**Etiology of Cardiac Arrest in the Absence of Manifest Structural Heart Disease –
Update from the CASPER Prospective Cohort**

by

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Abstract

Background: The Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) enrolls patients with apparently unexplained cardiac arrest and no evident cardiac disease, and aims to identify the underlying conditions responsible for the cardiac arrest through systematic clinical testing. A combination of exercise testing, drug provocation, electrophysiological testing, advanced cardiac imaging, and targeted genetic testing may unmask the cause of cardiac arrest when a cause is not apparent.

Methods and Results: The first 200 survivors (48.6 ± 14.7 years, 41% female) of unexplained cardiac arrest from CASPER, from 14 centers across Canada were evaluated to determine the results of investigation and follow-up risk of recurrence. Patients were free of evidence of coronary artery disease, left ventricular dysfunction or evident repolarization syndromes. Advanced testing determined a probable or definite diagnosis in 41% of patients. During a median follow-up of 3.15 ± 2.34 years, 23% of patients had either a shock from their ICD or appropriate anti-tachycardia pacing or both. The annual ICD appropriate intervention rate was 0.16 per year (SEM=0.14), with no clear difference in intervention rate between diagnosed and undiagnosed subjects, or between those diagnosed with a primary electrical versus structural etiology.

Conclusions: Obtaining a diagnosis in previously unexplained cardiac arrest patients requires systematic clinical testing and regular follow-up to unmask the cause of cardiac arrest. Nearly half of apparent unexplained cardiac arrest patients ultimately received a diagnosis, allowing for improved treatment and family screening. A substantial proportion of patients received appropriate ICD therapy during follow-up.

Preface

Parts of this thesis were reproduced from the article “Life Threatening Causes of Syncope: Channelopathies and cardiomyopathies” (1) with the permission of Elsevier.

The author (AH) was first author, responsible for the literature review and the writing of this manuscript. The manuscript for this thesis has been submitted. The author (AH) was first author, responsible for the data analysis and the writing of the manuscript.

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List of Abbreviations

ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
BrS	Brugada Syndrome
CA	Cardiac Arrest
CASPER	Cardiac Arrest Survivors with Preserved Ejection Fraction Registry
CCS	Canadian Cardiovascular Society
CCT	Coronary Computed Tomography
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
ECG	Electrocardiogram
ERS	Early Repolarization Syndrome
ERP	Early Repolarization Pattern
FH	Familial Hypercholesterolemia
HCM	Hypertrophic Cardiomyopathy
ICD	Implantable Cardioverter Defibrillator
IHRD	Inherited Heart Rhythm Disorders
LBBS	Left Bundle Branch Block
LQTS	Long QT Syndrome
MRI	Magnetic Resonance Imaging
NSVT	Non Sustained Ventricular Tachycardia
PVC	Premature Ventricular Contractions
RBBB	Right Bundle Branch Block
RV	Right Ventricle
SAECG	Signal Average ECG
SCD	Sudden Cardiac Death
SIDS	Sudden Infant Death Syndrome
SMVT	Sustained Monomorphic Ventricular Tachycardia
SUD	Sudden Unexplained Death
SVT	Sustained Ventricular Tachycardia
VT	Ventricular Tachycardia

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Dedication

To my parents

Chapter 1: Literature Review

1.1 Introduction

Cardiovascular disease is an epidemic, responsible for approximately 1/3 of all deaths in Canada. With nearly 1 death every 7 minutes attributable to heart disease or stroke (2) it is costing Canadian tax payers over 20.9 billion dollars in physician services, hospital costs, lost wages and decreased productivity (3). Approximately half of all heart disease deaths are sudden (4), with over 300,000 North Americans experiencing an out of hospital cardiac arrest per year (5) and half of those sudden cardiac deaths (SCD) are the first reported cardiac event (6). Unfortunately, the survival rate under these circumstances is estimated to be as low as 7.6% (7) with age having an inverse correlation to survival.

The most common underlying etiology of cardiac arrest in the general population is coronary heart disease (58%) (8); however, coronary heart disease is only responsible for 6% of cardiac arrests in young adults (between ages 10-35), suggesting an increased incidence of other causes including inherited heart rhythm disorders (IHRD) in this demographic (9). IHRD cause cardiac arrhythmias that are commonly caused by ion channelopathies, or related to structural abnormalities, a group responsible for approximately 1/3 of sudden cardiac deaths in the young (10). The etiology of sudden cardiac death is difficult to diagnose when structural heart abnormalities are not present and approximately 18% of autopsies do not result in a diagnosis (11) and approximately 5% of all patients who experience a sudden cardiac arrest are without obvious structural heart disease or an external cause (12, 13). The proportion of unknown diagnoses which may be due to IHRD is currently difficult to determine, as the channelopathies underlying

most IHRD do not generally result in obvious gross anatomical abnormalities. A study in a tertiary care center in the Netherlands studied first and second-degree family members of patients that suffered a sudden unexplained cardiac arrest between the ages of 1-50 years. Results from this study found that 33% of patients had an inherited cause of cardiac arrest by investigating surviving family members, listed in Figure 1 (11).

Figure 1: List of Diagnosis and Percentages for Sudden Unexplained Death Families in a Single Tertiary Center in The Netherlands. IVF diagnosis was made in probands with the risk locus at 7q36, present in patients with familial IVF (11). LQTS=Long QT Syndrome, CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia, BrS=Brugada Syndrome, ARVC=Arrhythmogenic Right Ventricular Cardiomyopathy, IVF=Idiopathic Ventricular Fibrillation, FH=Familial Hypercholesterolemia, HCM=Hypertrophic Cardiomyopathy

IHRD are a group of cardiac disorders that predispose to rapid ventricular arrhythmias, leading to syncope, sudden cardiac arrest due to ventricular fibrillation, or

sudden cardiac death. IHRD often go undiagnosed until affected individuals experience an unexplained cardiac arrest (UCA) and/or death. These tragic events may manifest in young, seemingly healthy adults. A recent study in Ontario, Canada, found that over 10 years, 80 children had a sudden unexplained death, with 30% believed to be associated with lethal arrhythmias (14). IHRD are often unrecognized as individually some diseases are rare, however the estimated incidence for the entire population of some form of an IHRD is approximately 1 in 400, resulting in a significant, albeit under reported, impact on families and communities worldwide (15). Increased research is allowing for improved recognition and screening of IHRD, and the media has highlighted recent cases of SCD in high profile athletes bringing IHRD research to the world stage (16). It is hoped that improved recognition of signs and family history of IHRD can be translated into improved diagnosis of the disorder leading to effective prevention.

Presently, the various forms of IHRD such as Brugada Syndrome (BrS), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Early Repolarization Syndrome (ER), Long QT Syndrome (LQTS) and Short QT Syndrome (SQTS) are often diagnosed only after the presentation of a patient who has experienced a symptom of the IHRD (17). Although IHRD research is relatively new, with Brugada Syndrome first described in 1992 (18), folklore has described presumed Brugada Syndrome for much longer. Brugada Syndrome is characterized in south East Asian populations where young men would die in their sleep. Communities in Laos explained these deaths as the responsibility of a “nightmare spirit” named *dab tsog* (19). Diagnosis for SCD in other cultures were referred to as *lai tai* (“died during sleep”) (20) in Thailand, *bangungut* (“moaning and

dying during sleep”) in the Philippines (21), and *pokkuri* (“sudden unexpected death at night”) in Japan (22). While the knowledge of the etiology of disease has continued to evolve, more research needs to be conducted to understand these diseases and allow for diagnosis and effective prevention of sudden death. Unfortunately, the death of seemingly healthy children or young adults is often the first sign of IHRD in a family, leaving families to cope with the loss of a loved one. Furthermore, many of these conditions may be inherited, resulting in concern for relatives who may have an undiagnosed IHRD (23).

The Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) enrolls participants that have experienced an UCA, and are without obvious phenotypic signs of heart disease. These patients require advanced diagnostic testing to determine a diagnosis. The objectives of this study are to study the participants enrolled in CASPER to improve the characterization and management of these UCA patients. As well, we aim to determine the efficacy of diagnostic tests currently used for this population, and to determine the utility of genetic testing.

Diagnosing the etiology of an unexplained cardiac arrest allows for improved direction in patient treatment, as well as family screening to identify others at risk of a cardiac arrest. With the absence of coronary artery disease and a normal ejection fraction, diagnosis may be elusive and requires specialized IHRD clinics. IHRD clinics are multidisciplinary clinics involving electrophysiologists, nurses, genetic counselors and technicians. Patients entering the clinic undergo multiple diagnostic tests (Figure 2), and, due to their often-familial nature, provide a full family history, which may direct genetic testing.

Figure 2: Flow Diagram Depicting Order of Clinical Diagnostic Testing (24)

ECG=electrocardiogram, SAECG=Signal-Averaged ECG, CCT=Cardiac Computed Tomography, Echo=Echocardiogram, MRI=Magnetic Resonance Imaging, EP=Electrophysiology

1.2 Clinical Diagnostic Testing

1.2.1 Patient History

One of the most important “tools” at the physician’s disposal is the collection of a thorough patient history (25) as patient history and physical examination can result in a diagnosis approximately 50% of the time when a patient presents with syncope, a symptom which may be caused by an underlying IHRD (26, 27). Therefore, identifying what questions to ask is imperative to the diagnosis. As the IHRD are often familial in

nature, a complete family history is essential (Table 1). Questions regarding drowning and motor vehicle accidents are especially important to ask, as many patients may not associate these events with their family diagnosis. Genetic counselors are typically central to an IHRD focused clinic, with expertise in history collection and pedigree construction (28).

Table 1: Questions to Ask When Diagnosing Channelopathies

Does the patient have a history of syncope?
Is there a history of syncope or cardiac arrest in the patient's family?
Are there any relatives in the patient's family who have had a sudden unexplained death?
Is there a history of drowning in the patient's family?
Is there a history of crib death in the patient's family (sudden infant death syndrome, SIDS)?
Have there been any suspicious motor vehicle accidents?
Has the patient experienced cardiac symptoms, such as chest pain, or palpitations?

Syncope is defined as a sudden transient loss of consciousness with postural failure due to inadequate cerebral perfusion with spontaneous recovery (1, 29, 30). The incidence of syncope has been reported as 6.2 people per 1000 person-years (31), and the majority of cases are benign in origin. Syncope may have neurological or cardiovascular origins, however syncope may have a life-threatening etiology if caused by ventricular arrhythmias stemming from an IHRD. Therefore, details of the attack can often lead to a diagnosis. Table 2 is a summary of the clinical features of IHRD syncope, neurogenic syncope and seizures. An eyewitness will allow for a first hand account of event, which can be useful in the diagnosis. Minor muscle twitching and urinary incontinence are common with syncope, and thus IHRD patients are often mistakenly diagnosed with seizures. Seizures are often associated with muscle spasms, a characteristic that is mostly not associated with syncope. Seizures are typically longer in duration, with arrhythmic

syncope characterized by an abrupt onset and complete resolution of symptoms that is relatively brief (often < 30 seconds).

Recognizing the events leading up to the cardiac event will also help determine a diagnosis. Neurally mediated syncope is typically associated with upright posture, the sight of blood, or fear of venipuncture (32). Patients will also typically be “warned” as they will experience pre-syncope before the episode. Patients with syncope or a cardiac arrest due to an IHRD, however, rarely experience any presyncope before their events. While some patients experience palpitations leading up to the event, most patients will not have a prodrome (33).

Lastly, the time to complete recovery is an important diagnostic criterion when differentiating between types of syncope and seizures. Typically, the patient feels completely recovered after syncope due to an IHRD within seconds of the event, while neurogenic syncope and seizures typically take much longer for the patient to feel completely recovered (33).

Table 2: Differentiation Between Inherited Heart Rhythm Disorders Syncope, Neurogenic Syncope and Seizures

History	IHRD	Vasovagal	Seizures
<i>Before Episode</i>			
Precipitant	Often none	Prolonged standing, fear, emotional stress, pain	Sleep deprivation, repeated stimuli
Presyncope	Sometimes	Often	Rare
Relationship of Episodes to Posture	None	Usually standing	None
Palpitations	Sometimes	Sometimes	None
Prodrome	Palpitations	Warmth, diaphoresis, nausea, visual blurring	Aura
Onset	Sudden	Usually Gradual	Sudden
<i>During Episode</i>			
Duration	Seconds to minutes	Usually less than a minute	Variable, can be longer than several minutes
Seizure Activity	Unlikely	May have involuntary stiffening	Always
<i>After Episode</i>			
Time to Complete Recovery	Seconds to minutes	Minutes	Minutes to Hours

The symptoms leading to the event are also very important for differentiating between the IHRD. Table 3 distinguishes between the activities that can cause a cardiac arrest amongst the IHRD. One of the obvious questions to ask when a patient has had syncope or a cardiac arrest is whether the patient was exercising or at rest when the episode occurred. Though events may happen under many circumstances, this is often very helpful in distinguishing between IHRD and other mechanisms and will help determine the focus of more intensive testing.

Table 3: Activities Leading to Sudden Cardiac Arrest

Channelopathy	Activity
LQTS	Exercise, auditory stimuli, strong emotion, rest and sleep (LQT3 only)
SQTS	Unknown
BrS	Rest or sleep
ARVC	Exercise
CPVT	Exercise or emotional stress

1.2.2 Medical Pedigree

Often constructed by a genetic counselor, the medical pedigree is a graphic representation of a family, outlining the family's health history and genetic relationships (Figure 3) (34). A medical pedigree provides a picture for the physician to interpret signs of IHRD in the family. Standardized nomenclature for the development of medical pedigrees has been developed (34), and has been adopted in specialized IHRD clinics.

Figure 3: Example of a Medical Pedigree

1.2.3 Electrocardiogram

Originally invented in 1855 by Kollicker and Mueller (35), the electrocardiogram (ECG) has evolved to be the most important diagnostic tool for an

electrophysiologist to detect abnormal electrical conductivity of the heart. All patients in the CASPER registry undergo at least one ECG, with many receiving multiple ECG to determine changes over time due to disease progression.

Despite a modest 5% diagnostic yield, an electrocardiogram (ECG) should be performed in all patients presenting with signs of an IHRD. When attempting to identify a IHRD, the ECG is analyzed for abnormalities in QT duration, T wave morphology, U waves and repolarization (36).

1.2.3.1 Procedure

Patients receiving an ECG may lie in the supine position, or sit in a chair during the ECG. Sensors, called electrodes or leads, are attached to the skin to record the electrical activity of the heart. The recording is digitized on acquisition, and printed on a paper record, called an electrocardiogram, which is interpreted by a trained physician. The 12-lead ECG is composed of 12 separate leads, and can be broken up into different groups, the limb leads, and the chest leads. Leads I, II, III, AVR, AVL and AVF make up the limb leads, and V₁, V₂, V₃, V₄, V₅, V₆ are the chest leads. Multiple leads are used to view different vectors of the same cardiac activity. Therefore, the electrical activity looks slightly different in each lead due to a change in the angle of the “reading” (35). Typical ECG recording are 12 seconds, but longer ECG recordings may occur with the use of Holter Monitoring (see 1.2.4).

1.2.4 Holter Monitor Testing

The Holter Monitor is an ECG that is worn by the patient during a 24-48 hour period. The portable, battery-powered device is worn using a shoulder strap or belt loop, with 3-5 skin electrodes attached for continuous monitoring. The patient is required to

keep a diary of activities and symptoms during the recording. The device also has a button that may be activated if the patient experiences an event to allow the ECG reading to be correlated to the event to determine if it was associated with an arrhythmia (37). Holter Monitors may contribute to a diagnosis by detecting PVCs in diseases such as ARVC, or rarely detects a symptomatic arrhythmia, wherein the ECG recording is diagnostic of the mechanism of the arrhythmia and its correlated diagnosis (e.g. Long QT and torsades de pointes). While Holter monitoring is valuable as a diagnostic tool, it is not without its limitations. As outlined by Subbiah *et al.*, the size of the Holter monitor may prevent the patient from sleeping or exercising which is often when the patient experience arrhythmia (Table 3). Furthermore, many arrhythmias are rare, and will not occur within the 24-48 hour period. Lastly, there is variability in the recollection of activation events, leading to inaccurate symptom-rhythm correlation (37). Limitations of the Holter monitor has resulted in a relatively low diagnostic yield, with a study by Linzer *et al.* finding that Holter monitoring had a diagnostic yield of 19% in patients experiencing symptoms of syncope or presyncope (38).

1.2.5 Signal Averaged ECG

Signal-averaged ECG (SAECG) encompasses a variety of technologies that uses signal-processing techniques to improve resolution of the ECG. Conventional ECGs are unable to detect small changes in signals, but SAECG is able to record microvolt-amplitude signals non-invasively (39). SAECG identify potentials, called late potentials, which are high frequency, low amplitude signals that continue after normal depolarization is complete. These late potentials are believed to represent regions of the myocardium that display slow conduction, which may cause reentrant circuits and

subsequent ventricular tachyarrhythmia's (40). SAECG may also be performed to identify regions of scar tissue, often caused by myocardial infarction, by identifying fractionation of late potentials. Fractionation occurs when bundles of myocardium lack electrically tight connections due to separation by scar tissue (41).

1.2.6 Exercise Stress Test

Many diseases, including LQTS and CPVT, are masked during rest and require exercise to expose phenotypic abnormalities. There are multiple protocols available for treadmill exercise testing, however, CASPER typically uses a modified Bruce protocol. Patients undergo a 12-lead electrocardiogram while in a supine (lying with face up) position, then another immediately upon standing, and continuously during treadmill exercise testing (42). 12-lead ECGs are obtained at 1-minute intervals during exercise, at peak exercise, and at 1-minute intervals during a 6-minute recovery phase (43). QT intervals are investigated to determine if exercise caused prolongation of the QT interval. The patient is also monitored for ventricular arrhythmias, which may suggest CPVT or less frequently QT mediated torsades de pointes. When measuring the QT interval, a corrected interval (QTc) is used to account for changes in heart rate. Bazett's formula is used to calculate the QTc interval and is defined as: $QTc = QT / (RR \text{ interval})^{1/2}$ where $RR \text{ interval} = 60 / \text{heart rate}$ and is measured in lead II or V5 (44, 45). Up to four different techniques have been identified to measure QT interval (46) however CASPER uses a technique that has been defined in previous studies, with the end of the T wave defined as the intersection of the maximum downslope of the ST segment with the isoelectric line of the T-P segment (Figure 4) (47). This technique has been validated by Postema *et al.* in a

study where 151 medical students were able to accurately, and reproducibly, measure the QTc interval in prolonged and normal QTc interval ECGs (46, 47).

Figure 4: How to Determine QT Interval to Calculate QTc, modified from Postema *et al.*

(47)

1.2.7 Drug Infusion Testing

Drug infusion testing is used to unmask arrhythmias when arrhythmias are undetectable on a standard 12-lead ECG. Drug infusions included in the CASPER registry include epinephrine, isoproterenol and procainamide.

1.2.7.1 Epinephrine Infusion

Epinephrine infusions are typically administered to unmask LQTS (48-50) or CPVT (24, 51, 52). Initially, a peripheral IV is started and a baseline ECG is recorded. Upon completion of the baseline ECG, patients are infused with epinephrine, beginning with 0.05 mcg/kg/min for 5 minutes. In five-minute intervals, the epinephrine infusions are increased to 0.10 mcg/kg/min and 0.20 mcg/kg/min and ECGs are performed during

the infusion (50). Epinephrine infusions are discontinued if the blood pressure drops below 80 mm Hg, or rises above 200 mm Hg. If the patient experiences ventricular tachycardia or polymorphic ventricular tachycardia, greater than 10 premature ventricular contractions (PVCs) per minute or previously absent T wave alternans, or experiences symptoms of headache and/or nausea, the epinephrine infusion is concluded (49). Symptomatic patients due to the epinephrine infusion receive metoprolol, a potent beta-blocker that decreases heart rate and myocardial contractility (53).

The frequencies of PVCs are determined with a 1-minute rhythm strip recording after five minutes of infusing the patient with epinephrine. Non-sustained ventricular tachycardia, defined as persistent ventricular tachycardia between 3-30 seconds, and sustained ventricular tachycardia, defined as persistent ventricular tachycardia for longer than 30 seconds, are also recorded. Furthermore, QT intervals and heart rate are measured at the end of each 5-minute period, allowing for the calculation of QTc.

1.2.7.2 Procainamide Infusion

Procainamide is a potent sodium-channel blocker and infusions are typically performed to unmask Brugada Syndrome (BrS). Procainamide infusions are typically performed after the epinephrine infusion in UCA patients, and are initiated after a 30-minute washout period (54). Patients are infused with 15 mg/kg of procainamide to a maximum of 1 g over 20 minutes. ECGs are recorded every 10 minutes during infusion and every 30 minutes after infusion, for up to 1 hour (51).

1.2.7.3 Isoproterenol Infusion

After the infusion of Procainamide, patients suspect for BrS with ≥ 1 mm ST elevation may be infused with Isoproterenol, a beta-adrenergic agonist (55), at 2 $\mu\text{g}/\text{min}$ for 30 minutes. Like the metoprolol is for epinephrine infusion patients, isoproterenol is the “antidote” that counters the effect of procainamide on Na^+ channels. ECGs are recorded for every 15 minutes and ST segments are analyzed for the response in ST segments and evaluated for diagnostic criteria of BrS.

1.2.8 Electrophysiological Testing

Electrophysiological (EP) testing is a general term used to describe the testing of the interaction between the physiology (often pathology) of the heart and the effects of programmed stimulation of the heart. EP testing requires both recording of the electrical characteristics of the heart and pacing. EP studies can lead to diagnosis by measuring alterations in the speed of conduction, the direction of the impulses and whether an arrhythmia is induced. It can be broken down into recording of the intervals in the heart, the amplitude and distribution of signals (voltage and activation mapping) and the evaluation of the induced responses of the heart to programmed pacing maneuvers. Furthermore, EP studies allow for the initiation of pacing from multiple sites to enhance the ability to induce potential culprit arrhythmias (56). Multiple protocols of pacing may be used (Table 7) and in the CASPER study, EP testing typically refers to a protocol that aids in the diagnosis of patients by programmed electrical stimulation (PES) and electro-anatomical mapping.

1.2.8.1 Patient Preparation and Procedure

Prior to the procedure, patients are required to be fasting for at least 6 hours, and may require IV fluid infusion during the procedure to prevent dehydration and subsequent vasovagal syncope (56). Antiarrhythmic drugs are held for at least 4 drug half lives (typically 2-3 days).

Once the patient arrives in the EP laboratory, patients are attached to a 12-lead ECG, a non-invasive blood pressure cuff, pulse oximetry to measure the patient's oxygen saturation during sedation, and defibrillation pads. Defibrillation pads are required as PES may induce life-threatening arrhythmias and require cardioversion or defibrillation (56).

Once the patient is sedated, paired electrode catheters to allow for pacing and recording are inserted into the patient. Typically four catheter electrodes are used, and their location of insertion is determined by the area of interest. Once inserted, differing stimulation techniques (Table 4) are utilized to potentially induce an arrhythmia (56).

Table 4: Types of Pacing Conducted During EP Studies

Simple pacing	Pacing, or delivery an electrical shock, at a constant rate below 300 beats per minute (bpm)
Rapid pacing	Pacing at a constant rate of 300 bpm or over
Delivery of single and multiple timed extrastimuli following sensed beats	Involves the addition of extrastimuli following normal heart rhythm (sinus rhythm) or tachycardia.
Delivery of extrastimuli following a paced drive train	Often used to determine if there is a reentry circuit. The investigator will “drive” the beat by introducing stimuli at a fixed length, often 500 or 600 msec. The investigator will then introduce a second, premature stimuli. The typical protocol is 8 fixed beats at 600 msec, followed by a premature stimuli at 400 msec. The interval to the premature stimuli is then shortened by 10-20 msec, until the myocardium is no longer captured. (57)

1.2.8.3 Electroanatomical Mapping

Electroanatomical mapping uses magnetic technology to detect regions of the heart with fibrosis that may cause arrhythmias (57, 58). Electroanatomical mapping uses a basic physics concept that a metal coil placed in a magnetic field will generate an electric current. A miniature passive magnetic field sensor is embedded in the tip of a mapping catheter, which can detect the strength of each field, and the subsequent position of the catheter in 3D space. The investigator can manipulate the catheter over the endocardial surface of the heart, generating a three dimensional reconstruction of the chamber of interest of the heart with electrogram voltage and activation timing (58). This technology may be used to determine regions of the heart that are causing arrhythmias (such as reentry circuits), or regions with low amplitude endocardial electrograms.

Electroanatomical mapping has been shown to be effective in the diagnosis of ARVC

patients, identifying regions of the heart that have been infiltrated by fibro-fatty tissue with low amplitude electrical signals (59).

1.2.9 Echocardiography

The echocardiography, or echo for short, is a noninvasive imaging technique that uses ultrasonic waves to determine structural or function abnormalities (60). A cross section of the heart may be taken to identify anatomical changes, looking for differences in chamber size or anatomical size, which may lead to a diagnosis (61).

Echocardiography was performed in CASPER patients as a left ventricular ejection fraction (LVEF) of less than 50% was considered an exclusion. Reduced LVEF is seen in patients with known heart disease such as a cardiomyopathy (62), heart failure (63) or a previous myocardial infarction (64). Due to its high prevalence, Hypertrophic Cardiomyopathy (HCM) one of the most frequent causes of SCD despite a relatively low risk of SCD in HCM patients (28) and reduced LVEF is a marker of HCM in both adult and pediatric populations (62, 65). Therefore, a reduced LVEF is an explainable cause of cardiac arrest and an exclusion factor for CASPER.

1.2.10 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imaging technique that may also be used to determine the LVEF of a patient, or more important in CASPER, to determine the presence of ARVC or other more subtle changes. Table 5 highlights the major and minor criteria for ARVC patients.

Gadolinium is a useful agent that improves the contrast between tissue types in patients undergoing an MRI. MRI with gadolinium enhancement aids in the detection of

myocarditis, sarcoidosis and the identification of fibrofatty infiltration in ARVC patients (66, 67).

1.2.11 Coronary Angiogram

A coronary angiogram is an invasive procedure that measures blood flow in the coronary arteries, identifying regions of arteries that are narrowed due to the deposition of plaques in the walls of the arteries. Narrowing or occlusion of the arteries may decrease blood flow to the heart, resulting in a decrease in required oxygen supply to the myocardium or myocardial infarction, increasing the risk for sudden cardiac death (8). The CASPER study excludes patients with coronary artery disease with >50% stenosis as coronary artery disease is an explainable, and common cause of a cardiac arrest (8).

1.2.11.1 Procedure

The coronary angiogram procedure typically takes between 30 to 60 minutes. Patients are given a mild sedative during the procedure, and a small incision is made in the groin or arm of the patient over the femoral or radial artery. A catheter is then inserted through the incision into the artery, where it is guided retrograde to the heart, where the physician will inject contrast into the coronary arteries. Fluoroscopy is used to determine the flow of the dye through the arteries, potentially identifying regions of stenosis due to coronary artery disease (68).

1.2.12 Coronary Computed Tomography

Coronary Computed Tomography (CCT) is a noninvasive technique that uses high resolution CT to identify coronary artery disease (69, 70). The uses of the electron beam allows for the elimination of coronary motion artifacts, with improved contrast and

spatial resolution (71). CCT is recognized as a viable technique to identify coronary artery disease (72).

1.2 Inherited Heart Rhythm Disorders

In general, arrhythmias can be separated into the bradyarrhythmias and tachyarrhythmias. The tachyarrhythmias may then be broken down into the site of origin, either the ventricular, or supraventricular tachyarrhythmias. The ventricular arrhythmias may be caused by the IHRDs, defined as either a mutation in an ion channel (channelopathy) or structural heart disease (Figure 5) (1).

Figure 5: Arrhythmia Categorization

1.3.1 Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) has an estimated prevalence ranging from 1:1000 to 1:5000 (73-75). Typically, ARVC involves mutations in the genes encoding desmosomes. Mutations in desmosomal genes lead to altered desmosomal protein structures and subsequent weakening of the binding of

cardiomyocytes, leading to the deposition of fibrofatty tissue between the cardiomyocytes, causing a disruption of the electrical signaling of the heart. These alterations in electrical signaling are responsible for the development of scar tissue that leads to slow conduction, the substrate for reentrant pathways and ventricular tachycardia that causes palpitations, syncope, ventricular tachycardia (VT), ventricular fibrillation (VF) and/or cardiac arrest (76-79). Since ARVC was first included in the literature in 1982 (80), characteristic findings and disease progression have been identified. In the early stage of the disease, infiltration of fibrofatty tissue of the myocardium is localized, typically affecting the “triangle of dysplasia”, comprised of the right ventricular inflow and outflow tract, and the right ventricular apex (80). Further disease progression is variable among patients, but infiltration may persist in regions of the right ventricle (RV) and the left ventricle (81), typically sparing the interventricular septum.

In 1994, the first task force criteria were developed for the diagnosis of ARVC, based on structural, histological, ECG, arrhythmic and familial conditions of the disease (78). In 2010, the task force criteria were modified with the inclusion of quantitative imaging techniques and genetic test results (82). Diagnostic criteria are outlined in Table 5. Multiple diagnostic tests are required to meet the criteria required for the diagnosis of ARVC.

Table 5: 2010 Diagnostic Criteria for ARVC. Definite Diagnosis: two major, or one major and two minor or four minor criteria from different diagnostic categories. Probable Diagnosis is considered when patient has one major and one minor or three minor criteria from different diagnostic categories. A possible diagnosis when the patient exhibits one major or two minor criteria from different diagnostic categories (82).

<u>Structural Changes</u>	Major	Minor
2D Echocardiogram	Regional akinesia, dyskinesia, or aneurysm and 1 of the following: 1. PLAX RVOT $\geq$ 32mm 2. PSAX RVOT $\geq$ 36mm 3. O fractional area change $\leq$ 33%	Regional RV akinesia or dyskinesia and 1 of the following: 1. PLAX RVOT $\geq$ 29 to $<$ 32mm 2. PSAX RVOT $\geq$ 32 to $<$ 36mm 3. O fractional area change $>$ 33% to $\leq$ 40%
MRI	Regional akinesia, dyskinesia or dyssynchronous RV contraction and 1 of the following: 1. Ratio of RV end-diastolic volume to BSA $\geq$ 110 mL/m ² (male) or $\geq$ 100 mL/m ² (female) 2. RV ejection fraction $\leq$ 40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: 1. Ratio of RV end-diastolic volume to BSA $\geq$ 100 to $<$ 110 mL/m ² (male) or $\geq$ 90 to $<$ 100 mL/m ² (female) 2. RV ejection fraction $>$ 40% to $\leq$ 45%
RV Angiography	Evidence of regional RV akinesia, dyskinesia or aneurysm	
<u>Tissue Characterization</u>	Major	Minor
RV Biopsy	Residual myocytes greater than 60% by morphometric analysis (or $<$ 50% if estimated), an endomyocardial biopsy of a $\geq$ 1 sample showing fibrous replacement of the RV free wall, with or without fatty replacement of tissue	Residual myocytes between 60% to 75% by morphometric analysis (or 50% to 65% if estimated), an endomyocardial biopsy $\geq$ 1 sample showing fibrous replacement of the RV free wall, with or without fatty replacement of tissue
<u>Abnormalities During Repolarization</u>	Major	Minor
ECG	In individuals greater than 14 years of age, T wave inversion in right precordial leads (V ₁ , V ₂ , and V ₃) or beyond with no evidence of complete right bundle branch block QRS $\geq$ 120 ms)	In individuals younger than 14 years of age, T wave inversion in leads V ₁ and V ₂ with no evidence of complete RBBB or in V ₄ , V ₅ , or V ₆ . In individuals less than 14 years of age with complete RBBB, T wave inversion in leads V ₁ , V ₂ , V ₃ , and V ₄

<u>Abnormalities During Depolarization</u>	Major	Minor
ECG and SAECG	Epsilon wave in the right precordial leads V ₁ , V ₂ , V ₃ by ECG	In the absence of a QRS duration of ≥ 110 ms on the standard ECG, late potentials by SAECG in ≥ 1 of 3 parameters: filtered QRS duration ≥ 114 ms; duration of terminal QRS $< 40\mu\text{V}$ (low-amplitude signal duration) ≥ 38 ms; root-mean-square voltage of terminal 40 ms $\leq 20\mu\text{V}$. Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V ₁ , V ₂ , or V ₃ , in the absence of complete RBBB
<u>Arrhythmias</u>	Major	Minor
ECG and Holter	Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis	Nonsustained or sustained ventricular tachycardia of RVOT configuration, LBBB morphology with inferior axis or of unknown axis > 500 ventricular extrasystoles per 24h (Holter)
<u>Family History</u>	Major	Minor
Patient History	<p>If the patient has one of the following:</p> <ol style="list-style-type: none"> 1. ARVC/D confirmed in a first-degree relative who meets current Task Force criteria. 2. ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative. 3. Identification of a pathogenic mutation 	<p>If the patient has one of the following:</p> <ol style="list-style-type: none"> 1. History of ARVC/D in a first-degree relative but unable to determine whether the member meets current Task Force criteria. 2. Premature sudden death (< 35 years of age) due to suspected ARVC/D in a first-degree relative. 3. In a second degree relative, ARVC/D confirmed pathologically or by current Task Force criteria

The ECG is an important diagnostic tool for ARVC, as outlined in the ARVC task force criteria (Table 5) (82). T-wave inversion, or the presence of epsilon waves in the precordial leads (V₁-V₃) are the main ECG diagnostic characteristics to be aware of. Sustained or non-sustained ventricular tachycardia with left bundle branch morphology is

highly suggestive of ARVC as well (82), but may be more apparent with a prolonged recording time with the use of a Holter Monitor. The SAECG may also contribute to diagnosis as the fibrofatty replacement of the myocardium in ARVC patients may cause late potentials, contributing as a minor criteria for the diagnosis of ARVC (82).

A MRI may determine the presence of akinesia, dyskinesia or dyssynchronous RV contraction with a decrease in RV end-diastolic volume or reduction in RV ejection fraction (82). MRI with late gadolinium enhancement may also be used to differentiate scar from healthy tissue, and the recognition of fibrous or fatty tissue in ARVC patients (83). A study by Borgquist *et al.* identified 102 patients with a definite diagnosis of ARVC, and retrospectively compared task force criteria with the use of echocardiography compared to MRI. The study found that a significant number of patients did not meet the task force criteria with the echocardiography criteria, but were fulfilled by the MRI criteria (84). Further evidence for the use of MRI is a study by White *et al.* where imaging was compared with non-MRI imaging versus MRI imaging in 125 patients who were resuscitated from sudden cardiac death (SCD) or experienced sustained monomorphic ventricular tachycardia (SMVT). Results from the study found that myocardial disease was identified in 51% of patients using non-MRI imaging, compared to 74% with the use of a MRI ($p=0.002$). Furthermore, the use of MRI imaging resulted in a change in diagnosis in 50% of patients, including 18% with acute myocardial injury (85). Results from this study identify the value of MRI in the diagnosis of patients who have experienced an UCA.

ARVC is familial in 30-50% of cases (86, 87). While there are a number of genes responsible for ARVC, the majority of cases are caused by mutations in five genes that

make up components of the desmosome: plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin (JUP) (88).

1.3.2 Brugada Syndrome

Brugada Syndrome (BrS) was originally characterized in 1992 (18), and is an IHRD with a prevalence in southeastern Asian countries of approximately 0.5-1:1000 (89). BrS has a much lower prevalence in caucasian populations (90, 91) and men are at a 5.5-fold higher risk of sudden death compared to women (89). Currently, it is unknown why men have a more severe phenotype compared to women, however higher testosterone levels have been suggested as a cause and may explain why symptom severity between sexes is no different in the pediatric population where testosterone levels in both sexes are lower (92). BrS symptoms rarely occur during exercise, with BrS patients at most risk while resting, sleeping or when the patient has a fever (33). The hallmark characteristic of BrS is the presence of persistent ST-elevation in precordial leads V_1 and V_2 (18). Since it was first characterized, the definition of Brugada Syndrome has evolved to include three different ECG types, designated based on the shape of the ST segment elevation (Figure 6). Type 2 ST elevation (saddle shaped) is the most common form of ST elevation (17), with Type 1 exhibiting an inverted T wave with a coved ST elevation of ≥ 2 mm in at least 2 leads of V_1 to V_3 . Type 3 may be morphologically similar to Type 2 or Type 3, but with ST elevation of ≤ 2 mm (93). The presence of syncope is an important risk factor as the presence of syncope in patients with a Type 1 ECG pattern has a greater risk of cardiac arrhythmic events (94, 95). Patients suspected of BrS may have a second ECG upon testing, but with the precordial leads raised by two intercostal spaces, which improves the sensitivity to detect a Brugada

pattern (Figure 7) (96). When BrS is suspected but not apparent on an ECG or Holter monitor, a procainamide infusion can provoke BrS type arrhythmias (54).

Figure 6: Three Types of Brugada Syndrome Based on ECG ST Elevation Pattern.

Figure 7: ECG High Lead Locations for Improved Sensitivity of Detection of Brugada Syndrome

Late potentials identified with the SAECG may be used for the risk stratification in BrS patients (97), with one study of 43 BrS patients finding that 22 (91.7%) of 24 patients in the symptomatic group and in 7 (36.8%) of 19 patients in the asymptomatic group exhibited late potentials. Kaplan-Meier curves were plotted for event-free survival according to late potentials, showing a significant difference between patients that had late potentials, compared to those who did not (log rank, $p=0.003$) (97).

Currently, 12 different genes have been associated with Brugada Syndrome, all of which encode proteins responsible for the components of sodium, potassium or calcium channels. Denaturation of these ion channels result in decreased sodium or calcium inward current, or an increase in potassium outward current (33). Accelerated inactivation of sodium channels at higher temperatures may be responsible for the increased risk of SCA during febrile state (98). The yield of genetic testing in Brugada Syndrome is 20-30%, with the vast majority attributed to the SCN5A gene, which is responsible for encoding proteins that form the channel responsible for the inward sodium current I_{Na} (99).

1.3.3 Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare ion channelopathy with an estimated prevalence of 1:10 000 (33). CPVT is caused by mutations in genes associated with calcium channels, leading to increased intracellular calcium levels. Mutations in two genes account for 60% of CPVT patients (28). The

cardiac ryanodine receptor RyR2, is much more common than a mutation in the gene CASQ2, a gene responsible for cardiac calsequestrin (33). Increased levels of intracellular calcium may lead to the propagation of the action potential and premature ventricular contraction (PVC), resulting in subsequent polymorphic ectopy or biventricular VT (100). Typically, CPVT symptoms occur within the first two decades of life and usually occur during exercise or during emotional stress (101-103).

An exercise stress test may be used to unmask CPVT, as it has been found that over 80% of symptomatic CPVT probands experience ventricular arrhythmias during exercise testing (101-104). Typically, exercise testing provokes premature ventricular contractions (PVC) (101). PVCs are often followed by the appearance of couplets and non-sustained polymorphic or bidirectional ventricular tachycardia (101, 105). While exercise stress testing is useful to aid in the diagnosis of CPVT patients, currently there are no guidelines that point to a definite diagnosis of CPVT with exercise stress testing (105).

1.3.4 Early Repolarization Syndrome

Early repolarization (ER) in the young is typically benign, with an approximate prevalence between 5%-13% in the general population (106, 107), but in some populations it may be a marker for an increased risk of ventricular fibrillation and/or sudden cardiac arrest (106). ER syndrome is defined as ≥ 1 mm of QRS slurring and/or notching, with QRS-ST junction (J-point) elevation in at least two sequential leads, excluding leads (V₁-V₃) (106-108). The slope of the ST segment is often helpful in assigning potential risk in ER (107). A recent study by Kim *et al.* studied 25 SCA survivors with ER patterns, finding that the prevalence of an ER pattern with a horizontal

ST segment was greater in patients surviving SCA, compared to healthy controls (109). Currently, six genes have been identified in ER syndrome patients, including KCNJ8, CACNA1C, CACNB2b, CACNA2D1, ABCC9 and SCN5A. ER is caused by mutations in genes encoding potassium, calcium and sodium channels, resulting in decreased sodium or calcium currents, or an increase in potassium current (110).

At the current time, there are no validated techniques to provoke the ER pattern in patients, although recent evidence has suggest the Valsalva maneuver may be useful (110). ER characterization is in its infancy, and our understanding of cellular and genetic mechanisms, and resultant clinical decision-making are in rapid evolution.

1.3.5 Long QT Syndrome

Long QT Syndrome (LQTS) has a prevalence of approximately 1:2500 and a ten-year untreated mortality rate of approximately 50%, with those with a previous event at a higher risk than asymptomatic patients (111, 112). LQTS is characterized by prolongation of the corrected QT interval (QTc), typically > 460 msec in a male and 480 msec in a female, however females are at greatest risk when the QTc interval is greater than 500 msec. (33). A hallmark of LQTS is the presence of polymorphic ventricular tachycardia called torsades de pointes (113). Torsades de pointes means “twisting of points” and is characterized by the appearance of the polarity of the QRS complex spiraling around the baseline of the ECG (Figure 8) (114). Lengthened QT intervals are a sign of prolonged repolarization, which can occur due to mutations in potassium or sodium channels in cardiac myocytes. Prolonged repolarization may cause early afterdepolarizations, which increases the risk of torsades de pointes and can lead to syncope or SCD (115). Those with LQTS may be at particular risk during exercise, such

as running, or swimming, as the QTc interval fails to shorten during exercise, leading to syncope or SCA (116).

Figure 8: ECG of Torsades de Pointes in a Young Woman with Exercise Induced Syncope, Subsequently Diagnosed with Type 2 Long QT Syndrome

The ECG is required for diagnosis of LQTS because it is required to calculate the QTc interval. The normal upper limit of the QTc interval is 460 msec; however, 99% of normal men and women will have a QTc of less than 470msec and 480msec, respectively (117). As noted above, a QTc interval of ≥ 500 msec is diagnostic of LQTS. However, up to 27% of genotype positive LQTS will have what is considered a normal QTc interval of <440 msec (118). Furthermore, the presence of T wave morphology changes typical of LQTS supports its diagnosis (Figure 9). Maximum and minimum QT interval are also recorded to allow for the calculation of QT dispersion, defined as the range of the QT intervals (119).

Figure 9: T-wave Morphology in 3 Most Common Types of LQTS

The epinephrine infusion is often used to unmask disease as 50% of LQTS patients have a normal or borderline QT interval at rest (120). Abnormal QT intervals were previously described in a large study by Ackerman *et al.*, as an absolute QT prolongation of 30 msec, and this value was used for the CASPER study (50). Rhythm strips are assessed by blinded investigators, and analyzed for PVC count and non-sustained and sustained tachycardia information. A 30-minuted washout is performed after the last epinephrine infusion, with ECGs performed every ten minutes. Interestingly, exercise stress testing has differing effects depending on the type of LQTS. Wong *et al.* found that during exercise, LQT1 patients had increased QTc prolongation compared to LQT2 patients (43). Furthermore, the transition from supine to standing can lead to a LQTS diagnosis, as it has been found that LQT2 patients have a significant increase in QTc interval when standing, compared to controls subjects (healthy volunteers) (42, 43).

LQTS is a familial condition with 15 genes identified since 1995, with mutations in potassium channels, sodium channels, calcium channels and membrane adaptor proteins. (33). However, 92% of patients that are gene positive for LQTS have one of the three most common types of LQTS, caused by mutations in one of three ion channels (Table 6) (28). Type 1 LQTS occurs due to a loss of function genetic mutation in a potassium-channel subunit-encoding gene KCNQ1. Similarly, type 2 LQTS is caused by a loss of function mutation in the gene KCNH2, a gene also responsible for the

production of a component of a potassium-channel. Type 3 LQTS differs in that it occurs due to a gain of function mutation in the gene SCN5A, a gene that encodes a sodium channel (33). All of these mutations result in a prolonged QT interval (Figure 10).

Table 6: The 3 Most Common Types of LQTS

LQTS	LQT1	LQT2	LQT3
Gene	KCNQ1	KCNH2	SCN5A
Type	Loss of function in K Channel (slow)	Loss of function in K Channel (rapid)	Gain of function in Sodium Channel
Typical Conditions	Physical or emotional Stress	At rest, sudden noises or post partum	Rest or during Sleep
ECG	The most likely to have a normal ECG	Notched or low amplitude T waves	Least likely to have a normal ECG
Prognosis	Good with Beta Blockers	High Risk	May require sodium blockers

Figure 10: LQTS Action Potential and Resulting ECG Due to Mutation in Ion Channels

1.3.6 Short QT Syndrome

Short QT Syndrome (SQTs) is currently the most rare of the known channelopathies. SQTs is characterized by the presence of a QTc interval of ≤ 300 ms or, a QTc < 360 ms with one of the following: a pathogenic mutation, a relative with SQTs, a family member with a sudden unexplained death at ≤ 40 , or if the patient has survived a VT/VF episode without heart disease (33). The common genes associated with SQTs are associated with LQTS but have opposing effects (Table 7). Individuals with type 1 SQTs have a gain of function mutation in the potassium channel KCNH2, while individuals with type 2 and type 3 SQTs have gain of function mutations in the potassium channels

KCNQ1 and KCNJ2 respectively (28). These gain of function mutations increase the release of potassium from the cardiomyocyte, increasing the rate of repolarization, subsequently resulting in a shortened QT interval, causing atrial and ventricular fibrillation (Figure 11) (121). Further confusing the diagnosis is that SQTs has also been associated with mutations in the calcium channels CACNA1C and CACNB2, both of which have been linked to Brugada Syndrome (33).

Table 7: Types of SQTs

SQTs	SQTs1	SQTs2	SQTs3
Gene	KCNH2	KCNQ1	KCNJ2
Type	Gain of function in K ⁺ Channel (rapid)	Gain of function in K ⁺ Channel (slow)	Gain of function in K ⁺ Channel
ECG	Peaked T-Waves, Shortened QT Interval	Peaked T-Waves, Shortened QT Interval	Peaked T-Waves, Shortened QT Interval

Figure 11: SQTs Action Potential and Resulting ECG Due to Mutation in Ion Channels

1.3.7 Short-Coupled Idiopathic Ventricular Fibrillation

Short-coupled idiopathic ventricular fibrillation (SCIVF) is a relatively new form of ventricular fibrillation currently used to explain a cause for cardiac arrest. This diagnosis is not to be confused with Idiopathic Ventricular Fibrillation (IVF), a term used to define a patient with an unexplained cardiac arrest where diagnostic testing was unable to determine a diagnosis (122, 123). This paper refers to the IVF patients as unexplained cardiac arrest probands. SCIVF probands are characterized by short-coupled PVCs prior to the T-wave during polymorphic VT, leading to VF and subsequent syncope or cardiac arrest (124). The short-coupled PVCs are believed to originate from the His-Purkinje fibers (124). SCIVF is difficult to diagnose, as patients need to be monitored during the event and patients from CASPER were diagnosed after the index event, when the ICD recorded the rhythm

leading up to follow-up events. With improved understanding of this mechanism, it has been found that probands with the SCIVC mediated cardiac arrest respond well to Quinidine, ensuring long-term efficacy in preventing future events (125).

1.4 Genetic Testing

The role of genetic testing in the clinical diagnosis of IHRD has continued to develop with the progress of cardiovascular genetic knowledge. Typically, genetic testing is performed in patients with a definite clinical diagnosis to enable family screening, provide prognostic information or to confirm a diagnosis when a patient has a less compelling phenotype (126). Genetic testing is not recommended for the screening of asymptomatic patients without clinical evidence of disease. With an increased role for genetic testing in specialized arrhythmia clinics, the involvement of trained genetic counselors has been recommended by the Canadian Cardiovascular Society (CCS) guidelines for patient counseling, the interpretation of genetic data, and the development of medical pedigrees (Figure 3) (126). However, genetic testing raises ethical issues in stigma, privacy, insurance and employment discrimination. Physicians have a “duty to warn”, especially when suspect IHRD patient employment may be a danger to society, such as a bus driver or airline pilot (126). However, the lines are blurred when considering the purchase of life or travel insurance policies, where insurance companies many refuse to cover patients with a genetically proven IHRD, or charge costly premiums. These are all issues that the physician and genetic counselor need to consider when ordering genetic testing for a patient.

1.4.1 Long QT Syndrome - Guidelines

The Canadian Cardiovascular Society recommends that genetic testing for LQTS be performed when the patient has survived a cardiac arrest or experiences syncope, and shows signs of QT prolongation on the resting ECG. Furthermore, genetic testing should be performed with a borderline QT interval and the presence of abnormal T-waves, as seen in Figure 9, or if the patient is being screened due to a confirmed genotype positive first-degree relative. Lastly, asymptomatic patients with QT prolongation suspected of having LQTS should have genetic testing (126).

1.4.2 Brugada Syndrome - Guidelines

The Canadian Cardiovascular Society recommends that genetic testing be performed in patients with a Type 1 ECG pattern. This includes patients that have had a previous cardiac arrest, experiences syncope, or are asymptomatic. Patients may also be screened for BrS if the patient has a genotype positive first degree relative (126).

1.4.3 Arrhythmogenic Right Ventricular Cardiomyopathy - Guidelines

The CCS guidelines recommend that patients that meet the Task Force Criteria for ARVC, should undergo genetic testing. Furthermore, suspected ARVC patients that do not meet the Task Force Criteria are recommended to have genetic testing, along with patients with a genotype positive first degree relative. Patients with a first degree relative with clinical ARVC, but are not phenotype positive, are not recommended to have genetic testing due to the sporadic nature of ARVC (126).

1.4.4 Catecholaminergic Polymorphic Ventricular Tachycardia - Guidelines

CPVT patients should receive genetic testing if they are clinically suspected for CPVT, or for family screening due to a genotype positive first degree relative. Due to the infancy in diagnosis of ER syndrome and SQTS, currently there are no guidelines for genetic screening.

1.4.5 Sudden Unexplained Death and Sudden Infant Death Syndrome

Sudden unexplained death (SUD) is defined as unexplained cardiac death, with the onset of symptoms 1-hour previous to death, with no known history of heart disease or other form of fatal disease (28, 127). If the patient is less than 1 year of age, died during sleep, and has had a thorough autopsy with no explanation for the death, the patient is diagnosed with SIDS (128). The CCS and Heart Rhythm Society (HRS) recommends that patients resuscitated from sudden cardiac death be clinically screened for IHRD before the arrangement of genetic testing (28, 126). In the case of SUD and SIDS, the CCS and HRS recommend that a thorough clinical examination of first-degree relatives to screen for the presence of an IHRD. At the physicians discretion, the physician may also order screening of the most frequent IHRD causing genes, including the KCNQ1 and KCNH2 genes, which are responsible for 90% of genetically confirmed LQTS cases, and SCN5A, the most commonly affected gene in BrS (126).

1.5 Therapeutics

1.5.1 Drug Therapy

Antiarrhythmics may be prescribed for the management of arrhythmias, however, with the exception of beta blockers, the current guidelines recommend antiarrhythmics only as an adjunct therapy. Antiarrhythmics may also perpetuate the problem and need to be prescribed with care (129). For example, many of the antiarrhythmic drugs are QT prolonging and not recommended for patients with LQTS. A full list of the QT prolonging drugs can be found at www.qtdrugs.org.

Beta blockers are recommended in the guidelines for the safe and effective prevention of ectopic beats and arrhythmias in conditions such as LQTS and CPVT (129). Beta blockers are effective in slowing the sinus rate by the competitive inhibition of sympathetic activating adrenergic receptor mediated pathways (129). Beta blockers may also inhibit excess calcium release by the ryanodine receptor (130). A recent study (131) has also found the effective use of beta blockers in LQT1 patients, effectively shortening the QT and QTc interval during exercise-induced faster heart rates, and lengthening the QT and QTc interval during rest.

Alternate drug therapies include the administration of electrolytes in electrolytic imbalanced patients, such as the administration of potassium in hypokalemic patients (129). Furthermore, ACE inhibitors, angiotensin II receptor antagonists and aldosterone blockade with spironolactone or eplerenone have been associated with a decrease in SCD through reverse remodeling of the myocardial substrate (129, 132, 133).

1.5.2 Implantable Cardioverter Defibrillators

Since 1998, the American College of Cardiology and American Heart Association (134) has recommended an implantable cardioverter defibrillator (ICD) in response to cardiac arrest and in 2000, the Canadian guidelines made the same recommendation (135). Three large trials, including the AVID trial (136), CIDS trial (137), and CASH trial (138) all found a reduction of death when an ICD was implanted compared to the use of drug therapy, and together, found a reduction in the risk of sudden cardiac death by 50% (139). In 2012, ICD therapy was improved with the results of the MADIT-RIT study. The MADIT-RIT study changed the way physicians program the ICD, with delayed therapy programming associated with a decrease in inappropriate shocks and a decrease in all-cause mortality (140). Current guidelines recommend the implantation of an ICD as the gold standard for the secondary prevention of cardiac arrest (141), and most physicians will also prescribe the conjunctive use of drug therapy (129).

1.5.3 Ablation

Radiofrequency ablation is a procedure that may be used to ablate the origin of the VT. As with the IHRD, when there is no apparent structural heart disease, ablation procedures typically have a good prognosis when a single VT presents from the RV with a LBBB inferior axis morphology, or from the LV, with a RBBB morphology (142-145). A recent study (146) has also found the benefit of ablation in IVF patients. Patients diagnosed with IVF were recruited, and the origin of the premature ventricular beats were ablated, and followed for a median time of 63 months. Results from the study found long-term freedom from VF or VT recurrence, with only 18% of patients experiencing

recurrence of VF or polymorphic VT (146). Furthermore, ablation has been shown to be successful in patients diagnosed with IHRDs, including Brugada Syndrome (147) and ARVC (148).

Chapter 2: Research Paper¹

2.1 Purpose

The current study evaluated the standardized approach of patients with unexplained cardiac arrest, with the goal to determine an optimal testing strategy that diagnoses IHRDs, excludes IHRDs when appropriate and informs the nature and need for cascade screening of family members. Strategies for diagnostic pathways need to be streamlined to ensure patients receive optimal testing for diagnosis determination, without excessive use of health care resources. This may lead to improved patient outcome and utilization of health care resources.

2.2 Hypothesis, Objectives and Specific Aims

Hypothesis: Systematic testing can be used to determine an etiology in patients who have suffered an unexplained cardiac arrest. Results from the CASPER study will allow for the creation of diagnostic pathways, aiding in the diagnosis of patients who have experienced an unexplained cardiac arrest.

Objectives: The overarching goal of this study is to understand those who are most vulnerable to suffer an unexplained cardiac arrest and diagnose the underlying condition. Furthermore, the goal is to determine the risk of secondary cardiac events and to determine the efficacy of diagnostic clinical testing and genetic testing, specifically:

1. To improve the characterization of UCA patients
2. To improve the management of patients and families in whom UCA has occurred.

¹ This manuscript for this research project has been submitted.

3. To determine the efficacy of diagnostic tests currently used for this population.
4. To determine the effectiveness of genetic testing for this population.

The objectives of the study will be completed by fulfilling the following specific aims:

1. To compare age, sex, and cardiac symptoms (presyncope, syncope, palpitation, and chest pain) in probands diagnosed with unexplained cardiac arrest and those with an established cause for cardiac arrest after diagnostic testing.
2. To compare the prevalence and severity of cardiac symptoms before and after UCA and compare the difference in cardiac symptoms between UCA patients and diagnosed CA patients.
3. To determine the efficacy of genetic testing and factors associated with positive genetic testing.
4. To calculate efficacy of each diagnostic test.
5. To compare the yield of testing for detection of structural versus electrical causes of CA.
6. To determine optimal diagnostic pathways for UCA probands
7. To determine whether clinical testing results predict of future events
8. To determine whether having a diagnosis is predictive of future events
9. To compare future events in patients with a diagnosis, comparing structural versus electrical explanations for CA

2.3 Methods

2.3.1 Overview

The Cardiac Arrest with Preserved Ejection Fraction Registry (CASPER) enrolls patients from 14 investigator-affiliated centers across Canada. The sites included in the registry are: University of British Columbia, British Columbia, BC Children's Hospital, British Columbia, Royal Jubilee Hospital, Victoria, British Columbia, University of Calgary, Alberta, the University Health Network, Ontario, St. Michael's Hospital, Ontario, Western University, Ontario, McMaster University, Ontario, University of Ottawa, Ontario, Université Laval, Québec, Université de Montréal, Québec, Queen's University, Ontario, Dalhousie University, Nova Scotia. The registry is ongoing, but the patients in this study were enrolled in the registry since its commencement date on January 1, 2004, until July 1, 2013. Cases enrolled in the study have suffered a cardiac arrest of unknown etiology or experienced syncope with polymorphic VT, and their first-degree family members. First-degree relatives of sudden death victims have also been included. Over 700 participants from Canadian inherited heart rhythm specialty clinics have been included in CASPER, with over 300 participants experiencing an unexplained cardiac arrest. Participants enrolled in the registry who have suffered an unexplained cardiac arrest are defined as probands. The probands enrolled in CASPER are without evident heart disease or obvious phenotypic traits of inherited heart rhythm disorders and therefore require systematic and advanced testing to determine an underlying diagnosis.

2.3.2 Participant Selection

Cardiac arrest patients were eligible for enrollment if they had experienced an unexplained cardiac arrest with documented cardiovascular collapse with ventricular

tachycardia or fibrillation requiring DC cardioversion or defibrillation to restore sinus rhythm. Follow-up testing demonstrated normal left ventricular function (left ventricular ejection fraction $\geq 50\%$), excluding the possibility of a cardiomyopathy, and normal coronary arteries, defined as no coronary artery with less than 50% stenosis (narrowing of artery) (51). Patients were not excluded if they had transient left ventricular dysfunction or QT prolongation immediately after the cardiac arrest if these resolved promptly. Patients suspected to have LQTS were excluded and defined as persistent resting $QTc > 460$ msec for males and > 480 msec for females (149, 150) and patients with reversible causes, such as marked hypokalemia (serum $K^+ < 2.8$ mmol/l) or a drug overdose were excluded as well. Furthermore, patients were excluded if imaging identified hypertrophic cardiomyopathy or if they experienced commotio cordis, wherein a patient experiences a cardiac arrest caused by a physical blow to the chest wall that triggers a ventricular arrhythmia (151). Lastly, patients with Type I Brugada ECG with ≥ 2 mm ST elevation in V_1 and/or V_2 or hemodynamically stable sustained monomorphic ventricular tachycardia with a QRS morphology consistent with recognized forms of idiopathic ventricular tachycardia (outflow tract or apical septal) were also excluded (152).

2.3.3 Inclusion Criteria

1. Survivor of an unexplained cardiac arrest (UCA) requiring treatment from a first responder to re-establish a normal heart rate
2. Enrolled before December 1, 2013

2.3.4 Exclusion Criteria

1. < 12 years of age

2. Probands enrolled who have experienced syncope caused by polymorphic ventricular tachycardia
3. Coronary artery disease (stenosis >50%)
4. Reduced left ventricular function (left ventricular ejection fraction (LVEF) <50%)
5. Persistent resting QTc>460 msec for males and 480 msec for females
6. Reversible cause of cardiac arrest such as marked hypokalemia (<2.8 mmol/l) or drug overdose sufficient in gravity without other cause to explain the cardiac arrest
7. Hemodynamically stable sustained monomorphic ventricular tachycardia with a QRS morphology consistent with recognized forms of idiopathic Ventricular Tachycardia (outflow tract or apical septal)
8. Type I Brugada ECG with ≥ 2 mm ST elevation in V₁ and/or V₂
9. Unwilling or unable to provide consent

2.3.5 Data Extraction

Data were accessed through a web-based database. Data were extracted into an .xml format, where they were converted into an excel file and analyzed. Critical fields were identified, and patients were sorted by completeness of data and those with >90% data completion was included in the study. Patients with >10% missing data were excluded from the study. Patients with intact data had a data quality review and sites were prompted to complete missing data. This included missing data pertaining to the tests themselves, such as a missing parameter for a test, and also missing tests, which were required to support the diagnosis, such as an exercise test to support the diagnosis of

LQTS. Once the data set was closed, descriptive statistics were performed, followed by multivariate analysis to predict outcome. The first 200 probands with sufficient data were included in the analysis.

2.3.6 Clinical Testing

Patients received standard testing to determine the cause of the cardiac arrest (Figure 2). Standard testing included continuous ECG telemetry for at least 72-hours, echocardiography, and coronary angiography and/or cardiac CT and/or cardiac MRI (cMRI) in select younger patients. Patients that met the enrollment criteria received additional testing where applicable, including an exercise stress test, signal-averaged ECG (SAECG), cMRI with gadolinium, and procainamide and epinephrine challenge. SAECG were considered positive based on established testing guidelines (153). Testing was performed according to the algorithm outlined in Figure 2. Investigators had discretion to perform testing as guided by the clinical presentation and results of previous testing. Thus a patient with a cardiac arrest during exertion may not have undergone procainamide provocation if standard and high precordial lead ECGs were not suspicious for Brugada changes. Patients remained in the study if they were unable or unwilling to undergo recommended specific tests.

Cardiac MRI was analyzed by an expert and assessed for evidence of ARVC, sarcoidosis, myocarditis, unrecognized myocardial infarction or other explanatory causes. Right ventricular (RV) angiography and RV biopsy was performed in select cases where ARVC was suspected. ARVC diagnosis was based on the 2010 ARVC task force criteria (82).

12-lead ECGs were performed as close to the cardiac arrest as was available and analyzed by investigators. Early repolarization was defined as ≥ 0.1 mV J point elevation (QRS-ST junction) in at least 2 leads, either as slurring or notching in the inferior lead (II, III, and aVF), lateral lead (I, aVL, and V₄ to V₆), or both (106, 154-156). Coronary spasm was diagnosed when patients experienced ≥ 2 mm of transient ST elevation, with non-sustained polymorphic VT and angiographic evidence of vasospasm.

Holter monitors were determined to be abnormal if there were recordings of NSVT, VT, or greater than 1000 PVCs during a 24 hour period of monitoring. In a population of a variety of cardiovascular disorders, PVCs were found to range from 37-1801 per hour (157), but have also been recorded in healthy individuals (158, 159), so this study used a conservative amount when identifying an abnormal number of PVCs.

Electrophysiological (EP) testing was performed at the investigators discretion, using standard protocols that permit up to 3 ventricular extra stimuli at 2 drive cycle lengths for induction of ventricular arrhythmias (160). Electro-anatomical mapping was performed in select cases where ARVC was suspected.

Exercise stress tests were performed using a Bruce or modified Bruce protocol. Patients underwent a 12-lead ECG while in a supine position, immediately when standing, and continuously during treadmill exercise testing (42). 12-lead ECGs were obtained at 1-minute intervals during exercise, at peak exercise, and at 1-minute intervals during a 6-minute recovery phase (43). Procainamide and epinephrine infusions were performed using standard techniques, including 10 mg/kg procainamide infusion over 20 minutes (to a maximum of 1g), and continuous epinephrine infusion up to 0.20 μ g/kg/minute (54), with 12-lead ECGs performed at baseline and before the

administration of each dose (48, 49, 51, 161-166). A procainamide test was considered positive when an increase in ST₂₀ elevation >1 mm or a >1 mm of new ST₂₀ segment elevation was observed in response to procainamide (164).

2.3.7 Determination of Diagnosis

Advanced testing was used to determine a diagnosis and patient diagnosis was ranked as definite, probable or possible (Table 8). Investigators were asked to review the entire patient record including the nature and context of symptoms, family history, and results of clinical and genetic testing and render a working diagnosis, with a qualitative descriptor of the strength of the diagnosis (ie. definite, probable or possible) based on the weight of the evidence. The working diagnosis could be revised over time based on events during follow-up, and/or repeat clinical and genetic testing. For the purpose of classification and comparison, patients were divided into two groups; diagnosed based on a definite or probable diagnosis, and undiagnosed based on unexplained cardiac arrest or only weak evidence of a diagnosis (possible diagnosis, single inconclusive test)

Table 8: Strength of Diagnosis

Level of Diagnosis	Definition of Diagnosis Strength
Definite*	Both clinical and genetic testing led to a diagnosis, or clear clinical evidence
Probable**	Clinical testing or genetic testing was positive
Possible***	One or more of the clinical tests were considered borderline, but inconclusive

* Example: MRI of myocarditis, biopsy for sarcoidosis, dramatic early repolarization after arrest, all other tests negative

**** Example:** exercise or epinephrine induced QT prolongation and swimming related cardiac arrest, but genetic test is negative. One major and one minor ARVC Task Force criteria.

***** Example:** failed QT shortening with exercise that was not compelling ($QT_c < 500$ msec), with a negative epinephrine challenge and genetic test. Possible ARVC based on 2 minor Task Force criteria

2.3.8 Genetic Testing

Targeted genetic testing was performed on the basis of phenotype detection after clinical testing was complete. Testing was accessed on the basis of clinical testing from commercial vendors. Prior to access to clinical genetic testing in 2007, limited research testing assessed 7 patients. Genomic DNA was isolated from blood lymphocytes and screened with direct sequencing performed on suspected culprit genes.

2.3.9 Follow-Up Data

Patients were seen every 6-12 months and, when applicable, ICDs were interrogated for the presence of ICD shocks or anti-tachycardia pacing (ATP) and determined whether they were appropriate by the local investigator. ATP was only included when it was responsible for termination of the ventricular tachycardia as ATP may also occur during charging of the ICD prior to shock. Patients whose cardiac arrest was > 3 months prior to enrolment were excluded from the follow-up to eliminate ascertainment bias favoring an apparent good prognosis. Patients required a minimum of 12 months follow-up to ensure sufficient time for events to occur. Outcome ascertainment was not blinded to the patients clinical history or working diagnosis.

Symptoms were recorded and cardiac events were defined as the presence of syncope, palpitations, recurrent cardiac arrest, or ICD events including shocks or ATP. So-called idiopathic VF was divided into unexplained VF and short-coupled idiopathic ventricular fibrillation (SCIVF) based on ECG monitoring or review of ICD therapy events. These patients had short-coupled onset of premature ventricular contractions (PVC) prior to the T-wave during polymorphic VT, leading to VF (124). SCIVF patients were treated as diagnosed due to recent studies suggesting the benefit of quinidine in this population (125).

2.3.10 Statistical Analysis

Statistical analysis was performed using SPSS software (version 22, Cary NC). Continuous variables were compared by using the 2-tailed Student *t* test for continuous variables, and the Fisher's exact test for categorical variables. *P* values <0.05 were considered significant. Continuous variables are expressed as mean $\pm$ SD. Cox regression models were constructed and hazard ratios and time to first event, including ICD shock and/or ATP, were calculated and compared between those with a diagnosis and those without. Cox regression models were also constructed for those with a diagnosis, comparing time to first event and hazard ratios in patients with a structural diagnosis, to those with an electrical diagnosis. These models were adjusted for age and sex of the patients.

Statistical analysis was performed to determine if any factors were predictive of future events. Diagnostic testing, including: adrenaline, CCT, EP, MRI, procainamide, SAECG and stress tests were read by investigators and determined to be normal, borderline, or abnormal, whereas angiograms and Holter monitors were either normal or

abnormal. Most ECGs were considered to be normal based on inclusion criteria of the study, however QRS duration has been linked to future events (167), therefore QRS duration was included in the model, ranking QRS duration as <80, 81-100, 101-120, and >120. Lastly, genetics was included in the model, where genetics was reported as normal, variant of unknown significance, or pathogenic. A Spearman correlation was used to determine whether any of the testing was correlated with future events. Models using linear regression were also constructed, aiding to determine whether any group of diagnostic testing was predictive of future events.

Chapter 3: Results

A total of 200 patients were enrolled between January 1, 2004 and December 1, 2013 from 14 sites across Canada (Table 9). Patients had a mean age of 48.6 ± 14.7 years (range 18-88 years) and 81 patients (41%) were female. Baseline demographics were similar between the definite/probable diagnosed (41%) and undiagnosed/possible groups, with 95% of the cohort undergoing an ICD implant after the cardiac arrest. There was no difference between ICD implantation rates in patients with and without a diagnosis ($p=0.207$). Symptoms reported prior to cardiac arrest included pre-syncope (6%), syncope (21%), palpitations (9%), and chest pain (12%), with no significant difference between those with and without a diagnosis.

Table 9: Patient Demographics and Diagnostic Information. *=Significant p-value

	All n=200	Diagnosed n=81	UCA n=119	P-Value
Age (Year $\pm$ SD)	48.6 $\pm$ 14.7	47.9 $\pm$ 14.6	49.0 $\pm$ 14.5	$p=0.674$
Age at Cardiac Arrest (Year $\pm$ SD)	41.5 $\pm$ 14.7	39.8 $\pm$ 14.9	42.7 $\pm$ 14.5	$p=0.943$
Females (%)	81 (41)	35 (43)	46 (39)	$p=0.559$
ICD Implantation	190 (95)	79 (98)	111 (93)	$p=0.207$
HR	75.9 $\pm$ 21.7	73.0 $\pm$ 18.3	77.9 $\pm$ 23.6	$p=0.075$
QT	398.0 $\pm$ 50.3	398.0 $\pm$ 48.6	398.0 $\pm$ 51.6	$p=0.470$
QTc	437.9 $\pm$ 49.2	429.6 $\pm$ 37.9	442.6 $\pm$ 54.7	$p=0.081$
LVEF	57.4 $\pm$ 9.7	57.1 $\pm$ 8.8	57.6 $\pm$ 10.2	$p=0.160$
Diagnosis n(%)				
ARVC	14 (7)	14 (17)		
BrS	7 (4)	7 (8)		
Coronary Spasm	7 (4)	7 (8)		
CPVT	10 (5)	10 (12)		
DCM	2 (1)	2 (2)		
ER	13 (7)	13 (16)		
SCIVF	5 (3)	5 (6)		
LQTS	18 (9)	18 (22)		
Myocarditis	3 (2)	3 (4)		
Other	2 (2)	2 (4)		
UCA	119 (60)	0 (0)		
Symptoms				
Presyncope	12 (6)	4 (5)	8 (7)	$p=0.765$
Syncope	41 (21)	21 (26)	20 (17)	$p=0.153$
Palpitations	17 (9)	5 (6)	12 (10)	$p=0.441$
Chest Pain	23 (12)	8 (10)	15 (13)	$p=0.654$
Genetics				
Had a mutation	22 (11)	20 (25)	2 (2)	$p=0.0001^*$
Pathogenic	13 (7)	13 (16)	0 (0)	$p=0.0001^*$
VUS	9 (5)	7 (9)	2 (2)	$p=0.033^*$

ICD=Implantable Cardioverter Defibrillator, HR=Heart Rate, LVEF=Left Ventricular Ejection Fraction, ARVC=Arrhythmogenic Right Ventricular Cardiomyopathy, BrS=Brugada Syndrome, CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia, DCM=Dilated Cardiomyopathy, ER=Early Repolarization, IVF=Idiopathic Ventricular Fibrillation, LQTS=Long QT Syndrome, UCA=Unexplained Cardiac Arrest

After enrollment, 68 (34%) patients initially received a diagnosis. Patients with unexplained cardiac arrests were continuously monitored and evaluated resulting in 81 (41%) patients receiving a diagnosis with 26 definite diagnoses (13%) and 55 probable diagnoses (28%, Figure 12). Diagnoses were based on phenotypic evidence in 63 patients (32%), genetic evidence in 11 patients (6%) and both phenotypic and genetic evidence in

7 patients (4%). Eight probands had a change in their diagnosis during follow-up as more information became available. In total, 158 patients (79%) received some form of genetic testing, with 13 patients genetically positive for a probable or definite disease causing mutation (Table 10).

Figure 12: Working Diagnosis for CASPER patients. N=200 patients. 41% of patients received a diagnosis. Of those that received a diagnosis, 28 (35%) had an underlying structural condition (blue), and 53 (65%) had a primary electrical disease (red).

Table 10: Patients with Pathogenic Mutations and Positive Clinical Testing

Patient ID	Diagnosis	Strength	Mutation	Type	Age	Sex	HR	QTc	Adrenaline	Procainamide	Additional Test of Interest	Follow-Up
21	LQTS	Definite	KCNH2	Pathogenic	30	Female	57	458	Abnormal	Normal	Abnormal Stress Test	No reported follow-up events
157	CPVT	Definite	RyR2	Pathogenic	34	Female	61	444	Abnormal	Not Performed	Abnormal Stress Test	Lost to follow-up
181	CPVT	Probable	LMNA, RyR2	Pathogenic	46	Female	77	487	Abnormal	Normal		Lost to follow-up
244	Early Repolarization	Probable	PKP2	Pathogenic	49	Female	65	425	Normal	Normal		Lost to follow-up
256	ARVC	Probable	DSP	Pathogenic	50	Female	57	390	Abnormal	Abnormal	Abnormal Stress Test Normal MRI, Borderline SAECCG	No reported follow-up events
269	ARVC	Probable	PKP2	Pathogenic	58	Male	57	419	Normal	Normal	Abnormal ECG, Borderline SAECCG	Lost to follow-up
969	ARVC	Probable	PKP2	Pathogenic	31	Male	63	404	Not Performed	Not Performed	Abnormal MRI	Experienced palpitations
1400	LQTS	Probable	KCNQ1	Pathogenic	21	Male	51	436	Not Performed	Not Performed	Abnormal Stress Test	Lost to follow-up
4157	Brugada Syndrome	Probable	SCN5A	Pathogenic	79	Male	57	429	Not Performed	Borderline		Experienced multiple episodes of syncope, ICD shocks and ATP
4199	Brugada Syndrome	Definite	SCN5A	Pathogenic	49	Male	87	446	Not Performed	Abnormal		No reported follow-up events
4318	ARVC	Probable	TMEM43	Pathogenic	40	Male	75	Not Recorded	Not Performed	Not Performed	Abnormal MRI, Abnormal RV Biopsy	No reported follow-up events
4349	ARVC	Probable	DSG2	Pathogenic	68	Male	63	416	Not Performed	Not Performed		No reported follow-up events
4351	ARVC	Probable	DSP	Pathogenic	45	Male	76	383	Not Performed	Normal	Normal MRI, Borderline SAECCG	No reported follow-up events

Patients received an average of 6.9 ± 1.75 tests at baseline as part of their cardiac arrest evaluation (median 7). Some tests were repeated during follow-up or when results were borderline, resulting in each patient undergoing 8.3 ± 2.44 tests (median 8). The majority of the patients underwent a cMRI (77%), exercise stress test (73%) and SAECG (67%). Provocative drug infusion was performed, with 136 patients (68%) undergoing an epinephrine infusion, and 131 patients (66%) undergoing a procainamide infusion. EP testing and Holter monitor were performed less frequently, with 31% and 28% patients undergoing these tests, respectively. Few patients underwent RV angiography (4%) or RV biopsy (5%). Table 11 shows complete results of all the clinical testing.

Table 11: Summary of Total Numbers of Clinical Testing

	Baseline	Total	Abnormal	Borderline	Normal
Epinephrine	136	136			108
CPVT			15	13	
LQTS			13	14	
Angiogram	147	147	27	0	120
CCT	23	23	1	0	24
ECG	200	315	36	0	279
Echo	186	271	0	0	271
EP	62	64	19	0	45
Exercise Stress Test	146	186	9	13	164
Holter	57	66	13	0	53
MRI	153	158	36	5	117
Procainamide	131	135	12	4	119
RV Angio	8	8	2	2	4
RV Biopsy	9	9	2	1	6
SAECG	133	151	47	13	91

Further investigation was performed, targeting diseases where multiple clinical tests may contribute to the diagnosis. Epinephrine infusions and exercise stress tests are diagnostic for LQTS and CPVT, and were compared amongst diagnosed patients (Figure

13 and 14). Six tests were evaluated based on the ARVC task force criteria (Table 5) to determine the diagnostic capabilities for the detection of ARVC (Figure 15).

Figure 13: Diagnostic Testing Used to Identify a Diagnosis of LQTS

Figure 14: Diagnostic Testing Used to Identify a Diagnosis of CPVT

Figure 15: Diagnostic Testing Used to Determine a Diagnosis of ARVC

Figure 16 outlines the specific tests responsible for each diagnosis. Cardiac MRI was the most effective form of clinical testing with 19% of patients, including six with ARVC, receiving a diagnosis due to structural abnormalities. The benefits of cMRI in ARVC patients has been well documented with its inclusion into the modified ARVC task force criteria (82), however cMRI was also effective in the diagnosis of coronary spasm and myocarditis. Thirteen (16%) patients were diagnosed with the use of exercise stress testing. Over a quarter of the diagnosed cohort were diagnosed with LQTS or CPVT, both of which are characterized by potentially lethal arrhythmia's arising during exercise-induced activation of beta-adrenergic receptors. Seven patients (3 CPVT, 4

LQTS) had borderline exercise stress testing, directing investigator initiated testing to epinephrine infusion, which led to a diagnosis in four more patients. Overall, provocative drug testing was effective, with epinephrine infusion responsible for the diagnosis of 12 patients (15%), where an exercise stress test was negative or borderline, and procainamide testing was responsible for six of the seven patients that were diagnosed with BrS. The other BrS patient had a borderline procainamide, but with genetic testing was found to be a carrier of a pathogenic SCN5A mutation. Sensitivity and specificity of testing was calculated for patients diagnosed with LQTS, CPVT and Brugada Syndrome (Table 12).

Table 12: Sensitivity and Specificity of Clinical Testing

	Sensitivity	Specificity
Brugada Syndrome		
Procainamide Infusion	83%	94%
LQTS		
Exercise Stress Test	30%	82%
Epinephrine Infusion	31%	93%
CPVT		
Exercise Stress Test	38%	82%
Epinephrine Infusion	50%	99%

Sensitivity and Specificity of testing, compared to definite or probable diagnosis

Figure 16: Primary Test Responsible for Diagnosis

160 (80%) patients were followed after their cardiac arrest and diagnostic testing. Patients that were not followed had experienced cardiac arrest > 3 months prior to enrolment, and would thus have introduced ascertainment bias in natural history assessment, i.e. the enrollee had to survive to be enrolled, artificially increasing survival in the follow-up cohort. The mean duration of follow-up was 3.15 ± 2.34 years. The 155 patients with an ICD were evaluated; 25 patients (16%) experienced an appropriate ICD shock during their follow-up (median time to first shock 2.22 years, Table 13). Twenty-

five patients (16%) experienced ATP (median time 1.04 years) and 15 patients (10%) experienced both a shock and ATP. The overall rate of experiencing any appropriate therapy (ATP or shock) in ICD recipients was 0.16 per year (SEM=0.14). There were no significant differences between ICD events, including shock ($p=0.076$) or ATP ($p=0.185$) when comparing patients with and without a diagnosis, though there was a trend to more events in the diagnosed patients. Symptoms at follow-up, including palpitations, syncope, and deaths were ascertained during follow-up, detailed in Table 14. In patients that were diagnosed, there was a higher frequency of syncope ($p=0.029$) compared to those without a diagnosis (13% vs. 3%) ($p=0.029$). Two patients died during follow-up, one with a diagnosis of sarcoidosis who died of VT storm due to lead failure and the inability to deliver high voltage therapy. This patient was originally diagnosed with ARVC, but sarcoidosis was discovered at autopsy, allowing for the diagnosis of a first-degree family member with rare familial sarcoidosis. The second patient that died was diagnosed with LQTS and eventually died from malignancy.

Table 13: ICD Events, Comparing Patients with and without a Diagnosis

	All n=155	Diagnosed n=66	UCA n=89	P-Value
Average Follow-up Time (years), n$\pm$SD	3.15 $\pm$ 2.34	3.68 $\pm$ 2.23	2.75 $\pm$ 2.34	$p=0.865$
Median Follow-up Time (years)	3.03	3.20	2.40	
Median Time to First Event (years)	1.3	1.17	1.72	
<u>ICD Shocks, n (%)</u>				
Received an Appropriate Shock n (%)	25 (16)	15 (23)	10 (11)	$p=0.076$
Median Time to First Shock (years)	2.22	2.05	2.62	
<u>ATP, n (%)</u>				
Received Appropriate ATP n (%)	25 (16)	14 (21)	11 (12)	$p=0.185$
Median Time to First ATP (years)	1.04	1.02	1.07	
<u>ATP and/or Shock, n (%)</u>				
Appropriate Shock and Appropriate ATP n (%)	15 (10)	8 (12)	7 (8)	$p=0.416$
Either Appropriate Shock or Appropriate ATP n (%)	35 (23)	20 (30)	15 (17)	$p=0.054$
<u>Inappropriate treatment</u>				
ICD Shock, n (%)	25 (16)	13 (20)	12 (14)	$p=0.378$
ATP, n (%)	8 (5)	5 (8)	3 (3)	$p=0.287$

Table 14: Follow-up Events, Comparing Patients with and without a Diagnosis.

*=Significant p-value.

	All n=160	Diagnosed n=67	UCA n=93	P-Value
Experienced Symptoms	33 (21)	16 (24)	17 (18)	$p=0.431$
Palpitations	23 (14)	10 (15)	13 (14)	$p=1.000$
Syncope	12 (8)	9 (13)	3 (3)	$p=0.029^*$
Death	2 (1)	2 (3)	0 (0)	$p=0.174$

Survival models were constructed using Cox regression analysis to compare the time to first ICD shock, time to first ATP, and time to first event (shock or ATP) in patients with and without a diagnosis (Figure 16). Unadjusted and adjusted (age and sex) hazard ratios were calculated and are listed in Figure 17 and Table 15. There was a strong association between ICD shock and ATP ($p<0.001$). Patients that experienced ATP as their first detected event were also more likely to experience a subsequent ICD shock ($p=0.03$).

Figure 16: Time to First event, Comparing Patients with and without Diagnosis. Cox Regression curves illustrating time to first ICD event, including A) Time to first shock ($p=0.226$), B) time to first ATP ($p=0.248$), and C) time to first event (shock or ATP; $p=0.208$).

Figure 17: Hazard Ratios for Future Cardiac Events

Table 15: Adjusted and Non-adjusted Hazard Ratios

	Unadjusted Hazard Ratio			Adjusted Hazard Ratio		
	P-Value	HR	95% CI	P-Value	HR	95% CI
Age						
≥50	0.159	1.637	0.824-3.251	0.193	1.581	0.794-3.147
<50		0.611	0.308-1.213		0.633	0.318-1.260
Sex						
Male	0.189	1.615	0.790-3.303	0.168	1.664	0.806-3.435
Female		0.619	0.303-1.266		0.601	0.291-1.240
Patient Type						
Diagnosed	0.314	1.413	0.721-2.767	0.229	1.515	0.770-2.982
Undiagnosed		0.708	0.361-1.386		0.66	0.335-1.299
Diagnosis Type						
Structural	0.634	1.26	0.487-3.262	0.889	1.073	0.400-2.878
Electrical		0.794	0.307-2.055		0.932	0.347-2.502

For patients with a diagnosis, comparisons were made between those with underlying structural heart disease and those with primary electrical disease (Table 16).

Fifty-three patients (65%) had underlying primary electrical disease and 28 (35%) had underlying structural heart disease. In follow-up, there was no difference in symptoms between these two groups (Table 17). In comparing ICD events at follow-up, there was a trend towards increased ATP in patients with structural heart disease compared to electrical disease (Figure 18, HR=2.73, 95% CI=0.672-7.030, $p=0.077$).

Table 16: ICD Events Comparing Those with Electrical Heart Disease and Structural Heart Disease

	Electrical n=45	Structural n=23	P-Value
Average Follow-up Time (years), n±SD	3.65 ± 2.39	3.71 ± 1.92	$p=0.161$
Median Follow-up Time (years)	3.08	3.25	
Median Time to First Event (years)	1.02	0.7	
<u>ICD Shocks, n (%)</u>			
Received an Appropriate Shock n (%)	11 (25)	4 (17)	$p=0.548$
Median Time to First Shock (years)	2.22	0.34	
<u>ATP, n (%)</u>			
Received Appropriate ATP n (%)	6 (14)	8 (35)	$p=0.063$
Median Time to First ATP (years)	0.99	0.53	
<u>ATP and/or Shock, n (%)</u>			
Appropriate Shock and Appropriate ATP n (%)	5 (12)	3 (13)	$p=1.000$
Either Appropriate Shock or Appropriate ATP n (%)	11 (26)	7 (30)	$p=0.774$
<u>Inappropriate treatment</u>			
ICD Shock n (%)	12 (28)	1 (4)	$p=0.025^*$
ATP n (%)	2 (5)	3 (13)	$p=0.333$

Table 17: Cardiac Events During Follow-Up, Comparing Those with Electrical Heart Disease and Those with Structural Heart Disease

	Electrical n=43	Structural n=24	P-Value
Experienced Symptoms	11 (25)	5 (21)	$p=0.769$
Palpitations	6 (14)	4 (17)	$p=0.737$
Syncope	6 (14)	3 (13)	$p=1.000$
Death	1 (2)	1 (4)	$p=1.000$

Figure 18: Time to First Event, Comparing Structural vs. Electrical Heart Disease. Cox Regression curves illustrating time to first ICD event, including A) Time to first shock ($p=0.631$), B) time to first ATP ($p=0.077$), and C) time to first event (shock or ATP; $p=0.492$).

Analysis was performed to determine if there was a correlation between positive clinical testing and future cardiac events, or if positive clinical testing was predictive of future events. Spearman correlation and linear regression modeling was performed with neither having any significant results (Appendix).

Chapter 4: Discussion

The current study has shown that with systematic advanced testing, a clinical diagnosis can be determined in approximately half of patients presenting with an unexplained cardiac arrest. A variety of diagnostic testing techniques are required as the unexplained cardiac arrest patients make up an eclectic group of diagnoses, which includes both primary electrical diseases and latent structural causes. CASPER excluded patients with coronary artery disease, the most frequent cause of cardiac arrest (5), and overt structural heart disease, so it would be expected that more patients would have primary electrical disease as the culprit of the cardiac arrest. Patients that were diagnosed subsequently were offered family screening to identify additional relatives at risk of a cardiac arrest.

As has been previously reported (168), many of the diseases identified in CASPER are diverse, dynamic and have overlapping phenotypes. Seven percent of patients were diagnosed during follow-up, as phenotypes became more evident or more information became available about the underlying disease. Furthermore, eight patients had a change in their diagnosis, due to overlapping phenotypes or borderline clinical testing. These results highlight the importance of continuous follow-up and monitoring of patients as phenotypes may become more evident, or more information may become available to allow for diagnosis, and subsequent refined treatment options and family screening.

Since the initiation of CASPER in 2004, continued research has led to the acceptance of new mechanisms responsible for cardiac arrest, including short-coupled IVF and early repolarization (106, 124, 156). Five (6%) patients that received a diagnosis

were identified with short-coupled IVF and 13 (16%) received a diagnosis of early repolarization. While the SCIVF diagnosis is still in its infancy with regards to diagnostic testing and mechanisms, Belhassen *et al.* (125) have shown that SCIVF patients respond well to Quinidine treatment and therefore warranted this assigned diagnosis with its therapeutic implications. It is not known to be familial, which warrants further study to determine mechanisms. The SCIVF diagnosis could only be made in patients being monitored at the time of the VF, either through telemetry or during follow-up events recorded by their ICD, so the diagnosis required a second cardiac event after the index event while the patient was being monitored. Therefore, 2.5% of the overall unexplained cardiac arrest population may be an underestimation of the number of patients where the SCIVF mechanism may be responsible for the cardiac arrest. This will require continuous monitoring for secondary events to gain a clearer picture of its prevalence.

Early repolarization has been reported to have a prevalence of approximately 5-13% in the general population (106, 107), and, in this study, early repolarization was the sole diagnostic finding associated with the cardiac arrest in 13 (7%) patients. Full results may be found in a previously published study (169), however the study by Derval *et al.* included patients with early repolarization with approximately one-third having other substrates for cardiac arrest (169). For purposes of strict definition, patients in the current analysis received a diagnosis of early repolarization if it was the only known reason for the cardiac arrest.

As previously stated, coronary artery disease is the most likely culprit for cardiac arrest, and CAD should be ruled out for all patients presenting with a cardiac arrest.

When the patient is without obvious phenotypic heart disease and is considered an unexplained cardiac arrest patient, based on the results from Table 11 and Figure 16, cMRI should be performed, as it was the single most useful test for diagnosing patients with UCA. CMRI was useful in the diagnosis of patients with structural heart disease, including ARVC, DCM, coronary spasm and myocarditis. Once structural heart disease has been ruled out, investigators should direct their attention to the diagnosis of primary electrical diseases. Patient history and an ECG are the foundation for evaluating the UCA population. When the ECG is not diagnostic, the patient history and ECG findings may direct the investigator to further testing. The SAECG should be performed in conjunction with the ECG as it was useful in the diagnosis of patients, with approximately 1/3 of SAECG considered abnormal and subsequently contributing to diagnosis. From the patient history, if the UCA occurred during exercise or during stress, the investigator should direct their attention to the diagnosis of LQTS, ARVC or CPVT.

From a strictly diagnostic yield perspective, epinephrine infusions should be performed next as it allows for the diagnosis of CPVT and LQTS. Abnormal testing was found in 11% and 10% respectively. Our previous reports regarding epinephrine challenge raised concern that specificity may be a concern, in contrast to procainamide infusion (51, 162). Both tests appear to be appropriate with a modest yield, but require contextual interpretation because of inherent limitations in reproducing specific pathogenic findings. If the cardiac arrest occurred during rest, the patient should undergo a procainamide infusion, as it was the best test for diagnosing Brugada Syndrome. Despite a high rate of positive testing, the EP testing should be used as a last resort as the EP testing was responsible for a diagnosis in only one patient with ARVC, and is

invasive. Based on the evidence from this study, a diagnostic pathway has been proposed in Figure 19. Lastly, if ARVC is suspected because the ECG demonstrates inverted T-waves, and/or the SAECG and MRI are diagnostic of ARVC but do not fully meet the task force criteria, investigators should consider performing an RV angiogram and/or RV biopsy. Genetic testing should be performed to confirm a diagnosis and used to identify family members who may be susceptible to future cardiac events due to IHRD.

Figure 19: Proposed Diagnostic Pathway

The ICD intervention rate in the current study was higher than anticipated in a cohort with preserved cardiac function and a latent substrate for cardiac arrest. We were unable to detect a difference in event rate between those with a diagnosis to those without a diagnosis, including time to first ICD shock, time to first ATP and time to first event (shock or ATP). This study is underpowered to determine a significant difference between the two groups, but early indications suggest that those with a diagnosis may have more severe phenotypes and therefore are more likely to have a follow-up event

(Table 13 and 14). Conceptually, this may be related to disease severity, but given that the comparator by definition has unexplained cardiac arrest, mechanistic explanations cannot be explored unless a cause becomes evident. Future studies may demonstrate that the ability to diagnose patients is a form of risk stratification for future events. Furthermore, the underlying disease type may also be a factor, as Figure 18 shows trends for decreased time to first event in those with underlying structural disease ($p=0.077$), and those with structural disease are twice as likely to receive ATP during follow-up than those with electrical disease. The current study has not yet accrued sufficient follow-up to determine if these trends are real and have diagnostic or therapeutic implications.

Lastly, overall numbers of ICD shocks and ATP were calculated for a median of three years, where 25 (16%) patients received ICD shocks and 25 (16%) received appropriate ATP. Previous studies have reported that those with a previous cardiac arrest due to VF are at a higher risk of second events,(170) but results from studies investigating follow-up ICD events in unexplained cardiac arrest patients have been mixed (146, 171, 172). This study supports the HRS guidelines for implantation of ICD in those with an unexplained cardiac arrest (122). While this study was not powered to provide a robust estimate of annual shock rate, the annual shock rate of 16% was similar to populations previously reported in primary prevention populations (140, 173) but greater than heart failure populations with results from SCD-HeFT reporting an annual shock rate of 7.5% (174).

Chapter 5: Conclusion

This study represents a rare cohort of individuals who have suffered an unexplained cardiac arrest, and represents the largest cohort studied to date. Overall, this study shows that with advanced testing, investigators are able to determine a diagnosis in approximately half of previously unexplained cardiac arrest patients. Over two-thirds of the patients had a potentially inherited mechanism of disease, allowing for family screening and identifying those at risk of a cardiac arrest. Continued monitoring is imperative as these primary electrical diseases or latent structural causes are often dynamic and phenotypes may become more evident with repeated testing, or recording of events that lead to a diagnosis. Furthermore, results from this study highlight the potential for diagnosis to aid in risk stratification to determine those whom are more likely to have a future cardiac event. This study also provides physicians with strategies for identifying underlying conditions, and provides annual shock rates to communicate to patients, and to develop strategies to mitigate shock risk.

As is expected with rare diseases, our cohort is relatively small, making reporting on the ICD event rate difficult with few actual events. An increase in follow-up and more ICD events rates may provide insight into annual shock rates and allow for the determination of clinical tests that may be predictive of future events. Furthermore, patients included in this study represent the patients who have survived a cardiac arrest, and results from this study may not be applicable to non-survivors of a cardiac arrest, unexplained after an autopsy report. Procainamide was the only sodium channel blocker used for the detection of Brugada syndrome, as it is the only sodium channel blocker available in Canada.

The total number of events is low in this population, which will require an increased number of events to allow for improved analysis. Future directions of this study are to continue to monitor the patients enrolled, and to continue to enroll other patients to increase the cohort and subsequent number of cardiac events. More events may also shed light on the prevalence of SCIVF in the population. Furthermore, we recently received a grant from the Rare Disease Foundation to conduct a study on ICD programming in this cohort. In 2012, the MADIT-RIT study changed the way physicians program the ICD, with delayed therapy programming associated with a decrease in inappropriate shocks and a decrease in all-cause mortality(140). Participants enrolled in MADIT-RIT included those with ischemic heart disease who received an ICD for primary prevention (140). We aim to determine whether there is a comparable benefit in those without coronary artery disease or underlying reduced heart function (dilated cardiomyopathy), who undergo ICD implantation for secondary prevention due to a previous unexplained cardiac arrest. Lastly, a future goal is to conduct research to better understand environmental risks that may be associated with increased risks in cardiovascular events in patients with previous UCA. This may include: pollution, nutrition, physical activity and exposure to non-cardiac drugs influence risk. For example, in 2010, the American Heart Association stated that short-term increase in air pollution may have lead to the early mortality of thousands of individuals in the United States alone, by methods which may include QT interval prolongation due to intraventricular conduction delay (175-178). Diesel exhaust is a major source of traffic-related air pollution and has been shown to cause vasoconstriction of blood vessels in human subjects, but no studies have studied the effect of diesel exhaust on repolarization (179). Furthermore, while the effects of air

pollution on cardiovascular disease are concerning, the evidence has mostly relied on epidemiological studies and have involved healthy populations (175, 180-187). Few studies have completed randomized control trials in high-risk populations. A future goal is to conduct a randomized control trial comparing UCA patients to normal, healthy volunteers, to determine whether UCA patients are at a high risk for cardiac events due to air pollution, and whether recommendations should be made regarding occupation and location of residence.

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Appendices

Appendix 1: Spearman correlation to determine correlation between clinical testing and ICD events

Correlations

			Age	Sex	Event	Diagnosed	Ad_In_CPVT		Angiogram	ECG_88_100	EP	Hol_PVC	Hol_NSVT	Hol_SVT
Spearman's rho	Age	Correlation Coefficient	1.000	-.067	.151	-.002	-.007	-.046	.350**	.120	-.106	-.062	-.066	-.068
		Sig. (2-tailed)	.	.400	.057	.978	.928	.561	.000	.285	.182	.441	.409	.395
		N	159	159	159	159	159	159	159	81	159	158	158	158
Sex	Sex	Correlation Coefficient	-.067	1.000	-.089	.001	.208**	.284**	-.196*	.073	-.066	.151	.160*	.157*
		Sig. (2-tailed)	.400	.	.265	.985	.008	.000	.013	.519	.408	.058	.044	.048
		N	159	159	159	159	159	159	159	81	159	158	158	158

		Age	Sex	Event	Diagnosed	Ad_In_CPVT		Angiogram	ECG_88_100	EP	Hol_PVC	Hol_NSVT	Hol_SVT
Event	Correlation Coefficient	.151	-.089	1.000	.154	.048	.031	.144	.093	.068	-.039	-.022	-.025
	Sig. (2-tailed)	.057	.265	.	.052	.545	.695	.069	.406	.395	.629	.787	.751
	N	159	159	159	159	159	159	159	81	159	158	158	158
Diagnosed	Correlation Coefficient	-.002	.001	.154	1.000	.096	.049	-.020	.034	.073	.040	.047	.059
	Sig. (2-tailed)	.978	.985	.052	.	.227	.536	.800	.761	.361	.618	.555	.463
	N	159	159	159	159	159	159	159	81	159	158	158	158
Ad_In_CPVT	Correlation Coefficient	-.007	.208**	.048	.096	1.000	.761**	.056	.139	.153	.069	.059	.055
	Sig. (2-tailed)	.928	.008	.545	.227	.	.000	.483	.216	.054	.388	.463	.492
	N	159	159	159	159	159	159	159	81	159	158	158	158

		Age	Sex	Event	Diagnosed	Ad_In_CPVT		Angiogram	ECG_88_100	EP	Hol_PVC	Hol_NSVT	Hol_SVT
—	Correlation Coefficient	-.046	.284**	.031	.049	.761**	1.000	-.070	.045	.205**	.124	.113	.106
	Sig. (2-tailed)	.561	.000	.695	.536	.000	.	.378	.692	.010	.120	.158	.187
—	N	159	159	159	159	159	159	159	81	159	158	158	158
Angiogram	Correlation Coefficient	.350**	-.196*	.144	-.020	.056	-.070	1.000	.183	-.120	-.033	-.049	-.045
	Sig. (2-tailed)	.000	.013	.069	.800	.483	.378	.	.102	.133	.680	.538	.571
Angiogram	N	159	159	159	159	159	159	159	81	159	158	158	158
ECG_88_100	Correlation Coefficient	.120	.073	.093	.034	.139	.045	.183	1.000	.122	.112	.112	.112
	Sig. (2-tailed)	.285	.519	.406	.761	.216	.692	.102	.	.277	.321	.319	.318

		Age	Sex	Event	Diagnosed	Ad_In_CPVT		Angiogram	ECG_88_10_0	EP	Hol_PVC	Hol_NSV_T	Hol_SVT_T
ECG_88_10_0 EP	N	81	81	81	81	81	81	81	81	81	81	81	81
	Correlation Coefficient	-.106	-.066	.068	.073	.153	.205**	-.120	.122	1.000	-.028	-.015	-.026
	Sig. (2-tailed)	.182	.408	.395	.361	.054	.010	.133	.277	.	.730	.847	.745
EP Hol_PVC	N	159	159	159	159	159	159	159	81	159	158	158	158
	Correlation Coefficient	-.062	.151	-.039	.040	.069	.124	-.033	.112	-.028	1.000	.988*	.993**
	Sig. (2-tailed)	.441	.058	.629	.618	.388	.120	.680	.321	.730	.	.000	.000
Hol_PVC Hol_NSVT	N	158	158	158	158	158	158	158	81	158	158	158	158
	Correlation Coefficient	-.066	.160*	-.022	.047	.059	.113	-.049	.112	-.015	.988**	1.000	.997**
	Sig. (2-tailed)	.409	.044	.787	.555	.463	.158	.538	.319	.847	.000	.	.000

		Age	Sex	Event	Diagnosed	Ad_In _CPV T		Angiogram	ECG_88_10 0	EP	Hol_ PVC	Hol_ NSV T	Hol_ SV T
Hol_N	N	158	158	158	158	158	158	158	81	158	158	158	158
SVT	Correlation	-	.157	-	.059	.055	.106	-.045	.112	-	.993	.997*	1.00
Hol_S	Coefficient	.068	*	.025						.026	**	*	0
VT	Sig. (2-tailed)	.395	.048	.751	.463	.492	.187	.571	.318	.745	.000	.000	.
Hol_S	N	158	158	158	158	158	158	158	81	158	158	158	158
VT	Correlation	-											
MRI	Coefficient	.260	.079	.094	.034	-.061	-.064	.033	.009	.029	-.007	-.020	-.014
	Sig. (2-tailed)	.001	.319	.240	.666	.449	.421	.677	.935	.716	.934	.807	.858
MRI	N	159	159	159	159	159	159	159	81	159	158	158	158
Proc	Correlation	.166		.169	.057	.429**	.384	.154	.116	.054	.074	.060	.063
	Coefficient	*	.122	*			**						
	Sig. (2-tailed)	.036	.126	.033	.476	.000	.000	.053	.304	.501	.356	.451	.435

		Age	Sex	Event	Diagnosed	Ad_In_CPVT		Angiogram	ECG_88_100	EP	Hol_PVC	Hol_NSV_T	Hol_SVT
Proc SAEC G	N	159	159	159	159	159	159	159	81	159	158	158	158
	Correlation Coefficient	-.023	-.078	.230**	.173*	.088	.051	-.009	.217	.158*	.043	.081	.067
	Sig. (2-tailed)	.769	.329	.004	.029	.270	.521	.912	.051	.047	.588	.311	.406
SAEC G Stress	N	159	159	159	159	159	159	159	81	159	158	158	158
	Correlation Coefficient	-.077	.086	.144	.183*	.245**	.212**	-.022	.088	.159*	.203*	.224*	.217**
	Sig. (2-tailed)	.333	.283	.071	.021	.002	.007	.782	.435	.046	.010	.005	.006
Stress Genetics	N	159	159	159	159	159	159	159	81	159	158	158	158
	Correlation Coefficient	-.057	.028	.088	.226**	-.016	.084	-.043	-.016	.056	.039	.033	.041
	Sig. (2-tailed)	.478	.729	.270	.004	.842	.293	.589	.890	.480	.630	.678	.610

		Age	Sex	Event	Diagnosed	Ad_In_CPVT	Angiogram	ECG_88_100	EP	Hol_PVC	Hol_NSV_T	Hol_SVT_T
Genetics	N	159	159	159	159	159	159	81	159	158	158	158
Time												
Genetics	Correlation											
Time	Coefficient	.020	.076	.180*	.154	.247**	.149	.071	.190*	.061	.079	.080
Time	Sig. (2-tailed)	.800	.343	.023	.052	.002	.061	.692	.017	.448	.324	.318
	N	159	159	159	159	159	159	81	159	158	158	158
Time												

Appendix 2: Linear regression model to determine predictability of future ICD events based on clinical testing

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Step 1 ^a								
age	.000	.018	.000	1	.991	1.000	.965	1.036
sex(1)	.462	.517	.800	1	.371	1.588	.577	4.372
time	-.001	.001	.590	1	.442	.999	.998	1.001
event(1)	-1.475	.833	3.140	1	.076	.229	.045	1.169
adrenaline			3.058	3	.383			
adrenaline(1)	.734	.596	1.516	1	.218	2.084	.647	6.708
adrenaline(2)	1.333	.789	2.857	1	.091	3.793	.808	17.801
adrenaline(3)	.580	.882	.433	1	.511	1.787	.317	10.067
angio			3.870	2	.144			
angio(1)	-1.092	.616	3.144	1	.076	.336	.100	1.122
angio(2)	-.365	.791	.213	1	.644	.694	.147	3.273
cct			3.109	3	.375			
cct(1)	-1.163	1.036	1.262	1	.261	.312	.041	2.378
cct(2)	-1.965	1.532	1.645	1	.200	.140	.007	2.822
cct(3)	-.986	1.073	.843	1	.359	.373	.046	3.059
ecg			.983	4	.912			
ecg(1)	.944	1.647	.328	1	.567	2.569	.102	64.801
ecg(2)	.418	1.167	.128	1	.721	1.518	.154	14.965

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
	ecg(3)	.677	.895	.572	1	.449	1.968	.341	11.363
	ecg(4)	.854	.925	.852	1	.356	2.349	.383	14.395
	ep			.597	2	.742			
	ep(1)	.376	.506	.552	1	.458	1.456	.540	3.927
	ep(2)	-.081	.784	.011	1	.918	.922	.198	4.285
	holter			2.527	2	.283			
	holter(1)	.998	.628	2.527	1	.112	2.713	.793	9.284
	holter(2)	-20.264	8638.533	.000	1	.998	.000	.000	.
	mri			2.150	3	.542			
	mri(1)	-.354	.563	.395	1	.530	.702	.233	2.115
	mri(2)	-21.444	27104.160	.000	1	.999	.000	.000	.
	mri(3)	.480	.675	.506	1	.477	1.616	.431	6.061
	procainamide			2.861	3	.413			
	procainamide(1)	-.393	.536	.538	1	.463	.675	.236	1.929
	procainamide(2)	-1.098	1.632	.453	1	.501	.333	.014	8.170
	procainamide(3)	1.216	1.072	1.286	1	.257	3.374	.412	27.606
	saecg			1.447	3	.694			
	saecg(1)	.617	.561	1.210	1	.271	1.854	.617	5.567
	saecg(2)	.146	.895	.027	1	.870	1.158	.200	6.696

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
	saecg(3)	.542	.685	.625	1	.429	1.719	.449	6.582
	stress			4.738	3	.192			
	stress(1)	-.207	.547	.143	1	.705	.813	.278	2.375
	stress(2)	1.684	.892	3.564	1	.059	5.390	.938	30.974
	stress(3)	.122	.707	.030	1	.863	1.129	.283	4.512
	genetics			2.467	3	.481			
	genetics(1)	-.068	.470	.021	1	.885	.934	.372	2.348
	genetics(2)	1.746	1.164	2.252	1	.133	5.731	.586	56.060
	genetics(3)						4149256		
		38.264	14060.565	.000	1	.998	9924996568.000	.000	.
	event(1) by time	.001	.001	1.281	1	.258	1.001	.999	1.002
	Constant	-.450	1.811	.062	1	.804	.638		

a. Variable(s) entered on step 1: age, sex, time, event, adrenaline, angio, cct, ecg, ep, holter, mri, procainamide, saecg, stress, genetics, event * time .