UNIVERSITY OF SOUTHAMPTON

RELATION OF FETAL GROWTH TO ADULT CORONARY HEART DISEASE: A STUDY OF LEFT VENTRICULAR MASS AND ARTERIAL COMPLIANCE IN SOUTH INDIAN ADULTS

Retrospective cohort study of men and women born in Mysore, South India during 1934-53

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AUTHOR'S CONTRIBUTION

I was involved with the planning, fieldwork, data collection and part of the analysis and writing up from the first Mysore study which was led by Dr Claudia Stein under the guidance of Dr Caroline Fall. In the follow up study, I led the project team. I performed all the echocardiography and arterial compliance measurements myself after undergoing appropriate training. I carried out the statistical analysis and interpretation of the data myself, with assistance from Dr Caroline Fall, Dr Christopher Martyn and Miss Rosie Shier. I typed the thesis and prepared the manuscript with help from Mrs Jane Pearce.

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ABSTRACT

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RELATION OF FETAL GROWTH TO ADULT CORONARY HEART DISEASE: A STUDY OF LEFT VENTRICULAR MASS AND ARTERIAL COMPLIANCE IN SOUTH INDIAN ADULTS

By K Kumaran

Studies in the UK, Europe, USA and India have shown that low birthweight and other indices of reduced fetal growth are associated with an increased risk of coronary heart disease (CHD) in adult life. Small size at birth has also been associated with risk factors for the disease, including increased left ventricular (LV) mass and reduced arterial compliance. During 1993-95, a study on 517 men and women born in the Holdsworth Memorial Hospital, Mysore, South India between 1934 and 1953, and whose weight, length and head circumference at birth had been recorded, showed that small size at birth was associated with an increased rate of CHD. I examined the hypothesis that the link between reduced fetal growth and adult CHD in this population is mediated by increased LV mass and reduced arterial compliance.

In the follow-up study of 435 men and women during 1996-97, I measured systolic and diastolic blood pressures, LV mass (using 2D and M-mode echocardiography) and compliance in three arterial segments (derived from pulse wave velocity {PWV} using the non-invasive technique of photoplesythmography; higher the PWV, lower the compliance).

The mean LV mass was 149 g (SD 37) in men and 125 g (SD 32) in women. The mean PWV was 4.14 m/s in the aorto-radial, 3.28 m/s in the aorto-femoral and 13.59 m/s in the femoro-postreior tibial segments. Higher LV mass was associated with an increased risk of CHD ($p=0.05$). LV mass and PWV were positively correlated with each other and with systolic and diastolic blood pressures, non-insulin-dependent diabetes mellitus, plasma glucose, insulin, proinsulin, 32-33 split proinsulin and serum triglyceride concentrations ($p<0.05$ for all), independently of age, sex and body size. In addition, LV mass correlated negatively with fasting serum HDL-cholesterol concentration ($p=0.02$). Unlike studies in Western populations, small size at birth was not associated with increased blood pressure or LV mass, nor with reduced arterial compliance. On the contrary, systolic blood pressure and LV mass were higher in subjects who were longer at birth, rising by 1.64 mm Hg (95% CI – 0.08 to +3.37; $p=0.06$) and 1.63 g/m^2 (95% CI 0.13 to 3.13; $p=0.03$), respectively, per one inch increase in birth length, independently of adult size. Arterial compliance was higher in those whose mothers were lighter ($p=0.02$) or had smaller pelvic (external conjugate) diameters.

Both LV mass and PWV in this Indian population are low compared with Western populations, though as in the West, higher LV mass is associated with an increased risk of CHD. Greater LV mass and reduced arterial compliance are associated with an adverse coronary risk profile, especially with features of the Insulin Resistance Syndrome (hypertension, raised triglycerides and lower HDL-cholesterol, non-insulin-dependent diabetes mellitus and insulin resistance, and central obesity). The higher prevalence of CHD in Indian men and women of lower birthweight, shown in an earlier study of the same cohort, cannot be explained by changes in blood pressure, LV mass or arterial compliance. The association of raised blood pressure and LV mass with longer length at birth suggests that the way in which the intrauterine environment influences CHD differs between Indian and Western populations.

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PUBLICATIONS ARISING FROM THE WORK DESCRIBED IN THIS THESIS

1. Kumaran K, Fall CHD, Martyn CN, Vijayakumar M, Stein C, Shier R. Blood pressure, arterial compliance, and left ventricular mass: no relation to small size at birth in South Indian adults. *Heart* 2000; **83**: 272-7.

2. Kumaran K, Fall CHD, Martyn CN, Vijayakumar M, Stein C, Shier R. Left ventricular mass and arterial compliance: relationship to coronary heart disease and its risk factors in South Indian adults. *Int J Cardiol 2002;* **83**: 1-9.

ABBREVIATIONS

BMI	Body mass index
BSA	Body surface area
CHD	Coronary heart disease
CI	Confidence interval
cm	Centimetre
EC	External conjugate
ECG	Electrocardiogram
g	Gram
IC	Intercristal
IS	Interspinous
kg	Kilogram
l	Litre
lb	Pound
LV mass	Left ventricular mass
LVH	Left ventricular hypertrophy
m	Metre
mm	Millimetre
mmol	Millimoles
nmol	Nanomoles
pmol	Picomoles
PWV	Pulse wave velocity

Chapter 1 INTRODUCTION

Part I – Coronary heart disease

1.1 Global importance of coronary heart disease

Worldwide, coronary heart disease (CHD) accounted for approximately 6.3 million out of a total of 50.5 million deaths in 1990 (1). It is a major cause of mortality in most countries. As well as being the leading cause of death, CHD also causes considerable disability. The two major categories of cardiovascular disease, CHD and stroke presently account for 9.7% of global DALYs (disability adjusted life years, the sum of years lived with disability and the number of years of life lost due to premature mortality) (2).

1.2 The pathology of coronary heart disease

CHD occurs due to the atherosclerotic narrowing of the coronary arteries (3). This results in the obstruction of blood supply to the myocardium leading to myocardial ischaemia and, consequently, to angina. The narrowing may be further complicated by thrombo-embolic events, leading to myocardial infarction and death.

There is some argument that the process of atherosclerosis begins early in life with the formation of 'fatty streaks'. These are made up of macrophages, monocytes, smooth muscle cells and lipid cells in the intima of the arterial wall (4). They have been observed at about 10 years of age in the coronary arteries but as early as one year of age in the aorta (5). Fatty streaks occur in all populations irrespective of gender or adult coronary heart disease rates (5). They appear to cause no obstruction and it is unclear whether they are precursors of atherosclerosis.

The atherosclerotic fibrous plaque appears around 20 years of age and is characterised by the proliferation of smooth muscle cells and accumulation of lipid rich plaques, macrophages and connective tissue in the thickened intima of coronary vessels which

protrude into the lumen of the artery (6). Complications such as ulceration, thrombosis, haemorrhage and mineralisation may occur in these lesions after 30 years of age, leading to angina or myocardial infarction (6). Although the exact mechanisms are unclear, the most widely accepted explanation for the process of atherosclerosis is the 'response to injury' hypothesis (3). This proposes that it is a response to metabolic or structural injury to the arterial endothelium. It suggests that biochemical (e.g., free radicals) or mechanical (e.g., raised blood pressure) damage leads to the proliferation of smooth muscle cells and infiltration by macrophages and lipid cells (3). Continued endothelial damage stimulates thrombus formation (3).

1.3 Epidemiological features

1.3.1 Time trends - rise and fall of coronary heart disease in Western countries

The changes over time in the incidence of CHD offer an interesting study, the curve broadly resembling that of an epidemic. The incidence rose steeply at the turn of the century in the developed Western nations and soon became the commonest cause of death. In England, the age adjusted mortality from CHD in people aged 40-75 years increased by over 450% between the years 1921 and 1945 (7). While this rise was apparent in both sexes, it was more marked in men than in women. This rise in mortality continued until the early 1970s. In the United States of America, age adjusted mortality rates from CHD showed a doubling in men and women aged 35-74 years between 1940 and the mid 1960s (8).

After this steep rise, rates of the disease are now falling in most developed nations. The decline in CHD mortality in the UK began in 1973-74 and occurred in all districts of England, Wales and Scotland (9). This decline, roughly 12-15% between 1973-74 and 1979-80, was greatest in people aged 35-44 years. By 1985, the overall decline in CHD mortality reached 15% in people aged 30-69 years (10). The fall in CHD mortality began

earlier and was more marked in the USA. Between 1968 and 1976, age adjusted mortality rates from CHD fell by nearly 21% (11-13). This decline continued and the decrease in CHD mortality reached 36% by 1982 (12). The Framingham study, in a comparison of three cohorts of men aged 40-59 years in 1950, 1960 and 1970, showed that there was also a decrease in the incidence of CHD over the years (14). This suggests that the decline in CHD reflects a fall in the incidence of the disease, rather than just improved case survival. There is also good evidence that the trends are not due to changes in diagnosis or classification of disease (11,12).

1.3.2 Geographical variations

There are marked variations in CHD mortality rates between countries and even within different regions in the same country. The disease reached its peak earlier in the United States, and mortality rates began falling almost a decade earlier, than in England. The fall in mortality rates was also more pronounced in USA and Australia when compared to England (14). In the 1940s mortality was higher in London and the southern part of England than in the northern region and Wales (15). This has now reversed; currently mortality is higher in northern England (16). These differences in mortality rates between various regions remain largely unexplained. For example, in the UK, fat consumption and smoking levels failed to explain differences in CHD mortality between towns in the northern and southern regions of the country (17).

1.3.3 Shift in CHD from affluence to poverty

Another interesting change with time has been the relationship of CHD to social class. Initially mortality from CHD was higher in the upper social classes and it was thought to be a disease associated with prosperity (7,15,18). There was a gradual shift with time such that the disease increased steadily in the lower social classes while remaining relatively stable in the higher social classes. This trend continued and in the 1950s CHD

was higher in the lower social classes compared to the upper social class in England (16,18). There were similar trends in other developed countries. Just as the rise was more marked initially in people from the upper social class, so was the decline. Standardised mortality rates (SMRs) in England show an overall decline between the years 1970-72 and 1979-83 (10). While there was a reduction of about 15% in SMRs in people with non-manual occupations in all the regions of England, Scotland and Wales, there was a slight increase in SMRs in people with manual occupations (10). Currently, CHD in the UK seems to be a disease of the lower social classes.

1.4 Aetiology of coronary heart disease: The 'risk factors' concept

While considerable progress has been achieved in the diagnosis and treatment of CHD, its precise aetiology remains obscure. The rapid changes in incidence of CHD over time suggest important environmental causes for the disease, and resulted in a search for environmental factors that might be responsible. Since CHD initially appeared to be a 20th century 'Western' disease, attention was directed to the significant changes in the modern adult lifestyles of people in industrialised countries.

Such changes included an increase in the dietary consumption of fat (especially saturated, mainly animal, fat), obesity, decreased physical activity and an increase in cigarette smoking (19-21). Of these, dietary fat emerged as the main focus of attention. Populations which consumed a high fat diet tended to have higher mean concentrations of total and LDL cholesterol in comparison to populations whose diet contained low levels of fat (19,20,22). Further studies showed that the prevalence of atherosclerosis was also higher in populations with a high fat content in their diet compared to populations with a low fat diet (19,20). A strong association was demonstrated between hypercholesterolaemia and increased rates of atherosclerosis and CHD (23,24). Evidence showed that the atherosclerotic lesion was an accumulation of lipids including

free and esterified cholesterol (19). All these findings led to lipids being implicated in the aetiology of atherosclerosis and CHD and an increased intake of saturated dietary fat and cholesterol was therefore considered detrimental (19-21). This was supported by evidence from studies showing that a lowering of serum cholesterol concentrations was accompanied by a reduction in CHD mortality (21,25). Increased levels of triglycerides as well as an increased ratio of total to HDL cholesterol were also associated with an increased risk of CHD (26,27). In fact, some considered dietary fat intake to be the pivotal cause of CHD (19,20,22,23).

However the role of dietary fat as the main cause of CHD is controversial (28,29) and other lifestyle factors were also independently associated with an increased risk of CHD. Obesity was also shown to be associated with a higher risk of CHD (30,31). People who were physically more active had less severe disease and a lower mortality rate from CHD compared to people who were less active (32). Death rates from all causes were higher by 68% in smokers and mortality rates from CHD for smokers were nearly twice that of non-smokers (33-35). All these led to the suggestion that CHD was a result of adult lifestyle and therefore modification of lifestyle would control CHD. In fact, the fall in CHD over the past three decades has been attributed to a decrease in dietary fat intake and reduction of smoking rates (12,13,19,36).

Apart from 'lifestyle' factors, a number of physical and metabolic factors have been shown to be associated with CHD. These include hypertension, diabetes mellitus, hyperinsulinaemia, raised levels of clotting factors and central obesity (19-21,37-43). Raised systolic and diastolic blood pressure have been independently associated with an increased risk of CHD (19-21,37). Raised plasma insulin concentrations and diabetes have also been linked to higher rates of CHD as well as with increased concentrations of serum triglycerides, serum total and LDL cholesterol, and decreased HDL cholesterol

(38-43). In addition, other risk factors that have been identified include a family history of CHD, male sex, lower social class, short stature and stress. Recent studies have also demonstrated associations between CHD and raised levels of homocysteine (44), with Chlamydia pneumoniae infection (45), and with reduced antioxidant levels (46). There are also interactions between metabolic and lifestyle factors: obesity is associated with diabetes, hypertension and an adverse lipid profile; smokers have higher levels of clotting factors; and diabetics are also more prone to be hypertensive.

All these findings have led to the 'risk factor' concept. The above mentioned variables are associated with an increased risk of developing CHD but no single variable is the *'cause'* of CHD. CHD is considered a multifactorial disease which people may or may not develop depending upon the number of risk factors they accumulate or avoid. This is supported by the fact that higher levels of risk factors predict more disease (19-21,37) and a reduction in risk factor levels decreases the risk of CHD, as shown by the MRFIT and European Multiple Risk Factor Intervention trials (47,48).

1.5 Known risk factors do not fully explain the epidemiology of CHD

The known risk factors do not, however, accurately predict the occurrence of CHD within individuals (49), geographical variations in the incidence of CHD (20,37), and changes in the incidence of CHD with time, especially the recent decline. For a man falling into the lowest risk groups for smoking, serum cholesterol levels, blood pressure and pre-existing symptoms of CHD, the most common cause of death in still CHD, at least in the UK (50). Differences in blood pressure, smoking rates or serum lipid concentrations do not explain the variations in CHD prevalence across the world or within countries (19-21,37).

It is true that medical treatment of CHD has improved over the years, and that the levels of some CHD risk factors such as cholesterol concentrations and smoking rates have

fallen in some populations (36,51). Therefore a combination of primary prevention by modification of lifestyle and secondary prevention by medical treatment of CHD were assumed to be the main reasons for the decline in CHD mortality (51,52). Recommendations were made to bring about changes in lifestyle to shift the population distributions of risk variables and to identify and treat high risk individuals to control CHD (51). Analysis of the beneficial effects of improved medical management of CHD, and control of its known risk factors have failed to however demonstrate conclusively that these factors explain the decline in CHD mortality (53).

1.6 Early life origins of coronary heart disease

After years of being associated with adult lifestyle, it was therefore surprising when epidemiological studies first showed that the origins of CHD could lie with 'poverty' in the early life environment. This was first suggested by Rose who observed that siblings of patients with CHD had a 50% higher infant mortality rate compared with siblings of controls (54). Their parents also had an almost four-fold higher risk of premature death (<45 years) compared to controls. Rose suggested that these findings may reflect poor socio-economic conditions, or that CHD tended to occur in individuals who came from a 'constitutionally weaker stock'. Later, in 1984, a study of civil servants in England showed a 61% increase in CHD for men in the shortest group compared to those in the tallest group, independently of all other risk factors (55). This was attributed to differences in adult height acting as a 'marker for critical factors operating from early in life'.

A study in Norway by Forsdahl first showed that geographical variations in CHD mortality in the 20 counties of Norway between 1964-67 correlated significantly (r=0.79) with infant mortality between 1896-1925 (56). The variations in CHD death rates did not correlate with current infant mortality rates. He suggested that a poor standard of living in early life, for which infant mortality was a surrogate measure, followed by affluence in later life was

a risk factor for CHD. Forsdahl also showed a correlation between current serum cholesterol levels and past infant mortality rates in these communities (57). There were no differences in current standard of living between these areas. He proposed that poverty in childhood and adolescence followed by later prosperity resulted in increased cholesterol levels and therefore increased the risk for CHD.

Soon after that, geographical studies in the UK conducted by the MRC Environmental Epidemiology Unit, Southampton demonstrated that the two to three-fold differences in death rates from CHD in different parts of England and Wales correlated strongly ($r=0.73$) with past differences in infant mortality rates in these areas (58), supplementing the earlier evidence from Norway. CHD mortality correlated with both neonatal and post neonatal mortality in these studies. Low birthweight is an important cause of neonatal mortality while post neonatal mortality is related to poor living conditions.

Barker interpreted these findings as indicating that CHD could have its origins during fetal life, much before exposure to the external world (59). Since low birthweight is a major determinant of neonatal mortality, he suggested that it was the likely link between infant mortality and death from CHD in later life. He proposed that CHD could be the result of maternal undernutrition (due to the effects of poverty) causing fetal undernutrition and undernutrition in infancy. These may increase susceptibility to later affluence. This hypothesis offered an explanation for the change in CHD with regard to socio-economic class. People belonging to upper socio-economic classes would have become affluent earlier and experienced the rise in CHD but would have also benefitted earlier from improvements in maternal undernutrition and fetal growth. People belonging to lower socio-economic class would go through both these phases in a delayed manner.

1.7 Low birthweight - a risk factor for coronary heart disease

To extend this hypothesis, the focus then moved on to studies in individuals and the MRC Environmental Epidemiology Unit, Southampton started a systematic research programme. A study in Hertfordshire, UK showed, for the first time in individuals, an inverse association between weight in infancy and adult coronary heart disease (60). Standardised mortality ratios decreased from 111 in men who weighed less than 18 lb at one year to 42 in those who weighed more than 27 lb. An association between low birthweight and increased CHD mortality was also demonstrated for the first time in the Hertfordshire study (60,61). Standardised mortality rates from CHD in men fell progressively from 102 in groups who weighed less than 5.5 lb at birth to 66 in those who weighed 10 lb or more (60). The corresponding SMRs for women were 83 and 49 (61).

Since then, further studies in the USA, India, Finland and Sweden have shown that reduced growth in utero, as measured by small size at birth, is associated with an increased risk of morbidity and mortality from coronary heart disease (62-65). The associations appear to be with smallness for gestational age (i.e., retarded fetal growth) rather than smallness due to prematurity.

1.8 The 'fetal origins' hypothesis

These findings have led to the "fetal origins" hypothesis proposed by Barker. He suggested that CHD has its origins in fetal life "programming" whereby sub-optimal fetal growth, due to fetal undernutrition during vulnerable periods of development, permanently damages organ structure and/or physiology thus leading to a breakdown of homeostatic mechanisms in later life (66-68). Organs grow mainly during 'critical' periods of rapid cell division during intra-uterine life. This growth depends upon an adequate supply of nutrients. The fetus adapts to a diminished supply of nutrients by slowing the rate of cell division, especially in tissues undergoing 'critical' periods at that time, to get over the crisis. Barker proposed that these adaptations persist and result in the

permanent reduction of cell number, changes in the distribution of cell type or lasting changes in hormonal or metabolic activity, thus leading to the development of disease in adult life (66-68).

1.9 Shape of the body at birth and CHD and its risk factors

It has been demonstrated that as well as birthweight, the shape of the body at birth as indicated by length, head circumference and ponderal index (ratio of birthweight to birth length) is also related to adult CHD. Babies who are thin at birth, as measured by ponderal index, those who have a small head circumference or short length have an increased risk of mortality from CHD (69,70). In addition to its association with CHD, reduced fetal growth has also been linked with higher adult levels of known cardiovascular risk factors. These include hypertension, non-insulin dependant diabetes mellitus, raised serum lipids, raised clotting factors and central obesity (69-80). These risk factors have been associated with low birthweight and also with 'disproportionate' fetal growth as indicated by particular patterns of newborn sizes and shapes. Thin babies with a low ponderal index (weight relative to length^3), babies who were short in relation to their head circumference and babies with a high placental weight relative to birthweight developed raised blood pressure in adult life (75,76). Thin babies also developed non-insulin dependant diabetes and syndrome X (the combination of insulin resistance, non-insulin dependent diabetes, hypertension, central obesity and dyslipidaemia) in adult life (71, 79). A reduced abdominal circumference predicted raised serum cholesterol and fibrinogen levels in adult life (73,74,80). In fact, in many instances, other birth measurements are more strongly related to CHD and its risk factors than birthweight alone. This implies that they provide more information about the important aspects of fetal growth than birthweight alone.

1.10 Fetal growth and shape of the body at birth

The growth velocity for various components of the fetus differ during the course of intrauterine life (81). Increase in crown-heel length occurs rapidly after the 10th week of gestation reaching peak growth velocity around the end of the second trimester. The increase in weight follows a similar pattern except that the peak velocity is reached around 32-34 weeks of gestation. Accumulation of fat occurs mainly in the last 10 weeks of pregnancy. The growth of the head shows a relatively uniform rate of increase throughout pregnancy. The growth of the placenta is greater than that of the fetus during the first half of pregnancy and slows down in the second half of gestation. At 34-36 weeks the growth of the fetus slows down possibly as a result of the available space in the uterus becoming occupied.

Fetal undernutrition during different periods of intrauterine life may affect some parameters of growth more than others, resulting in a variety of new-born shapes and body proportions at birth. The shape of the body at birth may therefore reflect the period of 'hit' during intrauterine growth.

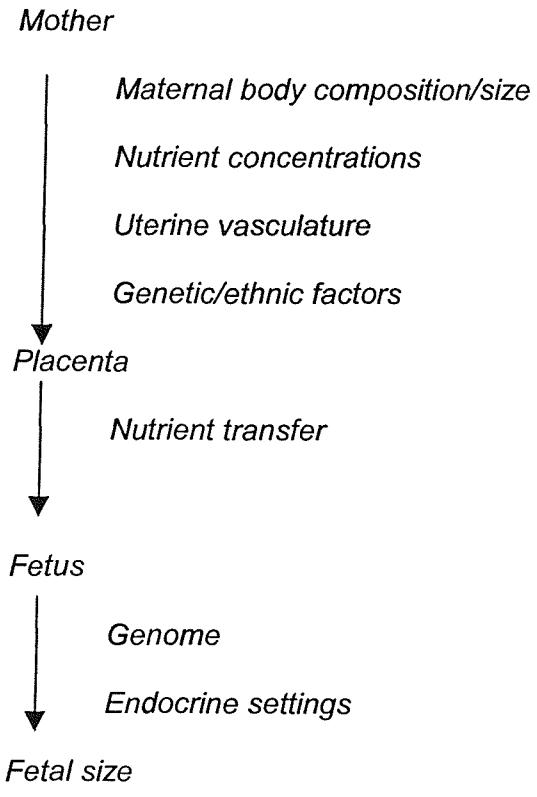
In 1971, after a series of observations on new-borns, Miller et al suggested that intrauterine growth retardation (IUGR) resulted in four patterns of neonatal body shapes (82): abnormally short babies, babies who were long in relation to their head circumference, babies with reduced soft-tissue mass (thin babies), and babies with excess fat or fluid. However this study did not distinguish the timing of the insults that resulted in IUGR. In 1984, Villar et al suggested that there were two main patterns of IUGR new-borns (83): proportionately small babies with normal ponderal index, and disproportionate babies with low ponderal index. He suggested that the first group of babies were born to women who were chronically malnourished and so experienced fetal undernutrition throughout pregnancy while the second group experienced an insult in late gestation. The babies in the second group were more likely to experience catch-up

growth in infancy. More recently Barker has suggested that undernutrition at different periods of intrauterine life produced 3 different phenotypes (84):

1. Undernutrition in early pregnancy leads to a lowered resetting of growth trajectory and results in a proportionately small baby with low birthweight, small head circumference and short length,
2. Undernutrition in mid-pregnancy, as a result of disturbed feto-placental relationship, results in a low birthweight, thin baby and
3. Undernutrition in late pregnancy sustains brain growth at the expense of the trunk and results in a short baby with normal birthweight.

1.10 Factors influencing fetal growth

Fetal growth and size is believed to be influenced by a number of factors. The important influences are shown schematically:



Of these, maternal size has been shown to play the major role in determining the size of the offspring at birth. In a large study containing 25 datasets from all over the world, maternal height, weight and body mass index (BMI) as well as the weight gain during pregnancy predicted birthweight (85). Low maternal pre-pregnant weight was the best predictor, and explained almost 50%, of low birthweight and IUGR (85). Other studies have also shown that maternal anthropometry is a good predictor of the birthweight of the offspring (86-88).

Maternal anthropometry may reflect nutrition; BMI and weight gain during pregnancy are considered indicators of current nutrition while maternal height is considered to be an indicator of childhood nutrition. Weight is a composite of the two. Poor maternal nutrition at these different stages may cause fetal growth retardation, and lead to adult disease in her offspring. At present there are few data available in which disease outcomes can be linked back to measurements of maternal size. Martyn et al showed that smaller maternal pelvic size, which could serve as an indicator of maternal size and nutrition, was associated with an higher risk of stroke in the offspring in adult life (89). A high BMI in mothers of short stature was shown to be associated with increased mortality from CHD in the offspring in a follow-up study of a large cohort in Finland (64).

Race, ethnic origin and genes are believed to influence patterns of fetal growth and size at birth (86). There are wide variations in birthweight and neonatal body proportions around the world (85,86). It is not known whether these reflect ethnic genetic differences or variation in maternal size and nutritional status (86). Studies assessing relative influences of maternal and paternal factors show that it is the maternal factors which play an important role in determining fetal growth while paternal influence is minimal (90). For example, it has been shown that half-siblings born to the same mother have similar birthweights while those born to the same father do not (90). Experiments in which Shire

and Shetland ponies were crossed showed that the foals were larger when the Shire horse was the mother although the genetic composition of the two crosses were similar (91). This may also be because small mothers 'constrained' the growth of their fetuses (92,93). Mothers who were themselves low birthweight babies tend to give birth to low birthweight babies (94). Also mothers who have failed to achieve their full growth potential because of adverse circumstances in their own childhood may produce smaller fetuses (93).

There are associations linking specific genes with birthweight. Recent reports suggest that a common allelic variation (class III) at the variable number of tandem repeat (VTNR) locus in the promoter region of the insulin gene (III/III genotype) was associated with an increase in birthweight (95). This variation has also been associated with insulin resistance and impaired glucose tolerance and diabetes. However these associations are independent of each other suggesting that factors which restrict growth and increase susceptibility to adult disease act independently of the insulin gene VNTR. It has also been suggested that a heterozygous mutation in the glucokinase gene may cause a defect in the sensing of glucose by the pancreas, and cause both low birthweight and hyperglycaemia after birth (96). The sex of the fetal genome also plays a role in birthsize. For example, male infants have been shown to have higher birthweights and a lower risk of intrauterine growth retardation when compared with female infants (85,86). The fetal genome is believed to aim to reach a target size based on its 'growth potential'. Maternal or fetal undernutrition may adversely affect fetal growth leading to smaller size at birth by re-setting of target size (97,98).

The placenta is responsible for feto-maternal exchange and therefore it is not surprising that fetal growth is also believed to be influenced by placental size, structure and function. However the placental mechanisms remain poorly understood. Maternal

undernutrition and smoking may adversely affect placental growth (85-87,99). Recently Godfrey et al showed that women who had a high intake of carbohydrates in early pregnancy followed by a low intake of proteins in late pregnancy tended to have reduced placental size and gave birth to thin infants (100).

Fetal growth is also influenced by endocrine systems. Insulin, insulin-like growth factor 1 (IGF-1), growth hormone and cortisol are important hormones regulating fetal growth (101-106). In adverse conditions, these hormonal axes are altered and may lead to reduced fetal growth. While insulin, IGF-1 and growth hormone mainly affect cell accretion, cortisol affects cell differentiation (101,104). Depending on the timing and extent of insult, fetal growth and maturation are adversely affected at different stages of gestation.

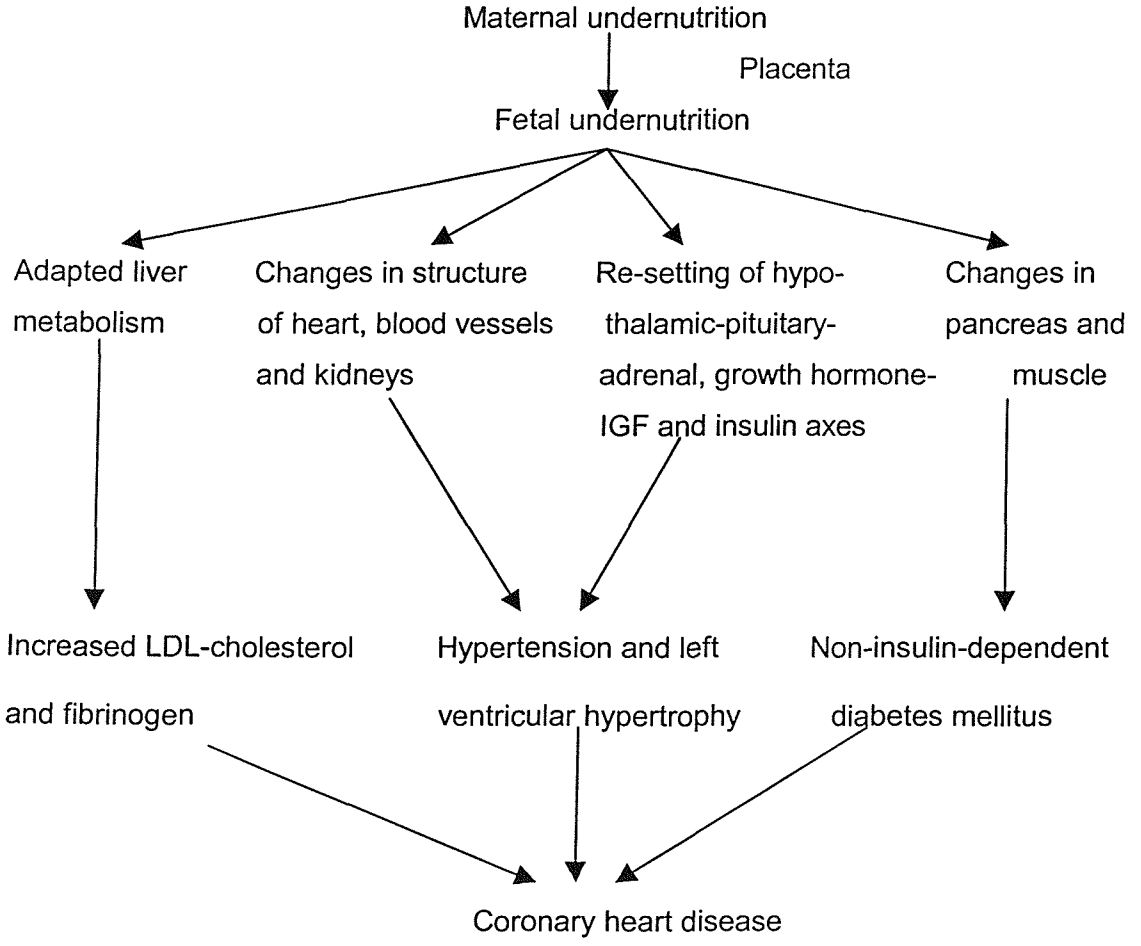
1.11 Proposed mechanisms linking fetal growth to adult disease

Barker has proposed a framework linking fetal growth to adult disease (98). Growth of the fetus is restricted by the nutrients and oxygen it receives from its mother. The fetus adapts to undernutrition by slowing down its rate of growth, alterations in metabolism and hormonal axes with changes in tissue sensitivity, redistribution of blood flow and enlargement of placenta. These changes persist and permanently alter the structure and function of organs leading to adult disease. This may occur through two principal mechanisms:

1. Undernutrition results in alterations in fetal blood flow which lead to preferential perfusion of the brain at the expense of the trunk. If sustained, they may lead to reduced growth of the abdominal organs, reduced muscle mass and stunting at birth. This results in permanently altered structure and function of the liver leading to altered lipid metabolism and raised serum lipid concentrations, the pancreas altering glucose/insulin metabolism and resulting in non-insulin dependent diabetes mellitus,

and kidneys leading to hypertension. Reduced blood flow in the large arteries of the trunk and legs may also be associated with reduced elastin deposition, less compliant arteries and subsequent hypertension. Diversion of oxygenated blood to the brain at the expense of the trunk also increases the load on the heart and peripheral resistance leading to left ventricular hypertrophy and, eventually CHD.

2. Undernutrition results in hormonal alterations and permanent re-setting of the hormonal axes. It may reduce secretion of, and sensitivity to insulin and IGF-1 resulting in re-setting of the IGF-growth hormone and hypothalamic-pituitary-adrenal axes which may persist resulting in hypertension and non-insulin dependent diabetes mellitus, and eventually CHD.



Part II – Coronary heart disease in India

1.12 CHD trends in Indians

Rates of CHD are now rapidly increasing in the developing world including India (107-109). The burden of CHD seems to be shifting to the developing nations (107). While the percentage of deaths attributable to CHD in most developing countries is still less than in developed countries, the absolute numbers of deaths are higher due to the large populations involved (107,108). In India, even the percentage of deaths attributed to CHD is higher than in Western countries (1,107). Another alarming factor is the earlier age of CHD deaths in India compared to the developed countries (107,108).

A recent epidemiological study of coronary heart disease in an urban population of Delhi reported a prevalence of 9.67% in adults between the ages of 25 and 64 (110). The prevalence has increased by about eight times in adult urban populations from 1.05% in 1960 to 9.67% in 1995 (109,111). The rise in rural populations has been less marked, increasing from 2.03% in 1974 to 3.70% in 1995 (109,111).

Indians also seem to have an increased susceptibility to CHD in comparison to other races (112,113). Studies in the UK, Singapore and Trinidad have shown that morbidity and mortality from coronary heart disease is higher in South Asian immigrants than in the general population (114-118). Mortality due to CHD in Indians living in the UK is 38% higher in men and 43% higher in women compared to Europeans with the greatest difference occurring in young men in whom the relative risk is two-fold higher (114,115,118).

This susceptibility seems to be aggravated by migration to Western societies and by change to an urban lifestyle. Migrants from the Indian subcontinent to the UK had a more adverse coronary risk profile compared to their siblings in Punjab who did not migrate

(119). In a study of coronary artery disease and its risk factors in rural and urban populations of North India, Singh et al reported a significantly higher prevalence of coronary disease as well as a less favourable risk profile in the urban population in comparison to the rural population (120).

As well as rural-urban differences, there are regional differences in the prevalence of CHD in India. Within India, people from the southern region seem to have a higher prevalence of CHD when compared to people from other regions. A retrospective study of mortality due to coronary disease among railway employees in different regions of India in 1967 reported a significantly higher rate in South Indians (121). More recently Beegom et al in a study in 1994 showed that the prevalence of CHD in South Indians was about 60% higher in comparison to North Indians (122).

While these studies may have been performed on different populations using varying methods, they may not be exactly comparable. However, in spite of these factors, there seems to overwhelming evidence suggesting that rates of CHD in Indian populations are high, and that these rates are continuing to rise.

1.13 Transition in India

Currently India is going through a period of epidemiologic transition. Morbidity and mortality due to infectious diseases are declining while there is a rise in that due to non-communicable diseases: coronary heart disease, diabetes and hypertension. Projected statistics suggest that deaths due to circulatory diseases will be the leading cause of mortality in India by 2015 (123). The mortality rate due to circulatory problems has increased over the years and is expected to nearly double between 1985 and 2015 from 145 to 295 per 1,00,000 population in men and from 126 to 239 per 1,00,000 in women,

while there is an expected reduction in the overall mortality rate and deaths due to infectious diseases (108,123).

This epidemiologic transition is associated with demographic transition (107). Economic development and increasing urbanisation are leading to changes in lifestyle. These include increased fat consumption, reduced physical activity, obesity, smoking, overcrowding and stress (107,108,124). The average life expectancy is rising, partly due to a steady decline in the number of deaths occurring in infancy and childhood. This has resulted in increased numbers of middle-aged and older adults and it is therefore likely that more people will survive to ages where vascular diseases become apparent (107,124). The burden of CHD in India is therefore expected to be enormous in the near future and is an important public health problem.

1.14 Failure of classical risk factors to explain the high rates of CHD in Indians

The high rates of coronary heart disease in Indians are not explained by known risk factors (112,113,125). However it must be pointed out that there is no published prospective study in an Indian population. Most available data is from cross-sectional or case-control studies. A recent study from an industrial hospital in South India reported that the prevalence of CHD in their subjects did not correspond with high levels of known risk factors such as serum cholesterol concentrations, hypertension and smoking (126). Cross-sectional studies have shown that the concentrations of total serum cholesterol are generally lower in Indians than in Western populations (112-114,127). While levels of blood pressure and prevalence of hypertension are no higher than in Afro-Caribbean populations, rates of CHD are higher in Indian populations (112,113,115,127). Among men, rates of smoking are similar in Indian and Western populations (112,113), but whereas the prevalence of CHD in Indian men and women is similar, very few Indian women smoke. The one 'classical' risk factor which is markedly associated with CHD in

Indian populations is non-insulin dependent diabetes mellitus (NIDDM) (112,113,127). Indian populations have a higher prevalence of NIDDM compared to Western populations. This is associated with insulin resistance, higher concentrations of triglycerides and lower concentrations of HDL cholesterol (127) which form the components of the 'Insulin Resistance Syndrome' or Reaven's Syndrome (128). While absolute levels of BMI are lower, Indians tend be centrally obese (127). Therefore CHD in Indians seems to be associated with features of the 'Insulin Resistance Syndrome'. Recent evidence suggests that Indians have increased levels of lipoprotein (a) (129) and apolipoprotein B (129) and as these are believed to be genetically influenced, CHD in Indians may have a genetic basis.

1.15 The fetal origins hypothesis as a possible explanation for the high rates of CHD in Indians

It has been suggested that the high rates of CHD and NIDDM in the Indian population are due to a "thrifty genotype" (130). This hypothesis implies that disease-causing genes persist at a high level in the population because they confer a survival advantage in times of poor nutrition, but lead to disease in a setting of adequate food supply and sedentary lifestyle. The fetal origins hypothesis offers an alternative explanation (131). This suggests that poor fetal growth, especially generations of undernutrition, predisposes Indian populations to developing CHD; this is aggravated by exposure to other risk factors in later life.

1.16 Implications for India

India has an exceptionally high rate of low birth weight babies with approximately 30% of the population having a birth weight of less than 2.5 kgs (132,133). Maternal factors are considered to be the leading causes for this high incidence of IUGR and low birth weight babies (133,134). Specifically, these include: poor maternal anthropometric status - low

weight, body mass index and height, low age at marriage, anaemia of pregnancy and maternal undernutrition. If low birthweight is an important risk factor for adult CHD, India will be especially vulnerable due to the vast numbers of poorly nourished infants who have been born in the past few decades. The gradual but steady decline in infant mortality and childhood mortality rates will lead to a higher proportion of such infants surviving to adult life when their hypothesised susceptibility to CHD may become apparent. If the fetal origins hypothesis is relevant to India, public health strategies to arrest the 'epidemic' of CHD should include interventions to improve the growth and nutrition of girls and women. Measures to control adult risk factors may be most effectively targeted to people of low birthweight.

In 1991, the MRC Environmental Epidemiology Unit, Southampton decided to initiate a programme of research in India. A systematic survey of over 300 old hospitals in India led to the discovery of the Mysore birth records and the first study in an Indian population, of the long-term outcome in relation to size at birth.

Chapter 2 THE MYSORE BIRTH RECORDS AND THE FIRST MYSORE STUDY

2.1 Background

During 1993-1995 Dr C E Stein and I carried out a study of coronary heart disease (CHD) and its risk factors in 40-60 year old men and women born in the Mary Calvert Holdsworth Memorial Hospital (MCHMH), Mysore, South India where detailed birth records have been kept on every birth since 1934. This was the first study to explore associations between fetal growth and coronary heart disease in an Indian population. The full findings of the first Mysore study form the subject of Dr CE Stein's thesis. I will present here the major findings relating to CHD which are relevant to my own study, and have been reported in detail in our earlier papers (63, 135) as these results are necessary for putting my own data in context.

2.2 Methods

2.2.1 Setting

In the search for a suitable centre for the proposed research study, over 300 hospitals throughout India were contacted. Of the 3 hospitals with suitable birth records, the MCHMH was selected because the stable population of Mysore made it feasible to trace prospective subjects. The hospital was established as a charitable mission hospital in 1905, and is in a crowded and relatively poor area of the city. Since its inception it has been one of the major centres offering quality care in Mysore. Due to the hospital's reputation, it attracted and, continues to attract patients from all socio-economic classes.

The hospital has well-maintained birth records since 1934 which contain the weight, length and head circumference of babies at birth (Appendix 1; Figure 2.1). These measurements were recorded routinely by one of three midwives under an agreed protocol over the period between 1934 and 1953. The records also contain details of parents' names, address, occupations, religion or caste and the mother's obstetric

history. About 55% of the records contain maternal pelvic measurements; these were recorded for most primiparous and some multiparous women. Some mothers (roughly 40%) attended the antenatal clinic and their records also contain their weight at each antenatal visit. The records do not provide useful information on gestational age and placental weights as there are few records with accurate measurements.

2.2.2 Selection of subjects

The subjects for the first Mysore study were traced by a door-to-door survey of a three square kilometre area around the hospital in a central part of the city which was delineated by main roads (Appendix 1; Figure 2.2). Four field workers surveyed every household in this densely populated area asking people whether they were born in the hospital. Population census details were collected from all the households surveyed, including the total number, age and sex of all members living in each household. The survey included approximately 7800 households and covered a population of over 52,000 people. For people who said they were born in MCHMH, the names of their parents, order of siblings, address and parents' occupation at the time of birth, date of birth and any special features of the pregnancy were obtained on a 'tracing form' (Appendix 1; Figure 2.3). 1311 people said that they were born in the hospital as singletons and were 40 years or older. Since there was no detailed map of Mysore city covering all these streets, we recorded the location of these potential subjects by creating a large scale map (Appendix 1; Figure 2.4).

We aimed to trace 500 people who were born in the hospital during a twenty-year period between 1934 and 1953. Records of all the 8,883 live births during that period were entered on a database and the people traced by survey were matched to their birth records using strict matching criteria. Matching people to their birth records was not easy as many of the subjects did not know their correct age or date of birth. The birth records did not contain the names of the babies and therefore had to be matched on the names of

both parents, address at birth, and order and sex of siblings. There were inconsistencies in spelling parental names as names had been transcribed from Indian languages into written English. Computerised birth records were matched to parental names on the tracing form using a program devised to link names phonetically. After the computer program had identified a probable match, the original birth record was scrutinised in comparison to the information on the tracing form by either Dr C E Stein or myself. The criteria on the 'tracing flow chart' (Appendix 1; Figure 2.5) were applied to identify a 'definite match'. Details that did not match were verified by further open-ended questioning of the prospective subjects by the field workers who were blind to the information on the birth records. The study only included people whom we were able to match to their birth records with certainty. The breakdown of the figures is given below:

8883 live births between 1934-53 entered on database

↓

52,000 people surveyed (7800 households)

↓

1311 possible traces

↓

536 definite traces matched to their birth records

↓

517 participated in the study.

2.2.3 Investigations

We were able to identify and match 536 people with their birth records. 517 (96%) subjects participated in our study conducted between 1993-95. These subjects were invited to attend a clinic for physical examination and investigations after an overnight fast of 12 hours. Subjects underwent a standard 12-lead ECG and blood pressure recording. They also underwent a 75 gm 2 hour glucose tolerance test (136) in which blood was

drawn at 0, 30 and 120 minutes for measurement of plasma glucose and insulin levels. Fasting concentrations of serum total and HDL cholesterol, serum triglycerides, plasma fibrinogen and factor VII were also measured while serum LDL cholesterol concentration was calculated. We also measured subjects' height, weight, hip and waist circumferences and four skinfolds (triceps, biceps, subscapular and suprailiac). The Rose-WHO questionnaire was administered to collect history of chest pain; details of current medication, previous medical history, smoking, alcohol consumption and socio-economic status were also collected. The Kuppuswamy score (137), which uses information on family size, housing, education, occupation and income, was used to assess socio-economic status.

The presence of coronary heart disease was determined by the presence of one or more of the following criteria:

- typical angina according to the Rose/WHO chest pain questionnaire (138);
- ECG Minnesota codes 1-1 or 1-2 (Q and QS waves) (139);
- or a history of coronary artery angioplasty or bypass graft surgery.

2.3 Results

I will only present the results which are relevant to my own study.

The age range of the 517 men and women was 38-60 years (mean 47 years). 25 (9%) men and 27 (11%) women had coronary heart disease as diagnosed by our criteria; 14 (2.7%) had Q waves on ECG, 41 (7.9%) had symptoms of angina, and one had a history of coronary artery bypass surgery. The prevalence of CHD rose with increasing age, from 8% in men aged less than 45 years to 10% in men aged 45 years and over, and from 6% to 13% in women of similar age groups. The prevalence was similar in Muslims (10%), Hindus (10%) and Christians (13%). The percentage of CHD was higher in men of lower socio-economic class but there was no difference between social classes in women.

CHD and birthsize

The prevalence of CHD was higher in men and women who had lower birthweight, shorter birth length and smaller head circumference at birth. These results are shown in Table 2.1. These trends were stronger among participants aged 45 years and over ($p<0.05$ for all birth measurements). There was no relation with ponderal index at birth. The trends between CHD and size at birth were similar in men and women.

Table 2.1

Percentages of men and women with coronary heart disease according to birth measurements

	All men and women			
	n	% with		
		Angina	Q waves	CHD
Birthweight (lb)				
- 5.0	62	8	2	10
5.1-5.5	87	10	2	11
5.6-6.0	111	9	5	13
6.1-6.5	121	8	4	11
6.6-7.0	77	8	1	9
>7.0	59	3	0	3
All	517	8	3	10
P for trend				0.09
Birth length (in)				
-18	193	11	5	15
18.1-19	169	7	1	7
>19	150	6	2	8
All	512	8	3	10
P for trend				0.03
Head Circ at birth (in)				
<13	80	11	1	13
13	227	9	3	11
-13.5	204	5	3	7
All	511	8	3	10
P for trend				0.08

p values adjusted for age and sex

CHD and maternal size

Mothers of lower weight had smaller babies, who as adults had a higher prevalence of CHD. The highest prevalence of CHD (20%) was in those who weighed less than 5.5 lbs at birth and whose mothers weighed less than 100 lbs. In contrast there were no cases of CHD in those who weighed more than 6.5 lbs at birth and whose mothers weighed more than 100 lbs (Table 2.2)

Table 2.2

Frequency of coronary heart disease according to birthweight and mother's weight in pregnancy

Birthweight (lb)	Mother's weight (lb)		
	<100	>=100	All
-5.5	20% (40)	8% (13)	17% (53)
5.6-6.0	9% (22)	14% (22)	11% (44)
6.1-6.5	9% (23)	8% (26)	8% (49)
>6.5	6% (16)	0% (47)	2% (63)
All	13% (101)	6% (108)	9% (209)

CHD risk factors

Subjects with CHD were older and shorter than those without the disease and had higher systolic blood pressures, a more adverse lipid profile and higher concentrations of plasma glucose and insulin (Table 2.3)

Table 2.3

Risk profile of men and women with and without CHD (Mean (SD))

	MEN		WOMEN	
	With CHD (n=22)	**Without CHD (n=215)**	**With CHD (n=23)**	**Without CHD (n=175)**
General characteristics				
Age (years)	**51.5**(5.5)	**49.3**(4.7)	**51.2**(5.0)	**49.2**(4.7)
Height (cm)	**164.7**(6.3)	**165.6**(6.0)	**150.9**(7.7)	**151.7**(6.4)
Body mass index (kg/m2)	**23.2**(3.3)	**23.0**(4.0)	**25.0**(4.6)	**25.4**(5.2)
CHD risk factors				
Systolic blood pressure (mm Hg)	**136**(21)	**131**(16)	**133**(14)	**132**(19)
Diastolic blood pressure (mm Hg)	**82**(13)	**80**(11)	**76**(11)	**77**(11)
Serum triglycerides (mmol/L)*	**1.8**(1.8)	**1.7**(1.7)	**1.7**(1.6)	**1.5**(1.7)
HDL-cholesterol (mmol/L)	**0.9**(0.2)	**0.9**(0.2)	**0.9**(0.2)	**1.0**(0.2)
LDL-cholesterol (mmol/L)	**3.7**(1.0)	**3.1**(0.8)	**3.0**(0.6)	**3.2**(0.8)
Total cholesterol (mmol/L)	**5.3**(1.2)	**4.9**(1.0)	**4.7**(0.7)	**4.9**(0.9)
Fasting insulin (pmol/L)*	**41**(3)	**48**(2)	**74**(2)	**54**(2)
30-min insulin (pmol/L)*	**335**(2)	**382**(2)	**447**(2)	**379**(2)
120-min insulin (pmol/L)*	**342**(3)	**329**(2)	**464**(2)	**393**(2)
Proinsulin (pmol/L)*	**9.0**(2.5)	**7.8**(2.4)	**7.6**(2.0)	**6.3**(2.1)
32-33 split proinsulin (pmol/L)*	**9.2**(2.6)	**8.4**(2.9)	**9.3**(2.3)	**8.3**(2.4)
Fasting glucose (mmol/L)*	**5.5**(1.5)	**5.1**(1.3)	**5.7**(1.5)	**5.3**(1.3)
30-min glucose (mmol/L)*	**8.1**(1.4)	**8.4**(1.3)	**8.4**(1.4)	**8.0**(1.3)
120-min glucose (mmol/L)*	**6.7**(1.5)	**6.4**(1.4)	**7.5**(1.4)	**6.9**(1.3)
Waist/hip ratio	**0.91**(0.06)	**0.91**(0.06)	**0.85**(0.06)	**0.83**(0.06)
Subscapular/triceps skinfold ratio	**1.84**(0.47)	**1.83**(0.48)	**1.37**(0.30)	**1.28**(0.32)
Plasma fibrinogen (g/L)	**298**(54)	**310**(80)	**341**(56)	**339**(60)
Factor VII (g/L)	**117**(37)	**112**(37)	**135**(39)	**124**(40)

* Geometric mean and SD

CHD risk factors and birthsize

The prevalence of NIDDM was higher in those who were shorter at birth (p=0.07) and in those who had a higher ponderal index (p=0.05) independently of age, sex and adult BMI. The highest rates of diabetes were in those who were short at birth with a relatively high birthweight. Fasting insulin and 32-33 split proinsulin were inversely related to birthweight only in men. The 30 minute plasma insulin concentration tended to be lower in subjects who had a higher birthweight and ponderal index at birth independently of age, sex and adult body size. The 120 minute insulin concentration showed a similar trend with birthweight. None of the other CHD risk factors showed any statistically significant

associations with any of the birth measurements. However, systolic blood pressure tended to be higher in subjects of longer length at birth (p=0.07).

Table 2.4

Relation of birth measurements to CHD risk factors: unadjusted Pearson correlation coefficients

	Birth weight	Length	Head Circumference	Ponderal Index
Blood pressure				
Systolic	0.08	0.11	-0.02	-0.04
Diastolic	0.09	0.09	<0.01	-0.02
Glucose				
Fasting	0.08	<0.01	<0.01	0.06
30 minutes	0.13	0.05	0.08	0.05
120 minutes	0.09	0.02	0.06	0.06
Insulin				
Fasting	0.03	0.01	<-0.01	<0.01
30 minutes	-0.03*	0.08	<-0.01	-0.10*
120 minutes	<-0.01*	0.05	0.05	-0.06
Proinsulin	0.09	0.06	0.04	0.01
32-33 split proinsulin	0.03	0.02	<0.01	<-0.01
Lipids				
Total cholesterol	0.05	0.06	-0.05	-0.02
LDL cholesterol	0.04	0.09	-0.07	-0.05
HDL-cholesterol	0.02	-0.02	<0.01	0.03
Triglycerides	0.01	-0.01	-0.01	0.02
Central obesity				
Waist/hip ratio	0.13	0.10	0.08	0.01
SS/TR	0.01	0.07	0.06	-0.06
Clotting factors				
Fibrinogen	<-0.01	0.03	- 0.09	-0.03
Factor VII	0.03	-0.05	0.08	0.14

*** p<0.05**
****p<0.01**
p values adjusted for age, sex and adult body size

CHD risk factors and maternal size

Prevalence of NIDDM, and plasma proinsulin and 32-33 split proinsulin concentrations were higher in subjects whose mothers were heavier during pregnancy or had larger pelvic diameters, independently of age, sex and current body size. None of the other CHD risk factors were significantly related to maternal size.

2.4 Summary

- The prevalence of CHD in Mysore defined by standard criteria was 10%, which is similar to rates elsewhere in India (109, 110) and in Western populations. This study therefore confirmed that rates of CHD have reached significant levels in India.
- Our findings that CHD was associated with low birthweight, small head circumference and short body length at birth are consistent with those from studies in Western countries and reflect similar associations between high rates of CHD and poor fetal growth in an Indian population. These body proportions are thought to result from fetal adaptations to undernutrition throughout gestation, with reduction in growth of the head, body length, and soft tissues.
- Ours was the first study to establish a link between CHD and low maternal weight. The finding that mothers with lowest weights had the smallest offspring, who as adults had the highest rates of CHD, is consistent with ideas about maternal undernutrition causing impaired fetal growth which leads to adult CHD.
- The Mysore subjects were not only insulin resistant but also had insulin deficiency. The findings suggest that this population is intrinsically different from Western populations with different associations between fetal growth and adult diabetes.

2.5 Rationale for my follow-up study

To elucidate mechanisms that may be responsible for these associations, I decided to focus on two further cardiovascular measurements that have been shown to be related to poor fetal growth in Western populations, left ventricular mass and arterial compliance. These were carried out in the same cohort of men and women and form the subject of my project and the remainder of this thesis. Oral consent was obtained from the subjects prior to the clinic visit and ethical permission for the study was obtained from the Ethics Committee of the MCHMH.

Chapter 3 LEFT VENTRICULAR MASS

3.1 Introduction

3.1.1 Relation with coronary heart disease

Increased left ventricular (LV) mass is known to predict increased morbidity and mortality from CHD (140-148). In the Framingham prospective study, an increment in LV mass of 50 g per metre of height in men over 40 years of age was associated with a 49% increase in the incidence of coronary heart disease (1400). In women the corresponding figure was 57%. In elderly people over 60 years, the risk of death from CHD for a similar increase in LV mass rose by 67% in men and 60% in women (141). The Framingham Heart Study showed that in people with CHD, those with left ventricular hypertrophy (LVH) had a worse prognosis than those without (143-145,147,148). LVH is also associated independently with an increased risk of sudden death (149), ventricular arrhythmias (150,151) and congestive cardiac failure (152).

3.1.2 Pathophysiology

The pattern of left ventricular hypertrophy (LVH) is determined by the type of cardiac overload. Volume overload produces eccentric hypertrophy (increased ventricular mass in proportion to cavitary volume) and pressure overload leads to concentric hypertrophy (increased ventricular mass out of proportion to cavitary volume) (153). Concentric hypertrophy usually results from hypertension and is more common than eccentric hypertrophy. The raised peripheral resistance in hypertension creates a pressure overload (154-157) leading to replication of sarcomeres, an increase in cell width, ventricular wall thickening and concentric hypertrophy without an increase in the number of myocytes. Although concentric LVH maintains systolic function at near-normal levels, left ventricular relaxation is impaired with long-standing pressure overload (156,157). Thus concentric LVH represents a cardiac end-organ manifestation of hypertension (156).

The mechanisms by which LVH leads to an increased risk of CHD are not known and a number of possible explanations have been offered. The increased tissue mass that occurs in LVH results in a greater myocardial oxygen demand which may promote the development of ischaemia or infarction when coronary blood flow is compromised.

The heart receives its blood supply during diastole. When ventricular relaxation is impaired, as in LVH, the coronary blood flow is adversely affected. An additional contributing factor to the development of ischaemia is the extrinsic vascular compression caused by the hypertrophied ventricle which also results in diminished coronary flow.

The hypertrophied ventricle has a disproportionate increase in the extracellular collagen matrix relative to the rate of capillary growth (158,159). This relative decrease in capillary density is manifested pathophysiologically as increased minimal coronary vascular resistance (least resistance to coronary blood flow), when measured during maximal coronary flow (160). The main regulator of microvascular tone, the endothelium, is damaged in hypertension and LVH. This contributes to disordered coronary flow regulation and a decrease in coronary flow reserve (the difference between basal and maximal coronary blood flow) (161). The increase in minimal coronary vascular resistance and a decrease in coronary blood flow reserve contribute to the development of myocardial ischaemia (161).

Thus a combination of increased myocardial demand, extrinsic vascular compression, increased minimal coronary vascular resistance and decreased coronary flow reserve may lead to myocardial ischaemia even without the presence of large-vessel atherosclerotic coronary artery disease.

LVH is also associated with an increased incidence of ventricular tachycardia and

arrhythmias though the mechanisms for this remain unexplained. This may be another factor responsible for the increased CHD mortality seen with LVH (150,151).

It is also possible that the association between LVH and CHD is because they share common risk factors including obesity, age and raised blood pressure (156,157,162-164). Therefore increased left ventricular mass may promote CHD in a causal manner or may merely serve as a marker of other risk factors.

3.1.3 Factors affecting LV mass

LV mass is higher in men than in women and increases with rising systolic blood pressure and with increasing body size (164-170). Other factors that have been associated with an increased left ventricular mass include ageing, hyperinsulinaemia, non-insulin dependent diabetes mellitus, increased triglycerides, reduced HDL cholesterol levels, increased nor-adrenaline, increased subscapular skinfold thickness and greater physical activity (171-182).

Obesity and an increased subscapular skinfold thickness are independently associated with increased LV mass (171,173,174,176). Obesity tends to cause eccentric hypertrophy probably because of its tendency to result in volume overload (153,156,157). The rise in systolic blood pressure with increasing age may be responsible for the increased LV mass in older people (163,170,172). Insulin receptors have been identified in myocardial cells and vascular smooth muscle cells (183). Insulin resistance and hyperinsulinaemia are believed to cause vascular and cardiac hypertrophy (184-186) by stimulating protein synthesis. The increased LV mass in diabetics and in those with dyslipidaemia is thought to be due to associated insulin resistance (177,181,182). Nor-adrenaline also promotes myocardial hypertrophy (184,185) and increased sympathetic activity may also be associated with insulin resistance (177). Increased physical activity has also been weakly associated with increased LV mass (170,175).

These factors, however, do not explain all the variation in adult LV mass (187).

3.1.4 Early life influences on LV mass

There is evidence that the differences in adult LV mass may be influenced by factors acting early in life. A study in Hertfordshire by Vijayakumar et al showed that men who were small at birth and one year had raised LV mass in adult life (188) (Table 3.1). Another study in Paris on subjects between 8 and 24 years of age demonstrated that a low weight in infancy and at 2 years of age was associated with increased left ventricular mass in later life (189), although no significant relation was found with birth weight.

Table 3.1

Geometric mean left ventricular mass according to weight at one year and birth weight

	Men (n)	LV mass (g)	LV mass adjusted BSA
Weight at a year (lb)			
<=18	8	239	246
-20	31	204	210
-22	61	212	212
-24	64	199	197
-26	24	191	190
>26	14	190	184
Birthweight (lb)			
<=5.5	8	240	241
-6.5	26	207	209
-7.5	63	202	205
-8.5	64	201	199
-9.5	32	196	193
>9.5	9	221	216
All	202	203	204
Geometric SD		1.26	1.25

(Reproduced from Vijayakumar et al, reference 188)

It was proposed that factors acting early in life could 'programme' the cardiovascular system resulting in increased LV mass and consequently, adult CHD (188). Cardiac growth and fetal circulation are believed to be affected by impaired fetal growth which may adversely affect the development and functioning of the cardiovascular system.

3.1.5 Cardiac growth

The human heart grows fastest in fetal and infant life (190,191). An increase in cardiac mass occurs due to an increase in the number (hyperplasia) or volume (hypertrophy) of myocytes or a combination of the two processes (191,192). Increase in cell number stops during the first year of postnatal life (191,192). The increase in cardiac mass after that is due to hypertrophy alone (191,192).

After the high rates of cardiac growth in fetal and early postnatal life, the increase in cardiac weight is proportional to the increase in body size in children and in adults throughout the first half of life (193,194). This results in a fairly constant relationship of cardiac weight to body size. Subsequently cardiac mass increases in old age, irrespective of body size. The mechanisms responsible for this are not clear, but an increased afterload due to the raised blood pressure which accompanies ageing may contribute.

3.1.6 Fetal circulation and contrast with postnatal circulation

The fetal circulation differs from the postnatal circulation in two specific hemodynamic features (195):

1. Volume: In fetal life, the ventricles pump blood in parallel and the cardiac output is equal to the sum of the outputs of the two ventricles. The right ventricle has a larger radius than the left ventricle and consequently a greater stroke volume, the ratio of right ventricular output to left ventricular output ranging between 1.2 and 1.3 (195,196). In postnatal life, the stroke volumes of the ventricles are equal.

2. Pressure: During intrauterine life, the right and left ventricles have common atrial filling pressures and common arterial outflow pressures. It is recognised that at the time of birth the left ventricle undergoes rapid increase in mass in relation to its increased load while the right ventricle remains unchanged or even undergoes slight regression so that RV/LV ratio decreases after birth (195,196). This is due to the physiologic decrease in pulmonary vascular resistance after birth while there is a great increase in systemic vascular resistance.

Thus, in fetal life the right ventricle has a greater workload than the left ventricle, a situation which reverses after birth.

3.1.7 Changes in cardiac dynamics in intrauterine growth retardation

During fetal life, the left ventricular output is directed through the ascending aorta mainly to the brain. The output of the right ventricle is directed to the lower body and placenta. Hemodynamic studies have shown that intra-uterine growth retardation (IUGR) affects some fetuses by causing increased blood flow through the left side of the heart (197,198) and reducing the relative contribution of the right ventricle to the total cardiac output to about 47% (197). This increases the load on the left ventricle. A study in Cleveland, USA on fetal cardiac size in normal and IUGR fetuses showed that those with IUGR had an increased cardiac mass due to left ventricular free wall hypertrophy (199).

The redistribution of blood flow in IUGR fetuses is believed to be a reflex aimed to spare blood flow to the brain. In the process, blood flow to the abdominal organs and lower body is compromised (197,198,200). These changes are believed to occur due to increased placental resistance, which affects pulmonary blood flow ejecting through the ductus into the descending aorta, and thus causes a fall in pulmonary artery flow velocity. A complementary increase in aortic blood flow velocity occurs as a result of vasodilatation in the cerebral and coronary circulations.

3.1.8 Proposed hypothesis linking poor fetal growth to increased left ventricular mass

Although the results of the earlier studies on the relationship between adult LV mass and early life factors are stronger with weight in infancy, effects in fetal life may be responsible for these findings. Barker proposed that fetuses which are undernourished at different times during gestation are born with different patterns of growth and body shapes (refer Chapter 1,section 1.10). A fetus experiencing undernutrition in early pregnancy slows its growth rate, is born proportionately small with low birthweight, and has low weight in infancy (84,98). A fetus which experiences undernutrition during the second trimester is born thin with low birthweight, experiences catch-up growth in infancy and has a normal weight at one year (84,98). A fetus which is undernourished during mid-late gestation sustains brain growth at the expense of trunk, is short at birth with a normal birthweight but has a lower weight at one year because of growth failure in infancy (84,98). In his framework for fetal programming of adult CHD, Barker suggested that babies with either of the latter two patterns of fetal growth are prone to developing adult CHD. The short 'brain-sparing' fetus is thought to develop raised blood pressure as well as increased serum concentrations of LDL cholesterol and fibrinogen, and the thin fetus develops higher blood pressure, insulin resistance and non-insulin dependant diabetes (98). Both may result in CHD in later life.

The short baby is believed to respond to nutrient deprivation by redistribution of blood flow of blood flow to the brain at the expense of limbs and abdominal organs. This is accompanied by an increased afterload on the left ventricle. It has been suggested that the increased load placed on the left ventricle in intrauterine growth retardation leads to a permanent increase in LV mass and a higher risk of LVH in adult life. Impaired growth in utero is also believed to cause alterations in the hormonal axes and result in persistent changes in hormones such as insulin, insulin-like growth factor I and growth hormone, which regulate growth and are known to influence cardiovascular structure. Either of

these routes may be responsible for the 'programming' of raised LV mass in adult life (98,188).

The Mysore records contain length and head circumference at birth in addition to birthweight and provided an opportunity to examine the relation between left ventricular mass and body proportions, as well as weight, at birth. The earlier Mysore study showed an association between lower maternal weight during pregnancy and an increased risk of CHD in the offspring and I therefore also examined the relation between maternal weight and adult LV mass in the offspring. This was the first study to look at the relationship of size at birth to adult LV mass in an Indian population and the first community based study of LV mass and its relations with CHD and its risk factors in India.

I hypothesised that babies with impaired fetal growth, in particular 'short' babies with a relatively greater head circumference would have increased LV mass in adult life as a result of 'programming' during fetal life.

3.2 Methods

3.2.1 Methods of measuring LV mass and LVH

LV mass is measured by echocardiography, a technique which has been validated in prospective studies by comparison of antemortem echocardiographically measured LV mass with post-mortem LV mass measured by chamber dissection (201-203).

LVH can be diagnosed by chest x-ray, electrocardiography (ECG) and echocardiography. In correlation with autopsy studies, the accuracy as well as the sensitivity and specificity of echocardiography in diagnosing LVH is higher than ECG and chest x-ray (203). The Framingham study also showed echocardiography to be more sensitive than the ECG in diagnosing LVH and in predicting the progression of CHD (204).

3.2.2 Procedure

In my study conducted during 1996-97, LV mass was measured by 2D and M mode echocardiography. All the scans were done by myself using either a Larsen and Toubro Sigma 1 AC or Larsen and Toubro Clarity machine. I underwent basic echocardiographic training with the team of technicians at the Royal South Hants Hospital, Southampton and further training with Dr M Vijayakumar, Consultant Cardiologist, Vijaya Hospitals, Madras. Echocardiographic data were collected on a data collection form (Appendix 2; Figure 3.1) and also recorded using a commercial video cassette recorder (Sony 550) for review by Dr Vijayakumar.

Measurements were made according to the recommendations of the American Society of Echocardiography (205). Subjects were placed in the left lateral decubitus position (Appendix 2; Figure 3.2). Using the parasternal long axis view, the M mode cursor was placed perpendicularly to the long axis of the left ventricle at the level of the chordae tendinae making sure that the interventricular septum and the posterior cardiac wall were visualised clearly throughout the cardiac cycle (Appendix 2; Figure 3.2). ECG leads were

attached during the echocardiographic examination and the ECG in standard lead II was considered. All measurements were made in M mode, and M mode prints were taken with a video printer (Sony UP930) using high density printing paper.

Measurements were made from these prints using a digitiser (Genitiser GT-1212B). The first deflection of the QRS complex of the ECG was considered as the end diastolic point and measurements made at the vertical line drawn through this point included interventricular septal thickness at end diastole (IVSD), posterior cardiac wall thickness at end diastole (PWTD) and left ventricular internal diameter at end diastole (LVEDD). They were made using the leading edge to leading edge technique i.e., from the inner portion of the outer line to the outer portion of the inner line (Appendix 2; Figure 3.3). Left ventricular diameter at end systole (LVESD) was obtained by calculating the distance from the lowermost portion of the interventricular septum to the posterior cardiac wall. The average value of five different cardiac cycles was used in the analysis, as shown in the data analysis form (Appendix 2; Figure 3.1). LV mass was calculated from these parameters using a validated standard formula, LV mass = $0.8[1.04\{(IVSD+LVEDD+PWTD)^3 - LVEDD\}^3] + 0.6$ gm (206). Relative wall thickness (RWT), a sensitive indicator of concentric hypertrophy, was calculated using the formula, RWT= 2(PWTD/LVEDD) (207).

Weight was measured to the nearest 0.5 kg using a Seca scale. Height was measured to the nearest 0.1 cm using a portable Harpenden stadiometer. Body surface area was calculated using the formula: $0.007184 \times [\text{weight (kg)}]^{0.425} \times [\text{height (cm)}]^{0.725}$ (208).

In all echocardiographic studies, a proportion of individuals cannot be assessed because of an inadequate echocardiographic window or inability to obtain the correct angle of view. The percentages of inadequate examinations are known to be higher in older subjects, and range between 20 and 30% in other published studies

(140,141,147,148,172). These figures however, refer to populations with a mean age greater than the Mysore subjects by 9-20 years. I excluded the following subjects from the analysis:

1. Subjects with a poor echocardiographic window where the interventricular septum and the posterior cardiac wall could not be visualised clearly and simultaneously throughout the cardiac cycle
2. Subjects in whom it was not possible to obtain the correct echocardiographic angle i.e., where the M mode cursor could not be placed perpendicularly to the long axis of the left ventricle
3. Subjects with rheumatic heart disease, hypertrophic cardiomyopathy and left ventricular aneurysm, conditions which tend to cause cardiac enlargement in their own right and can be diagnosed by echocardiography.

3.2.3 Intraobserver variation

I repeated the echocardiographic LV mass measurements in 10 subjects within a month of their initial examination. Paired t tests showed no significant differences in LV mass between the two measurements. I also repeated the digitisation of echocardiographic prints on a further 21 subjects; these also showed no significant differences. The data are presented in Appendix 3.

3.3 Statistical methods

Birth measurements were made in pounds and inches, and were often rounded, creating clumping of data. Plasma glucose, insulin, proinsulin, 32-33 split proinsulin and serum triglyceride concentrations had a skewed distribution and were logarithmically transformed to obtain a normal distribution curve. Data analysis was done using the SPSS/PC 5.1 statistical computer package. Data was analysed by tabulation of means and multiple linear and logistic regression, using continuous variables as appropriate.

3.3.1 Analysis of LV mass

LV mass was analysed in two ways:

a) as a continuous variable, and

b) as a dichotomous variable, comparing subjects with and without LVH.

To create the LVH variable, I selected a subset of people from the cohort who were normotensive (systolic and diastolic blood pressures of less than 140 and 90 mm Hg respectively), were not on any cardiac or anti-hypertensive medication, did not have CHD or diabetes and had a BMI of less than 30 kg/m^2. Subjects who had a LV mass (indexed for BSA) greater than 2 standard deviations from the mean value of this subset were defined as having LVH (209,210). The calculation was made separately for men and women (cut off values for men and women 104 g/m^2 and 89 g/m^2 respectively) although the sexes were then combined to examine relationships with CHD and its risk factors, and fetal and maternal measurements.

3.4 Results

3.4.1 Characteristics of the subjects

Eight people from the original sample of 517 had died. 435 (85%; 237 men and 198 women) of the remaining 509 agreed to take part in the study. Their characteristics are shown in Table 3.2, and showed expected male-female differences in body size. 62% of the men in the study had smoked at some point while 47% continued to do so. 21% of men reported alcohol consumption. Only one woman reported smoking and alcohol consumption. 46% of the subjects were classified as belonging to lower social classes. The majority of our subjects were Muslims while Hindus formed the second largest religious group.

Table 3.2

Mean (SD) characteristics of the Mysore men and women

	Males (n=237)		Females (n=198)		All (n=435)	
Age (years)	**49.5**	(4.8)	**49.5**	(4.8)	**49.5**	(4.8)
Weight (kg)	**63.3**	(12.4)	**58.5**	(13.0)	**61.1**	(12.9)
Height (cm)	**165.5**	(6.1)	**151.6**	(6.5)	**159.2**	(9.4)
Body mass index (kg/m^2)	**23.1**	(4.0)	**25.4**	(5.1)	**24.1**	(4.7)
Body surface area (m^2)	**1.68**	(0.17)	**1.52**	(0.17)	**1.61**	(0.19)
% current smokers	**47**		**<1**		**26**	
% ex-smokers	**15**		**0**		**8**	
% drink alcohol	**21**		**<1**		**12**	
% lower social class	**47**		**45**		**46**	
% Hindus	**36**		**41**		**39**	
% Muslims	**53**		**51**		**52**	
% Christians	**11**		**8**		**9**	

There were no statistically significant differences in age, sex, social class, adult height and weight between those who participated in our second study and those who did not. Similarly there were no statistically significant differences in age, sex, height, weight, systolic blood pressure and socio-economic class between those who were or were not

included in the analysis, although the subjects on whom adequate echocardiograms could not be obtained were older (mean age 51.0 years Vs 49.2 years).

Table 3.3 shows the mean birth dimensions of the men and women in the study. Male babies were larger in all measurements than female babies.

Table 3.3

Mean (SD) birth measurements of the Mysore men and women

	Men		**Women**		**All**	
Birthweight (g)	**2785**	(410)	**2707**	(401)	**2749**	(401)
Length (cm)	**47.9**	(3.1)	**47.6**	(3.0)	**47.8**	(3.0)
Head circumference (cm)	**33.7**	(1.7)	**33.2**	(1.6)	**33.5**	(1.7)
Ponderal index (g/cm^3)	**25.7**	(5.0)	**25.4**	(5.0)	**25.6**	(5.0)

I compared body size in this cohort of men and women with that of the cohorts in Hertfordshire and Sheffield where earlier studies examined the relation of size at birth to adult LV mass and arterial compliance. The Mysore subjects were smaller at birth in all measurements, and shorter and lighter in adult life (Table 3.4).

Table 3.4

Mean characteristics of the Mysore men and women and comparison to UK data

	Mysore		**Hertford**		**Sheffield**	
	Men	Women	Men	Women	Men	Women
Current						
Age (yr)	49.5	49.5	66.8	66.2	50	50
Weight (kg)	63.3	58.5	79.1	67.7	81.1	68.8
Height (cm)	165.5	151.6	172.0	160.0	172.4	160.1
BMI (kg/m^2)	23.1	25.4	26.6	26.3	27.3	27.3
At birth						
Birthweight(g)	2785	2707	3514	3427	3269	3141
Length (cm)	47.9	47.6			50.8	50.5
Head circ (cm)	33.7	33.2			34.5	34.0
Ponderal index (kg/m^3)	25.7	25.4			24.9	24.4

Birth length and head circumference not measured in Hertford.

Since all the cardiovascular outcomes are strongly related to adult body size, it is important to describe the link between adult size and size at birth. Higher birthweight was associated with higher adult weight (men:r=0.2, p=0.001, women:r=0.25,p<0.001), height (men:r=0.3, p<0.001, women:r=0.22,p=0.001), body mass index (men:r=0.12, p=0.05, women:r=0.16, p=0.01) and body surface area (men:r=0.28, p<0.001, women:r=0.29,p<0.001). Longer length at birth was associated with greater adult body size only in women (weight: r=0.24, p=0.001; height: r=0.17, p=0.01; BMI: r=0.18, p=0.01; BSA: r=0.25, p<0.001). The corresponding correlation coefficients for men were 0.08, 0.10, 0.05 and 0.09 (p>0.05 for all). Greater head circumference at birth was associated with higher adult weight (men:r=0.16, p=0.01, women:r=0.15,p=0.02), height (men:r=0.19, p=0.003, women:r=0.15,p=0.03), body mass index (men:r=0.11, p=0.08, women:r=0.1, p=0.1) and body surface area (men:r=0.18, p=0.004, women:r=0.2,p=0.005). Ponderal index at birth was not significantly related to adult body measurements.

Maternal weight during pregnancy and pelvic diameter correlated positively with birthweight and ponderal index in both sexes (p<0.05 for all). There were no significant correlations with length at birth. Head circumference at birth correlated positively with maternal weight in women and with pelvic diameter in men (p<0.05 for all). Higher maternal weight was also associated with a greater adult body size in their male offspring while both maternal weight and pelvic size correlated positively with the adult body size of female offspring.

3.4.2 Cardiac dimensions

Of the 435 men and women who underwent echocardiography, I excluded 54 (13%) from the analysis because of an inadequate echocardiographic window or incorrect angle, and 2 who had hypertrophic cardiomyopathy. My analysis was therefore restricted to 379 people (207 men and 172 women). Cardiac dimensions are shown in Table 3.5. All were normally distributed.

Table 3.5

Mean (SD) cardiac dimensions in the Mysore men and women

Cardiac dimensions	Men (n=207)		Women (n=172)		All (n=379)	
Interventricular septal thickness (mm)	**10.6**	(1.7)	**9.9**	(1.6)	**10.3**	(1.7)
Posterior wall thickness (mm)	**8.8**	(1.1)	**8.5**	(0.9)	**8.7**	(1.0)
Left ventricular end-diastolic diameter	**45.1**	(4.1)	**42.5**	(3.5)	**43.9**	(4.0)
Left ventricular end-systolic diameter	**27.3**	(3.6)	**24.8**	(2.8)	**26.2**	(3.5)
Left ventricular mass (g)	**149**	(37)	**125**	(32)	**138**	(37)
Relative wall thickness	**0.4**	(.06)	**0.4**	(.06)	**0.4**	(.05)

Mean LV mass was lower in this Indian population than in Western populations. The mean LV mass was 203 g in men and 156 g in women in the Hertfordshire cohort (aged 60-66 years). Data from the Framingham study show that the mean LV mass in a sample of 18-90 year-olds was 202 g in men and 136 g in women.

3.4.3 LV mass and sex, body size and age

Mean LV mass was greater in men (149 g, range 67-265 g) than in women (125 g, range 59-240 g) ($p<0.001$) and strongly correlated with body size, rising with increasing weight ($r=0.62$), height ($r=0.42$), body mass index ($r=0.42$) and body surface area ($r=0.64$) ($p<0.001$ for all measurements of body size).

Of the body size measurements, surface area (BSA) was most closely related to LV mass. For subsequent analyses, I therefore adjusted for body size in the traditional way, by indexing LV mass with BSA (LV mass/BSA) (205,211). On adjusting for body size, the difference in mean LV mass between the sexes diminished [LV mass/BSA in men=88 g/m^2 (SD 18); and women=82 g/m^2 (SD 16)] but remained statistically significant ($p=0.001$). On indexing with BSA, LV mass was still higher in the Framingham cohort compared to the Mysore subjects (102 g/m^2 and 83 g/m^2 in men and women respectively).

LV mass also rose with increasing triceps, biceps, subscapular and suprailiac skinfold measurements as well as with higher waist and hip circumference and a greater waist to hip ratio (Table 3.6) in both sexes. Correlations were similar at all skinfold sites. Even after indexing with BSA, the relationships with waist circumference, hip circumference, and waist-hip ratio remained strongly statistically significant in both sexes ($r=0.27$, $p<0.001$; $r=0.24$, $p=0.001$; $r=0.26$, $p<0.001$ and $r=0.24$, $p<0.001$; $r=0.20$, $p=0.01$; $r=0.18$, $p=0.01$ in men and women respectively). In contrast, the relationship of LV mass/BSA with subscapular and suprailiac skinfold thickness was of borderline statistical significance and that with triceps and biceps skinfolds disappeared.

Table 3.6

Correlations between LV mass and skinfold measurements and waist and hip circumference

	Men		Women	
	r	p	r	p
Triceps	0.35	<0.001	0.43	<0.001
Biceps	0.23	0.001	0.44	<0.001
Subscapular	0.34	<0.001	0.43	<0.001
Suprailiac	0.36	<0.001	0.44	<0.001
Waist circ	0.53	<0.001	0.57	<0.001
Hip circ	0.53	<0.001	0.55	<0.001
Waist-hip ratio	0.42	<0.001	0.31	<0.001

LV mass/BSA tended to rise with increasing age in both sexes ($r=0.12$, $p=0.09$ in men and $r=0.16$, $p=0.03$ in women). This effect of age on LV mass diminished, and was no longer statistically significant, when systolic blood pressure was added to the regression equation ($p=0.4$ and 0.5 in men and women respectively).

3.4.4 LV mass and adult 'lifestyle' factors

There were no statistically significant relations between LV mass/BSA and smoking status, alcohol consumption, or with current social class.

3.4.5 LV mass and blood pressure

LV mass was strongly related to systolic (r=0.41; p=<0.0001) and diastolic (r=0.36; p=<0.0001) blood pressure, rising with increasing blood pressure (Tables 3.7 and 3.8). These relationships were independent of age and body size. LV mass/BSA was significantly greater in the 112 subjects with hypertension (95 g/m^2) compared with the 267 without hypertension (80 g/m^2) (p for difference <0.001).

Table 3.7

Mean (SD) LV mass and LV mass/BSA in men and women according to systolic blood pressure

Systolic BP (mm Hg)	Men			Women		
	n	LV mass (g)	LV mass/ BSA (g/m^2)	n	LV mass (g)	LV mass/ BSA (g/m^2)
<108	37	129 (24)	78 (12)	33	112 (25)	77 (14)
108-	42	146 (28)	86 (15)	38	114 (21)	75 (11)
116-	44	144 (27)	86 (16)	32	118 (24)	77 (12)
131-	47	154 (35)	88 (16)	36	136 (34)	86 (18)
145+	37	177 (47)	102 (23)	33	146 (39)	95 (20)
All	207	149 (36)	88 (18)	172	125 (32)	82 (17)
p value		<0.0001	<0.0001		<0.0001	<0.0001

Table 3.8

Mean(SD) LV mass and LV mass/BSA in men and women according to diastolic blood pressure

Diastolic BP (mm Hg)	Men			Women		
	n	LV mass (g)	LV mass/ BSA (g/m^2)	n	LV mass (g)	LV mass/ BSA (g/m^2)
<67	29	133 (30)	82 (16)	41	112 (22)	75 (12)
67-	40	138 (22)	82 (12)	37	119 (26)	78 (13)
73-	44	146 (31)	86 (16)	38	127 (33)	81 (15)
79-	47	151 (37)	88 (18)	32	139 (36)	90 (18)
86+	47	169 (46)	97 (23)	24	137 (38)	91 (22)
All	207	149 (36)	88 (18)	172	125 (32)	82 (17)
p value		<0.0001	<0.0001		<0.0001	<0.0001

LVH was also strongly associated with blood pressure and hypertension. The 55 people with LVH had higher systolic (146 mm Hg Vs 123 mm Hg) and diastolic (84 mm Hg Vs 75 mm Hg) blood pressures compared to the 324 without LVH (p for difference <0.001 for both). 69% of those with LVH were hypertensive compared with 23% in the non-LVH group. People with hypertension had a relative risk of 7.5 (95% CI 4.1 to 14) of having LV hypertrophy. The cross tabulation of this association is demonstrated in Table 3.9.

Table 3.9

Relation between hypertension and LV hypertrophy: Number (%) of people with and without LV hypertrophy tabulated against those with and without hypertension

		Hypertension		
		No	Yes	
LV	No	250 (78%)	74 (22%)	324 (100%)
Hypertrophy	Yes	17 (31%)	38 (69%)	55 (100%)
		267	112	379

Odds ratio* = 7.5 (95% CI 4.1 to 14)

(* adjusted for age and sex)

The relation of LV mass with CHD and its risk factors and with fetal and maternal measurements were similar in the two sexes. I therefore combined the sexes for all further analyses.

3.4.6 LV mass and CHD

LV mass was higher in men and women with CHD compared with those without the disease (Table 3.10). This association was strongest with 'hard' ECG evidence of ischaemia; men and women with Q waves on ECG had a markedly higher LV mass than those without, while men and women with a history of symptomatic angina alone did not have a significantly greater LV mass than those without.

People with CHD also had a higher prevalence of LVH (odds ratio=1.61, 95% CI .71 to 3.71). Corresponding figures for those with major Q waves and angina were 2.62 (95% CI .72 to 10.41) and 1.14 (95% CI .42 to 3.12) respectively.

Table 3.10

Mean (SD) LV mass and LV mass indexed by BSA according to presence or absence of CHD

CHD	n	LV mass (g)	LV mass/BSA (g/m^2)
Absent	340	137 (35)	84 (17)
Present	39	149 (46)	91 (22)
p* value		0.03	0.02
Major Q waves on ECG			
Absent	369	137 (36)	85 (18)
Present	10	169 (42)	101 (21)
p* value		0.01	0.007
Angina according to Rose questionnaire			
Absent	348	138 (36)	85 (17)
Present	31	144 (45)	89 (21)
p* value		0.2	0.2

(* p values obtained by logistic regression and adjusted for age and sex)

3.4.7 LV mass and CHD risk factors

I examined the relationship of LV mass to known risk factors for CHD including impaired glucose tolerance (IGT) and non-insulin dependant diabetes (NIDDM), plasma glucose, insulin and pro-insulin concentrations, serum lipid concentrations (total, LDL and HDL cholesterol and triglycerides) and plasma fibrinogen and factor VII concentrations.

In both sexes, LV mass and the prevalence of LVH were greater in those with NIDDM and IGT than people with normal glucose tolerance. This difference was less marked, but still present, after adjustment for age and body size (Table 3.11). The prevalence of LVH was also higher in people with NIDDM (27%) and IGT (20%) compared to those with normal glucose tolerance (10%) (p for difference<0.01).

Table 3.11

Mean (SD) LV mass and LV mass indexed by BSA according to diabetic status

Status	n	LV mass (g)	LV Mass/BSA (g/m^2)
Normal	251	134 (34)	84 (17)
IGT	68	147 (35)	87 (17)
Diabetic	55	151 (44)	90 (21)
All	374	138 (36)	85 (18)
p* value		<0.0001	0.01

(*adjusted for age and sex)

LV mass also rose with increasing fasting plasma glucose concentrations (Table 3.12). Similar associations were present with the 30 (p=0.01) and 120 (p<0.001) minute glucose values. On adjusting for age and body size, the relationships with the fasting and 120 minute values remained statistically significant (p=0.001 and 0.005 respectively).

Table 3.12

Mean (SD) LV mass and LV mass indexed by BSA according to fasting plasma glucose concentrations

Glucose (mmol/l)	n	LV mass (g)	LV Mass/BSA (g/m^2)
<4.3	71	132 (39)	83 (18)
4.3-	80	131 (31)	82 (16)
4.8-	73	135 (33)	84 (17)
5.2-	82	143 (35)	87 (17)
5.9+	72	151 (42)	90 (20)
All	378	138 (36)	85 (18)
p* value		0.0002	0.001

(* adjusted for age and sex)

LV mass tended to rise with increasing fasting plasma insulin concentrations (Table 3.13). There were similar findings with fasting pro-insulin and 32-33 split pro-insulin ($p<0.001$ for both) and with 30 and 120 minute insulin concentrations ($p=0.08$ and <0.001 respectively). The relationships were stronger with fasting and 120 minute insulin concentrations which reflect insulin resistance, compared with the 30 minute insulin concentration which reflects insulin secretion. On adjusting for age and sex, only the relationship with fasting insulin remained statistically significant.

Table 3.13

Mean (SD) LV mass and LV mass indexed by BSA according to fasting plasma insulin levels

Insulin (pmol/l)	n	LV mass (g)	LV Mass/BSA (g/sq m)
<24	68	123 (35)	82 (20)
24-	78	131 (29)	84 (16)
39-	79	137 (33)	85 (16)
68-	66	146 (39)	86 (18)
112+	76	155 (41)	90 (21)
All	367	138 (36)	85 (18.0)
p* value		<0.0001	0.01

(* adjusted for age and sex)

Unadjusted LV mass was greater in subjects with higher fasting concentrations of serum triglycerides ($p<0.0001$), total cholesterol ($p=0.02$) and LDL cholesterol ($p=0.03$) and showed a progressive reduction with increasing levels of HDL cholesterol ($p=0.002$). On adjusting for body size, the relationships with triglycerides and HDL cholesterol concentrations remained statistically significant. There was no correlation between LV mass and serum fibrinogen and clotting factor VII concentrations. The findings are summarised in Table 3.14.

Table 3.14

Relation between LV mass, LV mass/BSA and risk factors for CHD: simple correlations and significance values obtained using multiple linear regression

	LV mass		LV mass/BSA	
	r1	**p1**	**r2**	**p2**
Fasting glucose	0.18	<0.001	0.13	0.001
30 minute glucose	0.15	0.01	0.07	0.2
120 minute glucose	0.23	<0.001	0.14	0.005
Fasting insulin	0.29	<0.001	0.13	0.01
30 minute insulin	0.09	0.08	0.01	0.6
120 minute insulin	0.19	<0.001	0.06	0.15
Pro-insulin	0.37	<0.001	0.16	0.002
32-33 split pro-insulin	0.27	<0.001	0.07	0.1
Total cholesterol	0.13	0.02	0.02	0.5
LDL cholesterol	0.13	0.03	0.03	0.4
HDL cholesterol	- 0.22	0.002	- 0.14	0.02
Triglycerides	0.29	<0.001	0.17	0.001
Fibrinogen	0.04	0.9	0.03	0.5
Factor VII	0.11	0.09	0.04	0.9

r1 = simple correlation with LV mass

p1 = significance on multiple linear regression with LV mass adjusting for age and sex

r2 = simple correlation with LV mass/BSA

p2 = significance on multiple linear regression with LV mass/BSA adjusting for age and sex

3.4.8 LV mass and size at birth

Unadjusted LV mass was related to weight, length and head circumference at birth, rising with increasing birthweight (p=0.001), length (p=0.003) and head circumference (p=0.04) [Table 3.15]. These trends appeared to largely reflect the greater adult body size of bigger babies, because on adjusting for current body size, only the relation with length (Table 3.15) remained statistically significant. LV mass indexed by BSA rose from 80 g/m^2 in the lowest length group to 87 g/m^2 in the highest length group (p=0.03). The prevalence of LV hypertrophy also increased with increasing length, from 3.8% to 22.9% (p=0.008) across the range of length groups (Table 3.15). The relationships with length persisted even after adjusting for adult height (p=0.01 and 0.04 for LV mass and LV mass/BSA respectively). There were similar trends when the sexes were examined individually. The association between length and adjusted LV mass was no longer statistically significant (p=0.3) if systolic blood pressure was added to the regression equation. The strength of the association between birth length and LVH also diminished on adding systolic blood pressure to the logistic regression equation (p=0.08). There was no relation between ponderal index at birth and LV mass, LV mass/BSA or LVH

Table 3.15

Mean (SD) LV mass, LV mass/BSA and prevalence of LVH according to birth measurements

Birthweight (g)	n	LV mass (g)	LV mass/BSA (g/m^2)	% LVH
<2400	78	127 (33)	83 (18)	9
2400-	75	133 (32)	83 (16)	15
2650-	72	142 (38)	85 (18)	15
2835	63	134 (30)	85 (17)	11
3000+	91	152 (40)	88 (19)	20
All	379	138 (36)	85 (18)	14
p* value		0.001	0.2	0.1
Length (cm)				
<45.5	52	126 (33)	80 (15)	4
45.5-	119	138 (33)	85 (16)	12
47.0-	117	137 (37)	85 (18)	15
50.0+	87	146 (41)	88 (20)	23
All	375	138 (36)	85 (18)	14
p* value		0.003	0.03	0.008
Head circum-ference (cm)				
<33	62	129 (35)	83 (17)	10
33-	167	136 (34)	85 (17)	14
33.5-	74	140 (36)	84 (18)	15
34.5+	71	149 (43)	87 (19)	20
All	374	138 (36)	85 (18)	14
p* value		0.04	0.4	0.4
Ponderal index (kg/cm^3)				
<21	68	138 (42)	85 (19)	16
21-	80	132 (34)	84 (18)	15
24-	73	148 (38)	90 (20)	23
26-	71	133 (28)	83 (14)	9
29+	83	139 (38)	84 (17)	10
All	375	138 (36)	85 (18)	14
p* value		0.7	0.2	0.1

(* adjusted for age and sex)

3.4.9 LV mass and 'brain-sparing'

I expected babies with a higher head circumference to length ratio, a surrogate measure of experiencing the 'brain-sparing' effect in utero to have increased LV mass. There were no relationships between LV mass and LV mass/BSA, and head circumference to length ratio (Table 3.16). Although the prevalence of LVH rose with increasing head circumference to length ratio, there were no clear trends even though the association was statistically significant (Table 3.16). When length and head circumference were added simultaneously in a regression model, the relationship with LVH was significant with length alone ($p<0.01$) suggesting that the association was due to the effect of longer length rather than greater head circumference.

Table 3.16

Mean (SD) LV mass, LV mass/BSA and prevalence of LVH according to head length ratio

Head length ratio	n	LV mass (g)	LV mass/BSA (g/m^2)	% LVH
<0.678	77	146 (41)	88 (20)	23
0.678-	92	130 (34)	82 (17)	9
0.706-	102	141 (35)	87 (19)	15
0.723+	82	134 (35)	82 (15)	9
All	373	138 (36)	85 (18)	14
p value		0.2	0.1	0.03

3.4.10 LV mass and maternal measurements

There was no association between LV mass, LV mass/BSA and LVH, and maternal weight during pregnancy (Table 3.17). Unadjusted LV mass was positively related to maternal external conjugate pelvic diameter, intercristal diameter and interspinous diameter (Table 3.17), rising with increasing pelvic diameters ($p=0.02$, 0.07, 0.06

respectively). These relationships disappeared after adjusting for birth size. There were no associations between LV mass/BSA or LVH and maternal pelvic measurements.

Table 3.17

Mean(SD) LV mass, LV mass/BSA and prevalence of LVH according to maternal measurements

Maternal weight (lb)	n	LV mass (g)	LVM/BSA (g/m^2)	% LVH
<94	42	142 (35)	89 (19)	19
94-	58	130 (37)	80 (17)	7
108-	53	141 (32)	86 (16)	19
All	153	137 (35)	84 (17)	14
p* value		0.1	0.9	0.4
EC (cm)	N	LV mass (g)	LVM/BSA (g/m^2)	%
<17.8	40	136 (37)	86 (18)	17
17.8-	90	139 (31)	85 (15)	11
19.0+	74	146 (39)	89 (17)	24
All	204	141 (35)	87 (17)	17
p* value		0.02	0.1	0.3
IC (cm)				
<24.1	60	136 (31)	86 (15)	17
24.1-	61	138 (36)	86 (20)	15
25.4+	87	146 (39)	88 (18)	19
All	208	141 (36)	87 (18)	17
P* value		0.07	0.5	0.1
IS (cm)				
<21.6	53	139 (30)	87 (14)	17
21.6-	57	138 (35)	86 (20)	14
22.9+	98	144 (39)	87 (18)	19
All	208	141 (36)	87 (18)	17
p* value		0.06	0.5	0.1

(* adjusted for age and sex)

3.4.11 Concentric hypertrophy: Relative wall thickness (RWT)

RWT was similar in both sexes (0.4). It was strongly related to body size, rising with increasing weight (r=013, p=0.009), height (r=0.12, p=0.01) and BMI (r=0.22, p<0.001). Surprisingly, there was no correlation with BSA. RWT also rose strongly with age (r=0.20, p<0.001). It showed no associations with smoking, alcohol consumption, physical activity or social class.

Relation with blood pressure

RWT was strongly related to both systolic (r=0.36; p<0.001) and diastolic (r=0.31; p<0.001) blood pressures, rising with increasing blood pressure. These associations were independent of age and current body size. People with hypertension had a greater RWT than those without (p<0.001). This was true in both sexes and was independent of age and BMI.

Relation with CHD and its risk factors

RWT showed no relationship with CHD. Nor were there any links between RWT and major Q waves on ECG or angina. Higher RWT was however, associated with an adverse coronary risk factor profile. These findings are summarised in Table 3.18. RWT was significantly higher in people with diabetes (p<0.01) and rose with increasing fasting glucose concentrations (p<0.01), independently of age, body size and sex. When systolic blood pressure was also added to the multiple regression equation, the significance of these associations diminished but remained statistically significant. RWT was not significantly related to fasting insulin levels after adjusting for body size. It was however, related to fasting pro-insulin and 32-33 split pro-insulin concentrations, even after adjusting for age, sex, body size and systolic blood pressure. RWT was also significantly greater in those who had higher concentrations of triglycerides and total and LDL cholesterol levels, independent of age, sex and body size. The association with triglycerides became statistically non-significant after including systolic blood pressure.

HDL cholesterol was only weakly related to RWT. RWT was positively related to clotting factor VII concentrations (p=0.02), after adjusting for age, sex and body size. There was no relation with plasma fibrinogen concentrations.

Table 3.18

Relation between RWT and CHD risk factors: simple correlations and significance values obtained using multiple linear regression

Variable	Correlation (r)	p1	p2
Fasting glucose	0.23	0.0004	0.004
Fasting Insulin	0.18	0.12	0.19
Pro-insulin	0.26	0.0008	0.008
32-33 split proin	0.27	0.0002	0.0007
Triglycerides	0.18	0.005	0.06
Total chol	0.25	0.0001	0.0002
LDL chol	0.20	0.0009	0.0007
HDL chol	0.06	0.02	0.1
Factor 7	0.18	0.02	0.02
Fibrinogen	0.11	0.2	0.1

p1= significance on multiple linear regression with age, sex and body size

p2= significance on adding systolic blood pressure to the above equation

Relation with birth measurements

RWT was not related to birthweight. As with LV mass, there was a weak association with length at birth. RWT rose with increasing length (p=0.03), independently of age, sex and BMI. On adding systolic blood pressure to the multiple regression equation, this trend was no longer statistically significant (p=0.1). There was an inverse association between RWT and ponderal index at birth (p=0.02). On including systolic blood pressure this relationship also weakened (p=0.07). This relationship appeared to be due to the effect of longer length than due to any effect of lower birthweight. There were no relationships between RWT and head circumference.

Relation with maternal measurements

There were no significant correlations between RWT and maternal weight or pelvic size.

3.5 Summary

This part of the study examined the relation between LV mass and CHD, risk factors for the disease, and fetal growth.

Mean LV mass was greater in men than women and rose with increasing age, body size and blood pressure. These results are consistent with findings in Western populations. LV mass and percentages of subjects with LVH were greater in those with diagnosed CHD. This relationship was more strongly related to ECG evidence of CHD. Increased LV mass was also associated with an adverse coronary risk profile including NIDDM, higher concentrations of plasma glucose and insulin, higher serum triglyceride concentrations, lower HDL cholesterol concentrations, and with central obesity.

Increased LV mass was unrelated to small size at birth, suggesting that the association between adult CHD and small size at birth in our earlier study on the same cohort cannot be explained by changes in LV mass. Contrary to my hypothesis, LV mass rose with increasing birthlength. This finding did not appear to be explained by the longer length of male babies or by the higher LV mass in taller subjects. These findings are discussed in greater detail in the final chapter.

Chapter 4 ARTERIAL COMPLIANCE

4.1 Introduction

4.1.1 Significance of arterial compliance to the cardiovascular system

The term compliance refers to the distensibility or elasticity of the arteries. The major arteries perform two main functions (212-214). They act as conduits to supply blood from the left ventricle to all the various organs and tissues of the body; this is well known. The other main function, which is relatively less well known, is their function as a 'windkessel' (212-214). In systole, the left ventricle contracts against a closed mitral valve to expel incompressible blood at a high pressure into the aorta. The elastic properties of the aorta allow it to expand to accommodate this stroke volume (roughly 70-75 ml) and minimise the rise in blood pressure and left ventricular afterload. In diastole, the elastic recoiling of the aorta propels blood forward against a closed aortic valve. The next ventricular contraction occurs roughly when pressure declines to about two-thirds of the peak systolic pressure. This mechanism serves to supply blood at a steady flow throughout the arterial system by maintaining adequate pressure as well as smoothening the pulsatile flow from the heart. If compliance is reduced, this cushioning effect is impaired leading to increased systolic pressure, decreased diastolic pressure and raised pulse pressure. The decreased compliance also reduces coronary blood flow (which occurs only in diastole) and increases left ventricular afterload.

4.1.2 Aortic compliance

4.1.2.1 Elastin

The compliance of the aorta is due to the presence of elastin, a long-lived scleroprotein (212,215-217). Elastin is characterised by a low elastic modulus indicating it is highly extensible. It can be extended to over twice its normal length before it breaks and forms 30-70% of the dry weight of major arteries (215). The properties of elastin result from its molecular structure (218,219). It is made up of covalently cross-linked desmosines rich in

hydrophobic but, poor in hydrophilic amino acids. During stretch, water molecules associate with non-polar side chains disrupting the hydrophobic arrangement. Aggregation of non-polar groups in turn expel water to revert to their original hydrophobic arrangement and this causes recoil. Therefore the presence of elastin enables aorta to stretch in response to pressure and revert to its original form when stress is removed.

4.1.2.2 Inter-relationship between elastin and collagen

Another protein, collagen, also forms a prominent part of vessel structure and provides much of the tensile strength (212,216,218,220). Collagen is characterised by high stiffness, reflected in a much higher elastic modulus (over 100 times greater than elastin). It breaks when extended by 10% of its original length. Elastin and collagen function together (212,214,218,220,221). At low and moderate pressures, elastin fibres stretch and distribute stress equally throughout the wall. As blood pressure rises further, stress is borne increasingly by collagen. At pressures over 200 mmHg, collagen fibres take over completely and absorb the stress, becoming resistant to further stretch of vessel wall. Therefore as blood pressure rises, arteries become functionally stiffer. This inter-relationship between collagen and elastin allows for arterial expansion over a range of pressures and prevents vessel rupture.

4.1.2.3 Structural arrangement of elastin and collagen in the vessel wall

The structural arrangement of elastin within the arterial wall is important. The tunica media forms the largest part of the vessel wall and is the major determinant of its mechanical properties. It is made up of lamellar units arranged in an orderly manner (219). Elastic fibres (of which elastin is the major component – 90%; the remaining 10% is made up of microfibrillar proteins) are arranged in concentric lamellae and are seen as thick fibres while finer elastin fibres form networks between them. This provides extensibility to the vessel and distributes stress evenly throughout the wall. Collagen fibres are interspersed between elastin lamellae and are arranged circumferentially. So

far no physical attachment between elastin and collagen fibres have been demonstrated. Smooth muscle cells are dispersed mostly parallel to elastic laminae while some are arranged longitudinally.

4.1.2.4 Changing distribution with distance from heart

The distribution of elastin and collagen differ in relation to distance from the heart (212,216,220). The proportion of elastin becomes gradually less with increasing distance from the heart while the opposite is true for collagen. Animal studies estimate the relative proportions of elastin and collagen to be 60 and 40% in thoracic and 30 and 70% in extra-thoracic arteries respectively (212,215,217). Elastic laminae are greater in number in the blood vessels near the heart (which are more elastic) while they are fewer in vessels away from heart (which are more muscular). This suggests that the lamellar unit is responsible for elastic function. Therefore the arteries close to the heart are the most compliant. This may reflect the particular importance of the windkessel function of the aorta (see section 4.1.1).

4.1.3 Factors known to affect arterial compliance

Arterial compliance is known to be related to age, sex, body size, blood pressure, atherosclerosis, NIDDM and insulin resistance (214,216,217,222-232). With ageing, elastin fibres undergo rupture due to the wear-and-tear effect caused by the cyclic repetitive stress on the vessel wall. These fibres are not re-generated (see below). Stress is therefore increasingly transferred to collagen leading to decreased compliance and increased pulse pressure. Collagen is also synthesised in response to arterial wall stretch causing further reduction in compliance. The gradual loss of elastin and its replacement with collagen explains the reduction in compliance that occurs with ageing.

Arterial compliance is decreased in women compared to men, and is lower in those with greater body size (214,216,217,222). It has been suggested that men have reduced

compliance because of their greater body size. The association between greater body size and reduced compliance is believed to be mediated through blood pressure. However, the exact mechanisms for these findings remain speculative.

Arterial compliance is strongly related to blood pressure (224-229) although the temporal association between the two remains unclear. Reduced compliance may play a role in the initiation and/or perpetuation of raised systolic blood pressure. When compliance is reduced, systolic blood pressure and pulse pressure rise. This rise in pressure leads to synthesis of collagen in response to stretch of the arterial wall. The effects of ageing tend to amplify this. Raised blood pressure also causes increased wear-and-tear on the vessel wall. This causes further reduction in compliance leading to a positive feedback loop. The process is self-limiting at a point where a particular pulse pressure causes no further stretch of vessel wall. Evidence also suggests that the rise in blood pressure cannot solely account for the decrease in compliance. While drug treatment of hypertension may bring blood pressure down to normal limits, compliance may continue to be low depending on the type of drug used (225,226). It has also been shown that subjects with borderline hypertension have lower levels of compliance than would be expected from their blood pressure alone (214). Other studies have shown that in hypertensives, the reduction in compliance may occur before the rise in blood pressure occurs (225,233). Reduced compliance has also been linked to LVH (229,234,235). It is probable that the increased afterload as well as the raised systolic pressure associated with reduced compliance lead to LVH.

Atherosclerotic arteries have been shown to have reduced compliance (214,217,236). There is a strong relation between arterial stiffness measured by non-invasive ultrasonography in vivo and the severity of atherosclerosis in pathology specimens at necropsy. This may be due to the accumulation of smooth muscle cells, lipids, macrophages and calcium in the arterial wall (214,217). It may also be that the intima of

vessels with reduced compliance is more susceptible to atherosclerosis from injury due to pulsatile stress (214).

NIDDM and insulin resistance have been associated with reduced compliance (230-232). It has been suggested that the thickening of the vessel wall and the associated accelerated atherosclerosis in NIDDM may lead to a reduction in compliance. While the exact mechanism between insulin and compliance remains unclear, it is possible that the vascular hypertrophy associated with hyperinsulinaemia may lead to reduced compliance (232).

4.1.4 Reduced compliance as a cardiovascular risk factor

Reduced compliance has been associated with an increased risk of cardiovascular disease including CHD and stroke (214,216,217, 233,236-239). Aortic compliance assessed by MRI was lower in patients with CHD compared with normal healthy age-matched volunteers (224). In another study, aortic stiffness index (assessed by ultrasonography) was higher in patients with myocardial infarction compared to normal volunteers (239). Aortic compliance assessed by doppler ultrasonography was also found to be lower in normotensive CHD cases compared with normotensive controls even though they had similar blood pressures (236). The coronary arteries receive all their blood supply only in diastole. Therefore reduced compliance (which lowers diastolic blood flow due to impaired elastic recoil of aorta) may cause myocardial ischaemia, especially when oxygen demand is increased. As mentioned above, reduced compliance has also been associated with a number of known risk factors for CHD. The temporal association is however, unclear as all of them are also closely related to one another. Therefore reduced arterial compliance may be linked to increased risk of CHD either independently or through its association with CHD risk factors.

4.1.5 Reduced compliance and fetal growth

Apart from the factors mentioned above, little is known about the determinants of arterial compliance. Recent evidence from a study in Sheffield has raised the possibility that decreased compliance may have its origins in impaired growth in utero (240). This study showed that compliance in the aorto-iliac and femoro-popliteal arterial segments in middle-aged adults were lower in those who were born with lower weight or smaller abdominal circumference at birth (Table 4.1). Martyn et al suggested that babies with reduced fetal growth may have impaired synthesis of elastin resulting in the development of blood vessels which have reduced compliance in later life (240,241).

Table 4.1

Mean pulse wave velocity in aorto-iliac and femoro-popliteal-tibial arterial segments according to measurements made at birth

	Mean pulse wave velocity (m/s)					
	Aorto-iliac	p value	n	Femoro-popliteal -tibial	p value	n
Birthweight (lb)						
<=5.5	9.1		11	12.8		10
-6.6	8.5		37	12.4		45
-7.5	8.6		73	11.5		79
-8.5	8.3		58	10.7		60
>8.5	8.6	0.5	15	11.3	0.05	19
Abdominal circumference (in)						
<=11.5	9.3		44	13.1		48
-12.25	8.3		42	10.8		46
-13	8.4		62	11.1		73
>13	8.0	0.01	45	10.8	0.03	44

Pulse wave velocity is inversely related to compliance

(Adapted from Martyn et al, reference 240)

4.1.5.1 Importance of early life effects on elastin synthesis: Critical periods of elastin growth

Elastin synthesis occurs almost entirely during fetal and early postnatal life (215,242-244). Studies in human abortuses have demonstrated soluble elastin fragments (tropoelastin) at around 2 months of gestation (215,244). These fragments undergo cross-linking to produce mature elastin. Synthesis of elastin continues during the remainder of gestation reaching a peak in late gestation and continuing into early postnatal life. After that the rate of elastin synthesis decreases and stops around 3-6 months of postnatal life (215,244).

Elastin has a long half-life (212,215). This has been estimated by studies measuring the racemisation of L-aspartate, where the presence of D-aspartate correlates with time elapsed since protein synthesis (245,246). It has been shown that the age of elastin correlates with the age of the subject; this is consistent with elastin being laid down in early life with no appreciable synthesis thereafter. This suggests that any disruption in normal growth of elastin during fetal life may have permanent consequences (247). Evidence from rat studies show that fetal growth inhibition by administration of methotrexate during a period of rapid cellular growth in the developing aortic wall affects its DNA content leading to a permanent reduction in elastin content (248).

4.1.5.2 Factors influencing elastin growth

The factors that determine elastin growth are not yet clearly defined. There is some evidence to suggest that blood flow and growth factors in fetal life may play a role. In rabbits, ligation of one external carotid artery during fetal life produced a reduction in DNA content and elastin content in the ipsilateral artery compared with the artery on the opposite side (249). In humans, a necropsy study showed that in children who were born with a single umbilical artery, the ipsilateral iliac artery was elastic while the contralateral artery was thin walled and muscular (250). In such cases, the entire placental flow would

have been through the common iliac artery on the side of the existing umbilical artery. In living children aged 5-9 years, those born with a single umbilical artery had more compliant iliac arteries on that side than in the opposite iliac artery suggesting that these changes persist (251).

IGF-1 is an important growth factor in intrauterine life. It is influenced by nutrient concentrations in fetal blood and fetal IGF concentrations are reduced in IUGR (101,106,252,253). IGF-1 has been shown in vivo to increase tropoelastin gene transcription (252). Lower IGF-1 concentrations in poorly growing fetuses may therefore lead to reduced elastin synthesis.

4.1.5.3 Possible link between poor fetal growth and reduced arterial compliance

Fetal undernutrition during critical periods of organ growth and maturation may cause decreased synthesis of elastin, permanently affecting the structure of blood vessels. Due to the relative decreased ratio of elastin in relation to collagen, the compliance of the aorta and other large arteries is likely to be reduced. This may occur by either of the mechanisms mentioned below.

Growth retardation in utero causes an alteration in fetal blood flow – the 'brain sparing' effect, which preserves blood flow to the brain thereby maintaining its supply of oxygen and nutrients at the expense of the abdominal organs and limbs (refer Chapter 3, section 3.1.8). This altered flow may impair elastin synthesis during critical periods of blood vessel development.

Poorly growing fetuses also have an abnormal IGF-1 axis. It is possible that this also reduces elastin synthesis.

4.1.6 Pulse wave velocity and arterial compliance; physical principles

The compliance or elasticity of a substance is characterised by its elastic modulus (212,213). For an elastic substance, within certain limits, strain (i.e., the deformity) is proportional to stress (i.e., the force) and is expressed as its elastic modulus (212). Arteries can be considered as visco-elastic cylindrical tubes filled with an incompressible fluid, blood. In response to a pressure change, the wall of the artery dilates radially. The circumferential elastic modulus relating to the radial expansion of the artery in response to the stress of a pressure change is given by Peterson's modulus, $E_p=\Delta PR/\Delta R$ where ΔR is the change in radius due to pressure change ΔP (usually the pulse pressure) and R is the mean radius. Therefore a substance with a low elastic modulus dilates more in response to a pressure change.

The elastic property of the arterial wall also plays an important role in determining the velocity of propagation of a pulse wave. This is given by the equation, $c=(Eh/2R\rho)^{1/2}$ where E is the elastic modulus, h is the wall thickness, R is the radius and ρ is the density of blood. The assumptions underlying this equation are that the tube is filled with an incompressible fluid and has a very thin wall. This equation shows that arteries with a low elastic modulus have a low pulse wave velocity and are more compliant.

In practice, it is easier to calculate the velocity of a propagation wave by measuring the distance travelled by a pulse wave between two points and dividing it by the transit time rather than calculating it from the formula using the elastic modulus, wall thickness and radius. The velocity thus obtained is useful as a surrogate measure of elasticity. It is possible to measure the velocity of the pulse pressure wave or flow wave or dilatation wave. The shape of the pressure wave depends on the duration of systole, mean arterial pressure, vasomotor tone, pulse wave velocity and wave reflections (212). The pressure wave rises to a peak and falls in an approximately exponential manner in the ascending aorta. The pattern remains similar in the thoracic aorta and the arteries to the upper

limbs, head and neck. As the distance from the heart increases, there is a shortening in the amplitude and a delay in the foot of the wave, while the peak of the pressure wave remains almost synchronous in the various segments.

The flow wave pattern depends on ventricular preload, ventricular contraction and ventricular afterload (212). In humans, two flow wave patterns are seen in the ascending aorta. In younger people, the wave has a rounded peak with a smaller secondary positive wave. In adults the wave rises to a late peak with a more gradual fall. In the descending thoracic aorta, the peak is more rounded with an incisura and a prominent secondary wave. In the upper limb arteries the incisura is sharper with a more significantly peaked secondary wave. As the distance from the heart increases, the secondary wave becomes more prominent.

The dilatation or diameter wave depends upon the radial stress exerted (due to pressure) on the vessel wall and the condition of the wall (212). This wave has an almost upright upstroke, a peak and then a gradual, almost exponential, downslope in the ascending aorta. The patterns are similar in the descending aorta and upper limb vessels. With increasing distance from the heart as in the lower limb arteries, the downslope becomes sharper.

In all these waves, measurements are made at the foot of the wave as high frequency waves which get attenuated are present at the foot and are least likely to suffer from interference due to wave reflections (212).

4.1.7 Methods of measuring compliance:

Compliance can be measured by intra-arterial catheterisation, doppler ultrasonography and photoplesythmography (212,214,216,217,254-256). All these techniques are similar

in that they calculate the velocity of wave propagation by measuring the transit time taken for a wave to traverse a given distance. Intra-arterial catheterisation is used to measure the pressure wave velocity in which catheters tipped with pressure transducers are inserted over two points of an artery and pulse wave velocity calculated. Flow wave velocity can be measured by doppler ultrasonography. In this procedure, two continuous doppler wave transducers are placed over two separate points of the artery and pulse wave velocity calculated. The velocity of the dilatation wave can be measured by the principle of photoplesythmography. I used this method to measure pulse wave velocity; the method is described in below in section 4.2.1.

4.1.8 The Mysore cohort and study

The Mysore cohort provided an opportunity to test whether small size at birth was associated with reduced arterial compliance in adult life and whether this was one possible mechanism by which poor fetal growth led to adult CHD in this Indian population. In particular I was interested to examine arterial compliance in relation to neonatal body proportions which might suggest brain-sparing: higher head circumference to birthweight ratio and higher head circumference to length ratio.

After commencing the project and while reading-up the background, I also decided to compare the compliance between the right and left radial arteries. The right and left radial arteries have different embryonic origins – the right arises from the brachiocephalic arch and is preductal while the left is from the left subclavian, a direct branch of the aorta, and is postductal. In growth retarded fetuses with alteration of blood flow, there is increased blood flow through the left ventricle while the flow from the right ventricle through the ductus arteriosus is relatively reduced. Therefore it is possible that the right brachial segment may receive relatively more blood flow than the left and may consequently be more compliant.

4.2 Methods

4.2.1 Procedure

In my study, pulse wave velocity was measured by a non-invasive optical method using the principle of photoplesythmography (256). This involves measuring the velocity of the pulse dilatation wave by detecting its passage between two probes positioned a known distance apart on the skin above the arteries. The probes consist of an infra red emitter and detector. Infra red radiation from the emitter passes into the skin, vascular tissues and blood. When the wave of dilatation passes the probe the volume of blood in the vicinity increases and the amplitude change is detected by the infra red detector. This output is captured by an analog-to-digital-converter at a rate of 1 kHz, interfaced to a computer (Appendix 4; Figure 4.1). The hardware consists of a multiplexer, analog-to-digital converter and variable gain amplifier. The software allows the capture, real-time display and storage of the signals from the detectors as well as detecting the foot of the systolic upstroke and measuring the time delay between the two sites.

This method has been validated against measurement of pulse wave velocity obtained using intra-arterial catheterisation, and yields similar estimates to those obtained using doppler ultrasonography that has been shown to give reproducible estimates of arterial compliance (255,256).

This method was used to calculate the transit time taken for a wave of contraction originating in the left ventricle to reach the peripheral arteries. This involved placing probes over the heart and over the peripheral artery. The probe over the heart records the ECG and the probe over the peripheral artery records the pulse wave tracing (Appendix 4; Figure 4.2). The transit time is calculated as follows: Verticals are drawn at the deflection of the QRS complex of the ECG and the beginning of the upstroke of the pulse wave (Appendix 4; Figure 4.1). The customised computer program measures the

time delay between these two verticals (transit time). The distance between the probes is measured using a measuring tape. Pulse wave velocity is calculated as the distance between the probes divided by the transit time. Pulse wave velocity is inversely proportional to arterial compliance. Thus a higher pulse wave velocity indicates a stiffer arterial wall and reduced compliance. Pulse wave velocity was measured directly in the following segments: aorto-radial (both sides), aorto-femoral and aorto-posterior tibial. Pulse wave velocity in the femoro-posterior tibial segment was calculated from the values obtained for the aorto-femoral and aorto-posterior tibial segments by dividing the distance between the points by the difference in transit times. All information was entered on a data collection form (Appendix 4; Figure 4.3). I was trained by Dr Christopher Martyn, Consultant Epidemiologist, MRC Environmental Epidemiology Unit, Southampton.

4.2.2 Intraobserver variation

I repeated the recording of pulse wave traces in all arterial segments in 10 subjects within a month of their initial examination; t tests there were no significant differences between the two measurements. These data are presented in Appendix 5.

4.3 Results

Of the 435 men and women who participated in this study, only one woman refused the arterial compliance measurement. A further six were excluded from the analysis of the aorto-femoral segment because of inadequate trace quality. The left radial artery trace was recorded only in 417 subjects as I decided to record this segment only after starting the data collection. This analysis therefore includes:

434 subjects (237 men and 197 women) for the aorto-right radial and aorto-posterior tibial segments,

428 subjects (236 men and 192 women) for the aorto-femoral and femoro-posterior tibial segments, and

417 subjects (224 men and 193 women) for the aorto-left radial segment.

Pulse wave velocity in the right and left aorto-radial, right aorto-femoral and right aorto-posterior tibial segments was normally distributed while that in the right femoro-posterior tibial segment was skewed. Data were logarithmically transformed to obtain a normal distribution curve.

4.3.2 Pulse wave velocity and sex, age and body size

Mean pulse wave velocity tended to be higher in men than in women in four of the arterial segments measured (Table 4.2). There was no statistically significant difference in pulse wave velocity in the femoro- posterior tibial segment between the two sexes (Table 4.2).

Table 4.2

Mean (SD) pulse wave velocity in the Mysore men and women

Segment	Men (n=238)	Women (n=197)	All (n=434)	P value
Aorto-Rt radial	4.32 (0.45)	3.92 (0.40)	4.14 (0.47)	<0.01
Aorto-Lt radial	4.25 (0.52)	3.87 (0.43)	4.07 (0.51)	<0.01
Aorto-femoral	3.35 (0.51)	3.19 (0.50)	3.28 (0.51)	<0.01
Aorto-posterior tibial	5.86 (0.66)	5.63 (0.58)	5.71 (0.64)	<0.01
Femoro-posterior tibial*	13.46 (1.54)	13.60 (1.58)	13.59 (1.56)	0.5

* Geometric mean and SD

Pulse wave velocity in this Indian population was lower than that of a population from Sheffield in the UK, measured using the same technique (Phillips N, unpublished data, Table 4.3). The UK subjects were however, older (age 69-72 years) than the Mysore cohort.

Table 4.3

Mean pulse wave velocity in the Sheffield men and women

Pulse wave velocity (m/s)	Men (n=102)	Women (n=42)	All (n=144)
Aorto-Rt radial segment	**4.83**	**4.20**	**4.65**
Aorto-femoral segment	**4.74**	**4.14**	**4.56**
Aorto-posterior tibial segment	**6.73**	**5.92**	**6.49**

The relationships of PWV with age, body size and coronary heart disease risk factors were similar in the two sexes and, as for LV mass, they have been combined in the following analyses.

Mean pulse wave velocity rose with increasing age in both sexes and in all arterial segments ($r=0.08$ to 0.24; $p<0.05$ for all), except for the femoro-posterior tibial segment. On including systolic blood pressure in the regression model, the relationship between age and pulse wave velocity in both the radial segments was no longer statistically significant ($p=0.3$ and 0.2 in the right and left radial segments respectively) while those in the aorto-femoral and aorto-posterior tibial segments remained statistically significant ($p<0.001$ and $p=0.004$ respectively).

In men, mean pulse wave velocity increased with increasing weight, height, BMI and BSA in the four arterial segments measured directly ($r=0.12$ to 0.40). There were similar trends in women; however height was unrelated to pulse wave velocity in women ($r=0.01$ to 0.14). The relationships with body size tended to be weaker in women. Pulse wave

velocity in the femoro-posterior tibial segment was unrelated to height in both sexes although it tended to rise with increasing weight, BMI and BSA (r=0.10 to 0.15). Since BSA was the body size measurement most strongly correlated with PWV, it was used to adjust for current size in subsequent analyses. On adjusting for BSA, the difference in pulse wave velocity between the two sexes diminished but remained statistically significant ($p<0.05$ to <0.01).

4.3.3 Pulse wave velocity and adult 'lifestyle' factors

Pulse wave velocity was unrelated to smoking, alcohol consumption or socio-economic status.

4.3.4 Pulse wave velocity in the right and left radial arteries

I compared the velocities in the right and left radials to see whether there were any significant differences between the segments. Although pulse wave velocity in the left artery was slightly lower (4.07 m/s Vs 4.14 m/s; Table 4.2), this difference was not statistically significant. Both segments showed similar trends in relation to CHD risk factors as well as maternal and fetal measurements.

As there was no significant difference between PWV in the two radial segments, and the aorto-posterior tibial segment is a 'combination' of the aorto-radial and femoro-posterior tibial segments, I have restricted presenting the following results to the aorto-right radial, aorto-femoral and femoro-posterior tibial segments.

4.3.5 Pulse wave velocity and blood pressure

Pulse wave velocity in all arterial segments was strongly related to blood pressure, rising with increasing systolic and diastolic blood pressures (Tables 4.4 and 4.5) although it was weaker in the femoro-posterior tibial segment in comparison to the other segments (Tables 4.4 and 4.5). PWV in this segment showed a stronger correlation with ankle

blood pressure (r=0.14 and 0.16 for systolic and diastolic blood pressure respectively) than arm blood pressure (r=012 for both systolic and diastolic blood pressure). Men and women with hypertension had higher pulse wave velocities in all segments than those with normal blood pressure (Table 4.6).

Table 4.4

Mean pulse wave velocity (m/s) according to systolic blood pressure

Systolic blood pressure (mm Hg)	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
<108	3.97 (80)	3.06 (80)	11.55 (80)
108-	4.04 (90)	3.16 (90)	13.75 (90)
116-	4.16 (84)	3.22 (81)	14.56 (81)
131-	4.19 (93)	3.40 (90)	13.81 (90)
145+	4.30 (87)	3.53 (87)	14.48 (87)
All	4.14 (434)	3.28 (428)	13.59 (428)
p value	<0.001	<0.001	0.009
p* value	<0.001	<0.001	0.03

*adjusted for age, sex and body size; figures in parentheses indicate number of subjects

Table 4.5

Mean pulse wave velocity (m/s) according to diastolic blood pressure

Diastolic blood pressure (mm Hg)	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
<67	3.95 (84)	3.08 (84)	12.55 (84)
67-	4.05 (83)	3.18 (82)	13.20 (82)
73-	4.14 (93)	3.31 (92)	12.80 (92)
79-	4.19 (85)	3.28 (82)	15.03 (82)
86+	4.33 (89)	3.51 (88)	14.73 (88)
All	4.14 (434)	3.28 (428)	13.60 (428)
p value	<0.001	<0.001	0.004
p* value	<0.001	<0.001	0.01

* adjusted for age, sex and body size; figures in parentheses indicate number of subjects

Table 4.6

Mean pulse wave velocity in those with and without hypertension

Segment	Pulse wave velocity (m/s)	
	Without hypertension (n=298)	With hypertension (n=137)
Aorto-Rt radial	4.09	4.24
Aorto-femoral	3.19	3.46
Femoro-posterior tibial	13.06	14.73

4.3.6 Pulse wave velocity and pulse rate

A higher pulse rate was associated with a greater pulse wave velocity in all the arterial segments (r=0.10 to 0.28; p=0.05 to <0.001). These relationships persisted and remained statistically significant even after including age, sex, body size and systolic blood pressure in the multiple regression model.

4.3.7 Pulse wave velocity and LV mass

Except for PWV in the femoro-tibial segment, mean pulse wave velocity tended to rise with increasing LV mass, even after adjusting for body surface area (Table 4.7). Pulse wave velocity tended to be higher in men and women with LV hypertrophy (aorto-Rt radial 4.19 Vs 4.13; aorto-femoral 3.42 Vs 3.24; femoro-posterior tibial 14.58 Vs 13.46 m/s in those with and without hypertrophy respectively).

Table 4.7

Relation of pulse wave velocity to LV mass: simple correlations and significance values obtained using linear regression

Segment	LV mass		LV mass adjusted for BSA	
	r	p	r	p
Aorto-Rt radial	0.21	<0.001	0.08	0.1
Aorto-femoral	0.21	<0.001	0.15	0.004
Femoro-posterior tibial	0.06	0.3	0.01	0.8

4.3.8 Pulse wave velocity and CHD

There were no statistically significant differences between pulse wave velocity in any of the arterial segments in subjects with and without CHD (aorto-Rt radial 4.15 Vs 4.06; aorto-femoral 3.27 Vs 3.33; femoro-posterior tibial 13.60 Vs 12.93 m/s in those without and with CHD respectively). Similarly there were no statistically significant relationships with major Q waves on ECG or angina.

4.3.9 Pulse wave velocity and risk factors for CHD

I examined the relationship of pulse wave velocity to known risk factors for CHD (Table 4.8).

Pulse wave velocity in the aorto-femoral and femoro-posterior tibial segments tended to be higher in people with NIDDM and impaired glucose tolerance compared to those with normal glucose tolerance (Table 4.8), and in those with higher fasting, 30 and 120 minute plasma glucose concentrations (Table 4.9). PWV in the radial segments were not significantly related to glucose concentrations. The strongest relationships were with PWV in the distal arterial segment (femoro-posterior tibial segment).

PWV tended to rise with plasma insulin concentrations (Table 4.9). The relationships between the various arterial segments and insulin diminished on adjusting for current body size. There were similar, indeed stronger correlations between PWV and plasma pro-insulin and 32-33 split pro-insulin concentrations (Table 4.9). The strongest relationships were with PWV in the proximal arterial segments (aorto-radial and aorto-femoral segments.

Pulse wave velocity was higher in subjects with raised serum triglyceride concentrations (Table 4.9). None of the other lipids showed any relation with pulse wave velocity. Pulse wave velocity also tended to be higher in those with a greater waist to hip circumference

ratio. There were no relations between pulse wave velocity and either factor VII or fibrinogen concentrations.

Table 4.8

Mean pulse wave velocity according to glucose tolerance

	Pulse wave velocity (m/s)		
	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
Normal	4.13 (288)	3.25 (288)	12.81(288)
Glucose intolerance	4.17 (75)	3.32 (75)	15.18 (75)
NIDDM	4.13 (65)	3.42 (64)	15.33 (64)
All	4.14 (428)	3.28 (422)	13.59 (422)
P value	0.8	0.01	<0.001

Figures in parentheses indicate numbers

Table 4.9

Relation of pulse wave velocity to risk factors for CHD: simple correlations and significance values obtained using linear regression

	Aorto-Rt Radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
Fasting glucose	0.04	0.15*	0.15**
30 min glucose	0.16	0.15	0.15**
120 min glucose	0.06	0.10	0.16*
Fasting insulin	0.10	0.16	0.12
30 min insulin	0.14*	0.12	<0.01
120 min insulin	0.12*	0.11	0.15*
Proinsulin	0.22*	0.26*	0.15*
32-33 split proinsulin	0.18*	0.22*	0.13
Total cholesterol	0.05	0.10	0.06
LDL cholesterol	0.02	0.05	0.02
HDL cholesterol	- 0.07	0.01	- 0.07
Triglycerides	0.16	0.16	0.16**
Waist/hip	0.38*	0.29*	0.09
SS/TR	0.23	0.10	0.06
Fibrinogen	- 0.05	0.06	<0.01
Factor VII	0.06	0.04	0.09

* p <0.05

** p <0.01

(p values adjusted for age, sex and BSA)

4.3.10 Pulse wave velocity and birth size

Mean pulse wave velocity tended to rise with increasing birthweight; on adjusting for current body size this relationship disappeared (Table 4.10). There were no significant relations between pulse wave velocity and length, head circumference or ponderal index at birth (Table 4.10). However pulse wave velocity in the femoro-tibial segment had a weak inverse association with ponderal index, which persisted after adjusting for age, sex, and BSA.

Table 4.10

Mean pulse wave velocity (m/s) according to birth measurements

Birth weight (g)	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
<2400	4.12 (86)	3.25 (86)	13.74 (86)
2400-	4.05 (88)	3.19 (87)	13.87 (87)
2650-	4.12 (82)	3.28 (79)	13.46 (79)
2835-	4.07 (70)	3.26 (69)	12.94 (69)
3000+	4.26 (108)	3.38 (107)	13.46 (107)
All	4.14 (434)	3.28 (428)	13.60 (428)
p value	0.02	0.02	0.6
p* value	0.9	0.8	0.3
Birth length (cm)			
<45.5	4.13 (57)	3.29 (56)	12.55 (56)
45.5-	4.06 (135)	3.24 (132)	13.46 (132)
47.0-	4.19 (133)	3.31 (132)	13.32 (132)
50.0+	4.14 (105)	3.29 (104)	14.30 (104)
All	4.14 (430)	3.28 (424)	13.59 (424)
p value	0.2	0.6	0.1
P* value	0.8	0.8	0.6
Head circumference (cm)			
<33.0	4.08 (70)	3.29 (69)	14.01 (69)
33.0-	4.13 (192)	3.26 (190)	13.07 (190)
33.5-	4.14 (86)	3.32 (84)	13.46 (84)
34.5+	4.17 (81)	3.29 (80)	14.01 (80)
All	4.14 (429)	3.28 (423)	13.59 (423)
p value	0.2	0.7	0.6
P* value	0.8	0.9	0.4
Ponderal index (kg/cm^3)			
<21	4.12 (83)	3.27 (83)	13.74 (83)
21-	4.14 (89)	3.22 (88)	14.15 (88)
24-	4.14 (82)	3.29 (81)	14.01(81)
26-	4.12 (81)	3.29 (79)	13.33 (79)
29+	4.14 (95)	3.33 (93)	12.55 (93)
All	4.14 (430)	3.28 (424)	13.59 (424)
p value	0.8	0.3	0.08
P* value	0.8	0.8	0.06

* adjusted for age, sex and BSA; figures in parentheses indicate number of subjects

4.3.11 Pulse wave velocity and 'brain-sparing'

While I expected higher PWV (lower compliance) in subjects who may have been subjected to 'brain-sparing' effects in utero, as measured by higher head circumference to length ratio, there were no significant relationships between them (Table 4.11).

Table 4.11

Mean pulse wave velocity (m/s) according to head circumference to length ratio

Head circumference to length ratio	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
<0.678	4.18 (107)	3.36 (106)	13.60 (106)
0.678-	4.17 (109)	3.25 (109)	13.87 (109)
0.706-	4.10 (117)	3.28 (115)	13.60 (115)
0.723+	4.10 (95)	3.25 (92)	12.81 (92)
All	4.14 (428)	3.28 (422)	13.59 (422)
p value	0.2	0.2	0.3
P* value	0.8	0.6	0.3

* adjusted for age, sex and BSA; figures in parentheses indicate number of subjects

4.3.12 Pulse wave velocity and maternal size

Mean pulse wave velocity tended to be higher in men and women born to mothers who had been lighter during pregnancy; this was statistically significant for the aorto-femoral (Table 4.12) and left radial segments. Pulse wave velocity in the aorto-posterior tibial segment tended to be higher in those whose mothers had smaller external conjugate pelvic diameters; there were no relationships with any of the other arterial segments (Table 4.12). There were no relationships between pulse wave velocity and maternal intercristal and interspinous pelvic size (Tables 4.12)

Table 4.12

Mean pulse wave velocity (m/s) according to maternal measurements

Maternal weight (lb)	Aorto-Rt radial segment	Aorto-femoral segment	Femoro-posterior tibial segment
<94	4.11 (45)	3.34 (45)	12.81 (45)
94-	4.11 (72)	3.26 (72)	13.20 (72)
108+	4.02 (59)	3.15 (56)	15.49 (56)
All	4.08 (176)	3.25 (173)	13.87 (173)
p value	0.2	0.05	0.04
p* value	0.2	0.02	0.2
External conjugate diameter (cm)			
<17.8	4.13 (46)	3.29 (46)	14.44 (46)
17.8-	4.13 (111)	3.39 (111)	12.55 (111)
19.0+	4.04 (84)	3.25 (81)	14.01 (81)
All	4.10 (241)	3.33 (238)	13.46 (238)
p value	0.2	0.4	0.9
p* value	0.2	0.2	0.6
Intercristal diameter (cm)			
<24.1	4.08 (69)	3.30 (68)	13.46 (68)
24.1-	4.15 (73)	3.36 (73)	13.20 (73)
25.4+	4.08 (103)	3.31 (101)	13.60 (101)
All	4.10 (245)	3.33 (242)	13.46 (242)
p value	0.9	0.9	0.9
p* value	0.5	0.3	0.9
Interspinous diameter (cm)			
<21.6	4.10 (58)	3.34 (57)	12.68 (57)
21.6-	4.14 (71)	3.33 (71)	14.01 (71)
22.9+	4.08 (116)	3.31 (114)	13.46 (114)
All	4.10 (245)	3.33 (242)	13.46 (242)
P value	0.6	0.7	0.6
P* value	0.3	0.1	0.7

* adjusted for age, sex and BSA; figures in parentheses indicate number of subjects

4.4 Summary

In this part of the study, PWV (a surrogate measure of arterial compliance) was related to CHD and its risk factors, and to fetal and maternal characteristics.

PWV was higher in men than in women and rose with increasing age and body size. It was unrelated to smoking, alcohol consumption, socio-economic class or physical activity.

PWV was strongly related to blood pressure, rising with increasing systolic and diastolic pressure. It was also higher in those with a greater LV mass. Although unrelated to CHD, higher PWV was associated with an adverse coronary risk profile. As with LV mass, PWV was most strongly related with features of the insulin resistance syndrome. PWV tended to be higher in those with NIDDM and impaired glucose tolerance compared to those with normal glucose tolerance especially in the femoro-posterior tibial segment. It was also higher in those with raised plasma insulin and serum triglyceride concentrations.

PWV was unrelated to small size at birth. There were no significant associations with head circumference to length ratio, a surrogate measure of 'brain-sparing'. However it tended to be higher in those whose mothers were lighter (aorto-left radial and aorto-femoral segments or had a smaller external conjugate pelvic diameter (aorto-posterior tibial segment). There were no significant differences between PWV in the right and left radial segments. These findings will be discussed in the final chapter.

Chapter 5 BLOOD PRESSURE

5.1 Introduction

Although blood pressure was examined in the first Mysore study, I analysed blood pressure data in this study because of two main reasons:

- LV mass and arterial compliance are strongly related to blood pressure (see sections 3.4.5 and 4.3.5 respectively)
- Blood pressure is strongly related to brithweight in other populations (see section 5.1.4 below)

5.1.1 High blood pressure as a CHD risk factor

High blood pressure is a known risk factor for CHD and has been associated with an increased risk of mortality from CHD in prospective studies (257,258). There does not appear to a threshold limit for blood pressure; it is a continuous and normally distributed variable, and the risk of CHD increases linearly with increasing pressure (259). Although the exact mechanisms by which raised blood pressure leads to CHD are not clear, it is believed to damage the intima and media of arteries and increase atherosclerotic plaque formation (260,261). It also increases left ventricular afterload.

5.1.2 Known determinants of blood pressure

Blood pressure increases with increasing age and greater body weight is associated with higher blood pressure (260). Blood pressure varies widely within individuals according to their mental state and activity and also with different times of the day (260). It is raised by anger, fear, pain, stress, cold and exertion and decreases during sleep (260). There are wide variations in blood pressure between populations; it is not known whether they reflect genetic or environmental influences (259).

5.1.3 Aetiology of hypertension

In the vast majority of cases, hypertension is 'essential' or 'idiopathic', that is without a known definite cause. Although a small minority of cases can be ascribed to be secondary to renal artery stenosis or pheochromocytoma, the fundamental cause of essential hypertension is unknown. Factors believed to play a role in the initiation of hypertension include vascular overload and increased vasomotor tone (260,261). These may have their origins in endocrine or hormonal disturbances or sympathetic nervous system activity.

5.1.4 Fetal origins of high blood pressure

Raised blood pressure has been consistently associated with low birthweight in many studies across the world and has been suggested as one possible link between poor fetal growth and adult CHD (262-264). There are a number of possible mechanisms by which poor fetal growth could either initiate or amplify raised blood pressure (98):

- Blood pressure is known to 'track' and in children the rise of blood pressure with age is related to growth. Therefore postnatal 'catch-up' growth in children of low birthweight may amplify changes established in utero and lead to hypertension.
- Poor fetal growth may also result in reduced numbers of nephrons which in turn may lead to increased glomerular capillary pressure and subsequent hypertension.
- Fetal undernutrition may cause permanent changes in the hypothalamic-pituitary-adrenal axis which in turn resets homeostatic mechanisms controlling blood pressure and thus result in hypertension.
- Poor fetal growth preserves blood flow to the brain at the expense of the trunk; the alteration in fetal circulation may lead to permanent changes in the structure of arteries and cause raised blood pressure.

In this study, blood pressure was analysed in relation to CHD and its known risk factors as well as to fetal growth.

5.2 Methods

Systolic, diastolic and mean blood pressure in the right arm were recorded using an automated recorder (Dinamap 800) with the subject supine and rested for 10 minutes. Blood pressure was recorded after echocardiography and before recording pulse tracings. Subjects who had a systolic blood pressure of over 140 mm Hg and/or a diastolic blood pressure of over 90 mm Hg were classified as being hypertensive (265).

5.3 Results

5.3.1 Blood pressure and sex, age and body size

Mean systolic blood pressure was similar in both sexes (127 mm Hg). Mean diastolic blood pressure was slightly higher in men than in women (78 mm Hg Vs 74 mm Hg), although this was not statistically significant. Both systolic and diastolic pressure tended to rise with increasing age (r=0.20 and 0.12 respectively; p<0.01 for both; Table 5.1).

Table 5.1

Mean (SD) systolic blood pressure according to age

Age (yr)		Systolic blood pressure (mm Hg)		
	n	Men	n	Women
<45	42	123 (18)	37	120 (21)
45-	110	125 (21)	80	126 (23)
50-	40	130 (29)	53	129 (19)
55+	45	133 (23)	28	138 (30)
All	237	127 (22)	198	127 (23)
P value		0.007		0.001

Systolic pressure was strongly related to adult body size in both sexes, rising with increasing weight, BMI and BSA (r=0.28, 0.28, 0.25; p<0.001 for all in men and r=0.13,0.18,0.09; p=0.05, 0.01, 0.1 in women respectively). Systolic pressure was unrelated to height. BMI was the body size measurement most strongly correlated with systolic pressure (Table 5.2) and was used to adjust for adult body size in subsequent analyses.

Table 5.2

Mean (SD) systolic blood pressure according to BMI

BMI (kg/m^2)		Systolic blood pressure (mm Hg)		
	n	Men	n	Women
<20	55	120 (25)	26	124 (25)
20-	55	121 (17)	34	127 (26)
23-	58	128 (21)	34	121 (21)
25-	43	135 (20)	50	129 (22)
28+	26	140 (21)	54	132 (23)
All	237	127 (22)	198	127 (23)
P value		<0.001		0.01

Diastolic blood pressure also correlated strongly with body size, rising with increasing weight ($r=0.16$; $p<0.01$), height ($r=0.13$; $p<0.01$), BMI ($r=0.09$; $p=0.05$), BSA ($r=0.19$; $p<0.01$).

5.3.2 Blood pressure and 'lifestyle' factors

Both systolic and diastolic blood pressures were similar in smokers and non-smokers and were unrelated to alcohol consumption. They showed no relation to current socio-economic status.

5.3.3 Blood pressure and CHD

People with CHD had higher systolic and diastolic blood pressure when compared to those without (132 mm Hg Vs 126 mm Hg; 78 mm Hg Vs 76 mm Hg). There were similar relations with both ECG changes (130 mm Hg Vs 126 mm Hg; 78 mm Hg Vs 76 mm Hg) and with angina (133 mm Hg Vs 126 mm Hg; 78 mm Hg Vs 76 mm Hg).

Systolic and diastolic blood pressure showed similar relations with CHD risk factors, and birth measurements although the relationships with diastolic blood pressure tended to be weaker. I have restricted the presentation of tabulations in the following results to systolic pressure alone while mentioning significant results with diastolic pressure.

5.3.4 Blood pressure and CHD risk factors

Higher systolic pressure was associated with an adverse CHD risk profile (Table 5.3). Systolic blood pressure was higher in subjects with diabetes (138 mm Hg) and impaired glucose tolerance (129 mm Hg) than in those with normal glucose tolerance (124 mm Hg) (p for difference <0.001). These relations persisted on adjusting for body size, age and sex. Mean systolic blood pressure tended to rise with increasing plasma glucose levels (fasting, 30 minutes, 120 minutes). These relations were statistically significant even after adjusting for age, sex and body size.

Mean systolic blood pressure tended to rise with fasting and 120 minute plasma insulin levels while it was unrelated to the 30 minute concentration. On adjusting for age and body size, the relations with the fasting and 120 minute insulin concentrations disappeared. Mean systolic blood pressure tended to rise with increasing serum triglyceride concentration; this relationship persisted even after adjusting for age, sex and body size. There were no relations with serum total, HDL and LDL concentrations. There were no relationships between systolic blood pressure and factor VII or fibrinogen concentrations.

Table 5.3

Systolic blood pressure and known CHD risk factors

	Regression co-efficient	95% CI	p value
Fasting glucose (mmol/L)	1.22	0.32 to 2.13	0.008
30 min glucose (mmol/L)	1.14	0.20 to 2.09	0.01
120 min glucose (mmol/L)	1.17	0.34 to 2.00	0.005
Fasting insulin (pmol/L)	1.22	-167 to 4.12	0.4
30 min insulin (pmol/L)	-2.65	-5.75 to 0.44	0.09
120 min insulin (pmol/L)	0.25	-2.67 to 3.17	0.8
Triglycerides (mmol/L)	6.19	2.24 to 10.13	0.002
Total cholesterol (mmol/L)	1.23	-0.89 to 3.35	0.2
LDL cholesterol (mmol/L)	0.14	-2.38 to 2.67	0.9
HDL cholesterol (mmol/L)	5.05	-4.34 to 14.44	0.2
Fibrinogen (g/L)	-0.01	-0.04 to 0.02	0.6
Factor VII (g/L)	0.02	-0.02 to 0.08	0.3

p value adjusted for age, sex and BMI

Mean diastolic blood pressure tended to greater in people with diabetes (81 mm Hg) and impaired glucose tolerance (77 mm Hg) than in those with normal glucose tolerance (76 mm Hg) (p for difference 0.001). Higher diastolic blood pressure was associated with increasing fasting, 30 minute and 120 plasma glucose levels, even after adjusting for age, sex and body size (p=0.04, 0.03 and 0.001 respectively). It was unrelated to plasma insulin concentrations. Raised diastolic pressure was associated with higher serum

triglyceride concentrations (p=0.001), after adjusting for age, sex and body size. It was unrelated to serum total serum cholesterol, LDL cholesterol and HDL cholesterol concentrations. Diastolic pressure was unrelated to fibrinogen or factor VII concentrations.

5.3.5 Blood pressure and size at birth

Systolic blood pressure tended to rise with increasing birthweight (p=0.1) and birth length (p=0.02) while it was unrelated to head circumference or ponderal index at birth (Table 5.4). The relation with birthweight disappeared on adjusting for adult BMI reflecting the larger body size of those who were bigger at birth. The relation with birth length however persisted. Systolic blood pressure rose by 1.64 mm Hg (95% CI –0.08 to 3.37) per one inch increase in birth length. There were similar findings for percentages of people with hypertension (Table 5.4). People with hypertension also tended to have a lower ponderal index (Table 5.4). This, however, appeared to be due to the effect of birth length alone. In a regression model containing both birthweight and birth length, there was no significant effect of birthweight on systolic blood pressure (p=0.8), while the relationship with birth length persisted (p=0.07). Diastolic blood pressure was unrelated to size at birth.

Table 5.4

Mean (SD) systolic blood pressure and % of hypertension according to birth measurements

Birthweight (g)	n	Sys BP (mm Hg)	% hypertension
<2400	86	125 (18)	27.9
2400-	88	123 (23)	28.4
2650-	82	129 (24)	39.0
2835-	71	129 (21)	32.3
3000+	108	129 (26)	30.5
All	435	127 (23)	31.5
P value		0.6	0.4
Birth length (cm)			
<45.5	57	124 (18)	24.5
45.5-	135	126 (21)	27.4
47-	134	126 (24)	32.8
50+	105	131 (24)	39.1
All	431	127 (23)	31.5
P value		0.06	0.07
Head circ (cm)			
<33	70	128 (21)	38.5
33-	193	126 (22)	30.5
33.5-	86	129 (220	34.8
34.5+	81	126 (25)	24.6
All	430	127 (23)	31.5
P value		0.5	0.2
Ponderal index (kg/m^3)			
<21	83	129 (23)	38.5
21-	89	126 (20)	32.5
24-	83	129 (26)	34.9
26-	81	127 (23)	27.1
29+	95	125 (22)	25.2
All	431	127 (23)	31.5
P value		0.1	0.02

p value adjusted for age, sex and BMI

5.3.6 Blood pressure and maternal size

There were no relationships between systolic blood pressure and maternal weight during pregnancy (Table 5.5) or with maternal pelvic size (Tables 5.5). Nor were there any associations between diastolic blood pressure and maternal size.

Table 5.5

Mean (SD) systolic blood pressure and % of hypertension according to maternal measurements

Maternal wt (lb)	Sys BP (mm Hg)	N	% hypertension
<94	129 (21)	46	30.4
94-	126 (20)	72	26.3
108+	128 (25)	59	30.5
All	127 (22)	177	28.8
P value	0.6		0.6
External conj (cm)			
<17.8	132 (26)	46	41.3
17.8-	129 (23)	111	34.2
19.0+	127 (23)	84	33.3
All	128 (24)	241	35.5
P value	0.3		0.6
Intercristal dia (cm)			
<24.1	131 (23)	69	42.0
24.1-	128 (23)	73	35.6
25.4+	128 (24)	103	31.1
All	128 (24)	245	35.5
P value	0.2		0.1
Interspinous dia (cm)			
<21.6	130 (24)	58	39.6
21.6-	129 (24)	71	36.6
22.9+	128 (24)	116	32.7
All	128 (24)	245	35.5
P value	0.6		0.4

p value adjusted for age, sex and body size

5.4 Summary

Both systolic and diastolic blood pressure showed expected relations with age and current body size, rising with increasing age and BMI. Diastolic, but not systolic pressure, was related to adult height. Neither systolic nor diastolic pressure showed any relation to smoking, alcohol consumption, and socio-economic class.

As expected, systolic blood pressure tended to be higher in the men and women with CHD. Higher systolic pressure was also associated with an adverse coronary risk profile. There were similar relations with diastolic blood pressure.

Higher systolic blood pressure was unrelated to small size at birth. This findings contrasts with findings in western studies. On the contrary, it was associated with longer birth length. These unexpected and interesting findings will be discussed in the final chapter. There were no relationships between systolic blood and maternal weight during pregnancy, nor with maternal pelvic size. Diastolic pressure was unrelated to size at birth or to maternal measurements.

Chapter 6 DISCUSSION

6.1 The study cohort

The study was performed in a sample of South Indian men and women born in one hospital in Mysore between 1934 and 1953 and whose size at birth and maternal characteristics had been recorded. Although only a small percentage of people born in the hospital during that period were traced, there are no reasons to suspect that there were any systematic differences between those traced and not traced as there were no significant differences between them in birth measurements. In terms of birth data, this population is unique.

These birth records were discovered after a search of over 300 hospitals in India. Of the three hospitals with birth records of this quality and age, Mysore was considered a place with sufficient population stability to enable us to trace a large sample of men and women. They were a subset of men and women who were traced by house-to-house survey of central Mysore in 1993-94 and participated in our earlier study on the relationship between fetal growth and coronary heart disease and its known risk factors in which they were assessed for prevalence of CHD and were measured for a number of CHD risk factors. The methods used were highly reproducible. We obtained high participation rates from the cohort; 96% of those traced attended our clinic for the earlier study while 85% returned for this study.

6.2 Limitations of the study

This cohort was not a true 'population' sample. The study was restricted to people who were born in a mission hospital in Mysore between 1934 and 1953, who were still alive, lived locally and who gave us sufficient information to be able to match them to their birth records with certainty. Most deliveries at that time took place either at home or in the government hospital in the city. It is not clear what factors influenced these families to choose the MCHMH for delivery. However, since the hospital enjoyed a good reputation

and was a charitable organisation, the families were probably a mix of poor and well off people. Many babies, especially those of low birthweight, would have died in infancy. The sample is therefore unrepresentative of all births in Mysore during that period.

Although the survey was carried out in a relatively poor area of the city, just over half the participants were from upper rather than lower social class. This may reflect greater accuracy in obtaining information for tracing and matching from this group. The study sample had a higher percentage of Muslims compared to the population distribution either in Mysore or the rest of India. This is explained by the fact that the hospital is situated in an area which is predominantly Muslim. Our study sample is therefore unrepresentative of the inhabitants of modern Mysore city.

In spite of these deficiencies, this was a large sample of healthy men and women. They were similar in weight and height to other urban South Indian populations (266). Their rates of CHD, NIDDM and hypertension were similar to rates obtained in other studies on populations in urban India (109,266,267). It is not possible to compare LV mass and PWV as there are no previously published data in healthy Indian adults. Although 12% of the subjects were excluded from the analysis of LV mass, this figure is no more than expected from other published results, and those excluded seemed similar to those included.

6.3 Outcome variables and their relation to CHD and its risk factors

6.3.1 LV mass

Higher LV mass was associated with greater body size and obesity. Similar relations have been found in previous studies (147,162,164,169-174,176). This is probably because obesity is associated with an increased circulating volume and cardiac output. Mean LV mass was greater in men than in women even after adjusting for their greater BSA. While this is consistent with findings from other studies (162,169,171,173) there do

not appear to be any clear reasons for this difference. It is possible that men have a greater LV mass relative to their body size in comparison to women.

Mean LV mass in this Indian population was low compared with Western populations, even after allowing for their smaller mean body size. The mean LV mass was 149 g in men and 125 g in women; after indexing by BSA, the values were 88 g/m^2 and 82 g/m^2 respectively. The mean LV mass was 203 g in men and 156 g in women in a cohort from Hertfordshire, UK aged 60-66 years (188). Data from the Framingham study show that the mean LV mass in a sample of 18-90 year-olds (mean age 51 years) was 202 g in men and 136 g in women (140,144,147). After indexing by BSA, the mean was 102 g/m^2 in men and 83 g/m^2 in women. The lower blood pressure levels in our population may account for this difference. However a racial difference in LV mass cannot be ruled out; in a recent study, young Black Afro-Americans had a greater LV mass than young White Caucasians even after taking into account differences in body size and blood pressure (268).

LV mass rose with increasing age, a relationship which was no longer statistically significant after adjusting for systolic blood pressure. This finding is consistent with studies in the West (140,162,163) and suggests that the effect of age on LV mass is mediated through the rise in systolic blood pressure that occurs with increasing age. LV mass is known to be positively related to blood pressure and hypertension (165,166,168-172,174) and this was true in my study also. Higher systolic blood pressure leads to increased left ventricular afterload and causes myocardial hypertrophy.

Consistent with findings from Western studies, men and women with CHD had a greater LV mass than those without (140-146). The mechanisms by which increased LV mass leads to CHD is not clear. It may be that the increased tissue mass that occurs in LVH results in increased myocardial oxygen demand; this may promote the development of

ischaemia when coronary flow is compromised. It has also been suggested that LVH is associated with an increase in coronary vascular resistance (161), a decrease in coronary blood flow reserve (160) and an increased incidence of ventricular tachycardia and arrhythmias (150,151) which may also contribute to the development of myocardial ischaemia. It is also possible that they are associated because they share common risk factors including obesity, age, raised blood pressure, diabetes mellitus, hyperinsulinaemia and an adverse lipid profile.

In my study, LV mass was higher in people with diabetes and impaired glucose tolerance, and in those with higher insulin concentrations. All these relationships were independent of age, sex and body size. LV mass tended to be higher in those with raised triglycerides as well as in those with lower concentrations of HDL cholesterol, independently of age and body size. Total cholesterol was unrelated to LV mass after adjusting for body size. LV mass was also higher in those with greater central obesity. LV mass has been correlated with CHD risk factors in Western populations. It has been associated with diabetes mellitus and raised fasting glucose concentrations (178,179), hyperinsulinaemia (180,182), insulin resistance (177,181), higher concentrations of triglycerides and total cholesterol, and lower concentrations of HDL cholesterol (171,172). In this Indian population, greater LV mass is associated with features of the Insulin Resistance Syndrome (glucose intolerance, hypertension, hypertriglyceridaemia, low HDL cholesterol concentrations and central obesity). Insulin resistance and hyperinsulinaemia may explain the associations between LV mass and CHD and its risk factors as hyperinsulinaemia is associated with vascular hypertrophy as well as an adverse lipid profile.

6.3.2 Arterial compliance

Higher PWV was associated with greater body size. The reasons for this are unclear although it has been described earlier (216,222-224). The associated higher blood

pressure may play a role but does not fully explain the effect. Mean PWV was also greater in men than in women; this difference persisted after even allowing for their larger body size.

Mean PWV in this population was lower than that obtained by an identical method in a population in Sheffield, UK (Phillips N, personal communication). However the Sheffield cohort was older and had higher systolic blood pressure and these factors may have been responsible for their greater PWV. PWV rose with increasing age except in the femoro- posterior tibial segment, suggesting that central but not peripheral arteries become less compliant with advancing age. Elastin is the major determinant of compliance in the aorta and a greater collagen to elastin ratio in the vessel wall is associated with reduced compliance (212-214). The more peripheral arteries tend to contain less elastin in relation to collagen (214,216). Therefore the gradual loss of elastin with ageing and its replacement with collagen may be more significant in the central arteries.

PWV was strongly related to blood pressure, rising with increasing systolic and diastolic pressure. The temporal association between PWV and blood pressure is unclear. Within physiological pressure limits, the compliance of the aorta is responsible for smoothening the pulsatile flow from the heart as well as maintaining an adequate pressure head throughout the cardiac cycle (212-214,225,226). The aorta expands during ventricular systole to accommodate the stroke volume (about 75 ml) and minimises the rise in blood pressure as well as left ventricular load. During diastole, its elastic recoil promotes blood flow forward against a closed aortic valve. If compliance is reduced, this function is impaired leading to increased systolic, lowered diastolic and raised pulse pressure. The vessel responds to the stretch on its wall caused by the raised pressure by synthesising collagen. This causes further reduction in compliance and a positive feedback loop is established. This is enhanced by ageing, where the wear-and-tear effect of the cyclical

repetitive stress damages elastin fibres, which are replaced with collagen. However the process if self-limiting at a point where a particular pressure causes no further stretch of the vessel wall. Therefore reduced compliance may initiate or amplify the process of hypertension. Higher PWV was also associated with an increased LV mass. Reduced compliance leads to raised systolic pressure, increased LV afterload and may promote LVH (229,235).

PWV was not related to CHD, but was associated with higher levels of known risk factors for the disease, including diabetes, raised plasma glucose, insulin and serum triglyceride concentrations. Other studies have shown that reduced compliance is associated with diabetes (230,231). It is suggested that diabetes may be associated with reduced compliance through its association with accelerated atherosclerosis, hypertension or by promoting smooth muscle hypertrophy. Insulin resistance has also been associated with reduced compliance (231,232) although the exact mechanism of this relation appears unclear. The lack of an association between PWV and CHD is surprising, particularly considering that both factors are related to LV mass, blood pressure and other risk factors for CHD in this study. I speculate that the link between PWV and CHD is not strong enough on its own in this population to clearly establish an independent association and that the effects are mediated by other risk factors.

6.3.3 Blood pressure

Both systolic and diastolic blood pressure showed expected relations with age and current body size, rising with increasing age and BMI. Diastolic, but not systolic pressure, was positively related to adult height.

As expected, systolic blood pressure tended to be higher in the men and women with CHD. Higher systolic pressure was also associated with an increased prevalence of

NIDDM and with higher concentrations of serum triglycerides. There were similar relations with diastolic blood pressure.

In summary, in this Indian population, greater LV mass and reduced arterial compliance are associated with an adverse CHD risk factor profile, especially with the features of the Insulin Resistance Syndrome (glucose intolerance, hypertension, hypertriglyceridaemia, low HDL cholesterol concentrations and central obesity) (128). Our earlier study on the same cohort has suggested that, consistent with other studies in Indian populations, they are insulin resistant (135). Hyperinsulinaemia promotes vascular hypertrophy either by a direct action or through increased sympathetic activity (269). This may lead to hypertension, increased LV mass and reduced compliance. Hyperinsulinaemia has also been associated with an increased risk of CHD (38,40,42,43). Insulin resistance has also been associated with lipid abnormalities including raised serum triglyceride concentrations and reduced HDL cholesterol concentrations (40,42). It is therefore possible that hyperinsulinaemia and insulin resistance may underlie the development of CHD in this population and serve as the link between LV mass, arterial compliance and CHD risk factors.

6.4 No relation to small size at birth

Left ventricular mass, arterial compliance and blood pressure have been suggested as possible factors linking poor fetal growth to adult CHD. The main aim of this study was to examine whether these variables could be the possible link between small size at birth and adult CHD as shown in an earlier study on the same population.

There was no association between small size at birth and increased LV mass or blood pressure, nor with reduced arterial compliance. Contrary to my hypothesis, neither higher LV mass or blood pressure, nor reduced arterial compliance were associated with a decreased birthweight/head circumference ratio or increased head circumference/length

ratio, measures which are though to reflect brain sparing. On the contrary, systolic blood pressure, LV mass and rates of hypertension and LV hypertrophy were higher in people of longer crown-heel length at birth, independently of adult size. These findings were surprising and interesting as they differ from findings obtained in Western studies (69,70,75,76,188,240,262,). Although unrelated to size at birth, arterial compliance was lower in men and women born to lighter mothers with smaller pelvic diameters.

This lack of association between the cardiovascular outcomes measured and small size at birth was most striking for blood pressure which, in a large number of published studies, has shown an inverse relationship to birthweight (262). There are reasons why such a relationship, if present, may have been obscured in this population:-

6.4.1 Inadequate sample size or power

Formal calculations of sample size or power were not made at the beginning of the study due to the following reasons:

- The First Mysore Study had shown significant associations between small size at birth and adult coronary heart disease
- I was confident of getting sufficient numbers to match those of earlier studies which had shown relationships between small size at birth and adult LV mass and arterial compliance (references 188 and 240) in Western populations
- Since no new subjects could be recruited for the follow-up study, the practicalities of the project demanded that our team attempted to ensure the maximum possible participation rate from the original cohort.

However, while analysing the data after conclusion of the study, the issue of sample size and power was examined as a possible reason for the lack of an association between small size at birth and adult LV mass, arterial compliance or blood pressure. While this is

something that cannot be corrected for retrospectively, the two sets of calculations shown below (using the association between length at birth and LV mass – the only significant relationship discovered in this study) suggest that the numbers were indeed sufficient, and that the lack of an association between small size at birth and adult LV mass, arterial compliance or blood pressure is not due to a lack of power in the study.

a. **Sample size for comparing means:**

Based on a significance level of 0.05 and 80% power, it would have been sufficient to have had 63 people in each group to demonstrate the association between LV mass and birthlength in four groups that is shown in Table 3.15 (Chapter 3, page 55). That amounts to a total of 252 people while birthlength was available for 375 people in the study (although it must be noted that the first group consisted of only 52 people while the other groups had approximately 100 people).

b. **Sample size for size of effect:**

At a significance of 0.05 and 80% power, a sample size of 375 subjects would have detected a relationship if the true change in LV mass was only 1.7 gm per one cm increase in birthlength. This is smaller than the actual unadjusted size of effect that was found in the study (approximately a 2.5 gm change in LV mass per one cm change in birthlength) suggesting that even a smaller sample size would have demonstrated this effect.

6.4.2 The birth records contain insufficient information

The association between low birthweight and raised blood pressure has been shown to be strongest in those born at full term (270). The Mysore records do not contain gestational age, and it was not possible to distinguish between low birthweight due to prematurity and that due to retarded fetal growth. This would tend to reduce the strength of associations between low birthweight and raised systolic pressure. The records also do not contain information on placental weights. Studies in UK have suggested that the

relationship between low birthweight and raised adult blood pressure is strongest in those born with relatively large placentae in relation to their birthweight (76).

6.4.3 Insufficient range of birth size

Earlier this century, many babies of low birthweight died during infancy or early childhood. The loss of babies at the lower extreme of birthweight may have reduced the power of this study. The men and women studied were larger at birth compared to all the deliveries in the hospital during the same period (mean birthweight 6.1 Vs 5.9 pounds, length 18.9 Vs 18.8 cm, head circumference 13.2 Vs 13.1 cm). However there were no statistically significant differences in birth measurements between the study sample and all the deliveries in the hospital, or between those who agreed to participate and those who did not. Another possible reason for the lack of a relation with small size at birth may be the fact that the mean birthweight was considerably lower compared to babies born in the West. It may be that the association between small size at birth and raised systolic pressure is apparent only when there are small as well as large babies i.e., a sufficiently wide range.

6.4.4 Different patterns of fetal growth

It may be that the absence of an association between high blood pressure and lower birthweight in this population is explained by different patterns of fetal growth. It has been suggested that raised blood pressure is linked to undernutrition in mid-late gestation resulting in the fetus switching down its growth (98). India is characterised by generations of undernutrition. It is possible that Indian fetuses down-regulate growth early in gestation, remain small and either avoid adaptations or adapt differently.

6.4.5 Lack of postnatal catch-up growth

The Mysore men and women were smaller than Western populations not only in size at birth but also in adult size. A recent study from Sweden showed that higher blood

pressure was related to small size at birth only in men who had grown into tall adults (271). The authors' interpretation of this finding was that in an affluent country like Sweden adult height is a good index of people's genetic growth potential. Tall men who were small at birth were therefore likely to have suffered a greater degree of intra-uterine growth retardation than short men. An alternative explanation is that a combination of growth retardation in utero, followed by catch-up growth postnatally, leads to raised blood pressure (272). It is possible that the short adult height of the Mysore population (median height in men 168 cm, considerably lower than the median of 176 cm in Sweden), suggesting poorer post-natal as well as pre-natal growth, may have prevented a rise in blood pressure in lower birthweight men and women. A similar association with blood pressure has been found in those who are small at birth but become obese as adults (98,273). The Mysore men and women remain relatively non-obese in adult life and this may have prevented the rise in adult blood pressure seen in Western populations.

6.4.6 Treatment of adult hypertension

Approximately 13% of our subjects were on anti-hypertensive medication, including ACE inhibitors and beta-blockers, which not only lower blood pressure but also cause regression of LV hypertrophy (274,275). This may have been another contributing factor. However the results were similar even when subjects on medication were excluded from the analysis.

This study provided no evidence, therefore, that increased blood pressure and LV mass, and reduced arterial compliance, are related to reduced fetal growth in this Indian population. This suggests that the association between reduced fetal growth and coronary heart disease, found in our earlier study of these men and women, is not mediated by changes in blood pressure, LV mass or arterial compliance.

6.5 LV mass, systolic blood pressure and longer length at birth

Higher systolic blood pressure and LV mass were associated with longer length at birth. These associations were of borderline statistical significance, and may have arisen by chance. They may reflect the fact that longer babies become taller adults (r=0.18), and taller adult height is, in turn, associated with higher LV mass and diastolic blood pressure. The associations with longer length at birth were, however, still present after adjustment for adult height. A trend of increasing systolic blood pressure with increasing length at birth has been described earlier in UK adults and children, but not highlighted (75,77). The same studies showed higher blood pressures in people who had a low weight for length or ponderal index at birth and in people with a lower head circumference/length ratio at birth. Although similar trends were found with these birth ratios in Mysore, these were clearly due to the increased length component *alone* whereas in the UK the relationships were reflective of longer length *in relation to lower birthweight or smaller head circumference.*

Apart from effects on the cardiovascular system of the intra-uterine brain-sparing reflex, another mechanism which has been proposed to explain the link between small size at birth and adult cardiovascular disease is the re-programming of hormones, such as insulin, IGF-I, growth hormone and cortisol, which regulate fetal growth (101-106,276-278). These hormonal changes may be the principal fetal adaptations which link fetal growth to adult disease in Indian populations. I propose two speculative hypotheses as to how this might occur.

It has been suggested that the under-nourished fetus increases cortisol secretion, and develops insulin resistance, as mechanisms to slow down growth in the face of an inadequate nutrient supply (98). Cortisol has an important role in promoting tissue and organ maturation towards term and modulates growth only during late gestation and in adverse circumstances when nutrient supply is restricted. The timing of the cortisol surge

may have important long term consequences. This is supported by evidence that treatment of pregnant rats and sheep with low dose dexamethasone during early gestation led to persistently raised blood pressure in the offspring (279). It has been suggested that reduced fetal growth resulting in elevated cortisol concentrations may permanently programme the hypothalamic-pituitary-adrenal axis and underlie the development of hypertension and insulin resistance (280). It has also been shown that there is a correlation between morning plasma cortisol concentrations and fasting insulin concentrations in adults. It is possible that the generations of undernutrition in India cause a surge in cortisol production earlier than usual as a fetal adaptation. The increased cortisol secretion may result in insulin resistance and be associated with a concurrent surge in insulin. The elevated levels of these hormones may result in cardiac hypertrophy and raised blood pressure through their known action on promotion of vascular growth and these changes persist in later life. The actions of these hormones on skeletal growth may result in increased birth length of these babies. Our earlier study showed that impaired fetal growth was associated with increased adult insulin resistance and hyperinsulinaemia (135) and this proposed hypothesis may offer an explanation for my findings.

Fetal undernutrition in early gestation

↓

Increased cortisol, insulin resistance and hyperinsulinaemia

↓

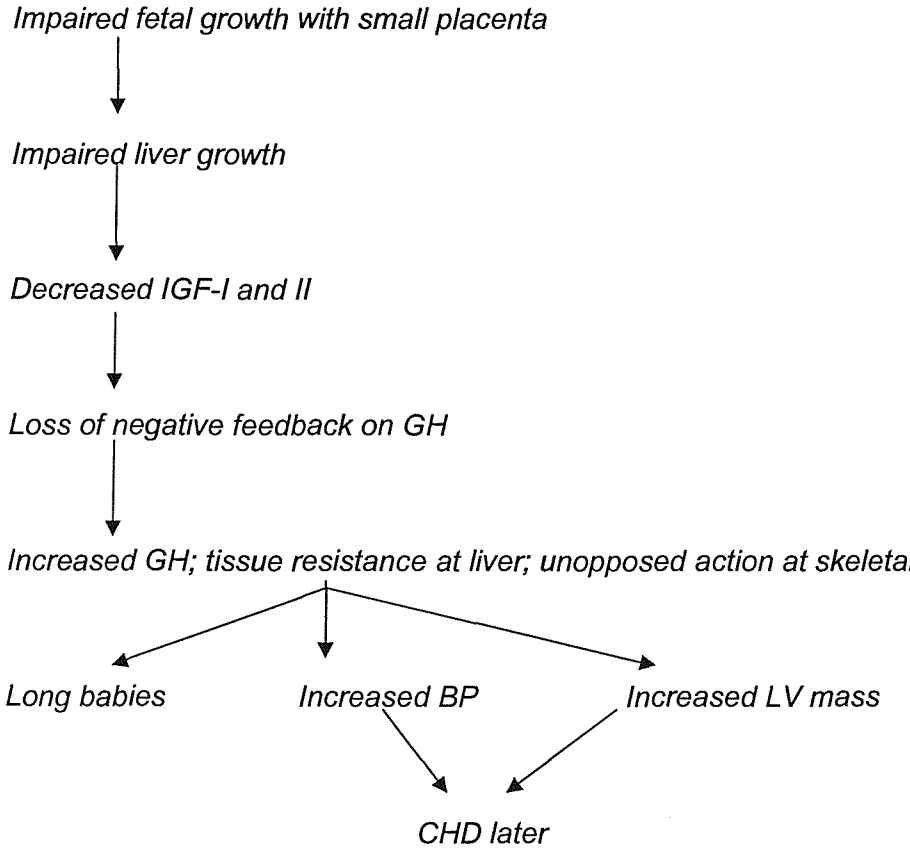
Promotion of vascular and skeletal growth

↓

Increased blood pressure, LV mass and birth length

Another speculative hypothesis is that these babies may have a disturbance in the IGF-growth hormone axis. Concentrations of IGF-I and II are lower in long babies with low

birthweight and small placentae (Godfrey K, personal communication). These babies also have smaller abdominal circumferences, thought to reflect reduced liver growth. It is possible that these babies have hepatic growth hormone resistance, lower levels of IGF-I and IGF-II, loss of the negative feedback effect of IGF-I on growth hormone, and elevated circulating growth hormone concentrations which is allowed to act unopposed at non-hepatic sites. Growth hormone is known to promote cardiac hypertrophy and may have caused an increase in cardiac mass and blood pressure which may have persisted. Its unopposed action on skeletal tissues would have resulted in an increase in length of these babies.



6.6 Arterial compliance and maternal size

Although unrelated to size at birth, arterial compliance in our study was reduced in men and women whose mothers had a low body weight when they booked into the antenatal clinic, and smaller pelvic diameters measured at term. This could be a chance finding as

the results were of borderline significance and were not present in all arterial segments. However reduced external conjugate diameter suggests poor nutrition during skeletal growth in childhood and adolescence (281). Recent evidence from Mysore suggests that pelvic size correlates with maternal height and body fat (Hill J, personal communication). Therefore mothers with smaller pelvic diameters may be short or thin or both. It is possible that maternal undernutrition may result in elastin deficiency and modify the structural development of blood vessels in the fetus causing them to become stiffer and less compliant in later life without reduction in overall birthsize. This may be the route through which smaller pelvic size is associated with an increased risk of stroke in the offspring, as shown in a recent study in Britain (282).

6.7 Summary and conclusions

1. LV mass, arterial compliance and blood pressure were examined in a large sample of healthy South Indian adults. This is the first time that these cardiovascular variables have been described in an Indian population. Mean LV mass, PWV and blood pressure were all low compared to values obtained in studies in Western populations.
2. LV mass and arterial compliance were examined in relation to CHD and its risk factors. Consistent with findings from studies in Western populations, increased LV mass and reduced arterial compliance were associated with an adverse coronary risk profile especially with insulin resistance and features of the IRS (hypertension, hypertriglyceridaemia, low HDL-cholesterol concentrations and central obesity).
3. LV mass, arterial compliance and blood pressure were examined in relation to fetal growth and measurements of maternal size. Neither increased LV mass or blood pressure, nor reduced arterial compliance were related to small size at birth. This suggests that the association between small size at birth and increased risk of adult CHD, as shown in our previous study in the same cohort, is not mediated through changes in LV mass, arterial compliance or blood pressure. The lack of a relationship

with low birthweight, particularly for blood pressure, is striking in view of the consistency of this finding in many other populations.

4. Increased LV mass and raised systolic blood pressure were associated with longer length at birth. These associations may be due to alterations in endocrine axes during fetal life.
5. Arterial compliance was reduced in men and women whose mothers were lighter during pregnancy and had smaller external conjugate pelvic diameters. Maternal undernutrition may cause reduced fetal elastin deposition and be responsible for this association.

6.8 Future research

Ultrasound studies of Indian fetuses show that femur length corresponds closely to Western fetal growth standards throughout pregnancy. In contrast, fetal head and abdominal circumferences fall below Western curves from early in the third trimester. This suggests that skeletal growth is relatively spared in Indian fetuses. In future research in India, it would be useful to study the endocrine correlates of fetal growth patterns, by measuring cord blood concentrations of cortisol, growth hormone and IGFs, and by assessing the growth hormone-IGF and hypothalamic-pituitary-adrenal axes in childhood and adult life.

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APPENDIX 1

4252060

66

Holdsworth Memorial Hospital, Mysore City

Maternity Case Sheet

No. 1367. 1368 (14.21Da

Name SITA

Husband's name:- RAMA

Age 38 yrs Race Sweepers. Para 8th

No. of Years After Marriage 12 yrs.

Address Ediga.

Occupation House-wife

Admitted at ♀ S.D.H. A.H. - 30-5-42 Confined 30.5.42. Discharged 6/6/42. normal.

PREVIOUS HISTORY 1st N.D. here. H.c.v. died & chicken pox after 7 yrs. 6th N.D at home H.c living 9 yrs

2nd N.D at home H.c died & fever after 1½ yrs 7th N.D at home F.c living 6 yrs.

3rd N.D at home F.c she died & fe chicken.

4th N.D at home F.c dead after 9 days.

5th N.D at home F.c living 1½ yrs

No of Living Children Dead Abortions

Date of L.M.P. Date When Labour Expected

Whether Examined at Home No.

PRESENT CONDITION getting fairly good contraction

cervix prolapsed.

Breasts B.P.

Urine S.G. Reaction Albumen Sugar

Measurements

Interspinal 8½" Intercristal 9½" External Conjugate 7" P.I.S. 2¾"

EXAMINATIONS P. A. Full term. P.O.A. Head fixed. F.H.S. good.

Date	Time	Type of Pain	Degree of Dilatation	Membranes	Presentation	Sutures Fontaneles	Capt.	F.H.	P.	T.	REMARKS	Examined by

TREATMENT GIVEN DURING LABOUR S E.

LABOUR

Time Pains Began ♀ A.H. 30.5.42.

" Membranes Ruptured ♀ at 8.15 A.H. 30.5.42.

" Full Dilatation at 8.25 A.H. 30.5.42.

" Birth of Child at 9. A.H. 30.5.42

" Birth of Placenta at 9.10 A.H. 30.5.42.

Duration of Labour

	Hrs.	Mts.
1st Stage	3	25
2nd "		25
3rd "		10.
Total	4 hrs	10 minds

Placenta—Condition Complete.

Insertion of Cord Lateral

Length of Cord 18" Date of Separation

CHILD

Date and Time of Birth 30.5.42 at 9. A.H.

Born Alive or Dead Alived.

Sex F-child.

Weight 6 lbs

Length 19"

Circumference of Head 12½" S.O.B. Bi.P.

S.M.B.

Kunjamma Jacob.

2.1 A typical birth record (names fictitious) A1.1

2.2 The survey area

A1.2

Social Worker : A/JK/K Date : 23.6.94

Full name : BHAGYA Religion/Caste : HINDU-SC-SWE

Present Address : ABCD, XYZ ROAD
MYSORE

Address when born : II EDIGA

Age : 53 Date of birth: | NK |

Mother : Alive / Dead ✓ Occupation : HOUSEWIFE

Full Name : SITA

Father : Alive / Dead ✓ Occupation : SWEEPER IN M.C.C

Full Name : RAMA

Mother's age when married : NK yrs

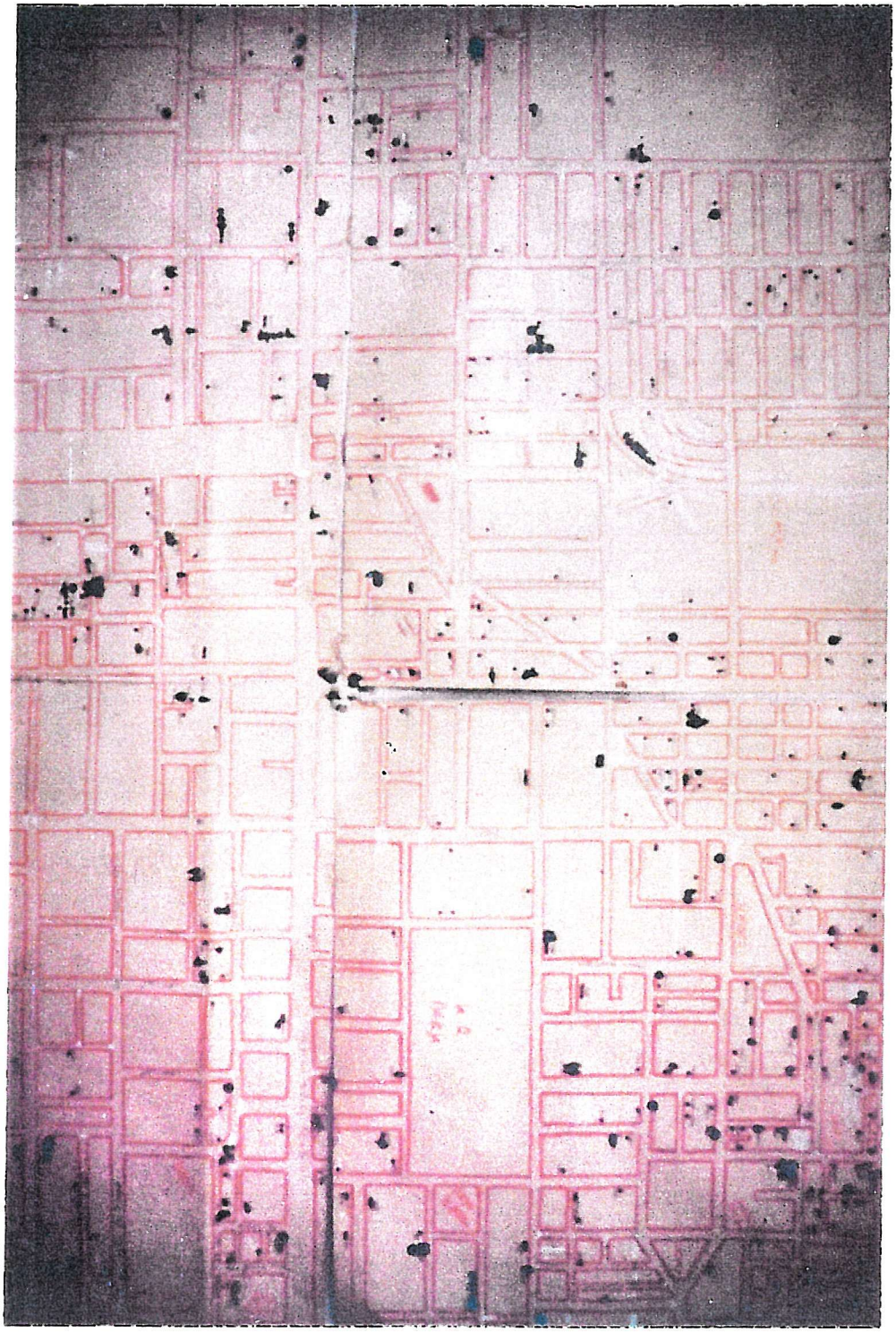
Mother's age at birth : NK yrs

No.	Brothers/ Sisters Name	age	sex	birthplace	alive/ dead	comments
1	MALE CHILD	NK	M	HOME	D	
2	MALE CHILD	NK	M	HOME	D	
3	FEMALE CHILD	NK	F	HOME	D	
4	FEMALE CHILD	NK	F	HOME	D	
5	RUKMINI	59	F	HOME	A	
6	LAKSHMANA	56	M	HOME	A	
7	BHAGYA	53	F	HMH	A	
8	RADHA	49	F	HMH	A	
9						
10						
11						
12						
13						

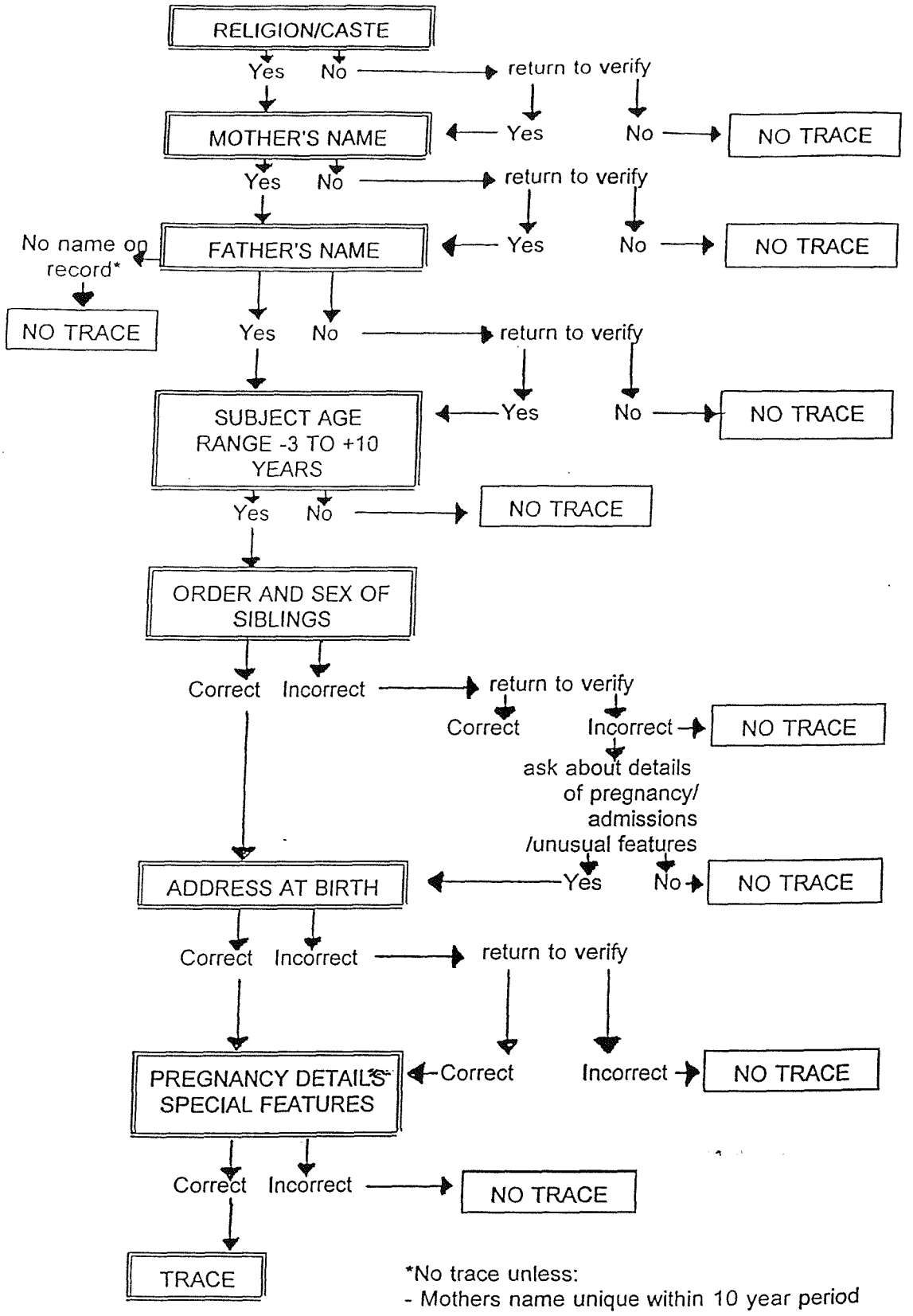
Comments about Mother - NIL -

Comments about Patient - NIL -

2.3 A tracing form with information collected during survey (names fictitious) A1.3



2.4 Large scale map of the survey area



*No trace unless:
- Mothers name unique within 10 year period
or
- address very specific (i.e. Door No.)
or
- special features (i.e. handicap)

2.5 Tracing flow chart

APPENDIX 2

MYSORE - ECHO (RESULTS)

ID NUMBER _____

NAME _____ _____ SEX M / F

MRC NUMBER _____

D.O.BIRTH _____

D.O.EXAMINATION _____

HEIGHT: CMS WEIGHT: KGS BSA:

S BP D BP M BP PULSE

ECHOGENICITY: GOOD ADEQUATE POOR

COMMENTS:

MEASUREMENTS:

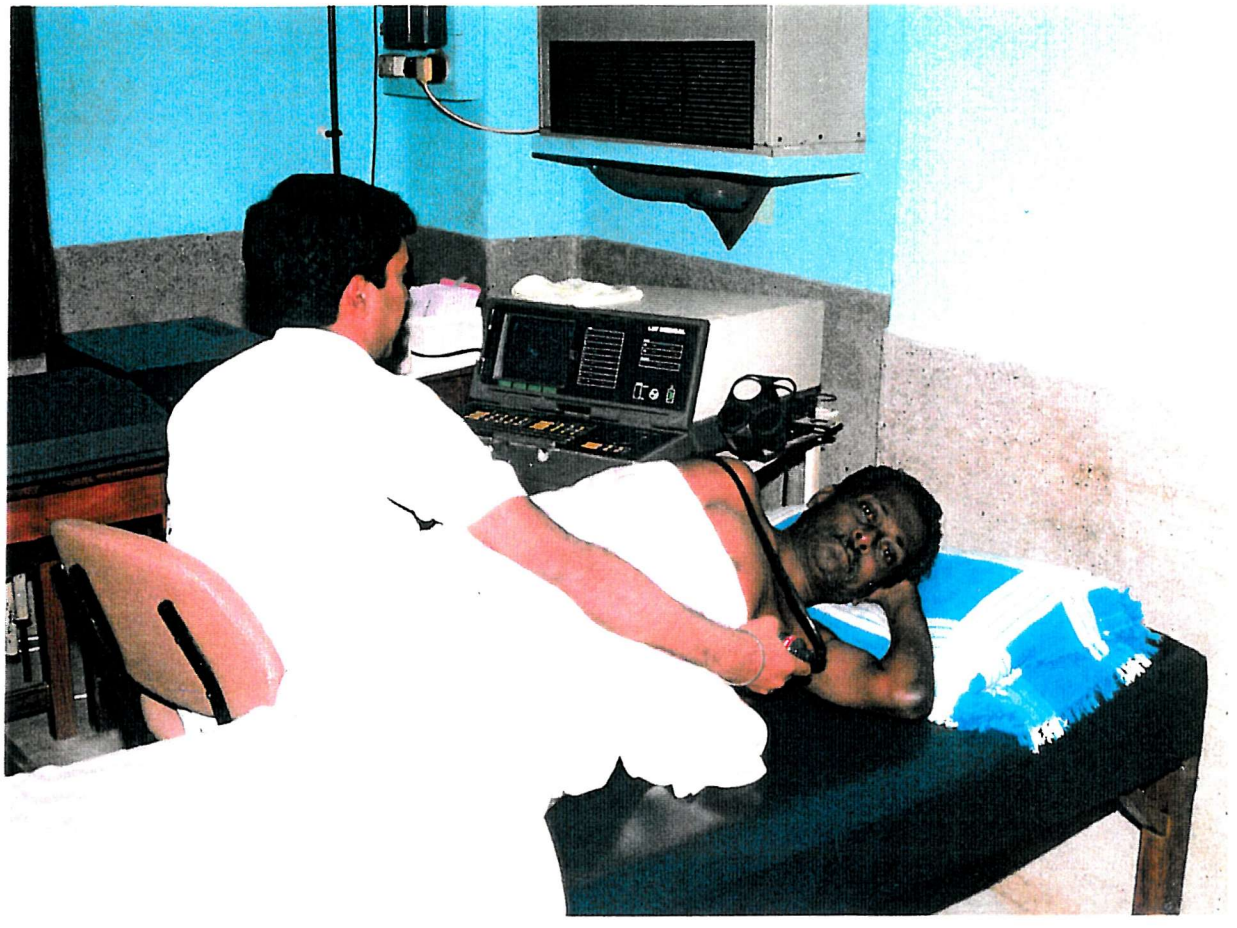
	1	2	3	4	5	AVE
IVS D						
PWT D						
LVID D						
LVID S						

1. LV MASS:

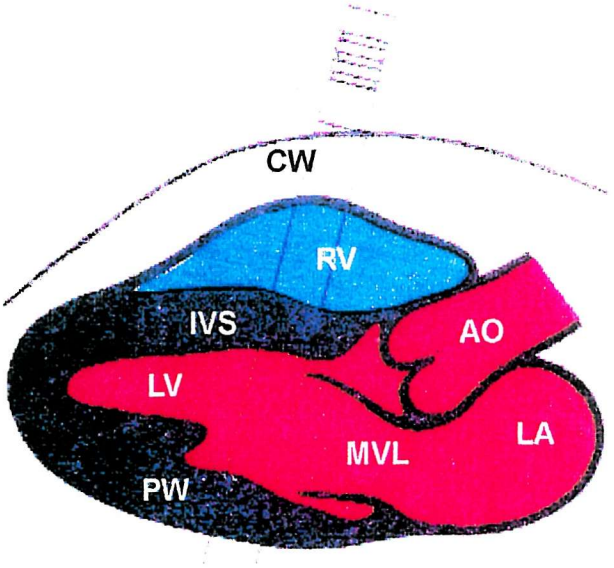
2. CARDIAC OUTPUT:

2. RWT:

4. T.P.R:

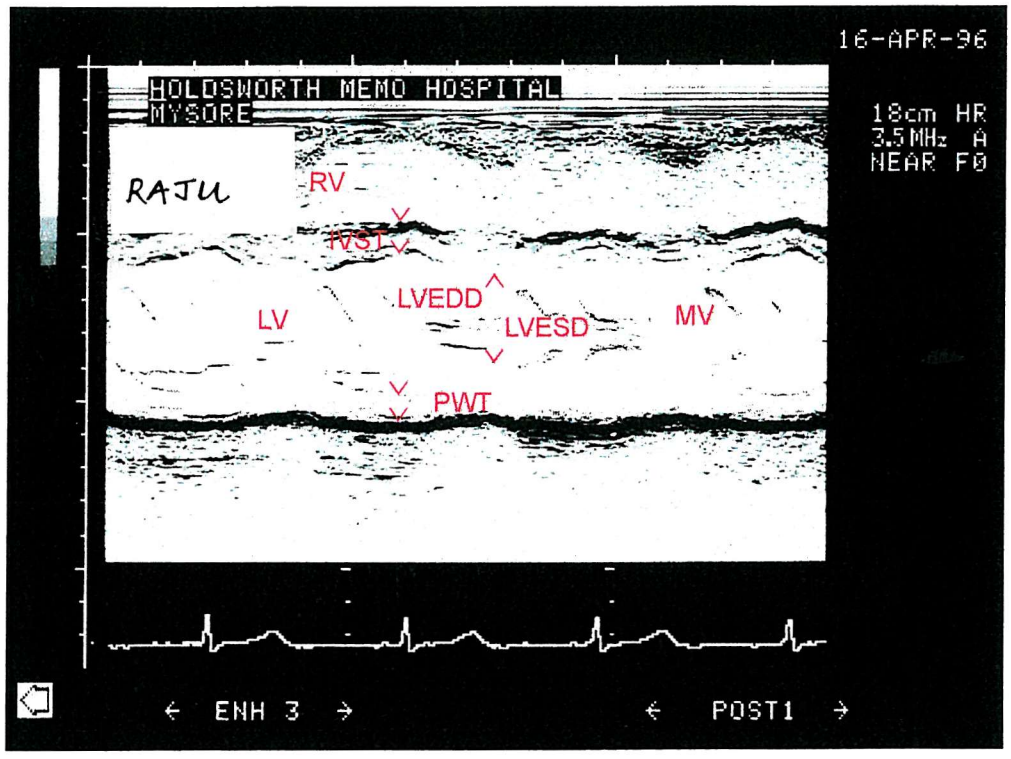


An Echocardiographic Examination.



Cardiac Structures Visualised in the Parasternal Long Axis View.

CW: Chest Wall
RV: Right Ventricle
IVS: Interventricular Septum
LV: Left Ventricle
PW: Posterior Wall
MVL: Mitral Valve Leaflets
LA: Left Atrium
AO: Aorta



M-mode Echocardiograph Print Illustrating the Measurements Made and the Structures Visualised.

IVST:	Interventricular Septal Thickness at end diastole
PWT:	Posterior Wall Thickness at end diastole
LVEDD:	Left Ventricular End Diastolic Diametre
LVESD:	Left Ventricular End Systolic Diametre
RV:	Right Ventricle
LW:	Left Ventricle
MV:	Mitral Valve

3.3 A M-mode print (name fictitious) **A2.3**

APPENDIX 3

Intra Observer Variation Data – LV mass

1. I re-digitised the echocardiographic prints of 20 subjects in the study in order to check the repeatability of the measurements. ANOVA and t-tests were used to examine systematic differences; there were no statistically significant differences in LV mass between the two measurements. The data are shown below.

Comparison of LV mass in 20 subjects whose echocardiographic prints were re-digitised

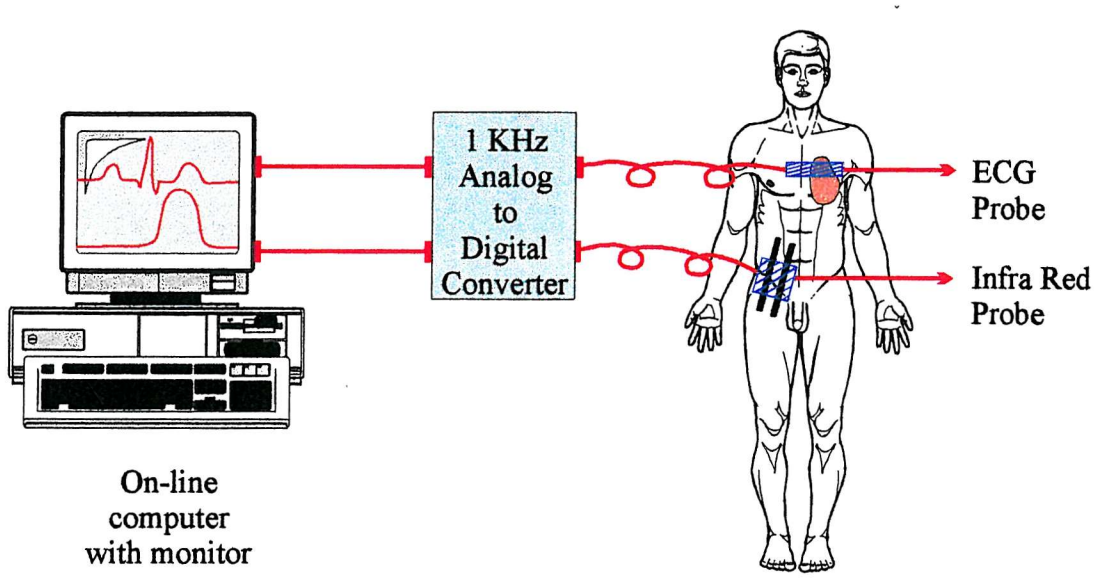
	LV mass (g)	
Subject number	**Original values**	**Repeat values**
1	136	140
2	143	142
3	148	151
4	92	90
5	128	130
6	137	134
7	157	153
8	174	169
9	146	143
10	124	126
11	166	169
12	134	137
13	134	131
14	153	157
15	106	108
16	130	126
17	145	150
18	110	107
19	129	133
20	115	119
21	82	84
Mean (SD)	132. 8 (22.8)	133.3 (22.7)
95% CI	122.4, 143.2	123.0, 143.6

2. I also repeated the entire echocardiographic procedure and recalculated LV mass in a further 10 subjects. Again, there were no statistically significant differences between the two examinations.

Comparison of LV mass measurements in subjects who underwent repeat echocardiography

	LV mass (g)	
Subject number	**Original values**	**Repeat values**
1	166	158
2	204	213
3	161	171
4	148	157
5	111	120
6	85	81
7	203	216
8	146	137
9	176	166
10	132	123
Mean (SD)	153.2 (37.7)	154.2 (41.5)
95% CI	126.3, 180.1	124.5, 183.9

APPENDIX 4



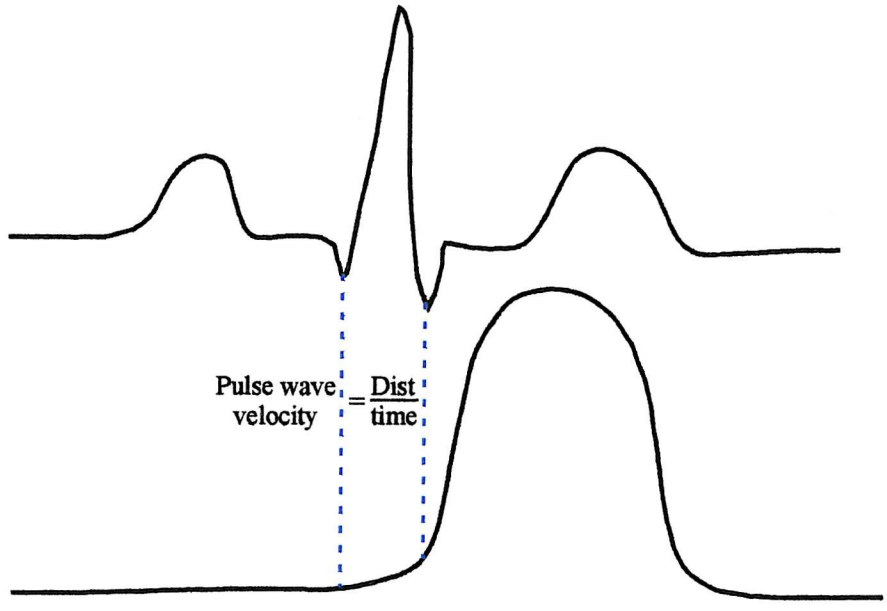
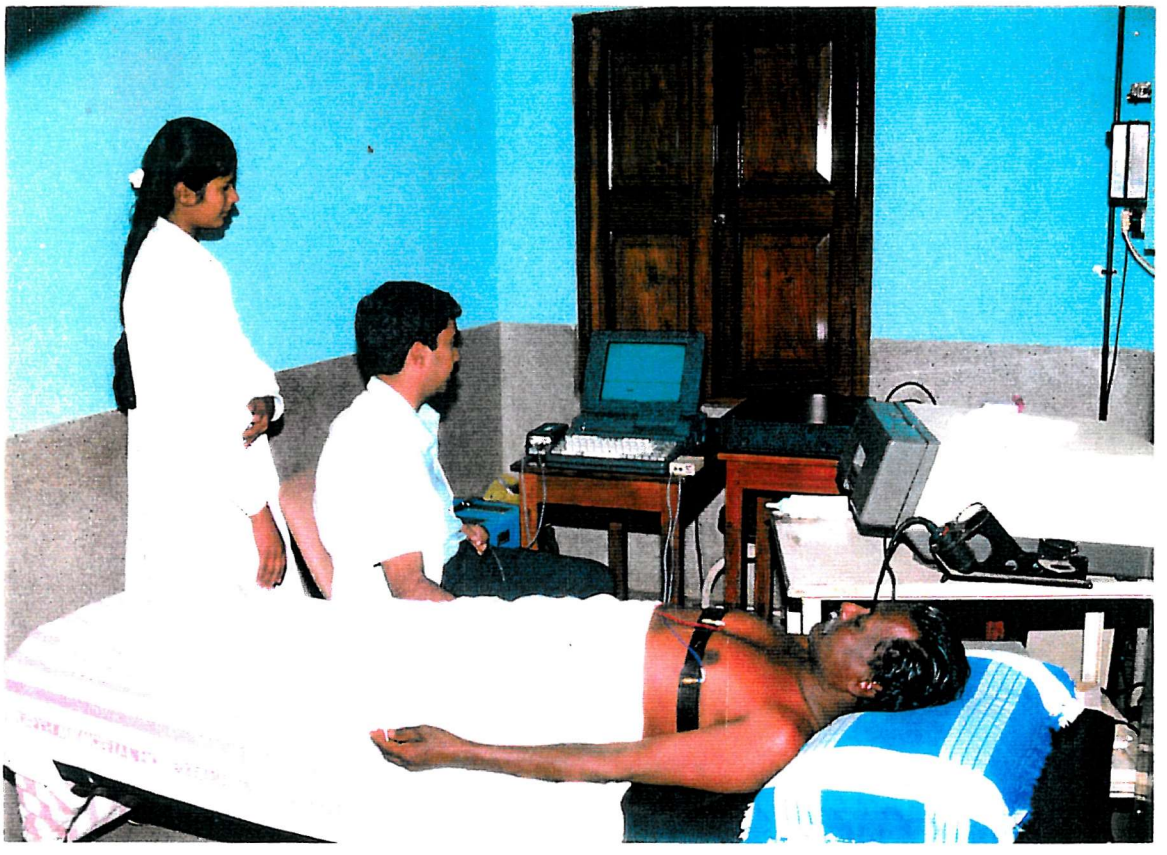
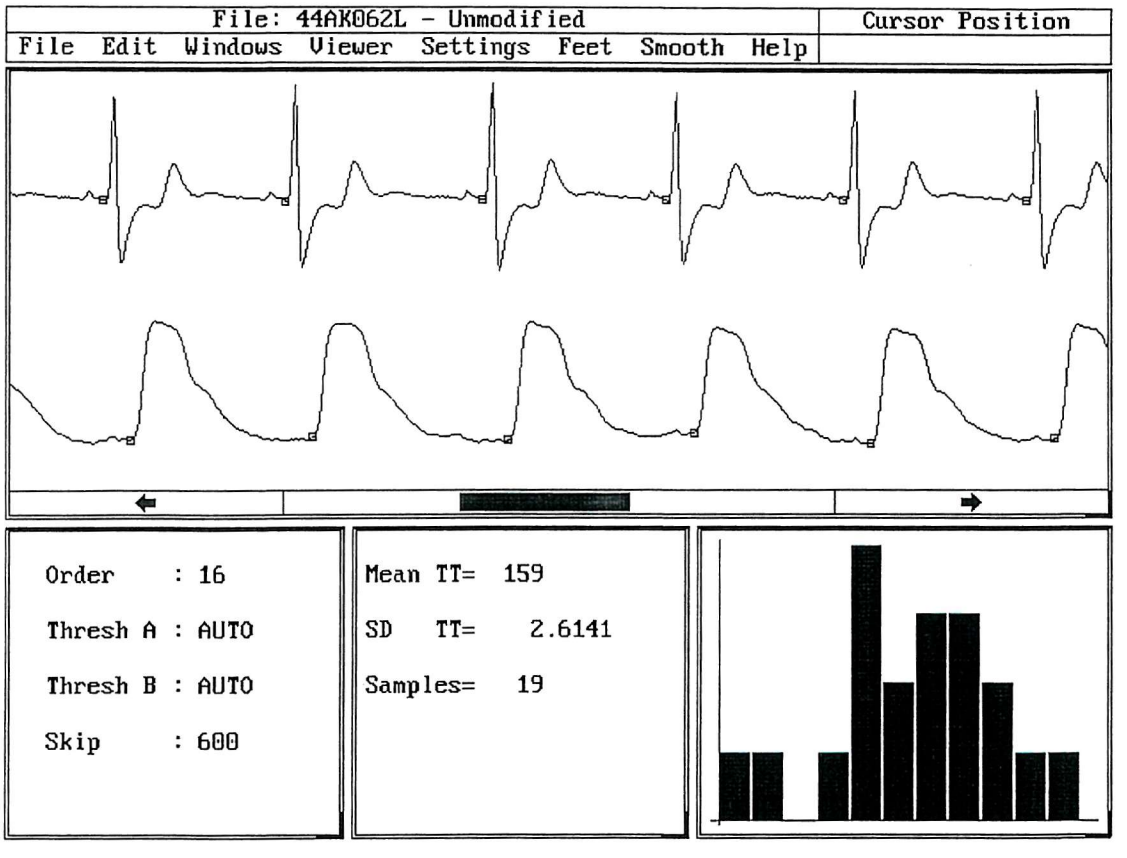


Illustration of the Principle of Recording Pulse Wave Traces and Measuring Pulse Wave Velocity and Arterial Compliance.



Recording pulse wave traces for measurement of arterial compliance.



Appearance of the ECG & pulse wave tracings on screen showing the calculated transit time.

MYSORE - COMPLIANCE (DATA COLLECTION FORM)

ID NUMBER _____

NAME _____

MRC NUMBER _____

DATE OF BIRTH(dd/mm/yy) _____

DATE OF MEASUREMENT(dd/mm/yy) _____

PROXIMAL	DISTAL	FILENAME	DISTANCE(CMS)
ECG	RT RADIAL	_____R	_____
ECG	LT RADIAL	_____L	_____
ECG	RT FEMORAL	_____F	_____
ECG	RT POST TIBIAL	_____P	_____

BRACHIAL	RT.	LT.
SYS BP	_____	_____
DIAS BP	_____	_____
MEAN BP	_____	_____
PULSE	_____	_____

ANKLE

SYS BP	_____
DIAS BP	_____
MEAN BP	_____
PULSE	_____

APPENDIX 5

Intra Observer Variation – Pulse wave velocity

I repeated pulse wave velocity in all the four arterial segments (aorto-right radial, aorto-left radial, aorto-femoral and aorto-posterior tibial) in 10 subjects. There were no statistically significant systematic differences between the two measurements (Table).

Comparison of PWV in the four arterial segments in subjects who underwent repeat measurements

	PWV (m/s)	
Subject number	**Original values**	**Repeat values**
	Aorto-right radial segment	
1	3.80	4.28
2	4.44	4.26
3	4.13	4.21
4	5.28	4.80
5	3.73	3.81
6	4.30	3.69
7	3.40	3.41
8	3.39	3.11
9	3.62	3.44
10	4.83	4.78
Mean (SD)	4.09 (0.63)	3.98 (0.58)
95% CI	3.64, 4.54	3.56, 4.39
	Aorto-left radial segment	
1	4.01	4.17
2	4.58	3.96
3	4.34	3.66
4	4.99	4.62
5	3.62	3.60
6	3.98	3.50
7	3.37	3.35
8	3.09	3.14
9	3.28	3.31
10	4.89	4.74
Mean (SD)	4.02 (0.68)	3.81 (0.55)
95% CI	3.53, 4.50	3.41, 4.20

	PWV (m/s)	
	Aorto-femoral segment	
Subject number	**Original values**	**Repeat values**
1	3.35	3.47
2	4.09	3.72
3	3.09	3.16
4	3.97	3.60
5	3.24	2.88
6	2.68	3.04
7	2.58	2.88
8	3.02	3.12
9	2.64	3.40
10	3.83	3.64
Mean (SD)	3.25 (0.56)	3.29 (0.31)
95% CI	2.85, 3.65	3.07, 3.52
	Aorto-posterior tibial segment	
1	5.52	5.23
2	6.23	5.45
3	5.56	5.37
4	6.14	5.88
5	4.79	5.26
6	4.47	4.58
7	5.08	5.12
8	4.98	5.33
9	5.20	5.50
10	6.06	6.31
Mean (SD)	5.40 (0.60)	5.40 (0.46)
95% CI	4.97, 5.83	5.08, 5.73