Design of a Mobile Kit for Cardiovascular Disease Screening in Resource Constrained Environments

by

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Abstract

In the past few decades global health has improved significantly and many countries have started to move away from high mortality rates due to infectious diseases. This trend has however been accompanied by an increase in chronic disease incidence, in particular Cardiovascular Diseases (CVDs). In countries that are making this epidemiological transition, such as India, chronic diseases are also a hindrance to economic health as a large portion of deaths occur when people are still active in the work force.

There are various policies that may be implemented to curb the burden of CVDs. These include population based approaches and high risk management strategies. In this thesis, the design of a mobile CVD Screening Kit to aid the screening of high risk subjects by low-skilled health workers is described. Focusing on India, a fertile ground where a mobile tool-kit may be implemented was identified at the intersection of: 1. Strong health worker schemes in primary care, 2. The diffusion of mobile phone technology and 3. Well developed CVD risk management strategies. The tools that constitute this CVD Screening Kit were tested at Sengupta Hospital and Research Institute, Nagpur, India. These tests showed that there is potential to develop the CVD Screening Kit further into a commercial product.

The main advantage of the CVD Screening Kit developed is that, differently from standard CVD risk factor analysis, it measures the root issue of many CVDs, i.e. arterial stiffness. Therefore, the CVD Screening Kit brings complex clinical analysis capabilities, that are generally only available in equipped hospitals, to the hands of low-skilled health workers working in primary care centres.

Although the CVD Screening Kit is still at an early stage of development, how it may be implemented in current public and private health programs that tackle CVDs, is also analysed in this thesis. Furthermore, it is discussed that introducing mobile phones to health workers, who are mostly female, may have a slow but strong impact on the independence and leadership of women.

Thesis Supervisor: Richard Ribon Fletcher
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Chapter 1

Introduction

The past century has seen a tremendous improvement in Global Health. According to the latest “Global Burden of Disease” Report published by Lancet, global average life expectancy has increased from 61.7 to 71.8 between 1980 and 2015 [Wang et al., 2016b]. This trend is remarkable and is set to continue in the next decades thanks to advancements in the understanding of our bodies and behaviours, together with improvements in medicine and technology. Nevertheless, there is still significant work to be done, especially in providing quality healthcare to the least fortunate.

Looking at the global relative incidence of various causes of death shows where there is scope for new understanding and the development of novel technologies or disease management strategies. Figure 1-1 shows various causes of death with the area of each box indicating the proportion of deaths with respect to the world total; the causes of deaths are categorised between Non-Communicable Diseases (NCDs) in blue and Infectious Diseases in Orange and Accidental deaths in green. Non-communicable diseases (NCDs) are diseases which are not transmitted from person to person and chronic, meaning that they may last for prolonged periods of time (e.g. Cancer and Asthma). Infectious diseases instead are transmitted from person to person via pathogens and usually last for shorter periods of time (e.g. Influenza and Meningitis). Figure 1-2 instead shows the global DALYs per disease. DALYs stands for Disability Adjusted Life Years, i.e. the number of years lost due to early death, illness or disability. In this Figure the burden held by NCDs decreases slightly because these tend to affect older age groups.
As indicated on the right side of Figures 1-1 and 1-2, the darkness of the colours in each box indicates the change in death/DALY burden between 1990 and 2015. This shows how shifts in
death cause clearly differ. For example drowning incidence has decreased while HIV burden has increased. This is further visualised in Figure 1-3 where only positive change is coloured. Here, aside from HIV and war, between 1990 and 2015, NCDs, are the cause of death which have increased the most with respect to the others.

Figure 1-3: Global Male and Female aggregate DALYs in 2015 with colour shade indicating positive change since 1990 (and grey for negative change); Key: Non-communicable Diseases, Infectious Diseases and Accidental Deaths [IHME, 2016].

As countries industrialise, develop economically and healthcare improves infectious diseases are slowly eradicated and NCDs begin to be the main sources of death. This trend was first described in detail by Omran in 1977 and coined: Epidemiological Transition [Omran, 1977]. Table 1.1 describes the original three Epidemiological Transition stages and a fourth one which was added by Omran recently in light of the improvements in management of NCDs. A country starts in Stage 1: Pestilence and Famine with a low life expectancy and may develop up to Stage 4: Delayed Degeneration where life expectancy has improved drastically and the main causes of death are delayed degenerative disease such as cancer and heart attack (i.e. NCDs).
Table 1.1: Epidemiological Transition [Omran, 2005]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pestilence and Famine</td>
<td>High and fluctuating mortality due to wars, low nutrition and epidemics.</td>
</tr>
<tr>
<td></td>
<td>Population growth low (if any) and volatile.</td>
</tr>
<tr>
<td>2. Receding Pandemics</td>
<td>Mortality starts to decrease as epidemics become rarer. Infectious diseases are the main source of death.</td>
</tr>
<tr>
<td>3. Degeneration</td>
<td>Epidemics curbed hence mortality decreases and stabilises. NCDs begin to have a larger impact on society as life expectancy increases.</td>
</tr>
<tr>
<td>4. Delayed Degeneration</td>
<td>Improved management of NCDs life expectancy is further increased.</td>
</tr>
</tbody>
</table>

Overall, the latest data shows that many countries are transitioning towards Stage 3 where NCDs become the main cause of death and disability. In fact, it is estimated that NCDs will be responsible for 75% of global deaths by 2030 and most of the new ones will occur in developing countries which are currently transitioning towards Stage 3 [Deaton et al., 2011]. It is therefore important for policy makers in countries where this epidemiological transition is occurring to realise that, while there may have been significant improvements in the reduction of infectious disease and malnutrition, health infrastructures have to be prepared for this new wave of NCDs.

Cardiovascular Diseases (CVDs) are part of the family of NCDs and are the leading cause of mortality globally. As illustrated in Figure 1-4, in 2015 CVDs accounted for about 32% of total deaths, surpassing the total number of deaths due to infectious diseases which include HIV, Tuberculosis and Malaria [IHME, 2016]. Amongst CVDs those which originate from Atherosclerosis, i.e. Ischaemic Heart Disease (IHD or Heart Attack)\(^1\) and Cerebrovascular Disease (Stroke), are the most dominant in both men and women as shown in Figure 1-5 [Deaton et al., 2011].

\(^1\)Also known as Myocardial Infarction
Figure 1-4: Global Male and Female aggregate Deaths in 2015 with CVDs in the Yellow Box and with box colour shade indicating change since 1990; Key: Non-communicable Diseases, Infectious Diseases and Accidental Deaths [IHME, 2016]

Figure 1-5: Distribution of varying types of CVD by Gender; Left: Male, Right: Female [WHO, 2011a]

Furthermore, aside from being the most prevalent CVDs, Heart Attack and Stroke are amongst the diseases which may be reduced significantly with appropriate risk reduction. This is illustrated in Figure 1-6, which is the same as Figure 1-4 however, the darker portion represents the relative

\[^2\text{Also the same as Figure 1-1}\]
amount of deaths that are caused by preventable behavioural risk factors such as: alcohol and drug use, dietary conduct, tobacco smoke and low physical activity.

It is of particular importance to recognize that currently 80% of CVD deaths occur in lower and middle income countries as, portions of their populations, begin to reach Stage 3 of the epidemiological transition (which should be viewed more as spectrum rather than discrete stages). In 2001 Yusuf et al. developed an Epidemiological Transition model especially for CVDs [Yusuf et al., 2001]. Table 1.2 is an adapted version of the one published by Yusuf et al. which shows the different stages of the transition, as well as regional examples which have been updated by the European Society of Cardiology in 2011. Furthermore, Yusuf et al. added a Stage 5 to the model in which he placed countries which had reached Stage 4 but, due to particular situations such as wars, had begun to see un uptake in mortality due to infectious diseases. This last stage is not included here as it is believed that countries/regions may oscillate backwards and forwards along the Epidemiological Transition model and that therefore Stage 5 in Yusuf et al. would be represented by a fall to Stage 3 (or further) in this adapted model.
Table 1.2: **Cardiovascular Epidemiological Transition** [Yusuf et al., 2001] †

<table>
<thead>
<tr>
<th>Development Stage</th>
<th>CVD Deaths as % of Total</th>
<th>Major CVDs</th>
<th>Region Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pestilence and Famine</td>
<td>5-10</td>
<td>Rheumatic Heart Disease, infections and nutritional Cardiomyopathies</td>
<td>Rural India and South America</td>
</tr>
<tr>
<td>2. Receding Pandemics</td>
<td>10-35</td>
<td>As above and hypertensive heart disease and haemorrhagic strokes</td>
<td>China</td>
</tr>
<tr>
<td>3. Degeneration</td>
<td>35-65</td>
<td>Stroke and IHD at young ages also due to increase in Diabetes and obesity</td>
<td>Urban India and former socialist economies</td>
</tr>
<tr>
<td>4. Delayed Degeneration</td>
<td>&lt;50</td>
<td>Stroke and IHD at old ages</td>
<td>Europe, Japan and the USA</td>
</tr>
</tbody>
</table>

† N.B. Regional example here are as of 2001

Transitions between different stages follow very complex dynamics, they are a function of disease, healthcare structure, economic development, climate and human behaviour. The industrialisation of a country’s economy, which often allows them to attempt a transition to Stage 3, is usually accompanied by significant changes in societal organisation and behaviour. These changes themselves may exacerbate the degenerative disease outlook in Stage 3. Urbanisation and globalisation drive changes in dietary habits, reduced physical activity and worsening environment conditions. People moving to urbanised centres increase their consumption of fats and sugars. Moreover, in cities manual labour greatly diminishes and air pollution is on the rise in developing countries. These factors together exacerbate CVD burden.

Overall, there is a strong trend towards CVDs having a large impact in countries which are developing and moving towards Stage 3 of the Epidemiological Transition Model. Furthermore, the economic conditions that enable these countries to improve healthcare delivery have shown to exacerbate CVD burden. It will therefore be critical in the coming years that policy makers in these countries equip their countries with the necessary resources and strategies to combat NCDs.
Chapter 2

Scope of this Thesis

The previous chapter introduced the Global Burden of Cardiovascular Disease as well as how the incidence modulates as a function of development. There are now a number of countries that have reached Stage 4 of the Epidemiological Transition Model first developed by Omran in 1977 [Omran, 1977]. These countries have been successful in reducing the burden of CVDs thanks to cutting edge policy strategies, disease management and medical advances. Many countries, such as India, that are reaching Stage 3 and seeking to move further, are not able to deploy all the advanced technology and medical expertise that countries in Europe and the USA have used to tackle CVDs. The incidence of Heart Attack and Stroke are increasing in India and the issue must be tackled both above and below the water surface as illustrated in Figure 2-1. The high incidence of Heart Attack and Stroke are held up by a very high diffusion of CVD risk factors in the population which have to be reduced lest they degenerate and lead to Heart Attack and Stroke.
Figure 2-1: Increasing rates in Heart Attack and Stroke are the evidence of a the prevalence of risk factors in the population [Iceberg, 2017]
This thesis describes the design and initial validation of a mobile CVD Screening Kit centred on a mobile phone developed to screen for CVD in resource constrained environments (focusing on India). There are three main parts to this thesis as shown below:

1. Context
2. Technology
3. Value

1. **Context**: This part describes a search for a fertile ground where a CVD Screening Kit may be developed to aid the reduction of CVD burden. A Medical Background is given in Chapter 3 - Cardiovascular Physiology and Pathophysiology and the main medical topic of this thesis: Atherosclerosis, will then be described in more detail in Chapter 8 - Pathology of the Vascular System. Policies used to tackle CVDs are described in Chapter 4 - Public Policy Approaches to Cardiovascular Disease Prevention. Followed by Chapter 5 - Burden and Treatment of Cardiovascular Disease in India. Once the context has been described fully it will be synthesized in Chapter 6 - Problem Statement and Proposed Solution.

2. **Technology**: The technologies developed for the CVD Screening Kit and their validation will be described in: Chapter 7 - Assessment of Cardiac Function, Chapter 9 - Basic Assessment of Vascular Health: Photoplethysmography and Chapter 10 - Advanced Assessment of Vascular Health: Pulse Wave Velocity.

3. **Value**: Finally, the value of the CVD Screening Kit designed will be evaluated in Chapter 11 - Public Health Impact and Chapter 12 - Conclusion.
Chapter 3

Cardiovascular Physiology and Pathophysiology

*Physiology* is the study of the normal function of living organisms and *Pathophysiology* is the study of abnormal function. In this section the physiology and pathophysiology of the Cardiovascular System, i.e. the heart and its vasculature, will be briefly presented together with the risk factors that lead to the majority of Cardiovascular Diseases (CVDs).

Figure 3-1: Leonardo da Vinci’s *Uomo Vetruviano* drawing with the heart at its anatomical center (heart not to scale) [Pescini, 2017]
3.1 Cardiovascular Physiology

The heart and its vasculature form a beautifully complex dynamic structure which perfuses every organ in the body, including the heart itself, with nutrient-rich blood. The heart is found in the anatomical centre of the body as shown in Figure 3-1. The Cardiovascular System functions may be analysed from three vantage points as shown in Figure 3-2: Mechanical, Vascular and Electrical. From a Mechanical standpoint the heart is a ‘perfusion pump’, the dynamics of which are governed by Electrical activation while the Vascular component distributes blood around the body [Edelman, 2016, Lilly, 2011].

![Figure 3-2: Heart Paradigm](image)

3.1.1 Mechanical Component

The muscular tissue of the heart is called myocardium, this muscle is the core element of the hearts perfusion power. The heart has of four main compartments: two atria and two ventricles separated by atrioventricular valves, as shown in Figure 3-3 and two main stages: Diastole and Systole. At the beginning of Diastole all atrioventricular valves are temporarily closed and the heart muscle is relaxing. Deoxygenated blood coming from the body flows into the right atrium and oxygenated blood from the lungs into the left atrium. As the pressure between the atria and respective ventricles decreases, the atrioventricular valves (tricuspid and mitral) open and blood flows freely from the atria into the ventricles. After a brief ventricle filling period the heart muscle contracts entering Systole. This contraction causes the atrioventricular valves to close and, following a period of ventricular iso-volumetric contraction, the aortic and pulmonary valves open, respectively.
directing blood to the body and to the lungs for oxygenation. As the heart subsequently relaxes the pressure outside the aortic and pulmonary valves becomes higher than the respective ventricles thus the valves close and the cycle repeats on average 2.5 Billion times in an average human lifetime [Edelman, 2016, Lilly, 2011].

![Figure 3-3: Schematic of the heart with the four main compartments, four major valves and main veins and arteries](image)

### 3.1.2 Electrical Component

The heart’s rhythm between Systole (contraction) and Diastole (relaxation) is controlled by a set of pacemaker cells found inside the heart which may be modulated by the brain. These pacemaker cells excite the heart electrically at regular intervals which cause the heart to contract and have enough time to relax before the next contraction. These electrical impulses create the typical ECG signal that is commonly associated with the heart [Edelman, 2016, Lilly, 2011].

### 3.1.3 Vascular Component

The role of the heart is to perfuse the body and itself with blood; it does this via the Vascular System. The vascular system is composed of two types of vessels: the arteries which carry oxygenated blood out of the heart and veins which bring blood back to the heart as shown in Figure 3-4. Deoxygenated blood enters the heart via the Inferior and Superior Vena Cava, passes through the lungs to be oxygenated and subsequently leaves the heart via the aorta to reach the whole body.
The heart perfuses itself via small vessels called coronary arteries. [Edelman, 2016, Lilly, 2011].

**Figure 3-4:** The circulatory system with vessels carrying de-oxygenated blood and oxygenated blood [TeachPE, 2017].

**Arterial System**

Of particular interest in this thesis is the Arterial System. The Arterial System is broadly comprised of three types of arteries: (i) Large Elastic Arteries (LEA), (ii). Long Muscular Arteries (LMA) and (iii). Arterioles. Figure 3-5 is a schematic of the Arterial System with example arteries labelled. The LEAs are found in the torso and are connected directly to the heart, they include the aorta and carotid arteries. These arteries provide a cushioning Winkessel effect on the blood: their compliance allows them to store blood during Systole and expel it during Diastole, thus providing a quasi stable flow of blood to the organs. LMAs are conduits for blood and may alter flow via muscular tone. They follow in series from the LEAs and distribute blood around the
body. Examples of LEAs are the Brachial and Femoral arteries. Arterioles are the last type of arteries and are found before the capillaries in various organs, they provide peripheral resistance and further ensure a steady continuous flow of blood to the organs [Nichols and O’Rourke, 2005]. The heart has its own set of special arteries called Coronary arteries. These arteries are connected to the base of the aorta and perfuse the heart itself with nutrients.

Figure 3-5: The Arterial System with examples of Long Muscular Arteries, Large Elastic Arteries and Arterioles [Haggstrom, 2009]
3.2 Cardiovascular Pathophysiology

Cardiovascular Pathophysiology is the study of Cardiovascular Diseases (CVDs). The most common ones are categorised in Table 3.1 with respect to the Cardiovascular component which they primarily affect. This categorisation of diseases is by no means discrete as the table suggests, all diseases affect all components to some degree. Each of the diseases will be described briefly now.

Table 3.1: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Vascular</th>
<th>Electrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathies</td>
<td>Aortic Aneurysm and Dissection</td>
<td>Arrythmias</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Atherosclerosis</td>
<td>Other electrical conduction and rhythm issues</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Valvular Heart Disease (e.g. Rheumatic Heart Disease)</td>
<td></td>
</tr>
</tbody>
</table>

**Arteriosclerosis** Arteriosclerosis describes a group of disease which cause arteries to become thick and stiff. Atherosclerosis is the most common type of Arteriosclerosis, a chronic inflammation and pathogenesis which involves lipids, thrombosis, elements of the vascular wall and immune cells\(^1\) [Edelman, 2016]. Atherosclerosis may affect all arteries in the body. When this condition affects the coronary arteries it is called: Coronary Artery Disease (CAD) and in late stages may provoke Ischemic Heart Disease (IHD), i.e. a shortage in blood supply to the heart which causes heart muscle death and may be fatal. IHD is commonly known as a *heart attack*. Similarly, atherosclerosis may cause an ischemia to the brain i.e. a *Stroke*. Strokes and Heart Attacks are the most common CVDs and represent Atherosclerosis at its acute stage [Lilly, 2011]. The pathophysiology of Atherosclerosis is illustrated in Figure 3-6.

---

\(^1\)Atherosclerosis: from the Greek "athere-", meaning "gruel" and "-skleros", meaning "hardness" [Lilly, 2011]
Figure 3-6: Pathogenesis of Atherosclerosis. A: Initial Lesion with a few *foam cells* but otherwise healthy artery, B: Fatty streaks begin to be visible as Lipid starts to accumulate in cells, C: An intermediate lesion is visible as lipids accumulates extra-cellularly, D: Atheroma develops as a lipid core forms (*yellow*), E: Fibroatheroma develops as the plaque becomes calcified and fibrotic, F: Atherosclerosis develops into complicated lesions which either constrict blood flow significantly themselves or may create thrombi (blood clots) which block blood flow causing a stroke or heart attack depending on where the lesion happens [Edelman, 2016, UCD, 2017]

**Aortic Aneurysm and Dissection**  This occurs when the Aorta, the artery directly connected to the heart, dilates and eventually ruptures causing a haemorrhage.

**Arrhythmias**  Arrhythmias are abnormal heart rhythms which occur when electrical conduction in the heart malfunctions impeding normal contraction and relaxation times.

**Heart Failure**  Heart Failure occurs when the demand for oxygen around the body exceeds the amount of supplied by the circulation of blood (not due to lack of oxygen from the lungs, but purely because the heart is incapable of ejecting enough blood at each stroke). This may occur due to many of the diseases described in this section. For example, as heart muscle deteriorates due to a cardiomyopathy the body will not receive enough oxygenated blood.

**Hypertension**  Hypertension is the abnormal level of Systolic and Diastolic Blood pressures outside the heart. Typical pressures are around 120/80 mmHg (Systolic Pressure over Diastolic Pressure).

**Cardiomyopathies**  Cardiomyopathies are diseases of the heart muscle. There are three main types: Dilated, Hypertrophic and Restrictive. They may be caused by a variety of toxic, inflammatory, genetic and metabolic causes.
**Congenital Heart Disease**  There are many different Congenital Diseases which arise from fetal malformations. These diseases are typically diagnosed before birth or during the first years of life if the baby survives.

**Peripheral Arterial Disease**  This is arteriosclerosis of the arteries in the limbs which may hinder circulation and create thrombi (blood clots) which cause ischemia in various organs. For example a thrombus may reach the lungs via the heart causing a *Pulmonary Embolism*.

**Valvular Heart Disease**  These are disease which affect heart valves. Nowadays replacements are possible which extend life expectancy significantly. A common precursor to Valvular heart disease is Rheumatic fever and in such cases is called *Rheumatic Heart Disease* (RHD). RHD is caused by repeated and ongoing infections of Acute Rheumatic Fever (ARF) and mostly affects young children although heart issues may surface with a time lag of several years. ARF is an infection by group A streptococcal bacteria. This fever may be cured readily with antibiotics, however, if left untreated ARF may affect the heart, joints and central nervous system. In particular, it may cause fibrosis of the heart valves. Heart valves are essential for the mechanical functioning of the heart. As fibrosis progress valves are not able to function properly and may both leak and/or constrict outflow. This is detrimental to the heart and will lead to heart failure [W HF, 2017].
3.3 Risk Factors

Aside from congenital issues the majority of CVDs are degenerative in nature meaning that they are chronic conditions which slowly worsen with time. This degeneration is accelerated by the presence of well defined risk factors. There are two types of risk factors associated with CVDs: (i) Modifiable risk factors and (ii) Unmodifiable risk factors. These are listed in Tables 3.2 and 3.3. Having one, or worse: multiple, risk factors, poses a person at risk of having a CVD. In general, CVD Risk is a holistic measure of the number and degree of risk factors a person has.

Table 3.2: Unmodifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Ageing is the prime inescapable risk factor. As one ages, in particular after the age of 55, the risk of coronary artery disease and stroke increases consistently even in perfectly healthy individuals because arteries naturally stiffen [World Heart Federation, 2016].</td>
</tr>
<tr>
<td>Demographic Characteristics &amp; Family History</td>
<td>Both Ethnic Origin and Family History may be risk factors. People of South Asian ethnic origin have a genetic predisposition to CVDs. Furthermore, having a first degree blood relative who has had coronary artery disease or a stroke before menopause for women or before 55 for men, increases level of risk [Nichols and O’Rourke, 2005, Edelman, 2016].</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender also plays a role, in fact men are more at risk until women reach menopause, after which both sexes share the same amount of risk [Lilly, 2011].</td>
</tr>
</tbody>
</table>
Table 3.3: Modifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hypertension is a disease which is also a risk factor for other Cardiovascular Diseases. It consists in chronic levels of systolic blood pressure (SBP) above 140mmHg and or diastolic blood pressure above 90mmHg</td>
</tr>
<tr>
<td>Abnormal Lipid Profile</td>
<td>Abnormal lipid levels consist in high levels of Blood LDL Cholesterol or low levels of HDL Cholesterol [Mayo Clinic, 2016]</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Tobacco use, both smoked and chewed increase risk significantly. Fortunately, thanks to the bodies ability to renew itself, stopping tobacco consumption reduces risk</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>Although true that a glass of red wine a day for women and two for men may reduce cardiovascular disease risk, excessive alcohol consumption is certainly detrimental [Edoardo Gronda, 2016]</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>Physical inactivity increases cardiovascular risk by 50% and obesity is a precursor to diabetes which is also a risk factor [Mayo Clinic, 2016]</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Diabetes causes damage to the arterial system acting as a precursor to Arteriosclerosis [Mitchell et al., 2004]</td>
</tr>
<tr>
<td>Body Weight</td>
<td>A well balanced diet is always beneficial for ones body and in particular helps reduce CVD risk especially if it reduces the amount of LDL Cholesterol</td>
</tr>
<tr>
<td>Psychological Burden</td>
<td>Chronic stress, Anxiety, Isolation and Depression are all conditions which do not only affect psychological condition but also physical health and may be detrimental for Cardiovascular Diseases.</td>
</tr>
</tbody>
</table>
This section will describe the three main strategies that policy makers around the globe may adopt to prevent CVDs [WHO, 2011a]:

- Surveillance and Monitoring
- Population Based Strategies
- Screening and High Risk Management

There are many nuances to these strategies and the level to which they are implemented, in terms of penetration, structure, medical expertise and technology, will vary depending on the resource constraints of the pertinent Health Ministry. Experience has shown that implementing all three strategies together enables synergies to arise and provide citizens with a good well-rounded protection against CVD.
4.1 Surveillance and Monitoring

Surveillance and monitoring involves geo-localising and aggregating medical records concerning CVDs, including CVD risk measurements, death counts, death age and cause ecc. This data aggregation enables epidemiologists to understand regions where CVDs are most prevalent, trends which are emerging and especially which strategies work [Beaglehole et al., 2011]. Furthermore, with the development of powerful computers, data analytic techniques are undergoing a renaissance and these tools may help epidemiologists understand the spread of CVDs in more detail than previously possible.

Efficient Surveillance and Monitoring is especially important in those countries, such as India and China, which are entering Stage 3 of the Epidemiological Transition model and are also undergoing deep demographic changes. With resource constraints, Surveillance and Monitoring allows for the appropriate allocation of resources into the other two policies in an effort to curb CVDs [Shah et al., 2010]. If surveillance is not performed, in particular in countries which are just now beginning to encounter CVD burden, there is a risk that CVD burden may be greatly underestimated. For example, as will be described in Section 5.1.1, CVD burden in certain rural regions in India has been significantly underestimated because of severe under-documentation of many deaths and death causes.
4.2 Population Based Strategies

Population based strategies of preventative care were first proposed by Rose et al. in 1992 [Rose, 1992, Deaton et al., 2011]. Rose et al. correctly believed that disease risk factors are not binary but that rather they appear as a spectrum in society. This means that a small decrease in risk factor prevalence amongst the whole population will remove many from the most vulnerable positions and reduce the worsening of risk factors over time in the rest of the population. Population based strategies of preventative care aim to reduce risk factor prevalence by media campaigns, increases in taxes on at risk products, subsidies on healthier goods, labelling of products and marketing restrictions [Beaglehole et al., 2011]. Furthermore, because society is a collective strategies that target all may also be self-reinforcing. Another reason to propose population based strategies is that knowing that certain risk factors lead to bad health, it would immoral not to divulge this information to the whole of society, rather than solely to those who are seeking health advice.

Many population strategies have shown to be very effective especially in European countries and in the United States of America where they have been implemented for a number of years. For example, national smoking bans in public areas have led to significant reductions in acute coronary events [Deaton et al., 2011]. These population based approaches are not always simple to implement. For example, reducing the incidence of obesity requires a deep understanding of complex cultural factors, availability to healthy food products and working conditions. Population strategies are in continuous evolution, for example recently an initiative by the European Union follows a successful French campaign EPODE in which town mayors and citizens are recruited to spread the importance of eating healthy food [Deaton et al., 2011].

In 2011 the Lancet NCD Action group and NCD Alliance proposed five priority interventions to reduce the burden of Non-communicable diseases (NCDs) globally but with a particular focus on developing countries. Four of these were population based approaches: 1). Tobacco control, 2). Salt reduction, 3). Improved diets and physical activity and 4). Reduction of hazardous alcohol intake. The only non-population based approach was the diffusion of technologies to measure risk together with the provision of essential drugs for high risk individuals. Overall, the authors of the Lancet paper comment that a combination of population and high-risk management strategies are necessary to significantly reduce the burden of NCDs.
4.3 Screening and Management of High Risk Patients

Screening and Management of High Risk Patients in primary care is a different strategy to population based interventions because these target specific high risk people. People in the at risk age group\(^1\) are generally screened for multiple risk factors and after risk factor aggregation models are used, the subjects is classified in a risk bracket and they are managed according to specific guidelines. It is important to target a wide population sample with these strategies because the two largest CVDs by death rates (Heart Attack and Stroke) are caused by Atherosclerosis which is mostly asymptomatic. Management strategies range from simply advising behavioural change, to medication subscription and, in the most severe cases, secondary care referral. There is a long history of risk predictive models to stratify people. Famously, the one derived from the Framingham Heart Study as well as the European SCORE model [Deaton et al., 2011]. It has been shown that risk score models are dependent on the particular population with which they were developed. For this reason the WHO has developed charts that may be used to identify risk in many subregions in the world in an effort to increase the screening capabilities in developing countries [Beaglehole et al., 2011].

The most recent risk screening models involve multiple risk factors as opposed to older ones which often focused on very few. The advantage of using multiple risk factors is that the there are far fewer false positives. This is because CVD risk factors form a continuum of risk, and therefore risk cannot be entirely described in a binary fashion. By reducing the false positive rate the number of people who are recommended medication reduces, thus cutting costs and the number of people who receive medication unnecessarily which may lead to adverse events [WHO, 2007b].

These screening strategies which stratify risk are particularly effective in settings with limited resources, where the objective is to optimise lives saved per unit cost. Furthermore, it has been shown that CVD interventions have a proportional reduction of risk irrespective of the initial level of risk [WHO, 2002]. Thus, if a fixed number of patients is treated, targeting high risk individuals is very efficient in terms of lives saved per cost. Moreover, the thresholds of risk at which certain measures are adopted may be modified by the competent entities in order to allocate resources appropriately.

\(^1\)Generally above 35 years
4.3.1 Assessment and Management of CVD Risk in Countries with a well developed Healthcare System

Assessment and management of CVD risk varies from country to country. Regular visits to primary care is the best way to monitor progression of CVD risk because treatment for risk reduction may start early on. In countries with a developed healthcare structure a primary care visit will suffice to detect if someone is at risk of developing a CVD or is already sick. If deemed necessary, in addition to the standard monitoring of heart sounds and blood pressure measurements, the patient will undergo certain particular tests to establish CVD risk fully. A sample of these tests which may be performed in equipped hospital structures is shown in Table 4.1. These tests may include an electrocardiogram to assess the electrical conduction of the heart and previous ischemia to the heart, an Echo-cardiogram to assess the hearts overall mechanical functionality, a treadmill test to assess degree of heart failure, blood tests to measure blood cholesterol and other pertinent parameters, vascular health analysis via a Doppler probe and finally a CT Heart Scan which shows how healthy the coronary arteries are. Once high risk individuals are identified they are prescribed appropriate medication and from then onwards undergo regular monitoring to keep track of the issue.

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Vascular</th>
<th>Electrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Sound and Blood Pressure</td>
<td>Cholesterol Blood Tests</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Echo-cardiogram</td>
<td>Doppler probe vascular analysis</td>
<td>CT Heart Scan</td>
</tr>
<tr>
<td>Treadmill test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.2 Assessment and Management of CVD Risk in Countries with a less developed Healthcare System

Access to modern facilities described above are not commonplace in many parts of the world. Most significantly there is a worldwide chronic shortage of medical professionals. In order to combat this the WHO has developed a *Guide for the Assessment and Management of Cardiovascular Risk* which they recommend to health care systems in low-resource settings. These guidelines have
two main components: 1). A Risk Assessment protocol similar to the Framingham Risk Score, 2). Patient Management Strategies for each level of risk. Importantly, this method has been designed to be performed by low skilled health workers [WHO, 2007b]. This method is widely used and has also been implemented in epidemiological studies to evaluate CVD risk in populations [Norman et al., 2014]. The Risk Assessment consists of charts that may be used to determine a persons 10-year risk levels of fatal or non-fatal cardiovascular event with the following information:

- Presence or Absence of Diabetes
- Gender
- Tobacco Consumption
- Age
- Systolic Blood Pressure
- Total Blood Cholesterol (Optional)

The presence of diabetes is tested by asking if they are already taking diabetic medication or with a urine of blood test, while total cholesterol level measurement requires a blood test.

Depending on the level of risk identified with the risk assessment a series of recommendations are made which range from behaviour change to medications to further care in secondary and tertiary care structures. These recommendations are highly effective if people comply to them regularly. However, it is important to note that compliance to medication and behaviour change are some of the hardest medical issues worldwide. This is another area where precise risk measurement may help because by showing patients their real risk of a fatal event may hopefully increase compliance to recommendations.

In recent years there have been great advantages in the medications for the reduction of CVD risk not only in terms effectiveness but also because of the expiry of patents which allow drug companies to produce generic variations of the original drug. This is particularly true in India where many of these generic drug manufacturers exist. Examples of these drugs are: Beta-Blockers (anti-hypertensive), Angiotensin converting enzyme inhibitors (anti-hypertensives), Statins (lipid

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2The user of such charts is also asked to bear in mind a list of other factors that may influence total risk such as previous CVD events [WHO, 2007b].
lowering drugs) and aspirin [Joshi et al., 2009, WHO, 2007b]. Furthermore, although not studied fully, researchers have started to develop poly-pills which contain a combination of CVD Risk reduction drugs in a single pill. A study published by Lancet claims that the cost of a poly-pill for CVD risk reduction would cost less than a dollar per person per year in India [Beaglehole et al., 2011]. Combining the drugs into a single pill may further increase compliance and greatly improve life expectancy. As an example of the effectiveness of these drugs: if a person is screened to have a maximum risk level in the WHO risk level measurement, CVD risk may be reduced by about 30% if blood pressure and cholesterol levels are reduced to acceptable levels via the intake of antihypertensives and statins [WHO, 2007b].

Figure 22. WHO/ISH risk prediction chart for SEAR D. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>&lt;10%</th>
<th>10% to &lt;20%</th>
<th>20% to &lt;30%</th>
<th>30% to &lt;40%</th>
<th>≥40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4-1: Chart used to determine 10-year Cardiovascular Risk knowing Age, Gender, Smoking habits, Systolic Blood Pressure and Cholesterol Level. SEAR D refers to a subregion that this table pertains to [WHO, 2007a]
4.4 Conclusion

Overall, all three main strategies are important to reduce the burden of CVDs. Governments should strive to strike a balance in allocating resources in each strategy. Referring to Figure 4-2: the dotted line represents a theoretical current distribution of 10-year CVD risk, High Risk individuals are represented by the area under curve to the right of the High Risk vertical line. The solid area represents the optimal distribution in which the present distribution has been shifted to the left as a whole via population based strategies and skewed towards the low risk region via high risk strategies.

Figure 4-2: Changes in 10-year CVD risk distributions when both population and high risk strategies are implemented [WHO, 2007a]
Chapter 5

The Burden and Treatment of Cardiovascular Disease in India

5.1 Burden of Cardiovascular Disease in India

India is one of the countries in the world that is suffering the most from CVD. The burdens in both rural and urban areas are particularly high compared to the rest of the world [Norman et al., 2014]. This relatively uncontrolled rise in burden is due to lack of awareness, access to primary care and low affordability of tertiary care which many Indians resort to due to the lack of primary care [Joshi et al., 2009]. This section will focus primarily on CVD Risk i.e. referring to the risk of developing Heart Attack and Stroke and also on Rheumatic Heart disease, which still has a significant impact especially in the rural population.

In the Introduction of this thesis rural India was placed at Stage 1 in the Epidemiological Transition. It will be shown in this section that perhaps Rural India is actually closer to Stage 3 as is Urban India. In fact, CVDs are expected to become the largest cause of death in India and the second cause of disability in the next two decades [Norman et al., 2014].

Figures 5-1 and 5-2 show the CVD Burden around the globe in terms of DALYs per 100,000 people for women and men respectively. Sub-Saharan Africa, Russia and South-East Asia are particularly hit by CVDs while Europe and the Americas less so.
Figure 5-3 shows aggregate proportional deaths in India in 2015 with only positive change shown in colour. It is clear from this figure that the incidence of Heart Attack and Stroke is increasing while Infectious disease (TB, Malaria, Diarrhoea ecc.) are declining aside from HIV. Of particular note is also the rise in Diabetes, a known risk factor to for Stroke and Heart Attack. It is important to also note that Rheumatic heart disease (labelled RHD) has also increased in incidence since 1990.
The reason why the Indian population suffers greatly from CVD is multi-factorial and in large described by the Epidemiological Transition which has been concomitant with:

1. Demographic shifts to urban and peri-urban areas
2. Increasing age profile
3. Lifestyle changes such as poor diet and physical activity
4. Genetic predisposition [Kumar, 2014].

70% of the Indian population lives in rural areas however every year about 10M move to urban and peri-urban areas [Allianz, 2011]. This means that more people are exposed to air pollution, tobacco consumption and less physical activity compared to in the rural areas. This is not to say that people in rural areas are free of risk factors. In fact it has been shown that increase in smoking and alcohol consumption is also increasing in rural areas.
Many of these CVD risk factors may be modified with behaviour change. In fact, it is estimated that almost 75% of CVD deaths in India are attributable to behaviour risks as shown in Figure 5-4 in which for each disease the darker colour represents the estimated deaths due to behavioural risk factors, thus potentially preventable [IHME, 2016]. These factors have contributed to a doubling of hypertension levels and a trebling of diabetes in the last 30 years in India [Yusuf et al., 2001].

5.1.1 CVD Incidence in Urban and Rural Settings

Incidence in Urban areas tend to be higher than in rural areas. A study performed by Joshi et al. showed that incidence of CVDs is 3-5% in rural areas and 7-10% in urban areas [Joshi et al., 2009]. Because 70% of the Indian Population lives in rural areas the total incidence is probably higher in rural areas [Bagchi, 2008].
Furthermore, the incidence in rural areas may be greatly underestimated. There are few and sparse studies that have surveyed CVD in India and these have mostly concerned urban areas [Joshi et al., 2009]. In rural areas 75% of deaths occur at home without physician certification and therefore no official death certificate is issued [Gaziano, 2009]. Furthermore there is not centralised death registry for CVDs [Yusuf et al., 2001]. This all contributes to the fact that the incidence of undiagnosed, uncontrolled and untreated CVD is significantly higher in rural areas [Gaziano, 2009]. This is also shown by various studies performed in rural populations. Mortality rates in rural Andhra Pradesh were north of 31% for Heart Attack and Stroke combined in a study conducted in 2009 [Joshi et al., 2009]. Another study performed in 2014 using the WHO risk prediction charts in rural Karnataka showed that 15% of the population was at > 30% risk and 28% was at > 20% risk, with Hypertension present in 35% of the population [Norman et al., 2014]. These numbers are particularly significant and paint a dire picture of the rural areas and highlight the lack of population based strategies and management of high risk individuals in rural villages. Moreover, in those rural areas where there is screening, there is often a severe lack of drug therapy compliance: a study conducted in Andhra Pradesh in an area where screening was happening, of the people with a diagnosed CVD only 14% used Aspirin, 41% took a blood-pressure lowering medication and 5% were taking lipid-lowering medication [Joshi et al., 2009].

Overall, since 2001, it seems that rural India has also progressed towards Stage 3 in the Epidemiological Transition, (as depicted in Table 5.1) skipping Stage 2 as there has been no significant rise in haemorrhagic stroke which is expected in Stage 2 [Gaziano, 2009]. This is of particular significance because on one hand it shows that infectious diseases are starting to be successfully eradicated and that on the other, an effort has to now be done to curb the rising incidence of CVDs and NCDs in general.

While it is true that Heart Attack and Stroke are increasing significantly and pose major issues, it is also true that in rural areas, non-degenerative types of CVD still have a significant impact. In particular Rheumatic heart disease (RHD), which as shown in Figure 5-3 is not only still present but also on the rise. The root cause of RHD is infectious, as it is repeated infections of Acute Rheumatic fever (ARF) which cause damage to the heart valves thus leading to RHD. ARF mostly impacts school children and in India the incidence is 100 to 200 per 100,000 children between the ages of 5 and 18 [Vijayalakshmi, 2012].
Table 5.1: Cardiovascular Epidemiological Transition [Yusuf et al., 2001]

<table>
<thead>
<tr>
<th>Development Stage</th>
<th>CVD Deaths as % of Total</th>
<th>Major CVDs</th>
<th>Region Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pestilence and Famine</td>
<td>5-10</td>
<td>Rheumatic Heart Disease, infections and nutritional Cardiomyopathies</td>
<td></td>
</tr>
<tr>
<td>2. Receding Pandemics</td>
<td>10-35</td>
<td>Ut supra and hypertensive heart disease and haemorrhagic strokes</td>
<td>Rural India</td>
</tr>
<tr>
<td>3. Degeneration</td>
<td>35-65</td>
<td>Stroke and Heart Attack at young ages also due to increase in Diabetes and obesity</td>
<td>Urban India</td>
</tr>
<tr>
<td>4. Delayed Degeneration</td>
<td>&lt;50</td>
<td>Stroke and Heart Attack at old ages</td>
<td></td>
</tr>
</tbody>
</table>

5.1.2 Ethnic Predisposition

India is not only faced with a raised burden in CVDs because of the Epidemiological Transition but also because of an ethnic predisposition which involves the whole south-asian population. Ethnicity comprises both genetic and cultural characteristics [Yusuf et al., 2001]. It is important to look at both when considering predisposition to CVDs due to ethnic backgrounds.

Regarding Genetic traits, studies on South-Asian migrant populations in the United States have shown that they are 3-5 times more likely to die from a CVD than the US average [Gupta et al., 2006]. In fact, the Indian phenotype is characterised by significant visceral adiposity (shown by larger waist-to-hip ratios), insulin resistance, higher C-reactive protein (measure of inflammation), raised triglyceride and abnormal low/high density lipoprotein balance (LDL/HDL) [Kumar, 2014]. All phenotypes which predispose the body to CVDs. It has also been found that migrant South Asians have LDL cholesterol levels similar to other populations however the particle size is smaller and these are prone to be atherogenic (i.e. promoting Atherosclerosis). Furthermore, HDL cholesterol particles, which shield against the damaging LDL cholesterol, are also smaller and as such provide less protection [Gupta et al., 2006].

Some of these genetic traits were previous environmental adaptations. Insulin resistance and raised triglyceride levels may be found in people who’s ancestors lived for many years with limited
nutritional resources and adapted to the lack of glucose by developing insulin resistance to ensure that the brain received enough glucose to function. The Indian descendant who is now leading a higher calorie diet easily becomes glucose intolerant and thus diabetic. These characteristics do not have to derive from the living environments of our ancestors, in fact a fetus that does not receive adequate nutrients during gestation has a higher chance of developing insulin insensitivity in adult life [Yusuf et al., 2001].

Furthermore, as people in various parts of the world adopt different lifestyles, the predispositions may be borne out of particular environmental factors that only portions of people of a certain ethnic/cultural origin face. In India saturated fats (namely clarified butter or ghee) are staple in cooking and anyone following this diet is at risk of obesity and high cholesterol levels, both significant risk factor for CVDs [Gaziano, 2009].

Overall, unfortunately, a mixture of cultural and genetic characteristics makes the South Asian population prone to CVDs. For now the solution to this is to be even stricter in the reduction of risk factors that promote CVDs.

5.1.3 Barrier For Development

CVDs are not only a large social cost to families but also a very large economic one to both individual families and countries. It is a strong driver towards poverty and, according to a study conducted in 2004, it is estimated that 2728 DALYs were lost per 100,000 people in 2010 in India due to CVDs [Columbia, 2004].

It is estimated that India is the country that has lost the most productive life years due to CVD than any other country around the globe. A total of 9.2M productive life years were lost among people between ages of 35-64 in the year 2000. This number is set to increase to a staggering 17m in 2030. Due to these worrying figures, the World Economic Forum considers Non-communicable diseases in general to be one of the main threats for development. The reason why so many productive life years are lost is because it is estimated that 64% of CVD deaths occur at a young age, between 35 and 64. On average in India people suffer their first CVD event (Heart Attack or Stroke) 6 years earlier than in the US [Columbia, 2004].
On a family scale the economic consequences of a family member dying from a CVD at a relatively young age are also dire. Weak prevention strategies lead many families to face the costs of tertiary care, it is estimated that more than 25% of hospitalized Indians fall beneath the poverty line. One quarter of families with someone who has a CVD face a catastrophic expenditure and 10% of these families enter poverty. This is because with weak prevention strategies people at risk are not detected early and only seek help when the CVD event happens. Furthermore, the largest source of poverty is widowhood, men are more susceptible to CVDs, only 15—20% of widows in India remarry and women employment between 35 and 64 is merely ~ 25%. In addition, because of demographic shifts percentage dependency, i.e. the percentage of a population that depends financially from someone else is set to increase from ~ 10% to ~ 20% between 2000 and 2040 and most dependants will be above 65 years [Columbia, 2004]. This means that more people will be susceptible to poverty if the person who provides financially for the family dies [Hammer et al., 2007, Beaglehole et al., 2011].
5.2 Treatment of Cardiovascular Disease in India

5.2.1 Introduction to Healthcare Provision in India

Healthcare is both a good and a service to society and as such healthcare suppliers charge a price for its provision. Healthcare may be either supplied publicly, financed through taxation, or privately under free market laws. In reality no nation on the planet has a system that is strictly bound to either of these two models [OECD, 2010]. The free market failures in healthcare are the externalities of diseases and the failure of insurance markets due to asymmetric information [Hammer et al., 2007]. To correct these failures governments may opt to regulate private insurance markets, provide public insurance schemes, deliver nation-wide plans to limit the externalities of diseases or render healthcare a public good through taxation.

India gained its independence from Britain in 1947 and in its early years envisaged that basic public health services would be provided to the population through taxation [Arora and Gumber, 2005]. This was overseen by the Ministry of Health and Family Health. However, lack of funding, geographical dispersion and a frail scheme for healthcare provision have meant that the service was never fully functional [Burns, 2014]. This means that people, throughout all levels of society, mistrust the public health system because of high medical staff absenteeism, low clinical care quality, low customer satisfaction and widespread corruption [Hammer et al., 2007]. Furthermore, the rural population remains overall under-provided in terms of healthcare, in fact 75% of doctors work in urban areas while 70% of the population lives in rural villages [Bagchi, 2008]. These failures have led the private market to flourish. To avoid people from making out-of-pocket payments the government launched a public insurance scheme in the 1980s and subsequently liberalized the market to incentivise the development of private insurance companies [Arora and Gumber, 2005]. Furthermore the government has developed insurance schemes that both private and public companies may supply. Nevertheless, as of 2011, due to the lack of common standards and over-regulation in the industry, only 20% of the population was covered by insurance and only 2% by private health insurance [Tk, 2011]. Despite the low level of insurance coverage, 85% of all visits to healthcare are to private providers, even for the poorest people. Consumers carry more than 70% of healthcare expenses and more than a quarter of all hospitalized Indians fall below the poverty line as a consequence of hospitalization fees [Tk, 2011].
5.2.2 Health Workers Schemes

To address the dire need of increased primary care in rural and peri-urban areas and thus reduce the need for tertiary care which places such a high burden on society, in 2005 the National Rural Health Mission (NRHM) was begun, which recently became the National Health Mission (NHM) with two subdivisions to serve both rural and urban areas [Foundation, 2015]. At the core of the National Health Mission is primary care delivered by trained health workers. These workers are in direct contact with the population and refer to secondary care if needed. Because of their vicinity to the people, especially in remote areas, they serve a very important role in screening and managing peoples healthcare [Gaziano, 2009].

Primary Healthcare in Rural Areas

In rural areas there are three types of infrastructure which serve as primary care centres: at the lowest level is the hierarchy Sub-health centres (SHC) with a coverage of about 5,000 people, followed by Primary Health Centres (PHC) (30,000 people) and finally Community Health Centres (CHC) (120,000 people). SHCs and PHCs serve as feeders to CHCs which include secondary care [Burns, 2014]. This is illustrated in Figure 5-5

SHCs are staffed by Accredited Social Health Activists (ASHA workers). These workers are selected women in villages who serve around 1000 people (200 families). They are trained as health educators and promoters but undergo very little nursing training. They do not reside at the SHCs but rather go door-to-door mostly promoting healthy behaviour and serve an important role in referring sick people to SHCs [Development, 2017]. SHCs also employ health workers called Aganwadi Workers (AWW) and Auxillary Nurse Midwives (ANM). AWWs are similar in scope and training to ASHAs but reside at the SHC. ANMs undergo a more rigorous training, are fully employed by the government and mainly stay at the SHCs although they often coordinate local events at villages such a the Village Health Nutrition days [Honey, 2017]. SHCs provide provide basic drugs, immunization, nutrition and health education, maternal health, pre-school education as well as checkups and referrals to CHCs [Burns, 2014]

PHCs are larger centers which are also used to promote prevention of diseases and educate the
population on medical issues. These centres are either staffed with a medical officer or regularly visited by a physicians or nurses. CHC are larger structures staffed by physicians in four different specialities: pediatrics, surgery, gynaecology and medicine [Burns, 2014].

![Diagram of Primary Healthcare Structure]

Figure 5-5: Primary Healthcare Structure. Across the whole of India, in both rural and urban areas there are 147,068 SHC, 23,673 PHC and 4,535 CHC

There are some shortfalls within this system of primary care delivery in rural areas. There is a severe lack of trained physicians and rampant absenteeism [Hammer et al., 2007]. Furthermore, the government has focused primarily on PHCs and CHCs leaving SHCs, which are the first contact to primary care for many people, under-provided. There is an estimated SHC shortfall of 12.5%. Moreover, even the PHCs and CHCs suffer from great equipment shortages. In fact it is estimated that 75% of CHCs, the largest of the three structures lack appropriate equipment [Burns, 2014].

Primary Healthcare in Urban Areas

In Urban areas there are about 4 times as many health-workers compared to rural areas. Primary care is provided by Urban Health Centres (UHC) or Urban Family Welfare Centers (UFWC) for every 100,000. Secondary care is provided by large public hospitals as well as private hospitals many of which charge according to wealth [Burns, 2014]. Despite this diffusion of healthcare, the urban poor also suffer from under provision. The National Urban Health Mission was set up to address this issue in 2013 and henceforth efforts have been made to design similar strategies to those in rural areas in urban slums. Urban PHCs and CHCs were set up in exactly the same fashion as the rural ones. SHCs were not required because the distances between the centres is significantly lower in urban areas. Including ASHAs, AWWs and ANMs and urban areas has not
only increased the provision of health but it has also raised education and awareness of health issues [NHM, 2013].

Private Provision of Primary Care

Despite the government's efforts to provide healthcare there is still significant under-provision of healthcare, in both rural and urban settings, which has led to many attempts by private initiatives and NGOs to bridge the gap. For example, the Swasth Foundation has developed a very functional model to provide affordable healthcare in urban slums and reasonable prices. They have a collection of small clinics in slums in Mumbai where they offer primary care including doctor or dentist visits, diagnostics, treatments, day care as well as secondary care such as consultation with a specialist. Their very efficient electronic medical records system allows them to keep track of people's health and plan delivery effectively. Because of their high quality and affordability even the poorest people often prefer to go to these private facilities where opening times are reliable and doctors are well prepared [Swasth, 2017].

In rural areas there are many NGOs who run schemes similar to those developed by the NHM i.e. training local health workers to perform essential medical practices with a few tools. Examples of these are the Antara Foundation, iKure and Arth Foundation [Antara, 2017, iKure, 2017, Foundation, 2017]. Engaging the locals by teaching them proper medical practices has proven successful and many other schemes are developing from this basic effective model.

5.2.3 Policies for Non-communicable Diseases

In 2012 the Ministry of Healthcare Family Welfare started the National Programme for Prevention and Control of Cancer (NPCDCS), Diabetes, Cardiovascular Disease and Stroke and in 2015 India pledged the 2013-2020 WHO Global Action plan for NCD [of Health & Family Welfare, 2013]. This Action Plan is made of nine points, the first of which is to reduce premature NCD deaths by 25% by 2020. The other points cover the reduction of critical risk factor prevalence and giving 80% of the population access to affordable basic technologies for diagnosis and essential medicines [WHO, 2015].

Before 2012 some states had started some small programs to deal with the increasing burden
of NCDs. With results from these initial plans the Ministry, in an attempt to achieve the WHO goals, developed the NPCDCS strategy with all three types of policy interventions; i.e. (i). Surveillance and Monitoring, (ii). Population Based Strategies and (iii). Screening and Management of High Risk Patients. The aim of the Ministry to introduce the NPCDCS was to support existing programs financially, start new ones and to provide a technical and logistics structure. The 2016 updated NPCDCS strategy is as follows [India, 2016]:

- Promote behaviour change by involving community, civil society and the media
- Start outreach camps to perform opportunistic screening
- Manage NCD by early diagnosis
- Build the capacity to perform prevention, early diagnosis, treatment at multiple levels of health care
- Provide primary, secondary and tertiary levels of healthcare with knowledge on cost-effective diagnosis and treatment
- Build database capacity to perform accurate surveillance of morbidity, mortality and risk factors

When the Ministry started planning the NPCDCS it realised that the Rural and similar Urban plans developed by the NHM worked well and their depth and diffusion was unparalleled by any other public healthcare structure. It was therefore decided to attempt to integrate the NPCDCS into the existing NHM framework as well as partner with some private hospitals and NGOs.

India may be divided into 640 health districts, each comprising about 1.8M people [Burns, 2014]. The Ministry decided to create a NCD Cell in each of these districts which would oversee and ensure implementation of the NPCDCS in their district. The staff employed in these cells include a Programme Coordinator, an Epidemiologist, Consultants, Accountants and Data Analysts. In March 2012 about 16% of all NCD cells had been developed with the objective of reaching full capacity by March 2017 [of Health & Family Welfare, 2013].
Each of these districts oversees a multitude of SHCs, PHCs and CHC. At a selection of CHC the Ministry decided to develop a NCD Clinic, i.e. the capacity to perform the tasks required to screen, manage, treat and refer to further secondary care structures. By March 2012 800 of these clinics were developed with an objective to reach 2500 by March 2017. These clinics provide specialised support including tests (blood tests, blood pressure measurement via spectrophotometer and ECG), as well as providing guidance to sub-centres on how to perform the task required by the NPCDCS. Table 5.2 shows the specific roles regarding CVDs, performed at each level of healthcare delivery as envisioned in the NPCDCS as specified by the Operational Guidelines released in 2013 [of Health & Family Welfare, 2013].

Table 5.2: NPCDCS Roles by Healthcare Center [of Health & Family Welfare, 2013]

<table>
<thead>
<tr>
<th>Health Facility</th>
<th>Services Offered</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHC</td>
<td>Promotion of behaviour change and opportunistic screening of Diabetes and Hypertension with glucometer kits and BP measurements</td>
</tr>
<tr>
<td>PHC</td>
<td>Ut supra and Treatment provision</td>
</tr>
<tr>
<td>CHC</td>
<td>Ut supra with screening performed with more advanced diagnostics including: blood tests, X-Ray ECG, ultrasound</td>
</tr>
<tr>
<td>District Hospital</td>
<td>Diagnosis and Management of CVD. These centres have more advanced instrumentation including: ut supra, CT Scan, MRI</td>
</tr>
<tr>
<td>Medical College</td>
<td>Research as well as mentoring ad training of district hospitals staff</td>
</tr>
</tbody>
</table>
At the SHC level ASHAs are trained to perform their duties as health activists to reduce NCD incidence by promoting healthy lifestyles such as the consumption of fresh fruit and vegetables, reduction of salt use and increased physical activity. As well as recommendations to have Blood Pressure tested at the SHC or upper structures [India, 2009]. ANMs are trained to measure BP and use a glucometer to measure diabetes. All more advanced diagnostics are performed upstream in the healthcare structure [of Health & Family Welfare, 2013].

Overall the government has set an ambitious plan which will hopefully bear fruit. The screening used at the SHC and also PHC is still very basic and does not use the recommended holistic risk factor approach proposed by the WHO, however it is a step forward in the attempt to reduce the economic and social burden of CVD.

**Rheumatic Heart Disease**

Despite the advances in infectious disease burden reduction, Acute Rheumatic Fever (ARF) together with its long-term possible effect: Rheumatic Heart disease (RHD), are still endemic in India, and, as shown in Figure 5-3 there has been a proportional increase in number of deaths since 1990. In the realm of CVDs the major focus has been on Heart Attack and Stroke in the adult population while RHD has been neglected somewhat [Vijayalakshmi, 2012]. Furthermore, in the past 50 years there has been no significant improvement in the diagnosis and management of ARF nor RHD [Kumar and Tandon, 2013]. ARF may be treated readily with antibiotic and anti-inflammatory treatments. These treatments may be administered by workers of the NHM at SHCs. To avoid repeated infections which will increase the probability of progressing to RHD secondary prophylaxis of patients who have had ARF must continue for about 5 years after the last acute manifestation of ARF. This is a significant burden and the reason why often the full prophylaxis is not followed and ARF progresses to RHD. It is important to note that most of the ARF patients are children and teenagers and as such most RHD cases occur under 30 years of age, i.e. before any significant risk from Atherosclerosis may arise.

If ARF is left untreated and progresses to RHD, treatment is extremely expensive and mortality and morbidity of these treatments remain high especially given the young age at the patients who receive these treatments. The only real interventions are either valve replacement or balloon valvotomy. These interventions possible are expensive (approximate $2k). Some rural areas which
have been fortunate to be protected by government insurance plans do not have to bear the cost but in many cases the costs have to be out-of-pocket [Mullen, 2014].
Chapter 6

Problem Statement and Proposed Solution

6.1 Problem Statement

To combat the large CVD burden in India the government is currently implementing both population based and high-risk management strategies. Population based strategies, through media campaigns and smoking regulation will help lower the average risk level of the population. Continued deployment of high-risk strategies will further help reduce the number of people at severe risk of having a CVD event. Only a combined effort to deploy these two policies simultaneously, together with strict surveillance, will foster a reduction in CVD incidence. This thesis will focus on describing a solution designed to aid the deployment of a high-risk management strategy for low resource constrained environments.

The structure of public rural and urban healthcare in India is very similar. After the rural structure first implemented by the National Rural Health mission proved successful, the government decided to deploy this structure in urban areas as well. The actual CVDs present in urban and rural centres is similar but not identical. Both have a high incidence of Atherosclerosis, while rural areas have a slightly higher incidence of rheumatic heart disease. This similarity in both primary health structure and disease incidence means that similar strategies may be developed for both areas.
The Ministry of Healthcare and Family Welfare, as well as individual states, have made great efforts to address the severity of CVD. Nevertheless, public primary care centres are far from being well distributed and efficient. This has led many private community health worker schemes to flourish. The National Health Mission (under the supervision of the Ministry) has realised this and is seeking to foster public-private partnerships to aid the public healthcare service. It is therefore important to address the problem of CVD incidence from both a public and private perspective. For example, iKure is a private community health worker service which after a few years of independent work are now being supported by the government in their mission to provide low-cost healthcare services to under-served populations [iKure, 2017].

There exist good management techniques, especially for low resource environments, that may be applied to people at risk of CVD, for example the ones provided by the WHO Hearts initiative [WHO, 2017]. These involve behaviour change suggestions and the prescription of various drugs. It is estimated that it would cost $1 per year to provide a poly-pill\(^1\) against CVD risk [Beaglehole et al., 2011, Joshi et al., 2009]. Studies have shown that this would increase life expectancy significantly in the high-risk population. Despite this there is a significant under-use of these management techniques. In order to be able to deploy these management techniques good risk assessment is essential to be able to stratify the population properly.

The current NPCDCS program includes rigorous risk screening however this only occurs at the CHCs and people will not travel the necessary great lengths to go there unless they are really sick. Because atherosclerosis is mostly asymptomatic, unless screening occurs at the lowest levels of the primary healthcare structure most people will not be screened. The problem is that there aren’t enough high-skilled personnel in the SHC or even PHC levels to be able to perform complicated risk screening tests. For this reason, as well for cost reasons the SHCs and PHCs only have very simple methods of measuring CVD risk. In the SHCs and PHCs the only tools available to the health-workers is a sphygmomanometer for Blood pressure and a glucometer to measure diabetes. Just these two measures are not enough to provide a holistic measure of CVD risk. Furthermore, blood pressure measurements are not always easy to perform. It is a rather complicated measurement to take and unskilled health-workers may not be able to use them appropriately. Furthermore, these devices need re-calibration often in order to maintain accurate data.

\(^1\)A single pill with a mixture of Statins, B-blockers and Aspirin
measurements [UBC, 2015a]. Moreover, only PHCs and above are allowed to administer treatment. This is highly inefficient if the person is screened at a SHC and then has to travel to a PHC for further screening and treatment prescription [Joshi et al., 2009]. This is probably done because of the low accuracy of the measurement at the SHCs. A holistic measure of CVD, which looks at multiple risk factors, as done at the CHCs is required to spread high risk management strategy effectively [Ndindjock et al., 2011].

Overall, the screening performed at the CHCs is too complicated to be adopted at the lower levels. It is complex, invasive, requires time, calibrated devices, uses non-reusable materials and is overall expensive. Furthermore, perhaps because of these reasons, these risk screening techniques are not widely spread across the country beyond CHCs and in CHCs themselves. A simpler technique to measure risk would be effective here as well and may help spread proper risk screening around the country.
6.2 Fertile Ground for Solution

There are three key factors which may be harnessed in an effort to provide effective measurement of CVD risk even at the lowest levels of primary healthcare system:

- Community Health Worker Schemes
- Good existing management strategies for high risk subjects
- Diffusion of Mobile phone technology

Both public and private community health worker initiatives provide access to a large portion of the population right at their doorstep [Jarvis et al., 2016]. Existing management strategies already in use mean that once a good measure of risk is deployed the use of such strategies will follow naturally [Gaziano, 2005]. Lastly, the growing diffusion of mobile phones and smartphones is remarkable and having health workers with a now powerful computer in their hands allows for the development of devices that exploit the computational power to perform advanced automatic analysis of signals [Foundation, 2015].

6.2.1 Diffusion of Mobile Phones in India

Mobile phones are present everywhere in India, from urban centres to deep rural areas. In fact 88% of households have a mobile phone [Bhattacharya, 2016]. This mobile phone is commonly shared within the household and has become an essential part in many daily lives. They are used for payments, to spread news from remote areas, to learn the prices of agricultural products as well as to receive weather information [Banerjee, 2014].

Recently India passed the mark of 1 Billion mobile phone subscribers and with 125M smartphones users the country has become the second largest market for smartphones on the planet (China is the first market) [Rai, 2016]. This means that about 17% of the population owns a smartphone. However, as phones are often shared, the number of actual users may be significantly higher. Overall, it is estimated that about 22% of people have access to internet via their smartphones [Poushter, 2016]. There is also a large second hand market for cellphones and smartphone penetration is set to increase significantly. In fact many large corporations, including Google, are planning to launch new cheaper ranges of their smartphones in India in the near future [Rai, 2016].
Overall, across India, mobile phones have been used to help health workers in five main ways: i). Training, ii). Digital Health records, iii). Task management and scheduling, iv). Awareness and Counselling v). Decision support tool [Foundation, 2015].

There are many private organisations who have sought to harness the power of mobile phones to improve the work of health workers. iKures Foundation provides health workers with smartphones and a proprietary mobile App that aids them in their work with medical records and recommendations [iKure, 2017]. Antara Foundation has developed an diagnostic App that with the aid of pictures allows health workers to screen for particular issues such as anaemia [Antara, 2017].

Introducing mobile phones or smart phones to health workers is by no means a solely private initiative. In fact, in 2016, India launched a Nation wide mobile health program to help health workers. This program powered by MOTECH, a mHealth solution developed by the Grameen Foundation with help from the Bill and Melinda Gates Foundation [Foundation, 2016]. The State of Madhya Pradesh recently supplied 80,000 SIM cards to ASHAs and ANMs and Uttar Pradesh has given mobile phones to many of its health workers. Furthemore, an on-line portal from the NHM provides a catalogue of many mHealth solutions that Health workers and their supervisors may test and use out in the field [Development, 2017, NHP, 2017].

A study conducted in Mysore, Karnataka, in 2012 showed that the vast majority of the health care workers in the area owned a mobile phone. This was in striking contrast to the fact that only 36% of the mothers which the health workers looked after owned a phone [Murthy, 2012]. This is may due to the fact that the health workers have a little more disposable income thanks to their job which allows them to buy a phone. Smartphones cost less than $50 in India and there is a proliferating second hand market [Bellman and Malhotra, 2016].

Overall, regarding primary health workers, although it being difficult to quantify, most AWWs and ANMs do have access to a mobile phone and increasingly smartphones as well [Honey, 2017]. This provides an unprecedented opportunity to harness the power of a miniature computer in the hands of a very diffuse community.
6.3 Introducing the CVD Screening Kit

6.3.1 Prior Art

Since the year 2000 a number of mobile phone based diagnostic tools for specific cardiovascular health monitoring have emerged. These new technologies have addressed both the needs of people in developing countries and wealthier countries. Table 6.1 shows a selection of tools categorised per Cardiovascular Component which they focus on. Not directly related to a Cardiovascular Components however relevant to CVD Risk: iHealth Labs have recently developed a multitude of mobile devices including a glucometer (measures the severity of diabetes) [iHealthLabs, 2016].

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Vascular</th>
<th>Electrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure measurement with external device: Withings and I-Health labs [iHealthLabs, 2016]</td>
<td>Lionsgate Technologies sell the PIERS device to measure pulse oximetry [UBC, 2015b]</td>
<td>Mobile ECGs have been developed by AliveCor that measure Atrial Fibrillation [Kardia, 2016]</td>
</tr>
</tbody>
</table>

Aside from the Apps in Table 6.1 there are many Apps on Appstores which claim that they are able to measure anything from Blood Pressure to Blood Oxygenation without an external device. However, none of the ones looked at have any reasonable degree of accuracy or published medical validation. The two main problems in resource constrained environments, and specifically in India, are Rheumatic Heart Disease and acute Atherosclerotic events (Heart Attack and Stroke). The clinically validated mobile tools such as those in Table 6.1 are very useful, however, none target the challenge of addressing cardiovascular disease screening for atherosclerosis as a whole. None seeks to address this issue in a holistic manner. CVD risk may be evaluated with a selection of these Apps however there is no device which attempts to look at the intrinsic mechanism of Atherosclerosis. There is no device made for resource constrained environments to

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2There are also other similar valid ones who are already commercially available or in the process to be
detect Rheumatic Heart Disease.

6.3.2 Proposed CVD Screening Kit

The CVD Screening Kit presented here contains a number of tools that, connected to a smartphone, enables health-workers of varying levels of training to screen for CVD risk in a holistic fashion. There are two main issues which this CVD Screening Kit tackles at the moment which, as has been described in this thesis, are the ones that carry the highest burden in India:

- Rheumatic Heart Disease
- Atherosclerosis, which leads to Heart Attack and Stroke

![Cardiac Function Assessment](image)
![Vascular Assessment](image)

Figure 6-1: Holistic CVD Risk Assessment Approach of the Cardiovascular Disease Screening Kit

The CVD Screening Kit aims to analyse the heart from two vantage points as shown in Figure 6-1: firstly Cardiac Function, the mechanics of the heart are analysed to screen for issues such as Rheumatic Heart disease. These will affect a young age group (between 15 and 30 years). Secondly, Vascular health is analysed to understand the degree of atherosclerosis in the subjects arteries i.e. the risk of having a Heart Attack or a Stroke in the short-term.

Table 6.2 shows the various devices in the CVD Screening Kit. Because health-workers have various levels of training it is unforeseeable that all would be able to work with all the tools. Therefore, the CVD Screening Kit has been split between a more Advanced Kit and a Basic CVD Screening Kit. The Basic CVD Screening Kit is significantly less capable of measuring cardiac health than the Advanced CVD Screening Kit, however, serves as a starting point to train the health-workers to use mobile phones and detect the most severe cases.
The Basic CVD Screening Kit is a very simple smartphone App that measures heart rate, breathing rate and heart rate variability by using the smartphones camera. This device may be used to screen for very severe cases CVD such as late Cardiac Failure or Arrhythmias. It is not a good holistic measure of cardiovascular disease health but may be used to train health-workers to using smartphones before progressing to the Advanced CVD Screening Kit.

Table 6.2: Cardiovascular Disease Screening CVD Screening Kit [Basic Kit, Advanced Kit]

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Device</th>
<th>Physiological Measurements</th>
<th>Vantage Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Smart-phone</td>
<td>Heart &amp; Breathing Rate, Heart Rate Variability</td>
<td>Cardiac Function</td>
</tr>
<tr>
<td>7</td>
<td>Stethoscope, Smart-phone</td>
<td>Abnormal Heart Sounds</td>
<td>Cardiac Function</td>
</tr>
<tr>
<td>9 &amp; 10</td>
<td>Arterial Stiffness Device, Smart-phone</td>
<td>Vascular Health</td>
<td>Vascular</td>
</tr>
</tbody>
</table>

The concept of the Advanced CVD Screening Kit functions is as follows: firstly, the Stethoscope is used to measure if there are any abnormal heart sounds which are indicative of mechanical issues such as rheumatic heart disease, cardiomyopathies and congenital issues. These issues are more pertinent to a younger age group. Congenital issues will have been diagnosed at a young age as they cause severe symptoms and RHD will generally involve a population below 30 (although RHD may progress later in life). This means that in older age groups, the stethoscope is not strictly needed for the risk assessment if this simplifies the use of the CVD Screening Kit. If a subject is found to have abnormal heart sounds with this device they will be referred to higher primary and secondary healthcare centres to receive further treatment because there is little that CHCs or SHCs may do about these issues. Secondly, the Arterial Stiffness device is used to screen for the level of atherosclerosis via Pulse Wave Velocity. As described in the Chapter 10, this measure of Pulse Wave Velocity, accompanied by other parameters collected will give an indication of the risk of having a heart attack or a stroke in the next 10 years. This measure is strictly unnecessary for subjects below 30/35 years of age and thus should not be used beforehand.
6.4 Mobile Applications

At the core of both the Basic and Advanced Kits is an Android mobile application. As shown in Figure 6-2, each Device has an independent App which may be called from the master Cardio App. This master App groups all the data for each patient from the different devices used. The first time the Cardio App is opened for a patient, a profile is created with a simple questionnaire (Age, Sex, Weight, etc.). With a new profile, the user may at this point select from a series of Apps which run independently of the Cardio App. Although these Apps run independently, data from each App is returned to the Cardio App for unified patient data storage. This is done such that in the future many other Apps, including non-proprietary Apps may be added to the Cardio App interface.

Figure 6-2: Cardio App Structure. Starting anti-clockwise from the left: 1. Records heart sounds from various locations on the body via a stethoscope, 2. This digital version of the WHO CVD Risk Score Charts which where mentioned earlier in this thesis was developed as a demonstration by David Houle, 3. The Basic CV Health App detects Heart Rate, Breathing Rate and Heart Rate Variability via the phones camera. 4. An Arterial Stiffness App collects data from the device that was developed to measure Arterial Stiffness.

Figures 6-3 and 6-4 show screenshots of the main Cardio App which was developed with the help of David Houle. This App is the core App of the CVD Screening Kit and allows the user to navigate the various tool specific Apps.
Figure 6-3: Screenshots from the Cardio App. 6-3a: First Screen where a new patient may be entered into the system or one may be selected by patient ID in the Saved ID Numbers section. 6-3b: Main Screen where various Apps may be selected, the standard questionnaire updated or a new patient initialised.

Figure 6-4: Screenshots from the Cardio App General initial Questionnaire required to enter a new patient
Chapter 7

Assessment of Cardiac Function

A Phonocardiography measurement is one of the first tests done by a doctor when performing a physical exam and is performed with a stethoscope. Via a stethoscope a doctor listens to the sounds that the heart makes while it beats. The stethoscope was originally an analog instrument invented by René Laennec in 1816 and recently there have been efforts to design digital versions of it that are able to record heart sounds as a doctor is performing the phonocardiography exam [Lilly, 2011].

The primary reason why doctors use phonocardiography is to check whether there are any abnormal heart sounds. A healthy heart rate is characterised by two main heart sound phases as shown in Figure 7-2. S1 occurs when the atrioventricular valves close before Systole and then just before Diastole when the tricuspid and aortic valves close. Abnormal sounds have different characteristics because they represent various diseases which affect the heart differently. In the majority of abnormal heart sounds cases either the two main heart sounds are very loud or soft, with respect to standard levels, or the systolic or diastolic phases of the heart cycle, which are usually silent, are not silent. These abnormal sounds during either Diastole or Systole are called murmurs [Lilly, 2011]. While Heart Sounds are usually around 200 Hz, murmurs have frequencies of above 400 Hz and are characteristic of heart valve issues such as rheumatic heart disease [Clifford, 2016].
There is a great opportunity to develop low-cost digital stethoscope that may collect data that may be input to machine learning algorithms able to automatically detect abnormal heart sounds. This Chapter firstly briefly describes the design and clinical validation of a low-cost digital digital stethoscope. Secondly, the development of Machine Learning algorithm for heart sound classification will be presented. This project however remains unfinished as the automatic classification of heart sounds has not yet been ported to an android application and therefore as a whole this project remains untested.
7.1 Device Design and Clinical Validation

A proprietary stethoscope had been previously designed for a study by the Mobile Technology Lab on Lung sounds [Chamberlain, 2017]. A standard stethoscope manufactured by Malhotra Surgical Industries (Approximately $20) was retrofitted with an omnidirectional electric condenser microphone (Approximately $0.2). The output of the microphone was connected to an audio jack and connected to a smartphone. Stethoscope pictures and design sketches are found in Appendix A.1. For this project a proprietary mobile App (Figure 7-3) was developed to record heart sounds from each of the four main phonocardiography body measurement sites.

Figure 7-3: Screenshots from the Heart Sound App Developed. 7-3a: Initial screen with possibility to enter Patient Name and ID. 7-3b: Screen for selecting heart sound measurement site: 1. Aortic, 2. Pulmonic, 3. Tricuspid and 4. Mitral 7-3c: Recording Screen from the Mitral Area

The stethoscope designed for the previous project in the lab worked well for lung sounds and an IRB approved study was developed to be performed at Sengupta Hospital and Research Institute, Nagpur India (COUHES number: 1511311987) to validate the feasibility of using the same stethoscope for the recording of heart sounds. Heart sound recordings from a selection of hospital patients, with and without heart sound defects, were collected to validate the use of the stethoscope for heart sounds.
The results from the proprietary stethoscope recordings showed that it works well for heart sounds as well. The signals collected are crisp and clear: it is possible to locate first and second heart sounds visually and audibly, as well as to detect abnormal heart sounds. Figure 7-4a is a sample of a signal from a healthy heart. The two heart sounds are clearly observed. Figure 7-4b instead shows a signal from a patient with aortic stenosis. The flow through the partial obstruction of the aortic stenosis creates a diamond shaped murmur where a healthy heart is usually silent [Lilly, 2011].

This initial validation showed the feasibility of using the low-cost digital stethoscope, originally designed to record lung sounds, for heart sounds. Aside from collecting data for post-analysis, at this stage there is no real applicability of the device. The following section of this chapter will explore how to make this device useful to health workers.

Figure 7-4: Left: Sample Stethoscope signal from a healthy patient. Four pairs of the two heart sounds (S1 and S2) are clearly identifiable. (N.B. Signal is filtered for high frequency noise). Right: Sample Stethoscope signal from Aortic Stenosis. The two heart sounds are not identifiable, only a diamond shaped murmur is present, typical of Aortic Stenosis (N.B. Signal is filtered for high frequency noise)
7.2 Machine Learning for Heart Sounds

In this section a Machine Learning Approach to Phonocardiography Analysis is presented which was done as part of MIT Course 6.867: Machine Learning. N.B. The work was done, in its entirety, in collaboration with Alex Yee.

7.2.1 Introduction

There is a great potential to use machine learning tools to automatically detect abnormal heart sounds. In fact, in the past few decades many research groups have shown the success of machine learning tools in screening for various abnormalities. However, these studies have not been performed on large and open data sets. The 2016 PhysioNet/Computing in Cardiology (CinC) Challenge was one of the first occasions in which multiple data sets from various sources were put together to design machine learning algorithms that would detect anomalies [Goldberger et al., 2000].

There was insufficient data collected with the digital stethoscope designed to be able to develop machine learning algorithms to detect abnormalities. Therefore, the data from the competition mentioned above was used. This section will describe the process of developing an algorithm that classifies stethoscope data as either normal, abnormal or unsure. The unsure class was included in the classification because often times the stethoscope recording is not excellent and must be repeated to have an accurate measure. Unfortunately this work was performed after the competition, however this enabled an analysis of how competitors had approached the problem and Figure 7-5 shows the competition results.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Entrant</th>
<th>Se</th>
<th>Sp</th>
<th>MAcc</th>
<th>Method note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Potes et al.</td>
<td>0.9424</td>
<td>0.7781</td>
<td>0.8602</td>
<td>AdaBoost &amp; CNN</td>
</tr>
<tr>
<td>2</td>
<td>Zabih et al.</td>
<td>0.8691</td>
<td>0.8490</td>
<td>0.8590</td>
<td>Ensemble of SVMs</td>
</tr>
<tr>
<td>3</td>
<td>Kay &amp; Agarwal</td>
<td>0.8743</td>
<td>0.8297</td>
<td>0.8520</td>
<td>Regularized Neural Network</td>
</tr>
<tr>
<td>4</td>
<td>Bobillo</td>
<td>0.8639</td>
<td>0.8269</td>
<td>0.8454</td>
<td>MFCCs, Wavelets, Tensors &amp; KNN</td>
</tr>
<tr>
<td>5</td>
<td>Horomi et al.</td>
<td>0.8848</td>
<td>0.8048</td>
<td>0.8448</td>
<td>Random Forest + LogitBoost</td>
</tr>
<tr>
<td>6†</td>
<td>Maknickas</td>
<td>0.8063</td>
<td>0.8766</td>
<td>0.8415</td>
<td>Unofficial entry - no publication</td>
</tr>
<tr>
<td>7</td>
<td>Plesinger et al.</td>
<td>0.7696</td>
<td>0.9125</td>
<td>0.8411</td>
<td>Probability-distribution based</td>
</tr>
<tr>
<td>8</td>
<td>Rubin et al.</td>
<td>0.7278</td>
<td>0.9521</td>
<td>0.8399</td>
<td>Convolutional NN with MFCs</td>
</tr>
<tr>
<td>17†</td>
<td>Voting of top N=38 algorithms</td>
<td>0.7120</td>
<td>0.9015</td>
<td>0.8068</td>
<td>Simple mode</td>
</tr>
<tr>
<td>43†</td>
<td>Sample entry</td>
<td>0.6545</td>
<td>0.7569</td>
<td>0.7057</td>
<td>See section 3</td>
</tr>
</tbody>
</table>

Figure 7-5: 2016 PhysioNet/Computing in Cardiology (CinC) Challenge Results [Clifford et al., 2016]
7.2.2 Datasets

3153 unique heartbeat sounds were drawn from the Open Access Database for the Evaluation of Heart Sound Algorithms [Goldberger et al., 2000]. These 3153 sounds were taken from 6 distinct databases at different institutions around the world and each used different equipment (data sets labelled A to F). Each heart sound was previously classified as either abnormal or normal. The noisiness metric was determined by a medical professional who considered whether the sound-file was of sufficient quality to judge the heart sound. Table 7.1 shows the distribution of these classifications over the 6 datasets. The source of normal heart sounds were healthy subjects while the abnormal heart sounds were from subjects with either heart valve defects and a few with coronary artery disease (CAD).

Table 7.1: Dataset Characteristics in Datasets A to F

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal, Non-noisy</td>
<td>276</td>
<td>73</td>
<td>20</td>
<td>26</td>
<td>146</td>
<td>31</td>
<td>572</td>
</tr>
<tr>
<td>Abnormal, Noisy</td>
<td>16</td>
<td>31</td>
<td>4</td>
<td>2</td>
<td>37</td>
<td>3</td>
<td>93</td>
</tr>
<tr>
<td>Normal, Non-noisy</td>
<td>116</td>
<td>295</td>
<td>7</td>
<td>26</td>
<td>1780</td>
<td>78</td>
<td>2302</td>
</tr>
<tr>
<td>Normal, Noisy</td>
<td>1</td>
<td>91</td>
<td>0</td>
<td>1</td>
<td>91</td>
<td>2</td>
<td>186</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>409</td>
<td>490</td>
<td>31</td>
<td>55</td>
<td>2054</td>
<td>114</td>
<td>3153</td>
</tr>
</tbody>
</table>

The competition organizers previously split the data between a training data set available to the public and a testing data set. It is important to note that the challenge organizers did not release the test set of the challenge. The challenge test set comprised heart sounds from the 6 distinct databases plus another two data bases which have not been released to the public. Therefore, the challenge withheld a set of data that would never be trained upon by the competition participants. Because of the limited data set available it was decided not to follow a similar approach, i.e. keep two datasets aside solely for testing and the public datasets were split randomly between testing (10%), validation (72%) and training (18%) with equal weights for each data set in each grouping. This difference in training data means that a direct comparison of the results achieved here and those shown in Figure 7-5 is not entirely possible.
7.2.3 Pre-Processing

Automatic classification of heart sounds occurs in two main steps. There are multiple heart cycles in each heart-beat recording and firstly each heart cycle must be identified and segmented into its four main phases (S1, Systole, S2 and Diastole). This is important as key abnormal sounds are dependent on the heart cycle phase. A sample signal labelled with the respective phases is shown in Figure 7-2. Secondly, features are selected from the separate heart cycle phases and finally classification algorithms are trained. The work described here will focus on the second part i.e. the classification. An algorithm developed by Springer et al. was used to segment the sound files into individual heart cycles and also to split each heart cycle into its four phases [Springer et al., 2016]. Springer’s algorithm is state of the art and uses a Hidden semi-Markov Model, augmented with the use of logistic regression for emission probability estimation and a modified Viterbi algorithm for decoding the most likely sequence of states [Springer et al., 2016]. Furthermore, the competition organizers also supplied manual segmentation for all the signals that may be used for training.

Compensating for Unbalanced Classes

As can be seen from Table 7.1 the Abnormal and Normal classes are unbalanced. Using unbalanced data sets hinders training. In fact, since 78% of the data overall is normal, simply classifying everything as normal would result in 78% accuracy. There are various techniques to solve this issue, including weighting the samples in the less numerous class more than the other or creating artificial samples. It was decided to randomly resample the data from the less numerous class until the classes were balanced.

Feature Extraction

The competition suggested a set of 20 features as a basis on which the competition organisers trained a Logistic Regression Classifier as a baseline score. The features are shown in Table 7.2 and these extract information about phase timings and magnitude differences between phases. Most of the defects affect the frequency of sound in one of the heart phases. In fact, many successful research groups which have used machine learning tools to classify heart sounds have used frequency analysis, either with discrete Fourier or wavelet transforms to extract features for heart sound classification [Ahlstrom et al., 2006, Akay et al., 1994].
Table 7.2: Standard Features - Mean Average and Standard Deviation of each of these measures were calculated for each PCG signal

<table>
<thead>
<tr>
<th>Time Heart Beat (THB)</th>
<th>TS/THB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time S1</td>
<td>TD/THB</td>
</tr>
<tr>
<td>Time Systole (TS)</td>
<td>TS/TD</td>
</tr>
<tr>
<td>Time S2 (Systolic Amplitude)</td>
<td>(S1 Amplitude)/(S2 Amplitude)</td>
</tr>
<tr>
<td>Time Diastole (TD)</td>
<td>(Diastolic Amplitude)/(S2 Amplitude)</td>
</tr>
</tbody>
</table>

It was decided to use a Short Time Fourier transform to extract power/frequency characteristics of the signal. S1 and S2 were treated as single elements and were assigned a single discrete window of the Short-Fourier Transform. Diastole and Systole are longer phases and to capture the modularity of abnormal heart sounds within these regions they were each split into four windows. This results in 10 windows for the Short-Fourier Transform. The results of the SFT may be visualized as a spectogram with three axis: time (discrete windows), frequency and power as shown in Figure 7-6. From each of the 10 SFT windows five frequency features were extracted: the frequency with the highest power and then the first four moments of frequency weighted by power were taken as features of the signal i.e. mean, variance, skewness and kurtosis.

Figure 7-6: Sample Spectogram on a portion of the signal. Two S1 phases are visible after 0 and 1 sec

Lastly, all the features were standardized, i.e. each feature over all the data was set to have $\mu = 0$ and $\sigma = 1$. This was done because the features are on many different scales and therefore regularization would not be fair in any model. Standardization was preferred over Min-Max scaling because this would leave the window open to explore dimensionality reduction techniques such as
Principal Components Analysis as the distribution of each feature would be maintained [Raschka, 2014].

Scoring Function

The challenge scored algorithms based on weighted sensitivity and specificity measures and the same will be done here. Sensitivity is shown in Equation 7.1, Specificity in 7.2 and the final Mean Accuracy scoring function in 7.3. This scoring function inherently compensates for unbalanced data in the test set as the Normal and Abnormal are separated between Sensitivity and Specificity respectively\(^1\). Table 7.3 show how to interpret the Scoring functions.

\[
Se = \frac{wa_1 \cdot Aa_1}{Aa_1 + Aq_1 + An_1} + \frac{wa_2 \cdot (Aa_2 + Aq_2)}{Aa_2 + Aq_2 + An_2} \tag{7.1}
\]

\[
Sp = \frac{wn_1 \cdot Nn_1}{Na_1 + Nq_1 + Nn_1} + \frac{wn_2 \cdot (Nn_2 + Nq_2)}{Na_2 + Nq_2 + Nn_2} \tag{7.2}
\]

\[
MAcc = \frac{Se + Sp}{2} \tag{7.3}
\]

Table 7.3: Rules for determining Mean Accuracy Scoring

<table>
<thead>
<tr>
<th>Reference Label</th>
<th>Weights</th>
<th>Algorithm Output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Abnormal</td>
</tr>
<tr>
<td>Abnormal, clean</td>
<td>(wa_1)</td>
<td>(Aa_1)</td>
</tr>
<tr>
<td>Abnormal, noisy</td>
<td>(wa_2)</td>
<td>(Aa_2)</td>
</tr>
<tr>
<td>Normal, clean</td>
<td>(wn_1)</td>
<td>(Na_1)</td>
</tr>
<tr>
<td>Normal, noisy</td>
<td>(wn_2)</td>
<td>(Na_2)</td>
</tr>
</tbody>
</table>

7.2.4 Logistical Regression

In the challenge the organizers implemented a Logistic Regression as baseline and achieved a Mean Accuracy of 0.71 (Test 0 in Table 7.4). The same was done here to see whether similar results were achieved and to learn more about the data.

\(^1\)N.B. data balancing is still necessary because this scoring function is not the Error function used to optimise the algorithm.
Implementation

A two-class (Abnormal and Normal) Regularized Logistical Regression model was implemented using the Scikit-learn toolbox [Pedregosa et al., 2011]. The model was trained with the balanced training set and the balanced validation set was used to decide on the regularization factor and mode (L1 and L2 were tested). The Negative Log-Likelihood of the Logistic regression to be minimized with L1 regularization is shown in Equation 7.4.

$$E_{LR}(w, w_0) = NLL(w, w_0) + \lambda ||w||_1$$ \hspace{1cm} (7.4)

To classify some outputs as unsure the validation set was used to find the optimal $\frac{\theta}{2}$ above which the probability of being in a class had to be, for data point to be classified in that class, otherwise it would be classified as unsure as shown in Equation 7.5 where 'P(z=Abnormal)' refers to the probability given by the Logistic Regression of data point z of being in class 'Abnormal'.

$$\begin{cases} 
\text{Abnormal} & P(z = \text{Abnormal}) \geq \frac{1}{2} + \frac{\theta}{2} \\
\text{Unsure} & \max(P(z = \text{Abnormal}, P(z = \text{Normal})) < \frac{1}{2} + \frac{\theta}{2} \\
\text{Normal} & P(z = \text{Normal}) \leq \frac{1}{2} + \frac{\theta}{2} 
\end{cases}$$ 

(7.5)

Results

The baseline results on the Automatic Heart Cycle Segmentation with Standard Features were calculated and shown under Test I in Table 7.4. The Mean Accuracy of Test I was very similar to the one computed as the baseline of the competition (Test 0).

Test II shows the results of the Automatic Segmentation using the Spectogram features. The Mean Accuracy of Test II is 10% better than for Test I. This shows how analysing the frequency of the sounds extracts more valuable information from the signal.

To test whether the Spectogram Features contained all the information provided by the Standard Features the two were combined in Test III. The hypothesis was that they would not, as the Spectogram Features do not contain information about phase lengths. Test III showed that in fact the two features used in unison performed better together.
Table 7.4: Logistic Regression Results on the Test Set

<table>
<thead>
<tr>
<th>Test</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic Segmentation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Manual Segmentation</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Standard Features</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spectogram Features</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Mean Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.660</td>
<td>0.658</td>
<td>0.748</td>
</tr>
<tr>
<td></td>
<td>0.710</td>
<td>0.711</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>0.514</td>
<td>0.837</td>
<td>0.839</td>
</tr>
<tr>
<td></td>
<td>0.877</td>
<td>0.877</td>
<td>0.847</td>
</tr>
<tr>
<td></td>
<td>0.720</td>
<td>0.686</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td>0.617</td>
<td>0.789</td>
<td>0.843</td>
</tr>
<tr>
<td></td>
<td>0.857</td>
<td>0.857</td>
<td>0.843</td>
</tr>
</tbody>
</table>

Lastly, the Manual Segmentation data was used with both the Standard and Spectogram Features (Test IV in Table 7.4). The Automatic Segmentation used in Tests I-III refers to the heart sound segmentation done automatically with Springer’s Algorithm [Springer et al., 2016]. The manual segmentation is the automatic segmentation corrected by health professionals. As shown the improvement with the Manual Segmentation data was minimal. The Logistic Regression trained with the Manual Segmentation data was tested with the Automatic Segmentation data in Test V. This Test showed the limitations of testing with the Manual data. In the real world the heart signals would not be manually segmented and therefore an automatically segmented heart signal would be given to the algorithm, as was tested in Test V. With this configuration the Mean Accuracy falls to 0.617. Both the Sensitivity and the Specificity greatly decrease. The Manual data excludes many noisy signals hence the algorithm trained on this data doesn’t learn how to deal with noisy signals and does a bad job at classifying the automatically segmented data. It was therefore decided to uses the automatically segmented data for the rest of algorithm development.
7.2.5 Neural Networks

At this point it was decided to explore how a Neural Network would perform on the data. Both Standard and Spectogram features were tested.

Implementation

A fully connected network with two hidden layers was used for the neural network architecture. The hidden layers all had ReLU activation functions with 0 bias as shown in Equation 7.6

\[ f_j(x) = \text{ReLU}(\sum_i^n w_{(i,j)}x_i + b_j) \quad (7.6) \]

A sigmoid function was chosen as the activation function of the output layer. This function is bounded by 0 and 1. A certainty threshold \( \theta \) tests whether the network outputs a confident output or not (i.e. unsure) as shown in Equations 7.7 and 7.8.

\[
\text{Class} = \begin{cases} 
\text{Abnormal} & \text{sigmoid}(z) \geq \frac{1}{2} + \frac{\theta}{2} \\
\text{Unsure} & \frac{1}{2} - \frac{\theta}{2} \leq \text{sigmoid}(z) \leq \frac{1}{2} + \frac{\theta}{2} \\
\text{Normal} & \text{sigmoid}(z) \leq \frac{1}{2} - \frac{\theta}{2} 
\end{cases} \quad (7.7)
\]

\[
\text{Where} \quad z = \sum_i^n w_{(i,j)}x_i + b_j \quad (\text{of final layer}) \quad (7.8)
\]

For the purpose of gradient descent optimization the unsure class was omitted because labels were only given for Abnormal and Normal. The loss function is the difference between the sigmoid output and the correct label plus a L2 regularization term to reduce over-fitting as shown in Equation 7.9.

\[
\text{Loss} = \sum_i |y_i - \text{sigmoid}(z)| + \lambda \sum |w|^2 \quad (7.9)
\]

The algorithm was developed with the Tensor-flow toolbox and a mini-batch gradient descent optimizer with batches of 200 data points per step [Marti Abadi et al., 2017].
Results

Results using the Standard Features and the Spectogram Features with an optimised network are shown in Table 7.5. It is shown that as with the Logistic Regression the best results are found with the Spectogram and Standard features together.

Table 7.5: Neural Networks Results on the Test Set

<table>
<thead>
<tr>
<th>Test Case</th>
<th>VI</th>
<th>VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Features</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spectogram Features</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.735</td>
<td>0.936</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.789</td>
<td>0.948</td>
</tr>
<tr>
<td>Mean Accuracy</td>
<td>0.762</td>
<td>0.942</td>
</tr>
</tbody>
</table>

7.2.6 Support Vector Machine

An attempt was also made to implement a SVM to classify heart sounds albeit unsuccessfully.

Implementation

The dual formulation of a kernelized soft SVM was used. The optimization problem was formulated based upon the dual formulation as shown in Equation 7.10.

\[
\begin{align*}
\text{maximize}_{x} & \quad -\frac{1}{2} \sum_{i}^{m} \sum_{j}^{m} \alpha_{i} \alpha_{j} y_{i} y_{j} K(x^{(i)}, x^{(j)}) \\
& + \sum_{i}^{m} \alpha_{i} - M \sum_{i}^{m} (\text{minimum}(C - \alpha_{i}, 0)) \\
\text{subject to} & \quad \alpha^{T} y = 0
\end{align*}
\]

(7.10)

A Gaussian Radial Basis Function was used as the kernel as shown in Equation 7.11.
\[ k(x, x') = e^{-\gamma|x-x'|^2}, \text{where} \quad \gamma = \frac{1}{2\sigma} \quad (7.11) \]

The sign function was used as the classifier to determine whether the output was Abnormal or Normal and, similarly to the Neural Network implementation a bandwidth of uncertainty (\(\eta\)) was added to classify a certain number of inputs as unsure as shown in Equation 7.12.

\[
\text{Class} = \begin{cases} 
\text{Abnormal} & \text{sigm}(z) \geq \eta \\
\text{Unsure} & -\eta \leq \text{sigm}(z) \leq \eta \\
\text{Normal} & \text{sigm}(z) \leq \eta 
\end{cases} \quad (7.12)
\]

Results

Table 7.6 shows the results of using the SVM. Combining the Standard and Spectogram features again showed superiority compared to using only the Standard features. However, the difference is not as striking as with the other methods. In fact, the sensitivity actually decreases when the Spectogram features are added. This may be due to the kernel being used. The Gaussian Kernel may not be appropriate for the distribution of the data once the extra Spectogram features are added to the model.

Table 7.6: Support Vector Machine Results on the Test Set

<table>
<thead>
<tr>
<th>Test Case</th>
<th>VIII</th>
<th>IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Features</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spectogram Features</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.726</td>
<td>0.649</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.681</td>
<td>0.853</td>
</tr>
<tr>
<td>Mean Accuracy</td>
<td>0.704</td>
<td>0.751</td>
</tr>
</tbody>
</table>
7.2.7 Discussion

Table 7.7 shows the final results for the models that were tested in this analysis. Results C in Table 7.7 refer to the best result of the competition. The Neural Network is the model that is able to understand the data better and perform its own feature importance extraction inherently without the restrictions that Logistic Regression or SVMs impose. The failure of the Gaussian kernel in the SVM method is highlighted by the fact that the Logistic Regression outperformed the SVM when all the features were included. The kernel was not able to represent the data well, while the less restrictive logistic regression was able to make significant improvements with the extra data.

Table 7.7: Final Results on Test Set

<table>
<thead>
<tr>
<th>Model</th>
<th>C</th>
<th>LR (III)</th>
<th>SVM (IX)</th>
<th>NN (VII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Features</td>
<td>n/a</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spectogram Features</td>
<td>n/a</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.942</td>
<td>0.839</td>
<td>0.649</td>
<td>0.936</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.778</td>
<td>0.847</td>
<td>0.853</td>
<td>0.948</td>
</tr>
<tr>
<td>Mean Accuracy</td>
<td>0.860</td>
<td>0.843</td>
<td>0.751</td>
<td>0.942</td>
</tr>
</tbody>
</table>

Of relevance is the fact that the features from the spectogram resulted in a significant improvement in mean accuracy. In fact, in the simple Logistic Regression model adding the spectogram features improved the mean accuracy by 10%. Machine Learning algorithms will only go so far as how good the data they are supplied with is.

It is noted that the specificity of the NN is far greater than that achieved in the competition. This is however an unfair comparison and highlights the issues with heart sound analysis from different sources. The difference in mean accuracy is most probably due to the fact that the testing set used here is different to that used in the competition. In the competition the testing set was composed of some of the publicly available data set data and data from two undisclosed data sets. Therefore, the algorithms developed here had seen samples from all data sets, the algorithms developed in the competition did not have this advantage.
7.2.8 Summary of Machine Learning Analysis

The differences in results due to the different test sets used highlight the failure of the machine learning algorithms employed to generalise on data sets from various sources. This is a problem and must be taken into account in the future when training algorithms for the stethoscope that was designed in the lab. It may be worth having algorithms trained solely on heart sounds collected from the device that will be deployed in the field, rather than with data from other sources. Or, if there is not enough data, a stronger weighting may be assigned to the sounds from the proprietary stethoscope. This will make the algorithms stronger and more robust for the sounds coming from the proprietary device.
7.3 Conclusion and Future Work

In this Chapter initial work on developing an automated phonocardiography exam was described. This is the core element of the Cardiac Function Assessment presented in the Problem Statement and Proposed Solution Chapter (Ch. 6): a low cost digital stethoscope which functions via a mobile phone application. Subsequently an algorithm capable of detecting abnormal heart sounds was developed. However, there currently is no bridge between the two components. Data collected with the proprietary stethoscope has not yet been tested with the algorithms developed to detect abnormal heart sounds. Furthermore, the heart sound analysis algorithms have not yet been ported to the mobile phone. Next in the pipeline is to port the algorithms developed into the mobile phone and then test the whole system in the field.

7.3.1 Microwave Cardiogram

Phonocardiography is a great tool to measure abnormal heart sounds, however, it does not offer a complete understanding of the heart’s mechanical function. Tools which offer a better visualisation of the heart are needed to complete a holistic cardiac Mechanical assessment. A heart echo-cardiogram exam, amongst many other useful applications, allows a doctor to understand exactly which and how heart valves are damaged, analyse Heart Failure and diagnose Cardiomyopathies. A similar tool would be invaluable in a comprehensive CVD Screening Kit.

![Figure 7-7: Heart Paradigm](image-url)
There have been recent advances in portable Echo-cardiograms, however, these still require expert use and are expensive. There has been past work in the lab on a low-cost Microwave Doppler probe which, connected to a mobile phone, may be used to measure heart function. This probe records a similar signal to an echo-cardiogram however outputs a 2D signal instead of a 3D signal [Fletcher and Kulkarni, 2010a, Fletcher and Kulkarni, 2010b]. The signal may show when heart muscle is degenerating due to an ischemia or a Myocarditis. In the future this tool may be developed further to offer a more comprehensive assessment of the hearts mechanical function.

Figure 7-8: Microwave Cardiogram Device connected to a Mobile Phone
Chapter 8

Pathology of the Vascular System

In essence, CVD risk, in terms of heart attack and stroke\(^1\), boils down to a measure of vascular health, or, more specifically, arterial health. It is in fact degenerated and diseased arteries which cause heart attack and strokes. Therefore, when measuring CVD risk it is important to measure arterial health precisely. This chapter is divided into four parts. In the first, more depth is given to the pathophysiology of Atherosclerosis. Secondly, existing Clinical methods to measure arterial health will be described. Thirdly, current measures arterial health in resource constrained settings will be described. Finally, two solution proposals will be presented and the implementation will be described in detail in Chapters 9 and 10.

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\(^1\)N.B. The following argument also pertains to the other degenerative CVD such as: Peripheral Arterial Disease, Valvular Heart Disease (except Rheumatic Heart Disease) and Aortic Aneurysm and Dissection. However, these diseases have a significantly lower burden and thus are not the main focus of this thesis.
8.1 Atherosclerosis and Arterial Stiffness

Atherosclerosis mostly affects the LEAs and the Coronary Arteries while LMAs are affected to a lesser degree [Vosse and Stergiopulos, 2011]. It is important to note that Arterial stiffening is not only part of the atherosclerotic pathogenesis but also a natural ageing process. Particular risk factors accelerate this degeneration leading to Heart Attack and Stroke.

Each heart beat creates a pressure wave that propagates from the heart along the whole arterial system [Vosse and Stergiopulos, 2011]. Arterial stiffening causes the speed and magnitude at which this pressure wave travels to increase. Thus augmenting Pulse Wave Velocity and Blood Pressure. In fact, Figure 8-1 shows pressure waves in a juvenile and an older adult. The increase in pressure magnitude with age in both aorta and radial artery is significant [ORourke et al., 2002].

![Figure 8-1](image)

Figure 8-1: Here are pressure waves in the ascending aorta and radial artery (the slightly delayed pulse). A). Young adult. B). Older human subject [ORourke et al., 2002].

The pressure waves in the arterial system are reflected where there are transitions in arterial properties such as geometry and compliance. In fact, looking at Figure 8-1, it may be observed that there is a *notch* in each of the waveforms, this is indicative of the superposition of forward and backward travelling waves. The pattern of transmission and reflection changes over time and is important as it affects the organs which receive blood from the heart.

Figure 8-2 represents a simplified model of wave reflections in a young Arterial System. The pulse starts at the heart and firstly travels in the LEAs and then in the LMAs. The Yellow interface is actually not so discrete but is rather quite continuous. In a young person the LEAs are flexible and compliant meaning that the pulse in them travels slowly. Because the LMAs are by nature stiffer the pulse will travel faster on them. Furthermore, at the yellow interface there will be sig-
significant pulse reflections as the difference in stiffness between the two arteries is significant. This is a healthy behaviour as it dampens the violent pulse travelling to the peripheries and vital organs [Mitchell et al., 2004].

![Simple Wave Reflection Model in a Young Arterial System with LEAs and LMAs](image)

Figure 8-2: Simple Wave Reflection Model in a Young Arterial System with LEAs and LMAs [Nichols and O’Rourke, 2005].

Figure 8-3 is the same simplified model of wave reflections as in Figure 8-2 but in an older Arterial System. As one ages LMAs are relatively unchanged while LEAs become stiffer and therefore start acquiring similar properties to the muscular arteries. At this point the pulse travels fast in both types of arteries and as the interface difference between the two arteries reduces the beneficial pulse reflection is also attenuated meaning that damaging strong pulses are delivered to the peripheries and organs [Nichols and O’Rourke, 2005].

![Simple Wave Reflection Model in an Old Arterial System with LEAs and LMAs](image)

Figure 8-3: Simple Wave Reflection Model in an Old Arterial System with LEAs and LMAs [Nichols and O’Rourke, 2005].

Figure 8-4 shows the changes in velocity with age in healthy aortic and brachial arteries, respectively LEAs and LMAs. Towards the end of the graph the speeds in the two vessels equalise. In a person with pathogenic atherosclerosis this may occur at a much earlier stage.
It is therefore important to realise when the LEAs are becoming too stiff because this is an indication of atherosclerosis and also that high pressure pulses are propagated all the way down to the rest of the arterial tree, which is not designed to withstand them [Mitchell, 2008]. CVD Risk is mostly associated with increased Blood Pressure (Hypertension) and Pulse Pressure i.e. the difference in pressure between Systole and Diastole. However, in the past two decades, arterial stiffening and thus changes in Pulse Wave Velocity and Wave Reflection have been accepted in the medical community as not only important markers of CVD Risk but as the root cause of Hypertension and increased Pulse Pressure. Therefore, it is well accepted that Pulse Wave Velocity and changes in reflection are amongst the most important determinants of stroke and heart attack i.e. CVD Risk [ORourke et al., 2002, Laurent et al., 2006].
8.2 Existing Clinical Methods to measure Atherosclerosis

There are a number of clinical methods that are used to measure the extent of Atherosclerosis that one has. Atherosclerosis affects all arteries, however, predominantly the coronary arteries and the LEAs. To measure the level of atherosclerosis in the coronaries the actual stiffness is not measured but various techniques are used to understand how obstructed the arterial lumen \(^2\) is. This is done with an angiogram: a X-Ray reactive liquid is injected in the blood stream of a patient while an X-Ray is performed. Another technique is a called CT-Calcium Scoring in which a series of X-Rays is taken of the subjects heart and the amount of calcium (atherosclerotic plaque) in each of the coronary arteries is measured [Sharma et al., 2010]. These methods indicate whether a subject has coronary artery disease, i.e. Atherosclerosis in the coronary arteries which leads to ischemic heart disease. The Angiogram and CT Calcium Scoring techniques are very accurate and paint a clear picture of the subjects coronary health. However, these precise methods are impractical for small primary health clinics in terms of cost as well as both technical and medical expertise required.

Atherosclerosis spreads across the coronary arteries and the LEAs and thus, the level of atherosclerosis may be measured effectively at the LEAs as well. The LEAs are more accessible than the coronaries and an actual measure of stiffness is simpler to attain. Doppler ultrasound has been used to assess the stiffness of arteries, such as the femoral and carotid arteries by simply looking at the distensibility of the walls. In recent years the most validated clinical measure of arterial stiffness has been the speed of the pressure pulse travelling on the aorta known as Aortic Pulse Wave Velocity (PWV\(_A\)). Equation 8.1 shows how PWV is related to the Young’s Modulus of the artery (\(E\)), where \(b\) is the thickness of the artery wall, \(r\) is the radius of the artery and \(\rho\) is the density of blood. Because all the variables in this equation change continuously along the arterial wall and within the same type of artery this equation is not used in practice to calculate \(E\) but rather the PWV value is quoted directly [ORourke et al., 2002].

\[
PWV = \sqrt{\frac{E \times \frac{b}{2r \rho}}}{8.1}
\]

\(^2\)The Lumen is the hollow part inside of a vessel
8.3 Current Cardiovascular Disease Risk Analysis in low Resource Settings

Cardiovascular Disease Risk is defined as the probability of having a stroke, heart attack or other cardiovascular diseases which are due to Atherosclerosis and the deterioration of the arterial system in general. Because of the existing methods to manage people at high risk of having a cardiovascular disease, simple methods to detect risk may be instrumental in reducing CVD burden, especially if this tool may be used by the least skilled health workers who undergo very little training.

There are many models which have been validated for many years which measure CVD very effectively by taking various measurements into account. For example the Framingham Risk Score or the equivalent European Systematic Coronary Risk Evaluation. Both these models use traditional risk factors to assess the risk of having a stroke or a heart attack and are used extensively in the medical profession [Sharma et al., 2010]. These tests, however, are for clinical use in well-equipped hospital structures. The WHO developed its own validated model that may be used in low resource environments. This model has worked very well and is effective at stratifying risk. Nevertheless, it suffers from two main issues:

1. Too complicated for low-skilled health-workers to use
2. Does not measure the exact extent of atherosclerosis

The WHO risk model is invasive as it requires a blood sample to test cholesterol and glucose levels (in a simplified version a urine test suffices however this reduces accuracy). The invasiveness of this technique, added to the often not completely sterile environment, increases the chances of infection. Many non-reusable materials are used to extract all the data for this model: expensive reactive paper strips are needed to analyse blood/urine samples, as well as vials for collection for example. Even if the vials are reusable they need to be sterilised and this takes time and effort. If the blood tests are performed in a lab instead of using hand-held point-of-care devices, samples need to transported to the labs and results sent back. This adds the complication of keeping samples refrigerated and safe. This whole process is expensive both in terms of monetary and logistics. Lastly, a blood pressure measurement is also needed for the WHO model and, although seemingly trivial, it is not the simplest measurement to take. Blood pressure measurement is performed with
a traditional sphygmomanometer in combination with a stethoscope. This is a cheap tool however it is technically challenging and may be inaccurate due to calibration drift unless calibrated every six months [UBC, 2015a]. It is technically challenging because soft Korotkoff sounds need to be auscultated with timely precision and the sphygmomanometer needs to be deflated at the correct speed otherwise these errors cause user-bias. Therefore, a sphygmomanometer is a very useful tool however not the easiest to use, especially by low-skilled health workers.

The WHO model is designed to be used in the field with low resources, because of this it fails to measure the exact level of atherosclerosis in a subject's arteries which a coronary angiogram performed expensively and invasively in a hospital may give for example. The WHO model takes into account several important risk factors but is not a precise measure of the actual issue, i.e. the level of atherosclerosis.
8.4 Proposed Cardiovascular Disease Risk Analysis in low Resource Settings

Overall, the WHO model is very effective and has had an impact in many regions around the world, however, it is unfit for use by the most low-skilled health workers, i.e. the front-line workers, the first representatives of primary care which many Indian people first come in contact with. The objective was to design a device with the following specifications:

- Easy to use for low-skilled health worker in SHC type structures
- Immediate measure, with no need of further lab tests for example
- Direct measure of atherosclerotic damage
- Similarly priced to current tools or cheaper
- Reusable
- Centred around a smartphone for data digitization and computing power

Bringing together the fertile ground envisioned in Chapter 6 two methods were envisioned to be able to measure the direct impact of Atherosclerosis on a subject’s arteries:

1. Vascular Assessment: Photoplethysmography (Chapter 9)
2. Vascular Assessment: Pulse Wave Velocity (Chapter 10)

Both technologies rely on a technology called Photoplethysmography (PPG) described in Section 8.4.1. The first measures a single PPG Signal while the second requires multiple PPG signals. The first attempts to measure arterial stiffening by analyzing the PPG waveform and how it changes with increased arterial stiffness (similarly to the effect on the pressure wave illustrated in Figure 8-1). The second instead attempts to measure a surrogate of $PWV_A$.

8.4.1 Photoplethysmography: Introduction

Aplethysmographis a device that measures changes in volume (typically air or blood) in a particular organ or the whole body. The first plethysmograph was built by Angelo Mosso during the latter part of the 19th Century. A diagram of Angelo Mosso’s invention is shown in Figure 8-5.
The change in air volume inside a glass vessel containing a forearm was measured as an indicator of change in blood volume. The word *Plethysmograph* comes from the Greek *plethysmós*: *increase* and *gràphein*: *to write*. Mosso gave the invention this name because the first plethysmograph marked the increase in blood with a metal pen (N in 8-5) on a sheet of rigid natural latex [Marco Galloni and Mara Fausone, 2016].

![Figure 8-5: Il Pletismografo, diagram drawn by Angelo Mosso in the late 19th Century [Marco Galloni and Mara Fausone, 2016]](image)

*Photoplethysmography (PPG) consists in shining a light on skin and measuring the reflected signal. The incoming light is attenuated by skin, blood and vessels, by three mechanisms: absorption, multiple scattering and reflection. Because the content of blood varies this technique is good for measuring blood content under the skin, the more blood present, the greater the overall attenuation as shown in Figure 8-6. The figure is strongest where there is low fat concentration and the area is well vascularized such as the ears and fingers [Challoner and Ramsay, 1974][Kamal et al., 1989].*
8.4.2 Other Possible Cardiovascular Health Measures via Photoplethysmography

The following is a list of Cardiovascular Health Parameters, aside from Arterial Stiffness, that may be measured with PPG (or at least have been explored by certain Research Groups), some of which will be explored in detail in Chapter 9:

- Heart Rate & Heart Rate Variability
- Respiratory rate
- Arrhythmias
- Valvular Issues
- Blood Oxygenation & Haemoglobin Content
- Stroke Volume and Cardiac Output
Chapter 9

Basic Assessment of Vascular Health: Photoplethysmography

A single Photoplethysmography (PPG) signal, captured anywhere on the body, carries a wealth of information; from standard Cardiovascular Health Parameters, Heart Rate to Arterial Stiffness. This section will explore how such information may be extracted using a PPG signal captured with a simple mobile phone camera.
9.1 Photoplethysmography via Smartphone Camera

Work done previously in the Mobile Technology Group resulted in a simple mobile application that is able to capture a PPG signal by using the flash as the light source and the camera as the optical sensor. Typically frame rates of around 30fps may be achieved. Figure 9-1 shows data being collected with a smartphone and Figure 9-2 shows a sample signal collected.

![Figure 9-1: Collecting PPG Data with a Smartphone](image)

![Figure 9-2: Sample PPG Signal from Smartphone](image)

In this Chapter two objectives will be explored. Firstly, the measurement of Standard Cardiovascular Health Parameters. This will form the basis of the Basic CVD Screening Kit described in Chapter 6. Secondly, the attempted measurement of Arterial Stiffness which will form the basis for the Advanced Assessment of Vascular Health in Chapter 10.
9.2 Standard Cardiovascular Health Parameter Extraction

In this section the extraction of Heart Rate, Heart Rate Variability and Breathing Rate will be discussed. Firstly, the past literature will be presented. Secondly, how these measurements were implemented in the smartphone App and validated will be described.

9.2.1 Background

Heart Rate

Heart rate (HR) determination is the first and essential component of cardiovascular health. Resting heart rate outside the normal range of 60-100 bpm is a first indicator of bradycardia if the HR is low and of tachycardia if HR is high [Clinic, 2016]. Heart rate is the most evident feature visible in the PPG signal and may even be read with the naked eye. Typically heart rate falls between 0.8-2Hz, hence an adaptive filter about these frequencies clears the signal from any other signal and the peak-to-peak intervals may be used to estimate Heart Rate [E et al., 2000, Johansson et al., 1999].

For noisy PPG signals, peaks are not always easily detected. In these cases, a frequency analysis of the signal is done to extract the dominant frequency within the acceptable range to determine heart rate [Fletcher et al., 2015]. In extremely noisy signals independent component analysis and blind separation may be used to extract HR [Poh et al., 2010].

Heart Rate Variability

Heart Rate Variability (HRV) refers to the variability in timing between heart beats in a given amount of time. HRV is a useful measure to learn about the interplay between the sympathetic and parasympathetic nervous system and assess cardiac health [Acharya et al., 2006]. Perhaps counter to intuition, a relatively high level of HRV is considered healthy, it is the extremely low and high values of HRV that must call for further attention. HRV has a very good association with lethal arrhythmias and thus is an important measurement which fortunately may be easily computed from a PPG signal [Malik, 1996].

In the past few years many cohorts of scientists have sought to standardize the measurement of HRV. There are two broad categories of measurements: those in the Time Domain and those in the
Frequency Domain. Below are a few examples from each category. Which one is best is a present matter of debate and it is probable that many are helpful to some degree and that some specific measures, especially when measured over prolonged periods of time (in the order of days), may be specific to certain diagnoses [Malik, 1996]. In the clinical environment, Time domain analysis has probably been dominant. Recently however, frequency analysis has gathered traction. It has been associated as an indicator of better understanding between the balance between sympathetic and autonomic nervous system. N.B. An NN interval is the time interval between two consecutive pulses.

Time Domain Analysis:

- SDNN\(^1\): Standard deviation of NN intervals
- SENN: Standard error of mean, i.e. the standard deviation of the mean NN interval
- SDSD: Standard deviation of differences between adjacent NN interval
- RMSSD: Root mean squared of successive NN interval differences
- pNN50\%: number of successive difference of intervals which differ by more than 50ms expressed as a percentage of the total number of ECG cycles analysed

Frequency Domain Analysis:

- Total power: Variance of all NN intervals
- ULF: Power in Ultra Low frequency range \(< 0.003\text{Hz}\)
- VLF: Power in Very Low frequency range 0.003-0.04Hz
- LF: Power in Low frequency range 0.04-0.15Hz
- HF: Power in High frequency range 0.15-0.4Hz
- LF/HF

Breathing Rate

Why do we have lungs? In 'Timaeus' Plato wrote: *But the gods, foreknowing that the palpitation of the heart in the expectation of danger and the swelling [...] of passion was caused by fire, formed

\(^1\)N.B. An NN interval is the time interval between two consecutive pulses.
[...] as a supporter to the heart the lung [...] as a soft spring, that, when passion was ripe within, the heart, beating against a yielding body, might [...] suffer less, and [...] join with passion in the service of reason [Plato, 2016].

Plato’s intuition was correct; the lungs really do have a quasi-symbiotic relationship with the heart. In fact, when we inspire thoracic pressure decreases causing the pressure difference between our extra-thoracic veins (namely the superior and inferior vena cava) and right atrium to increase, augmenting venous return to the right heart. This extra supply of blood is then directed out of the heart, through the lung alveoli and back to the heart to finally be ejected into the aorta. Because the PPG signal is essentially a measure of the volume of blood under the skin, this extra blood during inspiration is present in the PPG signal.

Hence, similarly to heart rate, breathing rate may be extracted from the PPG signal. A band pass filter at the appropriate frequencies on the PPG signal suppresses the cardiac frequencies and other noise, meaning that then calculating the inverse of the peak-to-peak interval of the signal will result in breathing rate [Johansson et al., 1999, E et al., 2000]. Alternatively, using a frequency analysis of a PPG signal, the first peak to be found at heart rate while the second at breathing rate as it will be the second most dominant frequency.
9.2.2 Device Design and Validation

A mobile App was designed to measure Heart Rate and Breathing Rate via Frequency Analysis. Furthermore, the HRV measure was also performed using frequency analysis (precisely the $LF/HF$ measure is displayed). The reason for opting for the frequency analysis rather than looking at the time domain and counting peaks is that this method is far more stable in noisy environments. Moreover, it was noticed that even with this method some results are not clear because the actual signal being collected is not clean. To improve on this Signal Quality Measures must be implemented in the future to ensure that the signal collected is of sufficient quality for frequency analysis to give accurate results. Figure 9-3 shows screen shots of the mobile App in operation.

![Figure 9-3: Screenshots from the Standard Cardiovascular Health App developed. 9-3a: Recording Screen, 9-3b: Results](image)

Figure 9-3: Screenshots from the Standard Cardiovascular Health App developed. 9-3a: Recording Screen, 9-3b: Results
9.3 Arterial Stiffness

In this section the measurement of Arterial Stiffness via a single PPG measure will be explored. Firstly, the past literature will be presented. Secondly, the device design and validation will be described. Finally, an account of an attempt to measure Blood Pressure which was pursued after understanding the failures of the Arterial Stiffness measures will be given.

9.3.1 Background

The PPG signal is affected by arterial stiffness and various research groups have sought to correlate PPG signal features to Arterial Stiffness Indicators. Many have been successful in finding these correlations as shown in Table 9.1. The most successful have shown that the relative height of the two peaks (Systolic and Diastolic Peak in Figure 9-4) in a single PPG beat, i.e. the Augmentation Index, is particularly indicative of arterial ageing and stiffening [Elgendi, 2012]. Augmentation Index is a measure of how much the pulse which bounces back from the peripheries affects the magnitude of the PPG signal in the downward slope i.e. the diastolic region. When this is measured in the finger, this measure is most indicative of stiffness of the peripheral vasculature and the Long Muscular Arteries in the arms, not the Large Elastic Arteries which are of most interest [Millasseau et al., 2000]. The Long Muscular Artery Index explored by Millasseau et al. is more indicative of LEA stiffness [Millasseau et al., 2000].

Table 9.1: Measurement of Arterial Stiffness via PPG

<table>
<thead>
<tr>
<th>PPG Feature</th>
<th>Arterial Stiffness Indicator</th>
<th>Framingham Risk Score</th>
<th>Pulse Wave Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentation Index</td>
<td>Age</td>
<td>[Millasseau et al., 2000, Takazawa et al., 1998, Padilla et al., 2006, Heffernan et al., 2012, Ht et al., 2016, Yousef et al., 2012, Pilt et al., 2014]</td>
<td>[Padilla et al., 2006]</td>
</tr>
<tr>
<td>Large Artery Stiffness Index</td>
<td>[Millasseau et al., 2000]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak to Peak Time(^2)</td>
<td>[Takazawa et al., 1998, Baek et al., 2007]</td>
<td></td>
<td>[Otsuka et al., 2006]</td>
</tr>
<tr>
<td>Crest Time(^3)</td>
<td>[Alty et al., 2007]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Derivative height Ratios(^4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

99
9.3.2 Device Design

Despite the success of various studies in showing correlations between PPG signal and Arterial Stiffness, no commercial product has ever been launched which gives a measure of Arterial Stiffness via single probe PPG. Furthermore, the literature reviewed does not present any automated, out of hospital solutions that health workers in the field may use. The studies are all performed with highly precise professional equipment which would not fare well outside specialised hospitals and expert technician hands.

It was decided to attempt to analyse (externally on a laptop) the data collected via the smartphone application (developed for the Standard Cardiovascular Health Parameters Extraction described earlier) to see if it were feasible to classify subjects in terms of health status according to PPG features.

9.3.3 Device Validation

To perform this feasibility study data was collected from two separate locations:

---

2Time between Systolic and Diastolic Peaks 9-4
3Time between start of PPG pulse to first (Systolic) peak
4See Figure 9-4
1. 26 Subjects at Sengupta Hospital and Research Institute in Nagpur, India (Age Group: >45 years)\(^5\):
   - Subjects with pre-identified heart failure, atherosclerosis and/or ischemic heart disease (16 Subjects)
   - Healthy Subjects (10 Subjects)

2. 21 Subjects at M.I.T. in Cambridge, USA (Age Group: 20-25 years)\(^6\):
   - Young healthy athletes (14 Subjects)
   - Young healthy but not particularly active subjects (7 Subjects)

Firstly, the data from Nagpur was analysed and it was noticed that as people aged and were sick with any heart disease, in general, as suggested by the literature the dichrotic notch was less visible. This is shown in Figure 9-5 where each colour represents a pulse from a different person and moving towards the right the dichrotic notch is more visible. Nevertheless, there were significant outliers, because of this and the small data sample available, it was not possible to categorise, with any reasonable accuracy, whether someone was healthy or not using the various PPG features.

Figure 9-5: Pulse Contour Analysis using Derivatives. Pulse from subjects with decreasing Arterial Stiffness (left to right)

\(^5\)COUHES Protocol: 1511311987
\(^6\)COUHES Protocol: 1511312006
Subsequently, the data from the M.I.T. study was analysed. Interestingly, here as well, there was a seeming distinction between the most athletic subjects and those healthy but who exercised less. This is shown in Figure 9-6 where the athletic subjects are found in Figure 9-6b. Although most subjects in this study, because of their young age had a visible Dichrotic notch, the athletes seemed to have a more pronounced one.

![Figure 9-6](image)

(a) Healthy but not particularly active  (b) Healthy and Athletic

Figure 9-6

Here as well however the data was not clear, even data from the same person was different in separate data collections and this was investigated further and two main sources of error were identified.

First of all, the sampling rate of 30 fps was deemed insufficient to capture the full complexity of the signal. It is sufficient to measure heart rate, however, the dichrotic notch is quite a subtle perturbation in the signal and thus often susceptible to noise and low frame rate.

Secondly, it was observed that the signal is particularly sensitive to the pressure applied by the subject on the camera. The pressure across the wall of a vessel, the $P_{\text{Trans-Mural}}$ is governed by Equation 9.1. $P_{\text{External}}$ is the external pressure applied to the vessel, for example a subject pressing their finger on the phone camera. PPG Amplitude is maximised when $P_{\text{Trans-Mural}} = 0$, i.e. when Equation 9.2 is valid. This is very significant as the dichrotic notch can be basically...
extinguished if too much (or little) pressure\textsuperscript{7} is applied to the device. Furthermore, these changes are so dramatic that the modulation in PPG amplitude due to changes in vertical displacement of the finger with respect to the heart are used to estimate Mean Arterial Pressure [Shaltis et al., 2008].

\begin{equation}
   P_{\text{Trans--Mural}} = P_{\text{Mean--Arterial}} - P_{\text{Hydrostatic}} - P_{\text{External}} \tag{9.1}
\end{equation}

\begin{equation}
   P_{\text{Mean--Arterial}} = P_{\text{Hydrostatic}} + P_{\text{External}} \tag{9.2}
\end{equation}

\textsuperscript{7}Within a reasonable tested range
9.4 Blood Characterisation

In this chapter a basic analysis of the PPG signal has been described. For the future, there is more information that may be extracted from a PPG, in fact, in past PPG has been most commonly used to measure Blood Oxygenation. This is standard practice all around the world thanks to its technique simplicity and low cost. To measure blood oxygenation light at two separate wavelengths (red and infrared) is shined onto the skin and the difference in absorption spectrum between oxygenated blood and de-oxygenated blood, as shown in Figure 9-7 may be compared to estimate blood oxygenation [Kamal et al., 1989, Nitzan et al., 2002]. This measurement may have various use cases as low blood oxygenation is a good marker of Cardiovascular Diseases such as Heart Failure. Most importantly such a device may replace the need for a separate Pulse Oximeter aside from the device developed.

![Figure 9-7: Absorption coefficient for Oxygenated and Deoxygenated Haemoglobin blood with respect to Wavelength](Challoner and Ramsay, 1974)

Recently efforts have been made to measure Haemoglobin content in blood with a similar technique to the one used to measure oxygenation [Abdallah et al., 2010, Wang et al., 2016a, Timm et al., 2015]. The Masimo Pronto is a product that has been FDA approved to measure Haemoglobin measures by using a very similar method described to measure Oxygenation level but with 7 different wavelengths. Considering the wide spread problem of Anemia in India it would be useful to include this measurement in the device developed here. This would add further functionality to the device and reduce the need for the paper strip method currently commonly
used to measure Hemoglobin.
9.5 Blood Pressure Measurement via Mobile Phone

After having understood the failures in measuring Arterial Stiffness an attempt was made to try to use what was going wrong to measure Blood Pressure via a mobile phone. Blood pressure is a key risk factor in every proper existing CV risk measurement algorithm. There have been many attempts to design a method to measure Blood Pressure without a standard cuff and many of these methods involve PPG signal.

Some research groups have sought to use features from PPG signal to train Machine Learning tools to measure blood pressure [Teng and Zhang, 2004, Grimaldi et al., 2011]. These methods did not show great levels of accuracy and extremely vulnerable to PPG noise as Arterial Stiffness measures.

Other researchers have tried to use models of the heart, for example the Windkessel model, to relate particular features from the PPG signal to Blood Pressure. [Choudhury et al., 2014] used a 2-element Windkessel model with good accuracy (±10 mmHg). This method seems to work relatively well and the authors suggest that a more precise model (such as the 3 or 4 element Windkessel Model) would improve results significantly. Nevertheless, this method requires calibration per person and therefore may be useful for continuous monitoring of a subject in a hospital structure but not for one-time measurements in the field.

Another method used in an attempt to measure Blood Pressure is by using the time lapse between the onset of a pulse to pulse arrival at an extremity. There are various ways of doing this, the underlying principle being that Pulse Wave Velocity, i.e. the speed of the pulse travelling on the arterial walls increases with increased Blood Pressure. Choudhury et al. used this method by using an ECG probe to measure the time of onset of the pulse and a PPG sensor on the finger to detect arrival [Choudhury et al., 2014]. Chandrasekan et al. and Junior et al. measured the onset of heart pulse by acoustically by using a smartphone Microphone. The former used two smartphones while the latter used the same smartphone to record both signals [Chandrasekaran et al., 2013, Junior et al., 2015]. The study led by Chandrasekan et al. developed into a commercial Company Auralife who sell their App on the Apple App Store and claim that it may be used as a guide but not as a medical tool. McCombie et al. devised a method of measuring the PPG signal
at the wrist and the finger and then using changes in hydrostatic pressure, caused by altering hand height with respect to the heart, with respect to pulse transit time to measure Blood Pressure. This last method requires a single Blood Pressure measurement per patient to be able to predict in the future. All these are interesting techniques however all require personal calibration every so often or rely on population data which may lead to bias and therefore none are suited for one-time measurements in the field.

Overall, the most interesting method to measure Blood Pressure was developed by Shaltis et al. who uses the principle that the signal from the PPG will have a maximum amplitude when transmural pressure equals to 0. Transmural pressure is governed by Equation 9.1. As shown in Equation 9.2, by keeping $P_{\text{External}}$ constant and measuring it with a pressure sensor, while altering $P_{\text{Hydrostatic}}$ and measuring it by calculating the relative height with respect to the heart with two accelerometers, when the PPG signal reaches a peak, meaning $P_{\text{Trans-Mural}} = 0$ then $P_{\text{Mean-Arterial}} = P_{\text{Hydrostatic}} + P_{\text{External}}$ and thus Mean Arterial Pressure is derived. Mean Arterial Pressure does not directly break-down in Systolic and Diastolic Pressure, however, it does provide indication of a subject's condition and this method was patented [Haruhiko H. Asada et al., 2006].

9.5.1 Attempt at Measuring Blood Pressure with a Mobile Phone

A similar method was devised such that accelerometers were not needed to measure BP and instead the vertical displacement from the heart (and thus the hydrostatic pressure) was found by knowing the lengths of the arm bones. I.e. with a subject lying in supine position, vertical displacement of the finger with respect to the heart may created by being a humerus under the heart, or a humerus plus a radius above the heart. As an initial test to see whether the change in PPG amplitude was detectable with a mobile phone a simple test assuming that contact pressure ($P_{\text{External}}$ in Equation 9.1) is irrelevant. This is of course an erroneous assumption, however by keeping the contact pressure constant a modulation in PPG amplitude due to hydrostatic pressure should still be observable.

A few tests were run and in fact, as Hydrostatic Pressure varied the PPG amplitude indeed modulated as is shown in Figure 9-8. These results highlighted the need for a measurement of
$P_{External}$ as the Mean Arterial Pressures calculated are incredibly low as shown in the sample result in Figure 9-8. Overall, this method looks like a promising method to measure Blood Pressure however it was not pursued further as energy and time was dedicated to the measurement of $PWV$. Nevertheless, this may be an interesting project to pursue in the future of the lab.

Figure 9-8: Modulation of PPG Amplitude as a function of Hydrostatic Pressure
9.6 Conclusion

Overall, the mobile phone PPG worked very well, as expected, to measure HR, BR and HRV. Nevertheless, the device validation showed that this method is not feasible for the measurement of arterial stiffness. This is because the prime PPG feature which mark Arterial Stiffness, i.e. the dichrotic notch is too susceptible to low frame rates available in low-cost mobile phones available in resource constrained environments and to changes in external pressure applied to the camera. To solve this issue it was attempted to set a methodological standard to control for the external pressure by attempting to ensure that only the health worker collecting the data was applying pressure and not the patient. Although partially successful this method was too vulnerable to human error. It was therefore decided to attempt to develop a device not dependant on such a delicate feature, especially considering that the device should work in the field and therefore be very robust. The development of such a device is described in Chapter 10.
Chapter 10

Advanced Assessment of Vascular Health: Pulse Wave Velocity

In this chapter the design process of a device built to measure a surrogate of Aortic Pulse Wave Velocity ($PWV_A$) will be described. This Chapter firstly includes a background on the gold standard measure of Pulse Wave Velocity: $PWV_A$ and its importance in measuring CVD risk. Secondly, clinically accepted methods of measuring $PWV_A$ and experimental methods which attempt to measure surrogates of $PWV_A$ will be explored. Thirdly, the device design will be described as well as its clinical validation. Lastly there will be a conclusion and discussion on future work.
10.1 Prognostic Value of Aortic Pulse Wave Velocity

It is now commonly accepted that Blood Pressure derives mostly from Arterial Stiffness and thus Atherosclerosis [ORourke et al., 2002]. As arteries degenerate they lose their elastic properties and become less compliant. Because of Arterial Stiffness is such an important precursor to increases in Blood Pressure and Pulse Pressure, it is widely hypothesized that Arterial Stiffness and thus the gold standard measure of Arterial Stiffness: $PWV_A$, is one of the most important risk factors for acute cardiovascular events caused by Atherosclerosis. Many studies have been performed to test this hypothesis and have validated it consistently both in clinical settings and also in epidemiological studies with general population. The fact that $PWV_A$ performs well in both clinical and general population studies is important because it shows that it may be used both as an indicator to screen people who appear to be asymptomatic, to catch the people at high risk, and also to stratify hospitalised patients. In certain clinical studies which previously had contradicting mortality results despite similar reductions in Blood Pressure, it has been shown that Arterial Stiffness is also a clarifying factor, showing that it is a stronger CVD event predictor than Blood Pressure. Furthermore, Arterial Stiffness has been shown to provide more prognostic information than standard stratification strategies which include: hypertension, diabetes, obesity, dyslipedemia and smoking. Overall, $PWV_A$ is regarded as an independent risk predictor for CVD events [Blacher et al., 1999, Sutton-Tyrrell et al., 2005, Laurent et al., 2006, Hansen et al., 2006, Journal, 2010, Mitchell et al., 2010, Liao and Farmer, 2014, Boutouyrie et al., 2014].

A study conducted in 1999 by Blacher et al. showed that $PWV_A$ is very strongly associated with Atherosclerotic damage and improved CVD risk prediction in patients with hypertension. At any given age of the subjects within the study $PWV_A$ was the best predictor of mortality. A $PWV_A > 13 \text{ ms}^{-1}$ itself was an extremely good predictor of mortality [Blacher et al., 1999].

An expert consensus document by Laurent et al. in 2006 concluded that a large body of evidence exists to support that $PWV_A$ has a higher predictive value than typical CVD Risk values calculated with classical methods that aggregate risk factor values. Furthermore, in 2010, Mitchell et al., for the Framingham Heart Study\footnote{The Framingham Heart Study is the largest ongoing study on Cardiovascular Disease. It was started after World War II with 5,229 residents of Framingham Massachusetts. It has been, and continues to be, instrumental in the understanding of Cardiovascular Pathology} conducted a medical study to analyse how well standard
risk factors were predictive of a major cardiovascular event. Multivariable models standardised for age, sex, blood pressure, anti-hypertensive medication, total and HDL cholesterol, smoking and diabetes showed that higher values of PWV were associated with a 48% increase in CVD risk [Mitchell et al., 2010].

Recently the European Society of Cardiology conducted a study published in the European Heart Journal in 2010 in which they sought to develop reference values for $PWV_A$ that may help clinicians make better use of this measure. A total of 16,867 subjects from 8 European countries took part in the study. This shows that, not only has $PWV_A$ acquired importance in the research realm, but is also gathering traction within the realm of medical practitioners [Journal, 2010].

There have also been other smaller studies performed with the general population which have showed the relevance of measuring $PWV_A$ to assess CVD risk. A study performed by Sutton-Tyrell et al. concluded that in an asymptomatic old population $PWV_A$ was in fact associated with CVD mortality [Sutton-Tyrrell et al., 2005]. Another study conducted on the general Danish population by Hansen et al. showed that $PWV_A$ predicted CVD outcomes better than traditional CVD risk factors [Hansen et al., 2006].

Overall, there is no doubt that $PWV_A$ is a very significant measure of CVD risk. This is mostly due to the fact, that, as an angiogram or a CT Calcium score, $PWV_A$ looks at the intrinsic health of a persons arteries. This is unlike typical risk factors which either focus on elements that cause atherosclerosis and vascular damage in general (as Diabetes and Cholesterol levels) or on the major effect of arterial stiffness i.e. Blood Pressure. Nevertheless, classical risk factors are extremely valuable and research has shown that a well defined analysis of CVD risk should be complement $PWV_A$ measurement with standard risk factor measurements [WHO, 2017].
10.2 Related Work and Prior Art

10.2.1 Existing Methods to Measure $PWV_A$

Measurement of Pulse Wave Velocity is the gold standard measure of Arterial Stiffness. It is easily reproducible, simple and accurate as well as being a good measure of CVD risk. However, $PWV_A$ itself is a surrogate of Arterial Stiffness and researchers are working to develop other methods to measure arterial stiffness more precisely [Cho and Kim, 2016]. These new methods mainly revolve around Echocardiography imaging. Nevertheless, for the objective of this thesis, it was decided to look at the most common and reproducible method to measure $PWV_A$ as these may be readily used to compare the values from the novel device being developed.

The objective is to measure Pulse Wave Velocity in the Large Elastic Arteries, the main arteries outside the heart affected by Atherosclerosis. To measure $PWV_A$ the Pulse Transit Time (PTT) and the distance between two arterial sites is needed. To do this a signal of the pressure wave travelling on the aorta is commonly measured simultaneously at the carotid and femoral arteries as depicted in 10-1. The difference in pulse arrival time is taken as the PTT. It is impractical to measure both waveforms simultaneously as finding the pulse of a single artery with a probe requires the full attention of a probe operator. To overcome this issue, single waveform measurements are taken and gated with an ECG measurement which enables post-combination of the wavelength

Figure 10-1: Measurement of $PWV_A$ [Laurent et al., 2006]
with respect to time to get $\Delta T$.

By knowing $\Delta t$ and $\Delta L$ (i.e. the distance between the carotid and the femoral artery), $PWV_A$ may be calculated as shown in Equation 10.1. It is important to realise that this equation is not an exact measure of velocity because the pulse originates from the heart and travels up the carotid and down the aorta, thus Equation 10.1 is not strictly correct, however, it is commonly used in the medical world. An alternative measure, which is also used (and more mathematically correct), is to calculate the distance as the subtraction of the heart to carotid artery distance and the heart to femoral artery distance.

$$PWV_A = \frac{\Delta L}{\Delta T} \quad (10.1)$$

The waveform may be measured in different ways, commonly using an Applanation Tonometry probe or a Doppler Ultrasound Probe [AtCor, 2015, Calabia et al., 2011].

### 10.2.2 Experimental Methods to Measure Surrogates of $PWV_A$

$PWV_A$, i.e. Aortic Pulse Wave Velocity is the gold standard measure for Arterial Stiffness. However, it is not practically simple to measure and perhaps this is the main reason why, although a great marker for CVD risk, its use is not as widespread as expected. Because of the impracticality of measuring $PWV_A$ especially in non-clinical settings, many researchers have sought to understand whether other surrogate measures of $PWV_A$, which are simpler to measure, were as significant, or at least close, to $PWV_A$ itself.

The Large Elastic Arteries are the ones most affected by Atherosclerosis and various studies have shown that only these are particularly indicative of CVD risk, while the Long Muscular Arteries do degenerate but more due to a natural process rather than a atherosclerotic pathogenesis. In fact, studies that study Pulse Wave Velocity in LMAs mostly conclude that they do have the prognostic value of the LEAs [Pannier et al., 2005]. Nevertheless, this has not discouraged researchers from looking at composite measures of PWV, i.e. measures that include both LEAs and LMAs.

The most studied studied surrogate measures have been Brachial-Ankle and Cardio-Ankle
Pulse Wave velocity. These measurements use pressure cuffs to measure pulse arrival time. This method is more practical than using the probes described earlier because the person taking the measurement simply has to put two cuffs at the appropriate locations without the difficulty which is involved in finding the Carotid and Femoral Arteries. Both methods have been linked to $PWV_A$ to some degree in various studies and Brachial-Ankle index is commonly used in Japan to measure CVD risk [Yamashina, 2002, Shirai et al., 2011, Perk et al., 2012, Cheng et al., 2016].

Two pulse start and arrival measurements, which are very simple and inexpensive, are the Electrocardiogram (ECG) and Photoplethysmography (PPG) respectively. This has lead to research groups to investigate whether it is possible to measure a surrogate of $PWV_A$ with PPG together with ECG and also with PPG alone.

Studies conducted by Allen et al. and Nitzan et al. have investigated Pulse Transit Times (PTT) between heart activation, measured with ECG, and arrival of the pulse to the Ears, Fingers and Toes, measured with PPG. The studies found statistically significant relationships between PTT and Age, Systolic BP and height. Thus concluding that these PTTs may be important measures of arterial stiffness [Allen and Murray, 2000, Nitzan et al., 2002, Allen, 2007]. A study conducted by Liu et al. also calculated velocities between the heart and the Ear, Finger and Toe and showed that there was variability in these measurements, however correlations were not made between the gold standard measure of Arterial Stiffness $PWV_A$ [Liu et al., 2011]. Finally, Mitchell et al. patented the idea of measuring different Pulse Wave Velocities by measuring heart activation via ECG and PPG arrival time at any location on the body [Mitchell, 2001].

In an effort to reduce the number of tools used, other research groups have sought to measure surrogates of $PWV_A$ with only PPG sensors. PPG sensors are extremely cheap and the signal is easily digitised for analysis. A study by Tsai et al. measured the pulse arrival time at the Ear, Toe and Finger and found a weak correlation between $Distance_{Finger-Toe}/Time_{Finger-Toe}$. This weak correlation is possibly due to the choice of distance measure used. The pulse starts at the heart and then simultaneously progresses to the Finger and to the Toe, thus dividing by the total distance between the Finger and Toe by the difference in arrival time, as is done in this study, is

---

2 An Electrocardiogram measurement does not necessarily require many electrodes. Just two electrodes are required if the activation of the heart is the only element of interest - as is with measuring PWV.
not exactly a measure of speed.

In a similar effort to use a single device to measure PWV, a company called 'Blumio’ has developed a method using a Microwave Doppler Probe to measure PWV between the shoulder and elbow with the objective of measuring Blood Pressure by finding a correlation between \( PWV \) and Blood Pressure [Metz, 2016].

Overall, there have been various efforts to reduce the complexity of measuring Pulse Wave Velocity. There is a tradeoff between how close a measurement is to the gold-standard \( PWV_A \) and how simple the measurement is to take. What follows is an attempt to simplify the measurement method without loosing the accuracy that \( PWV_A \) has in measuring arterial stiffness.
10.3 Device Design for PWV Measurement

This Section describes the Design of a device to measure surrogates of $PWV_A$. Before describing the actual final design and the Prior Design Process, i.e. the evolution of prototypes before reaching the final design is outlined.

10.3.1 Possible Approaches and Early Prototypes

**Google Cardboard design**

Various attempts were made to design a device that may measure PWV in the simplest way possible. Because a particularly clean signal is not needed to measure PWV, just the pulse arrival time is needed\(^3\), a different kind of PPG measurement technique may be used which is called Video-PPG [Fletcher et al., 2015]. The PPG method which has been described so far is called contact-PPG, in which, both the sensor and the light source are in contact with the subjects skin. In video PPG instead the light source and the sensor may be at a certain distance from the skin. The second key design factor taken into account is that hands, in most patients, may be moved to various parts of the body. To take advantage of these two factors, a device was designed out of cardboard which is placed on the forehead with space for the hand to be put inside on one half of the head as shown in Figure 10-2. Green LEDs illuminate the inside of the cardboard and a mobile phone camera is used to record a signal of both the hand and forehead in parallel, thus measuring PWV between these two body parts.

\(^3\)I.e. not any particular feature such as the Dichrotic notch

![Figure 10-2: Cardboard PWV Device Prototype.](image)

(a) Unfolded Cardboard Device  
(b) Folded Cardboard Device

Figure 10-2: Cardboard PWV Device Prototype. **A:** Velcro used to close the device, **B:** LEDs for illuminating the hand and forehead, **C:** Hole for smartphone camera, **D:** Curvature for forehead, **E:** Black to avoid reflections, **F:** Hole for hand to be inserted, **G:** Wires from LEDs, **H:** Connector Circuit, **J:** Battery
Unfortunately this first attempt was not as successful as expected. A signal was captured however as tonality of skin increased the signal became fainter and most importantly, as people age it was noticed that skin becomes more reflective, further attenuating the signal as light does not penetrate the skin as much. Considering that the target population is old and typically has a dark tonality of skin, this technique was not deemed appropriate. Furthermore, frame rate became an issue not because a precise PPG signal is needed but because the difference between the two pulses measured on the hand and forehead is very small and thus frame rates ≥100fps are needed for significant levels of accuracy and these are unattainable with simple low-cost smartphones.

Dual PPG design

Following from the failure described above it was decided to attempt using an external contact PPG Device to achieve the same objective, i.e. measure a pulse at the head and finger. A prototype was built (shown in Figure 10-3) and briefly tested.

![Figure 10-3: Contact-PPG PWV Device Prototype. A: USB Connection to smartphone, B: Wooden casing, C: Elastic Band, D: External PPG light Source and Sensor, E: Internal PPG light Source and Sensor](image)

This prototype brought back problems firstly encountered with the mobile phone PPG described in Chapter 9. It was difficult to explain to patients how much pressure to apply to their forehead. Furthermore, the signal from the forehead was not as clear as that from the finger. It was attempted to use the neck but this as well proved hard. These issues may have been perhaps solved with a better PPG sensor, however, due to the non-technical challenges encountered, namely subject compliance to rules, it was decided to work towards a more robust and solid solution that was even less contingent on a subject’s compliance to instructions. The following Rationale describes the development of such a technology, in which there is a net transition from dependence
on mobile phone processing and camera technology to an external device that solves the technical challenges and then relays results to a mobile phone.

### 10.3.2 Final Device Design: Arterial Stiffness Device

An Arterial Stiffness device was designed to attempt to measure a surrogate measure of $PWV_A$ with Photoplethysmography (PPG). PPG measurement is best done at body extremities, such as the Ears, Fingers and Toes, as illustrated in Figure 10-4. The PPG signal at these points has been shown in the literature to be robust and accurate [Allen, 2007]. Ideally, to measure $PWV_A$ precisely, a signal at the carotid artery and the femoral artery would have to be captured. Unfortunately this has been shown experimentally to be very hard with PPG. The carotid artery is difficult to locate on a persons neck and the signal strength is weak because the blood is under a thick layer of skin and a large walled artery. The femoral artery is found in the Groin as illustrated in Figure 10-4. In addition to similar problems to the carotid artery, the femoral artery is a delicate area that subjects may not be comfortable exposing. The measurement should not cause any stress that may alter the results. Overall, especially considering that a low-skilled worker will be using the device, it was decided not to attempt a measurement at the Carotid or at the Femoral Arteries, instead it was decided to use the Ear, Finger and Toe$^4$.

It is hypothesized that taking measurements from the three locations illustrated in Figure 10-4 will result in data to characterise the Pulse Wave Velocity in the Large Elastic Arteries and also to understand when the Pulse Wave Velocity in the Large Elastic Arteries becomes similar or even surpasses that in the Long Muscular Arteries. Figure 10-4 shows a simplified model of the Arterial System: most of the arterial segment between the H-F and G-T consists of Long Muscular Arteries aside from the very last portion of peripheral circulation, while the arterial segments between the H-G and H-E are predominantly Large Elastic Arteries apart from the peripheral vasculature at the Ears. The Pulse Transit Time between the Ear and the Finger will provide a relative measure of the speed in the Long Muscular Arteries in the arm as this is the main arterial segment between the ears and the Fingers. The Pulse Transit Time between the Ear and the Toe will hold information of both the Long Muscular Arteries and the Large Elastic Arteries however the latter should be more prone to change and thus alter the signal more.

$^4$All on the left side of the body for consistency
Figure 10-4: Simplified Model of the Arterial System with Large Elastic Arteries between H-G and H-E and Long Muscular Arteries between H-F and G-T where the letters stand for: Heart, Groin, Ear, Finger and Toe.

Figure 10-5: Illustration of the measurement platform including: PPG clip-on probes (Ear, Finger and Toe), Master board, and mobile phone with custom application for data collection.
10.3.3 Arterial Stiffness Device Hardware

Custom electronic modules were designed and assembled to collect PPG signals simultaneously and transmit them to a mobile-phone for data storage and are shown in Figure 10-5. The PPG devices each consist of two pairs of LEDs for illumination and a programmable gain op-amp photodiode circuit. The signals from each of the PPG modules was transmitted to a master board which then relayed the combined signals to a mobile phone.

10.3.4 Arterial Stiffness Device Signal Processing and Analysis

Mobile App

A custom mobile App was designed for android to store data and allow an operator to understand whether the signal is of good quality. Screen shots of the App are shown in Figure 10-6. An initial screen allows the user to retrieve a patient or enter a new one. The recording screen visualises data from each of the three probes simultaneously with the option to change lighting settings directly from the phone in case the signals are not optimal. For this initial stage of device development, the data processing was done on a laptop computer.

![Figure 10-6: Screenshots from the Arterial Stiffness App developed.](image-url)
Pulse Arrival Detection

The signals are filtered for high frequency noise and the pulse arrival time is calculated for each pulse using the *Intersecting Tangent Method* illustrated in Figure 10-7. At this point the transit time between the Ear and Toe and Ear and Finger may be calculated.

![Figure 10-7: Left: A sample synchronised signal from the Ear, Finger and Toe. Right: Illustration of the Intersecting Tangent Method used to estimate Pulse Arrival Time, where A is minimum in the pulse, B is the point of maximal upstroke, and C is the intersection between the horizontal and tangent lines drawn from A and B.](image)

10.3.5 Derivation of Pulse Wave Velocity

At each heart beat a pressure pulse travels from the heart to the Ear, Finger and Toe along different paths as shown in Figure 10-4. Because the device designed does not have an ECG measurement, the reference point for the onset of heart activation is assumed to be the ear. However, when the pulse reaches the ear it has already travelled a non-zero segment of the arterial structure. In order to compensate for this assumption, to get an appropriate measure of average velocity with the Pulse Transit Times that may be calculated with this device, the Heart to Ear distance has to be subtracted from the Heart to Finger and to Toe distances. Thus, Equations 10.2 and 10.3 are used to calculate the average velocities between between Ear and Finger \( (PWV_{EF}) \) and Ear and Toe \( (PWV_{ET}) \). For consistency, the same logic is used to measure \( PWV_A \) using the Doppler Probe (as described in Section 10.2.1).

\[
PWV_{EF} = (d_{Heart\rightarrow Finger} - d_{Heart\rightarrow Ear}) / t_{EF} \quad (10.2)
\]

\[
PWV_{ET} = (d_{Heart\rightarrow Toe} - d_{Heart\rightarrow Ear}) / t_{ET} \quad (10.3)
\]
10.4 Clinical Validation

To validate the use of the device designed in measuring Arterial Stiffness and degree of atherosclerosis a medical study was designed in close collaboration with Dr. Partho Sengupta and Dr. Shantanu Sengupta at Sengupta Hospitals and Research Institute in Nagpur, India, where the study was conducted. In this Section the study will be described and the results analysed.\footnote{This study methodology was approved by COUHES (Application Number: 1610714173) and by the Ethics committee at Sengupta Hospital and Research Institute Nagpur}

Objectives

1. Analyse the correlation between the measured $PWV_{EF}$ and $PWV_{ET}$ and the gold-standard measurement of $PWV_A$.  
2. Assess how well the device measures CVD Risk compared to the WHO model and to a gold-standard measure of Atherosclerosis in the Coronaries, i.e. Calcium CT Scoring.

10.4.1 Method

To test whether the device measurements are sufficient to distinguish between people with known Atherosclerosis and not it was decided to recruit subjects from two different population types:

1. Known CAD cases who have typically recently undergone CAD surgery or scheduled to do so.
2. People at Risk of having Atherosclerosis, i.e. patients with known Hypertension and/or Diabetes.

Taking into account the level of incidence of Atherosclerosis in the Indian population where the study was performed it was estimated that 25 subjects per study group would be sufficient to prove significance of the results. In addition three healthy young subjects were also recruited to compare the results of the device but did not participate in the other medical tests.

Objective 1: Correlation with Gold standard measurement

In order to correlate the experimental $PWV_{EF}$ and $PWV_{ET}$ with a gold-standard measure, $PWV_A$ was measured using an Echocardiogram coupled with an ECG. The GE Vivid E9 Ultra-
sound System used did not provide a direct measure of PWV and hence this calculation was done on a laptop computer once the data was collected.

**Objective 2: Comparison with standard Risk Assessment**

To be able to compare the device measurements with standard Risk Assessment all the parameters used in the WHO Risk Assessment were collected and each subject underwent a standard physical exam and completed a Subject Questionnaire with general health questions. Furthermore, because the WHO Risk Assessment is designed to be performed in the field and therefore is not as precise as tests which are usually performed in hospitals, a Coronary CT Calcium Score was performed on the subjects which were at Risk of developing CAD. This measurement assess the degree of calcification in the coronary arteries and is used to assess the severity of CAD [Sharma et al., 2010]. This will result in being able to find the subjects who were recruited as at Risk Subjects however are actually diseased. This test was not performed on the CAD population.

**10.4.2 Hypothesis**

The hypothesis is that $PWV_{ET}$ will be the derived measure most similar to the gold standard $PWV_A$ because both measures include the pulse travelling through the Aorta. With respect to $PWV_A$, $PWV_{ET}$ will also include the pulse travelling in the leg all the way to the foot, meaning that the two velocities will definitely not have an identical 1-to-1 relationship, however, there should be a correlation between the two. $PWV_{EF}$ should also be related to $PWV_A$ but since it looks almost uniquely at Long Muscular Arteries which do not degenerate that much, the correlation should be weaker. Furthermore, as $PWV_A$ increases, it is expected that $PWV_{EF} - PWV_{ET}$ will decrease in magnitude as $PWV_{ET}$ will be increase more significantly than $PWV_{EF}$.

As Pulse Wave Velocity is a direct measure of Arterial Stiffness, the main risk factor for CVDs, it is expected that the experimental Pulse Wave Velocity Measures, and especially $PWV_{ET}$, will be highly correlated with CVD risk measured via standard measures.
10.4.3 Results and Discussion

Analysis of Study Participants

Table 10.1 shows the key characteristics of the data collected. Of the 21 At Risk subjects, CT-Calcium scoring showed that 9 of these were in fact CAD patients. What is particularly interesting about this data set is that although most people are clearly unhealthy, i.e. are known CAD, hypertensive and diabetic patients; the standard risk factors measured, do not reflect this. Blood pressure, Lipid levels, A1c Values (measures of diabetes), ecc. are mostly within normal values and would be more representative of a slightly at risk group, not a group of whom almost half have undergone heart surgery because of CAD and almost half of the group at risk in fact has CAD.

Table 10.1: Data Characterization

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Subjects</td>
<td>42</td>
</tr>
<tr>
<td>Known CAD</td>
<td>21</td>
</tr>
<tr>
<td>At Risk (Actually CAD)</td>
<td>21 (9)(^6)</td>
</tr>
<tr>
<td>Ethnic Origin</td>
<td>South Asian</td>
</tr>
<tr>
<td>Males</td>
<td>25</td>
</tr>
<tr>
<td>Females</td>
<td>17</td>
</tr>
<tr>
<td>Age(^7)</td>
<td>57.9±10.5</td>
</tr>
<tr>
<td>Known Hypertension</td>
<td>41/42</td>
</tr>
<tr>
<td>Known Diabetes</td>
<td>24/42</td>
</tr>
<tr>
<td>Systolic Blood Pressure [mmHg]</td>
<td>131.4 ± 14.4</td>
</tr>
<tr>
<td>Diastolic Blood Pressure [mmHg]</td>
<td>78.1 ± 7.7</td>
</tr>
</tbody>
</table>

The reason for the seemingly paradoxical results is the fact that all subjects were under strict drug regimens and were being monitored at the hospital due to their status of being at risk or actually having CAD. Thus, the vast majority of subjects score very low on the WHO Charts

\(^6\)CAD was diagnosed with the CT Calcium Score Results

\(^7\)In ±x, x= 1 Standard Deviation
described in Sections 4.3.2 and 8.3. Nevertheless, although these standard measures of CVD risk factors showed that there was no significant risk, the results from the tests which looked at Arterial Health directly, showed a different picture. In fact, about 50% of the at risk patients who underwent the CT Calcium scoring test were diagnosed with CAD. Furthermore, 70% subjects had $PWVA$ values higher than 2 standard Deviations from normal mean values published by the European Society of Cardiology and only 5% of subjects were below the normal mean values [Journal, 2010]. These results paint a clearer picture of the subjects under analysis and show how important it is to utilise a measure of CVD risk that looks at Arterial Health directly. These sort of tests, such as $PWVA$, look at the intrinsic problem while standard risk factors, although extremely important and valid, do not have the strength to describe actual Arterial Health.

The drugs that people take to lower CVD Risk do also help reduce Arterial Stiffness, however the time frames and effects are different. For example a Diuretic may be used to reduce Blood Pressure by reducing the amount of volume in the CVD System. This reduces blood pressure very quickly, nevertheless, the arteries remain stiff. Only in the long term, with reduced stress on the arterial walls will the actual arterial stiffness will tend to decrease. N.B. with reduced Blood Pressure, PWV will also decrease because the stiffness caused by the blood pressure pushing against the arterial walls is relieved. However, the stiffness due to Arterial wall properties changing will remain and take longer to alleviate. Recently, because of the heightened interest and understanding of Arterial Stiffness, drugs which will directly act upon this are starting to be developed [Zieman et al., 2005]. Findings from this study show that these drugs may have a significant and positive impact on the reduction of CVD risk.

Overall, this shows that, the assumption that standard risk factors would be highly correlated with the novel $PWV$ measurement does not hold. This result would not be expected in a study with people not under the influence of drugs.

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8It is important to note that this comparison is valid however in an ideal case standard Values from the pertinent population would be more exact.
Sources of Experimental Error

Unfortunately there were significant sources of error in the study which lead to 13 of the 42 study participants to be excluded from the final analysis. There were four main issues: (1) Some of the data collected with the Doppler probe had unclear ECG tracings (used to time the pulse wave) and a few of these recordings had too low a time definition to make an accurate measurements of $PWV_A$. (2) The actual PPG devices developed did not work perfectly on each subject due to differences in skin tone and tissue composition. (3) It was hard to standardise body length measurements to measure PWV with both the echo-cardiogram and the Arterial Stiffness device developed. (4) 2 subjects had PAD which meant that the signal at the feet was very faint and almost undetectable. Improvements to eliminate these sources of error are found in the Conclusion of this chapter.

The Error Bars on the Arterial Stiffness Device Velocities in Figures 10-10, 10-11 and 10-12 are derived from assuming that the error in measuring distance is $\pm 1 \text{ cm}$. The error in the PPG pulse measurement is ignored as the measurement of error is significantly smaller compared to the error due to the distance measure. Nevertheless, it is important to note that there was a non-negligible standard deviation in the Pulse Transit Times measured. This increased as the quality of the PPG signal decreased and the Intersecting Tangent Method performed worse. In fact, a few study participants were excluded from the Figures because the PPG error (given by the standard deviation of the measurements) was too large, typically because one of the probes had a weak signal.

The Error Bars on the Echo Probe Velocities in Figures 10-10, 10-11 and 10-12 are derived from the error in distance treated in the same way as with the Arterial Stiffness device, together with the error in measuring the Pulse Transit time with the echo-cardiogram data given by the resolution of the echo-cardiogram image which varied throughout the study. Some subjects had very high errors due to low resolution of the echo-cardiogram data and these subjects were removed from the plots.
Pulse Wave Velocities in Study Subject Groups

First of all, the PWV measures as a whole are looked at here. Figure 10-8a shows how in general subjects with CAD had a higher $PWV_A$ than people only at risk. Nevertheless, the distinction is not as remarkable and is overlapping as shown by the error bars (1 Standard Deviation). This overlap is due to two main reasons. Firstly, age has a significant effect on Arterial Stiffness and therefore $PWV_A$ is not only dependent on whether a subject has CAD or not. Secondly, people at risk are also expected to have relatively High Arterial Stiffness because they are moving towards CAD.

Data from three healthy subjects$^9$ was also collected with the PPG devices. Mean averages are shown for $PWV_{ET}$ in Figure 10-8b. As in Figure 10-8a subjects at Risk have a slightly lower average $PWV_{ET}$ compared to CAD patients. The healthy subjects have a significantly lower average $PWV_{ET}$ because of their young age and very low CVD risk factor prevalence.

![Figure 10-8: Bar charts showing mean averages with error bars representing 1 Standard Deviation. On the left only the study subjects which underwent all tests are included. On the right a small sample of healthy adults was used to compare $PWV_{ET}$ values.](image)

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Figure 10-9 shows the relationship between $PWV_{ET}$ and $PWV_{EF}$. As is shown the relationship is very strong. What is important to note is that the $PWV_{ET}$ has a larger range than the $PWV_{EF}$, this is because the Elastic Arteries in the $PWV_{ET}$ are more affected by Atherosclerosis and therefore there is a greater variability. In Figure 10-9 the healthy people are marked in bordeaux. It is clear that these subjects have much lower pulse wave velocities in general and this is

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$^9$Age range: 23-25.

$^{10}$N.B. It may have been noticed that the velocities reported here differ from the ones in Figure 10-11 and 10-10. This is because for this bar chart the $PWV_A$ is calculated using the European standard method which was not used in the plots for consistency with the method used to measure $PWV_{ET}$ and $PWV_{EF}$ as explained in Section 10.3.5. Consistency is not maintained here because a discussion will be made with respect to the European Standard values.
promising for the development of a device that may screen for CVD risk.

![Figure 10-9: Relationship between \(PWV_{ET}\) and \(PWV_{EF}\). Key: Healthy people and CAD together with At Risk people](image)

**Figure 10-9**: Relationship between \(PWV_{ET}\) and \(PWV_{EF}\). Key: Healthy people and CAD together with At Risk people

**Analysis of relationship of \(PWV_A\) with \(PWV_{ET}\) and \(PWV_{EF}\)**

Figures 10-10 and 10-11 show the relationship between the two experimental measures of \(PWV\) and the gold standard measure, \(PWV_A\). As may be seen the correlation with \(PWV_A\) is stronger with \(PWV_{ET}\). This may be explained by the fact that the arteries involved in the \(PWV_{EF}\) measure are Long Muscular Arteries and therefore less affected by Atherosclerosis than the arteries involved in the \(PWV_{ET}\). Furthermore, there is a generally higher error with the \(PWV_{EF}\) measure as the distance between measurement sites and Pulse Transit Times are shorter.
Figure 10-10: Relationship between $PWV_A$ and $PWV_{EF}$

Figure 10-11: Relationship between $PWV_A$ and $PWV_{ET}$
Figure 10-12 is the same as Figure 10-11 however the subjects data points coloured green have a \( PWV_A \) within 2 standard deviations from the age dependent normal values of \( PWV_A \) from the European Society of Cardiology, while those in red are above this threshold [Journal, 2010]. As can be seen the healthier people are at the lower end of the velocities both in \( PWV_A \) and \( PWV_{ET} \). It is not possible to set a clean threshold because the velocity limits are age dependent and there is not enough data to extrapolate limits for different age groups.

**Analysis of relationship between** \( PWV_A \) **with** \( PWV_{EF} - PWV_{ET} \)**

As may be seen in Figures 10-10 and 10-11, \( PWV_{ET} \) is faster than \( PWV_{EF} \). This is because the aorta, which is the artery most prone to Atherosclerosis and increased \( PWV \), is found in the \( PWV_{ET} \). Furthermore, because of this the \( PWV_{ET} \) should increase more in speed with respect to \( PWV_{EF} \) as Atherosclerosis worsens, meaning that pulse waves are not reflected well any-more at the interface between the Large Elastic Arteries and the Long Muscular Arteries. This should mean that as atherosclerosis worsens \( PWV_{ET} \) should become ever more larger than \( PWV_{EF} \). This is proven by Figure 10-13 where \( PWV_A \) is plotted against \( PWV_{EF} - PWV_{ET} \).
Figure 10-13: Relationship between $PWV_A$ and $PWV_{EF} - PWV_{ET}$
10.5 Conclusion and Future Work

Not a particularly strong correlation was found between the gold standard $PWV_A$ and $PWV_{ET}$ or $PWV_{EF}$. Nevertheless, it is believed that this is mainly due to technical and experimental errors rather than a medical issue. Furthermore, the number of subjects was not high especially given the similarity between them. The hypothesis that $PWV_{ET}$ would be the experimentally derived measure most similar to $PWV_A$ and that $PWV_{EF} - PWV_{ET}$ would decrease in magnitude with degree of atherosclerosis were both confirmed, albeit weakly. It was not confirmed that $PWV$ in general was highly correlated to the standard CVD risk factors. This is because the vast majority of the subjects were under a strict drug regimen which reduced these magnitude of these risk factors. This issue however is of note because it showed that while measuring the standard risk factors is obviously important and clinically relevant, they may not elucidate arterial health fully, which more direct measures, such as Calcium CT-scoring and $PWV$ do. This shows how it is important to have a direct measure of Arterial Health when predicting CVD risk.

Overall, despite the not excellent results, it is believed that with improvements to the device and a different study design the device performance may be improved significantly and shown to be effective, especially when used in unison to other standard risk factor measures.

10.5.1 Device Improvements

With respect to the method to measure Arterial Stiffness attempted in Chapter 9, to measure the Augmentation index, the method explored in this chapter proved to be more robust i.e. collected more easily. This is because it is much simpler to measure pulse arrival time rather than the dichrotic notch as it is not affected by external or internal pressures. Nevertheless, now that a high frame rate external device has been developed it would be interesting to attempt to analyse the waveform of the signal to perhaps complement the PWV measurement.

Analysis of the waveform may also help identify patients with Peripheral Arterial Disease (PAD) which confounds the $PWV_{ET}$ measurement. PAD is an issue because it slows down the signal and therefore may result in a false positive. Previous studies have shown PAD may be diagnosed if there is a significant discrepancy between the Pulse Transit Time at the toes. To do this an extra device would have to be attached to the second toe. This may be done however it would
add extra components. In the future this option and that of analysing the actual waveform at the
toe should be explored to decide which path to automatically take to exclude patients with PAD.

Furthermore, because there are differences in skin tonality and tissue composition, to further
improve the signal from the devices built, an algorithm may be developed that will automatically
optimise signal quality by adjusting the brightness of the light source used in the devices. This
would increase the signal to noise ratio and render the detection of pulse arrival time simpler. An-
other aspect that would have improved the data would have been an improvement in the measure
of distance, essential to calculate velocity. In the study this was done with a measuring tape and
bone protrusions on the body were used to identify key points. This however often resulted in
measurements that were not directly linear because of body fat. In these cases it was attempted
to measure the distances by lifting the measuring tape from the body in order to have it flat with
respect to the ground. Aside from the fact that arteries do not follow straight lines (which is impos-
sible to correct for unless and MRI machine is used), perhaps better methodologies should be used
to measure the distance. One of the reasons that the results have high errors is that it is thought
that the distance error is possibly higher than the ±1 cm used in the calculation of the error bars.

Ideally a sensor would detect a signal from the femoral artery in the groin to get a precise mea-
sure of the velocity in the elastic arteries in the torso. In fact, a perfect correlation between the
PWV \( _{ET} \) and PWV \( _{A} \) is not possible because inherently they are two separate measures. It was
attempted to derive a model to extract the velocity in the torso but without a probe at the femoral
artery this is not possible; the measure available is an average velocity between the Ear and Toe and
it is not possible to split this into distinct components. An attempt was made to use the speed in
the arm (PWV \( _{EF} \)) as a proxy for the speed of the pulse in the leg to estimate the time period in the
leg and therefore the speed in the torso. This unfortunately did not result in anything promising.

Overall, it is important to note that the key result that was attempted to be extracted from this
study is the relationship between PWV \( _{ET} \) and PWV \( _{EF} \) with the standard CVD risk factors. A
great correlation with PWV \( _{A} \) i.e. the gold standard measure of CVD risk due to Arterial Stiffness,
is inherently not possible, however, PWV \( _{ET} \) and PWV \( _{EF} \) may hold more information and there-
fore finding the relationship between them and the standard risk factors would hopefully result in
pulse speed thresholds that may be used to stratify people at risk.
10.5.2 Experimental Improvements

Studying patients under strict drug regimen was definitely informative and highlighted the need for a precise measure of arterial health. However, this also confounded the results as it was not possible to correlate standard risk factors with $PWV$. In the future a study should be made with subjects who have not been previously diagnosed with a Cardiovascular Disease to be able to correlate standard risk factors with the experimental measures of $PWV$. Furthermore, this new study should be stratified by age group to account for natural changes in Arterial Stiffness according to age.

10.5.3 Other Applications of PWV: Maternal Health

The human body never undergoes such dramatic changes so rapidly as when a women becomes pregnant. During pregnancy the child’s heart develops and the mother’s heart undergoes incredible transformations. Within the first 14 weeks cardiac output\textsuperscript{11} increases by \sim 50\% and Systemic Vascular Resistance decreases by \sim 30\% due to the new placental circulation [Edelman, 2016]. These significant changes to the cardiovascular system are necessary for the healthy development of the child. One of the major issues that the mother may have during pregnancy is the development of hypertensive disorders which may lead to complications both to the mother and the child [Magee et al., 2008].

Hypertensive disorders affect \sim 10\% of pregnancies worldwide and Pre-eclampsia, which is the leading cause of maternal and perinatal morbidity and mortality, affects \sim 3\% of pregnancies [von Dadelszen et al., 2015, Hutcheon et al., 2011]. In Africa and Asia about 10\% of all maternal deaths are associated with Hypertensive disorders. The World Health Organization believes that most of these deaths may be avoidable through appropriate screening and treatment in time before health deteriorates [WHO, 2011b].

Previous efforts on early detection of pre-eclampsia have focused on measurement of blood pressure with a standard cuff method and urinalysis, respectively to check for high blood pressure and proteinuria. Various research groups have developed risk prediction models to understand the probability of a pregnancy to degenerate into a complicated one. The most important aspect of these models is the accuracy at which they stratify risk. Accurate risk stratification leads to an

\textsuperscript{11}\text{Cardiac Output} = \text{Stroke Volume} \times \text{Heart Rate [bpm]}
optimal distribution of resources as all risk levels receive the appropriate level of treatment. One of the most well known models to predict pre-eclampsia was developed at the University of British Columbia and is known as the fullPIERS model [Payne, 2014]. It has a predictive performance of AUC ROC: 0.88. This model requires is done in a clinical setting as it requires blood tests tests including Creatinine, AST, CBT [UBC, 2015b].

The fullPIERS requires laboratory tests and therefore may not be used in low resource environments at the forefront of primary care. The university of British Columbia has developed two solutions to compensate for this issue: 1). a miniPIERS model and 2). CRADLE - Community Blood Pressure Monitoring in Rural Africa and Asia: Detection of Underlying Pre-eclampsia [UBC, 2015a].

The miniPIERS screening is performed on a mobile platform on which results from a urine dipstick proteinuria test, systolic blood pressure, pulse oximeter and a clinical questionnaire (vaginal bleeding, chest pain, headache, etc.) are entered. This simplified version of the PIERS model achieved reasonable results (ROC AUC=0.76) however several practical limitations still remain. The reliance on non-reusable materials for the dipstick is a challenge both for supply and maintenance. Furthermore urine dipsticks have shown to be unreliable both because of human error in interpreting the colour and because they require additional measurements of the patient’s protein-creatinine ratio (PCR) or proper urine tests for confirmation [Phelan et al., 2004]. The pulse oximetry measure was added to the test because the hypertensive disorder causes blood oxygenation to decrease. Hypertension causes endothelial dysfunction which in turn causes pulmonary vasculature permeability to increase which impairs pulmonary diffusion, reducing oxygenation. Therefore the pulse oximetry measure is useful, however, it is an indirect measure of the endothelial dysfunction, of the vascular health, it would be useful to integrate a measure that is further upstream in the pathogenesis. Lastly, measuring blood pressure may be problematic in low-resource environments, to overcome this challenge the University of British Columbia developed the CRADLE project which includes an inexpensive (< 20$) electronic blood pressure monitor which requires very little training called 'BP 3AS1-2 Microlife' [Microlife, 2015].

Pre-eclampsia causes both the constriction of peripheral arteries and also larger arteries. The effect of both these symptoms is the increase in Blood Pressure [Tihtonen et al., 2006]. This
damage to the arterial walls is what then causes blood oxygenation to decrease. The gold standard measure for arterial stiffening is Pulse Wave Velocity (PWV). This measurement is typically used to screen for atherosclerosis. A study showed that PWV in the carotid-femoral and carotid-radial parts of the arterial tree were predictive of pre-eclampsia [Kaihura et al., 2009]. Furthermore, another study which involved a total of 183 women, showed that Brachial-Ankle PWV was more predictive than Blood Pressure measurement in predicting pregnancy-induced hypertension [Oyama-Kato et al., 2006]. This is probably because with PWV the actual damage to the arterial system is measured rather than the secondary effect of increased hypertension. Moreover, another study found that PWV has even more predictive value than some blood tests typically used to diagnose pre-eclampsia such as: serum levels of sFlt protein, uric acid, and 24-hr urine protein, and calcium excretion [Katsipi et al., 2014].

The device to measure $PWV_{ET}$ to measure general CVD risk may potentially be used to measure the severity of Pre-Eclampsia. It may be used by health workers in low-resource environments to screen for Pregnancy related Hypertensive Disorders before they lead to pre-eclampsia.
Chapter 11

Public Health Impact

This chapter will explore the value of the technology that has been described in this thesis. Firstly, the impact that the technology may have from a purely Public Health perspective will be presented. Secondly, it is also important to explore the behaviour of a novel technology within the social and institutional matrix where it is introduced [Marx, 1997]; all the technologies described in this thesis involve a mobile phone and the impact that mobile phones have on the lives of female health workers will be explored.
11.1 Public Health Value Proposition

In Chapter 6 Problem Statement and Proposed Solution two kits were presented, one Basic and the other Advanced. In this section the value of the Basic CVD Screening Kit and the most developed part of the Advanced CVD Screening Kit i.e. of the Advanced Assessment of Vascular Health: Pulse Wave Velocity, will be explored. Although these parts of the project are the most developed, they are still at a prototype phase and therefore their exact cost, final development and manufacturing are still unknown. Thus, the analysis described here is rather exploratory, however, still important to understand where the CVD Screening Kit developed may have an impact.

The first part of the Advanced CVD Screening Kit, i.e. the Cardiac Function Assessment, is yet incomplete, its functionality has not been proven and therefore will not be analysed here. Furthermore, its potential value in constrained resource environments is dubious. The only real cure for Rheumatic Heart Disease is heart surgery and, although situations are improving, this is commonly not an option for many people in India, especially in rural areas. In fact, the most cost-effective method to reduce the burden of Rheumatic Heart Disease is to screen and cure Acute Rheumatic Fever before it progresses to Rheumatic Heart Disease. It is nonetheless useful to continue work on digital Phonocardiophy as the technology may definitely be valuable in other scenarios.

It will be assumed for this discussion that the devices that will be analysed in this section have been developed further and that their measurements, together with standard survey questions on behaviour\(^1\), are indicative of precise levels of CVD risk similar to the ones in the WHO Risk Charts\(^2\).

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\(^1\)Such as Age, Weight, Height as well as smoking and alcohol consumption. N.B. to integrate these, a risk algorithm will have to be optimised with these data points.

\(^2\)See Chapters 4 and 8 for descriptions of the WHO Risk Charts
Fertile Ground for Solution

There were three main components of the fertile ground identified in Chapter 6 Problem Statement and Proposed Solution that may be exploited to aid government and private efforts to curb the burden of CVDs:

- Community Health Worker Schemes
- Good existing management strategies for high risk subjects
- Diffusion of Mobile phone technology

Community Health Worker Schemes and the diffusion of mobile phones has been previously discussed. The Screening and Management of people at risk has been described in Chapters 4 and 8, while the current treatment of CVD in India is described in Section 5.2. As mentioned in Chapter 4, CVD risk stratification and management is extremely valuable. Behaviour recommendations for low risk subjects and a mixture of risk reduction drugs for high risk individuals may reduce the risk of a CVD event by 50% [Gaziano et al., 2006]. It is estimated that, if people in the at risk age group are screened and managed appropriately, approximately 5.8 million deaths may be averted in India in the next 10 years. Furthermore, about 56% of these will be of people below the age of 70. This is extremely important as prevention of early age death reduces the risk of families falling into poverty by loosing their main source of income.

Overall, the benefits of good risk stratification, that the CVD Screening Kit developed provides, and subsequent management strategies are invaluable to reduce CVD burden due to Atherosclerosis in India. From a Government health perspective, currently the CHCs perform a strong screening for CVD and subsequent management 3, the SHCs and PHCs instead only perform opportunistic screening of Hypertension and Diabetes.

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3As the one proposed by the WHO for example, or any other holistic measure of Risk Factors
Design Criteria

The objectives of the Basic CVD Screening Kit were to provide a very simple tool that health workers with the lowest skill set may use to learn how to use a mobile phone and perform some basic tests. The design objectives of the Arterial Stiffness device (described in Chapter 8) were the following:

- Easy to use for low-skilled health worker in SHC type structures
- Immediate measure, with no need of further lab tests for example
- Direct measure of atherosclerotic damage
- Similarly priced to current tools or cheaper
- Reusable
- Centred around a smartphone for data digitization and computing power

As described in Chapter 8, the great advantage of measuring PWV is that it is an independent risk factor of CVD. This is the primary value of the device developed and, although it is recommended to use the most risk factors available to have a holistic measure of risk, this means that few other risk factors are needed to be measured to have a precise measure of CVD risk [WHO, 2017]. Furthermore, although not tested in a field trial yet, the device is easy to use, provides an immediate measure without the need of lab tests, is reusable and immediately digitizes the signal that may be evaluated immediately or communicated to a superior.
Costs and Benefits of the Current and Proposed Risk Assessment

This section will look into the estimated costs and benefits involved in implementing the proposed CVD risk assessment device. The key concept is that the device will fall into existing healthcare service frameworks, governmental or private. This means that all the training and operating costs will be absorbed by these organisations. Furthermore, it shall be assumed that the CVD Screening Kit will be used by programs who are already using, or have ready access to, mobile phones. There are two reasons for this assumption. Firstly, as mentioned in Section 6.2.1, mobile phones are incredibly diffuse and many initiatives, both governmental and private, already have them in use or are strongly pushing for their use with low skilled health workers. Therefore, it is not a challenge to find programs which already use mobile phones. Secondly, it is safer and more efficient to introduce mobile technology tools where similar products are already used. Rather than marketing the device together with a completely new technology (the mobile phone) existing ecosystems will be exploited first as many do exist and, subsequently, as mobile phones continue their diffusion around the country the CVD Screening Kit may be continue to be distributed.

Government and private initiatives to tackle CVDs are relatively similar and the government primary care structure will be the main focus of this section (i.e. the SHCs, PHCs and CHCs). CVD risk screening is currently performed at these centres and managed by the district NCD Cells. Healthcare facilities upstream may also be interested in this portable CVD Screening Kit, however, they mostly have access to more advanced CVD risk tests and are staffed with professional doctors who may perform them. The objective of this project is in fact to bring high quality screening capabilities down to the lowest primary care centres.

Table 5.2 and Figure 5-6 show how CVD risk screening is performed at the various governmental primary health centres. At SHCs only opportunistic screening of Diabetes and Hypertension with glucometer kits and BP measurements respectively. At PHCs the screening is the same, however, treatment is administered here. Finally, the CHC may perform the full risk measurement including blood tests and if necessary may also employ ECGs and Ultrasounds to have a better diagnosis once high risk has been established. Table 11.1 shows the current costs of the device and the use costs needed to perform risk screening at the various centres (Other risk factors needed for risk assessments, such as age and alcohol consumption are recorded via a survey).
Aside from the mobile phone for both Basic and Advanced CVD Screening Kit the Arterial Stiffness device consists of four components and cable connections\(^4\). Up till now the devices have been built in house and the cost of actually manufacturing the device will of course be different. To have an idea of at about how much the device could sell on the market at a minimum, prices of similar devices were explored. The device built is very similar to a standard pulse-oximeter, a device that uses Photoplethysmographic technology to measure blood oxygenation. Prices for these devices with on board display screens range from $10-20. Considering these prices and the simplicity of the device developed, the Basic and Advanced CVD Screening Kit may probably may be sold together with the mobile application between $30-40.

<table>
<thead>
<tr>
<th>Table 11.1: Primary Care Costs for CVD Risk Screening(^5)</th>
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<tr>
<td>Approximate Cost (USD)</td>
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<tr>
<td>Sphygmomanometer</td>
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<tr>
<td>Stethoscope</td>
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<tr>
<td>Urine Glucose and Albumin Test Strip</td>
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<td>Glucometer Device</td>
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<td>Glucometer Strips</td>
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<tr>
<td>Cholesterol Testing Device</td>
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<td>Cholesterol Testing Strip</td>
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The Basic CVD Screening Kit may be primarily used to train the lowest levels of health workers to use mobile phones i.e. the ASHA workers. The Basic CVD Screening Kit is very simple and measures key simple CVD health factors (Heart Rate, Breathing Rate and Heart Rate Variability). Abnormal values will be indicative of particularly serious cases and will be referred to higher levels of the healthcare system. However, this Basic CVD Screening Kit has very low risk assessment ability. The Advanced CVD Screening Kit with the \(PWV\) measurement device may be used by health workers who have been trained slightly more than ASHA workers, e.g. Aganwadi workers in the SHCs and the workers present in the PHCs and CHCs.

\(^4\)See Figure 10-5.

\(^5\)The approximate costs and usage rates stated here are estimated from various sources including [Mulligan et al., 2003, IndiaMart, 2017, Flipkart, 2017, NHS, 2009] and calculated with exchange rates on 30\(^{th}\) April 2017.
The Arterial Stiffness device in the Advanced CVD Screening Kit results in a measure of CVD risk. Current CVD risk Assessment in the SHCs and PHCs is performed with opportunistic measurements of BP (using a sphygmomanometer and stethoscope) and Glucose level to measure diabetes (using either urine Glucose colour strips or a Glucometer device with Glucometer strips which require a drop of blood). The hardware required to do this screening costs approximately $18-29 depending on which method is used to measure glucose. Then per patient there is a $0.15-0.20 strip cost. With more than 60 patients the costs of the current screening method would be equivalent to the proposed method. Considering that these devices have a life expectancy of between 3-5 years, there is no doubt that in the long term the proposed method, if the price estimate is in the correct range (or even too low), is cost-effective with respect to the current one. It offers a non-invasive, immediate, and simple method to measure CVD risk. The current method is invasive and complex since either urine or blood samples need to be taken and measuring Blood Pressure is not a simple task. The diagnosis of diabetes is very important because its progression often precedes CVD risk and because it leads to many complications (aside from CVD risk). It is therefore infeasible to propose that Glucose measurement be replaced by a Arterial Stiffness device in terms of Diabetes detection. Hence, the replacement of this device should be removed from the equation of cost-effectiveness of this device. Still, even if the Glucometer device is removed the remaining current cost of measuring Hypertension is approximately $18. This is possibly half of the cost of the new device however it is a holistically weak measure of CVD risk and a delicate one to measure as well. Furthermore, as mentioned earlier, sphygmomanometer require frequent calibration to maintain a precise measurement. The Arterial Stiffness device requires no calibration and is extremely simple to use hence very appealing to the lower primary care centres i.e. the SHCs and PHCs. It is probably unrealistic to replace all the sphygmomanometers with Arterial Stiffness Device as they are synonymous with health and there will definitely be some inertia holding back. However, this does not exclude that a NCD cell may decide to replace of few of them with the novel Arterial Stiffness device.

Overall, the Arterial Stiffness device has the potential to bring good CVD risk assessment down to the lower levels of primary healthcare. Currently only PHCs and above are allowed to administer CVD related drugs, although even SHCs are allowed to administer basic maternal and

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6Glucose measurement with blood is more accurate and precise
child health drugs and vaccinations. Bringing precise high risk CVD screening down to the lower health centres may also result in drugs being administered from these levels thus increasing diffusion.

At the CHC level of the healthcare structure primary care is advanced and there is a beginning of second care. At this level of healthcare delivery more blood tests are performed which both significantly improve CVD risk screening and cost as shown by the cost of measuring Cholesterol in Table 11.1. It is unforeseeable that the Arterial Stiffness device would replace the current devices used to measure CVD risk before high risk subjects are subjected to more advanced tests such as Echo-cardiography and ECG at CHCs. Blood test apparatus is valuable for a whole host of medical tests and the Arterial Stiffness device is not built to replace this. Nevertheless, preliminary screening may be significantly reduced in cost with the Arterial Stiffness device. Aside from cost, the Arterial Stiffness device may have a large impact on waiting times as it is much faster than having to wait for blood test results ecc. Because wait times can be very significant due to the lack of medical professionals this may be a very efficient method to reduce both costs and time as being able to only send people at high risk to the rest of the CVD risk assessment protocol by using a single measurement.

11.1.1 Conclusion

Overall, CVD Screening Kit may have a significant impact on the CVD risk screening capabilities at a range of healthcare centres, both public and private. The medical advantage is that the CVD Screening Kit measures an independent marker of CVD risk and therefore does not require a large array of other risk factor measurements to give a precise measure of risk, thus inherently reducing cost. Furthermore, it is non-invasive, easy to use and immediate. However, the whole discussion above and all these statements, need to be tested in the future, through a feasibility study and in depth market research. Nevertheless, the conclusion so far is that their is definitely potential for this CVD Screening Kit to have an impact and the best price estimate seems to be competitive with current solutions to CVD risk measurement.
11.2 The Impact of Mobile Phones on the Lives of Female Health Workers

The technology described in this thesis hinges on health workers possessing a mobile phone. In the past decade and a half mobile phones have had a large impact on how humans interact, communicate and access information all around the world. Who, twenty years ago, would have thought that sub-Saharan Africa would be at the forefront of mobile payments today? It is estimated that within similar developing countries 10 extra mobile phones per 100 inhabitants resulted in a 0.59\% increase in GDP between the years 1996 and 2003 [Lee, 2009]. The objective of this chapter is to understand the impact that mobile phones have once they have reached a health worker, who, in most cases in India, is a woman. Usefulness and impact of mobile phones in the health context will be briefly described, however, the main focus will be on the societal impact that the personal use of mobile phones has on female health workers.

In recent years, mHealth (Mobile Health) has spread incredibly around the world especially in projects which aim to improve the livelihoods of people in resource constrained environments. There have been many successful projects as well as certain failures. One of the main reasons why mHealth is attractive is because mobile phones are becoming extremely diffuse even in low-income areas and it seems natural to take advantage of the wide availability of these small, yet powerful, computers, to provide healthcare to people who are under-served by doctors and where the medical staff available has a very basic medical training.

The projects which employ mHealth are innumerable. In January 2016 the Indian Government started a nationwide mobile health program which aims to deliver mobile technology health tools to its front line health care workers [Foundation, 2016, BBC, 2015]. Federal State interest in mHealth is high and the Ministry of Health and Family Welfare recently compiled an on-line catalogue with recommended mHealth solutions [NHP, 2017]. At a State level, similar programs have already taken off and increasingly NGOs have started to use mobile health tools. Most notably, growing for-profit private initiatives that attempt to provide better quality healthcare in under-served areas, such as iKure, are also using mHealth as a key component of their healthcare delivery structure [iKure, 2017].
Stories of positive impact on healthcare care delivery are found worldwide. The first challenge that organisations face when implementing mHealth solutions is to teach the health workers how to use the mobile applications. This has proven difficult in some cases, however, there is clear evidence that with well designed applications and good training health workers may be taught to use these applications. These issues show that when designing the actual mobile application it’s of vital importance to work in close contact with the users. Furthermore, as mobile phones become more diffuse this barrier will reduce significantly. After successfully teaching health workers how to use these applications it is important to see the health impacts that these solutions have. An extensive systematic review on the literature performed by Braun et al. in 2013 showed mobile technology had good prospects to improve both the range and quality of services that health workers provide [Braun et al., 2013]. Large studies which involve mHealth projects with low skilled health workers have been successful; a study conducted by Diwan et al. collected syndromic surveillance data from 20,424 patients in rural India via a mobile application that low skilled health workers trained purposely to use for this project. The data had less under-reporting than government data [Diwan et al., 2015].

Direct interviews with the health workers involved in mHealth projects show that the impact that mHealth solutions go far beyond the medical health which they are providing. In a talk given to the MIT Tata Center students in 2017, the founder of iKure, Sujay Santra, talked about the great sense of pride that health workers in his program have about being able to help their community [iKure, 2017]. A health worker involved in an mHealth initiative in Bihar said about her mobile phone: I feel proud using this with women in my village. It increases my value in their eyes [Treatman et al., 2012]. In ‘Technology: The Emergence of a Hazardous Concept’, (1997), Leo Marx claims that technology is often seen as the single chief causative factor for modernisation and development. He is worried that this behaviour may lead to a neglect of moral and political standards in making key choices about the direction of society. Marx supports his thesis by claiming that society fails to view technology not only as a physical device, but also as an active component of the large complex social and institutional matrix of human life [Marx, 1997]. In the case of bringing a mobile phone to the hands of a female health worker it is important, for policy makers and society at large, to understand where they will play a role in the complex social matrix which constitutes human livelihood.
India is a very large country and generalisations about traditions and societal norms are weak representations of a rich and varied culture. The following observations are collected from a variety of sources and it is important to note that a wide spectrum, regarding each issue, may be observed in various locations in India. In many, and perhaps the most traditional areas of India, a patriarchal society is dominant. The effects of a male dominated society permeate through all age levels. India is one of the countries with the largest disparity between male and female newborns. Because of this sex-identification before marriage is illegal and punished by law. The male literacy rate from the 2011 census was 82.14% while the female one was 65.46%\(^7\) [indiafacts, 2011]. This is among the factors that results in only 27% of the Indian workforce being composed of women [Bellman and Malhotra, 2016]. This male dominance results in women having very little financial independence, are completely dependent on their husband and thus delegate significant household decision power. Furthermore, particularly in northern regions of India, women living in rural areas often marry with men from other villages causing significant loss of their known familial support system in the village of birth [Lee, 2009]. This also has an negative influence on the political and social say that a women has within her new village.

Disparities between men and women also extend to mobile phone use. 28% of women own mobile phones compared to 40% of men [Roy, 2012]. It is true that another 20% of women have access to a mobile phone through family or friends however this is not the same as owning one. Furthermore, internet access on mobile phones is also skewed towards men: 81% of men have access to internet while only 70% of women do [Bellman and Malhotra, 2016]. This disparity is due to various reasons. Many women cannot prove identity because they do not have a drivers licence, a utility bill or other documents without which it is impossible to buy a mobile service contract [Roy, 2012]. Some fathers do not let their daughters have mobile phones for fear that they will have a 'love marriage'. An extreme case of this behaviour happened in a village in Uttar Pradesh a few years ago where mobile phones were banned from unmarried women because of a few cases of elopement (NB: the ban did not extend to unmarried men) [Bellman and Malhotra, 2016].

May mobile phones be a catalyst for
the reduction of female/male disparities?

\(^7\)N.B. This significantly varies by State. For example, in Kerala both male and female literacy rates are north of 90% c.f. in Rajasthan the male literacy rate is country average while for females it is just above 50% [indiafacts, 2011]
Giving Mobile phones to health workers will not solve illiteracy, however, it may offer jobs to illiterate people. In fact, mobile phone applications have been developed that mostly work with audio messages without the need of much reading. A successful project in Uganda developed a mobile application with audio messages in the local dialect, images and diagrams which illiterate women were able to use. Obviously, only basic healthcare may be delivered in this way and this should not become a pretext to remain illiterate. However, by eliminating the need to fill paper forms, this technology has created a way by which even illiterate women may contribute to society; making them feel empowered by being part of the work force and helping them become financially independent [Vision, 2015, Lee, 2009]. Such technologies have also been deployed in India; in, Bihar, a region in northern India, an mHealth solution which requires minimal literacy level (it mainly plays back health information) has had a significant impact on helping young girls understand menstruation and practice good menstrual health [Treatman et al., 2012].

With good tools and well designed mobile applications health workers may definitely achieve much more in terms of healthcare support than if they did not have them. With mobile phones great amounts of information about diseases, and patients themselves may be stored digitally thus making them easily transferable to higher levels of healthcare, or used in hand-held symptom diagnostic algorithms. Moreover, data may be collected from external tools from varying manufacturers and similarly used. This means that women employed in these programs may have a significant impact and therefore are being hired by the government, NGOs and private organisations, there is no need (nor possibility) to employ a worker with higher skills. Overall, this gives a job opportunity to women which first of all means a start towards financial independence. Sujay Santra from iKure mentioned in a talk that with a little money at their disposal, the health workers in his program, are able to make some household decisions on their own as opposed to always relying on their husbands. Overall, this may hopefully lead to a stronger influence on house management and therefore reduce female/male disparity.

A paper published by Silva et al. in 2009 shows that mobile phone adoption is deeply dependent on how many people in a persons immediate surrounding have a mobile phone. Women who do not work as health workers nor own a mobile phone, if in contact with health workers with mobile phones may start to think about buying one themselves as they see the benefits of owning one. Many women in rural areas are self employed as artisans, for example in the batik print trade.
It has been shown that with mobile phones these women are able to circumvent the middle-man that usually sells their products. They are able to reduce information asymmetries to their advantage. Health workers who’s husbands do not own a mobile phone and work in farms may help them achieve similar results; knowledge of real crop prices in villages in Senegal via mobile phones has increased farmer profits dramatically [Rashid and Elder, 2009]. Furthermore, mobile phones may enable direct access to weather patterns which may further increase crop yields [Baird, 2016]. The effects of introducing mobile phones in a village via a health worker may potentially have radical effects on the economy of many other people in the village as they become more accustomed to this new tool.

Mobile phones have also had documented effects on marriage life. Especially in northern India many women leave their village of origin for marriage. In these areas land lines are often absent and mobile phones enable women to maintain there distant support groups which alleviates their loneliness and isolation. An Indian study by Dayoung Lee in 2009 found that mobile phones also significantly reduce cases of domestic violence on women, even more than having a better level of education [Lee, 2009]. This is a very positive effect that may derive from the social elevation acquired by the possession of a mobile phone, although, of course, it may derive from the fact that fairer husbands are both less likely to beat their wives and to more likely allow them to have a mobile phone.

Mobile phones enable women to be more independent and have a stronger voice within their community. An mHealth study in Bihar 85% of women participated felt more independent because of mobile phone ownership. Mobile phones enable women to create stronger social networks within their village and beyond which may help them find new jobs or find out interesting opportunities [Lee, 2009]. There are various groups that have started to promote local activism via the internet. CG Net is an audio based network initially developed by Microsoft in the Central Gondwana Region that gives a political activist voice to local communities which are otherwise completely isolated. All this emancipates women and gives them a voice on issues which they care about [Thies, 2017]. Overall, women health workers feel empowered and more credible within their society when using mobile phones to supply healthcare [Forum, 2013].

Many possible positive benefits of mobile phones on the livelihoods of women have been ex-
explored, they are not however a panacea for inequality and definitely will not solve issues over night, although they may definitely slowly help develop a society. Dayoung Lee showed that in India mobile phones have significantly reduced domestic violence, increased women’s autonomy in mobility and given economic independence. Nevertheless, issues such as child gender preference have not shown to improve yet. These deeper rooted social norms will take longer to eradicate however the emancipation of women will in the future hopefully lead to changes in this issues as well.

It is important to note that the vast majority of successful mHealth programs deal with maternal and child problems, meaning that health workers mostly interact with other women. In fact, a health worker quote mentioned earlier said that she feels proud of using her mHealth device with other women in her village, not men. Health workers have been mostly concerned with other women because of the prevalence of infectious diseases which affect maternity and their children. Now, with the advent of NCDs a different demographic will have to be looked after. Furthermore, in the age group before women start entering meno-pause, men are the most affected by CVDs (while later both are affected equally). This means that, in contrast to their routine work, health workers will potentially have to work with more men than women.

In an mHealth study in northern India in 2015, the authors of the study were initially concerned with the fact that women do not commonly interact with non-family men. They proposed that this could be potentially be solved via the female components of the patients family and in the study report no issues were reported. These concerns however raise important questions on implementation.

In the book *Geek Heresy*, Kentaro Toyama’s main thesis is that technology can only improve lives if the local populations behaviour dynamics are fully understood and the technology deployed accordingly [Toyama, 2015]. When the technology developed in this thesis is deployed for a feasibility study it will be vital to understand the relationship between the health worker and her patients works. It will be important to engage with both parties to have an understanding of how the device fits in the complex local social matrix which constitutes human livelihood. Furthermore, another relevant point that both Kentaro Toyama and his mentee Bill Thies both stress is that technologies can only amplify an underlying human behaviour: only if the health worker
scheme where an mHealth solution is itself healthy and solid will the device be able to thrive and create positive change [Thies, 2017]. It is therefore important that when selecting a location to perform a pilot study of this device that a good functioning health worker structure is chosen. The technology developed will unlikely be able to create change in a weak health worker structure. In fact in a study by De Renzi et al. it was described that mHealth tool worked well especially when the underlying healthcare structure was well managed [DeRenzi et al., 2011].

Overall, it is clear that when health workers start using mobile phones, initially given to them for work, for private use, they may have positive impact on the lives of these women. The phones may slowly act as a catalyst for change and emancipation. It is very important, for this to truly happen, that in a feasibility study (and further on if successful) to monitor both the medical impact and where mobile phones will fit in the social and institutional matrix of human livelihood. This will be invaluable to understand whether the project is successful as a medical device and at a social level.
The main objective of the project undertaken was to develop a Mobile CVD Screening Kit for resource constrained environments. In particular, for regions around the world that are facing an Epidemiological Transition towards higher Chronic Disease burden.

A CVD Screening Kit was developed with both a set of Basic Tools and Advanced Tools. The key element of the CVD Screening Kit, i.e. the Arterial Stiffness Device is potentially a very powerful tool as it may give low-skilled health workers the possibility of collecting very valuable data on a persons Arterial Health in the field, something that was previously only possible with large and costly hospital machines. Looking at the Heart Paradigm (Figure 12-1), the main focus of this thesis has been the analysis of the Vascular component of the heart because of its relevance to India.
Further work on this front is still needed before a finalised device is built and age specific standard measurement risk thresholds are developed. The second component of the CVD Screening Kit is the automated phonocardiography and is focused on the Mechanical component. This aspect of the project is at an earlier stage than the Arterial Stiffness Device and is an exciting project to move forwards.

The aim for the future of this project is to develop a comprehensive CVD Screening Kit accompanied by an ever evolving Mobile Application Suite. Moving forwards from the two main devices worked on, there are still many opportunities for more tools, or the augmentation of current tools, to provide a more holistic and complete CVD Screening Kit. Blood composition characteristics and maternal health applications, as well as tools that are currently being developed in the lab to assess heart Mechanical function, have already been discussed. Future advancements may be conceived in a similar way to the current tools, i.e. standalone devices that do not require expert interpretation, or for example, they may simply collect data that will then be sent to an expert for analysis. The Electrical component of the Heart Paradigm has so far been neglected in this thesis. The the most powerful tool to analyse the heart from this vantage point is the Electrocardiogram. An Electrocardiogram signal holds information about the electrical stimulation of the heart and also about past mild ischamias and changes in normal heart morphology such as heart hypertrophy. It may be relatively straightforward to attach conductors for a simple ECG measurement to the Arterial Stiffness Device and there have been successful implementations of automatic Electrocardiogram signal analysis algorithms. This will further expand the reach of the CVD Screening Kit.

There are many possible problematics with the implementation of the Mobile CVD Screening Kit developed that must be taken into account, aside from the technical issues which have been discussed. After risk measurement subjects have to comply to behaviour and drug regimen requirements for the screening to be actually effective. Behaviour change and drug intake compliance are two very hard problems which researchers in various domains have been trying to solve. Perhaps the knowledge of a personalised level of risk may nudge people into changing behaviour. Nevertheless, this remains a key possible problematic and how the risk measurement translates into a recommendation should in the future be well designed.
In India traditional medicine is still very much used and practised. In fact there is a Government Ministry of *AYUSH*, which deals with Ayurveda, Yoga, Naturopathy, Unani, Siddha and Homeopathy. There are certainly many truths in these ancient medical practices, reason why there is a government body which oversees their practice. However, there are certain issues which require allopathic medical attention and neither the people who are used to being treated with AYUSH medicine, nor the AYUSH practitioners, may be able realise when this is the case. While conducting medical studies in India, a patient arrived at the hospital in a dire state of severe heart failure and was fortunately saved. The doctors said that a day earlier the patient had gone to an Ayurvedic practitioner who had not noticed anything too worrisome. If the Ayurvedic practitioner had simply measured blood pressure he would have noticed that the patient was already in a critical state and the situation may have been handled in a simpler manner. The doctors said that these stories are not uncommon and not all end well. This shows that there may be some resistance with allopathic medicine and the fact that primary health workers have a simple tool to measure CVD risk is no guarantee that people will want to be tested, particularly because of the asymptomatic nature of Atherosclerosis. The AYUSH Ministry is not opposed to using technology and various AYUSH practices deal with feeling a patients pulse: in the practice of *Nadi-Pariksha* a patients wrist pulse is felt by the practitioner to assess health. There may therefore be ways of integrating the Arterial Stiffness Device with AYUSH practices. This will definitely broaden the scope of people that the device may screen.

Furthermore, resistance may also be met by Allopathic practitioners; the Arterial Stiffness Device developed may to some extent replace traditional Blood Pressure measurement\(^1\) and this may face some opposition. The Sphygmomanometer is synonymous with healthcare and both practitioners and patients may perhaps not feel comfortable if this device is not present.

Overall, the CVD Screening Kit designed in this thesis has shown to have potential to be developed further. Hopefully, with creative advances in both the technology and implementation strategies, the CVD Screening Kit will in the future be able to really help health workers screen for people at risk of CVD.

\(^1\)The Arterial Stiffness Device does not aim, nor is conceived, as a replacement to Blood Pressure measurement. However, there are situations, such as in the lowest primary care structures staffed with low-skilled personnel, where it may be better practice to use the Arterial Stiffness Device to assess risk.
Appendix A

A.1 Stethoscope Design


Figure A-2: Digital Stethoscope Assembled as in Figure A-1 with external Audio Jack
Figure A-3: Final Built Stethoscope
Bibliography


