PHYSICAL ACTIVITY AS A RISK FACTOR FOR ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY CAUSED BY A pS358L MUTATION IN TMEM43 IN NEWFOUNDLAND, CANADA

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ABSTRACT

The many benefits of regular physical activity (PA) have been well documented in the literature. PA has been shown to improve cardiovascular health and reduce the risk of cardiovascular disease. However, much less is known about the serious and sometimes fatal effects PA can have in individuals with certain rare cardiovascular diseases, such as arrhythmogenic right ventricular cardiomyopathy (ARVC). This cross sectional study sought to examine the association between PA and the onset and progression of ARVC caused by a p.S358L mutation in *TMEM43*. The sample consisted of 82 patients in who were diagnosed with ARVC caused by a p.S358L mutation in *TMEM43* and had received an implantable cardioverter defibrillator (ICD) as primary prophylactic (PP) treatment. Survival analyses were done on several clinical cardiac symptoms, cardiac test abnormalities, and demographic variables from prior to ICD implant using the Kaplan-Meier product limit method to determine their association with time to appropriate firing of the ICD. Relative risk (RR) was calculated using the Cox regression model. Having an abnormal 24 hour Holter monitor test result prior to receiving the ICD and reporting high levels of moderate to vigorous PA were found to be associated with appropriate discharge of the ICD with RR’s of 4.1 (CI 1.2-13.7) and 12.8 (CI 3.7-45.2) respectively. A multivariate Cox regression model showed high levels of moderate to vigorous PA and having an abnormal 24 hour Holter monitor result prior to ICD implant to be strongly associated with appropriate firing of the ICD with RR’s of 28.1 (CI 6.9-114.2) and 16.4 (CI 3.8-71.5). These results suggest that high levels of moderate to vigorous PA could play an important role in the phenotypic expression of ARVC caused by a p.S358L mutation in *TMEM43*. 
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Table of Contents
ABSTRACT .................................................................................................................. i
ACKNOWLEDGEMENTS ............................................................................................ ii
DEDICATION ................................................................................................................. iv
List of Tables .............................................................................................................. ix
List of Figures ........................................................................................................... x
List of Abbreviations ............................................................................................... xii
CHAPTER ONE: INTRODUCTION .............................................................................. 1
  1.1 Rationale .............................................................................................................. 1
  1.2 Aims and objectives ............................................................................................ 3
CHAPTER TWO: LITERATURE REVIEW .................................................................... 4
  2.1 Arrhythmogenic Right Ventricular Cardiomyopathy ........................................ 4
    2.1.1 History .......................................................................................................... 5
    2.1.2 Pathophysiology ........................................................................................... 6
    2.1.3 Diagnosis ....................................................................................................... 7
    2.1.4 Treatment ..................................................................................................... 8
    2.1.5 ARVC caused by a p.S358L mutation in TMEM43 in Newfoundland and Labrador ... 9
  2.2 Physical Activity and the Heart ................................................................. 12
    2.2.1 Measurements of Physical Activity .............................................................. 12
    2.2.2 Cardiovascular Benefits of Physical Activity .................................................. 13
2.2.3 Physical Activity Guidelines for Cardiovascular Health ................................. 14

2.2.4 Adverse Cardiovascular Adaptations to Physical Activity .............................. 15

2.3 Physical Activity and Arrhythmogenic Right Ventricular Cardiomyopathy .......... 17

2.4 Summary ........................................................................................................... 22

CHAPTER THREE: METHODS .................................................................................. 25

3.1 Ethical Considerations ....................................................................................... 25

3.2 Study Participants .............................................................................................. 26

3.3 Data Collection .................................................................................................. 29

3.3.1 In-person and phone interviews ..................................................................... 30

3.4 Physical Activity Assessment ............................................................................ 32

3.4.1 Modified Paffenbarger Physical Activity Questionnaire ................................. 32

3.4.2 Calculation of Physical Activity ...................................................................... 33

3.5 Data Analysis .................................................................................................... 34

CHAPTER FOUR: RESULTS .................................................................................... 37

4.1 Participant Characteristics .................................................................................. 37

4.1.1 Demographic Characteristics ......................................................................... 37

4.1.2 Clinical Characteristics .................................................................................. 37

4.1.3 Physical Activity Characteristics .................................................................... 38

4.1.4 Time to Appropriate Discharge of ICD .......................................................... 39

4.2 Kaplan-Meier Time to Event Analysis ................................................................ 40
List of Tables

Table 1: The prevalence of cardiac symptoms, cardiac test abnormalities, demographic data and self-reported physical activity in association to appropriate ICD discharge at > 240 beats per minute or death in patients who received an ICD as primary prophylactic treatment for ARVC caused by a p.S358L mutation in $TMEM43$. ................................................................. 58

Table 2: Multivariate cox’s regression analysis of covariates associated with appropriate ICD discharge at > 240 beats per minute or death in patients who received an ICD as primary prophylactic treatment for ARVC caused by a p.S358L mutation in $TMEM43$. ................................. 66
List of Figures

Figure 1: Hypothesized effects of physical activity in ARVC ......................................................... 24
Figure 2: Flow diagram of patients included in study. ................................................................. 29
Figure 3: Time from receiving ICD to experiencing first appropriate discharge of device. ......... 40
Figure 4: Time to first appropriate discharge of ICD in patients who experienced heart palpitations prior to receiving ICD. .................................................................................................................. 42
Figure 5: Time to first appropriate discharge of ICD in patients who experienced pre-syncope prior to receiving ICD ........................................................................................................................................... 43
Figure 6: Time to first appropriate discharge of ICD in patients who experienced chest pain prior to receiving ICD ...................................................................................................................................................... 44
Figure 7: Time to first appropriate discharge of ICD in patients who experienced syncope prior to receiving ICD ...................................................................................................................................................... 45
Figure 8: Time to first appropriate discharge of ICD by age of patient when ICD was received. 46
Figure 9: Time to first appropriate discharge of ICD in patients who had an abnormal ECG result prior to receiving ICD ................................................................................................................................. 47
Figure 10: Time to first appropriate discharge of ICD in patients who had an abnormal SAECG result prior to receiving ICD ....................................................................................................................... 48
Figure 11: Time to first appropriate discharge of ICD in patients who had an abnormal 24 hour Holter monitor result prior to receiving ICD ........................................................................................................ 49
Figure 12: Time to first appropriate discharge of ICD in patients who had an abnormal Echo result prior to receiving ICD ............................................................................................................................................. 50
Figure 13: Time to first appropriate discharge of ICD by sex .......................................................... 51
Figure 14: Time to first appropriate discharge of ICD by BMI prior to receiving ICD ................. 52
Figure 15: Time to first appropriate discharge of ICD by smoking status prior to receiving ICD. .................................................................................................................................................................................. 53

Figure 16: Time to first appropriate discharge of ICD in patients who reported participating in vigorous physical activity. .................................................................................................................................................................................. 54

Figure 17: Time to first appropriate discharge of ICD in patients who reported increased heart rate from physical activity more than three times per week. .................................................................................................................................................................................. 55

Figure 18: Time to first appropriate discharge of ICD by minutes per week of reported moderate to vigorous physical activity. .................................................................................................................................................................................. 56
List of Abbreviations

ACSM – American College of Sports Medicine
AD - Autosomal dominant
AHA- American Heart Association
ARVC- Arrhythmogenic right ventricular cardiomyopathy
BMI- Body Mass Index
BNP-B-type natriuretic peptide
Bpm – beats per minute
CDC – Centers for Disease Prevention and Control
CI-Confidence Interval
CPA-Compendium of Physical Activities
CSEP- Canadian Society of Exercise Physiology
cTnI- Cardiac troponin I
ECHO- Echocardiogram
ECG- Electrocardiogram
HR-Heart rate
ICD- Implantable cardioverter defibrillator
LVE-Left ventricular enlargement
MET- Metabolic equivalent
NIH – National Institutes of Health
NL- Newfoundland and Labrador
NOK- Next of Kin
PA-Physical Activity
PASP- Pulmonary artery systolic pressure
PI-Primary Investigator
PP- Primary prophylactic
PPAQ- Paffenbarger Physical Activity Questionnaire
PPARγ- peroxisome proliferator activated receptor gamma
PPRE- Peroxisome proliferator response element
PVC- Premature ventricular contraction
RR- Relative Risk
SAECG- Signal averaged electrocardiogram
SCD- Sudden cardiac death
TFC- Task Force Criteria
TP- Heart transplant
VA- Ventricular arrhythmia
VT- Ventricular tachycardia
WHO- World Health Organization
CHAPTER ONE: INTRODUCTION

1.1 Rationale

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart condition that can result in arrhythmias, heart failure and sudden cardiac death (SCD). It is most commonly characterized by fibrofatty replacement of the heart muscle quite often in both ventricles. Diagnosis of ARVC is often very difficult because many of the associated symptoms can be nondescript or even absent. ARVC is typically diagnosed using the Task Force Criteria (TFC) which uses a combination of known clinical test results and family history to create a diagnostic score [1]. The TFC has been modified in recent years to include the status of known disease causing mutations. Currently there are 12 known loci and eight identified genes for ARVC. While considered to be rare in the general population, with a prevalence of approximately 1 in 5000 [2] there are some regions of the world where it has been found to be more common. In Newfoundland, Canada extensive research has shown a strong genetic link in several families. Linkage analysis showed that the disease was at locus 3p25 and subsequent molecular work determined the causative gene to be TMEM43, with the causative mutation a p.S358L missense [3]. This discovery now allows for early and accurate pre symptomatic diagnosis of the disease allowing for timely prophylactic treatment, and a decrease in overall morbidity and improved survival. Treatment for this disorder is the implantable cardioverter defibrillator (ICD) which monitors heart rhythm and provides an electric discharge if a malignant heart rhythm is detected, returning the heart to a normal sinus rhythm.
Since the discovery of the gene responsible for causing ARVC in families from Newfoundland and the ascertainment of a large affected population, there has been increased interest in identifying other factors that may influence the penetrance and progression of the disease. One area of interest is the role that physical activity (PA) may play in disease progression.

Significant research has indicated that PA may put individuals with various genetic cardiovascular diseases, including ARVC, at an increased risk for SCD [4]. In a study examining SCD in adolescents and young adults in Italy [5] it was found that ARVC was associated with the greatest risk of SCD in young athletes. Another large postmortem survey of athletes in the United States found ARVC to be responsible for three percent of SCD [6]. In a 2006 study Kirchhof and his colleagues created a functional phenotype of ARVC in a mouse model and found endurance training accelerated the development of ARVC [7].

Decades of research have highlighted the importance of PA for controlling cardiovascular disease and other chronic illnesses. As such, it seems contradictory to suggest that with this cardiovascular disease PA may cause more harm than good in affected individuals.

The present study sought to examine the association between PA and the onset and progression of ARVC caused by p.S358L in \textit{TMEM43} in a population of patients from Newfoundland, Canada who had received an ICD as primary prophylactic treatment (PP) (treatment based on genetic results, not clinical cardiac results). Treatment was determined to be PP if the patient had no previously reported ventricular tachycardia (VT), no clinical diagnosis based on TFC but tested positive for the p.S358L mutation.
1.2 Aims and objectives

The primary objectives of this study were:

1. To retrospectively evaluate past PA practices in patients with ARVC due to p.S358L TMEM43 prior to receiving an ICD for PP treatment.

2. To determine if an association exists between reported PA in patients with ARVC caused by a p.S358L mutation in TMEM43 and time to appropriate discharge of their ICD.

The secondary objectives of this study were:

1. To assess other clinical cardiac symptoms and cardiac test abnormalities at the time of ICD implantation and determine their association to time to penetrance of ARVC caused by a p.S358L mutation in TMEM43 as determined by time to appropriate discharge of the ICD.

2. To assess other modifiable risk factors such as body mass index (BMI) score and smoking status at the time of ICD implantation and determine their association to time to penetrance of ARVC caused by a p.S358L mutation in TMEM43 as determined by time to appropriate discharge of the ICD.

This study will also serve to determine appropriate PA guidelines for patients who have received an ICD as PP treatment for ARVC caused by a p.S358L mutation in TMEM43. This will hopefully assist physicians, genetic counsellors and other health care providers on how to appropriately educate current and future patients with this specific mutation on safe PA guidelines.
CHAPTER TWO: LITERATURE REVIEW

In order to gain an adequate knowledge base for this study an extensive literature review was conducted. The search was broken down into three general areas. The first served to provide significant background information on ARVC. This included the cause, symptoms, diagnosis and treatment of the disease. This second served to acquire more knowledge about the genetic subtype used in this study. The third was performed to understand current theories and research examining the impact PA can have on the onset and progression of ARVC. The databases Pubmed, CINAHL and MEDLINE (OVID) were searched regularly from inception of the study until April 2016. The search used the following terms along with synonyms and related words: “Arrhythmogenic Right Ventricular Cardiomyopathy”, “Arrhythmogenic Right Ventricular Dysplasia”, “ARVC”, “ARVD”, “Physical Activity” and “Exercise”. The search was not limited by study design, date or language of publication.

2.1 Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a rare cardiovascular disease that can cause SCD in young men and women, particularly if it is left undiagnosed. It is characterized as the gradual fibrous and fatty replacement of the myocytes in the right ventricle (and frequently the left ventricle) of the heart which can eventually lead to fatal VTs and heart failure. To date there have been twelve different loci identified for ARVC, eight of which have been mapped to a specific gene sequence (i.e. the causative gene and underlying mutation (s) is known). The current research focused on a genetic form of ARVC caused by a p.S358L mutation in TMEM43 prevalent in Newfoundland, Canada.
2.1.1 History

Historical medical literature indicates that ARVC has likely been present throughout the ages, however, very little was known about the disease until half a century ago, in 1961, when the first known cases of the disease were documented and described [8]. At that time a review was published describing several cases of strong right atrial contractions of the right ventricular pressure curve, referred to as auricularisation [9]. It was not until the late 1970’s that a team of French cardiologists, led by Guy Fontaine, became the first group to name and describe the disease. The group called the disease arrhythmogenic right ventricular dysplasia. The term dysplasia was used because it was believed that the disease was caused by abnormal development of the right ventricle. Their report described six patients who had experienced sustained VT originating from the right ventricle [2]. The team also noted that fibrous fatty tissue was present throughout the myocardium and the patients had not previously been diagnosed with overt heart disease.

In 1982 Marcus and colleagues were credited as the first group to provide a clinical description of arrhythmogenic right ventricular dysplasia and noted that the disease had a tendency to run in families. This was revealed when the group described 24 cases of arrhythmogenic right ventricular dysplasia including two members of the same family [10].

As researchers became more knowledgeable about the disease the name was more revised, and became ARVC. This change in name reflected the understanding that the development of the disease was the result of progressive changes to the myocardium rather than abnormal development as previously thought [9].
In the thirty years since the first clinical description of ARVC there has been significant research by several groups, all with the common goal to more fully understand and explain the diverse and complex aspects of this unique disease.

2.1.2 Pathophysiology

ARVC is often described as a disease of the desmosomes, the very important intercellular adhesion cells in the heart muscle. The desmosomes provide mechanical connections between myocytes which aid in the electrical conduction of the heart muscle. Most known forms of ARVC have been genetically mapped to mutations in specific desmosomal proteins however others, such as *TMEM43* and the subject of this thesis, have been linked to other, non desmosomal, proteins found in the heart muscle [3]. The mutant desmosomal proteins can become very sensitive to the mechanical stress of the heart, especially over time. Repeated stress can cause myocyte death and the gradual fibrofatty replacement of the myocardium in the ventricles [11]. The fibrofatty replacement can cause thickening of the wall of the ventricle and can interfere with proper electrical conduction of the heart. Improper electrical conduction can lead to life threatening ventricular arrhythmias (VA).

Current research is interested in examining if modifiable risk factors are associated with causing more rapid fibrofatty replacement of the myocardium, thus expediting the disease progression and if there are potential factors that could help slow the fibrofatty replacement and preserve the myocardium in people affected with ARVC.
2.1.3 Diagnosis

ARVC is a gradual disease with changes to the heart muscle occurring slowly over time. It is often very difficult to diagnose in the general population because the symptoms can be subtle or non-existent. ARVC is often described as having four clinical phases. The first phase is referred to as the concealed phase. During this time no discernable symptoms are present even though the heart may be beginning to experience some structural changes. The second phase is the overt phase in which noticeable changes have started to occur in the heart and mild symptoms such as light-headedness or palpitations may be present. The third phase is weakening of the right ventricle. During this phase the right ventricle has become compromised and the patient would be at a high risk of experiencing a potentially life threatening arrhythmia. The fourth and final phase is characterized by the weakening of the left ventricle. During this phase the function of both ventricles is compromised and could result in heart failure. Risk for SCD is present during all four phases.

In 1994 an International Task Force created clinical diagnostic criteria for ARVC based on various known features of the disease[4], these guidelines separated symptoms into major and minor categories and are often referred to simply as the TFC. A positive diagnosis required the presence of a combination of 2 major criteria, 1 major and 2 minor criteria or 4 minor criteria. A serious shortcoming of the original TFC was that it was based predominately on the presentation of clinical symptoms. This inherently created an ascertainment bias, in that people with mild disease may never be diagnosed because they do not exhibit any symptoms or people with advanced disease may be undiagnosed if their first clinical symptom is SCD. Unfortunately ARVC, like most genetic diseases, can have variable expressivity or reduced penetrance which
can create difficulty in both diagnosing and determining how to treat the disease in different individuals. Variable expressively means that the disease can affect or be expressed differently in related individuals. Reduced penetrance means that even though an individual may have the gene mutation the disease may never fully manifest.

Overtime with technological advancements and increased knowledge of the disease several recommendations have been made to modify the original diagnostic criteria [1] and take into account genetic and other factors. The family history criteria were considerably revised and three new major criteria were created, these included; 1. ARVC confirmed in a first degree relative who met TFC 2. ARVC confirmed pathologically at autopsy or surgery in a first degree relative and 3. Identification of a pathogenic mutation categorized as associated or probably associated with ARVC. A table comparing the original and the revised TFC can be found in Appendix A.

### 2.1.4 Treatment

Currently there is no cure for ARVC; however several treatment options are available to patients that aim to control symptoms and prevent progression and potentially fatal arrhythmias associated with ARVC. With this being the case one of the most important factors in treating ARVC is early diagnosis.

In patients determined to be at a lower risk for ARVC antiarrhythmic drugs, such as sotalol and amiodarone (in combination with β-blockers) are often prescribed to help control the occurrence of VT. In high risk cases ICDs have become the preferred and recommended treatment method. The current recommendations are that unless clinical signs are present, then the ICD should not
be used for primary prevention [12]. For the genetic subtype highlighted in this study, primary prevention is the only method to stop early death [13]

Identifying and avoiding known risk factors can also play a very important in role in controlling the symptoms and progression of this disease. One of the primary objectives of the current study was to investigate PA as a potential risk factor in the genetic subgroup of ARVC caused by a p.S358L mutation in \textit{TMEM43}.

\textbf{2.1.5 ARVC caused by a p.S358L mutation in \textit{TMEM43} in Newfoundland and Labrador}

The province of Newfoundland and Labrador (NL) is considered to be genetically isolated making it an excellent location to study rare genetic diseases[14]. One genetic disease that is highly prevalent in NL is ARVC.

In the late 1980’s a family in Newfoundland, Canada was identified to have an autosomal dominant (AD) form of ARVC. This type of ARVC was found to be linked to the short arm of chromosome 3 at 3p25 [15]. Over the next several years many additional families were found to be linked to the same chromosomal area and could be identified by a set of DNA markers referred to as a haplotype. Extensive research began on this population, collecting data both retrospectively and prospectively, reviewing medical records and family histories, spanning over several generations. Data was collected on the patients with confirmed ARVC as well as their first degree relatives. Using the previously established ARVC TFC, new guidelines appropriate to this population were established to identify both low and high risk patients in this population. Originally, a patient was considered to be at a high risk of having ARVC if they had documented sustained VT or SCD before the age of 50, the presence of the known high risk DNA haplotype
after genetic testing, or they had been determined to be an obligate carrier (having a parent and offspring affected with ARVC).

In 1998 a cardiomyopathy genetics research clinic was established in St. John's Newfoundland at the Health Sciences Centre. At that time all patients born at an a priori 50% risk of ARVC (either affected themselves or had a first degree family member affected) were able to receive the genetic haplotype testing. ICDs were offered to all patients found to possess the high risk DNA haplotype and had an abnormal clinical test consistent with the ARVC TFC. In this population ICD therapy was shown prior to the causative gene being discovered to significantly decrease mortality in patients receiving the ICD for secondary or primary therapy for ARVC [15], a situation which has recently been confirmed with 10 years further follow up [16].

Over the next ten years a large cohort of 496 affected patients and their first degree relatives from fifteen different families were identified. This established population provided invaluable information about the disease. In 2008, using positional mapping, researchers were able to identify the gene *TMEM43* [3], and determined it to be caused by a p.S358L missense mutation. At that time all previously identified clinically affected patients were found to be mutation carriers. It was also concluded that males had disease associated symptoms, heart failure and death at a much younger age when compared to affected females [3]. With the gene discovery diagnosis could now be made directly following direct mutation analysis, allowing for diagnosis to be made before the onset of clinical symptoms and without requiring the presence of any abnormal clinical test results. This is of particular importance with this type of ARVC because
expression of the disease is highly variable and many affected individuals often do not fulfill TFC for diagnosis [16].

The extensive, multigenerational data collected from this cohort has been used to gain a better understanding of this disease and continue to improve diagnostic criteria to allow for earlier detection and appropriate treatment. In this population ICD therapy has shown significantly improve survival in both males and females [13, 15]. Because males were shown to develop symptoms at a younger age, all post-pubertal males who tested positive for the gene mutation were offered ICD therapy. Females who tested positive for the gene mutation were typically offered ICD therapy after they received an abnormal result on a clinical cardiac test [13]. An ICD was considered to be secondary prevention therapy if it was given following a clinically documented episode of sustained VT/VF. If no previous VT/VF had been reported before the ICD was implanted, treatment was considered to be primary prevention. The ICDs in this population were programmed to discharge (fire) when a patient experienced a sustained VT/VF or VT/VF of greater than 240 beats per minute (bpm). These limits indicate serious cardiac events and thus the time of a first appropriate discharge of the ICD is considered an event that would have been synonymous with death, had the ICD not been present. Analysis of ICD data in this population supports this theory [13].

Because of the high mortality associated with this genetic subtype of ARVC the genetic mutation testing and use of ICDs for treatment have been able to significantly improve disease associated mortality in this population. However, because the variable expression of the disease is wide it is
important for researchers to examine other risk factors that may contribute to penetrance and expression of this disease, such as PA.

2.2 Physical Activity and the Heart

PA is defined as any bodily movement produced by the skeletal muscles that requires energy expenditure [17]. PA can include exercise as well as non-exercise activities. Exercise is considered to be a planned activity that is structured and repetitive in nature with the intention to maintain or improve an individual’s health [18].

2.2.1 Measurements of Physical Activity

PA is often considered a modifiable risk factor for many diseases. As such, the measurement of PA is essential in epidemiological research to determine its association with a variety of health outcomes [19]. Numerous methods are available to measure PA both objectively and subjectively. The most practical and widely used method is the use of interviewer or self-administered questionnaires [20, 21]. Questionnaires often ask participants to recall PA habits over a defined period of time (past 24 hours, past week, past year and even lifetime). They are often inexpensive, easy to use for large groups and are minimally invasive to participants [21-24].

One of the most commonly used questionnaires, particularly in cardiovascular research, is the Paffenbarger Physical Activity Questionnaire (PPAQ), also referred to as the Harvard Alumni Activity Survey and the College Alumni Questionnaire [25].
There are objective measures to assess PA. The two most common methods are the use of accelerometers and direct cardiorespiratory testing. Accelerometers are devices, which are worn by participants to measure frequency, intensity and duration of PA for a specific period of time [26]. Cardiorespiratory testing is typically done in a laboratory setting, using a treadmill or cycle ergometer to measure maximal (or submaximal) oxygen uptake (VO2max). Both measurements have been shown to provide accurate estimates of PA; however they are often costly and can be very onerous to participants. Both of these methods are often used to assess the validity of PA questionnaires [27].

In research PA is often measured by the type of activity and its intensity. In 1993 the Compendium of Physical Activities (CPA) was created as a resource to promote consistency in PA measurement across research [28], it was updated in 2000 and again in 2011 [29, 30]. The CPA is an extensive list of common physical activities with corresponding intensity values. The intensities are measured using a value referred to as a metabolic equivalent or MET. The MET values were created based on pre-determined energy costs for certain activities [31]. A MET value of one is considered to be the amount of oxygen that is metabolized at rest while seated and is equivalent to 3.5 mL/kg/min of oxygen consumption [32].

2.2.2 Cardiovascular Benefits of Physical Activity

Decades of research have shown the irrefutable benefits of PA for cardiovascular and overall health. The American Heart Association (AHA) lists sedentary lifestyle as one of five major risk factors for cardiovascular disease, along with high blood pressure, abnormal blood lipids profiles, smoking and obesity[33]. Extensive research has shown that decreasing any of these risk factors could greatly reduce an individual’s chance of having a heart attack or experiencing
another cardiac event. Regular exercise and PA can play an important role in reducing several of these known risk factors [33-36].

2.2.3 Physical Activity Guidelines for Cardiovascular Health

With the many known benefits of PA for promoting health and preventing disease, guidelines were created to provide the public with healthy and safe PA recommendations needed to gain optimal health benefits. In 1996 the Surgeon General released a report with the intention to promote PA in the United States [37]. This report was supported by the Centers for Disease Control and Prevention (CDC), the American College of Sports Medicine (ACSM) and The National Institutes of Health (NIH) [38, 39]. Similar guidelines were also adopted in Canada by the Canadian Society of Exercise Physiology (CSEP) [40] and internationally by the World Health Organization (WHO) [17].

Current Canadian guidelines recommend, adults aged 18 to 64 years, should accumulate at least 150 minutes per week of moderate to vigorous intensity PA to achieve health benefits[40], with more PA providing greater benefits. American health organizations provide similar recommendations but also emphasize that for additional and more extensive health benefits, adults should increase their moderate to vigorous PA to 300 minutes per week[38].

These guidelines for minimal PA required for optimal cardiovascular benefits are well established, actively promoted and made readily available to the general public. Unfortunately, there are few resources available in terms of guidelines for whether or not an upper limit exists of how much PA is too much and may actually cause an individual more harm than good. With
more recent guidelines recommending even higher levels of weekly PA there may be a need to establish additional recommendations on how much is too much.

2.2.4 Adverse Cardiovascular Adaptations to Physical Activity

Individuals who are very physically active are often perceived to be healthy and can appear to be impervious to illness because of their superior level of physical fitness. Over the past several decades significant research has looked at the impact that high level PA can have on the cardiovascular system. It is well established that high levels of regular PA can cause structural and functional changes to the heart [5, 41, 42] often referred to as “athlete’s heart”. Changes can include increased cardiac mass and dilation of the both the atria and ventricles. These changes are typically not harmful and are considered a natural adaptation to training; however, there is significant evidence to suggest, that in some cases, these adaptations can become harmful and even fatal.

In 2006 a study was conducted using both biochemical and electrocardiographic assessments to examine myocardial injury after endurance exercise [43]. Twenty seven participants were evaluated one week before completing an ultra-endurance triathlon, as well as immediately after and one week later. Cardiac troponin I (cTnI) and B-type natriuretic peptide (BNP), known markers of myocyte damage were measured and right ventricular function was assessed. At baseline right ventricular function was normal in all athletes, post raced measurements showed significant right ventricular dysfunction. Both cTnI and BNP were significantly increased after exercise in 57.7% and 100% of participants respectably, indicating that myocardial injury had occurred. All levels returned to normal one week after the race.
This study hypothesized that the right ventricle, when compared to the left, is less capable of accommodating the sustained increased cardiac output experience during endurance exercise, and that the abnormal loading of right ventricular myocytes can result in damage and dysfunction. An increase in pulmonary artery systolic pressure (PASP) during exercise can also increase the afterload demands of the right ventricle causing damage. This study showed acute damage to the right ventricle following endurance exercise but speculated that repeated damage could lead to more serious chronic dysfunction such as VAs and even SCD.

Another study evaluated 46 high level endurance athletes who had participated in sports for more than two hours a day, three times a week for more than five years. All participants were being evaluated for symptoms associated with VA [44]. Using the original TFC for ARVC it was found that the right ventricle was implicated in 86% of the ventricular arrhythmias. After being followed up for a median of 4.7 years 18 of the 46 athletes (39%) had developed a major arrhythmic event, including nine who experienced SCD. This study was important because it showed that elite athletes presenting with arrhythmias often have a high level of irreversible right ventricular damage which can eventually result in severe arrhythmias and SCD. This indicates that endurance sports could play a major role in the development or progression of right VA and dysfunction.

There is often much attention when a young, athlete dies suddenly. The visibility of these cases in the media has led to an increased interest in research investigating the potential causes of death in these seemingly healthy individuals. For instance, in 2007, it was highly publicized when rising elite Spanish soccer player, 22 year old Antonio Puerta suddenly collapsed on the
field in the middle of a match. He was taken to hospital and later died. The autopsy indicated that complications from undiagnosed ARVC were responsible for his death [45]. Closer to home, in 2013, a 16 year old Quebec Major Junior Hockey League prospect from Nova Scotia died on the ice during training camp [46]. It was later revealed that he too had undiagnosed ARVC [47].

While there are many potential causes of SCD in young athletes, ARVC has frequently been implicated as one of the major causes.

2.3 Physical Activity and Arrhythmogenic Right Ventricular Cardiomyopathy

In the early 1990’s Corrado et al. [48] investigated the cause of SCD in 22 young competitive athletes from the Veneto region of Italy. They found that in 18 of the 22 cases death had occurred during or immediately following PA. The 6 patients (all male), diagnosed with ARVC all died during exercise.

In a subsequent study Corrado et al [5] sought to evaluate the risk of SCD in adolescents and young adults participating in competitive sports also in the Veneto region of Italy. They reported that PA was associated with a 2.5 times increased risk of SCD. They also reported that in SCD cases in patients with ARVC, athletes were significantly younger than non-athletes. It should be noted that the Veneto region of Italy is well known to have a high incidence of ARVC attributable to a genetic factor in that area [12, 49-52]. In 1994 Rampazzo and colleagues found the ARVC in that region was caused by a mutation in the TGFβ3 gene at 14q23-q24 and the incidence could be as high as 4.4/1000 [51].
Another Italian study evaluated 32 athletes, 28 males and 4 female, with a mean age of 23 and followed them for 6.7 years [53]. All athletes were previously asymptomatic but had been referred to the study centre for suspected or documented arrhythmias. The study took place before the original TFC for ARVC were established so diagnosis was based on a series of echocardiographic and angiographic test as well as clinical symptoms. Using these criteria all athletes were diagnosed with ARVC. During follow up severe symptoms developed in 50% of the athletes, 81% of the symptoms occurred either during or immediately following participation in sports, including two cases of SCD. This study concluded that ARVC was present in the athletic population, often with no clinical symptoms and it did not affect athletic performance. Unfortunately, it showed that athletes with ARVC are at a high risk of developing severe arrhythmic symptoms often during or following physical exertion. It was believed that PA could play a role in activating several arrhythmogenic mechanisms.

A study in the United Kingdom sought to examine the etiology of SCD in athletes [54]. They included 118 athletes in their study between 1996 and 2008. The athletes in this study were predominately amateur and recreational athletes. Researchers found that most deaths had occurred during or immediately following exercise. Cardiomyopathies were found to be the most common cause of death responsible for 62% of the cases. ARVC specifically, was attributable to 14% of the deaths.

More research was needed to further examine why PA was so strongly associated with the presentation of clinical symptoms and cardiac events in people with ARVC. It was well established that ARVC was a disease that can be caused by mutations in proteins responsible for
cellular adhesion of the cardiac myocytes known as desmosomes [11, 55-59]. Some of these proteins include plakophilin, plakoglobin, desmoglein and plakoglobin. It is believed that mutations in these proteins will lead to impaired adhesion and conductivity between the myocytes eventually leading to dysfunction of the right ventricle and fibrofatty replacement of the damaged myocytes. To further support the role of desmosomal damage as a cause of ARVC a mouse model was created [7]. Investigators also wanted to examine if mechanical stress, caused by PA could alter the phenotypic expression of ARVC. The investigators found by using heterozygous plakoglobin deficient mice they were able to create a functional phenotype of ARVC. Over ten months the plakoglobin deficient mice had both increased right ventricular volume and reduced right ventricular function and that left ventricular size and function had not been affected.

To test the effect of mechanical stress from PA the mice were put on a daily swimming program with the duration increasing from 5 to 90 minutes per day over eight weeks. The endurance training caused premature right ventricular dilation and dysfunction at 5 to 6 months of age. There was no difference in left ventricular size or function after the training program. This study showed that in an ARVC mouse model, right ventricular dysfunction and arrhythmias can be accelerated by endurance training. This indicates that mechanical stress, caused by physical exertion could impact phenotypic expression of ARVC.

The previous studies showed that ARVC can have variable phenotypic expression in a mouse model and that it can be influenced by environmental or modifiable risk factors, such as PA. A study by James et al. sought to investigate if exercise can influence penetrance of ARVC in
patients with desmosomal mutations [60]. The study included 87 participants, 46 male and 41 female with various desmososomal mutations. Their results showed that participants who were described as endurance athletes had a different presentation and clinical course when compared to their nonathlete counterparts. Athletes were found to have more clinical symptoms and develop symptoms at a younger age more often than nonathletes. This study showed for the first time in humans that the amount and intensity of exercise can increase the likelihood of developing VA and heart failure in people with ARVC with known desmosomal mutations.

Another study by Saberniak et al. [61] examined the impact that high level PA can have on myocardial function in patients with ARVC. As we saw before, during PA cardiac output is increased causing increased stress on the walls if the ventricles from volume overload [43, 62], this study used echocardiography and MRI to assess myocardial function in athletes and non-athletes. The revised TFC [1] were used to determine diagnosis of ARVC. Participants were considered to be an athlete if they reported participating in vigorous PA (activities with a MET value ≥ 6) for greater than 260 minutes per week for a minimum of 4 years. In total 110 participants were included in the study, 37 of whom were determined to be athletes. The results showed that athletes had reduced right ventricle and left ventricle function when compared to non-athletes. Athletes were also diagnosed with ARVC and had onset of VA at a younger age than non-athletes. This study indicates that exercise could aggravate and accelerate myocardial dysfunction in patients diagnosed with ARVC.

All the previously presented research has shown a strong association between PA and the onset and progression of ARVC. These studies have implicated mechanical stress on the right ventricle
and subsequent myocyte damage and dysfunction from increased cardiac output during PA as the primary culprit in the accelerated fibrofatty replacement of the right ventricles. However another pathway may also be involved accelerating the damage to the right ventricle and it may be of particular importance in ARVC caused by the p.S358L mutation in TMEM43.

Several studies have shown a reduction in the canonical Wnt/β-catenin signaling pathway in ARVC [55, 63, 64]. It is believed that plakoglobin can become separated from its desmosomal complex and then competes with β-catenin consequently suppressing the pathway. When the canonical Wnt/β-catenin pathway is suppressed the signaling pathway of the adipogenic transcription factor peroxisome proliferator activated receptor gamma (PPARγ) is activated. An activated PPARγ is able to activate a target gene when it binds to a peroxisome proliferator response element (PPRE) found on the gene.

Because of the vast clinical importance of PPAR’s, particularly their ability to regulate genes through PPRE’s a scan was done of the entire genome to identify target genes of PPAR [65]. One of the many target genes with a PPRE was TMEM43, the gene containing the p.S358L mutation in the families used in this study. This could indicate that if TMEM43 is part of the PPAR pathway, dysregulation could contribute to the fibrofatty replacement of the right ventricle and the mechanical stress created by PA may increase the amount of plakoglobin being separated from the desmosomes which in turn could upregulate PPARγ signaling and promote fibrofatty replacement to an even greater extent.
Additionally it is well established that PA is associated with the generation of PPARγ ligands which are needed to activate PPARγ signaling events [66-70]. The increased presence of these ligands in individuals with ARVC could be associated with the increased phenotypic expression of the disease in people who are more physically active.

2.4 Summary

Based on the current literature it is well established that in individuals diagnosed with ARVC, normal levels of myocardial stress can lead to damage and dysfunction of the right ventricle resulting in fibrofatty replacement of the myocardium. Research also indicates that in individuals with healthy hearts, excessive levels of myocardial stress, caused by high levels of PA, can lead to damage and dysfunction of the right ventricle, resulting in transient myocardial damage and fibrofatty replacement of the myocardium. As such it is hypothesized that in individuals diagnosed with ARVC, excessive levels of myocardial stress, caused by high levels of PA can lead to accelerated myocardial damage and dysfunction and subsequent fibrofatty replacement of the right ventricle. Figure 1 summarizes the hypothetical potential pathways to explain how PA may contribute to accelerated phenotypic expression of ARVC in affected individuals.

Currently there is a gap in the existing knowledge as to the various factors contributing to ARVC progression, specifically the role of physical activity on disease progression and expression.

The current study sought to evaluate PA levels in an established cohort of patients diagnosed with the genetic subtype of ARVC caused by the p.S358L mutation in *TMEM43* in
Newfoundland, Canada to determine if an association exists between high levels of PA and expression of disease.
Figure 1: Hypothesized effects of physical activity in ARVC

1 Figure was created by the author to summarize the hypothesized effects of physical activity in ARVC from the literature.
CHAPTER THREE: METHODS

3.1 Ethical Considerations

Ethics approval was obtained from the Human Research Ethics Board of the Faculty of Medicine, Memorial University of Newfoundland (Appendix B) and the Research Proposals Approval Committee (RPAC) of Eastern Health (Appendix C), HIC # 08.157.

Patients living in Newfoundland were first introduced to the study by their cardiologist when they attended an ICD clinic at the Health Science Center in St. John's, Newfoundland. The cardiologist explained the rationale, purpose, possible risks and benefits, as well as the requirements to participate in the study. Patients were then given the opportunity to review the consent form and ask questions before choosing to accept or decline participation in the study. If the patient agreed to take part in the study they had the option to meet with the primary investigator (PI) and complete the questionnaire at that time or take the questionnaire to complete at home and return later. Patients who were not scheduled to attend the ICD clinic for several months were informed of the study over the phone by the cardiologist. If they agreed to participate in the study consent forms and additional study information were sent to them the mail. Those patients were contacted by phone to complete the questionnaire after their signed consent forms were returned to the PI.

Patients living outside of Newfoundland and the next of kin (NOK) of deceased patients were introduced to the study over the phone by a genetics counsellor well known to the patients. The genetics counsellor explained the rationale, purpose, possible risks and benefits, as well as the requirements to participate in the study. If the patient or NOK agreed to take part in the study
consent forms and additional study information were sent to them the mail. Those patients and NOK were contacted by phone to complete the questionnaire after their signed consent forms were returned to the PI.

All patients and NOK were advised of the precautions that would be taken to ensure anonymity and confidentiality of all information. This included storing all collected information in a locked office that only investigators would have access to. All paper files were stored in the office in a locked filing cabinet and all electronic information was stored on a password protected computer with all personal identifiers removed.

3.2 Study Participants

An extensive dataset containing 496 patients (270 males, 226 females) had previously been established from a large study investigating the genetic epidemiology of ARVC in NL [3] and found to be part of a family that was segregating the TMEM43 p. S358L mutation. The cohort used for this study included fifteen families in NL. Data for the original cohort study was collected both retrospectively and prospectively using all available medical records. In total 1009 variables were collected on each patient and all data was stored in the original database. To be included in the study patients had to be born at an a priori 50% risk of inheriting ARVC caused by a p.S358L mutation in TMEM43. This therefore included all those now shown to be affected, all those now shown to be unaffected (who were born at 50% risk), obligate carriers and those remaining at a 50% risk because they have not yet been tested.

The current study was interested in investigating the association of clinical symptoms, cardiac test abnormalities and other demographic variables, specifically PA, at the time of ICD implant
and the progression and expression of their disease. As such the investigators were required to identify an accurate measurement to assess disease progression. Previous research on the original cohort had shown ICD therapy to significantly improve survival in affected patients, particularly males [13, 15]. This research has recently been added to and strengthened [13].

Recommendations were made at the time of the first paper [15] for ICD therapy to be used as both primary and secondary treatment in patients with a high genetic risk of ARVC caused by a p.S358L mutation in *TMEM43*. Typically ICD’s are programmed to discharge or “fire” when a potentially lethal arrhythmia occurs in the heart [71]. The rate at which the device fires is determined by the cardiologist who is sets up the device. Most devices will appropriately discharge when they detect any period of sustained VT. The previous papers on this cohort chose sustained VT at any rate or a rate >240 bpm to be an appropriate firing of the device [13, 15]. The rate of >240 bpm was chosen to reflect the worst events because at that rate the event would have been fatal, so a discharge at a heart rate (HR) of >240 bpm is considered an aborted death [15].

For the purpose of the current study, appropriate discharge of an ICD for sustained VT at any rate or VT >240 bpm was used as the measurement to determine advanced disease progression or phenotypic expression. The first criterion therefore, for study eligibility, patients had to have received an ICD as therapy for their disease. To ensure patients had a similar risk profile and did not already have advanced disease only patients who had received an ICD as PP therapy were included. The treatment was previously determined to be a PP therapy if the patient had no documented history of VT prior to implantation of the device. This information had been
recorded and was retrieved from the original database from the large cohort study. From the original 496 patients, 110 had received ICD’s. Of the 110 patients with ICD’s 82 had received the ICD as a PP therapy and were included in the current study (Figure 2).


3.3 Data Collection

Data collection took place from February 2009 to July 2010 and all new variables were added to the original dataset. All eligible patients (or NOK) were asked to completed a modified version of the PPAQ (Appendix D) [72], to assess the patients past PA habits in the year prior to receiving their ICD.
3.3.1 In-person and phone interviews

Data was collected from three groups of patients. One group included patients who were currently living and receiving treatment in Newfoundland. The second group included patients living and receiving treatment outside of Newfoundland and the third group included deceased patients.

All patients in the first group were in regular contact with a cardiologist and attended an ICD clinic at the Health Science Center in St. John’s, Newfoundland every 6 to 12 months. These patients were introduced to the study by their cardiologist when they attended the clinic for their regularly scheduled appointments. The study was explained to the patients by their cardiologist and they were given the opportunity to ask any questions. If they were interested in participating they were directed to meet with the PI at that time. The PI further explained the study, answered questions and obtained consent. Patients were then asked to complete a short questionnaire with the assistance of the PI. Patients were also given the option to take the questionnaire home and return it to the PI once completed, however all patients choose to complete the questionnaire at that time.

Information was collected from 56 patients who had attended the ICD clinic. Two patients had received heart transplants and were no longer required to attend the clinic. These patients were contacted and introduced to the study over the phone by the cardiologist. Both patients agreed to participate in the study and were sent consent forms in the mail. Once the consent forms were returned to the investigator, the PI contacted the patients by phone and administered the questionnaire.
Several patients were living in rural areas of the province and have their ICD's monitored by a specialist in central Newfoundland. These patients only attended the ICD clinic at the Health Science Center in St. John’s every twelve months. To ensure that the data was collected in a timely manner ten of these patients were contacted and introduced to the study over the phone by the cardiologist. If they agreed to participate they were sent consent forms in the mail. Once consent forms were returned to the PI the patients were contacted by phone and the questionnaire was administered.

The second group of patients were living and receiving treatment outside of Newfoundland. All of these patients were in regular contact with a genetics counselor in Newfoundland. The genetics counselor contacted each of these patients and informed them of the current study. If the patients agreed to participate they were sent a package from the PI. The package included: an instructions sheet clearly explaining what needed to be signed and returned to investigators; several “Release of Information” forms to allow researchers to receive any new information from clinics or hospitals attended by the patient that may be important for the study; two consent forms, one to be signed and witnessed and returned to investigators and the other to be kept for the patients personal records; and an addressed and prepaid envelope to return all information to the investigators. Once consent forms were returned and received the PI contacted the patients by phone and administered the questionnaire over the phone. Of the fourteen patients identified as living outside of Newfoundland thirteen were successfully contacted and participated in the study.
The final group included two patients who had received ICD's as PP treatment for ARVC caused by a p.S358L mutation in *TMEM43* but were deceased at the time of the study. NOK, who had previously been in contact with the genetics counselor, were identified and the genetics counselor made several attempts to contact these patients. One NOK was successfully contacted and agreed to take part in the study. Two consent forms were mailed to the NOK one to be signed and witnessed and returned to investigators and the other to be kept for their personal records. Once consent forms were returned and received the PI contacted the NOK by phone and administered the questionnaire over the phone. The NOK for the remaining patient was unable to be contacted and was therefore not included in this study.

All patients and NOK gave the investigators permission to use any previously collected information that would be useful for the current study. This included reviewing the patient files if necessary and utilizing any information from the preexisting dataset.

### 3.4 Physical Activity Assessment

#### 3.4.1 Modified Paffenbarger Physical Activity Questionnaire

For this study a modified version of the PPAQ (Appendix D) was chosen to retrospectively access the PA levels of the patients from the year before they received their ICD. This questionnaire was selected because it was valid and reliable and allowed patients to easily report previous PA habits. It was also considered to be a good questionnaire for accurately reporting moderate and vigorous PA [22].

For this questionnaire patients were first asked to report how many flights of stairs (1 flight= 10 stairs) and how many kilometers they typically walked each day. Next, they were asked to list
any sports, leisure and recreational activities they participated in during a typical week, as well as how many times per week and the amount of time spent doing the activities. The next section asked them to report seasonal activities that were only done at certain times throughout the year. They were asked to report how many weeks per year they did the activity and for how long they participated in it. The final question asked patients to report how many times per week they participated in an activity that caused their HR to increase or cause them to become short of breath.

3.4.2 Calculation of Physical Activity

Total PA was calculated by how many minutes per week patients reported being physically active. Each reported activity was assigned a MET value from the CPA [30]. Activities with a MET value of less than 3 were categorized as light PA. Activities with MET values between 3 and 5.9 were categorized as moderate PA. And finally all activities listed with a MET value of 6 or greater were categorized as vigorous activity. For each patient, the total minutes per week spent in each category of PA (light, moderate and vigorous) was calculated. For analysis three categories were created using the current PA guidelines and recommendations created by the American College of Sport Medicine [73], the Canadian Society of Exercise Physiology [40] and the World Health Organization[17]. These categories included: 1. Patients who were not meeting the current guidelines (reporting <150 minutes/week of moderate to vigorous PA), 2. Patients who were meeting the current guidelines (150-299 minutes/week of moderate to vigorous PA) and 3. Patients who were exceeding the current guidelines (≥300 minutes/week of moderate to vigorous PA).
3.5 Data Analysis

All new collected variables were added to the preexisting database in SPSS version 16. Analysis was completed using IBM SPSS Statistics version 19.

A cross-sectional analysis was performed to examine the association between self-reported PA and the expression of ARVC caused by a p.S358L mutation in TMEM43. The outcome variable of interest was defined as the presence or absence of the ICD appropriately firing. The primary exposure variable of interest was self-reported weekly minutes of participating in moderate to vigorous PA.

Survival analyses were performed to determine if associations existed between several possible covariates and the time to appropriate firing of the ICD using the Kaplan Meier product limit method and Cox regression analysis to determine relative risk (RR). A p-value of <0.05 was considered significant.

The analysis was performed for the presence or absence of cardiac symptoms prior to receiving the ICD as well as the age in which the ICD was implanted. The cardiac symptoms assessed included heart palpitations (a noticeable rapid or irregular heartbeat), pre-syncope (feeling of lightheadedness with loss of consciousness), chest pain and syncope (temporary loss of consciousness). Age in which the ICD was implanted was categorized into four groups; received the ICD before or equal to 30 years of age, 31-40 years of age, 41-50 years of age and greater than or equal to 51 years of age.
The results from four clinical cardiac tests prior to ICD implant were also examined. These tests included a 12 lead electrocardiogram (ECG), a signal average electrocardiogram (SAECG), a 24 hour Holter monitor test and an echocardiogram. These clinical tests were included because the presence of an abnormal result of one of these tests prior to ICD implantation could indicate a more advanced disease stage and be predictive of appropriate discharge of the ICD. The ECG was considered abnormal if it showed poor R wave progression. The SAECG test was deemed abnormal if the patient exhibited abnormal results on 2 of 3 previously recognized criteria [74]. The Holter monitor test is used to monitor the heart rhythm continuously for a period of time, in this case it was used for 24 hours. The presence of \( >200 \) premature ventricular contractions (PVC) on the 24 hour Holter monitor test was considered to be abnormal. The echocardiogram was considered abnormal if the patient exhibited left ventricular enlargement with left ventricular end diastolic diameter \( >112\% \) at 2 standard deviations above the predicted mean according to Henry’s formula [75].

Three demographic variables were evaluated, sex, BMI category (normal, overweight or obese) and smoking status (ever or never). BMI is a calculation in which a person’s weight in kilograms is divided by their height in meters squared. A BMI calculation of 18.5-24.9 is categorized as normal, a BMI of 25-29.9 is categorized as overweight, and a BMI of 30 or greater is considered obese.

Finally three variables accessing PA levels were used. These included reporting weekly vigorous activity (yes or no), reporting having an increased HR from PA (\( >3 \) times per week or \( \leq 3 \) times
per week) and reported weekly minutes of moderate to vigorous PA (<150 minutes per week, 150-299 minutes per week or ≥300 minutes per week).

Because of the well-known differences in the expression of ARVC caused by the p.S358L mutation in TMEM43 in males and females [3] sex was included in the final multivariate Cox regression analysis as well as any other variables found to have a p value of ≤0.05 from the univariate Cox regression analyses.
CHAPTER FOUR: RESULTS

4.1 Participant Characteristics

In total 82 patients were included in this study, several demographic, clinical and PA characteristics were either collected for this study or made available from the original database from the large previous cohort study.

4.1.1 Demographic Characteristics

Included in this study were 32 (39.0%) men and 50 (60.0%) women. The BMI was calculated for each patient from the year previous to receiving their ICD. The mean BMI for all patients was 27.9. Thirty patients (36.6%) were categorized as normal weight, 24 (29.3%) were categorized as overweight and 28 (34.1%) were categorized as obese. Smoking status was determined by the patients smoking status at the time of their implant. This was categorized as either having never smoked or having ever smoked. Thirty four (41.5%) patients reported having smoked at some point and 48 (58.5%) of patients reported that they had never smoked.

4.1.2 Clinical Characteristics

Extensive clinical variables were collected retrospectively and prospectively for the patients from the previous cohort study. To determine disease progression several pre-implant symptoms and clinical test results were reviewed. As mentioned previously patients were only included in the current study if they had received an ICD as a PP treatment. The presence of other clinical symptoms or abnormal pre-implant clinical test results did not exclude patients. Clinical symptoms reviewed included heart palpitations, presyncoope, chest pains and syncope. Fifty five (67.1%) patients reported experiencing heart palpitations at the median age of 27 years. Forty three (54.4%) patients reported experience presycope at the median age of 29 years.
Twenty two (26.8\%) patients reported experiencing chest pains at the median age of 31 years. Twenty (24.4\%) patients reported syncope at the median age of 26 years.

Prior to receiving their ICD patients were required to undergo several clinical tests to monitor their heart function. Having an abnormal result on any of the clinical tests may indicate a more advanced disease stage. For this study we reviewed the results of four pre-implant clinical tests, these tests included: 1. 12 lead electrocardiogram (ECG)  2. Signal Averaged electrocardiogram (SAECG) 3. A 24 hour Holter Monitor and an 4. Echocardiogram (Echo). Abnormalities for all clinical tests were determined by a physician in the cardiomyopathy clinic and reported in the original database. Forty one (50.6\%) patients had abnormal 12 lead ECG readings prior to have their ICD implanted. Twenty nine (39.7\%) had an abnormal SAECG’s, 51 (63.7\%) had abnormal Holter Monitor results and 42 (55.3\%) of the patients had an abnormal Echo (Table 1).

4.1.3 Physical Activity Characteristics

Using a modified version of the PPAQ patients were asked to retrospectively report their PA habits from the year prior to receiving their ICD.

Patients were asked how many times per week they engage in PA that caused their HR to increase, 44 (53.7\%) of patients reported this occurring more than 3 times per week and 38 (46.3\%) reported this occurring 3 times per week or less. Fifty-five (67.1\%) of patients reported some vigorous activity each week and 27 (32.9\%) reported no vigorous activity. Finally, 37 (46.3\%) patients reported that they were engaging in less than 150 minutes per week of moderate to vigorous PA, 14 (17.1\%) patients reported that they were engaging in 150-299 minutes per
week of moderate to vigorous activity and 31 (37.8%) patients reported that they were engaging in greater than 299 minutes per week of vigorous PA.

4.1.4 Time to Appropriate Discharge of ICD

The median age in which the patients received their ICD’s for PP treatment was 35.7 years. Twenty eight (34.1%) of the patients had their ICD’s implanted at 30 years or younger, 21 (25.6%) had their ICD implanted between the age of 31 and 40, 18 (21.9%) had their ICD implanted between the age of 41 and 50 and 15 (18.3%) patients had their ICD’s implanted after they were 50 years old.

Of the 82 patients included in this study 25 (30.5%) patients experienced an appropriate discharge of their ICD at a median age of 36.3 years (Figure 3).
Figure 3: Time from receiving ICD to experiencing first appropriate discharge of device.

4.2 Kaplan-Meier Time to Event Analysis

For this model several survival analyses were preformed to determine if associations existed between the various demographic, clinical and PA variables and the amount of time from receiving an ICD to the time of the first appropriate discharge of the ICD. The Kaplan Meier product limit method was used and a p-value of <0.05 was considered significant. Analyses were performed for the four cardiac symptoms; palpitations (Figure 4), pre-syncope (Figure 5), chest pain (Figure 6) and syncope (Figure 7), as well as patient age at implant (Figure 8). Additional
analyses were performed on the four clinical test results for 12 lead ECG (Figure 9), SAECG (Figure 10), Holter monitor (Figure 11), and Echo (Figure 12) as well as the demographic variables of sex (Figure 13), BMI (Figure 14) and Smoking Status (Figure 15).

Finally, tests were performed on three different measures of PA; reported vigorous PA (Figure 16), reported times per week HR was elevated from PA (Figure 17) and reported weekly minutes of moderate to vigorous PA (Figure 18). The variables associated with each Kaplan Meier analysis are tabulated in table 1.

In the analysis patients were indicated as censored if they had died, had an appropriate firing of their ICD or at the time of their last follow up in clinic.
Figure 4: Time to first appropriate discharge of ICD in patients who experienced heart palpitations prior to receiving ICD.
Figure 5: Time to first appropriate discharge of ICD in patients who experienced pre-syncope prior to receiving ICD.
Figure 6: Time to first appropriate discharge of ICD in patients who experienced chest pain prior to receiving ICD.
Figure 7: Time to first appropriate discharge of ICD in patients who experienced syncope prior to receiving ICD.
Figure 8: Time to first appropriate discharge of ICD by age of patient when ICD was received.
Figure 9: Time to first appropriate discharge of ICD in patients who had an abnormal ECG result prior to receiving ICD.
Figure 10: Time to first appropriate discharge of ICD in patients who had an abnormal SAECG result prior to receiving ICD.
Figure 11: Time to first appropriate discharge of ICD in patients who had an abnormal 24 hour Holter monitor result prior to receiving ICD.
Figure 12: Time to first appropriate discharge of ICD in patients who had an abnormal Echo result prior to receiving ICD.
Figure 13: Time to first appropriate discharge of ICD by sex.
Figure 14: Time to first appropriate discharge of ICD by BMI prior to receiving ICD.
Figure 15: Time to first appropriate discharge of ICD by smoking status prior to receiving ICD.
Figure 16: Time to first appropriate discharge of ICD in patients who reported participating in vigorous physical activity.
Figure 17: Time to first appropriate discharge of ICD in patients who reported increased heart rate from physical activity more than three times per week.
Figure 18: Time to first appropriate discharge of ICD by minutes per week of reported moderate to vigorous physical activity.
All results from the Kaplan-Meier analysis are presented in Table 1. No significant values were found for any of the clinical cardiac symptom variables or demographic variables.

For the clinical cardiac variables having an abnormal 24 hour Holter monitor result produced a significant result with a log rank p-value of 0.014. The other clinical cardiac variables did not produce significant results.

Finally, all three PA variables produced significant results. Having reported some vigorous PA produced a p-value of 0.023 and engaging in activities that increase heart greater than 3 times per week showed a p-value of 0.009. However participating in higher levels of weekly moderate to vigorous PA produced a p-value of 0.000.

**4.3 Cox’s Regression Analysis**

Univariate Cox regression analyses were performed on all covariates and RR was assessed. The same four variables produced significant p-values. Having an abnormal 24 hour Holter monitor result produced a significant result with a p-value of 0.023 and a RR of 4.1 (CI 1.2-13.7). Having reported some vigorous PA produced a p-value of 0.031 and a RR of 3.2 (CI 1.1-9.5). Engaging in activities that increase heart greater than 3 times per week showed a p-value of 0.013 and a RR of 3.1 (CI 1.3-7.4). Reporting greater than 300 minutes per week of moderate to vigorous activity produced a p-value of 0.000 with a RR of 12.8 (CI 3.7-45.2). All results are presented in Table 1.
Table 1: The prevalence of cardiac symptoms, cardiac test abnormalities, demographic data and self-reported physical activity in association to appropriate ICD discharge at ≥ 240 beats per minute or death in patients who received an ICD as primary prophylactic treatment for ARVC caused by a p.S358L mutation in *TMEM43*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>N*</th>
<th>%</th>
<th>Number of events</th>
<th>Median time to event</th>
<th>Log rank p values</th>
<th>Cox p value</th>
<th>RR</th>
<th>95% CI</th>
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<td>8.85</td>
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<td>%</td>
<td>Number of events</td>
<td>Median time to event</td>
<td>Log rank p value</td>
<td>Cox p value</td>
<td>RR</td>
<td>95% CI</td>
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<td>PVC’s/24hrs</td>
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<td>17</td>
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<tr>
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<td>32</td>
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<td>13</td>
<td>6.33</td>
<td>0.051</td>
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<td>61.0</td>
<td>12</td>
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<td>N*</td>
<td>%</td>
<td>Number of events</td>
<td>Median time to event</td>
<td>Log rank p values</td>
<td>Cox p value</td>
<td>RR</td>
<td>95% CI</td>
</tr>
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<td>7</td>
<td>-</td>
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<td>1.1</td>
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<td></td>
<td>Obese</td>
<td>28</td>
<td>34.1</td>
<td>10</td>
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<td>0.962</td>
<td>1.0</td>
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<td>2.6</td>
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**Physical Activity**
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<th>%</th>
<th>Number of events</th>
<th>Median time to event</th>
<th>Log rank p</th>
<th>Cox p</th>
<th>RR</th>
<th>95% CI</th>
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<td>55</td>
<td>67.1</td>
<td>21</td>
<td>6.56</td>
<td>0.023</td>
<td>0.031</td>
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<td>32.9</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.5</td>
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<tr>
<td>Reported increasing heart rate from physical activity</td>
<td>&gt; 3 times per week</td>
<td>44</td>
<td>53.7</td>
<td>18</td>
<td>6.56</td>
<td>0.009</td>
<td>0.013</td>
<td>3.1</td>
<td>1.3-7.4</td>
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<tr>
<td></td>
<td>≤ 3 times per week</td>
<td>38</td>
<td>46.3</td>
<td>7</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>7.4</td>
</tr>
<tr>
<td>Reported weekly minutes of moderate to vigorous physical activity</td>
<td>&lt; 150 minutes per week</td>
<td>37</td>
<td>45.1</td>
<td>3</td>
<td></td>
<td>-</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Category</td>
<td>N</td>
<td>%</td>
<td>Number of events</td>
<td>Median time to event</td>
<td>Log rank p values</td>
<td>Cox p value</td>
<td>RR</td>
<td>95% CI</td>
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<tr>
<td>activity</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>150-299 minutes</td>
<td>14</td>
<td>17.1</td>
<td>4</td>
<td>-</td>
<td>0.034</td>
<td>5.1</td>
<td>1.1</td>
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<tr>
<td></td>
<td>≥ 300 minutes</td>
<td>31</td>
<td>37.8</td>
<td>18</td>
<td>4.95</td>
<td>0.000</td>
<td>12.8</td>
<td>3.7</td>
<td>45.2</td>
</tr>
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*Frequencies may not total sample size due to missing values*
For the final model a multivariate Cox regression analysis was performed. This model allowed us to control for significant covariates. Sex was also included because of the well-known difference in expression of ARVC caused by a p.S358L mutation in \textit{TMEM43} in males and females. Having an appropriate firing of the ICD was used as the dependent variable. The model included male sex, having an abnormal pre-implant 24 Holter monitor result and engaging in 150-299 minutes/week of moderate to vigorous PA and engaging in greater than 299 minutes/week of moderate to vigorous PA as the covariates.

All results are presented in Table 3. Significant relationships were found for both male sex and abnormal pre-implant 24 hour Holter monitor result with p-values of 0.018 and 0.000 respectively and RR of 2.9 (CI 1.2-7.0) and 16.4 (CI 3.8-71.5). Engaging in greater than 299 minutes per week of moderate to vigorous activity showed a strong association with a p- value of 0.000 and RR of 28.1 (CI 6.9-114.2).

This model suggests that when controlling for sex and having an abnormal pre-implant 24 hour Holter monitor result, patients with ARVC caused by a p.S358L mutation in \textit{TMEM43} who engage in moderate to vigorous PA greater than 299 minutes per week are significantly more likely to experience an appropriate firing of their ICD when compared to patients who do not.
Table 2: Multivariate cox’s regression analysis of covariates associated with appropriate ICD discharge at ≥ 240 beats per minute or death in patients who received an ICD as primary prophylactic treatment for ARVC caused by a p.S358L mutation in *TMEM43*.

<table>
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<th>RR</th>
<th>95% CI</th>
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<td>Male</td>
<td>0.018</td>
<td>2.9</td>
<td>1.2-7.0</td>
</tr>
<tr>
<td>Holter Monitor</td>
<td>&gt; 200 PVC’s/24hrs</td>
<td>0.000</td>
<td>16.4</td>
<td>3.8-71.5</td>
</tr>
<tr>
<td>Reported weekly</td>
<td>150-299 minutes per week</td>
<td>0.061</td>
<td>4.9</td>
<td>0.9-25.9</td>
</tr>
<tr>
<td>minutes of</td>
<td>moderate to vigorous physical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activity</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥300 minutes per week</td>
<td>0.000</td>
<td>28.1</td>
<td>6.9-114.2</td>
</tr>
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</table>
CHAPTER FIVE: DISCUSSION

5.1 Overview of Results

This cross sectional study sought to determine if an association existed between retrospectively self-reported PA and the onset and progression of ARVC caused by a p.S358L mutation in *TMEM43*. Several clinical cardiac symptoms, cardiac test abnormalities and demographic variables from time of ICD implant were also examined to determine their association with time to appropriate ICD discharge.

5.1.1 Time to Event Analyses

For our study, first appropriate discharge of the ICD at any rate for sustained VT or at VT \( \geq 240 \) bpm was used as the measurement to indicate advanced disease stage or phenotypic expression of ARVC caused by a p.S358L mutation in *TMEM43*, as such time to the first appropriate discharge of the ICD was used as the dependent variable in our Kaplan-Meier time to event analyses and our Cox regression analyses. Previous research in this same population indicated that appropriate discharge of the ICD could be considered an event analogous to aborted death \[13\], and therefore an appropriate indicator of phenotypic expression of ARVC caused by a p.S358L mutation in *TMEM43*.

Data on several clinical cardiac symptoms prior to implantation of the patients ICD’s was well documented and reported for this population. Information was available on both the presence of clinical symptoms as well as the age in which clinical symptoms presented. The four clinical symptoms evaluated in this study included heart palpitations, pre-syncope, chest pain and syncope. The presence or absence of each the clinical symptoms were used as explanatory
variables in Kaplan-Meier and Cox regression analyses. None of the clinical symptom variables used in this study were shown to be predictive of time to appropriate discharge of the ICD. This result is not surprising because with this form of ARVC patients may be in the concealed phase of the disease with no evidence of clinical symptoms but still be at a high risk of a cardiac event. Previous research on this population showed that many patients are asymptomatic and that without appropriate ICD therapy, the first presenting symptom in many cases maybe SCD [15]. None of the clinical cardiac symptoms were used in the final multivariate Cox regression analysis.

Data was also available on the results of several clinical cardiac test results performed prior to implantation of the ICD. Of the four clinical cardiac test results that were examined only one test abnormality was associated with time to appropriate discharge of the ICD. Having evidence of greater than 200 PVC’s on a 24 hour Holter monitor prior ICD implantations was shown to be significantly associated with time to first appropriate firing of the ICD. Earlier studies, in this same population, showed that ectopy (a disturbance of the cardiac rhythm) occurred early in the natural history of the disease [16] and that having an abnormal 24 hour Holter monitor results of PVC’s >200 was the earliest sign of disease manifestation in both sexes.

In this same population in a multivariate Cox regression analysis showed that having an abnormal 24 hour Holter monitor result prior to ICD implantation was the only significant independent predictor of appropriate firing of ICD when compared to other clinical test result[13]. Because it was found to be a significant predictor of time to appropriate discharge of
the ICD in both the Kaplan-Meier and Cox regression analysis having an abnormal 24 hour Holter monitor result prior to receiving an ICD was used in the final Cox regression analysis.

Three demographic variables from the patients prior to receiving their ICD’s were also analyzed with Kaplan-Meier and Cox regression analyses to see if they were associated with time to first appropriate firing of the ICD. These included sex, if they had ever smoked or not and BMI, categorized as normal weight, overweight and obese. No demographic variables were associated with time to first appropriate firing of the ICD. However, sex was nearly significant with Kaplan-Meier and Cox regression analyses producing p-values of 0.051 and 0.058 and a RR of 2.1 (CI 1.0-4.9). Much of this data used males who had died, so limiting analyses to those with an ICD introduces a survivor bias: only males alive can be treated. So based upon the clear sex influence of this mutation documented, many times, sex was included in the final multivariate Cox regression analyses [3, 15, 16].

Finally three different measurements of PA were evaluated to determine if an association existed between patient PA levels prior to receiving their ICD and time to first appropriate firing of the ICD. All PA variables were derived from patient reported responses to the PPAQ. One question reported if patients had participated in any weekly vigorous activity. The second question reported how often patients report participating in PA which increased their HR, separated in to greater than 3 times per week or less than or equal to 3 times per week. The final question reported how many minutes per patients participated in moderate to vigorous activity. This question was divided in to 3 categories based on whether patients were not meeting, meeting or exceeding current PA recommendations for optimal health benefits [17, 38, 40]. Kaplan-Meier
and Cox regression analyses found all three measurements of PA to be associated to time to first appropriate firing of the ICD. The strongest association was found with the variable reporting the number of minutes per week patients reported participating in moderate to vigorous PA with p-values of 0.000 in both analyses and produced a RR of 5.1 (CI 1.1-23.1) in the group meeting current PA guidelines and a RR of 12.8 (CI 3.7-45.2) in the group exceeding current PA guidelines.

The final multivariate Cox regression analysis included male sex, having evidence of ventricular ectopy as determined by have a pre-ICD implant 24 hour Holter monitor test showing PVC’s ≥ 200 and both meeting and exceeding current PA guidelines for moderate to vigorous activity (reporting 150-299 minutes per week and ≥ 300 minutes per week respectively). The final results showed having preexisting ventricular ectopy and reporting participating in ≥300 minutes per week of moderate to vigorous activity to be strongly associated with time to first appropriate discharge of the ICD with RR’s of 16.4 (CI 3.8-71.5) and 28.1 (CI 6.9-114.2).

It should be noted that 58% (18/31) of patients who reported participating in ≥300 minutes per week of moderate to vigorous PA experienced an appropriate discharges of their ICD, while only 8% (3/37) patients who reported participating in <150 minutes per week of moderate to vigorous PA experienced an appropriate discharges of their ICD. Additionally, the three patients who reported the most minutes per week of moderate to vigorous PA all experienced an appropriate discharge of their ICD’s.
The results of this study are consistent with two previous studies. One involving 87 ARVC patients with four different desmosome mutations carriers [60] and another involving 110 ARVC patients with eight different pathogenic mutations [61], thus to date this is the largest study of its kind involving a patients with the same ARVC genetic mutation.

### 5.2 Clinical Implications

The results from this study may be very clinically important. Our results show strong evidence between PA and the phenotypic expression of ARVC caused by a p.S358L mutation in *TMEM43*. In the largest, genetically homogeneous, study to date we found high levels of weekly moderate to vigorous activity prior to receiving an ICD as PP treatment to be strongly associated with the time to first appropriate discharge of the ICD. The risk remained high even when the previously identified risk factors of evidence of ventricular ectopy and male sex were controlled for.

This data suggests that guidelines should be created to advise affected individuals about the risks associated with participating in high levels of moderate to vigorous PA. Similar guidelines for participation in recreation and leisure time PA have already been created for other genetic cardiovascular diseases [76, 77], but may need to be modified for this population.

Despite current PA guidelines for optimal health benefits [38] patients with ARVC caused by a p.S358L mutation in *TMEM43* should be cautioned to avoid prolonged periods of high intensity PA.
Modifying their PA habits could significantly influence the progression and expression of ARVC caused by a p.S358L mutation in *TMEM43*.

5.3 Study Limitations

5.3.1 Physical Activity Measurement

Using a retrospective interview based PA questionnaire may have had an impact on our study findings. Patients were asked to report PA habits from prior to having their ICD implanted; as such our measurement of PA relied heavily on the patient’s ability to recall past PA habits. This inherently introduced error in the form of recall bias which could have an impact on the accuracy of the reported data [78].

The questionnaire used in this study, the PPAQ, was originally designed to measure recreational and leisure time activities that are often more likely to be moderate to vigorous in nature [25]. With this being the case, daily, lighter intensity activities, such as occupational and household activities are more likely to be excluded or under reported [22]. This questionnaire relied heavily on what activities the patients considered to be PA.

Additionally, because of the many well-known health benefits of PA our patients may have been more inclined to over report their PA habits to appear more socially desirable, creating a social desirability bias [78, 79].

For a more accurate measure of PA future studies could follow patients prospectively for a specified period of time and use accelerometers to objectively measure weekly PA [80].
5.3.2 Generalizability

Our results pertain only to ARVC caused by a p.S358L mutation in *TMEM43* in patients who received their ICD as a PP treatment therefore these results may not apply to other mutation carriers or be generalizable to other forms of ARVC with different mutations.

5.4 Study Strengths

5.4.1 Cohort Data

This study had the benefit of utilizing a detailed dataset collected from a large previously established genetically homogenous cohort. The extensive data for this cohort was collected both retrospectively and prospectively, spanning several generations. The gene responsible for this form of ARVC has been identified, allowing for all mutation carriers to be accurately diagnosed and identified through genetic testing. As such, this unique population from Newfoundland, Canada has been described as the largest single well characterized subtype of ARVC in the world [13]. The patients in this study have been followed by the same cardiac care team and nearly all decisions regarding ICD therapy were made by the same electrophysiologist in St. John’s, Newfoundland. While this type of ARVC is most common in Newfoundland, Canada it is also present in other populations.

Nearly all previous research on PA and ARVC has focused on ARVC involving desmosome mutations. While our results have shown to be consistent with other studies involving patients with several different forms of ARVC [60, 61] our study is the largest study of its kind involving patients with the same ARVC genetic mutation and the only study that has examined ARVC caused by a p.S358L mutation in *TMEM43* specifically.
5.4.2 Physical Activity Measurement

The PPAQ used in this study is one of the most commonly used questionnaires to measure PA in epidemiological studies [25]. Its reliability and validity has been continuously evaluated [22, 81, 82]. Studies have shown that typically participants more accurately report their moderate and vigorous PA [83]. When compared to objective accelerometer measurements the PPAQ provided similar estimates of moderate and vigorous activity [22] confirming it as a useful tool to assess weekly levels of moderate and vigorous activity. Because current PA guidelines provide recommendations for how much weekly moderate to vigorous PA is needed for optimal health benefits we were specifically interested in accessing the patients levels of weekly moderate to vigorous PA.

This study had the added advantage of all questionnaires being administered either in person or over the phone by the same investigator. This allowed for the questionnaire to be administered in a consistent fashion. It also gave patients the opportunity to ask questions and receive clarification if needed. Having the same interviewer administer questionnaires can improve the overall accuracy of the questionnaire [84].

5.5 Future Research

5.5.1 Pathogenic Pathways

Nearly all previous research investigating PA and ARVC has focused on forms of ARVC involving desmosomal mutations however this study has shown a strong association between PA and the progression of ARVC caused by a p.S358L mutation in *TMEM43*, a transmembrane protein. While our results have shown to be consistent with the desmosomal mutation studies
future research could involve examining the more specific pathogenic pathways which link ARVC caused by a p.S358L mutation in TMEM43 and PA. The TMEM43 gene has been found to be one of the many target genes of PPARγ, an adipogenic transcription factor [65] and PA has shown to generate PPARγ ligands [66] which activate PPARγ signaling. The increased PPARγ signaling, generated during PA, combined with the dysregulation of the PPARγ pathway from the p.S358L mutation in TMEM43 could contribute to accelerated fibrofatty replacement of the right ventricle in patients who are more physically active, thus promoting phenotypic expression.

5.5.2 Other Modifiable Risk Factors

Nearly two decades of research have been devoted to defining and identifying ARVC caused by a p.S358L mutation in TMEM43 in Newfoundland, Canada. The exact gene responsible for this disease has been discovered [3] allowing for early diagnosis and treatment in affected individuals. This type of ARVC has been shown to be highly variable in its phenotypic expression and the current study showed that progression and expression of ARVC caused by a p.S358L mutation in TMEM43 can be influenced when affected individuals participate in high levels of moderate to vigorous PA. This study suggests that PA is a modifiable risk factor that could be adjusted to decrease the burden this disease and improve outcomes. Future research could investigate the role other environmental and modifiable risk factors may have on the progression and expression of ARVC caused by a p.S358L mutation in TMEM43.

5.5 Conclusion

This study showed a strong association between patients who reported participating in a high level of weekly moderate to vigorous PA and the development and expression of ARVC caused by a p.S358L mutation in TMEM43. This association was found to be independent of the
previously established risk factors of male sex and ventricular ectopy prior to receiving an ICD for PP treatment. This association suggests that moderate to vigorous PA may play a role in promoting progression of this disease.

Minimizing participation in high levels of weekly moderate to vigorous PA may be important for patients diagnosed with ARVC caused by a p.S358L mutation in *TMEM43* and could play a role in minimizing adverse outcomes associated with the disease. New guidelines should be created to advise patients with ARVC caused by a p.S358L mutation in *TMEM43* on safe PA recommendations.

Because of the high variability in the phenotypic expression of ARVC caused by a p.S358L mutation in *TMEM43* future research must continue to examine the how genetic and environmental factors interact and influence progression and expression of this disease.
REFERENCES


43. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL: Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. Heart (British Cardiac Society) 2008, 94(7):860-866.


82


## APPENDICES

### APPENDIX A

<table>
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<tr>
<td>I. Global/regional dysfunction/structural alterations</td>
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<td></td>
</tr>
<tr>
<td>Major</td>
<td>• Severe dilatation and reduction of RVEF w/o (or only mild) LV impairment</td>
<td>• Regional RV akinesia, dyskinesia, or aneurysm</td>
</tr>
<tr>
<td></td>
<td>• Localized RV aneurysms (akinetic or dyskinetic areas w/diastolic bulging)</td>
<td>• and 1 of the following (end diastole):</td>
</tr>
<tr>
<td></td>
<td>• Severe segmental dilatation of the RV</td>
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<tr>
<td></td>
<td>By MRI:</td>
<td></td>
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<tr>
<td></td>
<td>• Regional RV akinesia or dyskinesia</td>
<td>• and 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>• Localized RV aneurysms (akinetic or dyskinetic areas w/diastolic bulging)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>• Mild global RV dilatation and/or EF reduction with normal LV</td>
<td>• or PSAX RVOT ≥32 to &lt;36 mm (correct body size [PSAX/BSA] ≥18 to &lt;21 mm/m²)</td>
</tr>
<tr>
<td></td>
<td>• Mild segmental dilatation of the RV</td>
<td></td>
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<td></td>
<td>• Regional RV hypokinesia</td>
<td>By MRI:</td>
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<td></td>
<td></td>
<td>• and 1 of the following:</td>
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<tr>
<td>II. Tissue characterization of wall</td>
<td></td>
<td>By 2D Echo:</td>
</tr>
<tr>
<td>Major</td>
<td>• Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
<td>• and 1 of the following:</td>
</tr>
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<tr>
<td>Minor</td>
<td>• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 60% if est.)</td>
<td>• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction</td>
</tr>
<tr>
<td></td>
<td>• Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
<td>• and 1 of the following:</td>
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<tr>
<td></td>
<td>• Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
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<td></td>
<td>• Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
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</tr>
<tr>
<td></td>
<td>• Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
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<tr>
<td>III. Repolarization abnormalities</td>
<td></td>
<td>By MRI:</td>
</tr>
<tr>
<td>Major</td>
<td>• TWI (V1, V2, V3) or beyond; &gt;14 yrs; in absence of complete RBBB QRS ≥120 ms</td>
<td>• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction</td>
</tr>
<tr>
<td>Minor</td>
<td>• TWI in right precordial leads (V2 and V3) (people age &gt;12 yrs, in absence of RBBB)</td>
<td>• and 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>• TWI in right precordial leads (V2 and V3) (people age &gt;12 yrs, in absence of RBBB)</td>
<td></td>
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<tr>
<td></td>
<td>• TWI in right precordial leads (V2 and V3) (people age &gt;12 yrs, in absence of RBBB)</td>
<td></td>
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<tr>
<td></td>
<td>• TWI in right precordial leads (V2 and V3) (people age &gt;12 yrs, in absence of RBBB)</td>
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85
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<thead>
<tr>
<th>IV. Depolarization/conduction abnormalities</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
</tr>
<tr>
<td>• Epsilon waves or localized prolongation</td>
</tr>
<tr>
<td>(&lt;110ms) of QRS complex in right precordial</td>
</tr>
<tr>
<td>leads (V1 to V3)</td>
</tr>
<tr>
<td>• Epsilon wave (reproducible low-amp signals</td>
</tr>
<tr>
<td>(btn end of QRS complex to onset of T wave)</td>
</tr>
<tr>
<td>in right precordial leads (V1-V3)</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>• late potentials (SAECG)</td>
</tr>
<tr>
<td>• LP by SAECG in ≥1 of 3 parameters in</td>
</tr>
<tr>
<td>absence of QRS duration of ≥1 10ms on</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>1. Filtered QRS duration (fQRS) ≥114ms</td>
</tr>
<tr>
<td>2. Duration of terminal QRS &lt;40μV (LAS</td>
</tr>
<tr>
<td>duration) ≥38ms</td>
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<tr>
<td>3. RMS voltage of terminal 40 ms ≤20μV</td>
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<tr>
<td>• TAD of QRS ≥55ms measured from nadir of</td>
</tr>
<tr>
<td>S wave to end of QRS, including R', in V1,</td>
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<td>V2, or V3, in absence of complete RBBB</td>
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<tr>
<th>V. Arrhythmias</th>
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<tr>
<td><strong>Major</strong></td>
</tr>
<tr>
<td>• LBS NSVT or sustained VT (neg or indet</td>
</tr>
<tr>
<td>QRS in II, III, and aVF and pos in aVL)</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>• LBBB sustained or NSVT (ECG, Holter, ETT)</td>
</tr>
<tr>
<td>• &gt;1000 ventricular extrasystoles per 24</td>
</tr>
<tr>
<td>hours (Holter)</td>
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<tr>
<td>• NSVT or sustained VT of RV outflow</td>
</tr>
<tr>
<td>configuration, LBI (pos QRS in II, III, and</td>
</tr>
<tr>
<td>aVF and neg in aVL) or of unknown axis</td>
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<tr>
<td>• &gt;500 ventricular extrasystoles per 24</td>
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<td>hours (Holter)</td>
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<tr>
<th>VI. Family History</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
</tr>
<tr>
<td>• Familial disease confirmed at necropsy or</td>
</tr>
<tr>
<td>surgery</td>
</tr>
<tr>
<td>• ARVC/D confirmed in FDR who meets TFC</td>
</tr>
<tr>
<td>• ARVC/D confirmed pathologically at</td>
</tr>
<tr>
<td>autopsy or surgery in FDR</td>
</tr>
<tr>
<td>• Pathogenic mutation (assoc or probably</td>
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<tr>
<td>assoc w/ ARVC/D) in pt under eval</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
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<tr>
<td>• Fam hx of SD (&lt;35yrs) due to suspected</td>
</tr>
<tr>
<td>ARVC/D</td>
</tr>
<tr>
<td>• Familial hx (clinical dx based on present</td>
</tr>
<tr>
<td>criteria)</td>
</tr>
<tr>
<td>• Hx of ARVC in FDR in whom not poss or</td>
</tr>
<tr>
<td>pract to determine if FM meets TFC</td>
</tr>
<tr>
<td>• Premature SD (&lt;35 yrs) due to suspected</td>
</tr>
<tr>
<td>ARVC/D in FDR</td>
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<tr>
<td>• ARVC/D confirmed pathologically or by</td>
</tr>
<tr>
<td>current TFC in 2ndDR</td>
</tr>
</tbody>
</table>
December 2, 2008

Reference #08.157

Ms. S. MacLaughlin
Clinical Epidemiology
Room 1756
Health Sciences Centre

Dear Ms. MacLaughlin:

RE: “The influence of exercise in arrhythmogenic right ventricular cardiomyopathy (ARVDS)”

This will acknowledge receipt of your correspondence, dated November 26, 2008

This correspondence has been reviewed by the co-chair under the direction of the Committee Full approval of this research study has been granted for one year effective November 6, 2008. This is to confirm that the Human Investigation Committee reviewed and approved or acknowledged the following documents (as indicated):

- Revised consent form, dated October 8, 2008 approved
- Telephone script, approved

This approval will lapse on November 6, 2009. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. The information provided in this form must be current to the time of submission and submitted to HIC not less than 30 nor more than 45 days of the anniversary of your approval date. The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- Your ethics approval will lapse
- You will be required to stop research activity immediately
- You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again

Lapse in ethics approval may result in interruption or termination of funding.
February 3, 2009

Ms. S. MacLaughlin  
Clinical Epidemiology  
Room 1756  
Health Sciences Centre  
300 Prince Philip Drive  
St. John’s, NL A1B 3V6  

Dear Ms. MacLaughlin:

Your research proposal “HIC # 08.157 — Exercise in arrhythmogenic right ventricular cardiomyopathy”, was reviewed by the Research Proposals Approval Committee (RPAC) of Eastern Health at its meeting on February 3, 2009 and we are pleased to inform you that the proposal has been approved.

The approval of this project is subject to the following conditions:

- The project is conducted as outlined in the HIC approved protocol;
- Adequate funding is secured to support the project;
- In the case of Health Records, efforts will be made to accommodate requests based upon available resources. If you require access to records that cannot be accommodated, then additional fees may be levied to cover the cost;
- A progress report being provided upon request.

If you have any questions or comments, please contact Donna Bruce, Manager of the Patient Research Centre at 777-7283.

Sincerely,

[Signature]

Mike Doyle, PhD  
Director of Research  
Corporate Strategy & Research  
Chair, RPAC

cc: Ms. Donna Bruce, Manager Patient Research Centre
APPENDIX D

P.I.D #:___________
Date: ____________

Patient Information

Last name: ______________________ First: ________________ Maiden:____________
Address: ___________________________________________________________________
___________________________________________________________________________

Phone #: (H) ________________ (W) ________________ (cell) ____________________

D.O.B. (DD/MM/YYYY): ________________________

Sex: M F  Height: ____________  Weight:_____________

Medical History

1) When were you first diagnosed with Arrhythmogenic Right Ventricular
Cardiomyopathy? _________________________

2) When did you receive your implantable cardioverter-defibrillator (ICD)? (DD/MM/YYYY)
_______________________________________

3) When did you receive your first appropriate shock from your the ICD? (DD/MM/YYYY)
_______________________________________

4) How many times has your ICD given appropriate shocks? _________________
Dates of shocks? (DD/MM/YYYY) 1._________________ 2._________________
3._________________ 4._________________ 5._________________ 6._________________

5) What activity were you doing at the time of the ICD discharge(s)?
1.__________________________________ 2.__________________________________
3.__________________________________ 4.__________________________________
5.__________________________________ 6.__________________________________

6) What activities were you doing the day of the ICD discharge(s)?
1.__________________________________ 2.__________________________________
3.__________________________________ 4.__________________________________
5.__________________________________ 6.__________________________________
PHYSICAL ACTIVITY ASSESSMENT
PLEASE ANSWER THE FOLLOWING QUESTIONS BASED ON YOUR DAILY PHYSICAL ACTIVITY HABITS DURING THE YEAR BEFORE YOU RECEIVED YOUR ICD, OR THE YEAR BEFORE YOU DEVELOPED SYMPTOMS WHICH PREVENTED YOU FROM EXERCISING.

1. How many flights of stairs did you usually climb up each day? (1 flights = 10 steps)
   _______________________________________________________

2. How many kilometers did you regularly walk each day? ______________

3. List any sports, leisure or recreational activities that you may have participated in during a typical WEEK that year. Only include the amount of time that you would have been physically active (i.e. actual time jogging, biking, brisk walking, gardening, carpentry, cutting wood, curling, mowing lawn, cleaning the house, calisthenics, etc.)

<table>
<thead>
<tr>
<th>Sport, Recreation or other physical activity</th>
<th># of times/ WEEK</th>
<th>Average time/ EPISODE Hours &amp; Minutes</th>
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<tbody>
<tr>
<td>1.__________________________________________</td>
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<td>2.__________________________________________</td>
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<td>3.__________________________________________</td>
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<td>4.__________________________________________</td>
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<td>5.__________________________________________</td>
<td>_______</td>
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<tr>
<td>6.__________________________________________</td>
<td>_______</td>
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</table>

4. List any OTHER sports or recreational activities that you may have participated in that YEAR. PLEASE REMEMBER SEASONAL SPORTS OR EVENTS.

<table>
<thead>
<tr>
<th>Sport, Recreation or other physical activity</th>
<th># of weeks/ year</th>
<th>Average time/ week Hours &amp; Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.__________________________________________</td>
<td>_______</td>
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<td>2.__________________________________________</td>
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<td>4.__________________________________________</td>
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<td>5.__________________________________________</td>
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<tr>
<td>6.__________________________________________</td>
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</table>

5. At least once a week did you engage in regular activity akin to brisk walking, jogging, bicycling etc. long enough to get your heart thumping or get you out of breath?
   _______yes ________no
   If yes, how many times per week? __________________