pressure. Indeed, diastolic pressure is now challenged as an adequate index of arteriolar tone and of the hypertensive state (O'Rourke, 1990). In the present study there was no difference in either resting systolic or diastolic blood pressures between the Interlake and the Selfoss subjects in part because of the study design.

8.3 Systolic Blood Pressure Response to Exercise

As indicated earlier, in the review of the literature, the definition of what constitutes an abnormal or exaggerated systolic blood pressure response to exercise varies considerably among investigators. Accordingly, as stated

above, ESBP was treated as both a categorical and continuous variable in the present study. ESBP \geq 200 mm Hg was used to identify subjects of special interest. The frequency of ESBP \geq 200 mmHg was significantly higher in the Interlake than in Selfoss for both males and females. This finding adds another variable to the constellation of cardiovascular and biochemical variables and other factors that have been found to differ in the two populations. It is not unreasonable to suggest that the same environmental risk factors such as stressful lifestyle, diet or physical inactivity that contribute to such phenomena as the higher prevalence and mortality rate for ischemic heart disease in the Interlake compared to Iceland may play a part in determining the differences in prevalence of exaggerated ESBP.

A second key finding was that the frequency of ESBP \geq 200 mmHg was significantly greater in males than in females both in the Interlake and in Iceland. The sex difference was also observed in a previous study of normotensive subjects from a mixed urban population where the frequency of ESBP \geq 200 mmHg was 40 per cent and 13 per cent in males and females respectively (Naimark *et al.*, 1990). Few studies reported in the literature include women. Wilson and Meyers, (1981) reported the frequency of exercise systolic blood pressure \geq 225 mmHg as 12 per cent in a population (n=3820) that included 425 (11%) women. In the present study, with almost equal representation of men and women, the frequency of an exercise systolic blood pressure \geq 225 mmHg was 16 per cent and 9 per cent (sexes combined) in the Interlake (n=138) and Selfoss (n=135) respectively.

The explanation for the higher frequency of an exercise systolic blood pressure \geq 200mmHg in male subjects compared to female subjects is not certain but it is worth noting that the levels of exercise intensity achieved by

the males was on average greater than that achieved by females (Interlake: mean workload in watts for males = 146 ± 32 and for females = 97 ± 19 ; Selfoss: mean workload in watts for males = 153 ± 39 and for females = 103 ± 29) Thus there may be females in the study population who are potential hyper-responders, in terms of exercise systolic blood pressure, but who did not achieve the level of exercise intensity required to make their hyper-responsiveness manifest. Astrand, (1965) suggested that at a given heart rate women normally employ a smaller proportion of their aerobic capacity than do men. Therefore, at similar heart rates the exercise systolic blood pressure in women would be expected to be lower. In our population mean exercise heart rate in women tended in fact to be higher than mean exercise heart rate in men, therefore it would be expected that exercise systolic blood pressure values in the two sexes should have been closer than they were.

As stated earlier the body mass is another factor that must be taken into account in studying hemodynamic variables. It is of interest to note that in male subjects in the Interlake and Selfoss, and female subjects in Selfoss there was no correlation between body mass index and exercise systolic blood pressure. There was however a significant correlation between exercise systolic blood pressure and body mass index among female subjects in the Interlake. Although the explanation for the difference between Interlake females and the other three subgroups is not clear it was deemed to be important to take body mass into account in the multivariate analysis of factors influencing left ventricular mass (see below).

8.4 Left Atrial Dimension Index (LADI) and Left Ventricular Mass Index (LVMI)

As stated earlier left atrial enlargement can occur in hypertension before the appearance of left ventricular hypertrophy. Atrial enlargement might occur independently of changes in the ventricle due to increased venous return resulting in increased atrial stretch and therefore according to Laplace's Law, an increased wall tension (Messerli *et al.*, 1978; Logan *et al.*, 1981). It has also been postulated that the enlarged atrium reflects atrial manifestations of diminished compliance of the "hypertrophying" left ventricular myocardium (Frolich *et al.*, 1971). The literature focuses almost entirely on the later stages of the disease process when left ventricular hypertrophy is evident electrocardiographically or echocardiographically. In the present study of apparently healthy individuals there was a surprisingly high prevalence of left atrial enlargement, commonly defined as $LADI \geq 2.0$ cm/m². The prevalence of left atrial enlargement in the Interlake was 23 per cent and 25 per cent for males and females respectively. In Selfoss the prevalence was 17 per cent and 18 per cent for males and females respectively. It is of considerable interest to note that in the 46 subjects with left atrial enlargement, the enlargement occurred in the absence of left ventricular hypertrophy in 41 cases, whereas in only 5 cases out of 16 subjects with left ventricular hypertrophy was left atrial enlargement absent. This is consistent with the view that left atrial enlargement is a common precursor of left ventricular hypertrophy. The magnitude of the difference is striking and suggests that left atrial enlargement might be useful as a marker for early hypertension. If left atrial enlargement were to be bimodally distributed it might constitute a phenotypic abnormality that may be used in combining

restriction fragment length polymorphisms technology with genetic linkage analysis to identify genetic markers (Horan and Lenfant, 1990)

LADI was significantly correlated with exercise systolic blood pressure in all subject groups but the females in the Interlake. There was no significant correlation between LADI and either supine resting systolic blood pressure or body mass index in any of the subject groups. The latter findings are consistent with reports in the literature demonstrating insignificant correlations between resting systolic blood pressure and electrocardiographic indices of left atrial enlargement and significant correlations between exercise systolic blood pressure and electrocardiographic left atrial enlargement (Naimark *et al.*, 1990). In the final multivariate regression models cardiac index was an independent predictor of LADI. This finding lends support to the concept that left atrial enlargement in early hypertension is, in part at least, related to a hyperdynamic circulation. Exercise systolic blood pressure was also an independent correlate of LADI in the final regression model except for females in the Interlake.

The finding of a significant correlation between left atrial enlargement, determined echocardiographically, and exercise systolic blood pressure in normotensive and borderline hypertensive subjects has not been reported previously.

As stated earlier the prevalence of left ventricular hypertrophy (LVMI ≥ 125 g/m² for males and ≥ 100 g/m² for females) in the total population ranged from 6 per cent to 11 percent, a prevalence somewhat lower than that reported in the Framingham study where the prevalence of left ventricular hypertrophy was 16% in men and 19% in women (age range 17-90 years). The explanation for the difference in prevalence is probably because hypertensives

were included in the Framingham population. (Levy et al., 1988). The extent of hypertrophy in our study (as reflected by LVMI) ranged from 100 to 268 gm/m². Since the frequency distribution of LVMI values is roughly unimodal and since precise separation of "normal" from "abnormal" is difficult, LVMI was considered as a continuous variable in the univariate and multivariate statistical analyses.

Several investigators have found exercise systolic blood pressure to be a better correlate of left ventricular hypertrophy in studies of hypertensives than resting systolic blood pressure. Naimark *et al.*, (1990) extended this observation to demonstrate an association between electrocardiographic left ventricular hypertrophy and exercise systolic blood pressure in a normotensive population - a finding suggestive of an increased risk of cardiovascular sequelae for the subgroup of normotensives with a high exercise systolic blood pressure. In the present study, these findings have been supported in that in multivariate analysis exercise systolic blood pressure in normotensive subjects is closely associated with left ventricular hypertrophy determined by the more sensitive technique of echocardiography. A positive correlation between left ventricular mass and maximum blood pressure during symptom-limited exercise was also noted in a more recent study (Michelsen et al., 1990). The latter investigation did not include females or borderline hypertensives or an examination of the relationship between atrial dimensions and exercise blood pressure.

Because obesity was not an exclusion criterion, a possible effect of body mass on cardiac dimensions and cardiac output was considered. It is of interest to note that there was no correlation between LVMI and body mass index in males in either the Interlake or Selfoss. Although univariate

analysis demonstrated a correlation between body mass index and LVMI among females in both the Interlake and Selfoss, multivariate analysis indicated that body mass index was not an independent predictor of LVMI in females. In the case of cardiac output, there was no correlation with body mass in males or females in either population. Consequently exercise systolic blood pressure and cardiac output were more important than body weight in determining cardiac dimensions in the populations studied.

In the present study the mean cardiac output at rest is significantly higher in subjects with high exercise systolic blood pressure, but the calculated resting peripheral resistance is similar in all subjects regardless of exercise systolic blood pressure status. These findings lend support to the suggestion proposed by Ulrych *et al.*, (1969), that the increased cardiac output may be achieved through a redistribution of peripheral intravascular volume toward the cardiopulmonary circulation, presumably as a result of venoconstriction, perhaps resulting from sympathetic overactivity.

In the pilot study of two groups of Interlake males (10 with ESBP \geq 200 mmHg and 10 with ESBP $<$ 200 mmHg) matched, according to age and body mass index it was shown that those with elevated exercise systolic blood pressure had significantly higher levels of mean plasma norepinephrine than those without. However no correlation was found between plasma norepinephrine levels and LADI and LVMI. Thus while the results are not inconsistent with the view that the blood pressure response to exercise may be influenced by the general level of sympathetic activity the data do not demonstrate that such activity is the mechanism for the increased cardiac output and structural cardiac changes in early hypertension. Similar conclusions were arrived at by Esler and Jennings, (1984). They pointed out

that the cardiac spill-over contributes only 2 per cent to the total entry of norepinephrine into the circulating plasma compartment and it may therefore prove to be impossible to detect increased sympathetic activity in the heart by measuring plasma norepinephrine levels. One must also consider the possibility that plasma norepinephrine may influence the heart indirectly through some intermediate compound to which norepinephrine is not related linearly thereby masking a correlation.

It is of interest to note that among the pilot study subjects, in the two year period between exercise testing periods, one subject with an exaggerated exercise systolic blood pressure who was normotensive at rest in 1988, had developed an elevated blood pressure at rest by 1990, and that the blood pressure of two subjects who were borderline hypertensives in 1988 was still elevated in 1990.

8.5 Statement of Conclusions in Relation to Hypotheses

Hypothesis i

The findings of the present study support the hypothesis that there is a difference in the prevalence of an exaggerated systolic blood pressure response to exercise between native Icelanders and Canadians of Icelandic descent. Both males and females of the Interlake population exhibit a higher prevalence of exaggerated exercise systolic blood pressure than do the males and females of the Selfoss population. With respect to the prevalence of cardiac abnormalities (left atrial enlargement and left ventricular hypertrophy) the findings were mixed. The prevalence of left atrial enlargement and left ventricular hypertrophy was significantly higher in in

the Interlake males than in the Selfoss males. However, while the prevalence of left atrial enlargement in Interlake females was significantly higher than in Selfoss females, there was no significant difference in the prevalence of left ventricular hypertrophy between females in the Interlake and females in Selfoss. The demonstration of an increased prevalence of a marker for early essential hypertension taken together with the higher atherogenic index noted in other studies indicates that the Interlake population may be in double jeopardy.

Hypothesis ii

The hypothesis that subjects who are normotensive at rest and who have an exaggerated exercise systolic blood pressure also have a higher prevalence of left atrial enlargement is supported by the findings of the present study. However, when the total study population is subdivided according to site and sex it was found that the hypothesis was supported for males in both the Interlake and Selfoss and for females in Selfoss but not for females in the Interlake. As noted earlier the most striking feature was the high prevalence of left atrial enlargement in the population, consistent with the view that left atrial enlargement is a precursor of left ventricular hypertrophy and might be useful as a marker for early hypertension.

Hypothesis iii

The hypothesis that subjects who are normotensive at rest and who have an exaggerated exercise systolic blood pressure also have a higher prevalence of left ventricular hypertrophy than normotensive subjects without an exaggerated exercise systolic blood pressure is supported by the findings of the present study. In the case of this hypothesis the association between an exaggerated exercise systolic blood pressure and an increased prevalence of left ventricular hypertrophy was observed in all four subgroups. Although there were a few cases where left ventricular hypertrophy was present without left atrial enlargement, abnormalities in atrial function such as delayed atrial emptying due to a stiffening ventricle may be present despite normal values for the left atrial index.

Hypothesis iv

The findings with respect to the hypothesis that borderline hypertensives with an exaggerated exercise systolic blood pressure have a higher prevalence of left atrial enlargement are analogous to the findings in relation to normotensives; that is, the hypothesis is supported for the total population and for males in both the Interlake and Selfoss, for females in Selfoss, but not for females in the Interlake.

Hypothesis v

The findings with respect to the hypothesis that borderline hypertensives with an exaggerated exercise systolic blood pressure have a higher prevalence of left ventricular hypertrophy are analogous to the findings in relation to normotensives; that is, the hypothesis is supported for the total population and for the four subgroups.

Hypothesis vi

The results of the present study support the hypothesis that the effect of exercise systolic blood pressure on left atrial enlargement and left ventricular hypertrophy is independent of the effects of age, body mass index and resting systolic blood pressure for the total population. However, when the total population was subdivided according to sex and site the independent effect of exercise systolic pressure was seen for all four subgroups in the case of left ventricular hypertrophy. In the case of left atrial enlargement the independent effect of exercise systolic blood pressure was seen for males in both the Interlake and Selfoss, and in females in Selfoss, but not in females in the Interlake.

Hypothesis vii

The results of a limited pilot-study to investigate the hypothesis that there is an association between plasma levels of catecholamines, at rest and during exercise, and the levels of exercise systolic blood pressure indicate that

subjects with an exaggerated exercise systolic blood pressure have higher levels of plasma norepinephrine than subjects without an exaggerated exercise systolic blood pressure. A correlation between plasma norepinephrine levels and cardiac dimensions was not observed but as stated earlier one must also consider the possibility that plasma NE may influence the heart indirectly through some intermediate compound to which NE is not related linearly thereby masking a correlation. It is also possible that a more extensive study, involving larger numbers of subjects, may reveal a correlation between catecholamine levels and exercise systolic blood pressure.

8.6 Significance of Findings

The data seem to indicate and support the thesis of a continuum or spectrum of hemodynamic and structural alterations in the progressive development of essential hypertensive disease. The increased cardiac output is associated with higher exercise systolic blood pressure and both of these variables predict the values of LADI and LVMI in the Interlake and Selfoss populations. The demonstration of an association between exercise systolic blood pressure and echocardiographic abnormalities, which is independent of the level of the resting blood pressure, is consistent with the contention that an increased exercise systolic blood pressure may be one of the early manifestations of the hypertensive state and may also be a means of identifying individuals who are at increased risk for the development of the cardiac sequelae of hypertension. A definitive explanation of the findings awaits further research, however certain possibilities seem plausible. One is that exercise systolic blood

pressure is a better reflection of the overall pressure load imposed on the left ventricular myocardium over time than is resting systolic blood pressure. A second explanation is that the pathogenesis of cardiac hypertrophy involves an enhanced reactivity to adrenergic drive through a growth effect, and since exercise is known to activate the sympathetic nervous system, a correlation between exercise systolic blood pressure and LVMI would be expected. In this connection it may be observed that all inducers of growth appear to exert their initial effects by a common mechanism involving coupling of mechanical and biochemical changes; namely, an increased load imposes increased pressure on myocytes and stretch of muscle fibres (possibly mediated by norepinephrine release) causes an increase in RNA transcription and enhanced protein synthesis (Wikman-Coffelt et al., 1979).

Convincing evidence on these questions must come from carefully controlled prospective studies of the clinical outcomes of normotensive and borderline hypertensive individuals who have an abnormal systolic blood pressure response to exercise but are otherwise normal. The findings in the present study justify pursuing a longitudinal project whereby it can be determined if those normotensive subjects with an exaggerated blood pressure response to exercise are at greater risk of developing hypertension than normotensive subjects without an exaggerated exercise systolic blood pressure. Mechanisms such as neurohumoral influences should be investigated in the total population, since the results of a pilot study in a small number of subjects suggest that there may be an association between high exercise blood pressure responders and plasma norepinephrine levels. However some other factors are being recognized as possibly being involved

in the structural and functional changes in the heart and blood vessels. These include growth factors, which may be linked to catecholamines or act independently, changes in membrane components, alterations in endothelial factors and changes in metabolic pathways in myocardial and vascular smooth muscle cells.

It will be especially important to study female subjects further since a much smaller proportion of females exhibited a high exercise systolic blood pressure when compared with male subjects. In particular it will be necessary to determine whether different criteria need to be developed for males and females with respect to the criterion level for identifying an exaggerated systolic blood pressure response to exercise.

Increasing attention is being paid to systolic pressure, as opposed to diastolic pressure, as a predictor of cardiovascular changes, in view of the relationship of systolic pressure to such physiological parameters as arterial stiffness. It will, therefore, also be of interest to determine if arterial stiffening, which is probably the consequence of repetitive cyclic stress and is the principle cause of increased systolic blood pressure in hypertensive individuals, is more pronounced in those with high exercise systolic blood pressure than in those without.

The Icelandic-Canadian Study will provide an ongoing opportunity for pursuing these and other lines of research.

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Table 1 Distribution of Male Subjects by Age

Age (years)	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
20-29	6	8	6	9
30-39	20	26	24	35
40-49	25	32	19	28
50-59	20	26	14	21
60+	6	8	5	7
Total	77	100	68	100

Table 2 Distribution of Male Subjects by Occupation

Occupation*	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Managerial, administrative	15	20	11	17
Social and natural sciences, engineering, mathematics, religion, teaching	5	7	3	5
Medicine, health, sports, recreation	1	1	1	2
Clerical	4	5	3	5
Sales	4	5	4	6
Farming, fishing logging,	9	12	2	3
Processing	20	26	19	29
Transportation, equipment operators	18	23	20	30
Unemployed	1	1	2	3
Total	77	100	65	100

* Three subjects not employed (retired); Interlake = 1(1%), Selfoss = 2(3%).

Table 3 Distribution of Male Subjects by Marital Status

Marital	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Married	69	90	55	81
Single	7	9	8	12
Widowed	1	1	1	1
Divorced	0	0	4	6
Total	77	100	68	100

Table 4 Distribution of Male Subjects by Smoking Habit

Smoking habit	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Current	23	30	23	34
Past	34	44	23	34
Never	20	26	22	32
Total	77	100	68	100

Table 5 Mean and Standard Deviation of Clinical Data of Male Subjects

Clinical Data	Interlake Subgroup IA N=77	Selfoss Subgroup IIA N=68	p value*
Age(years)	46 ± 11	43 ± 10	.10
Height (cms)	177 ± 6	179 ± 6	.10
Weight (kgs)	87 ± 13	85 ± 13	.17
BMI (kg/ht ²)	28 ± 4	25 ± 4	.02
BSA(kg/m ²)	2 ± .2	2 ± .2	.53
SBP supine(mmHg)	130 ± 12	129 ± 11	.61
DBP supine(mmHg)	80 ± 7	81 ± 7	.14
ESBP max(mmHg)	204 ± 21	194 ± 20	.006
HR rest(b/min)	67 ± 9	66 ± 9	.39
HR exercise(b/min)	157 ± 14	139 ± 18	.0001
Stroke volume(ml)	125 ± 35	127 ± 31	.83
Cardiac Index(L/m ²)	4 ± 1	4 ± 1	.80
Periph Res(mmHg/L)	13 ± 3	3 ± 3	.93
Workload(watts)**	146 ± 32	153 ± 39	.24
FH-Ht (≤ 55 yrs)	25 %	45 %	.02

* p value= the level of significance of a two sample t test; a probability ≤ 0.05 is considered significant; ** watt, [unit of power (work/time)] = 1 joule . s⁻¹ = 6.12 kpm . min⁻¹; Abbreviations: BMI=body mass index; BSA= body surface area;SBP=systolic blood pressure; DBP= diastolic blood pressure;ESBP=exercise SBP; HR= heart rate; b/min= beats /minuye; Periph Res=peripheral resistance; FH-Ht= family history of hypertension.

Table 6 Mean and Standard Deviation of Echocardiographic Variables of Male Subjects

Echo variables	Interlake Subgroup IA	Selfoss Subgroup IIA	p value*
LVMl (g/m ²)	91 ± 22 (65)	95 ± 34 (64)	.41
LVEDD (mm)	54 ± 5 (73)	54 ± 4 (63)	.67
LVEDDI (mm/m ²)	27 ± 3 (73)	27 ± 2 (63)	.90
LVESD(mm)	35 ± 5 (71)	34 ± 4 (67)	.15
LVlVS (mm)	7 ± 1 (67)	8 ± 2 (64)	.15
LVPW (mm)	8 ± 1 (68)	8 ± 2 (64)	.69
LVlVS/LVPW	.9 ± .1 (65)	1 ± .1 (64)	.09
LADI (cm/m ²)	1.9 ± .2 (73)	1.8 ± .2 (67)	.02
FS (percent)	36.0 ± 5.6 (71)	37.6 ± 5.7 (64)	.09

*p value-see legend Table 5; the figures in parentheses represent the number of subjects in each category. Abbreviations: LVMl= left ventricular mass index; LVEDD= LV end diastolic dimension; LVEDDI= LV end diastolic dimension index; LVESD= LV end systolic dimension; LVlS= LV interventricular septum;LVPW= LV posterior wall; LADI= left atrial index; FS= fractional shortening.

Table 7 Distribution of Male Subjects by ESBP

ESBP (mmHg)	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
< 190	15	19	30	44
190-199	17	22	12	18
200-209	13	17	10	14
≥ 210	32	42	16	24
Total	77	100	68	100

Table 8 Distribution of Male Subjects in the Interlake by ESBP and Resting SBP

Resting SBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 140	*15	14	13	17	59
	**100	82	100	53	
140-159	0	3	0	15	18
	0	18	0	47	
Total	15	17	13	32	77
	19	22	17	42	100

The figures in each cell are:

* Frequency

** Column percent

Table 9 Distribution of Male Subjects in Selfoss by ESBP and Resting SBP

Resting SBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 140	*27	10	7	7	51
	**93	77	70	53	
140 - 159	2	3	3	9	17
	7	23	30	56	
Total	29	13	10	16	68
	44	18	14	24	100

The figures in each cell are:

* Frequency

** Column percent

Table 10 Distribution of Male Subjects in the Interlake by ESBP and Resting DBP

Resting DBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 90	*15	13	12	26	66
	**88	87	92	81	
90 -95	2	2	1	6	11
	12	13	8	19	
Total	17	15	13	32	77
	22	19	17	42	100

The figures in each cell are:

* Frequency

** Column percent

Table 11 Distribution of Male Subjects in Selfoss by ESBP and Resting DBP

Resting DBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 90	*28	9	6	10	53
	**90	67	60	64	
90 - 95	1	4	4	6	15
	10	23	40	36	
Total	29	13	10	16	68
	44	17	15	24	100

The figures in each cell are:

* Frequency

** Column percent

Table 12 LADI According to ESBP in Interlake Male Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LADI cm/m ² (mean ± sd)	1.81 ±.23	1.87±.11	1.90±.21	1.87±.19
no. of subjects	16	14	44	74

Mean difference between exercise levels is not significant (p value=0.29)

Table 13 LADI According to ESBP in Selfoss Male Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LADI cm/m ² (mean ± sd)	1.75±.18	1.77±.13	1.86±.24	1.79±.20
no. of subjects	16	14	44	74

Mean difference between exercise levels is not significant (p value=0.16)

Table 14 LVMI According to ESBP in Interlake Male Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LVMI gm/m ² (mean ± sd)	84.75±21	84.70±20	95.26±23	91.00±22
no. of subjects	13	14	38	65

Mean difference between exercise levels is not significant (p value=0.22)

Table 15 LVMI According to ESBP in Selfoss Male Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LVMI gm/m ² (mean ± sd)	85.8±16	86.0±11	110.6±48	95.4±34
no. of subjects	28	13	16	67

Mean difference between exercise levels is not significant (p value=0.05)

Table 16 Univariate Correlation Coefficients Relating Male Subject Clinical Characteristics for Dependent Variables: LADI and LVMI

	LADI (cm/m ²)		LVMI(g/m ²)	
	Interlake N = 74	Selfoss N = 65	Interlake N = 65	Selfoss N = 67
Age (yr)	.15	.31 **	.30 **	.38 ***
BMI (kg/m ²)	.07	.14	.09	.13
Supine SBP (mmHg)	.18	.20	.12	.31 **
Supine DBP (mmHg)	.05	.10	.04	.03
ESBP (mmHg)	.23 *	.27 *	.33 **	.31 **
HR rest(b/min)	.07	.19	.04	.10
HR exercise (b/min)	.13	.17	.32 **	.22
FS (percent)	.0006	.06	.06	.13
Cardiac Index (L/m ²)	.43 ***	.34 **	.57****	.50****
Periph Res (mmHg/L/min)	-.18	-.15	-.19	-.14
Work Load (watts)	-.23 *	-.23*	-.02	-.20

Abbreviations as in legends for Tables 5 and 6 ; * $p \leq 0.05$; ** $p \leq 0.01$;
 *** $p \leq 0.001$; **** $p \leq 0.0001$.

Table 17 Parameters of the Final Multiple Linear Regression Model for Prediction of LADI (cm/m²) for Males in the Interlake

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP (mmHg)	0.0024	.27
Workload (watts)	-0.0020	-.34
Cardiac Index(L/m ²)	0.0828	.46
Intercept	1.3605	
R ² for model = 0.38 p<0.0001		

Abbreviations as in legend for Table 5.

Table 18 Parameters of the Final Multiple Linear Regression Model for Prediction of LADI (cm/m²) for Males in Selfoss

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP (mmHg)	0.0025	.26
Occupation (6-8)	-0.1021	-.25
Cardiac Index(L/m ²)	0.0628	.35
Intercept	1.1205	
R ² for model = 0.21 p<0.0056		

Abbreviations as in legend for Table 5.

Table 19 Parameters of the Final Multiple Linear Regression Model for Prediction of LVMI (gm/m^2) for Males in the Interlake

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP (mmHg)	0.2170	.21
HR exercise (b/min)	0.2637	.17
Cardiac Index(L/m^2)	13.6850	.66
Intercept	32.1318	
R^2 for model =	0.47	$p < 0.0001$

Abbreviations as in legend for Table 5.

Table 20 Parameters of the Final Multiple Linear Regression Model for Prediction of LVMI (gm/m^2) for Males in Selfoss

Variable	Regression Coefficient	Standardized Regression Coefficient
Age (years)	0.0565	.17
ESBP (mmHg)	0.2455	.15
Cardiac Index(L/m^2)	14.0232	.44
Intercept	24.0911	
R^2 for model = 0.51 $p < 0.0001$		

Abbreviations as in legend for Table 5.

Table 21 Distribution of Female Subjects by Age

Age (years)	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
20-29	6	10	7	11
30-39	15	30	25	37
40-49	16	26	18	27
50-59	24	34	17	25
Total	61	100	67	100

Table 22 Distribution of Female Subjects by Occupation

Occupation*	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Managerial, administrative	2	3	4	6
Social and natural sciences, engineering, mathematics, religion,teaching	11	15	4	6
Medicine, health, sports,recreation	7	10	1	1
Clerical	13	18	13	19
Sales	7	10	6	9
Farming, fishing, logging	6	8	6	9
Processing	4	6	18	27
Transportation, equipment operators	0	0	4	6
Total	50	82	56	83

* Twenty-two subjects not employed; Interlake = 7 (12%) housewives, 4 (6%) retired; Selfoss = 10 (15%) housewives, 1(1%) retired.

Table 23 Distribution of Female Subjects by Marital Status

Marital Status	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Married	56	92	62	93
Single	0	0	0	0
Widowed	3	5	2	3
Divorced	2	3	3	4
Total	61	100	67	100

Table 24 Distribution of Female Subjects by Smoking Habit

Smoking Habit	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
Current	23	37	28	43
Past	18	30	13	19
Never	20	33	26	38
Total	61	100	67	100

Table 25 Mean and Standard Deviation of Clinical Data of Female Subjects

Clinical Data	Interlake Subgroup IA N = 61	Selfoss Subgroup IIA N = 67	p value*
Age(years)	44 ± 10	40 ± 10	.06
Height (cms)	164 ± 5	166 ± 5	.03
Weight (kgs)	74 ± 16	73 ± 13	.72
BMI (kg/h ²)	27 ± 6	26 ± 4	.27
BSA(kg/m ²)	2 ± .2	2 ± .2	.77
SBP supine(mmHg)	123 ± 13	122 ± 15	.61
DBP supine(mmHg)	78 ± 9	78 ± 8	.92
ESBP max(mmHg)	188 ± 26	180 ± 21	.06
HR rest(b/min)	71 ± 10	69 ± 9	.32
HR exercise(b/min)	162 ± 11	147 ± 16	.0001
Stroke volume(ml)	98 ± 24	95 ± 21	.06
Cardiac Index(L/m ²)	3.8 ± 1	3.6 ± 1	.20
Periph Res(mmHg/L)	14 ± 4	15 ± 4	.37
Workload(watts)**	97 ± 19	103 ± 29	.20
FH-Ht (≤ 55 yrs)	45 %	37 %	.10

* p value= the level of significance of a two sample t test; a probability ≤ 0.05 is considered significant** watt, [unit of power (work/time)] = 1 joule . s⁻¹ = 6.12 kpm . min⁻¹; Abbreviations: as in Legend for Table 5

Table 26 Mean and Standard Deviation of Echocardiographic Variables of Female Subjects

Echo Variables	Interlake Subgroup IA	Selfoss Subgroup IIA	p value*
LVMI (g/m ²)	74 ± 15 (55)	69 ± 16 (62)	.09
LVEDD (mm)	49 ± 4 (61)	49 ± 3 (63)	.45
LVEDDI (mm/m ²)	28 ± 2 (61)	27 ± 2 (62)	.35
LVESD(mm)	31 ± 4 (61)	30 ± 3 (61)	.34
LVIVS (mm)	6 ± 1 (55)	6 ± 2 (63)	.15
LVPW (mm)	7 ± 1 (58)	6 ± 1 (67)	.06
LVIVS/LVPW	.9 ± .1 (60)	1 ± .1 (63)	.09
LADI (cm/m ²)	1.87 ± .18 (55)	1.78 ± .2 (67)	.01
FS (percent)	37.8 ± 5.2 (61)	38.4 ± 5.7 (62)	.53

p value(see legend Table 5);the figures in parentheses represent the number of subjects in each category. Abbreviations: LVMI= LV mass index; LVEDD= LV end diastolic dimension; LVEDDI= LV end diastolic dimension index; LVESD= LV end systolic dimension; LVIS= LV interventricular septum;LVPW= LV posterior wall; LADI= left atrial index; FS=fractional shortening.

Table 27 Distribution of Female Subjects by ESBP

ESBP (mmHg)	Interlake Subgroup IA		Selfoss Subgroup IIA	
	N	%	N	%
< 190	33	54	47	70
190 -199	8	13	7	10
200-209	5	8	5	7
≥ 210	15	25	8	13
Total	61	100	67	100

Table 28 Distribution of Female Subjects in the Interlake by ESBP and Resting SBP

Resting SBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 140	*32	7	5	11	55
	**97	88	100	73	
140-159	1	1	0	4	6
	3	12	0	27	
Total	33	8	5	15	61
	54	13	8	25	100

The figures in each cell are:

* Frequency

** Column percent

Table 29 Distribution of Female Subjects in Selfoss by ESBP and Resting SBP

Resting SBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 140	*45	4	3	3	55
	**96	75	60	38	
140-159	2	3	2	5	12
	4	25	40	62	
Total	47	7	5	8	67
	70	10	7	13	100

The figures in each cell are:

* Frequency

** Column percent

Table 30 Distribution of Female Subjects in the Interlake by ESBP and Resting DBP

Resting DBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 90	*33	7	5	11	56
	**100	88	100	73	
90-95	0	1	0	4	5
	0	12	0	27	
Total	33	8	5	15	61
	54	13	8	25	100

The figures in each cell are:

* Frequency

** Column percent

Table 31 Distribution of Female Subjects in Selfoss by ESBP and Resting DBP

Resting DBP (mmHg)	ESBP (mmHg)				Total
	<190	190-199	200-209	>210	
< 90	*41	5	5	4	55
	**87	71	100	50	
90-95	6	2	0	4	12
	13	29	0	50	
Total	47	7	5	8	67
	70	10	7	13	100

The figures in each cell are:

* Frequency

** Column percent

Table 32 LADI According to ESBP in Interlake Female Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LADI cm/m ² (mean ± sd)	1.86 ± .22	1.99 ± .16	1.85 ± .21	1.88 ± .18
no. of subjects	33	8	20	61

Mean difference between exercise levels is not significant (p value=0.41)

Table 33 LADI According to ESBP in Selfoss Female Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LADI cm/m ² (mean ± sd)	1.74 ± .21	1.84 ± .15	1.92 ± .15	1.85 ± .20
no. of subjects	47	7	13	67

Mean difference between exercise levels is significant (p value=0.0097)

Table 34 LVMI According to ESBP in Interlake Female Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LVMI gm/m ² (mean ± sd)	68.3 ± 13.0	74.1 ± 11.7	82.6 ± 15.5	74.6 ± 15.5
no. of subjects	31	6	18	55

Mean difference between exercise levels is significant (p value=0.0039)

Table 35 LVMI According to ESBP in Selfoss Female Subjects

	ESBP (mmHg)			Total
	<190	190-199	≥200	
LVMI gm/m ² (mean ± sd)	63.6 ± 11.1	77.6 ± 20.6	83.5 ± 16.9	69.0 ± 16.8
no. of subjects	47	7	13	67

Mean difference between exercise levels is significant (p value=0.0001)

Table 36 Univariate Correlation Coefficients Relating Female Subject Characteristics for Dependent Variables: LADI and LVMI

	LADI (cm/m ²)		LVMI(g/m ²)	
	Interlake N = 61	Selfoss N = 67	Interlake N = 61	Selfoss N = 67
Age (yr)	.10	.29 *	.37 **	.39 **
BMI (kg/h ²)	.17	-.06	.46***	.29 *
Supine SBP rest (mmHg)	.08	.25 *	.50****	.36 **
Supine DBP rest (mmHg)	-.01	-.02	.20	.15
ESBP (mmHg)	.04	.36 **	.52 ****	.40 ***
HR rest(b/min)	.05	.13	.06	.19
HR exercise (b/min)	.03	.16	.35 **	.43 ***
FS (percent)	.07	.20	.04	.02
Cardiac Index (L/m ²)	.22*	.26 *	.26 *	.35 **
Periph Res (mmHg/L/min)	-.18	-.15	-.19	-.20
Work Load (watts)	-.13	-.19	-.01	-.29 *

Abbreviations as in legends for Tables 5 and 6 ; * $p \leq 0.05$; ** $p \leq 0.01$;
 *** $p \leq 0.001$; **** $p \leq 0.0001$.

Table 37 Parameters of the Final Multiple Linear Regression Model for Prediction of LADI (cm/m²) for Females in the Interlake

Variable	Regression Coefficient	Standardized Regression Coefficient
FH-HT	0.1290	.33
Occupation(6-8)	-0.0181	-.33
Exercise Workload (watts)	-0.0027	-.27
Cardiac Index (L/m ²)	0.0710	.39
Intercept	1.7655	
R ² for model = 0.29 p<0.0008		
Abbreviations as in legend for Table 5.		

Table 38 Parameters of the Final Multiple Linear Regression Model for Prediction of LADI (cm/m²) for Females in Selfoss

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP (mmHg)	0.00296	.31
Cardiac Index (L/m ²)	0.05657	.30
Intercept	1.036	
R ² for model = 0.27 p<0.0053		
Abbreviations as in legend for Table 5.		

Table 39 Parameters of the Final Multiple Linear Regression Model for Prediction of LVMI (g/m^2) for Females in the Interlake

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP(mmHg)	0.2951	.51
FH-HT	5.4531	.18
Exercise Workload (watts)	-0.1580	.20
Cardiac Index (L/m^2)	7.8695	.54
Intercept	0.2519	

R^2 for model =	0.53	$p < 0.0001$

Abbreviations as in legend for Table 5.		

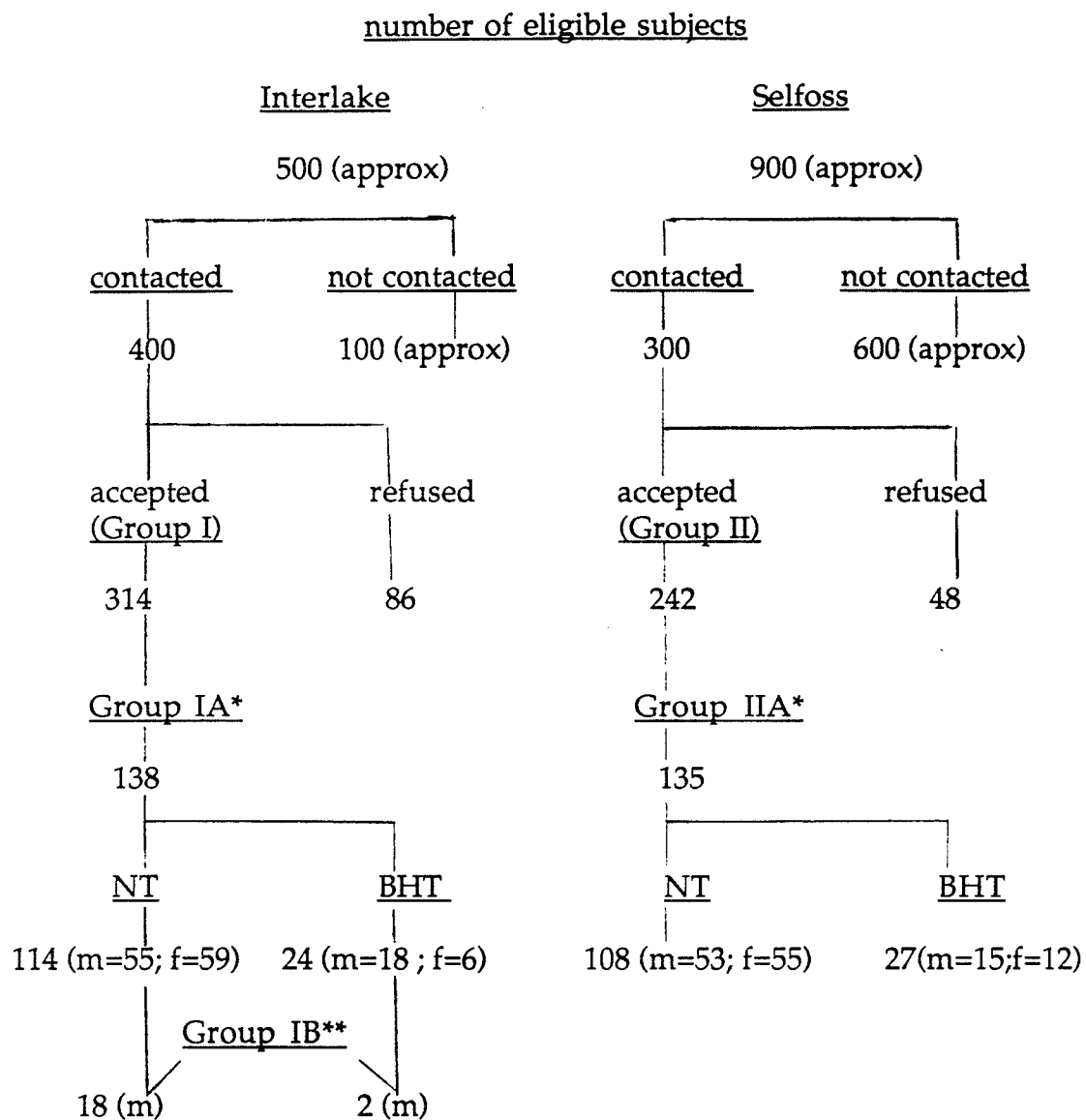
Table 40 Parameters of the Final Multiple Linear Regression Model for Prediction of LVMI (g/m^2) for Females in Selfoss

Variable	Regression Coefficient	Standardized Regression Coefficient
ESBP (mmHg)	0.1965	.25
HR exercise(b/min)	0.3257	.33
Cardiac Index (L/m^2)	6.1923	.41
Intercept	60.3181	

R^2 for model =	0.38	$p < 0.0001$

Abbreviations as in legend for Table 5.

Figure 1 Population Sampling Frame



Abbreviations: m= males; f=females; NT=normotensive; BHT= borderline hypertensive.

* see section 6.2.1 for criteria for selecting Groups IA and IIA

** see section 7.3 for criteria for selecting Group IB

Figure 2 Procedures Flow Chart for Sampling Frame

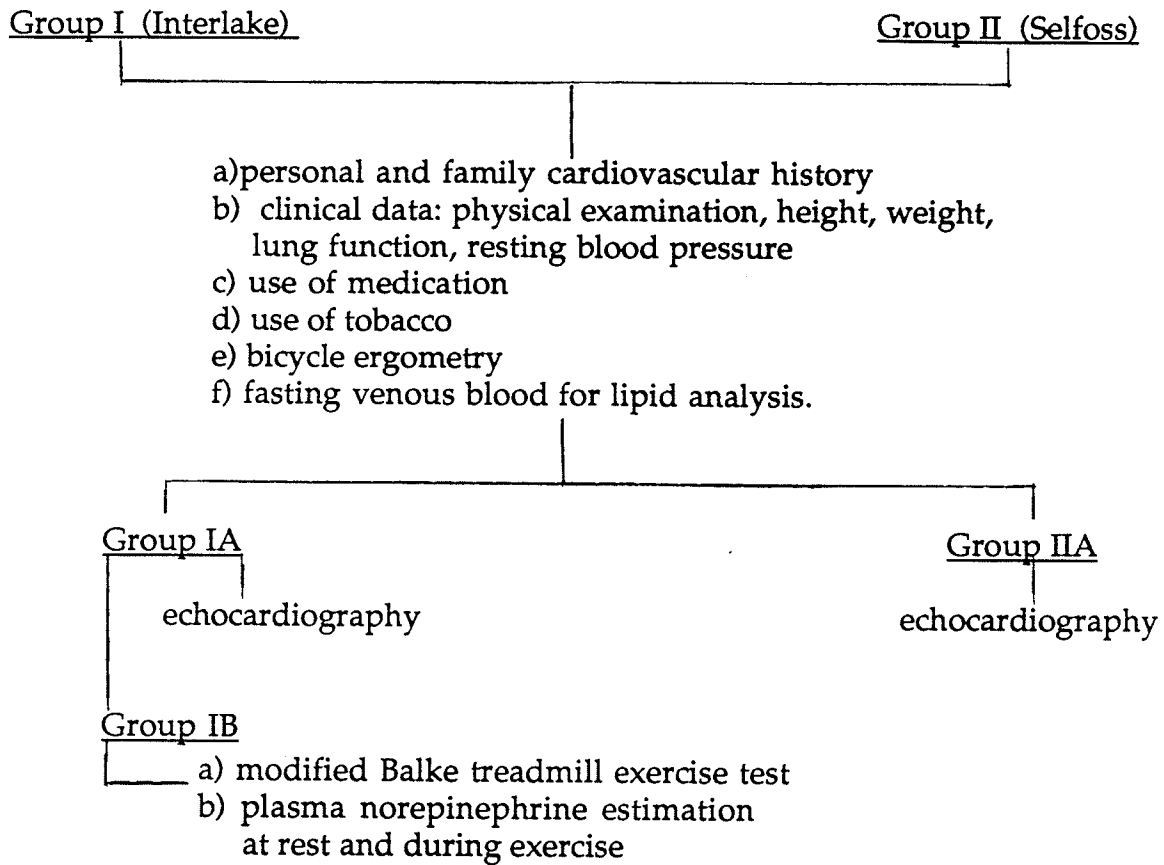
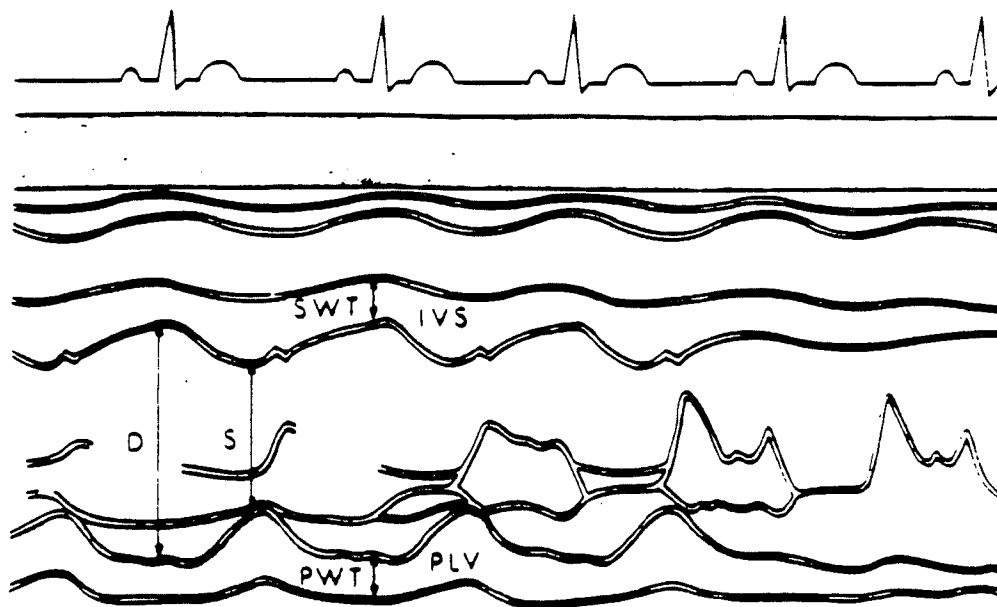


Figure 3 Diagram of the M-mode Echocardiogram*



Left ventricular measurements as recommended by the American Society of Echocardiography are shown. D = left ventricular diastolic dimension; S = left ventricular systolic dimension; SWT = septal wall thickness; IVS = interventricular septum; PWT = posterior left ventricular wall thickness; PLV = posterior left ventricular wall.

(* reproduced with permission from: Feigenbaum, D. Echocardiography Lea & Febiger, Philadelphia 1986)

Figure 4 Left Ventricular Mass Index for Males in the Interlake and Selfoss

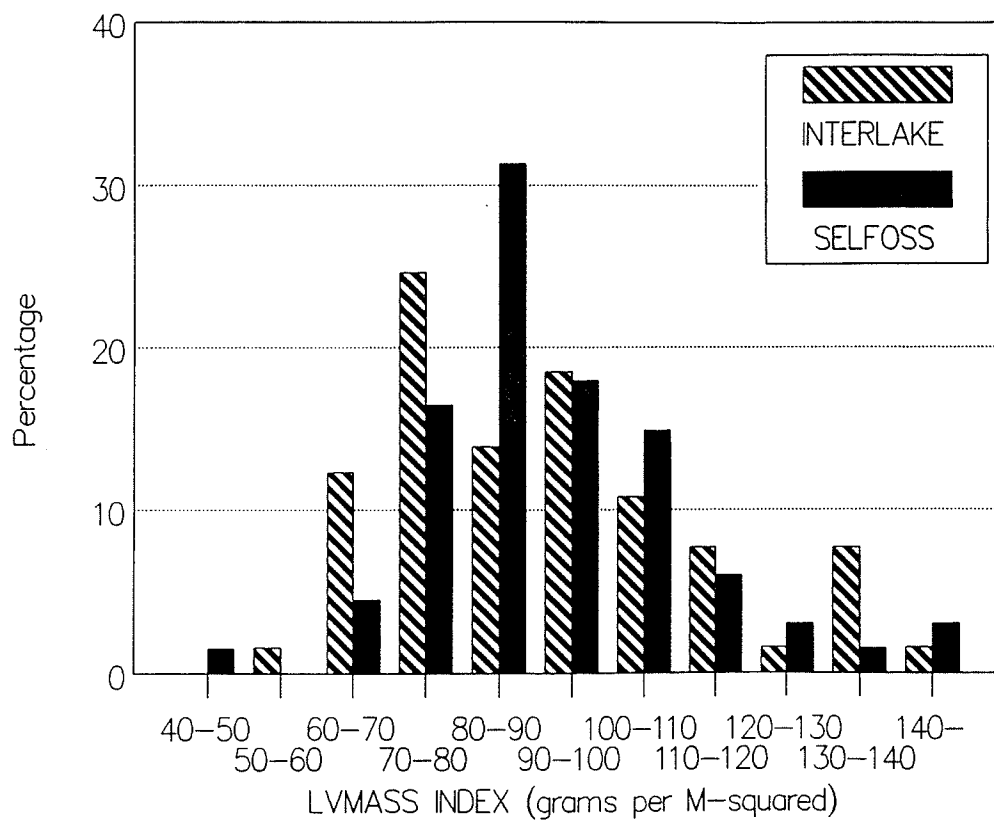


Figure 5 Left Atrial Dimension Index for Males in the Interlake and Selfoss

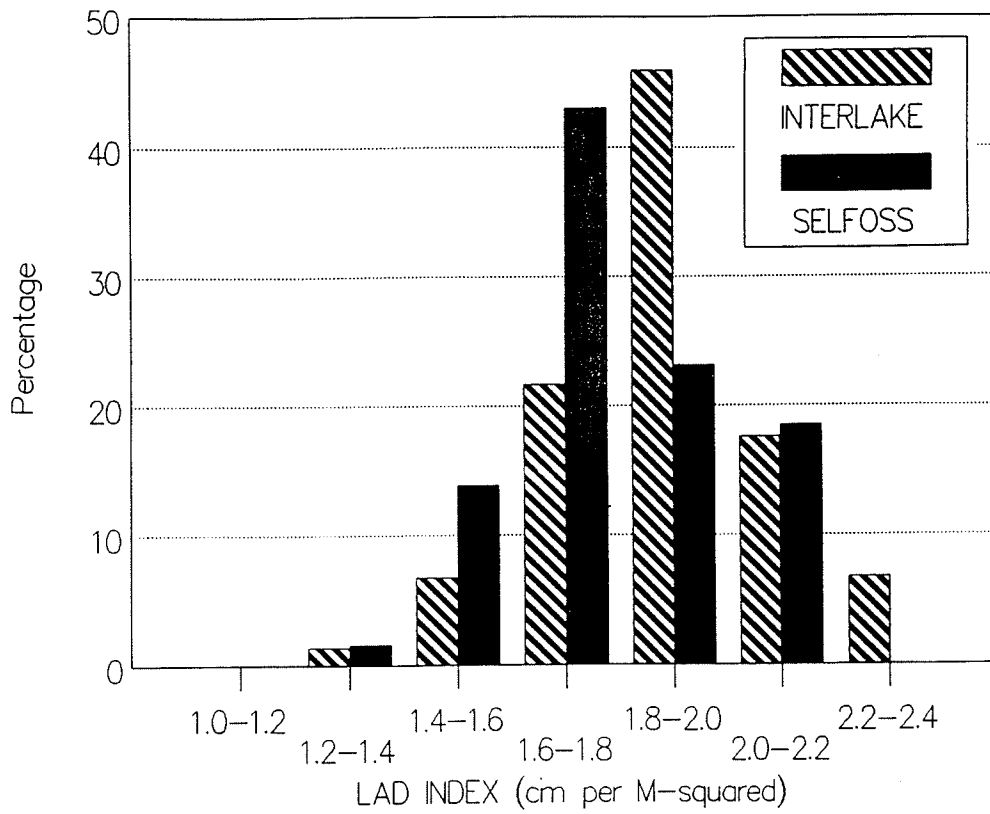


Figure 6 Left Ventricular Mass Index for Females in the Interlake and Selfoss

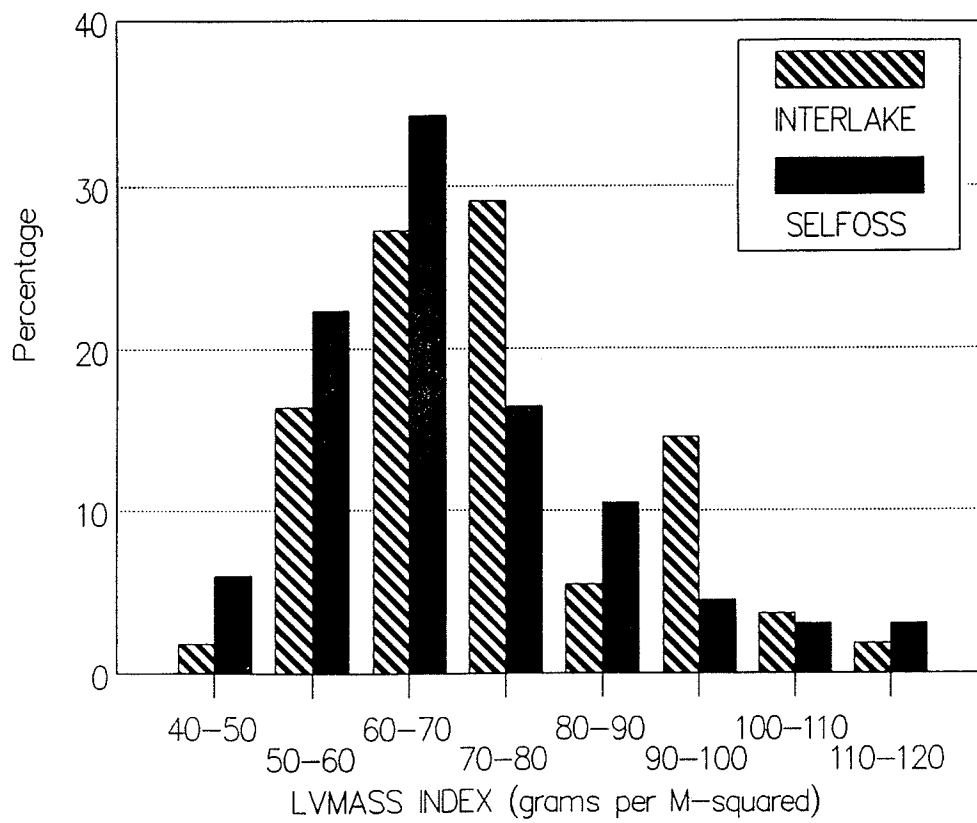


Figure 7 Left Atrial Dimension Index for Females in the Interlake and Selfoss

