Extracting Clinically-Actionable Information from Wearable Physiological Monitors.

by

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Abstract

In this thesis I examine several ways of extracting information from wearable monitors so as to help make clinical decisions. Wearable physiological sensors are developing rapidly, and pose a possible part of the solution to the demands of an aging population and rising health care costs. It is important that the data produced by such sensors be processed into information that is clinically relevant and will have an impact on the practice of medicine. I collected data in an ambulatory setting from several wearable physiological sensors, including electrocardiogram, arterial blood pressure, pulse plethysmograph, respiration and acceleration. Using this data set, I demonstrated a few approaches — including signal processing, and algorithms based on the application of physiological models — to extract clinically relevant information. These approaches are potentially of interest to both device makers interested in developing wearable monitors, and to clinicians who will be using such monitors in the future.
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Chapter 1

Introduction

This chapter puts forth the motivation for undertaking the study described in this thesis. I describe the goals of the project and the constraints on these goals. I then delineate my contributions specifically and give an outline of the document.

1.1 Motivation

Wearable medical monitors hold the promise of widespread use at low costs. Until now, such devices have been rudimentary and limited in their applications. Recent advances in integrated circuit technology have led to energy efficient, miniaturized devices suitable for long-term wearable use. Such technology has also led to lower costs, which is critical at the current time when concern for health care costs is rapidly growing. Despite being a possible inexpensive and ubiquitous solution for a variety of medical conditions, clinical adoption faces several challenges. Raw data from such devices may not be intuitive to a clinician and the large volume of data may render it useless. For example, most physicians do not look at the shape of blood pressure waveforms, but rather observe systolic, diastolic and mean values. It would also be impossible to fit a very long stretch of data into one plot and still be able to observe waveform shape. This work focuses on bridging the gap between the raw data recorded from wearable medical monitors and information provided to a clinician that can positively influence diagnosis and treatment of patients.
1.2 Scope of Project

The first step of this project was to collect data from a prototype cardiac monitoring device that includes a single-lead ECG and a 3-axis accelerometer. Additionally, a superset of physiologic data was collected with a variety of wearable and clinical sensors including an ECG, respiration, pulse plethysmograph and arterial blood pressure. It is reasonable to assume that such sensors could be packaged in a wearable form factor in the near future. The ultimate goal of such devices is to have them incorporated into routine clinical practice, so the data collected must be presented to clinicians in a way that they can act on. My task was to convert the raw data collected during our study into clinically relevant information.

1.3 Contributions

I started on this project designing the data collection setup and making arrangements at the Clinical Research Center at MIT where the experiments were conducted. I then supervised the data collection in conjunction with the study nurse and another member of our research group. I suggested modifications to improve the device software and protocol, ensuring higher quality data collection. I archived the data for processing and annotated much of it for further processing. I then sorted through the data and applied algorithms and models to derive clinically relevant information from the raw data.

1.4 Outline

The document starts with a background of physiology, technology for recording physiology (exercise physiology specifically) and what tests are used clinically. In Chapter 3, I explain the data collection setup and how the experiments were carried out. The data chapter (Chapter 4) provides an overview of the raw data to give an idea of what the different signals look like in a variety of subjects and during a variety of activities. Chapter 5 reviews what signal processing is commonly done on such signals and what
algorithms and models I used to extract information from our data. The discussion (Chapter 6) reviews the most important points covered in the document and provides an outlook of what the future may hold for wearable physiological monitoring devices.
Chapter 2

Background

2.1 Epidemiology of Cardiovascular Disease

According to the United States Centers for Disease Control (CDC), the top five causes of death in the United States for 2007 were [1]:

1. Heart disease: 616,067/year
2. Cancer: 562,875/year
4. Chronic lower respiratory diseases: 127,924/year
5. Accidents (unintentional injuries): 123,706/year

Heart disease and cancer are by far the leading causes of death. Of the two, heart disease is more manageable because it is confined to one organ system, has been studied for centuries, and many advances have been made in treatment [2]. Significant effort led to these new treatment efforts over the past several decades, including statins, antihypertensive agents, thrombolytic agents, agents for heart failure and antiarrhythmic agents [3]. Such treatments, coupled with improved prevention, are likely the reason for a steady decrease in the number of yearly deaths attributed to cardiovascular disease, as seen in Figure 2-1 [4]. It is also likely that such aggressive
Figure 2-1: Top causes of death in the US for 2007 as reported by the CDC. Note the log scale of the y-axis. Taken from [1].

Costly testing, hospitalization and treatments may be some of the reasons for the steady increase. For example, the CDC estimates that 6 million hospitalizations a year are due to cardiovascular diseases [6]. It is estimated that the total cost of heart disease has a price tag of $475 billion annually [7]. Though outcomes for heart disease are improving, the increasing costs are not sustainable, particularly given the aging U.S. demographics, and new solutions for diagnosing and managing these diseases must be found. Exercise, a healthy diet and not smoking are very low-cost solutions, and have been explored for decades [8]. Though such changes in lifestyle are important pieces of the solution, the data presented demonstrates the need for additional solutions.

It is also significant that the 3rd and 4th biggest killers are cerebrovascular disease and chronic lung disease. Cost of treatment of chronic lung disorders and hypertension follows just after heart conditions, cancer, trauma, and mental illness [9]. New solutions should also investigate ways to address these related problems.

Solutions need to reduce costs, must not impose a new burden on the time of the health care providers, must reach a broader population, and continue to improve patient outcomes. Cheaper technology, more efficient use of resources, and reduced
hospitalizations will all reduce costs. For example, it has been estimated that 1 in 10 hospitalizations is not necessary [10]. One challenge with monitoring cardiovascular and pulmonary conditions outside of a care setting, though, is that they often progress slowly and cannot be discovered early with a static view. Long-term wearable monitors pose one possible solution to reducing the cost of diagnosis and late-stage treatment by preventing people from having to come to the hospital while offering the hope of improved disease management and outcomes.

2.2 Cardiovascular Anatomy and Physiology

Anatomy is the study of the structure of living things. It involves studying static structures, including the examination of cadavers for human anatomy. Physiology is the study of the function of the body. Physiology is concerned with the behavior of specific parts of the body over time. Some quantities, such as internal temperature or blood pressure, are meaningful in as a single value taken at one time, but the vast majority of information is contained in the change of interacting variables over time. Physiology involves the identification of variables, the quantification of such variables, the recording of the values of those variables, and the relating of those variables to
Figure 2-3: Anatomy of the human heart. Taken from [11].

each other in a time dependent fashion to understand the mechanisms giving rise to the relationships among variables.

### 2.2.1 Cardiovascular Anatomy

#### Regions

The structure of the heart is shown in Figure 2-3 for reference. The heart is divided into four chambers, the two atria and the two ventricles. The atria receive blood from the periphery and propel it into the ventricles. The ventricles create the pressure for the blood to flow out of the heart. The heart is divided into the right and left heart, which pump blood to the lungs and the systemic circulation, respectively.

#### Valves

Just as there are four chambers in the heart, there are also four valves in the heart. The two atrioventricular (AV) valves open when the ventricular pressures drop below their respective atrial pressures so the atria can empty into the ventricles. The pulmonary and aortic valves prevent blood that has left the heart from leaking back into the ventricles. They open when the ventricular pressures rise above that of the
pulmonary artery and aorta, respectively, during contraction of the heart muscle.

**Blood circulation**

Blood enters the right atrium via the venae cavae and the coronary sinuses. From there it passes through the right AV (tricuspid) valve to the right ventricle. During ventricular contraction, it leaves the right ventricle through the open pulmonary valve and enters the pulmonary circulation via the pulmonary artery. In the lungs, the blood is oxygenated in the pulmonary capillaries. The oxygenated blood arrives back at the heart through the pulmonary vein, which empties into the left atrium. From the left atrium, blood passes through the left AV (bicuspid) valve and into the left ventricle. The left ventricle expels the blood from the heart through the aortic valve into the aorta and on to the coronary and systemic vasculature.

**Muscle force**

The myocardium, or muscle of the heart, is an involuntary muscle that contracts approximately once per second in the adult. The muscle wall in the atria is thinner than in the ventricles and only provide a small amount of pressure. Because the atria are situated above the ventricles, gravity and pressure differences provide most of the force needed to move blood into the ventricles, but the atria do contract to make sure the ventricles are filled. The right ventricular wall is smaller than the left as it only creates around 15 mmHg of pressure to send blood to the lungs. The left ventricle has much thicker walls to create the pressure (on the order of 100 mmHg) to send blood to the peripheral circulation.

**Electrical path**

The heart is an electromechanical coupling device, converting electrical energy into mechanical work. The sinoatrial (SA) node is located at the junction of the right atrium and the superior vena cava, and is the “pacemaker” of the heart. Normally, electrical impulses originate at the SA node and propagate in a highly organized fashion through the heart wall, or myocardium, to ensure synchronized mechanical
Conduction fibers travel throughout the walls of the atria and connect at the AV node. All electrical signals must go through this node, which is the only electrical coupling between the atria and the ventricles. The conduction fibers then travel down the septum (bundle of His - left and right bundle branches) between the ventricles and up the opposite sides of the ventricles, where they branch into the fine Perkinje fibers. Each impulse from the SA node leads to an atrial contraction, slows through the AV node, and then quickly depolarizes the ventricles to result in a coordinated contraction. See Figure 2-4 where the conduction system is shown in green. Following cardiac depolarization in each chamber, the chamber then repolarizes.

**Excitation-contraction coupling**

A sequence of events ensues at the cellular level to convert the electrical activation into mechanical force. The action potential arrives at the cell membrane and spreads to the interior, which increases the calcium conductance of special membrane channels.
Figure 2-5: Ion transport in cardiomyoctyes resulting in tension. The sequence of events that leads to tension is on the left with a diagram of the pathway on the right. Taken from [13].

and leads to an inward current of calcium ions. The subsequent increase in intracellular calcium concentration triggers the release of more calcium ions stored in the sarcoplasmic reticulum. The cytosolic calcium binds to troponin C which allows for the proteins actin and myosin to interact. According to the sliding filament theory, interdigitated protein filaments move relative to each other with one end of each filament anchored in place. Thick filaments, comprised of myosin, and thin filaments, comprised mostly of actin, slide along each other in opposite directions to produce tension. Calcium is not the only ion involved in the process, but the primary contributor. Figure 2-5 shows the detailed pathway that results in force generation. The balance of ions is returned to normal levels during repolarization.

2.2.2 Cardiovascular Physiology

Central component

The primary purpose of the cardiovascular system is to circulate blood to deliver nutrients and remove waste products. Cardiovascular physiology is therefore concerned with how the heart and circulation accomplish these goals. The heart operates by
contracting its muscle to create pressure in the ventricles of the heart. Pressurized blood then flows to regions of lower pressure, particularly the systemic circulation. The entire circulatory system therefore follows a pressure gradient from its peak pressure in the left ventricle, to lower pressure in the aorta to lower pressure in the arteries to the arterioles and so on, until the lowest pressure is achieved in the right atrium for a supine subject. The heart creates pressure by contracting, and then relaxes to prepare for the next contraction. These phases are termed systole and diastole, which together comprise one cardiac cycle or heart beat. One of the quantities of prime interest in this context is cardiac output, defined as the average volume of blood leaving the heart per unit time, typically calculated as liters/min. The cardiac output is determined by how often the heart can cycle (heart rate) and how much blood it can eject during each systole (stroke volume). The temporal profiles of key variables during the cardiac cycle are shown in Figure 2-6.

During diastole, the AV valves are open and blood empties from the atria to the ventricles. When the SA node fires, the atria contract to maximize the volume of blood in the ventricles. Towards the end of atrial contraction, the ventricles start to contract, closing the AV valves and opening the pulmonary and aortic valves when the ventricular pressures exceed that of the atria. At the end of systole, the ventricles relax. The pulmonary and aortic valves close and the ventricles further relax until the ventricular pressures are lower than that in the atria, at which point the AV valves open and blood begins to flow from the atria to the ventricles once more. Figure 2-7 shows the heart during diastole and systole with valve states and blood flow path. The ventricular pressure needs to be lower than the filling pressure for blood to fill the ventricle, but also greater than the aortic pressure to leave the left ventricle, so it ranges from 0 to around 120 mmHg.

**Peripheral component**

The relationship describing average blood flow through the peripheral circulation is

\[
Q = \frac{\Delta P}{R} \tag{2.1}
\]
where $\Delta P$ is the drop in pressure from the arterial to the venous side, and $R$ is the lumped (aggregate) resistance of the peripheral circulation. Equation 2.1 can also be applied to a local vascular segment. In this case, $\Delta P$ is the driving (perfusion) pressure of that vascular bed and $R$ is the local vascular resistance.

Not only do the various tissues of the body require different amounts of blood, they have time-varying blood requirements. During some activities, such as exercise, the proportions of blood going to various organs will need to change as compared to other activities. The cardiovascular system is beautifully designed to decouple the source from the periphery under normal physiologic conditions. Thus, local metabolic demands of tissue govern the local flow of blood by modulating the resistance in
Figure 2-7: Diagram of the heart during diastole and systole. The red arrows represent the flow of blood and the green lines represent the valves in the heart. Taken from [14].

Equation 2.1. Figure 2-8 shows a schematic of the circulatory system under resting conditions, with approximate percentages of blood divided amongst the various organ systems. The resistance of blood vessels is modulated by changing the diameter of the vessel in a nonlinear fashion as given by the Poiseuille equation:

\[ R = \frac{\eta L}{\pi r^4} \]  

where \( R \) is the resistance of the vessel, \( \eta \) is the viscosity of the fluid, \( L \) is the length of the vessel and \( r \) is the radius of the vessel. The Poiseuille equation only applies to laminar flow. Blood flow in the smaller vessels is generally laminar, but cannot be assumed to be at all locations [15]. The factors determining whether flow is laminar or not include the velocity of the fluid, the length of the vessel, the radius of the vessel, and the viscosity, which in blood is strongly dependent on the red blood cells. Although not strictly applicable to the cardiovascular (CV) system, the Poiseuille equation is still instructive as it shows the strong dependence of resistance on the vessel radius.

An additional property of the vasculature is the incremental compliance of the
vessel, which is defined as the change in volume for a given change in pressure:

$$C = \frac{\Delta V}{\Delta P}$$  \hspace{1cm} (2.3)

Compliance, the ability to store potential energy, is analogous to capacitance in an electrical circuit. The product of the resistance and the compliance is therefore a time constant for the energy stored in the elastic vessels of the circulatory system. The vast majority of the compliance can be found in the arteries and the vast majority of the resistance is in the arterioles.

### 2.3 Cardiovascular Control

The physiology described up to this point assumes an open loop system where the body is not receiving feedback to control the desired physiologic variables. In reality, the body does tightly control its internal environment, which is commonly referred
Figure 2-9: A basic control feedback block diagram. The setpoint for a given variable is the input on the left. The output tracks the setpoint as closely as possible given the constraints of the system.

2.3.1 Sensors

The primary variable of interest in the cardiovascular system is blood pressure. There are several ways this is measured in the body, with the predominant way being the baroreceptors [16]. In the wall of the carotid sinus and the aortic arch are stretch receptors, which indirectly sense pressure. When the pressure increases in the vessels and the walls are stretched, action potentials are fired in afferent nerves that connect with the brain stem. The carotid baroreceptors sense both increases and decreases in pressure, whereas those in the aortic arch primarily respond to increases. The baroreceptors are sensitive to the absolute value of pressure, but appear to be much more sensitive to changes in pressure and the rate of change of pressure.

Longer-term changes in blood pressure are sensed by the kidneys which are able to modulate a hormone response. Other sensors include the peripheral and central chemoreceptors, which are chemical sensors that sample the concentration of O$_2$ and CO$_2$. In the periphery they are located in the carotid bodies and the aortic bodies, where there is high blood flow. They primarily respond to decreases in partial
pressures of O₂ and increases in partial pressures of CO₂. In the brain, where the chemoreceptors are very sensitive, CO₂ is sensed by a change in pH.

2.3.2 Effectors

Sympathetic

The sympathetic system supports an enhanced response to stress, and counteracts the effects of the parasympathetic system, which works to keep the body at rest. In the sympathetic system, preganglionic neurons release acetylcholine, which stimulates postganglionic neurons to release epinephrine and norepinephrine, which in turn activate the effector mechanisms. These mechanisms include: an increased firing rate of the SA node, leading to increased heart rate; increased concentration of calcium ions in myocytes, leading to increased cardiac contractility; and increased smooth muscle contraction in the veins and arterioles, leading to increased venous tone and greater peripheral resistance. Other effects include dilated pupils, dilated bronchioles, and inhibited digestion.

In the cardiovascular system, the effectors above result in increased blood pressure and cardiac output. In the periphery, the increased resistance in the majority of arterioles results in a lower relative resistance in areas with higher metabolic demands, such as skeletal muscle or the brain, which leads to a proportionally greater blood flow to those areas. The sympathetic system has also been shown to contribute to a host of other reactions helping the body cope during exercise [17].

Parasympathetic

If the sympathetic system is thought of as the gas pedal of a car used to ramp up cardiac output, then it is necessary to have brakes when stopping sympathetic outflow is not sufficient. The parasympathetic system provides this action. In the parasympathetic system, acetylcholine is the primary neurotransmitter, interacting with muscarinic and nicotinic receptors to produce the effector mechanisms. The parasympathetic system primarily acts through stimulation from the vagus nerve,
Figure 2-10: Control feedback block diagram for the cardiovascular system. The control logic is housed in the brain stem where afferent fibers carry information from the sensors and efferent fibers carry information to the effector organs. Some effector mechanisms are shown in the green box and sensors in the blue box. Sample variables to control are blood pressure or cardiac output in the cardiovascular system and respiration rate in the cardiopulmonary system.

which has the opposite effect of what is described in the sympathetic section. Effects of the parasympathetic system include decreased heart rate and increased digestion.

**Balance**

In the past two decades, great emphasis has been spent trying to understand the autonomic control of the cardiovascular system. The prevailing hypothesis is that an imbalance of the sympathetic and parasympathetic responses leads to a greater risk of arrhythmias and sudden cardiac death, as demonstrated by direct recordings of vagal and sympathetic fibers [18]. It appears that vagal activation has an antifibrillatory effect, which has strong implications for risk assessment and implanting internal cardioverter defibrillators (ICDs) [19]. It has also been hypothesized that the degree of each response at rest can be used as an indication of cardiac health [20]. See Figure 2-10 for a simple block diagram of the feedback control of the cardiovascular system.

**2.3.3 Hormonal Feedback**

Nerves provide rapid feedback and modulate the cardiovascular system on short time scales. On longer time scales, chemical modulation can be used to regulate blood pressure. The Renin-Angiotensin II-Aldosterone System (RAAS) senses decreases in renal perfusion pressure, which then leads to the release of angiotensin II, which
results in increased thirst, increased peripheral resistance and sodium reabsorption, all of which help increase the arterial blood pressure.

2.3.4 Local Control

In addition to being controlled by the sympathetic system, the periphery can also be modulated on a local level. The prevailing hypothesis is that local metabolic demands control the resistance in local vessels. (Another hypothesis is that when smooth muscle is stretched, it contracts. This can explain how flow can remain constant with fluctuating blood pressure, but cannot explain active or reactive hyperemia.) Each organ reacts differently, but an increased local metabolic demand will translate into a decrease in resistance by decreasing smooth muscle tone via the nitrous oxide pathway, in order to increase blood flow.

2.3.5 Cardiopulmonary Coupling

This is an active area of research. It appears that there are incidental couplings that serve no apparent purpose, and intentional couplings that work together to ensure the delivery of oxygen and removal of carbon dioxide in the correct amounts to and from the body. It is possible that the mechanical couplings are not functional, such as sinus arrhythmia, which is the change in heart rate due to the change in thoracic pressure during breathing. On the other hand, there are working hypotheses that suggest the same neural source controls both systems to some degree, and that there is an ANS coupling.

Measurements of cardiac and respiratory functioning are connected by the fact that the impedance of the chest changes during respiration, which results in the modulation of the ECG signal.
2.4 Exercise Physiology

Some physiological variables are useful to analyze during a state of rest, but some information is much more revealing in the presence of a physiological stimulus. The study of the heart in a clinical setting has been extensive, especially the study of changes noted in a variety of illnesses. The vast majority of this information has been garnered from hospitalized patients, often in the supine position under tightly controlled circumstances. Much information can be obtained by testing how the cardiovascular system equilibrates at rest, however, further information can be obtained by probing the system during activity.

The most common clinical stress test is the exercise test. During such a test, the patient is monitored with various ECG leads while increasing the level of exercise. Subtle changes in the rate or morphology of the ECG in response to exercise allow cardiologists to diagnose a variety of disease conditions. Other tests have been validated, but are mostly used in research settings.

2.4.1 Physiological Response

It is clear that the increased metabolic demand of exercising skeletal muscle will require increased blood flow. The increased demands result in new setpoints in the control system, but the effectors and sensors remain the same. The literature explains some aspects of how this happens, but there is ample room for exploration. One challenge is that precise testing is hard to execute in exercise conditions, resulting in limited data.

Heart

The primary purpose of the heart is to pump blood through the body. The most valuable information in characterizing the performance of the heart is how much volume of blood is being pumped per unit time, which is known as cardiac output (CO) and is often reported in units of liters/min. The basic formula for calculating
cardiac output is:

\[ CO = HR \times SV \]  

(2.4)

where stroke volume (SV) is the volume of blood ejected from the heart during systole. The heart rate (HR) is largely governed by the sympathetic and parasympathetic branches of the nervous system which innervate the SA node in the heart. Their firing rate is determined by control logic in the brain, which uses several sensors in the body such as blood pressure and metabolic demand.

The stroke volume by definition is the difference between the end diastolic ventricular volume (EDVV) and the end systolic ventricular volume (ESVV). The ESVV is a function of the contractility of the ventricle, determined by the sympathetic tone and health of the myocardium, as well as the afterload, which is the arterial blood pressure that the heart has to pump against. The EDVV is a function of the compliance of the ventricle (which should not change significantly on short time scales) and the filling pressure, which relates directly to the total distending blood volume (TDBV) or the volume of stressed blood in circulation. TDBV is a function of total blood volume and venous tone.

To summarize, CO is the value that is of central interest in characterizing the heart, because it most directly relates the flow of oxygen and nutrients to metabolically active tissue. Several variables can be defined that contribute to CO, such as heart rate, filling pressure, contractility, and afterload.

The most apparent change during exercise is the increase in heart rate. Increased heart rate accounts for most of the increase in cardiac output, and has been shown to increase linearly with workload and oxygen uptake [21]. Stroke volume also increases, but only by 50% to 60% of normal resting stroke volume (whereas heart rate more than doubles). Research continues to examine how CO, HR and SV change during exercise, and how they depend on a variety of other variables such as age, gender, activity levels and smoking habits. For example, it has been demonstrated that heart rate during exercise decreases with age, but can be compensated by an increased stroke volume in healthy subjects [22].
As mentioned previously, stroke volume is modulated by filling pressure, contractility of the ventricles, and mean arterial pressure. Filling pressure is in part determined by intrathoracic pressure, which changes during the breath cycle, but is mostly modulated by changing blood volume and the venous tone. Blood volume changes as fluids are lost or consumed over a scale of minutes to hours. A change in venous tone results in a change of the total stressed blood volume in the circulation. An increased filling pressure will result in larger EDVV, thus increasing stroke volume.

Contractility can change by increasing or decreasing the tension generated by the myocardium. In conjunction with the afterload, contractility determines the end systolic volume. Although the cardiac output can increase by as much as 5-fold during activity, the mean ABP only increases slightly because of the large concomitant decrease in peripheral resistance. Measuring stroke volume in an exercising subject is a difficult task, and results are varied [23].

Another quantity that changes over longer periods of time is ventricular compliance. For example, as a result of hypertension, the myocardium may hypertrophy, resulting in a thickened left ventricular wall. Hypertrophy will decrease the compliance and therefore the EDVV, but the time scale is years.

**Periphery**

The entire peripheral system adjusts to accommodate exercise. Many organ systems such as the GI tract are less important during exercise, and blood flow to the gut is accordingly reduced during exercise. The skeletal and cardiac muscle on the other hand experience a large increase in blood flow. As mentioned previously, this is modulated by the local control of arteriolar diameter, and is the only acute response to exercise readily observed in the periphery. Long-term changes such as increased capillary density can have a significant effect. Damage to the cardiovascular system could manifest itself during exercise, but the mechanisms are diverse and not specific in their manifestations. It is therefore not likely possible to diagnose specific peripheral diseases with such data, but the data can still be useful in evaluating the vasculature.
response as a whole.

**Cardiac output function curves**

A convenient way of understanding what influences cardiac output, which is equal to venous return, is using cardiac and vascular function curves. The cardiac function curve shows how much blood the heart can pump and the vascular function curve shows how much blood can be returned through the vasculature to the heart. Both are plotted as a function of right atrial pressure. The actual cardiac output is the intersection of the two curves as seen in Figure 2-11. Each curve can change, resulting in a new cardiac output. When the cardiac contractility increases, a positive inotropic effect, the slope of the cardiac function increases and moves the intersection point higher. A change in the blood volume shifts the vascular function curve up or down, again resulting in a different intersection. Changes to TPR change both the cardiac function, as a result of a changed afterload, and the vascular function, as a result of changed flow to the veins. Figure 2-12 shows examples of how changes in the CV system result in CO changes.

### 2.5 Physiological Exercise Testing

Two significant advantages of exercise testing are the low cost and the ability to probe the system with external stimuli. There are two general goals with such tests, diagnostics and prognostics. For diagnostic purposes, several characteristics have been associated with certain conditions. For example, changes in the ST segment of the ECG are related to ischemia, which can be connected to coronary artery disease. The prognostic value of exercise tests is more subtle and less commonly used. Certain effects, like a delayed heart rate recovery, have been associated with a higher risk of mortality. While this may influence treatment, it does not necessarily give you information about what is wrong. It can also be used to evaluate damage following an event such as a myocardial infarction. A few conditions that can be evaluated with physiological testing (exercise and otherwise) include congestive heart failure,
Figure 2-11: The cardiac and vascular function curves provide insight into what determines cardiac output. The cardiac function curve is an indication of how fast and intensely the heart is beating. The other component affecting cardiac output is the amount of blood returned to the heart, or the venous return, which depends on the total distended blood volume. Taken from [16].

arrhythmias, respiratory disorders and sleep apnea.

2.5.1 ECG

The electrocardiogram (ECG or EKG) is a measurement of the voltages produced by the heart as measured at the surface of the body. Willem Einthoven demonstrated the first practical ECG measurement in 1903 and received the Nobel Prize in Medicine for it in 1927.

How it works

On a cellular level, each cell membrane has a transmembrane voltage based on the concentration of ions inside and outside of the cell, the ions of interest being sodium, potassium, calcium and to a smaller extent, chlorine. The cardiac muscle cells de-
polarize in the same manner as skeletal muscle, in that sodium channels open and sodium ions rush into the cell. This influx raises the resting membrane potential from around -85 mV to +40 mV. At the same time there are other slower ion channels whose conductance changes. The balance of the various ion channel conductances results in the shape of the action potential, which differs slightly depending on the location within the heart. Each action potential has five phases: a fast depolarization (0), a quick small repolarization (1), a plateau as the ion flows going in and out are

Figure 2-12: The above plots show what effects certain changes will have on the cardiac function and vascular function curves, which will change the cardiac output. Taken from [16].
equal (2), a repolarization tail (3), and a period of rest without activity (4). The phases are seen in Figure 2-13 with the approximate flux of ions.

![Cardiac Action Potential](image)

Figure 2-13: A cardiac action potential is shown with the five phases labeled and the associated exchange of ions across the cell membrane. Taken from [24].

The sum of all of these action potentials (time shifted according to where in the cardiac cycle they appear) is what the ECG is capturing as seen in Figure 2-14. In short, the ECG is the aggregate surface potential of all the depolarizations and repolarizations of all cells in the heart as they occur over the cardiac cycle. The features of the ECG occurring at specific times will therefore provide information about specific locations within the heart. Thus time points on the ECG encode for spatial regions in the heart. Boundaries are not always clearly defined because multiple areas may undergo depolarization or repolarization at the same time, resulting in overlap.

The utility of the ECG is enormous because the measurement reveals a great deal, yet is taken on the surface of the skin rather than needing direct access to the heart. The downside is that the electrical signal must travel through the tissue to the surface of the body, which attenuates and shapes the signal. The electrical propagation can be modeled using a current source inside a conducting medium, which for simplicity is modeled as a sphere of homogenous conductivity. The surface potential at a given
Figure 2-14: Action potentials at different locations in the heart and how they combine over the beat to result in the standard surface potential, which is the ECG. It can be seen that the electrical impulse travel slowly through the SA and AV nodes, distorting the shape of the template shown in Figure 2-13. Taken from [25].

location is given by the equation

\[ \Phi(R, \theta) = \frac{3M_0}{4\pi \sigma R^2} \cos \theta \]  

(2.5)

where \( M_0 \) is the current source, \( \sigma \) is the conductance of the torso, \( R \) is the distance from the source and \( \theta \) is the angle between the heart vector (which is the general direction of propagation of the action potential through the heart) and the lead vector (which is the line between the source and the observation point) [26]. The ECG measurement is the difference in potential between two such observation points. Equation 2.5 shows the importance of understanding what the ECG is when placing leads as
Figure 2-15: The basic ECG shape showing the P-wave, corresponding to depolarization of the atria; the QRS-complex, corresponding to the depolarization of the ventricles; and the T-wave, corresponding to the repolarization of the ventricles. Taken from [27].

the measured signal will depend strongly on placement.

Interpretation

Interpreting ECG waveforms involves examining the relative start time and shape of the various components: P-wave, QRS-complex and T-wave. These features are highlighted in Figure 2-15. Encoded in the shape is the magnitude and duration of each feature, which provides information about the conduction system. The presence of one feature without another may represent a block in conduction somewhere. A broadened feature may indicate slow conduction, such as when the signal travels through the normal myocardium in the ventricles instead of the Purkinje system. Sometimes the regular features might disappear altogether, as in ventricular fibrillation, when the normal conduction system is bypassed.
Clinical Relevance

The greatest clinical impact the ECG has had is detecting arrhythmias and extracting heart rate. There is a wide variety of arrhythmias that can be diagnosed by the trained eye looking at an ECG. Typically they can be characterized by location (the atria, the AV node and the ventricles), rate (bradycardia and tachycardia) and mechanism (ectopic). Premature contractions, tachycardia, flutter and fibrillation can take place in all chambers.

Some arrhythmias pose no risk to the patient, while others merit close watching even though nothing can immediately be done. Some arrhythmias, such as atrial fibrillation or serious tachycardias, can be treated with drugs or ablation. A propensity for a life-threatening arrhythmia such as ventricular fibrillation warrants implanting an ICD. A significant amount of effort has been invested in automatic detection of arrhythmias. For a more detailed treatment of specific arrhythmias see [26].

2.5.2 Respiration

There are various measurements of interest in the field of respiratory physiology. These measurements center around the volume of gas exchanged as well as the composition of the gas exhaled (composition of inspired gas changes relatively little and is not changed by physiology). The values can be examined per sample, per breath, or averaged. From waveform data, several key features can be extracted, such as tidal volume and respiration rate. Specific standard tests are used to extract other quantities, such as performing a complete inhalation/exhalation or forced exhaled vital capacity in one second (FEV₁).

The gas composition can be studied to analyze gas exchange at the level of the alveoli, but this should not change on a time scale of minutes to hours. Consequently percent composition of CO₂ can be used as an estimate of total volume expired.

Gas volume transfer is inherently a variable signal. Unlike the cardiovascular system which is regulated by the autonomic nervous system, the respiratory system can be overridden and controlled by the user; it does not necessarily have to follow
a periodic pattern as the electrical activity of the heart. It is therefore much more
difficult to distinguish between normal and disturbed breathing. Respiration rate is
derived from the volume exchange data and is therefore also an unsteady signal.

The most direct measurement of respiration is spirometry, which measures lung
function using a tube that the subject is required to blow on during exhalation. The
volume of the exhaled air can be measured in this way, or its composition can be
sampled. One challenge of spirometry is the cumbersome equipment, which is un-
comfortable and in some situations/environments impractical to use. Other methods
are available, such as measuring the expansion of the chest and abdominal cavities.
This option is attractive because of the ease of implementation. It is possible to cal-
ibrate such a measurement for accurate for volume, or simply possible to get relative
values from which respiration rate can be extracted.

2.5.3 Arterial Blood Pressure

Blood pressure, and specifically arterial blood pressure, is a key vital sign. The
heart acts as a pressure source, and there is a gradient of pressure throughout the
vasculature, from the aorta to the vena cava. Mean pressure is fairly constant in the
arteries, drops a little across the arterioles, and then drops significantly across the
capillaries, until it is close to atmospheric pressure in the veins. The value of greatest
interest is the arterial blood pressure (ABP). The systolic and diastolic values of
the arterial blood pressure are very easily determined using a pressure cuff and a
stethoscope. Disadvantages of this technique are that it is slow (10-20 seconds per
measurement) and only yields two values, the systolic and the diastolic pressures.

The most accurate way to measure ABP is by placing a pressure transducer di-
rectly in the radial or femoral artery as is done quite routinely in critical care settings.
This method will give a continuous waveform with time resolution dependent on the
sampling rate. The data is considered very reliable and can be high resolution. The
drawbacks of catheterization are pain, the need for trained personnel and restriction
of movement.

The one continuous-time noninvasive option that is available is a mix between the
preceding two. A small cuff is placed on the finger and its pressure is dynamically controlled pneumatically to maintain the volume of the cuff, so its pressure matches the pressure in the artery [28]. This option is not considered as accurate as a catheter, but is much easier to implement and can be portable.

2.5.4 Pulse Plethysmograph

Pulse plethysmography is a simple and elegant technology used ubiquitously in hospital settings. The sensor has two possible modes. The first uses two wavelengths of light to detect two different states of hemoglobin. When hemoglobin is completely bound to four oxygen molecules, one wavelength is more strongly absorbed. The other is absorbed when the hemoglobin is not bound to oxygen. The ratio of light absorbance through the finger at these two wavelengths provides an estimate of what percent of the possible amount of oxygen is present in the blood. This is referred to as pulse oximeter mode or spot oxygen saturation (SpO₂).

The second mode uses the fact the total incident light absorbed is a function of the volume of blood in the finger because blood strongly absorbs certain wavelengths. The waveform could then be used as an approximation for the ABP, but is not calibrated, as it depends on the compliance of the artery. This information can be used as an easy way to calculate heart rate.

2.5.5 Accelerometry

Accelerometers have made their way into everyone's pocket because they are inexpensive and can be placed in phones. Consequently they are inexpensive and easy to obtain. With an accelerometer, gravity must be taken into account; if one axis is directly facing away from the earth, that axis will read 1 G of acceleration. At a different angle there will be a trigonometric relationship with the angle between the accelerometer axis and gravity.
2.5.6 Stress Test Equipment

Other equipment commonly used for physiological testing is aimed at inducing a physiological response. This could be passive, such as a tilt table test, but more commonly it is an exercise test. A distinction should be made between isometric exercise and dynamic exercise. Isometric exercise involves minimal external movement, which increases the load on the left ventricle. Dynamic exercise is rhythmic muscular activity involving external movement. The motion in dynamic exercise is easier to translate into an estimated work load and is therefore preferred for testing. The disadvantage is that motion often is a source of noise in instrumentation.

The preferred methods of exercise in a controlled setting are cycling on a stationary bicycle or walking/running on a treadmill. The treadmill involves more muscle groups and subjects often perform slightly more work. It is also very simple to keep the exercise load constant by maintaining a constant speed on the treadmill. On a bicycle, pedaling speed is a large factor of workload and is controlled by the individual, thus varying over time. Another disadvantage of the bicycle is that individuals may be using upper body muscles, which would be undetected isometric exercise. The advantages of cycling include the individual’s upper body remaining still and the possibility of using a bicycle in the supine position for very unhealthy people. See [21] for more detailed information.

2.5.7 Protocols

Exercise protocols for cardiovascular testing were introduced as early as the 1950s for testing Air Force personnel [29]. Treadmill protocols are centered on speed and percent grade. Bicycle protocols can be estimated to achieve approximately the same level of energy expenditure. Some protocols fix the speed and only adjust the grade, while other protocols adjust both. The protocol introduced by Bruce in 1971 has remained the most popular, as indicated by surveys conducted in 1980 and 2000 [30, 31, 32]. Though these are still the most commonly used, it has recently been shown that smaller, more equal increments in workload are best [33]. Others have
concluded that the protocol should be tailored to the individual and the disease, but general guidelines recommend an 8-12 minute test duration [21].

Another approach is to ignore protocols and attempt to continuously ramp the workload to reach maximum oxygen uptake over a 10-minute time period. This approach is done by estimating the maximum, allowing the subject to warm up for one minute at a comfortable speed and then adjusting the speed and grade continuously until the maximum oxygen uptake (VO₂ max) is reach at the 10 minute mark.

It is also often useful to use the subject's perceived exertion. A Borg scale is from 6 to 20 and then converts to a 1 to 10 scale [34, 35]. This has strong limitations, but can be very convenient.

One recommendation for the postexercise period is to have subjects stand motionless for a few seconds after stopping exercise and then have the patient lie down. It has been shown that this can enhance ST-segment abnormalities instead of a cool down period [36].

2.5.8 Hypothesis

In our experiments we look at heart rate, mean blood pressure and pulse pressure. We also examine estimates of cardiac output and total peripheral resistance. In response to exercise, we would expect an exponential increase in cardiac output asymptotically approaching a steady state. Moderate exercise would likely result in a small and quick change, whereas a longer exercise period would result in an elevated and sustained cardiac output. We would also expect the total peripheral resistance to decrease according to the rate of increase of work load due to exercise.

Other maneuvers besides exercise also can provide valuable insight into cardiovascular control. For example the Valsalva maneuver is a common test that involves bearing down and increasing intrathoracic pressure for a period and then releasing. The increased pressure will decrease venous return and therefore reduce cardiac output. We would expect to see blood pressure drop and then, if the baroreceptors are working properly, an increase in heart rate to increase cardiac output. When pressure is released, venous return increases and consequently the cardiac output as well. The
increased pressure is sensed and the heart rate should drop.

Another easy maneuver is standing up. There is a sudden upward movement of the body against gravity, resulting in a decrease in venous return, causing blood pressure to drop. The pressure drop should be sensed by the baroreceptors, and sympathetic outflow should result in increased heart rate, cardiac output and TPR. The values will equilibrate at a steady state value if the subject remains standing.
Chapter 3

Prototype Device and Data Collection

We collected data from a prototype wearable cardiac monitor to evaluate performance and explore applications. We also collected other physiological signals from other wearable or potentially wearable devices to obtain a superset of physiological data that could be probed. In this chapter I will describe the experimental device in detail, as well as give an overview of the other equipment used. I will outline the process for obtaining approval for conducting the experiments and describe the documentation required. The next section details the protocol followed. The chapter ends by discussing some of the issues we faced with the prototype device and an outlook for future devices.

3.1 Wearable Cardiac Monitor

The wearable cardiac monitor evaluated in this thesis (Figure 3-1) was designed as a continuous, long-term, low-noise data recorder. The device is capable of recording single-lead electrocardiographic and 3-axis motion information continuously for up to two weeks.

It was designed in MIT’s Microsystems Technology Laboratories (MTL) by Eric Winokur in Prof. Charles Sodini’s group. The printed circuit board (PCB) was
fabricated by Advanced Circuits, Aurora, CO, and the electrical components were then put in place at MTL.

The device was designed in the shape of an 'L' on flexible PCB to capture different possible lead configurations. It is 10 cm long per side, with rounded corners, and weighs only 28 g. It is a light and somewhat adaptable device that can be worn directly on the chest using standard adhesion electrodes. It has five possible electrode sites to which disposable electrodes can be snapped in place. The sticky side of the electrode is then placed in direct contact with the skin, providing electrical contact and mechanical stability.

**Accelerometer**

The accelerometer sensor is an off-the-shelf component (ADXL345, Analog Devices, Cambridge, MA) which comes in a small (3 mm x 5 mm x 1 mm) plastic package with 14 leads that are soldered to the PCB. The sensor itself is a polysilicon structure suspended over the surface of a silicon wafer to provide resistance to force. A plate in the fixed plane and one in the moving structure are the two sides of a differential
capacitor. A schematic of this concept and the SEM of a similar device are seen in Figure 3-2. The device is capable of sensing +/- 8 G with 12-bit resolution, to give 4 mG's (1 G = 9.8 m/s²) per least significant bit (4 mG/LSB). It is an ultra-low current device, with current as low as 40 μA at a typical supply voltage of 2.5 V.

Figure 3-2: The upper diagram illustrates the principle behind a micromachined accelerometer in one axis. The fixed points are shown in green with black boxes around them. During acceleration, the beam (which is not fixed) moves and the fingers on the bottom move relative to each other, which movement can be measured as a change in capacitance. In the lower figure is an SEM of an Analog Devices ADXL202 showing the anchored points and the beam which is capable of moving. The smallest movement detectable is approximately 2pm. Images taken from [37].

**ECG**

The ECG sensor consists of 5 button connectors, an analog front end with configurable gain, and a ground drive circuit. The connectors were adapted from standard clinical
leads into which disposable snap electrodes directly connect. The ground drive circuit provides 0 to 2.7 V bias voltage and AC common mode rejection. Three of the five electrodes can be activated at one time, representing the ground, positive, and negative terminals. The configuration of the three can be set before starting data collection, but cannot be changed once it has started. See Figure 3-3 for a schematic of the ECG portion of the device.

![Figure 3-3](image-url)

Figure 3-3: The schematic of the monitor shows the three electrodes on the left along with the amplifier and common mode rejection. The MSP430 handles the analog-to-digital conversion and any digital signal processing. The data is stored in flash memory as seen on the right. Image taken from [38].

**Power management**

The power management circuit is simply a battery connected to off-the-shelf analog regulator circuits (TPS78227, TPS62200 - Texas Instruments, Dallas, TX). The circuit battery is a generic 4.2 V Lithium-Ion rechargeable battery. The power management maintains a constant 2.7 V for the rest of the components. The battery lasts approximately one month in data collection mode.

**Microcontroller**

The microcontroller is an off-the-shelf MSP430 processor from Texas Instruments. All of the analog-to-digital circuitry and a digital signal processing unit are on-board, which allows for real-time processing of data. Signal processing was not integrated
into the work of this thesis, but real-time algorithms can be implemented based on this thesis. The microcontroller communicates with all other circuitry on the PCB.

**Memory/USB**

The memory included on the device are five 64-megabit flash memory chips, for a total of 320 megabits. A USB communication adaptor (FT232RL - FTDI, Hillsboro, OR) connects to the microcontroller, allowing for configuration and transfer of data from the memory.

**Modes of operation**

Two modes of operation are possible: configuration and data collection. Both modes are accessed in software via the USB communication link. In configuration mode, a set of parameters, including electrode selection and gain level, are sent to the device. The data collection mode is started once the device is configured and only stops when the user requests the data that has been recorded. After the data collection has started, the device can be removed from the USB connector until the user wishes to download the data collected. At that point, the device will again need to be connected to a computer via the USB link. When connected to the communication link with the device powered off, the battery recharges.

**Placement**

Once the device is configured and data collection has started, it is ready to be attached to the subject. The electrodes are snapped onto the device and the plastic coating on each electrode removed to expose the sticky contact. All five electrodes are then snapped into place for greater mechanical stability, as opposed to only using electrodes for the three active locations (ground, negative and positive). The device can then be applied directly to the skin of the subject’s chest. Preparation of the skin may be desirable to enhance the signal quality, as described later. Care should be taken to place the device properly on the first try, as removal will leave adhesive residue. The electrodes should not be applied to the skin first, as alignment can then be difficult.
It is also more difficult to snap the electrodes into place since the human body will absorb a lot of the force used trying to press the device onto them.

Orientation on the chest will depend on the application, but standard lead configurations should be followed. The L-shape of the device allows for several different orientations, but the following principles should be kept in mind when selecting the orientation. The ground electrode provides a reference to be subtracted from the positive and negative terminals, and should be placed such that it will see approximately the same interfering variations as the positive and negative terminals (common mode rejection). One should keep in mind that the standard lead configurations have specific negative and positive terminal orientation. Getting the terminals backwards will lead to an inverted signal with reference to the standard configuration.

Safety

Care was taken in the design to prevent possible hazards to the subject. The device is flexible with rounded edges to prevent mechanical harm. The whole device is covered in a waterproof polymer coating to electrically isolate the electronics from the subject. Since the electrodes used have an impedance of approximately 100 kOhms, the maximum current that could possibly flow to the subject would be 27 μA, which is two orders of magnitude lower than what a human can perceive. The amount of power dissipated is 0.5 W/m² which is two orders of magnitude lower than the thermal energy that a human radiates. In summary, this is an extremely safe device for human subject use.

3.2 Equipment

3.2.1 Portapres

The arterial blood pressure (ABP) monitor used was a Portapres 152 (Finapres Medical Systems, Amsterdam, NL). This device is a non-invasive, portable device that estimates the continuous ABP waveform. A more accurate method to measure ABP
would be to place a catheter directly into a main artery that is connected to an external strain gauge, but this is very invasive and by the standards of non-critical care, would not be portable. Other cuff methods only give intermittent readings (1/min) and are cumbersome. The principle on which all Finapres systems are based is measuring the pressure required to maintain real-time control of the size of an artery [28, 39]. The finger is chosen as a convenient location to place a small cuff with a bladder that is capable of changing pressure rapidly via a pneumatic servo system. The cuff is also capable of measuring the relative blood volume in the finger via infrared plethysmography. A control feedback loop keeps the size of the artery constant, and the corresponding pressure of the cuff is the estimate of the pressure in the artery. Many studies have compared the accuracy of the Finapres device to other standard measurements such as intra-arterial recordings, with some varied results, but a survey of that literature showed that the measurement errors are statistically negligible [40, 41].

3.2.2 Pulse Plethysmograph

With a sensor placed on the finger, our Criticare 504-US (Criticare Systems Inc, Waukesha, WI) can measure the relative blood volume which correlates to diameter of the artery as well as oxygen saturation of the blood. The oxygen saturation changes by very small amounts in healthy adults (even during extended periods of breath-hold), and we therefore only recorded the pulse plethysmograph (PPG) waveform. Plethysmography is the measurement of the volume of an organ or tissue. Photoplethysmography is the use of infrared light to measure the relative volume of blood in arteries and arterioles by measuring the relative amount of light transmitted through the finger.

3.2.3 Clinical ECG

Tracing the ECG setup from the skin to the recorder, disposable 3M Red Dot multipurpose monitoring electrodes were used (medexsupply.com:3M-2560 - 3M, St Paul,
MN) with Welch Allyn ECG lead wires (medexsupply.com: WA-6200-05, Welch Allyn, Skaneateles, NY). The lead wires were connected to a common line which fed directly into the Criticare 504-US already mentioned, which has an input and output for ECG to simultaneously monitor along with PPG. The output from the unit was a single analog channel, and it appears that a bandpass filter is applied by the unit, with passband approximately 0.01-40 Hz, though exact specifications of the processing of the ECG signal are proprietary.

3.2.4 Respitrace

An Inductotrace System 10.9000 (Ambulatory Monitoring Inc., Ardsley, NY) was used to record the relative respiration waveform from the abdomen and the chest. The system consists of two elastic inductobands, an oscillator and a calibration unit. The bands are fabric with elastic inside to make them stretch, and a wire running through the fabric in a sinusoidal pattern. A cable clips onto the wires in the bands and connects to the oscillator. The oscillator provides a high frequency (300 kHz) AC current through the wire and measures voltage. If the inductance through the wires changes due to stretching of the wires, that is reflected as a change in the measured voltage. The calibration unit can be used with a spirometer to get an absolute measurement, but since we were only interested in tracking respiration rate, we did not calibrate our signal. Three channels can be collected: the abdomen, the chest and the sum of the two.

3.2.5 Data Recorder

An eight channel digital data recorder was used (RD135T, TEAC America, Montebello, CA) to convert the eight analog signals to digital, and then record them on digital tapes (Sony DDS3 125P and Maxell R-120DM). While using all eight channels, the default sampling rate is 12 kHz. Real-time visualization and control of the unit was achieved on a data collection laptop.
3.2.6 Additional Equipment

Two devices that did not contribute to the data, but were instrumental in collecting the data accurately were a time marker and signal generator. The time marker includes a switch and a voltage source such that when the custom-made switch is flipped, an analog pulse is generated. This signal can be used to mark events during experiments to easily find them in the data later. The signal generator was used to ensure data recording quality. With a 1 Hz input signal, it is possible to detect any data corruptions (drops or insertions) that are not exactly 1 s, and measure the length of such a corruption if it is less than 1 s.

3.3 COUHES Approval

The Committee On the Use of Humans as Experimental Subjects must give prior approval of any research at MIT involving the use of humans. This committee comprises physicians, professors, students, technicians, religious and community personnel who ensure that experiments comply with federal law and local ethics standards. The committee is updated on the status of the project, and all changes must be approved by the committee. A description of the three sections of the application is given below. See appendix A.1 for the application corresponding to the study presented in this thesis.

Basic Information

This section of the application focuses on the investigators involved in the study. The PI must be named along with brief qualifications for conducting the study. All other personnel involved must also be named and have completed the Human Subjects Training. Additional information that needs to be included are any collaborations, where the research will be conducted, and what the funding sources are.

Prof. George Verghese was the PI on the application, with several staff members and students included as personnel. The experiments were completed at the MIT Clinical Research Center and were funded by a gift from Texas Instruments.
Study information

The study section outlines the details of the study itself, starting with the purpose of the study and then the details of the protocol. A subsection entitled Drugs and Devices requires specific information on the use of drugs and experimental devices, as well as the use of radiation and diets in the study.

Our experiments include an investigational medical device, and one of the attachments provides a detailed description of the device, including safety considerations.

Human subjects

The third section is the longest and ensures that the study treats human subjects with care. The number of subjects projected and the age range of the population must be stated, along with any inclusion or exclusion criteria. If any vulnerable populations such as prisoners, employees, students, children, cognitively impaired or non-English speakers are included, justification must be made. Standard facts must be included such as how subjects will be compensated, what the potential risks are, and what the potential benefits are. There is a data handling section to ensure that privacy of subjects is maintained and the investigators must comply with all HIPAA regulations. Two very important sections are the adverse effects and informed consent. The former details how the investigators will detect and respond to any harm that happens to the study subjects. An informed consent document must be included exactly as it will be given to subjects to ensure that they know the details of the study and make a voluntary and informed decision about their participation.

We estimated 15 subjects ages 18-65 would be sufficient for a proof-of-concept study. Exclusions were based on health history (particularly cardiovascular diseases, surgeries or implants) and current health state (use of alcohol, pregnancy, sufficient sleep). We allowed the use of students because they represent healthy young adults who are ideal for this type of study. Our subjects were not compensated and were offered no direct benefits. Possible risks were outlined in detail, even though they were considered minimal. The types of data were delineated, along with how they
would be stored and secured. All our data was to be de-identified for processing. Precautions were taken to ensure no harm to subjects, and a method of contacting investigators after the study was put in place.

### 3.3.1 Accompanying Forms

In our application we also attached a description of the experimental device and the informed consent form. Also included was a questionnaire given to each subject to ascertain a healthy status at the time of the study.

### 3.3.2 Updates

Any changes to the application must be approved by COUHES prior to their implementation. This includes personnel changes; new personnel must provide documentation of having completed the human subjects training. Renewals must also be approved by the committee if the experiments extend beyond the original time period. All experimentation must stop until the renewal is approved by the committee. Our experiments extended beyond the original time frame and a renewal was approved. See appendix A.4 for the change of date request and appendix A.5 for the continuing review questionnaire required when continuing a protocol beyond the original end date.

### 3.4 Protocol

The process for collecting data includes recruiting subjects, consenting subjects, screening subjects, skin preparation, instrumentation, activities and follow-up.

#### 3.4.1 Recruiting

The initial subjects recruited were members of the lab. An advertisement approved by COUHES was placed around various locations on campus. Though approximately 10 people responded, not one of them successfully enrolled in the study. The primary
means of recruitment ended up being through the network of the investigators. The lack of compensation prevented a more general appeal. See appendix A.2 for the recruitment flyer.

3.4.2 Consent

Potential subjects were given a copy of the consent form prior to being consented, which allowed them to read it over carefully. The subjects were given a tour of the study setup if they desired and then reviewed the consent form and signed it with one of the PI's named on the COUHES application. Documentation was given to the CRC before any experiments started. See appendix A.3 for the consent form.

3.4.3 Screening Subjects

Before starting each of the experiments, the study nurse evaluated the health of each subject by taking vital signs. Each subject was also asked a series of questions to ascertain that they were in the proper physical and mental condition to undergo the testing, and that they knew what to expect during the testing.

3.4.4 Skin Preparation

One of the factors that can significantly affect the results of ECG measurements is the preparation of the skin directly under the electrodes. Hair and dead skin can add noise. Male subjects were given the option of shaving before the experiment, or the study nurse could shave a small patch on the chest with a disposable razor made for this purpose. The skin was then buffed with a rough pad to remove a layer of dead skin and encourage blood flow to the area. Finally, alcohol was used to clean the area and was allowed to dry. Effects of the preparation could include itchiness and discomfort for approximately one day, and was reduced by wearing loose clothing.

3.4.5 Instrumentation

After the skin preparation, the subject was instrumented in the following order.
Prototype device

Once the wearable device was switched to battery power, the memory registers of the device were cleared and the electrode configuration set with the custom software. The device was then removed from the USB cable, and the disposable electrodes were snapped into all five electrode locations. The sticky side of the electrodes was exposed by removing the plastic coverings, and the study nurse placed the device on the subject’s chest, with one side of the 'L' shape along the body’s long axis on the subject’s sternum, and with the other edge at a right angle above the left breast.

Clinical ECG

With the device in place, the disposable electrodes connected to the clinical leads were placed on the subject’s chest. They were placed with the ground electrode directly below the device in the center of the chest, the negative terminal placed directly to the left of the top left device electrode, and the positive terminal placed directly to the right of the top right device electrode. See Figure 3-4 for a picture of the prototype ECG device and the clinical ECG leads attached to a subject’s test. The ECG leads were then wrapped to the subject’s abdomen with Coban self-adherent wrap to prevent excessive movement. Once the ECG was in place, the subject was able to put on a shirt to wear throughout the experiment.

Figure 3-4: Wearable cardiac monitor and clinical ECG leads. On the left, the subject has only the wearable device connected via sticky electrodes under the device. On the right the clinical leads have been added in the same arrangement as the wearable device to give the same ECG lead projection.
Respitrace

The two bands were placed around the chest and the abdomen of the subject to fit snugly, but not tightly. The oscillator was then connected to the bands and fixed to the body with Coban wrap to minimize movement of the components.

PPG

The pulse plethysmograph sensor was placed on the index finger of the left hand. A piece of tape was placed around the sensor and finger to prevent the sensor from rotating while the subject was in motion.

Portapres

To reduce the load on the subject, the belt containing much of the electronics and the pneumatic pump was left on a cart close to the patient. The front-end unit was fixed to the left wrist of the subject with the velcro band attached. The sensor was then placed on the middle finger of the left hand and attached to the front-end unit. The sensor was placed snugly, but not tight enough to induce pain during the experiment. The Portapres was then initiated and calibrated. See Figure 3-5 for a picture of a fully-instrumented subject.

Sling

To keep the finger with the Portapres sensor close to the level of the heart, the subject’s arm was placed in a sling, with care taken not to put excessive pressure on the neck. The sling also served to prevent the subject’s arm from moving excessively, which would have introduced additional noise to the various instruments.

3.4.6 Activities

The subject was asked to engage in a series of activities, each of which was followed by a short rest period. The blood pressure signal was recalibrated after each activity.
Figure 3-5: The subject is wearing all physiological monitors. The PPG is on the index finger and the Portapres on the middle finger. The Respitrace bands are around the chest and abdomen. Underneath the subject’s shirt the wearable device and one of the clinical ECG electrodes are seen.

to ensure consistent accuracy. The subject performed the entire sequence of activities twice in a row, with each set of activities lasting approximately 40 minutes.

The subject was first asked to lie down on a bed in the CRC room in the supine position for 5 minutes. At the end of the 5 minutes the subject was helped into a sitting position on the edge of the bed for another 5 minutes. The subject was then helped to stand up for an additional 5 minutes. The subject was then asked to hop for 1 minute. This activity entailed repeatedly raising oneself on one’s toes, and leaving the ground only if the subject felt so inclined. After resting, the subject was asked to move their left shoulder to engage the chest muscles underneath the electrodes to stimulate muscle noise. The subject was then asked to perform a 10-second Valsalva maneuver, which involves holding one’s breath and straining to increase intrathoracic pressure.

At this point the subject was helped onto a treadmill and the speed was slowly increased to a comfortable walking pace. The speed for walking was usually around 2 mph. The subject was allowed to walk for up to 5 minutes, after which the speed was increased to a light run, typically around 4 mph. The subject was allowed to run for
up to 5 minutes, with the option of stopping at any time. At the end of running, the treadmill was stopped and the subject was allowed to recover for a couple of minutes. The last activity was to simulate stair climbing by repeatedly stepping onto and off the back of the treadmill for up to one minute.

After the subject had rested and any necessary adjustments were made, the set of activities was carried out one more time. A typical record from an experiment is seen in Appendix B.1.

3.4.7 Follow-Up

After the two rounds of activities were complete, the nurse once again took the vital signs of the subject to ensure recovery to normal values. The subject was questioned about the procedure and the device, and given the opportunity to privately share any concerns with the study nurse.

3.5 Experiments

Approval for the study was granted in the fall of 2009, but delays prevented setup until the spring of 2010. In March and April the clinical equipment was put in place and in May it was tested. From May to July the prototype device was tested and adjustments were made to the protocol to reduce noise. Starting in August, data was collected. Due to technical problems with the prototype device, the testing had to be suspended in October 2010.

3.5.1 Clinical Research Center (CRC)

The MIT CRC was established in 1967 with support from the NIH, to serve as a resource for non-clinical investigators to translate their research. The center provides the infrastructure including facilities, records and staff to support such research. We worked closely with Catherine Ricciardi R.N., to carry out the experiments. The center provided a controlled and safe environment for subjects to be instrumented
and perform simple activities.

3.5.2 Setup

As previously mentioned, the experiments were carried out at the CRC in a private room with a bed, a treadmill, and all of the instruments. All electrical equipment was placed on a portable cart. All sensors that need to be connected to control units and power were connected via cabling, and the cart could be moved to follow the subject. The cart was placed in between the bed and the treadmill on one side of the room, to minimize how much the subject had to move between activities. See Figure 3-6 for a picture of the setup in the CRC.

Figure 3-6: Experimental setup in the CRC. In the middle of the figure is the cart with all of the equipment for the physiological sensors and the data recording. In order from left to right, the ECG leads, finger plethysmograph, respiration bands and Finapres transducer are hanging from the pole. The bed on the right was used for resting in the supine position, and the treadmill on the left was used for walking and running.

3.5.3 Validation

Before starting experiments, it was important to evaluate the data from the various instruments and optimize performance. This process was much easier with the
commercial equipment. With the clinical ECG we experimented with various skin preparation techniques until we found the optimal noise reduction. The features of the ECG, including P-wave, QRS complex and T-wave, needed to be clearly visible, with minimal amounts of baseline drift and high frequency noise. During running we felt it sufficient to see the QRS complex. We also attached the ECG leads and the Respitrace oscillator to the body with Coban wrap after finding their movement induced noise and sometimes resulted in a loss of the signal. The key with the Respitrace signal was to see the peaks and valleys of breathing, to be able to estimate respiration rate. With the PPG we found that it was uncomfortable to have it taped tight, but no tape resulted in a noisy signal during movement. Our goal was to see the waveform shape, including the pulse reflection, during rest, and at least the peak during running. There was little to adjust for the Portapres, and we were pleased with the range of values it measured and the shape of peak, pulse reflection, and valley.

3.5.4 Data Archiving

The data from the clinical devices were recorded directly on digital tapes during experiments. After each experiment the data was read onto a PC, and the data from the device was also downloaded. The physical information sheets from the experiment were scanned and stored as a PDF. Each subject’s data was stored by medical record number, and no identifying information was kept outside the archive of the CRC. The raw data was digitally archived and also translated into easy-to-read MATLAB and WFDB formats.

3.6 Problems Solved

Issues that surfaced during experimentation included placement of the prototype device, insufficient amplitude resolution in the device ECG, and insufficient sampling rate of the accelerometer. By communicating with the device designers we were able to have modifications made and thus obtain significantly improved performance.
3.6.1 Device Placement

It was necessary to settle on an electrode configuration that would work for all subjects and be consistent throughout the experiments. The original idea had been to use a Lead II configuration to capture the P-wave better, but this would have meant that one side of the device would be aligned along the subject’s sternum while the other would run inferior to the subject’s left breast. This configuration would have potentially interfered with the anatomy and clothing of female subjects and was abandoned in favor of a Lead I configuration. To be consistent, the electrodes above the left breast were placed at the fourth intercostal space.

3.6.2 Insufficient ECG Resolution

The original amplitude resolution of the device had been set to 8 bits for convenient data storage. The A-D converter was capable of 12-bit representation. Due to the quantization noise seen in the data, the resolution was increased to 12 bits and the storage scheme changed to accommodate the increased data rate.

3.6.3 Insufficient Accelerometer Sampling Rate

The original sampling rate of the accelerometer was 2 Hz, which captured slow movements but was not high enough to capture quick movements, especially running on the treadmill. The low sampling rate made it possible to store longer stretches of data, but that was not necessary for this study. The rate was increased to 250 Hz to match that of the ECG, which also made alignment of the signals simpler.

3.6.4 Design Feedback

One convenient aspect of the non-commercial device was that we could share our findings directly with those developing the device, and they often were able to implement solutions. The shorter the time delay in this feedback loop, the quicker issues were resolved. I found that quick and accurate information passing was very effective, as
we often encountered problems the designers had not countered in their testing, and they found solutions to problems we did not realize we had.

3.7 Future Devices

The main problem with validating the data coming from the device was that one could not see the data in real-time. After recording the data, the only way to visualize it was to download them to a computer, which takes time. Further time is spent resetting the memory and restarting the device. So an experiment of 1 minute would have an overhead time of around 5 minutes. Robustness was also a big challenge, as our experiments wore down the devices and several had to be replaced.

3.7.1 No Feedback

One challenge was that when the prototype device was in operation, there was no feedback to the study personnel regarding whether or not the device was collecting data. The only way to determine whether data collection was proceeding properly was to try to download the data at the end of the experiment and look at it. Since the device was not designed to be particularly robust, it degraded over time. An LED was available on the device and was programmed to blink when the device was working properly. This did not give any information about the data; however, it did indicate that the device was recording data properly.

3.7.2 Robustness

As mentioned, the device was a prototype design and was not designed to be particularly robust. We discovered that normal handling of the device, particularly removing it from the subject, resulted in enough wear and tear for the device to fail over time. One hypothesis is that the ground drive circuit was too close to the edge of the device and solder connections eventually broke. The result was the data would get corrupted with 60 Hz noise, or the device would simply stop working. The problem
with the noisy data was that we could not assess data quality until the data had been downloaded at the end of an experiment.
Chapter 4

Data

4.1 Subject Population

Subjects were drawn entirely from an academic population. All 10 subjects were male; one female subject was tested, but the device failed and the data was not recovered. The majority of subjects were students in their twenties, with one outlier. The subjects were racially and physically diverse. All were in at least good health, with several subjects in excellent health. Table 4.1 shows the ages, health state, exercise level on a scale of 1-7 along with blood pressure and heart rate taken immediately before testing. All exhibited normal vital signs during screening. All subjects were informed prior to the experiments and freely consented according to IRB guidelines.

4.2 Data Representation Review

The “data deluge” is becoming a more common problem in medicine. The challenge is to take high dimensional data and long recordings, and represent it in a way that can be understood by the human mind. Typically the way such information is presented in the literature is in 2D tables or time series representations or well-established plots such as ROC curves or power spectra. The idea is to give a general feel for the data so that specific details of interest can be recognized and studied more closely.

Whether trying to condense data into something a doctor can use, or trying to
Table 4.1: Subject Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age</th>
<th>General Health</th>
<th>Ex. Level</th>
<th>Sys/Dia</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>11928</td>
<td>38</td>
<td>Excellent</td>
<td>4</td>
<td>118/76</td>
<td>64</td>
</tr>
<tr>
<td>14673</td>
<td>25</td>
<td>Excellent</td>
<td>6</td>
<td>114/62</td>
<td>68</td>
</tr>
<tr>
<td>14863</td>
<td>30</td>
<td>Excellent</td>
<td>?</td>
<td>122/78</td>
<td>72</td>
</tr>
<tr>
<td>14864</td>
<td>22</td>
<td>Excellent</td>
<td>4</td>
<td>118/60</td>
<td>72</td>
</tr>
<tr>
<td>14865</td>
<td>57</td>
<td>Good</td>
<td>3</td>
<td>112/70</td>
<td>72</td>
</tr>
<tr>
<td>14868</td>
<td>19</td>
<td>Excellent</td>
<td>4</td>
<td>104/60</td>
<td>58</td>
</tr>
<tr>
<td>14869</td>
<td>25</td>
<td>Excellent</td>
<td>?</td>
<td>112/76</td>
<td>70</td>
</tr>
<tr>
<td>14870</td>
<td>31</td>
<td>Good</td>
<td>4</td>
<td>128/68</td>
<td>72</td>
</tr>
<tr>
<td>14871</td>
<td>27</td>
<td>Excellent</td>
<td>4</td>
<td>104/60</td>
<td>52</td>
</tr>
<tr>
<td>14874</td>
<td>27</td>
<td>Excellent</td>
<td>4</td>
<td>104/60</td>
<td>56</td>
</tr>
</tbody>
</table>

include snapshots in a thesis, this is a difficult problem. Here I will give several snapshots that would not be practical in a medical setting. Summary statistics can be generated, but still only provide one angle of information.

4.3 Representative Data

All of the physiologic signals measured are periodic or quasi-periodic in nature. Each period can be examined individually to classify the shape of the beat in time or to extract specific features. One can look for changes from beat to beat, and also for what remains invariant. In this chapter there are several plots including a variety of signals from a variety of subjects performing various activities. Some specific things looked at are noise and patterns that depend on activity. The data is selected here to highlight different features that are significant.

4.3.1 ECG

All of the plots include two ECG recordings, one from the portable device (red) and one from the clinical device (blue). The magnitude of the red curve is accurate in mV on the scale, but the clinical magnitude could not be calculated in mV accurately. It is shifted up to display the two together.
Figure 4-1: The representation of the electrocardiogram during one heart beat shows the major features.

As mentioned in the background material in section 2.5.1, the shape of the ECG will depend on several factors, including equipment such as electrodes, placement of electrodes and electronics. Essentially the same electrodes and projections were used for both the portable and clinical devices, so the difference between the two should be largely due to the devices themselves.

The cartoon in Figure 4-1 shows the basic shape of an ECG, with the P-wave providing information about the atria, the QRS-complex providing information about the depolarization of the ventricles, and the T-wave providing information about the repolarization of the ventricles. The various segments and intervals are notable features giving insight into the circuitry of the heart. These features can be seen in most of the data below, though longer stretches, usually 20 seconds long, will be shown to demonstrate patterns.

The supine data in general was of excellent quality as seen in Figure 4-2. The largest source of noise while supine was 60 Hz noise that showed up strongly in the portable device because it did not have a good notch filter. It may have been that more 60 Hz interference was coupled into the body because the body was in contact with the bed over a large area. It is also likely that the equipment used for recording
Figure 4-2: These two figures demonstrate classic ECG waveforms representative of those obtained in the supine position, from the clinical device (blue) and the portable device (red).

was causing problems because it was around the same height as the bed and in close proximity to it. In general, this problem is very solvable, and applications where the subject is laying on their back should produce very clean data. It should be noted that the bottom two plots in Figure 4-3 are from the same subject. It was found that the prototype device was not very robust to noise, even within an experiment, which would be important in a final device.

Some of the data while sitting also had 60 Hz noise (see Figure 4-4), but most of it was also very clean. This data also could be useful since people spend much of their time sitting down. The standing data was similarly clean, except for brief stretches of noise as seen in Figure 4-5. This noise could be from muscle movement due to the subject shifting their weight, from talking or coughing, or something else.

The Valsalva maneuver is a simple, yet interesting test used to probe the autonomic nervous system. It involves straining, which requires muscle effort in the thoracic cavity, resulting in electrical activity in the chest which is picked up by the ECG. As opposed to the 60 Hz noise seen before, this muscle noise shows up in both the clinical ECG and the portable device. Though there is significant noise, the heart rate can often still be extracted. The saturations in the bottom right plot of Figure 4-6 may be due to loose electrodes.
Figure 4-3: All of the plots show the signal corrupted with 60 Hz noise much more pronounced in the portable device. The amount of noise varied widely between subjects and within a single subject’s record. It appears that, depending on the state of the prototype device, the proximity of our recording equipment, and position of the person, more or less noise was present. Note that the two bottom plots are from the same subject.
Figure 4-4: The 60 Hz noise sometimes showed up while sitting as seen in the start of the left plot, but this went away when the subject stood up. The majority of the data captured while sitting looks like that on the right.

Figure 4-5: The top plots are more typical and show classic ECGs, with little artifact. There was artifact, as noted in the bottom plots, which often had high frequency characteristics, likely muscle noise.
Figure 4-6: The Valsalva maneuver is important in cardiology, but can show up noisy on the ECG. Depending on the degree of straining, muscle noise is present as high frequency content. The bottom plots are quite corrupted with the bottom right plot having a major error in the portable device.
The hopping varied significantly between subjects. Some chose to rise up on their toes and some left the ground with decent force. The top plots of Figure 4-7 are unusually good and are likely the result of light hopping. The middle plots are typical, with baseline wander the result of tugging on the electrodes in the experimental device, but not in the clinical case where only lightweight wires were connected to the electrodes. The bottom right plot is a little perplexing and may be muscle noise.

The arm movement exercise also varied significantly among subjects. They were instructed to move their left arm to flex their chest muscles and add muscle noise. The top plots in Figure 4-8 show very clean results, which again may be because the subjects did not flex very strongly. The lower plots show the signature high frequency noise from muscles. It is possible to see how often the subjects were moving the muscle by noticing the periodic bursts. The baseline wander, which is especially noted in the bottom right, is likely the result of stress being put on the wires.

In general the ECGs taken during walking looked very good, as seen in the top row and bottom left plots in Figure 4-9. The bottom right had an unusually large amount of noise. The minimal amount of noise during walking is very encouraging because medium intensity exercise physiology tests can be performed with relatively little noise.

The typical running ECGs are seen in the top row of Figure 4-10. The middle row shows more baseline wander likely due to loose electrodes or perspiration. The bottom left plot shows a very noisy signal in the portable device. With filtering, it was usually possible to extract the heart rate, but there were some areas where this was not possible. The bottom right plot shows saturation, which occurred because of damage to the device during the experiment. Sometimes the device would recover, but again it showed the lack of robustness of the device.

The recovery period after exercise is very important because it provides insight into the autonomic cardiovascular physiology and is usually cleaner data than during activity. The data usually looked very good, but the most common problem was baseline wander, as seen in Figure 4-11, likely due to perspiration. In an adaptive filtering scheme it may be good to pay particular attention to baseline wander after
Figure 4-7: The plots represent the best (top row), typical (middle row) and worst (bottom row) ECGs during hopping. Noted in the typical data is that the clinical ECG performs better. It is likely that the mass of the device results in more force pulling on the electrodes, which leads to greater motion noise. The high frequency noise is likely muscle noise, which may vary according to the subject's body or the placement of the electrodes.
Figure 4-8: The plots represent the best (top row), typical (middle row) and worst (bottom row) ECGs during arm movement. The top plots are surprisingly clean while the middle plots show noise that is more expected – high frequency noise from the pectoralis and surrounding muscles picked up during each movement. The bottom row is of very poor quality; and it should be noted that the bottom right and middle right plots are from the same subject.
Figure 4-9: The ECG data during walking was generally very clean. The top plots and the bottom left show typical data, while the bottom right is an exception. The noise shows up in both devices, but is a little worse in the portable device. It may be that the subject held their trunk differently, so that muscle noise confounded the signal.
Figure 4-10: The top plots show representative data during running, the middle plots show noisier data, and the bottom plots are segments that are confounded by severe noise and artifact. There were some stretches like those on the bottom right that were unusable in one channel.
Figure 4-11: The recovery period after running was usually much cleaner than during running. Sometimes there was significant baseline wander, which may have been from loosening of the electrodes during running or the result of a poorer contact due to perspiration.

exercise to see if anything has changed with the electrode contact.

The stepping data overall looked very good (see Figure 4-12). Climbing stairs is a common daily activity, which could be good for stimulating cardiovascular physiology.

In general there were a few types of noise: baseline wander due to contact problems such as motion, loosening of electrodes, or perspiration; high frequency noise likely due to muscle motion underneath the electrodes; and 60 Hz noise, which can easily be mitigated through better filtering. The relatively low noise levels are very encouraging, given the physical activity taking place, and it should be possible to use the data to correlate cardiovascular changes with changes in activity.

It could clearly be seen that heart rate increased during periods of activity such as running. Something that is a little more subtle is the effect of breathing on the envelope of the ECG signal. Other changes may require longer stretches of data to extract the physiological importance.

4.3.2 Arterial Blood Pressure

The arterial blood pressure (ABP) waveform contains a wealth of information about cardiovascular state. Unfortunately it is difficult to measure, especially in an ambulatory environment. Each beat is less complicated than the ECG, as the pressure wave
Figure 4-12: The stepping data was usually a little noisier than the walking, but usually not nearly as bad as running.

only contains information from the left ventricular contraction and relaxation cycle. The basic waveform in one cycle can be seen in Figure 4-13. Although the shape alone is informative, the absolute values of the measurement are very important and the data presented is calibrated and displayed in units of mmHg.

The data collected is of the shape of the cartoon shown with variability in height of the reflected wave, which is sometimes completely absent. The majority of the time the ABP waveforms look like Figure 4-14 when the subject is not moving. There are occasional noisy segments, usually due to motion, as seen in Figure 4-15, but there were also areas of significant noise that were difficult to explain, as in Figure 4-16.

Physiologic variability is also an important factor. For example, Figure 4-17 shows two examples of significant physiologic variations probably due to the control system of the subject acting to control recovery from exercise. There is information in these variations that have been studied extensively with ECG, such as heart rate variability, but the relative difficulty of collecting ABP waveforms has limited the same kind of analysis with blood pressure signals.

During motion, the signal degrades somewhat. While walking, there is actually very little change in the structure and amount of noise (see Figure 4-18). There are interesting differences between the two subjects: though the heart rates of the two are very close, as well as the diastolic pressure, the systolic pressures differ by 40 mmHg.
Figure 4-13: A schematic representation of blood pressure during one heart beat. The minimum on the left is the diastolic value, which then rises quickly during systole until it reaches a maximum (systolic value). The smaller bump to the right is the reflection of the pressure wave.

Figure 4-14: On the left the subject is supine, with very periodic beats and a small reflected wave. The modulation on the envelope is likely due to breathing. On the right the subject is standing, with much more of a reflected wave noted, and a more variable baseline and pulse pressure. The majority of the data looks like the image on the right.
Figure 4-15: The noise in the left figure originates from movement of the sensor when the subject is moving their arm. The noise is within physiologic limits, but is obviously out of place and throws off the pulse pressure especially. On the right, during a Valsalva maneuver, the sensor stops working. It is not clear why, but it may have been the blood pressure dropping too low in a short period.

Figure 4-16: Sometimes the noise is hard to understand as it shows up in a relatively quiet period and doesn’t necessarily show up on the accelerometer as motion since the accelerometer is on the chest and the ABP transducer is on the finger. Sudden and short high frequency bursts may be a quick motion and the drop in all signal on the right may be when the sensors do not detect anything.
Figure 4-17: Illustrations of physiologic variability. The subject on the left had a peculiar heart beat pattern that varied significantly. This example shows the heart rate slowing down significantly in the middle, and both pulse pressure (i.e., systolic minus diastolic) pressure and mean blood pressure rising. On the right there is a lot of wander while the subject is recovering from running on the treadmill.

Figure 4-18: These plots of ABP during walking are very typical. There is some variation noted, but not a large amount of noise. The reflected wave can sometimes be noticed and is quite variable.
Figure 4-19: ABP during running. The top left figure shows a lot of variability and the top right shows less frequent, but greater variation. The source of each of these is uncertain, but important to recognize. The bottom plots exhibit less variability. It is noted that the reflected wave is often not visible.

Running changes the signal significantly, probably because of the tendency to swing one’s arms during running, which will change the pressure and add motion artifact (we tried to immobilize the arm with the transducer attached to it by placing the arm in a sling, but there was still some motion). The heart rate is clearly higher during running (Figure 4-19) and the reflected wave is often absent. There are noise sources and variations that are very peculiar and difficult to explain. It should be noted that subjects were running at different speeds and had different gaits, which would result in very different patterns. This variation is one of the challenges of measuring blood pressure at the finger. The majority of the noise likely came from moving the finger.
4.3.3 Respiration

Respiration is inherently a more variable signal because it is not as periodic as autonomically driven physiology. The respiratory system can operate automatically, but can also be overridden; there is no strict pattern. Also, breathing during speech is quite different than silent breathing. The non-periodicity makes it harder to interpret, and harder to derive quantities such as respiratory rate.

Respiratory rate can still be extracted with some degree of confidence. The depth of breathing may also be estimated by the amplitude of the signal. There is much to be learned from interpretation of the signal; it is just harder to do automatically.

A rather regular respiratory signal is seen on the left in Figure 4-20. Particularly during rest in the supine position, the signal was fairly periodic and stable. The amplitude corresponds to depth of breath and less regular breathing is noted on the right in Figure 4-20. The last breath on the right is a particularly deep breath. The amplitude is a relative value that depends strongly on body position. Figure 4-21 shows what effect a shift in body position has on the signal. Another interesting activity that shows up on the respiration is speech. It is possible to pick out intervals of speech, which have a distinctly linear characteristic, as seen in Figure 4-22.

With increased metabolic demands, the signal appeared to change more dynamically, as noted in Figures 4-23 and 4-24. It is also possible to see what activity the subject was engaged in based on the noise characteristics, but that was very device-dependent. During walking there are small deviations on top of the respiration signal and during running those deviations are much larger and more regular.

The device used was an older Inductotrace, with connectors that were susceptible to motion noise. For this reason the noise was particularly noted during running, and was very periodic. It was also noticed that in different positions, there were different contributions from the abdominal belt and the chest belt. For this reason, the sum of the two was used as a more consistent estimate of overall respiratory activity.

During increased metabolic demand, there will necessarily be an increase in oxygen needs. Increasing the flow of oxygen involves two mechanisms, namely increasing the
Figure 4-20: On the left is an example of quite regular and noise-free respiration. On the right is a much more typical recording with the subject taking irregular breaths of varied intensities, with the last breath being much deeper than the previous ones.

Figure 4-21: On the left the subject goes from standing up to a supine position. The ripple is the actual breathing signal, with the exponential decay of the local average being an artifact of the change in position and relative change in chest diameter. On the right the opposite is happening, when the subject goes from the supine position to sitting up.
Figure 4-22: The figure on the left shows periodic breathing with occasional interruptions that appear to be descending linearly. These regions correspond to talking, when the expelling of air may be more linearly controlled to maintain constant airflow. On the right is a more drastic example, with very quick breaths in and then linear regions corresponding to talking. This subject typically can talk for around 5 seconds before needing a breath.

Figure 4-23: On the left, the breathing rate is similar to that at rest, with fairly regular intervals, but more noise present due to the transducer. On the right, even more noise is present.
rate and the volume per breath. The respiration rate increases from 0.5 Hz in the supine case to 0.6-0.7 Hz during running. Though it is difficult to generalize the amplitude between subjects, it can be seen that during running there is also greater depth of breathing, resulting in more volume per breath.

4.3.4 PPG

Pulse plethysmography (PPG) is inherently a noisy signal; because of the optical components, it is very sensitive to motion. However, it is excellent for measuring heart rate, because only the maximum needs to be detected, and the implementation of hardware and software for this task is very straightforward. The pulse is seen in the dilation of the artery in the finger, as the pressure wave propagates and causes the blood vessel walls to expand. The little notch is the reflected wave, but is not always seen. The magnitude, frequency and morphology will all change, depending on the activity taking place. A very clean waveform is seen in Figure 4-25 on the left and a more typical waveform is on the right. More variation is noted in Figure 4-26 during standing and walking.

The most obvious noise is seen in Figure 4-27, where the signal in the plot on the right goes flat for a short period. This often happened during running, and may
Figure 4-25: PPG from two different sitting subjects. On the left the recording is very periodic, with little variation. On the right there is more variation, which is more typical, including change in baseline, amplitude, and height of the reflective notch.

Figure 4-26: The standing subject on the left shows a greater amount of variation, with little or no reflected wave detected. The heart rate is also greater than for the sitting subject in Figure 4-25. The figure on the right is very typical, with a little less variation in the amplitude, but showing variety in the notch during motion.
Figure 4-27: On the left the recording is typical of the PPG during running, with no notch noticeable and a fair amount of variation. On the right is significant variation, with some failure modes where the signal goes flat over time. This was not a rare occurrence during movement.

have been due to too much motion resulting in no signal from the transducer. The variation in height could be physiological or could be noise. The amplitude is not presented with units because a voltage is what is measured, which correlates with the volume of blood in the finger; the ordinate can be viewed as a rough estimate of artery diameter.

While sitting, the values approximately range from .25-.65 (there will be variation in between subjects) in arbitrary units. It appears that walking does not change the amplitude significantly, but during running the amplitude is much less, with the systolic value significantly lower and the diastolic value slightly higher. This corresponds well with the known fact that during exercise the resistance in worked muscles decreases, whereas in areas that do not require increased blood (and in particular the fingers, where the transducer is), the resistance is increased by decreasing the diameter of the arteries.

4.3.5 Accelerometers

The following plots show the 3-axis accelerometer data. In green is the y-axis (parallel to gravity), in brown the x-axis (perpendicular to gravity and in the plane of the chest), and in purple the z-axis (perpendicular to gravity and the plane of the chest).
Figure 4-28: This figure is a good example of a complete record of accelerometer data. The first transition is from standing to supine where the z-axis transitions from close to 0 G’s to almost 1 G. The values are very similar between sitting and standing, though the angle of the body may change slightly, accounting for the slight difference between the x and z axes. The solid regions of larger magnitude are oscillations packed closely. Note that there is always a 1 G gravity component present.

The data was originally sampled at 2 Hz with the first three subjects, to simply get an idea of body position. It was then switched to 250 Hz to match the ECG, in order to capture the details of movement like running. One thing to keep in mind is that gravity will always be present with a value of 1 G, though it may be distributed between the different axes with appropriate trigonometric terms. It should be kept in mind while interpreting the accelerometer data that they are indeed accelerations and not positions or velocities (which are perhaps more intuitive to conceptualize).

Figure 4-28 shows the three axes of the accelerometer over the complete set of all activities performed twice. The highest variation is seen in the axis parallel to gravity (green) because of the up and down motion during jumping and running. Figure 4-29 shows six other examples of complete accelerometer signals. The same basic pattern is followed, though the amplitude of variations differs from subject to subject as do noise levels. Figure 4-30 shows accelerometer signals for several different activities from the same subject, but is representative of all subjects tested.
Figure 4-29: The general pattern of the data is consistent across the subjects, though variations are noticeable. For example, 14673 bends over a little throughout the activities, especially hunching over while sitting. Subject 14869 on the other hand has very erect posture and exerted more effort during hopping. Subject 14870 exerted much more effort during the second time jumping. There were a few artifacts, such as the large deviations seen in 14869 and 14871. The large presence of the x and z axes in 14874 may have been a storage error.
Figure 4-30: The various activities are shown on shorter time scales in one subject. The transitions from standing to supine, supine to sitting and sitting to standing are all captured in the top left plot. Arm movement is seen in the top right, with little activity in the y-axis, and most in the x-axis. Hopping, middle left, shows most activity in the y-axis, with distinct spikes where the hop takes place, and with some other movement in between each hop. Walking, middle right, shows a pretty consistent pattern in each axis with the most interesting in the y-axis; there appears to be a bump with a sharp spike down interrupting it. Running, bottom left, has a much smoother shape because it is less complex in terms of specific impacts. Stepping, bottom right, is periodic, but has much less defined period shapes and a lot of variety.
4.4 Summary Statistics

Overall the quality of the data was impressive and could be used for extended analysis. It was also encouraging that many of the noise issues could be solved with better filtering and more robust designs. It could be expected that during periods of high activity the quality would go down, as was seen especially during running. It was noticed that during some activities like running, arm movement and recovery, there were specific failure modes that may possibly be addressed dynamically. In conclusion, the future is very promising for wearable physiologic signals.
Chapter 5

Analysis

This chapter will focus on three areas of signal analysis: signal processing, modeling and sensor fusion. I first review several signal processing techniques and some popular algorithms implemented for physiologic signals. One example of signal processing I explored was signal quality assessment. Regarding models, I review the Windkessel model which I applied to my data to estimate derived quantities that may be more relevant to clinical practice than raw data. Lastly I discuss sensor fusion, including how data from multiple sources can be represented together and how different sensors can increase the accuracy of derived quantities.

5.1 Signal Processing and Algorithms

Clinicians have traditionally looked at waveforms directly, but efficient algorithms and signal processing techniques have automated much of that work, and are even able to detect subtle changes the human eye is not able to. I will review here some common techniques and applications. ECG waveforms are perhaps the oldest and most commonly studied physiological waveforms that are processed, and much of the literature focuses on this signal. I will therefore focus on this specific measurement.
Filtering

Filtering is most commonly used as a pre-processing step to clean up data before applying other techniques like feature extraction or thresholding. It can be done as a batch process after data is collected, or in real time on microprocessors, a technology that has been implemented for use with the ECG for more than 25 years [42]. Removing noise can be done with standard FIR filters or with adaptive filters [43]. Kalman filtering is an example of computing the best estimate of noisy data [44]. A different application of filtering is to use filter banks to divide the signal into different frequency bands for detection of various characteristics [45]. Virtually all algorithms will include some form of filtering.

Transforms

Transforms are a powerful tool for representing data in different domains. The Hilbert transform for example can be used for QRS detection [46]. Another commonly used transform on which QRS-detection is based is the wavelet transform [47], [48]. Curve length transform is yet another transform used with QRS-detection [49]. The Fourier transform is used to visualize data in the frequency domain and is the most commonly used, with numerous applications.

Spectral Analysis

Examining physiological signals in the frequency domain can provide an important angle from which to examine data. One example is analyzing high frequency content for assessing risk of ventricular tachycardia [50]. This technique is commonly used in cardiovascular signals, with a large body of literature examining heart rate in the spectral domain [51] [52] [53].

Feature Extraction

With an ECG signal, feature extraction is used to find distinct repeating (or rare but relevant) morphological features, particularly the high frequency QRS complex,
to calculate heart rate [54]. More specific feature values can be extracted for more
detailed analysis and classification [55]. Features are typically extracted from the
time-domain signal, but can also be taken from other transform domains. Other
areas of application include the EEG, where features are not as distinct and research
on extraction is under development [56].

Algorithms

When a task is well-defined and its importance has been established, the problem
becomes algorithm development. New algorithms may involve techniques already
mentioned, or may lead to the creation of new techniques. QRS-detection is a promi-
nent example. The task is well-defined, with the input being the recording on one or
more ECG leads and the output being a series of event markers indicating the start
of the QRS complex. Several effective approaches with these inputs and outputs have
been implemented [57, 58]. A higher level approach in general is to combine various
algorithms in an attempt to increase accuracy [59].

A recent boost to signal processing in the physiological domain is the growth of
physiological data repositories such as the Physionet project [60]. By providing data,
algorithms can be tested and readily compared. Without such a resource, the data
collection and storage would be an enormous barrier to algorithm development.

5.2 Models and Estimation

Modeling is used to approximate physical behavior in a mathematically rigorous man-
ner. Such models provide insight into the dynamics of a system and allow for the
estimation or prediction of unknown variables. Such estimation is valuable when an
unknown variable is difficult or impossible to measure. An excellent example of the
advantage of estimation through modeling is the estimation of intra-cranial pressure
(ICP). Measuring ICP is very invasive and is only done in severe cases. By build-
ing a model based on variables that are much easier to measure, Kashif et al. have
demonstrated accurate estimation of ICP without using invasive methods [61]. In the
cardiovascular system, variables that are very difficult to measure, but provide intuitive information into the cardiovascular state of the patient are cardiac output (CO) and total peripheral resistance (TPR). Invasive methods are available for measuring CO accurately and are commonly used in critical care settings. There is no method available to measure TPR. This section explores model-based methods for estimating these two important variables non-invasively and in an ambulatory environment.

5.2.1 Windkessel

I use a very simple cardiovascular model, the Windkessel model. It is a three-element representation of the cardiovascular system using lumped components. The circuit equivalent is seen in Figure 5-1, with a current source representing the instantaneous CO, a linear capacitor representing the arterial compliance (AC), which stores energy with sufficient pressure, and a linear resistor for the total peripheral resistance (TPR), which is mainly comprised of the resistance of the arterioles. The arterial blood pressure (ABP) correlates to voltage in the electrical circuit.

![Figure 5-1: Circuit representation of the Windkessel model. CO - Cardiac Output, ABP - Arterial Blood Pressure, AC - Arterial Compliance, TPR - Total Peripheral Resistance.](image)

The differential equation relating the elements of the circuit is

\[
CO(t) = AC \ast \frac{dABP(t)}{dt} + \frac{ABP(t)}{TPR}
\]

(5.1)

where \(AC\) and \(TPR\) are assumed to be constant over time. Both \(ABP\) and \(CO\) have well known time-varying patterns as seen in Figure 5-2. It can be seen from the
ABP waveform that there is a reasonable approximation to a single exponential decay
during the transition from systole to diastole, which agrees well with Equation 5.1 for
any interval in which \( CO(t) = 0 \). The time constant of the system is \( \tau = TPR \times AC \).

![Graph showing arterial pressure and cardiac output profiles](image)

Figure 5-2: On the left is the profile of arterial pressure during one heart beat, and
on the right is the profile of cardiac output during one heart beat. It is noted that
the CO has a very steep rising slope and falls off with finite duration. Taken from
[62].

The CO waveform is a short pulse which rapidly increases with the onset of systole
and the opening of the aortic valve, has a short but finite duration, and drops back
down to zero when the aortic valve closes. The simplest way to model this behavior
is with an impulse of area equal to the stroke volume (SV), which is the area under
the \( CO(t) \) waveform in one beat. The main limitation of this approximation is that
the CO has finite width, and therefore some of the time dynamics of the CV system
will be compressed, but it is a relatively minor effect.

The AC term described above is the aggregate compliance of the arteries that the
blood leaving the heart sees. By definition, the compliance is the change in volume
per change in pressure, or in our case (under the impulsive approximation, which
implies all flow is absorbed by the compliance at the instant of ejection):

\[
AC = \frac{SV}{PP} \tag{5.2}
\]

Given the structure of the arteries, it is readily apparent that the assumption of a
linear compliance is open to challenge. The compliance will be determined by the
given volume in the vessel as well as the smooth muscle tone of the artery [63].
Also, the characteristics may not be constant. Despite these obvious limitations, it may be reasonable that the compliance is fairly linear over physiologically-relevant values and fairly constant over the time scale of our tests. Long-term changes in arterial compliance have been linked with age, exercise training and certain diseases [64][65][66]. Change in compliance is clearly an important topic, but not relevant on the timescale of hours or days which this work explores and is simply assumed to be constant.

The mean (as opposed to instantaneous) cardiac output is defined as the volume of blood exiting the heart in a given time period, or more specifically how much blood is ejected from the heart on each beat, multiplied by the number of beats per minute. We then arrive at the following equation (now and in all that follows we use CO to denote mean rather than instantaneous cardiac output):

\[ CO = AC * PP * HR \]  

Since \( AC \) is assumed to be relatively constant, the above equation shows that cardiac output is proportional to the product of pulse pressure and heart rate:

\[ CO \propto PP * HR \]  

Both pulse pressure and heart rate can be derived from the blood pressure waveform. HR can also be derived from the ECG and PPG waveforms. Equation 5.4 provides a very simple way to estimate (to within a scale factor) a difficult-to-measure but important and physiological value from two relatively accessible values.

Referring back to the Windkessel model, another valuable quantity can be estimated as well. The average of the voltage in the circuit over a heart beat can be divided by the average current to obtain the value of the resistor. TPR can then be estimated as

\[ TPR = meanABP/CO \]  

Since compliance is difficult to measure and we never calibrate, the cardiac output
estimate in Equation 5.4 has no physical units. The same is true for Equation 5.5 because CO is one of the terms. Values reported are therefore relative, and valuable over a subject’s record, but cannot necessarily be used to compare values among different subjects.

The main advantage of this estimation approach is its simplicity. Four values need to be extracted from each beat: the value of ABP at systole; the value of ABP at diastole; the mean ABP over the entire beat; and the distance between the same fiducial points on two consecutive beats, e.g., time of systole. With those data points, it is simply a matter of arithmetic operations to calculate CO and TPR. Such an approach could easily be implemented for execution in real-time with an on-board microprocessor. See 5-3 for two examples of such estimates.

5.2.2 Activity

Uptake of oxygen in the body is the best indication of metabolic needs and the load on the heart. Estimating this value has long been identified as important, but is a challenge. The most direct method is measuring chemical concentrations of air from the subject during exercise. This is a cumbersome method and a host of estimates have been developed. A convenient way to represent change in metabolic activity is with the unit MET, which is the body’s metabolic equivalent of power. One MET is equal to resting metabolic rate, which is approximately $3.5 \text{ O}_2/\text{kg/min}$. Less than 3 METs is considered light activity, 3-6 METs is medium, and more than 6 METs is vigorous [21]. A compendium of different activities has been compiled for quickly estimating the demands of a variety of activities, from running to yard work, an example of which is seen in Table 5.1 [67].

Accelerometers have long been seen as an attractive option for such estimations [68]. In 2000 an article examining differences between MET values and estimated METs from accelerometers showed discrepancies ranging from 30-60% [69]. Later studies showed that a tri-axial accelerometer matched reasonably well with doubly labeled water measurements [70]. It appears that accelerometers can be used for approximations of energy expenditure, but a single model has not been found to fit
Figure 5-3: Estimates of CO and TPR for two subjects. The CO is in blue, the TPR in green and the red will be explained in the next section. The plots exhibit some noise, but show consistency in responses, which held for all 10 subjects.

well with actual METs. Studies have turned to evaluating accuracy and applications with respect to specific populations, stratified by age, sex or medical condition [71, 72, 73, 74]. For other estimation techniques, see Ainslie et al. [75].
The interest of our study was not to track metabolic demand accurately, but to produce a general indicator of activity. In deciding how to represent activity, other variables besides the relationship with oxygen uptake should be considered, including necessary input variables and computational complexity. We decided on a very computationally simple method using only the data from the accelerometer. Additional information such as height, weight and gender could be useful, but was not incorporated. A more complicated approach would be to identify activities with the accelerometer and relate them to the compendium in Table 5.1. Then an adjustment could be made according to the energy in the accelerometer signal.

The physical activity (PA) estimation score used was the square root of the sum of the variances of each of the three axes of the accelerometer over a sliding window:

\[ PA = \sqrt{\sigma_x^2 + \sigma_y^2 + \sigma_z^2} \]  

(5.6)

with a window size of four seconds, and each window overlapping the next by one second. Aside from the computational simplicity, this measure carries physical units.
Figure 5-4: In color are the data from the 3-axis accelerometer over the course of one set of interventions. To aggregate this information into a single activity measure (plotted in black), we used the square root of the sum of the variances from each axis over a 4 second window.

of G's and excludes the gravity component, as long as body orientation does not change significantly over the window. The PA gives valuable insight into the relative load on a given subject over time, but cannot be confidently used to quantitatively compare activity across subjects.

5.2.3 Signal Quality Assessment

Background

Signal quality or its opposite, signal abnormality, are of interest in large data sets because they provide information on which parts of the data to examine. If the data is only noise, it should be ignored. Noiseless signals should be given substantial attention and need no filtering. Most data falls in between these extremes, and signal quality indicates to what extent. Previous methods have been based on how well different algorithms detect the same events [76] [77]. The key is identifying when the signals deviate from some normal. If noise sources are decoupled, shared information is physiologic and this approaches works well. Another approach is to examine when a waveform is likely not signal, based on its characteristics.
Signal Abnormality Index

I looked at deviations that were not physiologic by using the curve length transform (CLT) defined as

\[
CLT(w, i) = \sum_{k=i}^{i+w} \sqrt{\Delta t_k^2 + \Delta y_k^2},
\]

where \( w \) is the length of a sliding window, \( \Delta t_k \) is the time difference between consecutive data points and \( \Delta y_k \) is the difference in the magnitude between consecutive data points [49]. Using a window of appropriate length, the CLT was applied to the signal of choice. It can be assumed that physiological signals should be smooth and change on a relatively slow time scale, whereas noise will be higher frequency in nature, due to electronics or movement for example. The frequency of changes therefore indicates how likely the signal over a window is actually physiologic. The CLT can also pick up the magnitude of the deviations from a smooth signal. One advantage of this approach is its simplicity, involving only standard arithmetic operation. It could be run continuously and used to decide whether to store data or whether to filter or do further processing in real-time or decide what data to transmit. Figure 5-5 shows the relative noise level throughout the test for one subject, presented as a signal abnormality index.

5.3 Sensor Fusion

An area of physiological monitoring that has garnered increasing attention is that of combining information from multiple sensors to increase the usefulness of the data. Three examples of sensor fusion with our monitors and data are given.

5.3.1 Combining Multiple Signals

Traditionally the combination and evaluation of physiological signals has been left up to clinicians and researchers. For example, a physician will check vital signs, evaluating the values collectively and assessing the physiology based on his/her knowledge and experience. Such processing could be based on understanding of human physiol-
Figure 5-5: Signal abnormality in blue and physical activity in red. In general the quality of the signal degrades when the activity increases, but it can be seen that around 4700 s, corresponding to running on the treadmill the second time, the quality was poorer than the first time running on the treadmill, which started around 2000 s, even though the activity levels are comparable.

...ogy or simply pattern recognition. When working with a few values, this approach is efficient and tractable. When complexity reaches a certain point, however, it becomes too much for the mind to store and process. For example, physicians examine data instantaneously or in short stretches, but looking at an entire day or week of heart rate would not be practical. It has also been suggested that the mind can only process four variables at one time [78]. As data sets get larger and higher in dimensionality, it is increasingly less tractable for a clinician to process the information. There is much information in the relationships among the signals that is subtle. The number of relationships between variables is proportional to the square of the number of variables. It is only practical therefore that computers find more of the patterns and relationships among physiological variables.

From our data we had 8 signals: ECG on 2 devices, ABP, PPG, respiration, and 3 axes of acceleration. From these signals were derived several other values such as heart rate and respiration rate, as well as estimated values like CO, TPR, and PA. CO and TPR are a mix of information regarding heart rate and blood pressure. Our activity measure is a fusion of all 3 axes for a simpler representation. Plotting CO and PA together gives a good idea of how the heart is responding to an increased
workload. TPR and PA together give a good idea of how the vasculature responds to an increased workload. We reduced our data from several signals to two variables that are meaningful to examine in the context of cardiac monitoring. Figures 5-6, 5-7, 5-8, and 5-9 show CO, TPR, and PA all plotted together for a variety of subjects.

The data was remarkably consistent, showing strong responses, especially to running and vigorous jumping. The healthiest individuals showed rapid increases in CO and rapid decreases in TPR at the start of running. Most of the data was clear enough for interpretation, though when the device started to break down, the quality of the data was significantly reduced. The oldest subject showed slower dynamics; this aspect bears further study, as it may provide insight into the state of cardiac health of patients.

5.3.2 Redundancy

Many vital signs are not measured directly, but derived from other measurements. For example, heart rate is derived from ECG or PPG signals by looking for the repeated heart beat signatures and calculating HR based on the time interval between two successive beats. Uncertainty and inaccuracies arise from noise in the measured signal and from the algorithm utilized to extract features. Noise is typically mitigated by hardware design improvements or filtering. Algorithms typically fail to accurately detect a beat in the presence of noise. Failures include missed beats and misclassified beats, resulting in a heart rate that is too fast or too slow. Thresholds can be used to throw away outliers, but outliers can also be indications of real and problematic physiology.

Accurate information is very important in the context of false alarm reduction. Many alarms are based on thresholds that can easily be triggered by noise. One approach has been to increase the accuracy of algorithms, but there will always be noise an algorithm cannot handle and there will be sensors that fail. Fusion of signals to extract common information may reduce the need for further complicating algorithms and the need to constantly check false alarms.

I explored some ways of using redundant information in the measurements to
Subject 14865 was the oldest subject tested and showed a slower increase in CO, possibly reflecting a more mature heart as well as a slower autonomic response. The TPR also showed a slower response compared to the other subjects. Subject 11928 was a younger subject with quicker responses. The reason for the increases in CO become clear with the context of activity.
Figure 5-7: Subjects 14868 and 14869 show healthy responses, with rapid increases in CO at the onset of running. It is also noted that their CO levels remain generally higher during the second set of activities than during the first.

better estimate the calculated quantities. This approach works if noise in the different signals is decoupled or uncorrelated. For heart rate, our data indicates that the ECG and ABP noise are in fact sufficiently decoupled to allow improving accuracy
Figure 5-8: Subjects 14673 and 14870 have similar features to those in Figure 5-7. For subject 14673 the increase in PA during the jumping during the second set of activities. There is a corresponding increase in CO as expected.

significantly. The assumption is that when the values of beat intervals from two different sources differ greatly, one of the signals must be corrupted. In our case, the more physiologically viable option is chosen. If the two are close, the average
Figure 5-9: Subjects 14871 and 14874 exhibit noisier data than the previous subjects, likely because they were the last subjects tested and the device had degraded. The general responses are similar, but there are very noisy stretches. This ties into the discussion of when it is possible to trust data.

of the two is taken as the best estimate. This approach will fail only when the two signals deviate in the same way, in which case nothing can be done by this approach
to improve the signal. If both deviate, but by different amounts, we take the best of the two. One advantage of this approach with heart rate is that there are several physiological measurements from which it can be derived, so the accuracy will be improved with more signals such as ABP, PPG, and multiple leads of ECG if their noise sources are independent. Another example of redundancy could be improving our TPR estimate by looking at the pulse wave reflection in the ABP and PPG.

This approach is not new, but needs to be explored further and needs to find a greater clinical presence [76]. Similar models have been demonstrated in clinical settings, but we demonstrate it in an ambulatory setting where the need to mitigate noise is greater [79]. Figure 5-10 shows two examples of heart rate derived from ECG and ABP and heart rate estimated from the two signals.

5.3.3 Activity Triggered Snapshots

One major advantage of having accelerometer data is the context it provides for physiological changes. If an individual is wearing an ECG monitor and an HR spike is detected, it could be because of fear or exercise – those are two different physiological, despite some common manifestations. Similarly a sudden drop in blood pressure might be a concern, but not if it is known the person has just lain down. There is increasing interest in extracting information such as body position, activity level and adverse events such as falling from accelerometers [80]. As algorithms improve for such detection, information will be more accurate regarding movement of the body.

We looked at two different events and the accompanying physiology, one being the transition from supine position to being upright, and the other being recovery from activity. The first event is detected when the z-axis transitions from around 1 G for a period of time to 0 G and the y-axis transitions from 0 G to 1 G for a period of time. The corresponding physiological changes are plotted with enough time to see return to a steady state. If a person wore the device for a week, data would be recorder every day they got out of bed. The second event is detected when average activity level is above a certain threshold for a given time and transitions to below a lower threshold for another period of time. An example of such detection is seen in
Figure 5-10: The plots above show heart rate derived from ECG (blue) and ABP (black). Many deviations are seen where the heart rate suddenly drops or spikes. The bottom plots show the heart rate as estimated from the above data. Most of the large deviations have been removed. It is noted that two heart rate drops remain, around 1700 s and 4300 s. These are associated with Valsalva maneuvers and are in fact physiologic. A simple thresholding method would likely have removed these important data points.

Figure 5-11. The detection algorithm used is very basic, but worked well on the rest of the subjects. Figure 5-12 shows data from the first time arising from the supine position and data from recovery after exercise. ABP, CO and TPR waveforms are shown. As mentioned previously, an advantage of this approach is that snapshots that are useful distillations of the raw data can be presented to a clinician, to save time sifting through data or to save power by selective data transmission.
Figure 5-11: The PA is shown in red as has been displayed previously. The regions in time corresponding to getting up from a supine position (cyan) and recovery from exercise (black) are marked.
Figure 5-12: The plots above correspond to arising from a supine position and the plots below correspond to recovery from exercise. The plots on the left show ABP waveforms and the plots on the right show CO (blue) and TPR (green). These short data stretches (three minutes) provide key information that can be detected automatically as opposed to providing a clinician with an entire data set.
Chapter 6

Discussion and Outlook

6.1 Clinical Relevance

Up to this point wearable sensors have not made their way into everyday medicine, but have vast potential. We have presented results showing the possibility of estimating important quantities such as CO, TPR, and PA from data collected with wearable and portable sensors. Though not free of noise, the data shows clear patterns that can be explained by the underlying cardiovascular physiology. By using known physiology, we leverage the data we collect from wearable sensors and produce estimates that can be clinically relevant. We recognize the need for further development in several areas of this research.

With wearable devices being deployed in everyday settings and collecting large volumes of data, the paradigm for diagnostic and monitoring medical sensors will necessarily shift. It will be critical to present clean data to end-users, or at least methods for locating clean portions of data, as we have described. It is very likely that interpretation of such data will be based on established knowledge and validated models as opposed to pattern recognition and statistical methods alone. We believe that various cardiovascular conditions will be manifest in the estimates we have described. From a devices perspective, it is not unreasonable to think that future wearable sensors will include ECG, acceleration and ABP.

In research settings, many heart health scores have been proposed for risk strati-
fication. Examples include maximum exercise capacity, heart rate variability (HRV), heart rate recovery (HRR), and morphological variability [81, 82, 83, 84]. Significant correlations with mortality have been demonstrated in these cases, but the underlying mechanisms are generally still not well understood. The prevailing theory is that HRV and HRR can be used to estimate the performance of the autonomic response system [85]. Though HRV has been studied for decades and has promise, it has not found its way into the clinic. By reporting to physicians quantities that they are familiar working with, we increase the likelihood that they incorporate the information into their practice.

This approach is particularly attractive because it is not clinically disruptive. It is very difficult to change established practice in medicine; by introducing radical changes that disrupt work flow or add overhead in terms of money and time to the physician, they are much less likely to be adopted. We report quantities that are intuitive for physicians and can be absorbed quickly, using plots such as those we have shown.

Future work with this data will continue to focus on reducing the dimensionality of the data to provide clinically relevant information. It is also recognized that the data set used is limited in size, and larger data sets will be necessary to properly analyze these techniques.

6.2 Usage Models

Several usage models have been put forth, and we would like to clarify where we see the potential for impact. Principles of usage include minimal physician interaction, minimal data for a physician to review, and maximum positive predictive value. Home monitoring of those with heart conditions or those over a certain age would be ideal if the devices were cost-effective and easy to use. By doing a test over several days once a year, the physician could gather some statistics on the patient’s cardiac health. This would allow the physician to notice any changes from baseline over time. This usage model would require some scores for evaluating CO and TPR during exercise,
standing up or similar routine activities. Providing physicians with a few scores and plots would allow them to easily track patients from year to year to notice any change.

Another usage model would be for continuous monitoring such as in nursing homes. If a patient who was at high risk for an acute adverse heart event could continually wear a monitor, progress could be monitored on a time scale of weeks to watch for any warning signs. Research in this area is just starting, as extended wear sensors are being made more generally available.

A related area might be monitoring of low-risk hospital patients during their stay. Currently high risk patients can be relocated to the ICU where they are intensely monitored. Lower-risk patients might wear a pulse oximeter and have their vital signs taken on a schedule, but with inexpensive wearable monitors that process data in real-time, it might be easier to simply put one on every patient.

Another application space that has not been explored very much is world health. This application is particularly interesting because of the constraints of limited physicians and battery power. It would therefore be very useful to collect data in a portable setting, do some pre-processing, and transmit important information to a remote physician who could then make an assessment to be transmitted back. The biggest challenge may be that the market will have a hard time driving such a technology in a resource-poor setting.

6.3 To Device Makers

Through the experience of collecting data we were able to provide some feedback to the makers of the prototype device, and this can be generalized to a broader wearable medical device set of applications. The single most important factor when human testing is in the development loop is to do everything possible to shorten the development cycle. This has application to the development of the device, the protocol or the data analysis. Decreasing the feedback time dramatically decreases the development time. For example, when it took a long time to get data from the device, it was very hard to modify our protocol to get the cleanest data. When the
delay is reduced, the optimization can converge quickly and be useful. Time is also one of the huge advantages of on-board processing. When the processed data can be examined quickly, modifications can be made quickly to converge on solutions.

Another item is to have a set of usage models in mind to help drive testing. It is also extremely important to think about how well a device and data will be received by the medical community. A device will make no difference if it does not make it into the clinic; it must be attractive for adoption by clinicians.

6.4 To Clinicians

By participating in the development process we came to appreciate some of the challenges in developing such a device. First, it takes time to develop a device, and physicians would like things to get to them sooner. We are also aware that physicians time is very constrained and valuable. Given these constraints, I believe the key is that device makers need real feedback, not just what they think physicians will want.

Having collected some data and represented it, this should give a flavor of the idea of what can be done. Clinicians need to be willing to test new devices and provide feedback. Collaboration with designers is key.
Appendix A

COUHES Forms

A.1 Application

<table>
<thead>
<tr>
<th>Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects</th>
<th>Application # (assigned by COUHES)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>00090034</td>
<td>09/18/99</td>
</tr>
</tbody>
</table>

APPLICATION FOR APPROVAL TO USE HUMANS AS EXPERIMENTAL SUBJECTS (STANDARD FORM)

Please answer every question. Positive answers should be amplified with details. You must mark N/A where the question does not pertain to your application. Any incomplete application will be rejected and returned for completion. A completed CHECKLIST FOR STANDARD APPLICATION FORM must accompany this application.

I. BASIC INFORMATION

1. Title of Study
   Evaluation of a Wearable Wireless Cardiac Monitor

2. Principal Investigator
   Name: George C. Verghese
   Building and Room #: 10-140K
   Title: Professor of Electrical Engineering
   Email: verghese@mit.edu
   Department: EESCS
   Phone: 617-253-4212

3. Study Personnel
   All key personnel, including the PI, must be listed below, with a brief statement of qualifications and study role(s).
   Important Note: all key personnel are required to complete Human Subject training before work begins on the project.

<table>
<thead>
<tr>
<th>Investigator and Other Personnel [and Institution(s)]:</th>
<th>Qualifications: Describe briefly</th>
<th>Study role(s): (Check box to the right if person will be obtaining consent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Verghese, PhD</td>
<td>Signal processing, control theory</td>
<td>Principal investigator</td>
</tr>
<tr>
<td>Thomas Heldt, PhD</td>
<td>Medical engineering, signal processing, study design</td>
<td>Principal study coordinator</td>
</tr>
</tbody>
</table>

see Attachment I for list of further study personnel

4. Collaborating Institutions: If you are collaborating with another institution(s), then you must obtain approval from that institution’s institutional review board, and forward copies of the approval to COUHES.
   None

1 MIT key personnel: Individuals who contribute in a substantive way to the execution and monitoring of the study at or on behalf of MIT or affiliated institutions. Typically, these individuals have doctoral or other professional degrees, although other individuals may be included. In particular, investigator and staff involved in obtaining informed consent are considered key personnel.

APPLICATION FOR APPROVAL TO USE HUMANS AS EXPERIMENTAL SUBJECTS (STANDARD FORM) - revised 6/20/2009 - 1 -
5. Location of Research. If at MIT please indicate where on campus. If you plan to use the facilities of the Clinical Research Center you will need to obtain the approval of the CRC Advisory Committee. You may use this form for simultaneous submission to the CRC Advisory Committee.

MIT General Clinical Research Center

6. Funding. If the research is funded by an outside sponsor, please enclose one copy of the research proposal with your application. A draft of the research proposal is acceptable.

<table>
<thead>
<tr>
<th>A. Type of funding</th>
<th>B. Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Contract/Grant</td>
<td>□ Federal Government</td>
</tr>
<tr>
<td>□ Subcontract</td>
<td>□ Other Gov. (e.g. State, local)</td>
</tr>
<tr>
<td>□ Departmental</td>
<td>□ Industry</td>
</tr>
<tr>
<td>✗ Gift</td>
<td>□ Other Private</td>
</tr>
<tr>
<td>□ Other:</td>
<td>□ Departmental Funds</td>
</tr>
<tr>
<td>□ No Funding</td>
<td>□ Other:</td>
</tr>
</tbody>
</table>

Have funds been awarded?

☒ Yes ☐ Pending ☐ No

Award #, if known

Specify name of source designated above: Texas Instruments

7. Human Subjects Training. All study personnel MUST take and pass a training course on human subjects research. MIT has a web-based course that can be accessed from the main menu of the COUHES website. COUHES may accept proof of training from some other institutions. List the names of all study personnel and indicate if they have taken a human subjects training course.

George Verghese (human subjects test most recently renewed on 03/11/2009)
Thomas Heldt (human subjects test most recently renewed on 03/09/2009)
Faisal Kashif (human subjects test most recently taken on 12/10/2007)
Varun Chirravuri (human subjects test most recently taken on 02/03/2009)

8. Anticipated Dates of Research
Start Date: November 2009  Completion Date: November 2010

II. STUDY INFORMATION

1. Purpose of Study. Please provide a concise statement of the background, nature and reasons for the proposed study. Use non-technical language that can be understood by non-scientist members of COUHES.

By 2020, the number of people in the United States above the age of 65 is projected to grow by 44%, as about 80 million baby-boomers will have reached retirement age by then. Health-care budgets therefore grow to take up a larger and larger fraction of gross domestic product as individuals in that age bracket contribute disproportionately to health-care cost. Furthermore, it is obvious that the number of health-care providers cannot increase in proportion to the number of elderly. (In fact, the U.S. is already facing a shortage of nurses that is projected to reach over 1 million full-time nurses, or 38% of the projected demand, by 2020.) Consequently, there is a very strong need for improved monitoring of chronic disease conditions outside of expensive, high-acuity health-care environments (hospitals in particular), and also for improved health surveillance to
prevent the most catastrophic - and therefore costly - medical conditions and emergencies (such as, for example, heart attacks) from occurring.

The confluence of wireless, non-invasive, miniaturized, low-power sensor technology and ubiquitous low-cost wireless communication channels (cell phones, local-area networks) will enable the continuous acquisition, processing, and streaming of important vital-sign information for improved health monitoring inside and outside traditional health-care environments. Currently, few such vital-sign monitors exist that allow for recording of physiological information for periods of greater than 24 to 48 hours.

This study aims to characterize the performance of a prototype wearable wireless cardiac monitor that has the capability to record electrocardiographic and accelerometer data for up two weeks at a time without the need to exchange batteries or download the acquired data. In particular, this study aims to collect ECG and motion information from such a prototype while simultaneously recording vital-sign information using clinically approved medical devices. In this study, we focus on collecting data from healthy, adult volunteers during many physical maneuvers (resting recumbently, sitting, standing up, standing quietly, walking, light jogging, light jumping, arm reaching, simulated stair-stepping) commonly encountered during regular life. We will evaluate the performance of the prototype monitor against the data collected simultaneously from the approved clinical devices. Discrepancies in data quality will help drive improvements to the prototype design.

2. Study Protocol.

For biomedical, engineering and related research, please provide an outline of the actual experiments to be performed. Where applicable, provide a detailed description of the experimental devices or procedures to be used, detailed information on the exact dosages of drugs or chemicals to be used, total quantity of blood samples to be used, and descriptions of special diets.

For applications in the social sciences, management and other non-biomedical disciplines please provide a detailed description of your proposed study. Where applicable, include copies of any questionnaires or standardized tests you plan to incorporate into your study. If your study involves interviews please submit an outline indicating the types of questions you will include.

You should provide sufficient information for effective review by non-scientist members of COUHES. Define all abbreviations and use simple words. Unless justification is provided this part of the application must not exceed 5 pages.

Attaching sections of a grant application is not an acceptable substitute.

Before interested individuals are invited to an experimental session, they will be briefed on the background and scope of the study, on disqualifying medical conditions, and on the experimental protocol. Subjects will also be briefed on the prototype wearable wireless cardiac monitor and on the other medical instrumentation involved in the study. On the day of the experimental session, informed consent will be obtained and the subject will be asked to provide basic personal information, such as gender, age, body height, body weight, race, and ethnicity. Furthermore, the subjects will be asked to fill out a basic health-history questionnaire. Furthermore, the subject's resting heart rate, respiratory rate, and arterial blood pressure will be measured prior to instrumentation.

The subject will then be instrumented, which consists of attaching the prototype wearable wireless cardiac monitor to his/her chest using standard medical electrocardiogram (ECG) electrodes, and applying a second set of three ECG electrodes for measuring the ECG with a clinical electrocardiograph. Furthermore, a motion sensor (accelerometer)
and a temperature sensor will be affixed to the subject's chest, using standard medical tape. A pulse oximeter probe will be placed on a digit of the left hand, while pressure cuffs will be placed on the third and fourth digits of the right hand. Finally, elastic bands will be placed around the subject's chest and abdomen, respectively, to measure respiratory chest and abdominal wall excursions. Cables of the clinical ECG monitor, the arterial blood pressure monitor (Portapres), and the pulse oximeter will be affixed to a belt around the subject's waist to minimize the potential for the subject to trip or for the sensors to be torn off.

The study commences with the subject resting comfortably in the supine position on a bed or a medical-examination table for five minutes while baseline data is being collected. At the conclusion of the five-minute period, the subject is asked to get up from the recumbent position and to sit quietly on a chair for five minutes. (Given the level of instrumentation, it might be difficult for the subject to get up alone; the study personnel will aid in the process if/when necessary.) After the five-minute period in the seated position, the subject will be asked to get up and to stand quietly for five minutes. The subject will be allowed to contract his/her calf muscles or to gently step forwards/backwards or sideways if that improves comfort during the standing period. After the five-minute standing period, the subject is asked to hop lightly in place (light jumping) for up to one minute (the toes need not to lift off the ground). At the conclusion of the hopping period, the subject is asked to make horizontal in-plane movements with his/her left arm to engage the left pectoralis muscle (simulation of muscle noise in the ECG) for one minute. At the conclusion of the arm movement exercise, the subject will be asked to perform a 10-second Valsalva (straining) maneuver. At the conclusion of the Valsalva maneuver, the subject will be asked to step onto a treadmill and to walk comfortably (at speeds no greater than four miles/hour) for up to five minutes. At the conclusion of the walking period, the speed of the treadmill will be increased slowly until the subject jogs lightly and comfortably (at speeds no greater than seven miles/hour) for up to five minutes. At the conclusion of the five-minute period of light jogging, the speed of the treadmill is slowly reduced until the treadmill belt comes to a complete standstill. The subject will then be asked to stand behind the rear end of the treadmill and perform a simulated stepping exercise by repeatedly stepping onto the stopped treadmill and back down again. This exercise will last up to one minute.

This sequence of events will take approximately 30 minutes and will be repeated once for a total study duration of about one hour. The start and end of each intervention will be marked on the electronic data acquisition system with the help of an event marker.

At the conclusion of the final intervention, the study staff will remove the instrumentation and will give the subject the chance to freshen up. Finally, the subject will be asked to fill out an exit questionnaire before the experimental session concludes.

3. Drugs and Devices. If the study involves the administration of an investigational drug that is not approved by the Food and Drug Administration (FDA) for the use outlined in the protocol, then the principal investigator (or sponsor) must obtain an Investigational New Drug (IND) number from the FDA. If the study involves the use of an approved drug in an unapproved way the investigator (or sponsor) must submit an application for an IND number. Please attach a copy of the IND approval (new drug), or application (new use.).
If the study involves the use of an investigational medical device and COUHES determines the device poses significant risk to human subjects, the investigator (or sponsor) must obtain an Investigational Device and Equipment (IDE) number from the FDA.

**Will drugs or biological agents requiring an IND be used?**
- Yes [ ]
- No [x]

If yes, please provide details:

**Will an investigational medical device be used?**
- Yes [x]
- No [ ]

If yes, please provide details: see Attachment II to this document.

**4. Radiation**
If the study uses radiation or radioactive materials it may also have to be approved by the Committee on Radiation Exposure to Human Subjects (COREHS). COUHES will determine if you need COREHS approval.

**Will radiation or radioactive materials be used?**
- Yes [x]
- No [ ]

If yes, please provide details:

**5. Diets**

**Will special diets be used?**
- Yes [x]
- No [ ]

If yes, please provide details:

---

### III. HUMAN SUBJECTS

#### 1. Subjects

<table>
<thead>
<tr>
<th>A. Estimated number: 15</th>
<th>B. Age(s): &gt; 18; &lt; 65</th>
</tr>
</thead>
</table>

#### C. Inclusion/exclusion criteria

**i. What are the criteria for inclusion or exclusion?**
Exclusion criteria: known diagnosis or history of cardiovascular diseases (implanted cardiac pacemaker or defibrillator, hypotension or hypertension, coronary vascular disease, varicose veins, congestive heart failure, cardiac rhythm disturbances, or any medication for such conditions); history of fainting or postural hypotension; low exercise tolerance or history of shortness of breath; autonomic neuropathy; diabetes mellitus; use of alcohol, sedatives, or recreational drugs within 24 hours of participation; pregnancy; having slept less than six hours the night prior to participation or having slept less than 18 hours over the course of the three days prior to participation; skin sensitivity to medical adhesives (tape, electrodes) or electrode gels; history of balance problems; known diagnosis or history of respiratory disease; age less than 18 years.

**ii. Are any inclusion or exclusion criteria based on age, gender, or race/ethnic origin?**
- If yes, please explain and justify
  - Yes. Exclusion criteria apply for persons under the age of 18 as the focus of our investigation is primarily on health surveillance for the adult population in this first feasibility study of the device. On the recommendation of the Scientific Advisory Committee of MIT’s Clinical Research Center, we limit the upper age of participation to 65 years.

#### D. Please explain the inclusion of any vulnerable population (e.g. children, cognitively impaired persons, non-English speakers, MIT students), and why that population is being studied.

Many MIT students are healthy young adults, so we will include students in our study.

#### 2. Subject recruitment

Identification and recruitment of subjects must be ethically and legally acceptable and free of coercion. Describe below what methods will be used to identify and recruit subjects.
Recruitment to this study will be done primarily through the use of flyers but also through the word of mouth.

Please attach a copy of any advertisements/ notices and letters to potential subjects

3. Subject compensation
Payment must be reasonable in relation to the time and trouble associated with participating in the study. It cannot constitute an undue inducement to participate.

Describe all plans to pay subjects in cash or other form of payment (i.e. gift certificate)
There will be no compensation (cash, gift certificate, or other) for participation in this study.

Will subjects be reimbursed for travel and expenses?
No.

4. Potential risks. A risk is a potential harm that a reasonable person would consider important in deciding whether to participate in research. Risks can be categorized as physical, psychological, sociological, economic and legal, and include pain, stress, invasion of privacy, embarrassment or exposure of sensitive or confidential data.

All potential risks and discomforts must be minimized to the greatest extent possible by using e.g. appropriate monitoring, safety devices and withdrawal of a subject if there is evidence of a specific adverse event.

What are the risks / discomforts associated with each intervention or procedure in the study?
Instrumentation:
The Portapres device measures arterial blood pressure through the volume-clamp method, which applies a continuous, time-varying pressure to the finger at which arterial pressure is to be measured. While the device is especially designed for long-term blood pressure measurement, some people might consider this measurement uncomfortable. Furthermore, the subject will be instrumented with an electrocardiograph, an accelerometer, a pulse-oximeter, and an experimental medical device (our wearable, wireless cardiac monitor). In general, any electrical device connected to a subject poses the risk of electric shock.

Interventions:
The protocol includes quiet standing, walking and light jogging on a treadmill, as well as simulated stair stepping, and light jumping. Quiet standing might induce pre-syncope and syncope in some subjects. Walking and light jogging on a treadmill might pose the risk of exertion and falling off the treadmill. Finally, some subjects might consider simulated stair stepping and light jumping to be uncomfortable, especially if performed over longer periods of time.

What procedures will be in place to prevent / minimize potential risks or discomfort?
Instrumentation:
The Portapres device allows for switching of blood pressure measurements between two fingers to rest one finger while the device records pressure from a neighboring finger. This will reduce the level of discomfort experienced by the subject. The Portapres, electrocardiograph, and pulse oximeter are approved medical devices and therefore adhere to FDA electrical patient-safety standards. The accelerometer sensor does not directly measure bioelectric potentials or currents from the patient's body; it is therefore electrically isolated from the patient and poses no risk for electric shocks. The prototype
cardiac monitor is a low-power, low-voltage electronic device that poses minimal thermal or electric risk to the subject.

Interventions:
During the quiet standing phases of the protocol, study subjects will be encouraged to activate the muscle pumps in their calves by either shifting their weight from one leg to the other and back or by taking small steps back and forth. During the study, heart rate and blood pressure are monitored continuously. The experiment will be terminated immediately if heart rate rises excessively or drops precipitously (vasovagal syncope) or blood pressure drops noticably. (No hard thresholds can be given as our experience with prior clinical studies has shown that normal, healthy study subjects can present with a wide range of baseline heart rates and arterial blood pressures.) Furthermore, the study will be terminated immediately if the subject reports any signs or symptoms of pre-syncope (dizziness, blurred vision, shrinking of peripheral vision, sense of impending loss of consciousness).

While the study subject is on the treadmill during the walking and light jogging phases of the protocol, one member of the study staff will be standing behind the treadmill to catch the subject should he/she roll off the treadmill. Walking and light jogging will be limited to up to five minutes, while simulated stepping and light jumping will be limited to up to one minute each.

At the end (and if necessary at any earlier point of the sequence of interventions), subjects will be given the opportunity to rest, recover, and rehydrate.

The study will be performed at MIT's Clinical Research Center (CRC), and the nurse assigned to the study will provide assistance throughout the study protocol, which adds another layer of safety.

5. Potential benefits
What potential benefits may subjects receive from participating in the study?
Subjects will receive no direct benefits from participating in this study. However, subjects will be informed about any abnormal finding, such as arrhythmias, that might be detected during the study or during retrospective review of the data. In such cases, the data will be made available to the subject's physician for review and assessment, at the subject's request.

What potential benefits can society expect from the study?
The potential benefit to society derives from an in-depth evaluation of the wearable wireless cardiac monitor and the associated improvements in monitor design.

6. Data collection, storage, and confidentiality
How will data be collected?
Data will be collected (1) on paper, (2) by a dedicated data-acquisition system, and (3) on the prototype cardiac monitor. The data collection devices are all non-invasive (no penetration of skin). Written data will be collected in form of a health questionnaire and an exit questionnaire. Continuous physiological monitoring will be conducted using a single-lead ECG monitor (Hewlett Packard 1500A Electrocardiograph); a non-invasive, continuous blood pressure monitor (Finapres Medical Systems Portapres); a pulse oximeter.
Is there audio or videotaping? YES ☐   NO☒   Explain the procedures you plan to follow.

Will data be associated with personal identifiers or will it be coded?  Personal identifiers ☐   Coded ☒   Explain the procedures you plan to follow.

All research data collected during the experiment will be stored in de-identified electronic files. The coding of each subject's data will prevent linking a subject's personal information to the research data when it is analyzed or archived.

Where will the data be stored and how will it be secured?  All research data collected during this study will be stored in de-identified, electronic format on computers. We plan to make the de-identified data available to the research community through PhysioNet (www.physionet.org) or other such portals. The original signed consent forms will be kept in a locked cabinet at the Principal Investigator's or Study Coordinator's office.

What will happen to the data when the study is completed?  As outlined above, we plan to make the de-identified data available to the research community.

Can data acquired in the study affect a subject's relationship with other individuals (e.g. employee-supervisor, patient-physician, student-teacher, family relationships)?  The collected data cannot affect the subject's relationship with other individuals.

7. Deception   Investigators must not exclude information from a subject that a reasonable person would want to know in deciding whether to participate in a study.

Will information about the research purpose and design be withheld from subjects?  YES ☐   NO☒ If so, explain and justify.

8. Adverse effects.   Serious or unexpected adverse reactions or injuries must be reported to COUHES within 48 hours. Other adverse events should be reported within 10 working days.

What follow-up efforts will be made to detect any harm to subjects and how will COUHES be kept informed?  At the conclusion of the experiment, including the rest period, subjects will be asked to ambulate around the examination room under the supervision of the study personnel. The subjects will be asked whether they feel dizzy in the upright posture or have any other cardiovascular symptoms. If subjects do not report any symptoms, they will be discharged from the supervision of the study personnel. Subjects will be given the cell phone number of the Principal Investigator and the Study Coordinator to report immediately any symptoms of discomfort that might arise within 24 hours following the study session. Any serious events will be reported by telephone to COUHES immediately after such events are noticed or brought to the attention of the study personnel; a written memo will be delivered to COUHES within 48 hours. Adverse events will be reported to COUHES by e-mail within 10 days.

9. Informed consent.   Documented informed consent must be obtained from all participants in studies that involve human subjects. You must use the templates available on the COUHES web-site to prepare these forms. Draft informed consent forms must be returned with this application. Under certain
circumstances COUHES may waive the requirement for informed consent.

Attach informed consent forms with this application.

10. The HIPAA Privacy Rule. If your study involves disclosing identifiable health information about a subject outside of M.I.T., then you must conform to the HIPAA Privacy Rule and complete the questions below. Please refer to the HIPAA section, and to the definitions of protected health information, de-identified data and limited data set on the COUHES web-site.

Do you plan to use or disclose identifiable health information outside M.I.T.?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☒</td>
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</tbody>
</table>

If YES, then the subject must complete an Authorization for Release of Protected Health Information Form. Please attach a copy of this draft form. You must use the template available on the COUHES web-site.

Alternatively, COUHES may grant a Waiver of Authorization if the disclosure meets criteria outlined on the COUHES web-site.

Are you requesting a Waiver of Authorization?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☒</td>
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</table>

If YES, explain and justify.

Will the health information you plan to use or disclose be de-identified?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
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</table>

Will you be using or disclosing a limited data set?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☒</td>
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</tbody>
</table>

If YES, then COUHES will send you a formal data use agreement that you must complete in order for your application to be approved.

IV. INVESTIGATOR'S ASSURANCE

I certify the information provided in this application is complete and correct.

I understand that I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by COUHES.

I agree to comply with all MIT policies, as well all federal, state and local laws on the protection of human subjects in research, including:

- ensuring all study personnel satisfactorily complete human subjects training
- performing the study according to the approved protocol
- implementing no changes in the approved study without COUHES approval
- obtaining informed consent from subjects using only the currently approved consent form
- protecting identifiable health information in accord with the HIPAA Privacy Rule
- promptly reporting significant or untoward adverse effects

APPLICATION FOR APPROVAL TO USE HUMANS AS EXPERIMENTAL SUBJECTS (STANDARD FORM) – revised 6/2/2009)
Signature of Principal Investigator ___________________________ Date __________

Print Full Name and Title ____________________________________________

Signature of Department Head ___________________________ Date __________

Print Full Name and Title ____________________________________________

Please return 3 hard copies of this application (1 with original signatures) to the COUHES office E25-143b.
A.2 Recruitment Flyer

Recruiting Volunteers for Human-Subjects Study

We are recruiting volunteers for a human-subjects study, evaluating the performance of a novel wearable wireless cardiac monitor.

If you are interested, please contact thomas@mit.edu, 617-324-5005.
A.3 Consent Form

CONSENT FORM, WEARABLE WIRELESS CARDIAC MONITOR 1/7

CONSENT TO PARTICIPATE IN BIOMEDICAL RESEARCH

Evaluation of a Wearable Wireless Cardiac Monitor

You are asked to participate in a research study conducted by George Verghese, PhD, Thomas Heldt, PhD, and their students from the Research Laboratory of Electronics at the Massachusetts Institute of Technology. The results of this study may be published in de-identified form in a student thesis or scientific journal, and will be made available freely to the scientific community. You have been asked to participate in this study because you have volunteered and - based on the information you have provided - meet the minimum health and physical requirements for our study. You should read the information below carefully, and ask questions about anything you do not understand, before deciding whether or not to participate.

PARTICIPATION AND WITHDRAWAL

Your participation in this research is completely VOLUNTARY. If you choose to participate you may subsequently withdraw from the study at any time without penalty or consequences of any kind. The investigator may withdraw you from this research if circumstances arise that warrant doing so. Such circumstances include the emergence of evidence that you do not in fact meet the minimum health and physical requirements, or that during the study it becomes clear to the experimenter that you are becoming fatigued. If you choose to not participate or to withdraw at any point, it will not affect your relationship with M.I.T. or your right to health care or other services to which you are otherwise entitled.

You should not participate in this study if your answer to one or more of the following questions is "yes":

- Do you have a diagnosed heart or vascular condition? This could be a coronary heart disease, varicose veins, cardiac arrhythmias, congestive heart failure.
- Do you have an implanted cardiac pacemaker or defibrillator?
- Do you suffer from cardiac arrhythmias?
- Do you have a history of fainting, dizziness or low blood pressure upon standing up?
- Do you have skin sensitivity to medical adhesives (tape, electrodes) or electrode gels?
- Do you have a medical respiratory condition?
CONSENT FORM, WEARABLE WIRELESS CARDIAC MONITOR

- Are you are under the influence of alcohol, sedatives, or recreational drugs, or have you consumed alcohol or taken sedatives or recreational drugs in the past 24 hours?
- Is there the possibility that you might be pregnant?
- Do you have diabetes?
- Do you suffer from poor sensation in your legs or other neurological deficits?
- Do you have low exercise tolerance or develop shortness of breath easily?
- Have you slept less than 6 hours last night, or have you slept less than 18 hours in total in the last three days?

PURPOSE OF THE STUDY
The purpose of the research is to investigate the performance of a novel prototype wearable wireless cardiac monitor.

PROCEDURES USED IN THIS STUDY
If you agree to participate in this study, we would ask you to consent to the following:

- You will be asked to provide basic personal information such as age, gender, body height, body weight, race, and ethnicity.
- You will be asked to provide basic information about your current state of health and your health history.
- Prior to commencing the experimental protocol, the experimenters will take your heart rate, blood pressure, and respiratory rate, using standard clinical methods.
- Six non-invasive electrodes will be placed on the surface of the skin on your chest.
- Three of these electrodes will be attached to the wearable wireless cardiac monitor.
- The remaining three electrodes will be connected to a standard electrocardiograph.
- A non-invasive temperature probe will be placed on your skin.
- Non-invasive blood pressure cuffs will be placed on two of your fingers.
- A non-invasive sensor for your blood oxygen levels will be placed on one of your fingers.
- A small motion sensor will be affixed to your chest.
- During the experimental session, you might be asked several questions relating to your general sensation or questions about your well-being.
CONSENT FORM, WEARABLE WIRELESS CARDIAC MONITOR

- During the experimental session, you will be asked to
  - rest in the horizontal position for five minutes,
  - sit on a chair for five minutes,
  - stand for five minutes,
  - hop lightly in place for up to one minute,
  - move your left arm in a horizontal plane for one minute,
  - perform a brief straining maneuver,
  - walk on a treadmill at a comfortable speed for five minutes,
  - jog lightly on a treadmill at a comfortable speed for five minutes, and
  - step onto and off the stopped treadmill repeatedly for up to one minute.

- You will be asked to perform the entire cycle of interventions described above twice, possibly with rest in between.

- You might be asked to answer a series of questions at the end of the experimental session.

The total time for participation will be 2 hours at most.

You may terminate the experiment at any time by telling the experimenter you wish to stop.

POTENTIAL RISKS AND DISCOMFORTS

During the experiment you may experience one or more of the following:

- A pressure sensation at the finger at which your blood pressure is being measured. We can minimize potential discomfort by alternating the blood pressure measurement between two fingers.
- Skin irritation at the sites of electrode application.
- Electrical shocks. The electrical devices to which you will be attached pose minimal risk of electrical shocks as they are either designed for clinical use and therefore adhere to stringent electrical safety standards or are of such low electrical voltage and power that they don’t pose a risk.

Further discomfort might be experienced during the following interventions:

- Quiet standing:
  Some people experience dizziness or the feeling of impending loss of consciousness during quiet standing. We minimize this risk by limiting quiet standing to five minutes at a time and by allowing you to contract your calf muscles, by shifting your weight from one leg to the other, or by gently stepping forward/backwards or sideways. We will also be monitoring your heart rate and
arterial blood pressure continuously for any signs of abnormality.

- Light hopping/jumping:
  Some people might find light jumping inconvenient. We limit the time for this intervention to one minute and allow for vertical bouncing in which the toes need not lift off the ground.

- Walking/light jogging:
  Depending on your exercise tolerance, you might experience an increase in heart rate and sweating while walking or jogging on the treadmill. Furthermore, you might be at risk of falling off the treadmill. We will limit the treadmill’s speed to your comfort level for both the walking and light-jogging phase of the protocol. In any case, the speed will not exceed 4 miles/hour for the walking phase and 7 miles/hour for the light-jogging phase of the protocol. Furthermore, each of the two phases is limited to five minutes. You will be protected from falling off the treadmill by side rails and by members of the study staff who will be standing behind the treadmill to catch you in case you should trip.

- Simulated stair stepping:
  Some people might feel discomfort in stepping repeatedly onto and off the treadmill. We limit the time for this phase of the protocol to one minute to minimize such potential discomfort.

Members of the study staff will frequently ask you about your well-being to ensure your comfort, and will monitor your alertness through communication. You will be continuously monitored by at least two experimenters in the room.

The procedures may involve risks that are currently unforeseeable.

ANTICIPATED BENEFITS TO SUBJECTS
You will receive no benefits from this research.

ANTICIPATED BENEFITS TO SOCIETY
The potential benefits to science and society are a better understanding and possibly an improved design of a wearable wireless cardiac monitor. This in turn may provide improved health care for home-bound and high-risk patients.

PAYMENT FOR PARTICIPATION
You will receive no compensation for your participation in this study.
FINANCIAL OBLIGATION

Neither you nor your health insurance will be billed for your participation in this study.

PRIVACY AND CONFIDENTIALITY

The members of the research team and, if appropriate and requested by you, your physician and nurses are the only people who will know that you are a research subject. No information about you, or identifiable information provided by you during the research will be disclosed to others without your written permission, except if necessary to protect your rights or welfare, or if required by law.

After the experiment, all data and information collected during the experiment will be stored in an electronic database in de-identified format, which means that it will be impossible to trace the stored data and information back to you. We will make the de-identified data collected from this study freely available to the research community at large. This might involve posting data on Internet portals such as PhysioNet (www.physionet.org). When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience abnormally high heart rate, low blood pressure, drowsiness or dizziness, you may have to be discharged from the study, even if you would like to continue. The investigators, George Verghese, PhD or Thomas Heldt, PhD, will make this decision and will let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

EMERGENCY CARE AND COMPENSATION FOR INJURY

If you feel you have suffered an injury, which may include emotional trauma, as a result of participating in this study, please contact the person in charge of the study as soon as possible.

In the event you suffer such an injury, M.I.T. may itself provide, or arrange for the provision of, emergency transport or medical treatment, including emergency treatment.
and follow-up care, as needed, or reimbursement for such medical services. M.I.T. does not provide any other form of compensation for injury. In any case, neither the offer to provide medical assistance, nor the actual provision of medical services shall be considered an admission of fault or acceptance of liability. Questions regarding this policy may be directed to M.I.T.'s Insurance Office, (617) 253-2823. Your insurance carrier may be billed for the cost of emergency transport or medical treatment, if such services are determined not to be directly related to your participation in this study.

IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact:

<table>
<thead>
<tr>
<th>Principal Investigator:</th>
<th>Co-Investigator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>George C. Verghese (10-140K)</td>
<td>Thomas Heldt (10-140L)</td>
</tr>
<tr>
<td>77 Massachusetts Avenue</td>
<td>77 Massachusetts Avenue</td>
</tr>
<tr>
<td>Cambridge, MA 02139</td>
<td>Cambridge, MA 02139</td>
</tr>
<tr>
<td>(617) 253-4612</td>
<td>(617) 324-5005</td>
</tr>
</tbody>
</table>

RIGHTS OF RESEARCH SUBJECTS

You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you feel you have been treated unfairly, or you have questions regarding your rights as a research subject, you may contact the Chairman of the Committee on the Use of Humans as Experimental Subjects, M.I.T., Room E32-335, 77 Massachusetts Ave, Cambridge, MA 02139, phone 1-617-253 6787.

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.
CONSENT FORM, WEARABLE WIRELESS CARDIAC MONITOR

Name of Legal Representative (if applicable)

Signature of Subject or Legal Representative Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject or his/her legal representative and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

Name of Investigator

Signature of Investigator Date (must be the same as subject’s)

SIGNATURE OF WITNESS (If required by COUHES)

My signature as witness certified that the subject or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

Name of Witness
CONSENT FORM, WEARABLE WIRELESS CARDIAC MONITOR

Signature of Witness

Date (must be the same as subject’s)
A.4 Date Change

**APPLICATION FOR CHANGES TO AN APPROVED PROTOCOL**

Any change to a protocol that impacts human subjects must be approved by COUHES. If the change is minor and involves no more than minimal risks to subjects, an expedited review may be performed. All other changes are subject to a full Committee review.

1. **Title of Study**
   Evaluation of a Wearable Wireless Cardiac Monitor

2. **Investigator**
   Name: George C. Verghese  
   Building and Room #: 10-140K
   Title: Professor  
   Email: verghese@mit.edu
   Department: EECS  
   Phone: 253-4612

3. **Proposed Change.** Please provide a detailed description of the proposed changes, and indicate how these changes will affect the potential risks and benefits to the subjects. Define all abbreviations and use simple words. Unless justification is provided, this part of the application must not exceed 2 pages. NOTE: when adding study personnel state MIT or outside affiliation and include email address.

   We propose changing the expiration date of the protocol from Oct. 14, 2010 to Jan. 31, 2011.

   Please attach copies of all revised material (consent form, study protocol, recruitment, etc). Also, include a copy of all revised material with changes HIGHLIGHTED. Any incomplete application will be rejected and returned for completion.

   Signature of Investigator ___________________________ Date ____________

   Signature of Dept. Head ___________________________ Date ____________

   Please submit a signed hard copy of this application including all revised material to the COUHES office at E25-143b.
A.5 Continuing Review Questionnaire

<table>
<thead>
<tr>
<th>Massachusetts Institute of Technology</th>
<th>Existing COUHES #</th>
<th>Date of last approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Committee on the Use of Humans as Experimental Subjects</td>
<td>36</td>
<td>10/15/200</td>
</tr>
</tbody>
</table>

CONTINUING REVIEW QUESTIONNAIRE

Approval of your protocol by COUHES will, unless otherwise noted, expire one year after the date of the last approval. Before extending its approval for an additional period (usually one year) you must complete and return this form by the deadline for the COUHES meeting that will be held before your expiration date (see dates and deadlines: [http://web.mit.edu/committees/cohues/dates.shtml](http://web.mit.edu/committees/cohues/dates.shtml)). If this form is not received by the required date, the study will be administratively closed and research grants related to the study will be suspended. No further research with human subjects can be conducted under this protocol.

Please answer every question. Positive answers should be amplified with details. You must mark N/A where the question does not pertain to your application. Any incomplete application will be rejected and returned for completion. Do not use this form to request changes, attach an Application for Changes to an Approved Protocol form. If you are not requesting renewal of this protocol, you should submit this form to close the protocol.

<table>
<thead>
<tr>
<th>1. Title of Study</th>
<th>Evaluation of a Wearable Wireless Cardiac Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Principal Investigator</td>
<td>George C. Verghese Building and Room #: 10-140K</td>
</tr>
<tr>
<td>Name: George C. Verghese</td>
<td>Building and Room #: 10-140K</td>
</tr>
<tr>
<td>Title: Professor</td>
<td>Title: Professor</td>
</tr>
<tr>
<td>Department: EECS</td>
<td>Department: EECS</td>
</tr>
<tr>
<td>Phone: 253-4612</td>
<td>Phone: 253-4612</td>
</tr>
</tbody>
</table>

3. Are you requesting renewal of COUHES approval for this project?
   | NO ☐ YES ☒ |

4. Has there been a change in:
   | A. Responsible investigators? NO ☐ YES ☒ if yes, please explain: TWO PREVIOUSLY APPROVED INVESTIGATORS (VARUN CHIRRAVURI AND JERRY WANG) GRADUATED OR ENDED THEIR UROP IN OUR GROUP. |
   | B. Recruitment of subjects? NO ☐ YES ☒ if yes, please explain: |
   | C. Experimental procedure? NO ☐ YES ☒ if yes, please explain: |
   | D. Experimental drugs? NO ☐ YES ☒ if yes, please explain: |
   | E. Amount of blood drawn? NO ☐ YES ☒ if yes, please explain: |
   | F. Amount of radiation exposure? NO ☐ YES ☒ if yes, please explain: |
   | G. Other aspects of the study that affect the rights of the subject? NO ☐ YES ☒ if yes, please explain: |

5. STUDY PROTOCOL: (provide an outline of the approved current research)
protocol. You should provide sufficient information for effective review by non-scientist members of COUHES. Define all abbreviations and use simple words. Unless justification is provided, this part of the continuing review application must not exceed 2 pages.)
Because of technical difficulties with the delicate wireless experimental ECG monitor, we have fallen short of the recruitment target during the first year of study approval. We would therefore like to keep the protocol open until we have recruited all 15 subjects originally approved.

6. How many subjects have been studied?

<table>
<thead>
<tr>
<th>Since the last approval:</th>
<th>Since the start of the study:</th>
</tr>
</thead>
</table>

CONTINUING REVIEW QUESTIONNAIRE—revised 8/10/2010
Number of subjects approved for this study: 15
Number of subjects withdrawn from the study: (state reason for withdrawal, was Adverse Event report submitted?): 0

7. Have your subjects experienced any adverse effects since the last approval? All adverse effects must be reported to COUHES. If you have not reported an adverse event, please attach an adverse event reporting form.

| NO ☒ | YES ☐ |

8. Statement of Financial Interest

Have any of the financial interests of key personnel involved in the study changed since the last approval?

| ☐ Yes | ☒ No |

If yes, and unless already submitted, please attach a Supplement for Disclosure of Financial Interest for each change.

This supplement, together with detailed guidance on this subject and definitions of the highlighted terms, is available on the COUHES web.

9. Funding. If the research is funded by an outside sponsor, the investigator's department head must sign below. If not previously submitted, a copy of the research proposal is required (a draft is acceptable).

<table>
<thead>
<tr>
<th>A. Type of funding:</th>
<th>B. Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Contract/Grant</td>
<td>☐ Federal Government</td>
</tr>
<tr>
<td>☐ Subcontract</td>
<td>☐ Other Gov. (e.g. State, local)</td>
</tr>
<tr>
<td>☒ Gift</td>
<td>☒ Industry</td>
</tr>
<tr>
<td>☐ Other:</td>
<td>☐ Other Private</td>
</tr>
<tr>
<td>☐ No Funding</td>
<td>☐ Departmental Funds</td>
</tr>
<tr>
<td></td>
<td>☐ Other:</td>
</tr>
</tbody>
</table>

Have funds been awarded?

| ☒ Yes ☐ Pending ☐ No |

Award #, if known

Specify name of source designated above:

9. Funding. If the research is funded by an outside sponsor, the investigator's department head must sign below. If not previously submitted, a copy of the research proposal is required (a draft is acceptable).

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<td>☐ Other Gov. (e.g. State, local)</td>
</tr>
<tr>
<td>☒ Gift</td>
<td>☒ Industry</td>
</tr>
<tr>
<td>☐ Other:</td>
<td>☐ Other Private</td>
</tr>
<tr>
<td>☐ No Funding</td>
<td>☐ Departmental Funds</td>
</tr>
<tr>
<td></td>
<td>☐ Other:</td>
</tr>
</tbody>
</table>

Have funds been awarded?

| ☒ Yes ☐ Pending ☐ No |

Award #, if known

Specify name of source designated above: Texas Instruments

C. If Contract or Grant

Name of Contract or Grant:
Contract or Grant Number:

Contract or Grant Title:
OSP#:

10. Does your study require approval of any other committee (at or outside MIT)?

| NO ☒ | YES ☐ |

If yes, please attach current approval letters.

11. Have any results of the study been published?

| NO ☒ | YES ☐ |

If yes, please provide bibliographic information.

12. Informed consent

Please attach a copy of the informed consent document you are currently using. This should be the version most recently approved by COUHES.

If the requirement for informed consent has been waived by COUHES, please check this box ☐

Signature of Principal Investigator __________________________ Date __________

Print Full Name ____________________________________________
Signature of Department Head: ________________________ Date __________

Print full name and title: ______________________________ Date __________

Please return a signed hard copy of this application to the COUHES office at E25-143B.
Appendix B

Subject Record

<table>
<thead>
<tr>
<th>Personal Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject ID Number:</td>
</tr>
<tr>
<td>Age: 45</td>
</tr>
<tr>
<td>Body weight: 64 kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How would you rate your general health?</td>
</tr>
<tr>
<td>2. What is your normal activity level?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health History</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Are you allergic to any foods or medications? (Please list)</td>
</tr>
<tr>
<td>4. Are you allergic to anything else? (Please list)</td>
</tr>
<tr>
<td>5. When was the last time you consumed wine, beer or other alcoholic beverages?</td>
</tr>
<tr>
<td>6. When was the last time you took recreational drugs (e.g., marijuana, cocaine, etc.), stimulants, or sedatives?</td>
</tr>
</tbody>
</table>
HEALTH HISTORY FORM, WEARABLE WIRELESS CARDIAC MONITOR 2/3

7. Have you slept less than six hours last night?  
☐ No  ☐ Yes

8. Have you slept less than 18 hours in total over the last three days?  
☐ No  ☐ Yes

9. Is there a chance you might be pregnant?  
☐ No  ☐ Yes  ☐ Not applicable

10. Have you had any surgery in your lifetime?  
☐ No  ☐ Yes  
If so, please specify: __________

11. Have you ever had or do you have: (Please check all that apply)

☐ Skin conditions/sensitive skin
☐ Hearing problems
☐ Dizziness or vertigo (feeling of movement)
☐ Seizures
☐ Strokes / Transient ischemic attacks
☐ Head injury
☐ Bronchitis
☐ Emphysema
☐ Chronic pulmonary disease

☐ Abnormal heart rhythms (palpitations, arrhythmia)
☐ Angina or chest pain
☐ High blood pressure
☐ Low blood pressure
☐ Congestive heart failure or fluid in lungs
☐ Heart murmur
☐ Diabetes
☐ Anemia

☐ Vision problems
☐ Fainting/blackouts
☐ Headaches
☐ Parkinson’s disease
☐ Memory loss
☐ Asthma
☐ Shortness of breath
☐ Tuberculosis

☐ Pacemaker/Defibrillator
☐ Heart attack
☐ Pain in calves with walking
☐ Puffy ankles (edema)
☐ Rheumatic fever

☐ Thyroid problems
☐ Cancer
Health History Form, Wearable Wireless Cardiac Monitor

☐ Gastrointestinal bleeding
☐ Stomach problems (nausea)
☐ Liver disease (cirrhosis)
☐ Gall bladder problems

☐ Ulcers
☐ Hepatitis
☐ Kidney disease

13. Have you gained or lost weight over the last year?
☐ No  ☐ Yes
Personal Information

Subject ID Number: 14673

General Questions

1. How comfortable was the wearable wireless cardiac monitor?
   
   - [ ] Very comfortable
   - [ ] Somewhat comfortable
   - [ ] Neither particularly comfortable, nor particularly uncomfortable
   - [ ] Somewhat uncomfortable
   - [ ] Very uncomfortable

2. Please share with us anything about the comfort/discomfort of wearing the device that might help us improve its design.

   
   
   
   
   

---

156
CRC Protocol #: 608  
Nursing Flow Sheet 

PI: George C. Verghese  
Co-Investigator: Thomas Heldt 

Contact Info: 617-253-4612  
Contact Info: 617-324-5005 

DATE 10-1-2010 

☑ Consent signed 

☑ Time of Last Meal/ Snack: 12 □ AM □ PM Should be at least 2 hours post meal. 

☑ Temp 98°  

☑ BP 114/76 P 68 R 18 

☑ Height (no shoes) 176 cm  

☑ Weight with light clothing 64 kg 

☑ Brief Nursing Assessment: usual gd health OLc 

☑ Administer and review health questionnaire 

☑ Study procedures 

☑ Prepare Skin:  

☑ Shave 

☑ Abrade 

☑ Alcohol 

☑ Affix Board with leads @ 4 the intercostals space 

☑ Tape Battery 

☑ Affix Leads 

☑ Coban Lead wires around waist 

☑ Don T shirt  

☑ Apply 2 chest bands  

☑ Coban wires around waist 

☑ Apply Pulse Ox to finger: tape 

☑ Apply Finger BP cuff: tape  

☑ Wrist transducer (insert gauze) 

☑ Apply Sling
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mark</th>
<th>Minutes</th>
<th>Comments/Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Board Start</td>
<td></td>
<td>16:47:10</td>
<td></td>
</tr>
<tr>
<td>START Recorder</td>
<td></td>
<td>17:00:43</td>
<td>01</td>
</tr>
<tr>
<td>INITIAL Calibration</td>
<td></td>
<td>19:08:08</td>
<td></td>
</tr>
<tr>
<td>Calibrate</td>
<td></td>
<td>17:08:33</td>
<td></td>
</tr>
<tr>
<td>SUPINE: 5 min Start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>✓</td>
<td>17:09:54</td>
<td>02</td>
</tr>
<tr>
<td>Stop</td>
<td></td>
<td>17:11:57</td>
<td>03</td>
</tr>
<tr>
<td>SIT up quickly → rest</td>
<td></td>
<td>17:18:61</td>
<td></td>
</tr>
<tr>
<td>1 min → Calibrate</td>
<td></td>
<td></td>
<td>Board Light Blinking</td>
</tr>
<tr>
<td>Stand up: 5 min max</td>
<td></td>
<td>17:20:12</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>✓</td>
<td>17:21:20</td>
<td>04</td>
</tr>
<tr>
<td>Stop</td>
<td></td>
<td>17:21:12</td>
<td>05</td>
</tr>
<tr>
<td>Pseudo Hop: 1 min max</td>
<td></td>
<td>17:29:30</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>✓</td>
<td>17:30:31</td>
<td>08</td>
</tr>
<tr>
<td>Stop</td>
<td></td>
<td>17:30:21</td>
<td>09</td>
</tr>
<tr>
<td>Rest 1 min → Calibrate</td>
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<td>17:31:30</td>
<td>10</td>
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<tr>
<td>Valsalve: 10 sec</td>
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<td>17:35:34</td>
<td>12</td>
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<tr>
<td>Rest 1 min → Calibrate</td>
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<td>17:36:14</td>
<td>13</td>
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<tr>
<td>Treadmill walk: 4 mph</td>
<td></td>
<td>17:37:37</td>
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</tr>
<tr>
<td>Max Speed</td>
<td></td>
<td>17:38:00</td>
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</tr>
<tr>
<td>Start</td>
<td>✓</td>
<td>17:43:13</td>
<td>3.0</td>
</tr>
<tr>
<td>Stop</td>
<td></td>
<td>17:43:54</td>
<td></td>
</tr>
<tr>
<td>Treadmill increase slowly</td>
<td></td>
<td>17:47:34</td>
<td>6.0</td>
</tr>
<tr>
<td>to run: 7 mph</td>
<td></td>
<td>17:48:36</td>
<td>27</td>
</tr>
<tr>
<td>Max Speed</td>
<td></td>
<td>17:50:36</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>✓</td>
<td>17:51:18</td>
<td></td>
</tr>
<tr>
<td>Stop</td>
<td></td>
<td>17:52:18</td>
<td></td>
</tr>
<tr>
<td>Rest 1 min → Calibrate</td>
<td></td>
<td>17:53:19</td>
<td></td>
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<tr>
<td>Stepping: 1 min Max</td>
<td></td>
<td>17:55:32</td>
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<tr>
<td>Rest 1 min → end</td>
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<td>17:58:33</td>
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</tr>
<tr>
<td>Calibrate</td>
<td></td>
<td>17:59:34</td>
<td></td>
</tr>
<tr>
<td>Final Calibration</td>
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Investigator Signature: [Signature]  
Date: 10/1/10  
Research Nurse Signature: [Signature]  
Date: 10/1/10
Study Procedures: Work Sheet

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mark X 2</th>
<th>Minutes</th>
<th>Comments/Observations</th>
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<tbody>
<tr>
<td>INITIAL: Calibration</td>
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<tr>
<td>Calibrate</td>
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<tr>
<td>Supine: 5min Start</td>
<td>Start</td>
<td>5:54:30</td>
<td>Respiration</td>
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<tr>
<td></td>
<td>Stop</td>
<td>5:54:30</td>
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<tr>
<td>SIT up quickly→rest</td>
<td>Start</td>
<td>5:52:28</td>
<td>Board Blinking</td>
</tr>
<tr>
<td>1 min→Calibrate</td>
<td>Stop</td>
<td></td>
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<tr>
<td>Sit Up Quickly: 5min</td>
<td>Start</td>
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<td>23</td>
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<td></td>
<td>Stop</td>
<td>5:52:30</td>
<td>24</td>
</tr>
<tr>
<td>Stand Up→rest 1 min→Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>25</td>
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<tr>
<td>Stand up: 5 min max</td>
<td>Stop</td>
<td>5:52:30</td>
<td>26</td>
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<tr>
<td>Rest 1 min→Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>27</td>
</tr>
<tr>
<td>Pseudo Hop: 1 min max</td>
<td>Stop</td>
<td>5:52:30</td>
<td>28</td>
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<tr>
<td>Rest 1 min→Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>29</td>
</tr>
<tr>
<td>Move Lt/Rt Arm in plane: max 1 min</td>
<td>Stop</td>
<td>5:52:30</td>
<td>30</td>
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<tr>
<td>Rest 1 min→Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>31</td>
</tr>
<tr>
<td>Valsalver 10 seconds</td>
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<td>5:52:30</td>
<td>32</td>
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<td>Rest 1 min→Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>33</td>
</tr>
<tr>
<td>Treadmill walk: 4 mph</td>
<td>Start</td>
<td>5:52:30</td>
<td>Max: MPH 30</td>
</tr>
<tr>
<td>Max Speed</td>
<td>Stop</td>
<td>5:52:30</td>
<td>#Strides/Seconds 19</td>
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<tr>
<td>Treadmill increase slowly to run:7 mph</td>
<td>Start</td>
<td>5:52:30</td>
<td>Max: MPH 6.0</td>
</tr>
<tr>
<td>Max Speed</td>
<td>Stop</td>
<td>5:52:30</td>
<td>28</td>
</tr>
<tr>
<td>Rest 2 min→end Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td></td>
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<tr>
<td>Stepping: 1 min Max</td>
<td>Stop</td>
<td>5:52:30</td>
<td>34</td>
</tr>
<tr>
<td>Rest 1 min→end Calibrate</td>
<td>Start</td>
<td>5:52:30</td>
<td>35</td>
</tr>
<tr>
<td>Final Calibration</td>
<td>Stop</td>
<td>5:52:30</td>
<td></td>
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<tr>
<td>Stop Recorder</td>
<td></td>
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<tr>
<td>Stop Board</td>
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Investigator Signature: [Signature]
Date: 10/1/10
Research Nurse: [Signature]
Date: 10/1/10

159
Subject # 14673

- Administer exit questionnaire
- Exit BP 11/12 P 60 R 18

Comments: Tol procedures well

Signature: [Signature]
Date: 10/1/2010
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