Physical Exertion as a Risk Factor for Ventricular Arrhythmia: A Prospective Cohort Study

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The University of Western Ontario

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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PHYSICAL EXERTION AS A RISK FACTOR FOR VENTRICULAR ARRHYTHMIA: A PROSPECTIVE COHORT STUDY

(Thesis format: Integrated Article)

by

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Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

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London, Ontario, Canada

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Abstract

Episodes of physical exertion are associated with an immediately higher risk of cardiovascular events while physical activity over the long-term is cardioprotective. To assess the transient and long-term risk of ventricular arrhythmia (VA), we conducted a nested case-crossover study within a prospective cohort of 97 patients with implantable cardioverter-defibrillators (ICD). Within an hour of episodes of exertion, the risk of VA was 5.3 (95% CI 2.7 – 10.6) times greater compared to periods of rest. The association was higher among patients with aerobic fitness below the median (RR[relative risk]=17.5, 95% 5.2 – 58.5) than for patients with aerobic fitness above the median (RR=1.2, 95% CI 0.4 – 4.2, p-homogeneity = 0.002) and higher among patients who were sedentary (RR=52.8, 95% 10.1 – 277) compared to individuals who were not (RR=3.2, 95% 1.3 – 7.6, p-homogeneity=0.0002). We found no statistically significant difference in time-to-VA by aerobic fitness or sedentary behaviour. In this clinical cohort, there is an elevated risk of VA within an hour of exertion, particularly in patients with low aerobic fitness and sedentary behaviour.

Keywords

Case-crossover, ventricular arrhythmia, implantable cardioverter-defibrillator, exertion, sedentary
Co-Authorship Statement

The two manuscripts described here were authored primarily by Harpreet S. Chahal. Regular feedback on study design, data analysis, and interpretation was provided by supervisory committee and study collaborators.
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<thead>
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>Angiotensin-converting enzyme</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Anti-tachycardia pacing</td>
<td>ATP</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society class</td>
<td>CCS class</td>
</tr>
<tr>
<td>Echocardiographic monitoring</td>
<td>ECG monitoring</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>ICD</td>
</tr>
<tr>
<td>Metabolic equivalent of task</td>
<td>MET</td>
</tr>
<tr>
<td>Multi gated acquisition scan</td>
<td>MUGA scan</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>MI</td>
</tr>
<tr>
<td>New York Heart Association functional classification</td>
<td>NYHA class</td>
</tr>
<tr>
<td>Peak oxygen consumption</td>
<td>Peak VO$_2$</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>RCT</td>
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Chapter 1

1 Introduction

A ventricular arrhythmia is an abnormal heart rhythm that may prevent the ventricles of the heart from contracting in coordination with each other\(^1\). Ventricular tachycardia and ventricular fibrillation are two types of arrhythmia that may result in sudden cardiac death if they are not treated immediately. Patients at risk of fatal arrhythmia can be eligible to receive an implantable cardioverter-defibrillator (ICD), which can detect arrhythmia and deliver an electric discharge to correct abnormal rhythm. The ICD stores information on each episode of arrhythmia in its memory, which can then be analyzed as objective precisely timed assessments of ventricular arrhythmia.

During and shortly after an episode of physical exertion itself, there is a transiently elevated risk of myocardial infarction, stroke, and ventricular arrhythmia among individuals who are at high risk for these events\(^2\). Over the long term however, engaging in physical exertion is associated with a reduction in the baseline risk of cardiovascular events in both men and women. In this thesis, we explore these opposing roles of physical exertion in ventricular arrhythmia. We begin with a literature review where we describe the mechanisms of ventricular arrhythmia, along with a summary of its epidemiology, its treatment by implantable cardioverter-defibrillator (ICD), and its relationship with exertion. We outline objectives and hypotheses in Chapter 3 and detail study design and data collection in Chapter 4. In Chapter 5, we measure the immediate risk of ventricular arrhythmia following physical exertion. In Chapter 6, we assess the long-term risk of ventricular arrhythmia by aerobic fitness and sedentary behaviour. The final chapter discusses both studies in terms of their
contributions to the body of knowledge, their methodological strengths and limitations, and the implications for future research.

1.1 References


Chapter 2

2 Literature review

2.1 Mechanisms of ventricular arrhythmia

An arrhythmia or irregular heartbeat is characterized by abnormal electrical activity in the cardiac muscle, which may disrupt the mechanical function of the heart. Waves of depolarization cause contractions in the heart muscle. An arrhythmia can impair normal contraction by dysfunctional impulse formation, abnormal impulse frequency, or both. Arrhythmia occurs through three principle mechanisms called reentry, enhanced automaticity, and triggered activity, and patients with damaged myocardium from cardiovascular disease are at an increased risk of ventricular arrhythmia from each of these mechanisms\textsuperscript{1}. Scar tissue is created from prior myocardial infarction or generalized scarring from dilated cardiomyopathy and other cardiomyopathic processes. Islands of scar tissue in the myocardium increase the risk of arrhythmia through reentrant circuits. Tachycardia or rapid heartbeat can initiate due to an extrasystolic beat blocked in one direction around the scar and conducting in another\textsuperscript{2,3}. These extrasystolic beats are more common in patients with poor ventricular function, especially during exercise\textsuperscript{4-8}. In enhanced automaticity, arrhythmia is caused by an increase in the rate of phase 4 depolarizations of cardiac cells which increase impulse frequency. This regulation is under the direct influence of autonomic activity, which is considerably abnormal in patients with ventricular dysfunction\textsuperscript{9,10}. Triggered activity is another mechanism of
arrhythmia and is caused by delayed afterdepolarizations creating multiple abnormally initiated waves of depolarization.

2.2 Epidemiology of ventricular arrhythmia

Each year, approximately 40 000 Canadians die from cardiac disease\textsuperscript{11}. Approximately one half of these happen suddenly and are mostly due to ventricular tachycardia and ventricular fibrillation. A similar trend is observed worldwide; half of cardiac deaths across the globe occur suddenly, 80\% of which are attributed to ventricular arrhythmia\textsuperscript{12}. The risk of ventricular arrhythmia is higher in individuals who are older, male, and have lower ejection fraction\textsuperscript{13} – a measure of cardiac dysfunction. The risk of ventricular arrhythmia also varies across lifestyle and socio-demographic characteristics. Notably, the decreasing trend in sudden death due to cardiac cause from 1950 to 1999 was largely attributed to advances in its treatment and prevention\textsuperscript{14}.

2.3 Implantable cardioverter-defibrillator (ICD)

Patients at risk of ventricular arrhythmia are eligible to receive an implantable cardioverter-defibrillator (ICD), a device that is implanted in the upper chest. Rapid ventricular rates above a programmed threshold may indicate ventricular tachycardia or ventricular fibrillation and are treated by anti-tachycardia pacing (ATP) or shock therapy. Sensed events are recorded and assessed between different bipoles and allow for near-field recorded ventricular electrograms which detect arrhythmias, and far-field recorded electograms which assess atrial activity. With a review of both these recordings, an electrophysiologist may determine whether the arrhythmia originated in the ventricles
and if ICD therapy is appropriate`. While the ICD detects and treats arrhythmia, it does not by itself alter the risk of subsequent episodes of ventricular arrhythmia.

2.4 ICD implantation wait times

The majority of patients receive an ICD under the category of “primary prevention”\(^\text{11}\), indicating that they are identified as high risk for ventricular arrhythmia based on a poor ejection fraction and do not have a history of cardiac arrest\(^\text{15}\). After ICD implant, these patients may have a 25\% relative risk reduction and 8\% absolute risk reduction in all-cause mortality over 2 to 4 years compared to treatment by anti-arrhythmic medication\(^\text{15}\). Patients receiving ICD for primary prevention are considered ‘Priority Class 2’ by the Cardiac Care Network of Ontario and are assigned a target wait time of 56 days for implant. The London Health Sciences Centre is one of nine ICD implanting sites in Ontario and it has a median wait time of 36 days, with a mean of 27 patients waiting. The median wait time among all nine sites in Ontario from January-March 2008 was 30 days (range of 5-59 days) with an average of 164 patients awaiting ICD implant\(^\text{16}\). Current recommendations do not directly address the issue of patient activity level during wait for ICD implant\(^\text{17-19}\), a period where patients are unprotected against possibly fatal ventricular arrhythmia.

2.5 Physical exertion triggering ventricular arrhythmia

Among individuals with appropriate substrate, the mechanisms of ventricular arrhythmia can be potentiated by transient changes in autonomic tone, circulating catecholamines, electrolyte levels, oxygen desaturation, and pH balance – all of which occur during an
episode of physical exertion\textsuperscript{2}. While the precise link between a stress and ventricular arrhythmia is uncertain, there is evidence that population triggers like earthquakes and war and individual triggers like emotional and physical stress may precipitate ventricular arrhythmia among those who are predisposed\textsuperscript{20}. The association between episodes of physical exertion and ventricular arrhythmias have been documented in anecdotal reports, in observational case-crossover studies, and in experimental studies using exercise stress testing which incrementally increase the difficulty of exertion while concurrently monitoring heart rhythm\textsuperscript{21,22}. There have been two prior studies in patients with ICD which have reported a higher risk of ventricular arrhythmia immediately following physical exertion\textsuperscript{23,24}, but no study has examined if the heightened relative risk of ventricular arrhythmia following an episode of exertion varies by level of aerobic fitness or by sedentary behaviour.

### 2.6 Habitual physical exertion protecting against ventricular arrhythmia

Safe levels of habitual physical exertion are widely encouraged in older adults, even among those who have several comorbidities, low levels of fitness, or functional limitations preventing specific movements and activities\textsuperscript{25}. Habitual physical exertion reduces the risk of cardiovascular disease, coronary heart disease, hypertension, stroke, and can serve as effective therapy for many chronic conditions\textsuperscript{26}. Similarly, sedentary behaviour is associated with a higher baseline risk of cardiovascular events\textsuperscript{25}. This relationship may also exist between habitual physical exertion and ventricular arrhythmia; exertion over the long term may protect against arrhythmia by reducing
adrenergic activation and increasing vagal tone\textsuperscript{2}. After a monitored exercise training program, patients with ICD saw improvements in quality of life and peak aerobic capacity, an indicator of aerobic fitness\textsuperscript{27}. Further, higher levels of fitness\textsuperscript{28}, a byproduct of regular activity, and higher levels of habitual physical exertion\textsuperscript{29,30} are associated with a reduced risk of ventricular arrhythmia in patients with ICD. Habitual physical exertion may confer a protective advantage against ventricular arrhythmia, similar to its well-studied benefits for other chronic and acute cardiovascular illnesses.

There is evidence that physical exertion can act as both a risk factor and a protective factor for ventricular arrhythmia, the former in the form of transiently elevated short term risk and the latter in the form of long-term baseline risk reduction\textsuperscript{31}. It is also possible that the elevated short-term risk is lower in those who have higher levels of physical fitness as a result of their habitual physical exertion. These different associations of the outcome to the exposure across time, together with the possibility that the exposure is also an effect modifier, pose special methodological challenges to estimating these associations using epidemiological methods. Partially in response to these methodological challenges, groups of interventional cardiologists have been enrolling patients into prospective cohorts designed to conduct case-crossover analysis. In the next chapter we briefly describe the origins of a prospectively enrolled cohort of patients who underwent ICD implantation at the London Health Sciences Centre.
2.7 References


15. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular...


Chapter 3

3 Study methods

3.1 MOVE-IT: Monitoring Of Ventricular rhythm & Exercise – ICD sTudy

MOVE-IT was a single-centre prospective cohort study of 97 consecutive patients recruited from May 2009 to July 2012 in the London Health Sciences Centre in London, Ontario, Canada. The study protocol was approved by the Health Sciences Research Ethics Board (REB) and all participants provided informed consent. MOVE-IT was funded by the Heart and Stroke Foundation of Ontario to assess the short- and long-term risk of ventricular arrhythmia associated with physical exertion among patients with ICD.

3.1.1 Patient recruitment

All patients who received ICD implant in the London Health Sciences Centre in this period were considered for study enrolment. The decision to offer ICD was determined by consensus from a team of four cardiac electrophysiologists using evidence-based guidelines. Guidelines for primary prevention ICD implant are set by Canadian Heart Rhythm Society criteria as follows:

- Ischemic Heart Disease and
  - Post-MI > 1 month
  - Post coronary bypass > 3 months
- **Ejection Fraction < 30%**
  - **Appropriate medical therapy**
  - **No contraindications**

- **Non-Ischemic Heart Disease** and
  - **Ejection Fraction < 30%**
  - **NYHA class II/III**
  - **Appropriate medical therapy**
  - **Sufficient time since diagnosis (recommended 9 months) to exclude acute myocarditis or other transient causes of ventricular dysfunction**
  - **No contraindications**

Participants were categorized as “secondary prevention” patients if they had a prior cardiac arrest without reversible cause, or sustained ventricular tachycardia with an ejection fraction less than 40%.

Patients were excluded from the study if they met any of the following criteria:

- **Under 18 years of age**
- **Symptoms of angina with any of the following features: new onset; CCS class III or IV pending assessment; plan for revascularization**
- **Comorbid non-cardiac condition associated with anticipated survival less than 2 years**
- **Physical limitations precluding moderate exercise**
- **Participation in a concomitant research study that would conflict or affect outcome of this study**
- **Unwilling or unable to provide consent**
3.1.2 Study schedule

Patients underwent implantation of Medtronic, Guidant, or St. Jude ICD where the number of leads (ventricular +/- atrial) was determined by clinical scenario according to a team of electrophysiologists and the implanting physician. Patients returned for device interrogation 2 weeks after implant and every 6 months thereafter, in accordance with standard clinical practice. Study visits were timed to coincide with this clinical schedule; at the initial study visit, patients completed a structured medical questionnaire (appendix A) and underwent cardiopulmonary exercise stress testing to measure aerobic fitness. Patients who experienced symptomatic ventricular arrhythmia completed a post-therapy questionnaire (appendix B) administered over phone or at clinic visit by research nurse within 72 hours of device discharge. Electrograms for any recorded events were collected during device interrogation at scheduled study visits.

3.1.3 Sample size

Calculations for cohort size were based on the analysis planned to assess long-term risk of ventricular arrhythmia because it was expected to require the larger sample size. Pilot data indicated that ventricular arrhythmia occurred in approximately 20% of ICD patients per year, which is consistent with published data\(^1\). It was estimated that patients below median aerobic fitness would have a 35% annual incidence of ventricular arrhythmia and patients above median aerobic fitness would have a 15% annual incidence, which results in an estimated hazard ratio of 0.55. With this ratio, to detect a difference in freedom-from-ventricular arrhythmia using the Kaplan-Meier method with 80% power at a 2-sided alpha level of 0.05, 128 patients would be required\(^2\). With a conservative loss to follow
up of 10%, a total of 140 patients made the desired sample size. Ultimately, the achieved sample size was smaller than the desired size because recruitment and completion of cardiopulmonary stress testing was less than anticipated.

3.2 References


2. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Statistics in medicine. 1982;1:121-129.
Chapter 4

4 Objectives and hypotheses

In Chapter 5, we explore the immediate risk of ventricular arrhythmia following episodes of physical exertion. In this clinical population, we hypothesized that the risk of ventricular arrhythmia is elevated within an hour of physical exertion compared to periods of rest and within an hour of vigorous physical exertion compared to other times. Our secondary analysis in Chapter 5 compares this immediate risk of ventricular arrhythmia following physical exertion between individuals with lower levels of aerobic fitness and individuals with relatively higher levels of aerobic fitness, and between individuals who are sedentary compared to individuals who are not sedentary. We hypothesized that there is a higher risk of ventricular arrhythmia following exertion among individuals with lower levels of fitness and among those who are sedentary.

In Chapter 6, we explore time-to-ventricular arrhythmia over the study period and test if it differs by level of aerobic fitness or sedentary behaviour. We hypothesized that there is reduced time-to-arrhythmia among individuals with lower levels of aerobic fitness compared to those with higher levels of aerobic fitness, and that there is reduced time-to-ventricular arrhythmia among those who are sedentary compared to those who are not sedentary.
Chapter 5

5 Physical exertion and the immediate risk of ventricular arrhythmia

5.1 Introduction

There is consistent evidence that discrete episodes of physical exertion are associated with a transiently elevated risk of cardiovascular events including myocardial infarction and stroke in high-risk clinical populations. A few studies have described this association in ventricular arrhythmia, but none have examined if this risk varies by level of aerobic fitness or sedentary behaviour.

Although appropriate anti-tachycardia pacing (ATP) and shocks delivered by implantable cardioverter-defibrillators (ICD) may be life-saving, ICD therapy is associated with psychological distress and reduced quality of life\(^1,2\). Reducing sedentary behaviour is important for healthy aging in older adults\(^3\), but people with ICDs commonly report concerns that physical exertion will elicit a shock response so they may abstain from or engage in lower levels of physical activity to avoid shocks\(^4\).

In this study, we evaluated whether there is a higher risk of ventricular arrhythmia during and shortly after episodes of physical exertion compared to rest. We hypothesized that

\(^{1}\) A version of this paper is in press in the Canadian Journal of Cardiology
lower aerobic fitness, measured by peak VO$_2$, and sedentary behaviour would be associated with a higher risk of ventricular arrhythmia following isolated bouts of physical exertion.

5.2 Methods

5.2.1 Study population

The MOVE-IT study is a prospective cohort of 97 consecutive ICD patients recruited at the time of implant in the London Health Sciences Centre in London, Ontario, Canada from May 2008 to July 2012. Patients received primary and secondary prevention ICD implant based on criteria set by the Canadian Heart Rhythm Society$^5$. Patients were ineligible for the study if they met any of the following criteria: < 18 years of age, comorbid non-cardiac condition associated with anticipated survival < 2 years, or physical limitations precluding moderate exercise. Thirty therapies among 22 patients treated symptomatic ventricular arrhythmia, which makes the cohort for analysis.

5.2.2 Study design

The case-crossover design was developed to study the transient effect of an intermittent exposure on events with acute onset$^6$. Rather than comparing different exposure groups at the same time, the case-crossover design compares the same person at different times, using each person as their own control. As a result, there is no confounding by fixed (e.g. sex) or slowly varying characteristics. This requires collecting information on exposure (e.g. physical exertion) immediately preceding the outcome event (e.g. ventricular
arrhythmia) and comparing this with the expected frequency of exposure over a similar time period based on the study patient’s habitual pattern (appendix D).

5.2.3 Physical exertion

At the initial study visit, patients reported their average frequency and duration of light, moderate, and vigorous exertion activities over the last 6 months (appendix A) using the 15-point (scores ranging from 6-20) visual analogue Borg scale\(^7\) (appendix C) to gauge exertion intensity. Patients who reported no moderate to vigorous exertion in the past 6 months were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary. Information on timing of physical exertion and exposure to other possible behavioural precursors was also collected.

Patients who experienced symptomatic ventricular arrhythmia completed a semi-structured questionnaire within 72 hours of device therapy by telephone or at the clinic (appendix B). Patients reported the last time before device discharge that they had engaged in light, moderate, and vigorous exertion with the following response options: never, at the time of shock, 1/2 hour before, 1 hour before, 2 hours before, 3-6 hours before, 6-24 hours before, 1-2 days before, 3-4 days before, or ≥ 5 days before. In the questionnaire, patients also described the specific activity at the time of and immediately preceding ICD therapy, and their symptoms surrounding the event. Information on sexual intercourse and other potential triggers was also collected from the questionnaire and information on age, medical history, and medications was abstracted from medical records.
5.2.4 Aerobic fitness

A modified Bruce protocol\textsuperscript{8} was conducted 2 weeks after ICD implant to measure peak VO\textsubscript{2}. An initial 3 minute stage of 1.7 mph and 0% gradient (2.3 METs) was followed by 3 minute stages as follows: 1.7 mph at 5% grade (3 METs), 1.7 mph at 10% grade (4.6 METs), 2.5 mph and 12% grade (7 METs), 3.4 mph and 14% grade (10.2 METs), 4.2 mph and 16% grade (13.5 METs), 5 mph and 18% grade (17.2 METs). Peak VO\textsubscript{2} was measured continuously throughout the treadmill test using computerized online rapid gas analyzers for oxygen and carbon dioxide\textsuperscript{9} of the Vmax™ Encore Metabolic Cart (CareFusion, San Diego, CA). The treadmill test was performed adhering to accepted standards\textsuperscript{10}, with continuous 12 lead ECG monitoring and recordings at rest prior to exercise, at least every 3 minutes during exercise, peak exercise, and at 1-minute intervals for 6 minutes during recovery. Symptoms of chest pain, leg fatigue, and dyspnea were quantified using the Borg Scale. The exercise test was terminated when the subject could not continue due to symptoms (such as fatigue, dyspnea or chest pain) or if it was deemed medically necessary due to any of the following clinical findings: > 2 mm of horizontal or downsloping ST segment depression; persistent ≥10 mm Hg decline in systolic blood pressure; a hypertensive (systolic blood pressure > 280 mm Hg, diastolic blood pressure > 120 mm Hg) blood pressure response; or the development of significant arrhythmias. Written informed consent was obtained from each patient prior to exercise testing.
5.2.5 ATP or shock

Interrogation of the ICD provides a summary of detected arrhythmias; date, time, duration, therapies, and rhythm prior to onset are stored in the device memory. Electrograms were also available for each episode. The treating electrophysiologist and lead investigator (LJG) reviewed all stored electrograms to confirm included events.

5.2.6 Statistical analysis

In the case-crossover design, data are stratified on each individual event. In each stratum, the patient’s exposure in the hour preceding an event (hazard period) is compared to their expected frequency of exposure in a random hour based on their usual exposure time. We multiplied the usual frequency of activity by the usual duration of activity to calculate annual exposure time and we subtracted this value from total hours in a year to calculate annual non-exposure time. Using methods for sparse data, we calculated the Mantel-Haenszel incidence rate ratio (RR) for person-time and 95% confidence intervals comparing the observed exposure in the hazard period to the expected frequency of exposure. We evaluated whether this association was different between people above and below the median level of peak VO$_2$ in this sample and between individuals who were and were not sedentary. We compared these subgroups using a Wald $\chi^2$ test of homogeneity. Analyses were performed using macro in SAS 9.4 (SAS Institute, Cary, NC).
5.3 Results

A total of 30 events occurred among 22 patients (20 men, 2 women). Six (20%) were ventricular tachycardia, 12 (40%) were fast ventricular tachycardia, and 12 (40%) were ventricular fibrillation. Seven (23%) events were terminated by ATP alone, 12 (40%) by shock alone, and 11 (37%) by shock after ATP. The characteristics of the 22 patients who experienced symptomatic ventricular arrhythmia are presented in Table 5-1. The mean age of these study patients was 62.2 ± 7.6. The mean left ventricular ejection fraction was 26.9%, ranging from 15-42%. Twelve patients (55%) had a history of myocardial infarction, 6 patients (27%) had diabetes mellitus, and 21 (96%) were on beta blocker medication. Fourteen (64%) patients received primary prevention ICD, and 8 (36%) received ICD for secondary prevention.

Most ICD therapy (76%) occurred between 6AM and 6PM and an equal proportion of events occurred before and after 12:00PM (Figure 5-1). Sixteen (53%) therapies were delivered within an hour of physical exertion (14 light or moderate, 2 vigorous) and 13 (43%) events occurred during the episode of physical exertion.

The results of the case-crossover analyses are presented in Table 5-2. The risk of ventricular arrhythmia within an hour of any exertion was 5.3 (95% CI 2.7 – 10.6) times greater compared to periods of rest. The risk of ventricular arrhythmia was 23.3 (95% CI 5.8 – 91.9) times greater within an hour of vigorous exertion compared to other times. The risk of ventricular arrhythmia within an hour of any exertion was higher among patients with lower levels of aerobic fitness (peak VO$_2$ < 18.2 mL/kg/min) than for patients with higher levels of aerobic fitness (p-homogeneity=0.002). Similarly, this risk
was higher among habitually sedentary patients compared to patients who were not sedentary (p-homogeneity=0.0002). The results were not substantially different from sensitivity analyses that were restricted only to shock events.

5.4 Discussion

In this clinical population, there was a higher risk of confirmed ventricular arrhythmia within an hour of exertion compared to periods of rest. The association was stronger for patients below the median peak VO\textsubscript{2} than for patients with peak VO\textsubscript{2} above the median, suggesting that high aerobic fitness may lower the risk of ventricular arrhythmia following episodes of exertion. The association between an episode of exertion and ventricular arrhythmia was also stronger among those who were sedentary compared to those who were not sedentary.

Our results are consistent with prior research on exertion as an acute trigger of ventricular arrhythmia. Lampert et al.\textsuperscript{13} and Fries et al.\textsuperscript{14} reported a higher risk of ICD therapy immediately following an episode of exertion compared to other times. Additionally, previous research has shown that the relative risk of myocardial infarction and sudden cardiac death following episodes of physical exertion is higher among people who are sedentary\textsuperscript{15-17}. This is the first study to show that there is a higher risk of ventricular arrhythmia following episodes of physical exertion among those with lower levels of aerobic fitness and sedentary behaviour.

Exercise confers numerous long-term benefits\textsuperscript{18}, but isolated episodes of exertion are accompanied by transient changes that may induce ventricular arrhythmia among
individuals with appropriate substrate. Activation of the sympathetic nervous system from exertion leads to several mechanical, metabolic, and electrophysiological changes. Increased heart rate, ionotropy, blood pressure, and afterload increase myocardial oxygen demand, that may lead to ischemia and in turn precipitate ventricular arrhythmia. In addition, changes in electrolytes and pH may potentiate the risk of arrhythmia. Elevated levels of circulating catecholamines increase myocardial conduction velocity and membrane refractoriness, that may increase susceptibility to ventricular arrhythmia. Further, increased sympathetic activity increases calcium influx that may increase the amplitude of delayed afterpotentials, which can cause triggered automaticity and enhanced automaticity. Also, vagally-mediated recovery is typically delayed in patients with low ejection fraction, creating an elevated period of risk longer than the episode of exertion itself. The impact of these changes ultimately varies by individual characteristics; arrhythmic substrate may influence susceptibility to arrhythmia, but participation in habitual activity may protect against the brunt of each episode of exertion.

5.4.1 Strengths and limitations

By using each patient as his or her own control, the case-crossover design eliminates between-person confounding by all fixed and slow-varying characteristics – both measured and unmeasured. However, confounding by time of day is possible because ventricular arrhythmias are more likely to occur in the morning, when physical activity may also be more likely. However, the timing of both ventricular arrhythmias and physical activity among MOVE-IT patients were spread across the day. We prospectively
collected usual frequency and duration of physical exertion at the initial study visit so that occurrence of symptomatic ventricular arrhythmia could not influence a patient’s perspective on their physical activity habits. Further, in addition to assessing sedentary behaviour by self-report, we studied the impact of peak VO$_2$, an objectively collected measure of aerobic fitness.

All patients who reported activity at the time of therapy were also classified as active by the ICD’s activity sensor, which senses mechanical vibration using a single-axis accelerometer. However, several patients who reported being at rest during therapy were also classified as active by the ICD activity sensor. Although self-reported exertion at the time of ICD therapy may be over- or underreported by some patients, we used this measure because of concerns that the objectively recorded accelerometer data was too sensitive to small movements, does not measure exertion intensity, and only records activity at the time of device discharge. While this was a small study, we were still able to identify a statistically significant difference in the association between exertion and ventricular arrhythmia across levels of aerobic fitness and sedentary behaviour.

5.4.2 Conclusion

We found that there was a transiently elevated risk of ventricular arrhythmia within an hour of episodes of light, moderate, and vigorous exertion. Moreover, we found that this association as stronger among patients with lower levels of aerobic fitness and among patients with habitually sedentary behaviour.
5.5 References


Table 5-1. Baseline characteristics for 22 MOVE-IT patients experiencing symptomatic ventricular arrhythmia, mean ± SD or n (%)

<table>
<thead>
<tr>
<th></th>
<th>Full cohort°</th>
<th>Aerobic fitness below median†</th>
<th>Aerobic fitness above median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=22</td>
<td>n=9</td>
<td>n=9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.2 ± 7.6</td>
<td>60.9 ± 10.2</td>
<td>63.3 ± 6.0</td>
</tr>
<tr>
<td>Men</td>
<td>20 (91%)</td>
<td>7 (78%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Ejection fraction (%)* (by MUGA scan)</td>
<td>26.9 ± 7.3</td>
<td>28.0 ± 12.5</td>
<td>24.8 ± 5.3</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>116.6 ± 71.4</td>
<td>105.9 ± 11.1</td>
<td>115.6 ± 17.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71.4 ± 12.0</td>
<td>65.7 ± 9.3</td>
<td>73.9 ± 13.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3 ± 4.9</td>
<td>30.2 ± 6.3</td>
<td>29.2 ± 3.9</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>18.73 ± 5.80</td>
<td>13.9 ± 2.8</td>
<td>23.5 ± 3.4</td>
</tr>
<tr>
<td>Sedentary‡</td>
<td>8 (37%)</td>
<td>5 (55%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Indication for ICD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>14 (64%)</td>
<td>7 (78%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>8 (36%)</td>
<td>2 (22%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>12 (55%)</td>
<td>4 (44%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>7 (32%)</td>
<td>2 (22%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (55%)</td>
<td>3 (33%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Non-Ischemic cardiomyopathy</td>
<td>8 (36%)</td>
<td>4 (44%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (55%)</td>
<td>6 (67%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Valvular heart surgery</td>
<td>3 (14%)</td>
<td>1 (11%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Congenital heart surgery</td>
<td>1 (5%)</td>
<td>1 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Other Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (27%)</td>
<td>3 (33%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (55%)</td>
<td>5 (56%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (27%)</td>
<td>3 (33%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Cardiac medication history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>21 (96%)</td>
<td>9 (100%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>17 (77%)</td>
<td>7 (78%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>5 (23%)</td>
<td>2 (22%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>14 (64%)</td>
<td>7 (78%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7 (32%)</td>
<td>4 (44%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>2 (9%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Class 1 antiarrhythmic</td>
<td>3 (14%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

°4 patients did not complete cardiopulmonary exercise testing to determine peak VO₂
*4 patients did not have information on ejection fraction from MUGA scan
†Median aerobic fitness (peak VO₂) = 18.2 mL/kg/min
‡Patients who reported no moderate to vigorous exertion in the past 6 months at initial assessment were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary
Table 5-2. Relative risk and 95% confidence intervals of symptomatic ventricular arrhythmia within 1 hour of exertion among 22 MOVE-IT patients

<table>
<thead>
<tr>
<th>Ventricular arrhythmia within 1 hour of exertion</th>
<th>Relative risk (95% CI)</th>
<th>P- heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any exertion</td>
<td>16/22</td>
<td>5.3 (2.7 – 10.6)</td>
</tr>
<tr>
<td>Light or moderate exertion</td>
<td>14/22</td>
<td>4.9 (2.5 – 9.7)</td>
</tr>
<tr>
<td>Vigorous exertion</td>
<td>2/22</td>
<td>23.2 (5.8 – 91.9)</td>
</tr>
<tr>
<td>Aerobic fitness (peak VO₂)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above median°</td>
<td>3/9</td>
<td>1.2 (0.4 – 4.2)</td>
</tr>
<tr>
<td>Below median</td>
<td>9/9</td>
<td>17.5 (5.2 – 58.5)</td>
</tr>
<tr>
<td>Sedentary behaviour*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10/14</td>
<td>3.2 (1.3 – 7.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>6/8</td>
<td>52.8 (10.1 – 277)</td>
</tr>
</tbody>
</table>

*Median peak VO₂ = 18.2 mL/kg/min
*Patients who reported no moderate to vigorous exertion in the past 6 months at initial assessment were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary
Figure 5-1. Time of day of symptomatic ventricular arrhythmia among 22 MOVE-IT patients
Chapter 6

6 Freedom from ventricular arrhythmia by aerobic fitness and sedentary behaviour

6.1 Introduction

Habitual physical activity is widely recommended for older adults to reduce the risk of chronic disease, premature mortality, functional limitations, and disability\(^1\). A higher risk of cardiovascular disease in particular has been related to physical inactivity\(^2\). Some studies have described an increased risk of ventricular arrhythmia among individuals with lower levels of fitness and sedentary behaviour, however, other studies have found no significant improvement in risk after exercise therapy.

Ventricular arrhythmia can be monitored and immediately treated by an implantable cardioverter-defibrillator (ICD). An ICD may provide life-saving treatment through discharge of Anti-Tachycardia Pacing (ATP) or shock, but ICD therapy is associated with psychological distress and a reduced quality of life\(^3\).

In this chapter, we assessed the impact of aerobic fitness and habitually sedentary behaviour on freedom from ventricular arrhythmia. We hypothesized that lower levels of aerobic fitness, measured by peak VO\(_2\), and sedentary behaviour would reduce freedom from ventricular arrhythmia.
6.2 Methods

6.2.1 Study population

The MOVE-IT study is a cohort of 97 consecutive ICD patients in the London Health Sciences Centre in London, Ontario, Canada from May 2008 to July 2012. Chapter three describes the recruitment, inclusion criteria, and exclusion criteria of this study population in detail. In this chapter, we analyze all patients in the cohort, including those who did not experience ICD therapy for ventricular arrhythmia over the follow-up period.

6.2.2 Study design

MOVE-IT was a single-centre prospective cohort study. Patients were enrolled at the time of ICD implant. Patients returned for device interrogation 2 weeks after implant and every 6 months thereafter, in accordance with standard clinical practice. Baseline information on exposure (e.g. aerobic fitness and sedentary behaviour) was collected during the first study visit after implant and outcome status (e.g. ventricular arrhythmia) was collected in every subsequent scheduled clinic visit and any unscheduled clinic visit as well.

6.2.3 Physical exertion

Patients reported their physical exertion habits at an initial study visit, previously described in Chapter 5. Patients who reported no moderate to vigorous exertion in the past 6 months were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary.
6.2.4 Cardiopulmonary exercise stress testing

A modified Bruce protocol, described in Chapter 5, was conducted 2 weeks after ICD implant to measure peak VO$_2$, a proxy for aerobic fitness.

6.2.5 ATP or shock

Interrogation of the ICD provides a summary of detected arrhythmias; date, time, duration, therapies, and rhythm prior to onset are stored in the device memory. Electrograms were also available for each episode. The treating electrophysiologist and lead investigator (LJG) reviewed all stored electrograms to confirm appropriateness of therapy and ventricular origin of arrhythmia.

6.2.6 Statistical analysis

We constructed Kaplan Meier curves that calculated freedom from symptomatic ventricular arrhythmia. We tested if time to ventricular arrhythmia was different between people below and above the median level of peak VO$_2$ in this sample and between individuals who were and were not sedentary using the log-rank statistic. We plotted the log minus log of survival against the log of survival time between patients above and below median peak VO$_2$ and between patients who were and were not sedentary to assess proportionality of the hazard of ventricular arrhythmia between strata. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).
6.3 Results

The characteristics of the 97 patients in the cohort are presented in table 6-1. The mean age of these study patients was 60.9 ± 8.7. The mean left ventricular ejection fraction was 26.5%, ranging from 13-70%. 54 patients (56%) had a history of myocardial infarction, 33 patients (34%) had diabetes mellitus, and 91 (94%) were on beta blocker medication. 81 (84%) patients received primary prevention ICD, and 16 (16%) received ICD for secondary prevention. 42 (45%) patients reported sedentary behaviour.

The median length of follow-up was 2.6 years. Twenty-two patients (20 men, 2 women) had symptomatic ventricular arrhythmia. Five (23%) were ventricular tachycardia, 12 (54%) were fast ventricular tachycardia, and 5 (23%) were ventricular fibrillation. Seven (32%) events were terminated by ATP alone, 5 (23%) by shock alone, and 10 (45%) by shock after ATP. The mean peak VO\textsubscript{2} was 18.7 ± 5.8 mL/kg/min for patients who had ventricular arrhythmia and 17.7 ± 5.3 mL/kg/min for patients who did not have an event over the follow up period. Eight (36%) patients were sedentary among those who had ventricular arrhythmia and 34 (45%) were sedentary among patients who did not have ventricular arrhythmia.

There was no statistically significant difference in freedom from ventricular arrhythmia for patients below the median level of aerobic fitness compared to patients above the median level of fitness (Figure 6-1, p log-rank = 0.93). Also, there was no statistically significant difference in freedom from ventricular arrhythmia for patients who were sedentary compared to patients who were not sedentary (Figure 6-2, p log-rank = 0.83).
6.4 Discussion

We found no statistically significant difference in freedom from ventricular arrhythmia between patients above and below the median level of aerobic fitness and between patients who were and were not sedentary. While we found no association between aerobic fitness and time-to-ventricular arrhythmia, Cale et al.\textsuperscript{4} reported a 13% lower hazard of ventricular arrhythmia associated with a one unit increase in peak VO\textsubscript{2} in a univariate analysis of a prospective cohort of ICD patients. Self-reported sedentary behaviour was not associated with a statistically significantly different survival from ventricular arrhythmia in our study, but two studies have reported benefits in people with ICDs with higher levels of physical activity measured by the single-axis accelerometer permanently situated in the ICD. Conraads et al.\textsuperscript{4} found that increased levels of physical activity were associated with a reduced hazard of death or hospitalization from heart failure. Also, higher levels of physical activity at baseline and varying with time were associated with a lower risk of death before and after adjustment for demographic and device characteristics in a study of nearly 100 000 patients with ICD\textsuperscript{5}.

Elevated sympathetic drive reduces the threshold for ventricular fibrillation, thereby potentiating the risk of ventricular arrhythmia\textsuperscript{6}. The impact of this effect is magnified in the presence of poor ejection fraction\textsuperscript{7}, a risk factor common among all patients at risk of ventricular arrhythmia. Meta-analyses in patients with chronic heart failure show that habitual physical activity reduces baseline adrenergic tone\textsuperscript{8} and improves ejection fraction\textsuperscript{9}. Physical activity can also improve vagal regulation\textsuperscript{10}, which is blunted in patients with heart failure and enhanced in trained athletes\textsuperscript{11}. Increases in vagal tone
reduce the threshold for ventricular fibrillation experimentally\textsuperscript{12}, and are associated with reduced risk of ventricular arrhythmia in patients with ICD\textsuperscript{13}. With these mechanisms in mind, it is possible that physical activity may reverse autonomic dysregulation induced by cardiovascular disease and improve the electrical stability of the heart.

### 6.4.1 Strengths and limitations

We assessed aerobic fitness using peak VO\textsubscript{2} which is an objective measure obtained from the results of a cardiopulmonary exercise stress test. We also prospectively collected data on habitual physical exertion at the time of ICD implant. In this way, having or not having a ventricular arrhythmia did not influence a patient’s self-report of either sedentary or non-sedentary behaviour. As well, we recruited patients consecutively to reduce the potential of selecting patients based on specified characteristics apart from the inclusion and exclusion criteria.

Our study was limited by its sample size, which further reduced in our analysis assessing the impact of aerobic fitness. We had few events of ventricular arrhythmia and we did not use multivariable Cox regression in our survival model due to non-proportional hazards between our exposure groups in both analyses (Appendix E and F). Age, sex, and ejection fraction are a few factors associated with risk of ventricular arrhythmia. If these covariates are also associated with aerobic fitness or sedentary behaviour, they are potential confounders. Adjustment for lifestyle and socio-demographic characteristics may be an important consideration in measuring the association between the risk of ventricular arrhythmia and aerobic fitness and sedentary behaviour. Further, we
determined habitually sedentary behaviour from a self-reported questionnaire. Therefore, it is possible that sedentary behaviour may be over or underreported by some patients.

6.4.2 Conclusion

We found no evidence to suggest that there is a statistically significantly different freedom from ventricular arrhythmia between patients above and below the median level of aerobic fitness and between patients who were and were not sedentary in our study sample.
6.5 References


7. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles. Production of neurogenic


<p>| Table 6-1: Baseline characteristics of 97 MOVE-IT patients, mean ± SD or n (%) |
|---------------------------------|------------------|
| <strong>Full cohort</strong>                 |                  |
| n=97                            |                  |
| <strong>Age (years)</strong>                 | 60.9 ± 8.7       |
| <strong>Male</strong>                        | 78 (80%)         |
| <strong>Female</strong>                      | 19 (20%)         |
| <strong>Ejection fraction (%)</strong>       | 26.5 ± 9.2       |
| <strong>Blood pressure (mmHg)</strong>       |                  |
| Systolic                        | 113.7 ± 17.4     |
| Diastolic                       | 69.9 ± 10.2      |
| <strong>Body mass index (kg/m²)</strong>     | 29.5 ± 4.8       |
| <strong>Peak VO₂ (mL/kg/min)</strong>*        | 18.0 ± 5.4       |
| <strong>Sedentary</strong>                   | 42 (45%)         |
| <strong>QRS length (ms)</strong>             | 137.0 ± 30.5     |
| <strong>Cardiovascular history—n (%)</strong>|                  |
| Ischemic heart disease          | 52 (54%)         |
| Bypass                          | 20 (21%)         |
| Percutaneous coronary intervention | 16 (17%)     |
| Myocardial infarction           | 54 (56%)         |
| Non-Ischemic cardiomyopathy     | 36 (37%)         |
| Congestive heart failure        | 73 (75%)         |
| Valvular heart surgery          | 4 (4%)           |
| Congenital heart surgery        | 1 (1%)           |
| Peripheral vascular disease     | 2 (2%)           |
| <strong>Indication for ICD</strong>          |                  |
| Primary Prevention              | 81 (84%)         |
| Secondary Prevention            | 16 (16%)         |
| <strong>Other Medical history—n (%)</strong> |                  |
| Diabetes mellitus               | 33 (34%)         |
| Hypertension                    | 45 (47%)         |
| Hyperlipidemia                  | 40 (41%)         |
| Thyroid disease                 | 2 (2%)           |
| Chronic obstructive pulmonary disease | 13 (13%)      |
| <strong>Cardiac medication history—n (%)</strong> |                  |
| Beta blocker                    | 91 (94%)         |
| ACE inhibitors                  | 80 (82%)         |
| Angiotensin receptor blocker    | 16 (17%)         |
| Diuretic                        | 68 (70%)         |
| Digoxin                         | 26 (27%)         |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Full cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Class 1 antiarrhythmic</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>13 (13%)</td>
</tr>
</tbody>
</table>

*13 patients did not have information on ejection fraction
*Patients who reported no moderate to vigorous exertion in the past 6 months at initial assessment were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary
†30 (31%) patients did not provide consent to undergo exercise stress testing. The mean age of patients who did not provide consent was lower than those who provided consent (58.3 vs 62.0, p=0.05). There was a higher proportion of sedentary patients among those who did not provide consent (56%) than among those who did provide consent (40%, p=0.18).
Figure 6-1. Freedom from ventricular arrhythmia among 67 MOVE-IT patients stratified by aerobic fitness above and below the sample median

Kaplan-Meier Plot
With Number of Subjects at Risk

Log-rank test p = 0.93

Median aerobic fitness measured by peak VO₂ = 18.0 mL/kg/min
Patients who reported no moderate to vigorous exertion in the past 6 months at initial assessment were classified as sedentary and patients who reported any moderate to vigorous exertion were deemed not sedentary.
Chapter 7

7 Discussion and implications

In Chapter 5, we examined the immediate risk of ventricular arrhythmia following an episode of exertion. In our clinical population, we found that the risk of ventricular arrhythmia was higher within an hour of exertion compared to periods of rest, and that this association was stronger among patients with lower levels of aerobic fitness and among patients who were sedentary. In Chapter 6, we assessed the baseline risk of incident ventricular arrhythmia over the follow-up period and found no statistically significant difference in freedom from ventricular arrhythmia by level of aerobic fitness or sedentary behaviour in our sample. In contrast, several larger observational studies have found a higher risk of ventricular arrhythmia and cardiovascular events among individuals with lower levels of aerobic fitness and among those with lower levels of habitual physical exertion.

Our finding that there is an elevated risk of ventricular arrhythmia in the hour following physical exertion is consistent with the two prior case-crossover studies that examined this question in the ICD population. Lampert et al. reported a 3.87 (95% CI 1.97 – 14.8) times greater odds of ICD shock up to 15 minutes following self-reported mild-to-moderate physical activity compared to other times\(^1\). Fries et al. found similar results, reporting the relative risk of ICD shock as 7.5 (95% CI 5.2 – 11.1) times greater within 1 hour after physical stress compared to periods of rest\(^2\). Moreover, our finding that the immediate risk of ventricular arrhythmia following physical exertion is greater in people who are sedentary is consistent with previous studies that found that among people who
are sedentary, there is a higher immediate risk of myocardial infarction and sudden cardiac death following physical exertion. This is the first study to show that sedentary behaviour also elevates the immediate risk of ventricular arrhythmia following exertion, as do lower levels of aerobic fitness.

Based on our findings that the immediate risk of ventricular arrhythmia is lower among patients with relatively higher levels of aerobic fitness and those who are not sedentary, it is possible that an exercise regimen with an incremental increase in the intensity of exertion may help to minimize the risk of ventricular arrhythmias associated with isolated episodes of physical exertion by improving aerobic fitness. These improvements can be achieved among patients with ICDs. In a randomized controlled trial (RCT) of 52 men with chronic heart failure who had ICDs, exercise training improved aerobic fitness and quality of life within 8 weeks\(^3\). In a post-hoc analysis of over 1000 patients with heart failure and ICDs enrolled in an RCT, Piccini et al. found that randomizing sedentary individuals to exercise 3 times a week was not associated with the combined endpoint of appropriate and inappropriate shocks and all-cause mortality\(^4\). By increasing the frequency of exertion, the time at risk of exertion-induced ventricular arrhythmia would be higher in the intervention group compared to the control group. Therefore, the fact that there was no difference in risk of ventricular arrhythmia between the two groups may suggest that the exertion improved fitness and thereby lowered the risk of exertion-induced ventricular arrhythmias. In Chapter 6, we did not find a statistically significant difference in survival from ventricular arrhythmia by level of fitness or sedentary behaviour, but several larger observational studies have reported a higher baseline risk of ventricular arrhythmia and cardiovascular events associated with lower levels of fitness.
and sedentary behaviour. Even habitual activity at low levels of intensity is associated with a lower baseline risk of cardiovascular events\textsuperscript{5-7}, and it is possible that it also lowers the risk of ventricular arrhythmia from each episode of exertion.

### 7.1 Strengths and limitations

In Chapter 5, our study found that effect modification of the immediate risk of ventricular arrhythmia following physical exertion was robust across two independently collected measures. While sedentary behaviour is a self-reported and subjective measure whose interaction with the immediate risk of myocardial infarction and stroke has been studied before, we also demonstrated a similar increase in the immediate risk of ventricular arrhythmia among individuals with lower levels of aerobic fitness, an objectively collected metric.

This study was also strengthened through prospective measurement of baseline habitual physical exertion that was completed during the initial study visit. In this way, the occurrence of ventricular arrhythmia over follow-up could not influence a patient’s perspective of their self-reported participation in physical exertion. This study was however limited by the subjective and self-reported nature of the baseline physical exertion measurements. While patients were provided with a visual analogue scale to gauge intensity and given examples of common activities among older adults that would help capture all habitual physical exertion (e.g. gardening, yard work), it is not known how accurately these estimates reflect true participation in physical exertion in our population. Self-report was also used to classify exposure to physical exertion in the hour preceding ventricular arrhythmia, but because our interviews occurred within 72 hours of ICD discharge, it is likely that patients more accurately remember their level of exposure.
to physical exertion at the time of their first device-treated ventricular arrhythmia. It is important to note that while the ICD has an activity sensor which records whether or not a patient is “active” at the time of ventricular arrhythmia, it does not measure activity at any other moment in the hour before therapy. The ICD activity sensor is therefore limited in our purpose since the hazard period of transiently elevated risk lasts longer than an episode of exertion itself\textsuperscript{6}, notably because recovery from exertion is impaired in patients with poor heart function\textsuperscript{9} and benign ventricular arrhythmia during recovery is actually a stronger predictor of mortality than benign ventricular arrhythmia during exertion\textsuperscript{11}.

The case-crossover study design is self-matched and therefore eliminates confounding by fixed and slow-varying characteristics during the study period, such as age, sex, and comorbidities. Further, because exposure to physical exertion at baseline and immediately preceding the event were classified by the patient, it is likely that their perception of light, moderate, and vigorous exertion are consistent between these two compared time periods. While self-matched analysis eliminates the issue of non-exchangeability between persons, confounding within each person remains a possibility. If physical exertion is associated with another potential trigger of ventricular arrhythmia (e.g. sex, caffeine, time of day, stress) then it is possible that the association between exertion and ventricular arrhythmia is confounded by the co-exposure. In the MOVE-IT study, patients completed a semi-structured questionnaire after ICD discharge where they briefly described the minutes preceding ventricular arrhythmia (Appendix B), but it is possible that some co-exposures to physical exertion were intentionally or unintentionally omitted.
7.2 Conclusion and future directions

In this clinical population, there is an elevated risk of ventricular arrhythmia within an hour of physical exertion, especially among individuals with lower levels of aerobic fitness and with sedentary behaviour. Prior studies indicate that lower levels of aerobic fitness and habitually sedentary behaviour increase the baseline risk of ventricular arrhythmia and cardiovascular events. Future research is therefore necessary to design and evaluate activity recommendations that maximize the benefits of habitual activity and exercise training while minimizing the risk of ventricular arrhythmia associated with each episode of exertion.


7.3 References


Appendix A: MOVE-IT Baseline Survey

PHYSICAL ACTIVITY

LIGHT EXERTION

Since implantation, or in the past 6 months, on average how often do you participate in:

Light exertion physical activities, with normal breathing (corresponding to # 4 on the visual analog scale):
Time(s): ____ per □ day □ week □ month □ year

What is the usual duration of each episode of activity at this level? _____ □ hour(s) □ minutes

The following question concerns the usual time of the day that you perform light exertion physical activities. What percent of your light exertion activities occurs in the following time intervals? (the total percentages should sum to 100%)

6 AM - Noon ___% Noon – 6 PM ___% 6 PM – Midnight ___% Midnight – 6 AM ___%

What activity do you usually engage in at this level?___________________________________

MODERATE EXERTION

Since implantation, or in the past 6 months, on average how often do you participate in:

Moderate exertion physical activities, with deep breathing (corresponding to # 5 on the scale):
Time(s): ____ per □ day □ week □ month □ year

What is the usual duration of each episode of activity at this level? _____ □ hour(s) □ minutes

The following question concerns the usual time of the day that you perform moderate exertion physical activity. What percent of your moderate exertion physical activities occurs in the following intervals? (the total percentages should sum to 100%)

6 AM –Noon ___% Noon –6PM ___% 6 PM- Midnight ___% Midnight – 6AM ___%

What activity do you usually engage in at this level?

VIGOROUS EXERTION

Since implantation, or in the past 6 months, on average how often do you participate in:
Vigorous exertion physical activities, with panting; overheating (corresponding to #6 on the visual analog scale):

Time(s): ____ per □ day □ week □ month □ year

What is the usual duration of each episode of activity at this level? ______ □ hour(s) □ minutes

The following question concerns the usual time of the day that you perform vigorous exertion physical activity. What percent of your vigorous exertion physical activities occurs in the following intervals? (the total percentages should sum to 100%)

6 AM – Noon ___%  Noon – 6 PM ___%  6 PM – Midnight ___%  Midnight – 6 AM ___%

What activity do you usually engage in at this level? ________________________________

WALKING AND CLIMBING

Since implantation, or in the past 6 months:

1. How many city blocks do you walk each day? _____
   (assuming 1 km = 6 blocks)

2. What is your usual pace of walking?
   □ casual strolling
   □ average or normal
   □ fairly brisk
   □ striding

3. How many flights of stairs do you climb up each day? _____
   (assuming 10 steps = 1 flight)

<table>
<thead>
<tr>
<th>SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you have sexual intercourse? _____ times per</td>
</tr>
</tbody>
</table>

The following question concerns the usual time of day that you have sexual intercourse:

What percent of your sexual intercourse occurs in the following intervals?

6 a.m.-Noon ___%  Noon-6 p.m. ___%  6 p.m.-Midnight ___%  Midnight-6 a.m. ___%
Appendix B: MOVE-IT Post-therapy form

MOVE-IT PAPER FORMS
Post-ICD (Shock) Follow-up

POST ICD DISCHARGE

(Completed within 72 hours of ICD discharge, either via telephone or during clinic visit. If during clinic visit, please fill out follow-up clinic data form at the same time)

Please obtain the following information from the patient as soon as possible after a device discharge. Encourage the patient to give his or her best answer to each question.

Mean ICD-recorded heart rate over 30 seconds prior to ICD therapy: _______ bpm

DAY OF DISCHARGE

10. What time did you get up on the day of device discharge? ______ □ AM □ PM

11. What were you doing when the discharge occurred? □ no specific activity
   □ lying
   □ sitting
   □ standing
   □ walking
   □ running
   □ climbing stairs

12. Please write out the specific activity you were engaged in at the time of the shock:
   ________________________________

13. Please briefly describe the minutes immediately following the shock:

14. Were you having any symptoms before the device discharge? □ Yes □ No

   Symptoms before the discharge (please fill all that apply):

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration</th>
<th>How long before device discharge?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, discomfort, angina</td>
<td>Less than ½ hour</td>
<td>□</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Between ½ and 1 hour</td>
<td>□</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>Between 1 and 2 hours</td>
<td>□</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Greater than 2 hours</td>
<td>□</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>More than 2 hours but less than 2 days</td>
<td>□</td>
</tr>
<tr>
<td>Syncope</td>
<td>Other</td>
<td>□</td>
</tr>
<tr>
<td>Other(specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

56
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Time Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, discomfort, angina</td>
<td>Less than ½ hour</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Between ½ and 1 hour</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
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</tr>
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</tr>
<tr>
<td>Shortness of breath</td>
<td>More than 2 hours but less than 2 days</td>
</tr>
<tr>
<td>Syncope</td>
<td>Other</td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
</tr>
</tbody>
</table>

15. Did your symptoms go away after the shock?  
- Yes  
- No

16. Did you have any symptoms after the discharge?  
- Yes  
- No

**BEHAVIORAL PRECURSORS**

Before the device discharge, when was the last time you were engaged in:

Please select the closest option:

**Light exertion with normal breathing**  
(E.g.: mopping, normal walking (shopping), golfing with a car, sweeping, gardening with power tools)
- Never/Not applicable  
- At the time of shock  
- ½ hour before  
- 1 hour before  
- 2 hours before  
- 3-6 hours before  
- 6-24 hours before  
- 1-2 days before  
- 3-4 days before  
- 5 or more days before

**Moderate exertion with deep breathing**  
(E.g.: brisk walking, golfing on foot, ballroom dancing, slow dancing, slow biking, downhill skiing, cleaning windows, hanging wallpaper, interior painting, light restaurant work (like waiting tables))
- Never/Not applicable  
- At the time of shock  
- ½ hour before  
- 1 hour before  
- 2 hours before  
- 3-6 hours before  
- 6-24 hours before  
- 1-2 days before  
- 3-4 days before
☐ 5 or more days before

Vigorous exertion, panting/overheating, or exertion with gasping and much sweating:
(E.g.: sprinting, running, jogging, fast bicycling, football, mixing cement, hanging drywall, using jackhammer, speed walking, tennis, swimming, shoveling, pruning trees, heavy gardening, brick laying)
☐ Never/Not applicable
☐ At the time of shock
☐ ½ hour before
☐ 1 hour before
☐ 2 hours before
☐ 3-6 hours before
☐ 6-24 hours before
☐ 1-2 days before
☐ 3-4 days before
☐ 5 or more days before

Sexual intercourse
☐ Never/Not applicable
☐ At the time of shock
☐ ½ hour before
☐ 1 hour before
☐ 2 hours before
☐ 3-6 hours before
☐ 6-24 hours before
☐ 1-2 days before
☐ 3-4 days before
☐ 5 or more days before
Appendix C: Adapted Borg Visual Analog Scale used by MOVE-IT patients to report intensity of physical exertion

**Borg Rating of Perceived Exertion (RPE) Scale**

While doing this exercise, pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, combining all feelings of physical stress, effort, and fatigue. Don't consider yourself with any one factor such as the pain associated with breathing exertion intensity, but evaluate your total feeling of exertion. Try not to overestimate or underestimate your feelings of exertion to be as accurate as possible.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion at all</td>
</tr>
<tr>
<td>7</td>
<td>Very, very light</td>
</tr>
<tr>
<td>8</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td>Fairly hard</td>
</tr>
<tr>
<td>13</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td>Hard</td>
</tr>
<tr>
<td>15</td>
<td>Very hard</td>
</tr>
<tr>
<td>19</td>
<td>Very, very hard</td>
</tr>
<tr>
<td>20</td>
<td>MAXIMAL EXERTION</td>
</tr>
</tbody>
</table>

**Light Exertion with normal breathing**
(normal walking, flight of stairs, mopping, sweeping, light gardening)

**Moderate Exertion with deep breathing**
(brisk walking, moving table, pushing vacuum, bowling, playing golf and several flights of stairs)

**Vigorous Exertion with panting/overheating**
(sprint, running, jogging, fast bicycling, tennis, swimming, shoveling, and heavy gardening)
Appendix D: Case-crossover comparison schematic

Appendix E: Log minus log plot of the hazard of ventricular arrhythmia between individuals above and below the median aerobic fitness in 67 MOVE-IT patients.
Appendix F: Log minus log plot of the hazard of ventricular arrhythmia between individuals who were and were not sedentary among 94 MOVE-IT patients.
## University Educational Background

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Degree</th>
<th>Field of Study</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013–2015</td>
<td>Master of Science</td>
<td>Epidemiology &amp; Biostatistics</td>
<td>Western University</td>
</tr>
<tr>
<td>2009–2013</td>
<td>Bachelor of Medical Sciences</td>
<td>Honors Specialization in Physiology &amp; Pharmacology</td>
<td>Western University</td>
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</tbody>
</table>

## Research–specific Honours, Scholarships and Awards

<table>
<thead>
<tr>
<th>Agency</th>
<th>Award</th>
<th>Value</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Institutes of Health Research (CIHR)</td>
<td>Michael Smith Foreign Study Scholarship</td>
<td>$6 000</td>
<td>02/15 – 07/15</td>
</tr>
<tr>
<td>Canadian Institutes of Health Research (CIHR)</td>
<td>Frederick Banting and Charles Best Canada Graduate Scholarship</td>
<td>$17 500</td>
<td>2014 – 2015</td>
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<tr>
<td>Ontario Graduate Scholarship (OGS)</td>
<td>Queen Elizabeth II Graduate Scholarship in Science and Technology</td>
<td>$15 000</td>
<td>2014 – 2015</td>
</tr>
<tr>
<td>Ontario Graduate Scholarship (OGS)</td>
<td>Queen Elizabeth II Graduate Scholarship in Science and Technology</td>
<td>$15 000</td>
<td>2013 – 2014</td>
</tr>
<tr>
<td>Western University</td>
<td>Western Graduate Research Scholarship</td>
<td>$1 500 per term</td>
<td>2013 – 2015</td>
</tr>
</tbody>
</table>
Research Experience

02/2015 – 07/2015  
Visiting student  
(Dr. Murray Mittleman)  
Beth Israel Deaconess Medical Center  
Harvard Medical School
Boston MA, USA

05/2014 – 09/2015  
MSc student  
(Dr. Lorne Gula, Dr. Mark Speechley)  
London Health Sciences Centre  
Western University
London ON, Canada

02/2014 – 08/2014  
Collaborating student  
(Dr. Piotr Wilk)  
Middlesex-London Health Unit  
Western University
London ON, Canada

Selected Publications, Presentations and Abstracts

Publication  

Oral presentation  
Chahal HS, Mostofsky E, Mittleman MA, Suskin N, Speechley M, Skanes AC, Leong-Sit P, Manlucu J, Yee R, Klein GJ, Gula LJ. Impact of aerobic fitness and sedentary behaviour on immediate risk of ventricular arrhythmia following episodes of physical exertion. Canadian Society of Epidemiology and Biostatistics 2015 in Mississauga ON, Canada.

Poster presentation  