EFFECTS OF SPORT-SPECIFIC, INTERMITTENT HIGH-INTENSITY EXERCISE ON NOCTURNAL HEART RATE VARIABILITY AND GLYCEMIA IN ELITE ATHLETES WITH TYPE 1 DIABETES

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ABSTRACT

Type 1 diabetes (T1D) is associated with hypoglycemia and premature autonomic disturbance (using heart rate variability [HRV]) – both which have been implicated in sudden death. This study examined the effect of a single bout of intermittent high-intensity exercise (IHE) on nocturnal HRV in ten hockey players with T1D and ten teammates without T1D. HRV and BG were analyzed from 12am–6am following hockey activity and low activity days. Hockey-type IHE on a cycle ergometer decreased BG by -1.9 ± 2.8 mmol/L, while an actual hockey game increased BG by 1.0 ± 3.2 mmol/L. One participant experienced nocturnal hypoglycemia after a hockey game (lasting 230 min). A significantly better nocturnal HRV profile (QTc, SDNN, pNN50, RMSSD) was observed following the low activity day compared to the days where IHE took place ($p<0.05$). There was no difference in HRV between T1D and non-T1D participants. This study documented the unique ability of a hockey game to increase BG in youth with T1D. Furthermore, given that decreased HRV is commonly noted in youth with T1D, this study suggests that the onset of autonomic hindrances can be delayed in highly-active individuals.

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LIST OF ABBREVIATIONS

ANS autonomic nervous system

AV atrioventricular

bpm beats per minute

BG blood glucose

BMI body mass index; weight (kg)/height (m^2)

CAN cardiac autonomic neuropathy

CGM continuous glucose monitor

Ctrl-a control athlete (participant group of non-diabetic hockey players)

DIB dead in bed syndrome

EKG electrocardiogram

HF high frequency

HRV heart rate variability

HF/TP high frequency/total power; represents HF in normalized units

HITT high-intensity interval

HR heart rate

HRmax maximum heart rate

HRR heart rate reserve (HRmax-resting HR)

Hz hertz

IHE intermittent high-intensity exercise

LF low frequency

MSNA muscle sympathetic nerve activity

ms milliseconds

NN normal-to-normal

n.u. normalized units

pNN50 percent of normal-to-normal intervals that vary greater than 50 ms

PNS parasympathetic nervous system

QT Q-T interval; time it takes for a full heart beat contraction

QTc Q-T interval corrected for HR

RMSSD root of the mean of the squares of differences between beats

RPE rating of perceived exertion

RPMs revolutions per minute

RR R-R interval; time it takes for a full heart beat contraction

SNS sympathetic nervous system

SDNN standard deviation of normal-to-normal beats

T1D type 1 diabetes

T1D-a type 1 diabetes athletes (participant group of hockey players with type 1 diabetes)

T2D type 2 diabetes

TP total power

VLF very low frequency power

VO_2 volume of oxygen consumed

VO_2max maximum volume of oxygen consumed

WC waist circumference

LITERATURE REVIEW 1

1. Heart Rate Variability

Heart rate variability (HRV), in its most basic interpretation, refers to the beat-to-beat alterations in heart rate (1). While a seemingly straightforward concept, this method has been utilized for the effective diagnosis of early autonomic dysfunction since the 1960's, and is sometimes referred to as the window into autonomic control of the heart (91). Since its first conception as a medical tool, HRV has been used to assess various health impairments. On a more direct scale, it measures sympathetic and parasympathetic neural innervation at the level of the heart (1). The accessibility and sensitivity of this measure, combined with its ability to function as a surrogate measure of cardiac autonomic function, has led to its continued use in the present day (2).

The intrinsic heart rate (HR) generated by the sinoatrial node of the heart, without any neurohormonal input, is 80-100 beats per minute (bpm). However, it is well understood that a healthy individual has a resting HR between 60-80 bpm. This discrepancy is accounted for by the input of the parasympathetic nervous system (PNS) which decreases the HR, and the sympathetic nervous system (SNS) which increases the HR. At any given time, the HR is determined by the imbalance between parasympathetic and sympathetic innervation, which is constantly changing to meet bodily demands such as with stress or exercise. At rest, there is unevenness between the two branches, with the PNS dominating. With exercise, the sympathetic arm

dominates to increase the HR which helps to enhance blood flow to the working muscles.

With a healthy autonomic nervous system (ANS) the continuous neural stimulation to the heart alters the contraction of the myocardium in a very minute, but significant manner, leading to greater HRV. On the contrary, an impaired ANS results in reduced HRV which is associated with a poorer prognosis for a wide range of clinical conditions (1, 3, 4, 5). As such, HRV can be used as an indicator of autonomic function, but also of heart health.

1.1 HRV Assessment

An electrocardiogram (EKG) is commonly composed to quantify HRV in a convenient and non-invasive manner. A Holter monitor is often used as a reliable tool for assessing HRV. This small monitor can be set up in various configurations, including 3-, 5-, 7-, or 12-electrode placements (Appendix D). The electrodes are affixed to the anterior chest cavity and receive the electrical signals transmitted through the heart, which are then recorded on a memory card in the Holter monitor. This electrical profile can later be uploaded and converted for both power spectral density analysis and time domain analysis using the EKG tracing that is composed by the Holter monitor. In either method, the analyst must first scan the EKG tracing in order to exclude ectopic beats and artifact (1). After this point, the statistical parameters of the normal R-R intervals (NN intervals) can be derived in order to compute several time and frequency domain HRV indices (1).

1.2 Power Spectral Density Analysis (Frequency Domain Analysis)

Power spectral density analysis involves decomposing the variance between RR intervals into underlying frequencies that fall between 0.003-0.40 Hertz (Hz) (1). These frequencies can be further segmented to identify PNS and/or SNS predominance. A frequency between 0.003-0.04 Hz is termed very low frequency (VLF) and is believed to represent the SNS innervation (6), although several studies suggest it is influenced primarily by humoral and hormonal factors (1). Activity between 0.04-0.15 Hz is termed the low frequency (LF) band, and is believed to indicate a combination of both the SNS and PNS branches (1). The high frequency (HF) band (0.15-0.40 Hz) is believed to reflect the PNS or vagal activity (1). HF is also known as a respiratory band because it correlates to the NN variations that are observed with respiration (1). All power spectral bands are calculated in squared milliseconds (ms^2). Because the identified power in each frequency band is related to the total power, it is often recommended that power spectral bands be reported in normalized units (1). In this method, the low or high frequency power are expressed relative to the total power minus the very low frequency band (1). Utilizing this method, it becomes possible to infer that changes in low or high frequency power are reflective of a change in sympathovagal balance, and not just a mere change in the total signal strength (1).

1.3 Time Domain Analysis

The EKG tracings recorded by a Holter monitor can be partitioned into several meaningful variables. These values are the easiest to calculate (1), and include such

measures as QT length, QT length corrected for heart rate (QTc), R-R interval length, standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD), and percent of normal-to-normal intervals having a difference of >50 milliseconds (pNN50). Because these time domain indices reflect variance and variance increases over time, only HRV tracings of the same duration can be compared (1). In addition to these time domain measures, QT measurements are also informative. QT length represents the time required for a single beat to occur, from the initiation of Sinoatrial node depolarization to the end of ventricular repolarization. The QTc length is a more accurate measure, as it corrects the QT length for the heart rate itself (7). Bazett's formula is commonly used to derive the QTc by dividing the measured QT interval by the square root of the preceding RR interval ($QTc = QT/\sqrt{RR}$) (7). It is understood in literature that an efficient heart with healthy neural connectivity should contract quickly, with QTc remaining below 0.440 ms (8). Furthermore, Schwartz et al (9) suggested a probability-based diagnostic test for diagnosing long QT syndrome. The test is out of 9, and a score of 3 or more indicates high probability of long QT syndrome. Considering QTc alone, a QTc of over 480 ms in males or females receives 3 points, from 460-470 receives 2 points, and a QTc of 450 ms in males is 1 point. To reduce the likelihood of false positives, the QTc cut-off of >450 ms for boys or >460 ms for girls was used. Standard values published by the European Task Force (1) are included in Table 1.

Table 1. Summary of HRV indices and normal values of standard measures of HRV

HRV Measure	Meaning	Expected Values
***SDNN** **S**tandard **D**eviation of **N**ormal-to-**N**ormal beats	Overall HRV; higher is better	141±39 ms
***RMSSD** **R**oot of the **M**ean of the **S**um of **S**quares of **D**ifferences between beats	Index of vagal activity & parasympathetic activity at the heart; higher is better	27±12 ms
***PNN50** **P**ercent of adjacent **N**ormal-to-**N**ormal beats that differ by >**50** ms	Alterations of vagal activity, independent of circadian rhythms	n/a
VLF **Very **L**ow **F**requency	Sympathetic activity	n/a
LF **Low **F**requency	Combination of sympathetic and parasympathetic activity	1170±416 ms^2 54±4 nu
HF **High **F**requency	Parasympathetic activity	975±203 ms^2 29±3 nu
TP **Total **P**ower	Index of overall neural input to the heart	3466 ±1018 ms^2
**LF/HF Ratio	Reflection of sympathetic-to-parasympathetic balance	1.5-2.0
QT **Q** to **T** interval length	Duration of heart contraction, from depolarization to repolarization	n/a
QTc **Q** to **T** interval length **C**orrected for heart rate	Duration of heart contraction when corrected for heart rate; healthy ANS function should allow the heart to contract quickly regardless of heart rate	<0.440 ms
*Triangular Index	Estimate of overall HRV; larger is better	37±15

***taken over 24-hour recording, **taken over 5-minute recording**

1.3.a) SDNN

SDNN is often used as an estimate of overall HRV. Mathematically, SDNN is equal to the square root of the variance in NN intervals (1). The variance is equivalent to the total power of the spectral analysis. The actual value of SDNN depends on the length of the recording, with longer recording periods resulting in higher SDNN values. As a result, if comparing HRV results between or within individuals, it is imperative that the recording duration is identical. Typically, short-term (5-minute) recordings and 24-hour recordings are used for the assessment of SDNN (1). This measurement is reported in milliseconds, with larger values reflecting a better HRV profile.

1.3. b) RMSSD

RMSSD is an estimate of the short-term components of HRV (1). This measure estimates HF variations in the HR, using short-term normal-to-normal beats. Because HF waves predominantly represent PNS tone, RMSSD is thought to estimate PNS regulation of the heart. It also provides an index of vagal activity. Higher values are favourable.

1.3. c) pNN50

pNN50 reflects alterations in autonomic function that are primarily vagally-mediated (1). This measurement is independent of circadian rhythms, and is often depicted as a percentage, with larger values being favourable.

1.3. d) Triangular Index

The triangular index is an integral of the density distribution (ie number of NN intervals plotted on a histogram) divided by the maximum of the density distribution. This triangular index is said to be an estimate of overall HRV.

1.4 History of Heart Rate Variability

In the 18th century, Swiss scientist Albregth von Haller noted that a healthy heart beat was not regular, but rather displayed variations. While noted centuries ago, it was not until more recently that the clinical significance of this HRV was documented in the medical literature. In 1965, Hon & Lee noticed that alterations in beat-to-beat intervals preceded fetal distress, even before any change in HR could be detected (10). In 1977, Wolf et al showed an association of HRV and mortality, post myocardial infarction (11), and these findings have subsequently been confirmed (1, 3, 5, 12). Specifically, decreased HRV was noted in individuals recovering from a myocardial infarction, and those individuals with the greatest reduction in HRV also had the greatest risk for sudden death (13, 14, 15, 16). Linear methods such as time domain measures were most commonly used to assess HRV due to their simplicity, until Akselrod et al uncovered the abilities of power spectral analysis in 1981 (17). This new-found ability to quantitatively evaluate beat-to-beat cardiovascular control based on power spectral analysis of HR provided additional methods of assessing the same HRV measures. In 1996, a task force came together to publish measurement standards for HRV. To date, research on HRV measures continues to evolve.

1.5 Heart Rate Variability and Chronic Exercise

Healthy individuals typically have a high total power (TP) which represents greater overall ANS innervation (18), and a low LF/HF ratio due to the proportionately larger PNS innervation to the heart. This low LF/HF ratio is exaggerated even more so during sleep. Important to note is the fact that a healthier HRV profile, reflected by HRV indices, is observed in those who partake in habitual physical activity. Previous studies (19, 20, 21) have shown that measures of HRV tend to be better and higher in physically active compared to physically inactive, healthy individuals.

While those with type one diabetes (T1D) have lower HRV than those without, habitual physical activity has been implicated in increasing HRV in healthy children with initially low HRV (20, 22). The influence of physical activity level on autonomic function in T1D was first reported by Chen et al (90). This report suggested that a higher physical activity level was synonymous with higher HRV in children with T1D. It was also suggested by Chen and his colleagues that a decreased HRV is only present in children with T1D (mean age 10 years) with a low level of physical activity participation, but not in those with moderate-to-high levels of physical activity participation (90).

The experimental effects of exercise programs have proven themselves effective in improving HRV. While a moderate-intensity physical activity program may not improve HRV indices in those with definite or severe cardiac autonomic neuropathy (CAN), the outlook is more hopeful in diabetes patients with early involvement of CAN (34). Howorka et al (23) found that regular endurance training for 12 weeks increased HRV in individuals who scored relatively low on their battery of cardiovascular reflex

tests, but that these training-induced changes disappeared 4-6 weeks following training withdrawal. In a study by K. Javorka et al (24), the effects of a sports camp on youth with T1D who attended the camp either in the trained or untrained state was assessed. Trained individuals had significantly lower incidence of below-average HRV values at baseline. At the end of the camp stay, both groups experienced longer RR intervals (indicating a decreased resting HR) and increased HRV. Both groups also had an increase in total spectral power, largely due to an increased PNS output. When the percent improvements in HRV measures from camp activities were compared between trained and untrained subgroups with T1D, no differences were observed (24). This study provides an exemplary demonstration of the benefit that cumulative physical activity has on heart function, particularly due to its ability to increase parasympathetic activity and thus presumably heart efficiency as well.

1.6 Heart Rate Variability and Acute Exercise

It is widely accepted that improved physical fitness confers benefits to autonomic and heart function, as displayed by improved HRV measures. However it is important to also understand the acute effects that a single bout of exercise has on these systems. Pober (25) assessed the effects of a 1-hour cycling bout at moderate intensity, on HRV in healthy individuals. The results of the single bout of exercise on HRV were similar to published findings from long-term training; individuals experienced increased HF and decreased LF power at rest, indicating a shift toward increased PNS activity. This study

suggests that even a single bout of exercise may offer an acute cardioprotective effect, as reflected by the increased HF innervation.

1.7 Heart Rate Variability and Diabetes

HRV is frequently used to identify autonomic dysfunction at the earliest, sub-clinical stages (2). A long-term complication of type 1 and type 2 diabetes commonly includes progressive autonomic dysfunction which is characterized by early and widespread degeneration of small SNS and PNS fibers (26). Over time, this may progress to a diagnosable condition called diabetic autonomic neuropathy (DAN). Commonly-noted side effects of DAN include postural hypotension, persistent tachycardia, gastroparesis, gustatory sweating, and complications in the bladder and digestive tracts (1).

The suggested etiologies behind DAN include neurovascular insufficiency, autoimmune damage, metabolic insult to nerve fibers, and neurohormonal growth factor deficiency (27). In a technical review by Vinik et al (27), it was reported that the metabolic disturbances associated with type 1 and type 2 diabetes cause pervasive damage of peripheral nerves and blood vessels. The abundant presence of the ANS throughout the body exposes virtually all organs to the manifestations of autonomic dysfunction. It is therefore suggested that a person diagnosed with either type 1 or type 2 diabetes should be suspected of having at least subclinical disturbance of the ANS (27). A review by Ziegler et al demonstrated that the 5-year mortality rate in individuals diagnosed with diabetes is five times higher for those with diagnosed CAN than for those without (28). Therefore, the detection of these early disturbances, and an

understanding of the role of regular physical activity participation in ameliorating these disturbances are imperative in order to slow progression and subsequently better manage health complications (1).

Both short- and long-term HRV methodologies have successfully been utilized to detect DAN (16, 29, 30-34). The most common finding in the HRV profiles of individuals with DAN is a reduced power in all spectral bands (33, 35). Also commonly cited is a leftward shift in the LF/HF ratio, indicating proportionally larger sympathetic drive (34). This leftward shift represents parasympathetic withdrawal from the heart, which could presumably lead to an increased heart rate at rest and thus insufficiency and over-working of the myocardium.

Recently it has also been proposed that HRV be used as a predictor for type 2 diabetes (T2D). In a study by Mercedes et al (36), an 8-year follow up of healthy adults in the Atherosclerosis Risk in Communities (ARIC) study revealed that individuals who were diagnosed with T2D had a significantly lower LF, lower SDNN, and higher resting HR at baseline (36). This relationship existed independent of other factors such as waist circumference and physical activity level. These results suggest that ANS dysfunction may contribute to the development of T2D in healthy adults, rather than being a mere consequence of hyperglycemia in diabetes as previously thought.

1.8 Onset of HRV alterations in T1D

While it remains controversial as to when the first signs of reduced HRV can be detected in T1D, it is clear that impairments are not reserved for those of upper age

ranges. Chen et al (90) found that in children aged 8-13, both HbA1c and T1D duration were significant predictors of TP. This study also reported that individuals with a HbA1c above 8% and T1D duration greater than 4.5 years had significantly lower HRV than other persons without T1D. Similar findings were published by Kardelen et al, who concluded that in youth with T1D (mean age 12, mean HbA1c 9%) almost all time domain parameters were reduced (37). The same study showed that HRV indices reflected significant reductions in PNS activity and trends of increased SNS tone among youth with T1D. In a study by Warwick et al on 130 persons with T1D (38), a reduction of HRV could be detected as early as 1 year post-diagnosis, and this impairment worsened with increasing T1D duration. Other studies have documented diminished PNS activity in persons with T1D even before clinical symptoms of neuropathy were present (39- 41).

The research literature is equivocal, as several studies have suggested an association with poor metabolic control (42-48), age (49), and longer diabetes duration (43-46, 48-50), while other studies report no such association to alterations in ANS as measured by HRV (47, 51-53). Progressing through puberty has been previously associated with peripheral and autonomic neuropathy in most (54, 55) but not all (44, 45, 47, 48) studies. Studies by Massin et al (56) and Barkai and Kempler (57) emphasized the independent role of pubertal changes in the development of ANS disturbances, suggesting that reduced HRV could be observed at the onset of puberty. Massin's work (56) demonstrated that HRV indices were only significantly depressed in individuals aged ≥11 years. It is generally suggested that early puberty is a critical period for the onset of ANS disturbances in T1D.

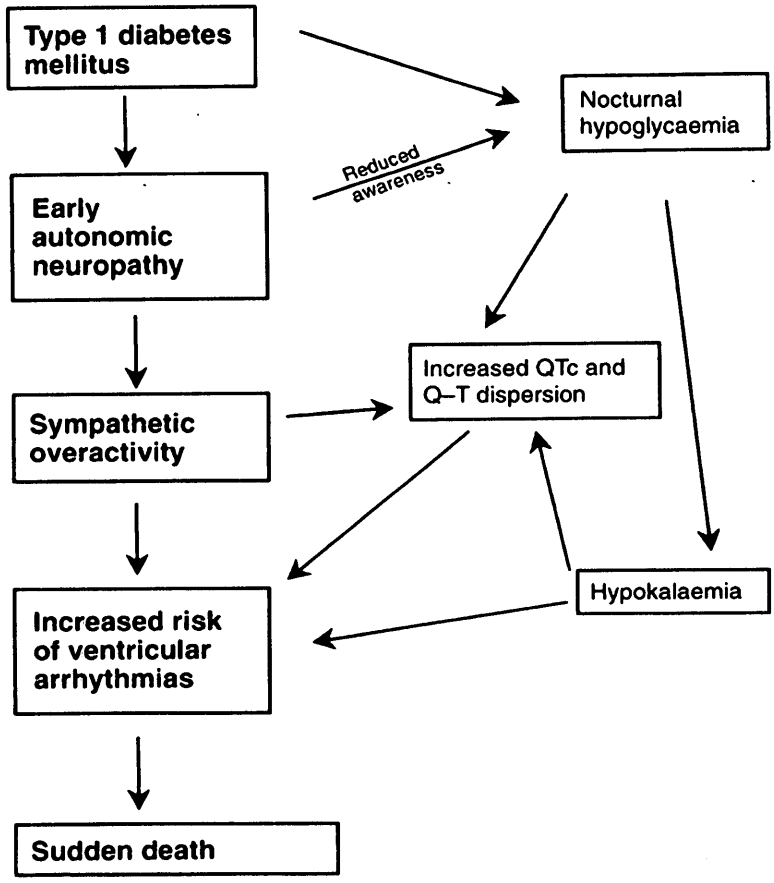
1.9 Heart rate variability and Dead in Bed Syndrome

A further issue that is implicated in ANS dysfunction in T1D is hypoglycemia. A previous episode of severe hypoglycemia blunts the ANS responses and awareness to subsequent drops in blood sugar (58-60). Absence of hypoglycemic symptoms and awareness is part of the syndrome called hypoglycemia-associated autonomic failure (60, 61), and has been implicated in the dead in bed (DIB) syndrome. While DIB only accounts for 6-11% of unexplained deaths in T1D (62), its extreme and elusive nature make it a pertinent area for research. In 1991, Tattersall and Gill reported 22 unexplained deaths in young patients with T1D (63). All of the deaths occurred at night, with the individuals being found the next morning in an undisturbed bed. This became the definition for DIB syndrome. In their study, the individuals were in seemingly good health the day before, however upon retrospective examination, many had recently experienced nocturnal hypoglycemic attacks. This study by Tattersall and Gill (62), along with many others (63-66), provide strong evidence that sudden death in youth with T1D may be related to hypoglycemic-induced cardiac arrhythmias. Because hypoglycemia rarely results in sudden death, it is believed that some other factors must predispose persons to this adverse event. As previously mentioned, autonomic neuropathy may impair the counter-regulatory response to hypoglycemia, thus it is hypothesized that dead in bed syndrome may be a consequence of both hypoglycemia and autonomic dysfunction that particularly impacts the heart. Additionally, there is evidence that reduced PNS activity contributes to cardiac electrical instability which could trigger ventricular dysrhythmias that could lead to sudden cardiac death (67).

During hypoglycemia, there is a notable elongation of the corrected QT interval (68). Hypoglycemia is also associated with increased plasma catecholamines and decreased serum potassium, both which are hypothesized to lead to QTc prolongation (69, 70). A follow-up study by Weston & Gill (71) looked at the relationship between nocturnal hypoglycemia and QTc intervals and found that not only was QTc elongation present with hypoglycemia, but the incidence of HR rhythm abnormalities was also significantly greater. Elongation of the QTc interval on ECG tracings of persons with T1D has been associated with sudden cardiac death when abnormal ANS function is also present (32, 72). Other research (73) suggests that hypoglycemia causes increased QTc and QT dispersion (QTd) in pre-pubescents and adults with T1D, independent of ANS dysfunction. Prolonged QTc interval can trigger ventricular tachyarrhythmias, even in the absence ANS dysfunction (73).

During sleep, a decrease in the LF/HF ratio is commonly observed (74), however in T1D, nocturnal LF predominance has been reported (34). Nocturnal hypoglycemia further increases the LF/HF ratio, indicating even greater sympathetic-to-parasympathetic imbalance (71). In a recent study on adults with T1D by Koivikko et al (75), HF did not change during nocturnal hypoglycemia, while LF increased. There was a significant negative correlation between LF power and glucose concentration (75). More importantly, hypoglycemia and increased sympatho-vagal imbalance are associated with lengthened QTc – a further risk factor for ventricular dysrhythmia (71). This relationship is depicted in Figure 1, published by Weston and Gill, 1999 (71).

Figure 1: Proposed explanation of the 'dead in bed syndrome' in T1D. Fatal ventricular arrhythmias may result from early autonomic neuropathy combined with hypoglycemia, and triggered by QT abnormalities.



2. Type 1 Diabetes Mellitus

Of the estimated 347 million cases of diabetes worldwide (76), the Canadian Diabetes Association suggests that 10% are believed to have T1D (77). Although less prevalent than T2D, T1D is associated with many long-term complications, as it is most commonly diagnosed in children and young adults and therefore requires life-long management. Currently, Canada has one of the highest reported incidence rates of T1D in youth under the age of 14, in the world (76). The incidence is increasing particularly in children under the age of 5 (78).

T1D is characterized as an autoimmune disease affecting the ability of the pancreas to secrete insulin to stabilize blood sugar levels (77). As a result, the tissues of the body rely on the injection of synthetic insulin in order to uptake and utilize circulating sugars (77). Because this typically-closed-loop homeostatic system has to be controlled through external manipulation, maintaining healthy blood sugar concentrations becomes a daily challenge for individuals with T1D. Without adequate insulin, these individuals experience elevated blood glucose (BG) levels called hyperglycemia. Slight hyperglycemia generally does not pose acute threats, and thus is often considered less problematic by persons with T1D. Nonetheless, it is important to limit the time spent in hyperglycemia, as high BG levels are associated with cumulative and chronic complications in the long-term. Typically, priority is given to avoiding low blood sugar, or hypoglycemia, in T1D due to the acute severe and life-threatening challenges that it can introduce. The primary challenge for individuals living with T1D is to sustain a healthy BG range, between 4-7 mmol/L (euglycemia). While this is largely a

balancing act between dietary carbohydrate consumption and insulin intake, this relationship is also under the influence of circulating hormones which makes management increasingly difficult with activities such as exercise and psychological stressors.

2.1. Type 1 Diabetes and Exercise

On one hand, the vast benefits of physical activity participation for those with T1D, including weight control, blood sugar control (79), and benefits on lipid profile (80, 81), make daily physical activity a compelling adjunct therapy. However, physical activity may also complicate the task of immediate blood sugar management, making it especially troubling for athletes with T1D (82). As such, determining the most suitable strategy for managing T1D with physical activity requires careful consideration of the type and intensity of physical activity to be performed.

2.1.a) Aerobic Exercise

Moderate-intensity physical activity occurs at around 40-59% of maximal exercise capacity (VO_2 max) (83), or 50-70% of heart rate reserve (HRR) (84), with a heavy reliance on aerobic metabolic processes. Aerobic activities typically include steady-state, endurance activities such as jogging, swimming, and cycling (26). Moderate-intensity physical activity is accompanied by greater glucose uptake by the muscle, which leads to a drop in BG in persons with T1D both during and after exercise (84). A common cause for this decrease is a relatively over-insulinized state in the body, resulting from insulin which, once injected in the body, remains in circulation for

several hours (82). As a result of the hyperinsulinemia, glucagon release is inhibited which therefore reduces hepatic glucose production (83, 84). Additionally, physical activity increases glucose transport out of circulation and into the working muscles due to the exercise-induced increase in insulin sensitivity. All of the above factors lead to an increased risk of hypoglycemia with exercise.

To prevent hypoglycemia with whole body, sustained, moderate-intensity activities, it may be advised to reduce insulin prior to the physical activity session, or supplement with carbohydrates during the activity that exceeds 15-30 minutes (84). The prescription for carbohydrate supplementation depends on not only the duration and intensity of the physical activity being performed, but the individual's starting blood sugar as well. Another technique to prevent hypoglycemia with whole body, sustained, moderate-intensity activities is to include short, maximal sprints in the session to counter the fall in blood glucose levels (83). One study (83) reported that when 20 minutes of easy pedalling on a cycle ergometer was performed in males with T1D, blood glucose levels continuously dropped both during and following the physical activity session. When a 10-second cycling sprint was introduced at the end of the 20-minute workout, the decline in BG was no longer apparent for 2 hours following the physical activity session.

2.1.b) High-Intensity Intermittent Training (HIIT)

HIIT training incorporates short bursts of maximal or near-maximal effort that cannot be sustained for long periods of time, and thus are separated by periods of lower intensity

physical activity. High-intensity exercise occurs at 80-100% of VO_2 max (83), or 70-85% of HRR (84), resulting in a greater production of lactic acid and larger reliance upon the anaerobic system. Because of the different metabolic processes which dominate at different exercise intensities, physiological responses vary accordingly, thereby adding to the difficulty of BG management in T1D.

In particular, the short sprints found in many sporting activities and spontaneous play in children, require intermittent bouts of high-intensity exercise, or IHE (85). During this type of physical activity or exercise, large demands are placed upon the body in a short amount of time, which requires muscle glycogen to be broken down for fuel. Catecholamine-mediated glucose production from the liver causes an elevation in BG during this type of exercise (86). Upon cessation of exercise, the catecholamine-driven inhibition on insulin is removed, insulin levels rise, and glucose is shuttled into the muscle to replace glycogen stores. In T1D, if there is insufficient circulating insulin at the onset of activity, an exercise bout can induce hyperglycemia. Furthermore, following exercise, it is difficult to know whether the GLUT4 transporters will sufficiently lower BG by replenishing glycogen stores, or whether an insulin bolus is needed to correct for the prevailing hyperglycemia. When individuals with T1D undergo intermittent high-intensity exercise (IHE), BG levels fall less rapidly compared to moderate-intensity exercise, and remain more stable in the hour following exercise despite doing more total work with IHE (87). This is partly explained by muscle glycogen which is used as fuel instead of circulating BG. As a result, there is a greater need for carbohydrate consumption both 30-60 minutes and 7-11 hours following exercise, when glycogen stores are being replenished (88). Failure to closely monitor BG trends after IHE may result in late-onset

hypoglycemia, which is particularly dangerous if experienced during nocturnal hours, while sleeping.

2.2 T1D and Hockey

From a brief glance at rosters of ice hockey players, it becomes evident that T1D does not limit individuals from reaching elite and competitive levels of this popular North American sport. As a result of its popularity among youth, well-rounded T1D care calls for established recommendations for effective T1D management with hockey. Such guidelines require efforts to study these individuals both observationally and experimentally, in both naturally-occurring and more tightly-controlled settings.

One reason that specific research is needed for athletes of this sport is because of the unique nature of hockey. In a pertinent study by Montgomery (89), hockey was characterized by high intensity intermittent skating with quick alterations in velocity and duration, and frequent body contact. The typical professional player performs for 15 to 20 minutes of a 60-minute game. Each shift lasts from 30 to 80 seconds with several minutes of recovery between shifts. The high-intensity bursts require muscular strength, power, and both anaerobic and anaerobic-aerobic endurance. On the other hand, the prolonged duration of the game and the need for quick recovery between shifts demands an efficient aerobic system. Peak heart rates during a shift on the ice exceed 90% of HRmax with average on-ice values of about 85% of HRmax. As a result of the various metabolic systems at play during hockey, and the dynamic nature of the sport, general guidelines for sport participation for persons with T1D require modification,

Despite both intra- and inter-individual differences with BG trends and physical activity participation, anecdotal reports of BG patterns with hockey activity display general trends. Individuals with T1D commonly report an elevation in BG with hockey games, with optimal performance occurring at a BG level between 8-10 mmol/L. Unfortunately guidelines specific to hockey players with T1D do not currently exist, as this is a largely un-researched area of T1D management. Widely-practiced recommendations for BG management with general IHE-type activities, such as hockey, are typically based on anecdotal reports, or strategies used for continuous "competitive activities" such as swimming and cycling (84).

For insulin pump users, some guidelines pertaining IHE include removing the insulin pump or reducing basal rates by 50-70% on the day of the activity (84). Further game-related recommendations include reducing meal boluses by 25-50% if a game is scheduled within 2-3 hours of that meal, and consuming 15-30 grams of carbohydrate per hour of activity, depending on the individual's playing time and intensity (84). If a game occurs in the night time, it is recommended to reduce basal rates by 10-20% overnight following extensive play in the evening, and to consume a bedtime snack to prevent nighttime hypoglycemia (84). These are recommendations made by one diabetes handbook, but have not been widely disseminated to the T1D population, perhaps because of a lack of scientific evidence behind them.

Because of the complications that arise with dysglycemia, it seems absolutely paramount to closely monitor BG in order to optimize sport performance and mitigate the health complications that can arise from poorly controlled BG. Because of the unique nature of hockey activity compared to other exercises and sporting activities, it is

important that research be conducted on this specific group of athletes to provide guidelines for future players. The current lack of research in this area leaves families of hockey players with T1D to discover their own strategies through trial and error. It can be frustrating for the children with T1D as well as their parents, and it can be dangerous if careful precautions are not taken to avoid extreme BG excursions. Additionally, mismanaged BG on the ice can prevent players from reaching their potential and can be discouraging, which ultimately prematurely ends their participation in hockey. With documented research, information and guidelines can be made available to parents, coaches, fellow athletes, and physicians, and can therefore assist with T1D management while encouraging continued participation in their chosen sport.

Summary

In sum, it is unknown what acute impact physical activity or exercise has on nocturnal HRV profile in individuals with T1D. Although it is commonly agreed upon that habitual physical activity offers benefits to HRV profile, the acute effects of physical activity participation on subsequent, nocturnal HRV remain largely unknown. This is an important area of research for athletes with T1D, who regularly participate in intense levels of physical activity. It has been published that overtraining leads to increased cardiac SNS tone during rest, as well as decreased overall HRV, signifying PNS or vagal withdrawal (41). Given the causal links between physical activity and night-time hypoglycemia, and between nocturnal hypoglycemia and worsened ANS function, this research aimed to assess whether a single bout of physical activity may predispose

individuals with T1D to worsened nocturnal HRV following the physical activity bout. If this is found to be the case, then it may help to explain why several reports of DIB have occurred in highly-active individuals (92, 93).

OBJECTIVES & HYPOTHESES 2

1) To observe the naturally-occurring trends of blood glucose levels with hockey participation.
   - While variances will occur between each participant, it will be interesting to note whether general trends are present during games, and in 24-hour recovery. Given the anecdotal reports of glycemic highs during games, we hypothesize that continuous glucose monitor tracings may reveal post-hockey hyperglycemia followed by an increased incidence of nocturnal glycemic lows. This could be due to over-correcting for the post-game high or due to insufficient carbohydrate consumption after the game.

2) To assess the immediate effects of highly-intense physical activity on subsequent nocturnal autonomic function in youth with T1D
   - Because of the correlation between hypoglycemia and worsened HRV, we hypothesize that acute HRV may be worse in participants with T1D following a hockey game, compared to their healthy controls. We predict that on a non-exercise day, no differences will be seen between T1D and non-T1D participants, due to the cardioprotective effects of exercise which may result in a delayed onset of ANS disturbances in these highly-active athletes with T1D.

3) To measure the relationship between nocturnal BG and ANS function

- We hypothesize that as has been previously published, periods of low BG will result in QTc elongation. We will further study the relationship between hypoglycemia, hyperglycemia, and ANS function by assessing other HRV parameters during hypoglycemia.

CONTRIBUTION OF THE AUTHORS 3

This project was conceived and designed through collaborative efforts involving Dr. Riddell, Dr. Jamnik, and myself. Subject recruitment and scheduling for lab visits was primarily my responsibility. Fitness assessments on participants were conducted by me, with assistance from members of the human performance lab which included Dr. Jamnik. I directed the hockey-type lab exercise protocols which were carried out with the assistance of several members of the fitness lab. Main contributors to the completion of the hockey-type lab exercise protocols include myself, Dr. Jamnik, Dessi Zaharieva, Robbie Gumieniak, Chip Rowan, Justin Sanderson, and Deandra Fillipo.

CGM insertion for participants was conducted by a qualified diabetes specialist – in most cases, Dr. Riddell. I was responsible for uploading the CGM data and pooling the data into Excel sheets. I also conducted all of the statistical analyses and composed all of the tables and figures seen in this thesis.

Northeast Monitoring received the original HRV file uploads and had a lab technician scan them for heart rate abnormalities. I learned how to run the software and ECG analyses myself, which allowed me to carefully scan through each of the participants' files and process the data using their software. I was blinded to the file name to protect from bias.

Dr. Riddell is the principle investigator and co-supervisor of this project. Dr. Jamnik is also a co-supervisor of this project.

METHODS 4

Ethics

This project was reviewed and approved by the Human Participants Review Sub-Committee at York University's Office of Research Ethics.

Recruitment

Endocrinologists and diabetes clinics in the Greater Toronto Area were contacted and supplied with recruitment flyers (Appendix A) for distribution at their clinics. Flyers were also posted in various arenas and hockey-centred fitness facilities through the Toronto area. Additional postings regarding the study were made online, through platforms such as Facebook and Twitter. Parents of youth who participated in a T1D-focused sports camp were also contacted via email. This word-of-mouth recruitment was targeted at rep-level hockey players between the ages of 13-21 who had been diagnosed with T1D at least 1 year prior. Upon initial contact with interested individuals, researchers inquired about pubertal level and age of diabetes diagnosis. A teammate for each individual was selected to function as a control participant. These individuals were chosen based on possessing similar attributes as our selected hockey players with T1D, such as age, sex, height, weight, and fitness level. The control participants completed identical measures to those with T1D, with the exception of the continuous glucose monitor and BG checks which were exclusively used for the persons with T1D.

Screening Tools

Based on parental or guardian report, individuals who had not yet commenced puberty were excluded from this study. Furthermore if the individual was newly diagnosed, played hockey at a non-competitive level, or played goalie, they were not included in the study. Finally, individuals with any diagnosed nervous system dysfunctions or retinopathy were excluded.

Each study participant was required to complete a PAR-Q+ (Appendix B) and if necessary, ePAR-med-X questionnaire (www.eparmedx.com) in order to screen for any contraindications to completing vigorous exercise as required by this study protocol. Minor assent forms were sent to participants under the age of 16 (Appendix C), while parental consent forms were supplied to their parent or guardian (Appendix D). For participants over the age of 16, informed consent forms were supplied directly to the participants (Appendix E). All aforementioned forms were emailed to the appropriate individuals before visiting the laboratory, in order to provide them with sufficient time to read them and present any questions to the researchers. Forms were collected at the initial laboratory visit.

Laboratory Measurements

1. Anthropometric Data. Weight was measured using a digital scale (Seca Alpha, *Germany*) with no shoes and light clothing. Waist circumference (WC) was measured using the National Institute of Health (NIH) protocol; the measuring tape was placed on the skin at the level of the iliac crest. Body fat percentage was determined through

bioelectrical impedance analysis (BIA) instrument (Tanita Scale, model TBF-612, *Arlington Heights, Ill*). Skinfold measurements were taken using Harpenden fat calipers at standard sites; biceps, triceps, subscapula, iliac crest and medial calf, as per the Canadian Physical Activity, Fitness and Lifestyle Approach (94). Markings were made at the skinfold sites as well as one centimeter below, first for where the fold was made and the second for the placement of the jaws of the fat caliper. BMI was calculated by using weight in kilograms divided by squared height in meters.

2. *Anaerobic Fitness*. Individuals were required to have a BG level of between 5-15 mmol/L in order to commence the protocols for anaerobic and aerobic fitness assessment. If individuals were below this threshold, one attempt was made to correct the low by administering 16 grams of carbohydrate (4 tablets of Dex4). A re-measurement was taken 15 minutes and 30 minutes after, at which point if the low was corrected, testing could proceed. If on the other hand, individuals were above the threshold upon entry to the laboratory, participants were recommended to consume water and could choose to take insulin or simply wait 15-minutes, at which point another BG reading was taken. Provided participants were within the appropriate range 15-30 minutes after their initial check, we proceeded with the testing measures. If individuals were not in the target BG range within that time span, the fitness testing was scheduled for another day. BG was checked with the individual's own hand-held device.

Anaerobic fitness was assessed using a 30-second Wingate protocol (95) on a Monark Ergomedic 894E Peak cycle ergometer. A 5-minute warm-up was administered on a cycle ergometer, during which time the Wingate protocol was explained to the participant. Resistance was calculated at 7.5% of the individual's body mass. Individuals

were placed at a seat height such that at maximal leg extension, a 10-15 degree angle remained at the knee joint. Participants were instructed to keep seated while pedaling as fast and hard as they could for the duration of the 30-second test. They were given the verbal cues "faster, faster, go" to accelerate their pedaling speed prior to the load being dropped for the all-out sprint. These cues were given to ensure that the participants were pedaling at their maximal cadence prior to the resistance setting in. Qualified fitness professionals administered the test while verbally encouraging the participant for its duration. The ergometers were connected to a Monark software program in order to continuously record the revolutions per minute (RPMs) and watts, which could later be used to determine peak power output and fatigue index. At the end of the 30 seconds, the resistance was removed and individuals remained on the cycle ergometer for a cool-down period. Following this, participants lay supine for a 30-minute recovery period, while active stretching and BG checks took place.

3. *Aerobic Fitness*. Following the 30-minute rest period, individuals participated in an incremental to maximum aerobic fitness test (VO_2max) provided their BG values were fairly stable and above 5 mmol/L. As per the Canadian Diabetes Association guidelines, 16 grams of dextrose tablets were administered to individuals whose blood sugar values were below this level. Polar heart rate monitors were worn to obtain their peak exercise heart rate during the test. A modified Astrand and Pollock (1978) incremental-to-maximum treadmill protocol was used for VO_2 max assessment. While walking on the treadmill, participants were familiarized with the general procedure and testing equipment. The protocol was designed based on incremental stages lasting 2 minutes in duration. The protocol for all individuals started at 3.5 mph at 0% incline, and then

proceeded to 5mph at 0% incline, and then 6mph at 0% incline. The stages that followed were tailored to individual biomechanics; some participants stayed at a speed of 6mph while others ran at 6.5, 7, or 7.5 mph. The protocol proceeded such that increases in intensity occurred once every 2 minutes, and once a comfortable running speed between 6 and 7.5 mph was reached for a participant, the speed was kept constant. To increase intensity from that point on, the incline was increased by 2% every 2 minutes. Individuals were verbally motivated to run continuously for as many 2-minute stages as possible. When the participant was unable to complete a full 2-minute workload, the speed was brought down to a walk for 2 minutes which marked the beginning of the supramaximal workloads. For this portion, individuals would run at the same speed as their final workload from the continuous portion, with the incline increased 2% higher than the previous workload. These workloads lasted 2 minutes, and were separated by 2-minutes of walking on the treadmill.

Open circuit spirometry, a form of indirect calorimetry, was used during the VO_2max assessment. The details of the open circuit spirometry involved the participant inhaling air from the atmosphere and expiring air through a mouth-piece attached to a two-way valve (Ewald Koegal Co, *San Antonio Texas*), connected to a hose and then to a 120L Tissot gasometer (Warren E Collins LTD. *Braintree, Massachusetts*), while wearing a nose plug. The fractional concentration of expired oxygen (F_EO_2) and carbon dioxide (F_ECO_2), and volume of air expired were measured in the final 30 seconds of each workload. From several of these recorded measurements, oxygen consumption (VO_2) and carbon dioxide production (VCO_2) could be calculated for each incremental stage. Oxygen and carbon dioxide concentrations of the expired air were analyzed

through rapid response gas analyzers (Applied Electrochemistry, Model S-3A and CD-3S, *Sunnyvale, California)*. Rating of Perceived Exertion (RPE) and HR were collected at the end of each stage. The VO_2 max test continued until volitional fatigue, or until the qualified exercise professionals concluded that physiological measures indicated that the participant had reached their VO_2 max.

Blood Glucose Monitoring

All participants with T1D were fitted with a blinded continuous glucose monitor (CGM; Medtronic iPro2). Sensors were injected in the upper buttock using an auto-injector, operated by qualified nurses or diabetes specialists. This sensor and iPro2 system allowed for continuous measurement of subcutaneous glucose concentration, taken every 5 minutes for up to 6 days. An adhesive patch was placed over the CGM to optimize comfort while participating in intense physical activity. Participants used their own glucometers to obtain BG measures a minimum of once every 8 hours, which would later act as calibration points for the respective CGM tracing. Participants were also provided with log sheets to record their meals, carbohydrate and insulin intake, and activities they partook in. Following completion of the study, CGMs were removed by the participant and collected by the researchers for upload and retrospective analysis.

Nocturnal BG was regarded as the continuous period from midnight (00:00h) to 6:00 AM (06:00h), and was isolated from the CGM for the nights following the lab exercise, low activity, and hockey game. These values were later pooled together and graphed to assess overall mean nocturnal BG trends and area under the curve following

the three collection days. As for the acute exercise bouts themselves, glucometer measurements were taken before and after completion of the hockey game and hockey-type laboratory exercise protocol in order to determine general BG trends with the two types of bouts.

Heart rate variability

1. *Technique*. Two commonly-used and accepted methods of assessing ANS function are muscle sympathetic nerve activity (MSNA) and HRV. While MSNA is considered the gold standard, it is an invasive measure which solely measures SNS activity from the peroneal nerve (96). For these reasons, a Holter monitor was selected as the most appropriate method for assessing HRV, a surrogate measure of ANS function for this study. All efforts were made to ensure that a continuous time period of 12:00-6:00 AM was analyzed for all participants. In the event that an extended length of artifact took place within the 6-hour time period (lasting 30 minutes or more), the time analyzed was extended past 6:00 AM to account for this lost time.

2. *Data Collection.* Similar to previous studies analyzing nocturnal HRV (97), HRV was analyzed from 12:00 am – 6:00 am using a Holter Monitor (Northeast Monitoring, DR 200 H/E) with a 5-lead configuration. These small monitors measured 8.6 cm long by 6.0 cm wide and 2.0 cm deep, and were worn in a pouch that attached around the hip. The sample frequency was 180 samples per second. These non-invasive monitors were worn on 3 nights within a 5 day span, to record the acute effects of a single bout of strenuous physical activity on nocturnal HRV. One of the 3 nights followed a regular

season hockey game which was played in the preceding evening. A Polar heart rate monitor was worn by each participant during this game, to collect HR fluctuations and therefore ensure the intensity of the exercise bout. Another of the 3 nights was to follow a laboratory-exercise protocol which simulated a hockey game in a controlled setting. A final recording night followed a low-activity day where no exercise was performed.

Participants were provided with a tight-fitting spandex shirt to wear over the Holter wires, which aided in the signal clarity picked up by the monitor. The monitor was kept in a pouch worn around the hip, and data was stored for each night on a formatted 2 GB SD card. Participants and their guardians were instructed how to set up the 5-lead configuration so that they could set it up independently at home. An instructional sheet and diagram depicting the configuration was also provided to the participants, and is located in Appendix F. Participants were instructed to sleep from 11:00 PM or earlier, until 6:00 AM or later, on the 3 recording nights. Individuals were also provided with a log-sheet (Appendix G) to record the activities they participated in during the day, any emotional stress experienced, the time they went to bed and woke up, and the time they started and ended the Holter monitor recording period. On the days where nocturnal HRV was to be recorded, participants were instructed to abstain from physical activities occurring outside of the design of the study. This included highly intense or high volumes of exercise, playing or practicing sports, and physically-demanding activities. If required by individual schools, participants were provided letters to request their exclusion from school physical activity classes.

3. *Data Analysis.* Data stored on the SD cards were uploaded remotely and sent for EKG analysis by an external company (Northeast monitoring, Mississauga, ON). Data

from each card was initially scanned for artifact and heart rhythm abnormalities by a trained technician, during the nocturnal EKG tracings stored on the card. Any abnormalities or true artifact were classified as such and excluded from the analyses. Because time domain measures depend on the length of the recording period, if a distorted signal (artifact) lasted 30 minutes or longer, the end-time of the analysis was extended accordingly.

Beat identification and classification were then performed by the automated computer program designed for these Holter recorders (LX Analysis, version 5.3 version D). Each QRS complex was then scanned by an individual who was blinded to the identity of the HRV study participant file, to ensure the correct markings of each beat classification. Following that, LX Analysis applied various mathematical algorithms to the EKG strips to calculate time and spectral domain measures in 5-minute intervals. Reported time domain measures included SDNN, RMSSD, PNN50, and several others. Power spectral domain measures such as VLF, LF, HF, TP, and LF/TP and HF/TP ratios were also calculated by LX Analysis. Several geometric measurements were also calculated, and included the logarithmic index and triangular index. An additional software program was developed by the software technicians at Northeast monitoring to analyze QT and QTc. This program was adapted to provide such analyses by applying Bazett's formula on data from 3-leads rather than the usual 12. Because only 3 leads were utilized, QT dispersion measures could not be determined. Six-hour averages were calculated for all HRV indices by the software program for the 12am-6am timeframe, and these values were used for subsequent intra- and inter-individual

analyses. All HRV parameters were defined according to international standards of measurements (1).

QTc was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$) (7). Prolonged QTc was identified using recent criteria suggesting that QTc of 0.450 In boys or 0.460 in girls revealed moderate risk of having long QT syndrome, QTc of 0.460-0.470 represented higher risk, and QTc of 0.480 represented almost definite diagnosis of prolonged QTc (98)

4. *Statistical Analysis.* HRV parameters were first analyzed by calculating each individual's mean value from their 6-hour nocturnal recording, each of the 3 recording nights. Means were then combined to compare differences between males and females, between T1D athletes (T1-a) and non-diabetic (control) athletes (Ctrl-a), and to compare values following the laboratory exercise protocol and after the hockey game, compared to after a low-activity day. HRV in exercise recovery was also assessed by collecting mean values from the 30-minute span, and comparing those values based on sex and T1D status. Means with standard deviations were calculated for all HRV variables, and T-tests were conducted to assess differences between groups. Significance was set at $p<0.05$.

Hockey-Type Exercise Protocol

1. *Design.* Individuals wore a coded polar HR strap and receiver during a regular hockey game that they played. These values were later observed for recognition of HR fluctuations during hockey games. Each sustained increase in the HR was assumed to

indicate a hockey shift, and subsequently studied for duration and intensity, as indicated by their HR. Each prolonged dip in the HR was associated with a rest between shifts, and was also analyzed for duration and intensity. From several of these game HR recordings, a standardized protocol (Appendix H) was developed for use during a laboratory-exercise protocol which simulated a hockey game in a controlled setting. This protocol consisted of three 20-minute periods of IHE on the same Monark Ergomedic 894E Peak cycle ergometer which was used during the Wingate test. The ergometers were hooked up to laptop computers which processed and recorded measures such as revolutions per minute (RPMs) and watt output. Each period was separated by a 10-minute rest period. As per the standard written protocol, participants were verbally instructed when to accelerate and decelerate their pedaling frequency. Verbal cues consisted of "go" "whistle" and "bench." On "go," participants were to simulate the effort that they would exert during a hockey shift. "Whistle" indicated a stoppage in play, where the player was allowed to either pedal on the bike with no resistance, or sit stationary. The term "bench" indicated a prolonged break, similar to when a player would be off the ice and sitting on the bench. During this time, the participant was to rest on the cycle ergometer. Resistance was set at 70% of the individuals Wingate resistance, or 5.25% of their body mass.

2. *In practice.* Individuals were instructed to treat the approach for the laboratory visit similar to what they would do for a regular hockey game. Most T1D participants consumed a carbohydrate-heavy meal before their hockey game, and reduced their insulin intake or preferred to suspend their insulin pump during hockey activity. As such, the same procedures, based on individual preferences, were recommended for the

hockey-type exercise protocol. The protocol was designed to take place between 3:30 and 4:30 PM; approximately 4 hours after their lunch was consumed.

Prior to beginning this protocol, participants with T1D were required have a BG level no lower than 5 mmol/L. If an individual was below this safety cutoff, one attempt was made to correct the low by administering 16 grams of carbohydrate (4 tablets of Dex4), or a self-chosen snack containing a similar amount of carbohydrate. A re-measurement was taken 15 minutes and 30 minutes after, at which point if the low was corrected, the hockey-type lab exercise protocol could ensue. If participants entered the laboratory with a BG level above 15 mmol/L, they were advised to consume water and could choose to take insulin or simply wait 15-minutes, at which point another BG reading was taken. Provided participants were within the appropriate BG range 15-30 minutes after their initial check, we proceeded with the hockey-type laboratory exercise protocol. If individuals were not within the safe BG range within the allotted time span, the lab exercise protocol was scheduled for another day.

To begin the lab exercise session, all participants were weighed and fitted with a Polar heart rate strap and Fitmate VO_2 max system (Image Monitoring). Heart rate and percent of VO_2 max were continuously monitored and recorded, as well as ergometer RPMs and Watts. BG checks were performed using the participant's own hand-held device, a minimum of once every 20 minutes. This occurred during the 10-minute break between periods, while participants could get off the cycle ergometers and walk around to stretch their legs. Participants were also encouraged to check their BG any time they wished. If at any time a participant with T1D had decreasing BG levels that were trending toward a potentially unsafe level, dextrose tablets were administered orally (16

grams of carbohydrate as per the Canadian Diabetes Association guidelines). Immediately following the completion of this exercise bout and a short cool-down period, a 5-lead Holter monitor was placed on each participant while they lay supine in a dark, quiet room for 30 minutes to assess post-exercise HRV. After the 30-minute period passed, the Holter monitor was removed.

RESULTS 5

In total, 14 males and 6 females were recruited for participation in this study, half of whom had T1D. Anthropometrics and fitness measurements are reported in Tables 2 and 3, respectively. Of note, individuals ranged in age from 13-17 and had all reached puberty according to parental report. One individual had been diagnosed with T1D less than the intended 1-year minimum, but was included in the study as they had surpassed the honeymoon period. Six participants were using insulin infusion pumps while 4 were utilizing multiple daily injections. All individuals with T1D had a control subject whom was matched in age, sex, and fitness level.

Of the 20 participants, 19 played ice hockey; 4 at the A-level, 4 at the AA-level, and 12 at the AAA-level or higher. One participant in the T1D group was a competitive lacrosse player and was included due to the similarity of lacrosse and hockey. This individual contributed HRV and CGM values from the laboratory exercise protocol and low activity day, but not from a game day. Their non-diabetic control also contributed HRV values from the laboratory exercise and low activity day, but not from a game. The remaining subjects participated in all 3 events included in the study design; laboratory exercise, low activity, and a hockey game.

This study did not aim to control BG values with exercise, and as such, meals and insulin were not controlled. Participants with T1D were free from disease complications, and were in fair to good metabolic control (mean glycosylated hemoglobin [HbA1c] 8.2 ± 0.7%) according to their last check-up by their physicians. Two individuals were participating in a drug trial at Sick Kids hospital, aimed at

preserving kidney function. The drugs administered by this study were an ACE inhibitor and a statin. While the individuals may have been receiving treatment or placebo at the time of this study, neither drug is believed to impact HRV.

Table 2. Individual anthropometric measurements for participants.

	Sex	Age (yrs)	Height (cm)	Weight (kg)	WC (cm)	Skinfolds (mm)	DD (yrs)	HbA1c
T1-a1	F	13.8	158	53.8	71.0	53.8	12.0	8.1
T1-a2	F	17.5	167	64.4	74.0	95.3	2.0	8.3
T1-a3	M	14.5	167	58.7	74.0	57.7	10.0	8.0
T1-a4	M	17.6	175	73.3	79.0	56.6	15.0	7.9
T1-a5	F	14.0	157	64.1	74.0	102.7	10.8	8.3
T1-a6	M	15.1	175	65.1	73.1	35.9	2.0	7.9
T1-a7	M	13.5	171	67.7	77.0		2.2	9.2
T1-a8	M	15.0	175	83.3	86.7	53.2	4.5	8.4
T1-a9	M	16.0	187	98.3	83.0		1.8	8.9
T1-a10	M	15.0	178	76.6	84.0	63.0	0.9	6.7
T1-a Average		**15.2**	**171**	**70.5**	**77.6**	**65.0**	**6.1**	**8.2**
Ctrl-a1	F	13.1	163	55.5	74.0	55.8	--	--
Ctrl-a2	F	17.2	170	57.3	73.0	49.9	--	--
Ctrl-a3	M	14.4	170	68.5	77.0	70.8	--	--
Ctrl-a4	M	17.9	174	75.6	83.0	62.4	--	--
Ctrl-a5	F	13.8	154	52.1	72.0	52.8	--	--
Ctrl-a6	M	15.8	173	61.3	71.0	33.5	--	--
Ctrl-a7	M	13.6	176	73.1	79.0		--	--
Ctrl-a8	M	15.0	184	84.8	89.0	39.2	--	--
Ctrl-a9	M	14.5	187	70.3	72.0		--	--
Ctrl-a10	M	15.2	167	71.4	83.0	53.2	--	--
Ctrl-a Average		**15.0**	**171.8**	**67.0**	**77.0**	**52.1**		
T-Test		**p=0.44**	**p=0.66**	**p=0.33**	**p=0.85**	**p=0.17**		

Ctrl-a represents the non-diabetic athletes with respective numbers that correspond to their matched participant with T1D.

Table 3. Individual fitness-related measurements for participants.

	HR min	HR max	Hockey level	VO_2 max mL O2/kg/min	Peak Power watts	Fatigue (%)
T1-a1	67	202	AA	56.2	471.9	46.4
T1-a2	57	209	A	51.8	567.0	39.3
T1-a3	51	190	AAA	59.0	647.4	48.0
T1-a4	51	192	Jr. A	49.8	735.3	51.7
T1-a5	48	186	AA	43.3	460.0	43.1
T1-a6	55	204	AAA	56.0	705.1	38.6
T1-a7	50	202	AAA	56.9	786.9	50.1
T1-a8	51	188	AAA	59.3	910.1	65.9
T1-a9	58	187	AAA	47.2		
T1-a10	54	197	A	58.9	747.4	39.0
T1-a Average	**54**	**196**		**53.9**	**670.1**	**46.9**
Ctrl-a1	65	204	AA	52.7	484.8	38.1
Ctrl-a2	59	201	A	54.8	528.5	33.8
Ctrl-a3	52	193	AAA	63.3	770.9	54.5
Ctrl-a4	44	194	AA	62.4	886.1	56.3
Ctrl-a5	63	189	AA	46.5	487.0	39.0
Ctrl-a6	43	203	AAA	53.0	772.3	56.7
Ctrl-a7	50	195	AAA	64.1	860.5	52.3
Ctrl-a8	53	195	AAA	61.1	1019.0	54.3
Ctrl-a9	52	193	AAA	51.8		
Ctrl-a10	43	201	A	52.2	635.4	54.5
Ctrl-a Average	**52**	**197**		**56.2**	**716.1**	**48.8**
T-Test	**p=0.49**	**p=0.51**		**p=0.21**	**p=0.14**	**p=0.58**

Ctrl-a represents the non-diabetic athletes with respective numbers that correspond to their matched participant with T1D.

Results:

A paired-samples 2-tailed T-Test revealed that there were no differences between groups based on any of the group characteristics. T1-a group had slightly higher sum of 5 skinfolds, indicating larger fat mass, however this trend was inconsistent between pairs, resulting in no statistical significance (p=0.17). Results from the fitness assessments revealed an overall mean VO_2 max of 55.0 ± 5.8 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ across all athlete participants (range 43.3-64.1). Results from the Wingate test revealed an average peak power output of 693.1 Watts$\cdot kg^{-1}$ across all athlete participants (range 460-1019). Results are summarized previously in Table 2.

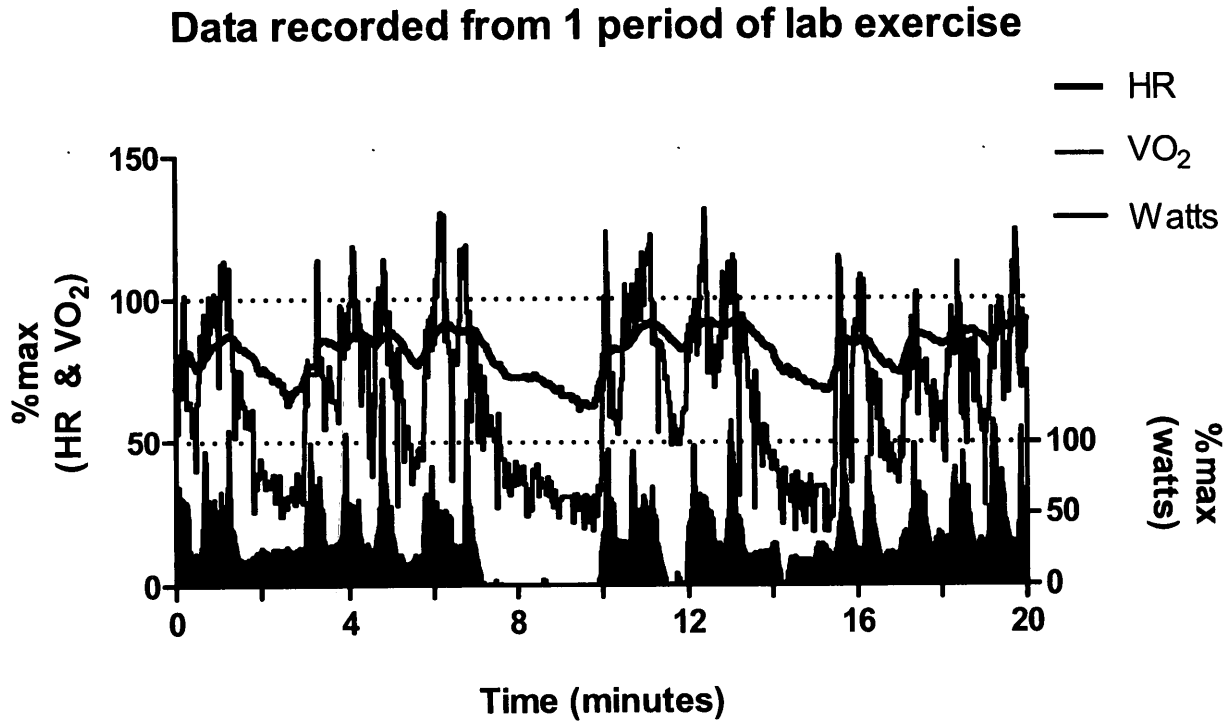
Hockey-Type Laboratory Exercise Protocol

Two participants had BG below the 5 mmol safety cut-off prior to starting the hockey-type laboratory exercise protocol. They were either treated with 16 grams of dextrose or a self-supplied snack which was similar to what they would consume at a hockey game if they were low. For both individuals, the single attempt was successful in correcting the low BG and thus it was deemed safe to proceed with the protocol.

All T1-a individuals attended the laboratory with their Ctrl-a teammate and completed the 20-minute protocol three times, representing three periods. Between the periods, 10 minutes of rest allowed participants to walk around, while the T1-a group could also check their BG, and consume dextrose tablets if necessary. One T1-a individual who had been treated with carbohydrate prior to exercise initiation, needed dextrose supplementation during the protocol. The exercise protocol is included in Appendix F.

VO_2, HR, and watt recordings from a representative period are included in Figure 2. On average, on-shift heart rates ranged from 85-100 % of HRR, with VO_2 ranging from 85-110% of max, as per their VO_2 max test results. Off-shift heart rates ranged from 60-70% of HRR, while VO_2 ranged from 30-50% of max.

Figure 2. Relative heart rate, VO_2 and power output during one repetition of the hockey-type laboratory exercise protocol



Hockey Game

Polar HR monitors with coded straps were worn by individuals during a regular season hockey game. Games ranged in length from 1 hour, to 1 hour and 15 minutes and occurred in the evening hours. All individuals' hockey games included 15-20 shifts, with HR continuously ranging from 185-205 while on the ice, to 130-140 bpm while on the bench between shifts. Peak HRs attained during games surpassed those seen in laboratory during the VO_2 max testing. All games included one 10-minute break for an ice resurfacing to take place.

Blood Glucose

Ten individuals with T1D wore the provided CGM and complete data was available for eight of them. One sensor was unable to be successfully uploaded, while another sensor came out of a participant before study completion. As a result, CGM data was available for eight of nine participants' hockey games, eight of ten individuals' laboratory exercise bouts, and nine of ten low activity days. For the two individuals whose CGMs were not functioning for the laboratory exercise bout, pre and post glucometer recordings were used instead. Pre and post glucometer recordings were also utilized for the 1 individual whose CGM was not working for the hockey game.

Pre- and post-activity BG changes from the laboratory exercise and hockey game sessions are included in Figures 3 and 4, respectively. Average starting BG for the laboratory exercise was 8.5 mmol/L, while average ending BG was 6.6 mmol/L, indicating a mean change of -1.9 mmol/L. Of the 10 individuals with T1D who completed

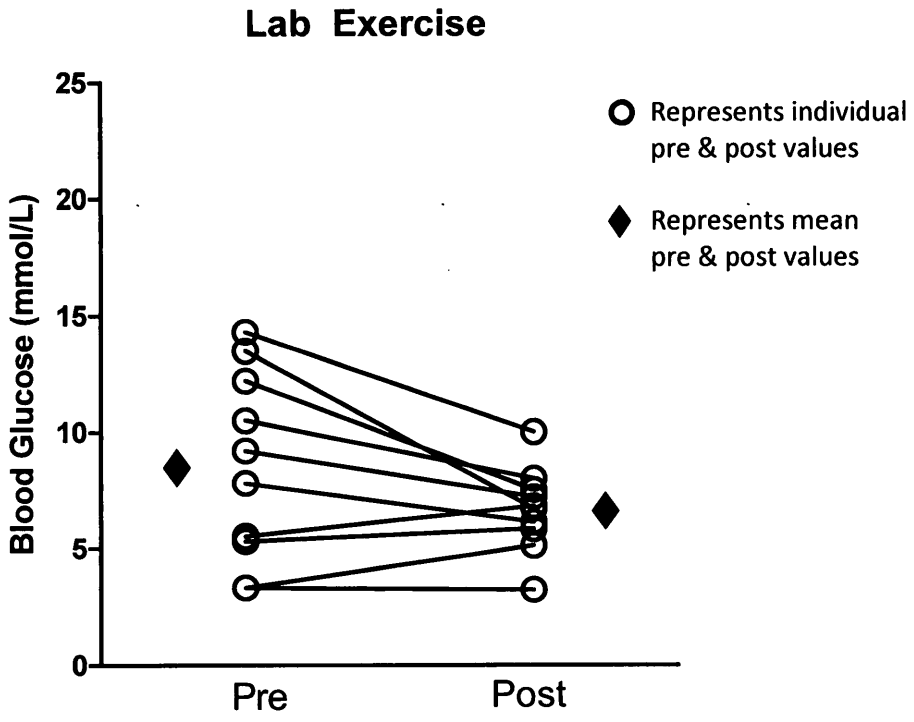
the laboratory exercise, 7 saw a decrease in BG while 3 experienced an increase. Average starting BG for the hockey game was 11.0 mmol/L, while average ending BG was 12.0 mmol/L, indicating a mean BG increase of 1.0 mmol/L. Of the nine individuals who contributed BG data from a hockey game, seven experienced an increase in BG from the start to the finish of their game, while 2 saw a decrease.

The inter-individual variations in nocturnal BG control (00:00h-06:00h) on each of the three nights can be viewed in figures 5a-c. Mean nocturnal CGM values were calculated across all participants, and the mean differences in BG control following a day where the lab exercise, no activity, or the hockey game took place, are found in figure 6. Area under the curve (AUC) analyses revealed that BG remained highest after lab exercise (4143 $mmol \cdot L^{-1} \cdot min^{-1}$), lower after a hockey game (3563 $mmol \cdot L^{-1} \cdot min^{-1}$), and lowest after a low activity day (3496 $mmol \cdot L^{-1} \cdot min^{-1}$). BG on the lab exercise night decreased, on average, 1.7 mmol/L from midnight until 06:00 in the morning. The tightest control was shown after the hockey game, with average BG values going from 9.3 mmol/L at midnight to 10.1 mmol/L at 06:00, displaying a 0.8 mM increase. BG on the low activity night experienced the greatest drop throughout the night, from 11.3 mmol/L at midnight, to 8.3mmol/L at 06:00. Individual CGM tracings from the nocturnal periods following lab exercise, low activity, and the hockey games are displayed in figures 5a, 5b, and 5c, respectively.

Of particular importance, retrospective CGM analysis revealed that one individual experienced prolonged nocturnal hypoglycemia following their hockey game, while having their HRV assessed. The CGM report from this night is included in Figure 7. Hypoglycemia onset was at 01:40h in the morning, and persisted through sleep until

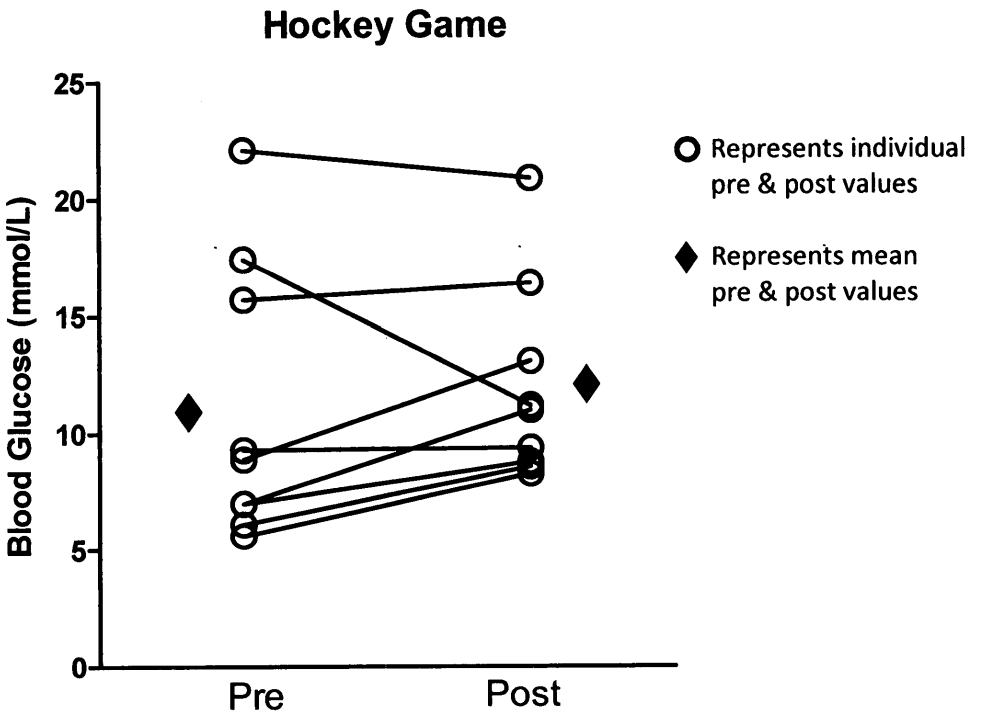
05:30h, for a total duration of 230 minutes. One additional participant had a hockey tournament during the time in which a CGM was being worn for the study. We pre-selected one night to assess this individual's post-hockey nocturnal BG and HRV, based on playing only one game in the preceding day, and wearing the Holter monitor at night. During this evening, BG management was good, however on the two other nights after hockey games, the individual experienced hypoglycemia which is worth reporting. On one night, the individual experienced 30 minutes of hypoglycemia, whereas on another night, 180 minutes of hypoglycemia occurred. These values were not included in any of the analyses included in this study.

Figure 3. Absolute BG concentrations immediately before and after the hockey-type lab exercise protocol, as reported by the CGM and validated by glucometer readings.



Average pre-laboratory exercise BG was 8.5 mmol/L, represented by the left-positioned diamond. Average post-laboratory exercise BG was 6.6 mmol/L, represented by the right-positioned diamond. Mean change with the hockey-type laboratory exercise protocol was -1.9 ± 2.8 mM.

Figure 4. Absolute BG concentrations immediately before and after individuals' hockey games, as reported by the CGM and validated by glucometer readings.



Average pre-hockey BG was 11.0 mmol/L, represented by the left-positioned diamond. Average post-hockey BG was 12.0 mmol/L, represented by the right-positioned diamond. Mean increase with a hockey game was 1.0 ± 3.2 mM.

Figure 5a. Continuous Glucose Monitor tracings taken from 8 participants during the nocturnal period (12:00AM – 6:00AM), following the hockey-type laboratory exercise protocol.

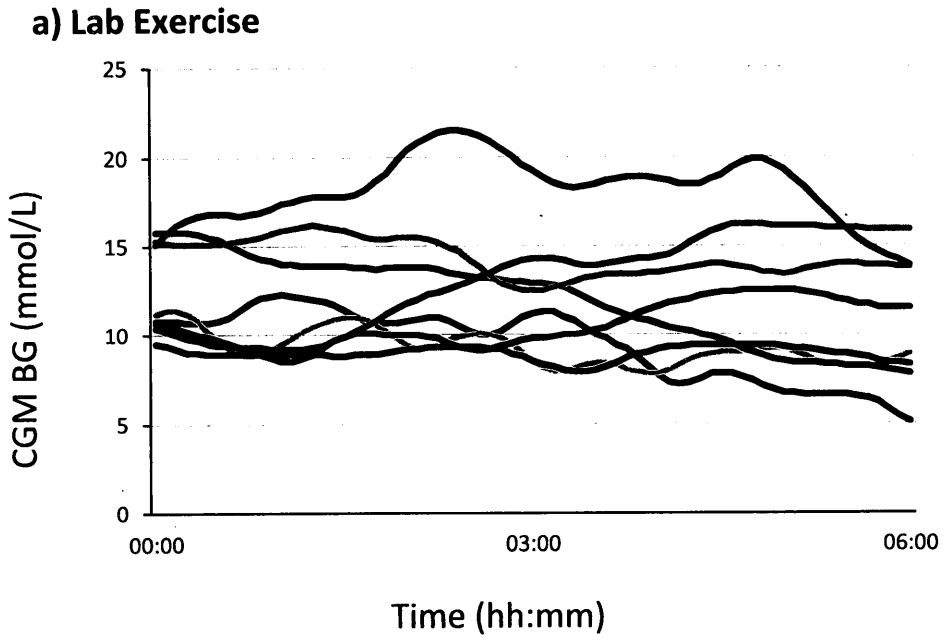


Figure 5b. Continuous Glucose Monitor tracings taken from 8 participants during the nocturnal period (12:00AM – 6:00AM), following the day of low activity

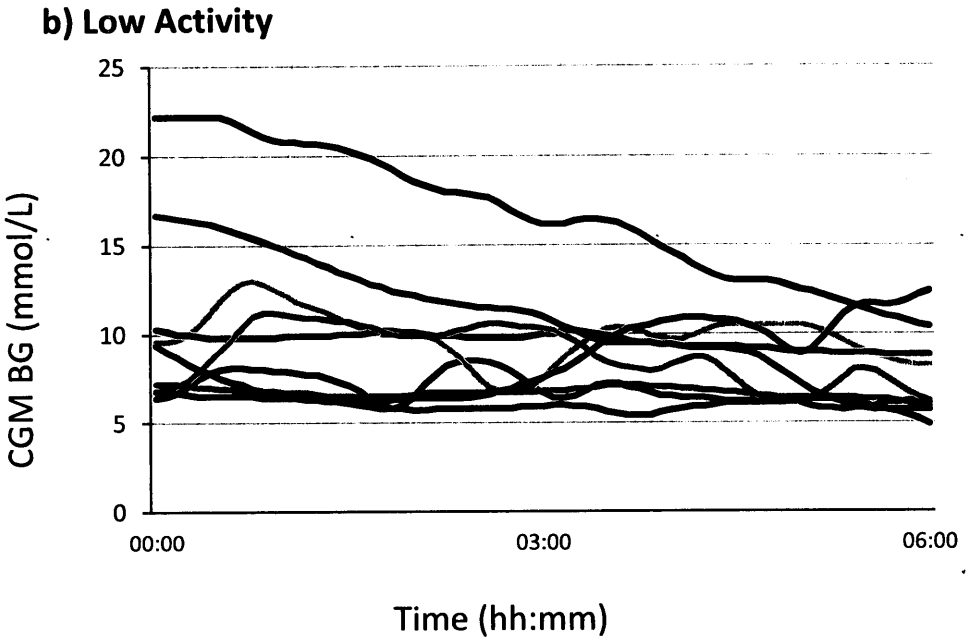


Figure 5c. Continuous Glucose Monitor tracings taken from 8 participants during the nocturnal period (12:00AM – 6:00AM), following individuals' hockey games

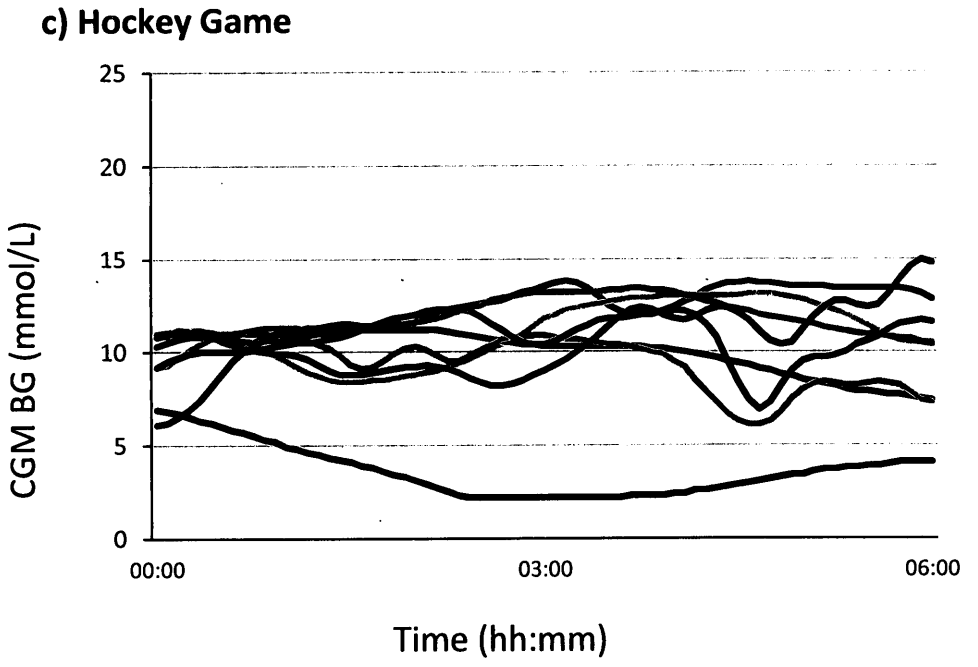
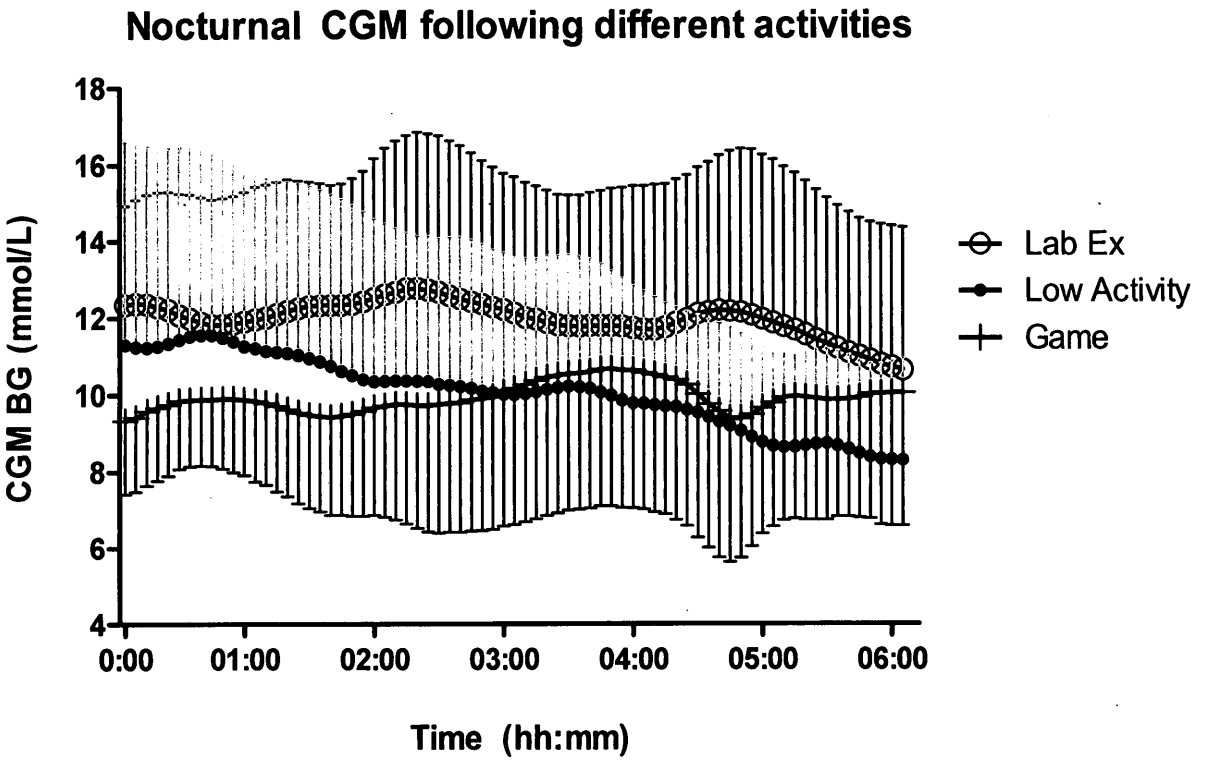
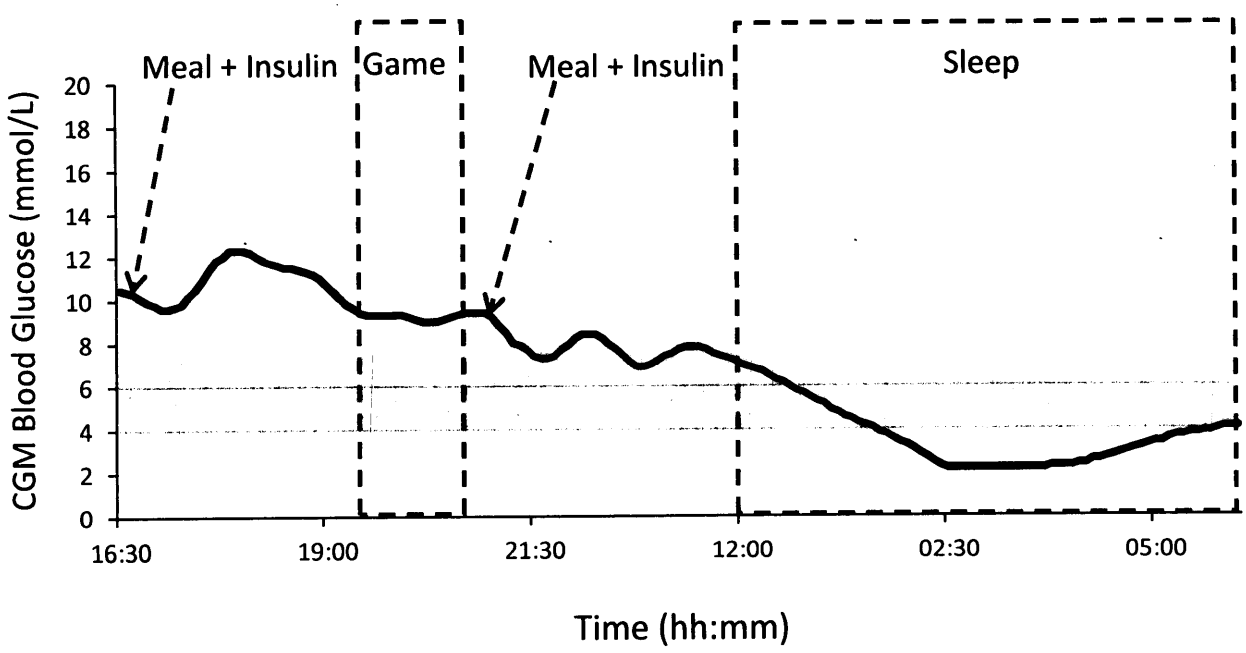


Figure 6. Mean nocturnal Blood Glucose concentration including bars of standard deviation recorded from midnight (00:00) to 6:00 AM (06:00) after participating in laboratory exercise, a low activity day, or a hockey game in the preceding day.



N=9 for lab exercise, N=9 for low activity, N=8 for game.
Lab exercise night saw a BG drop of 1.7 mmol/L (range: 12.4±2.6 to 10.7±3.7 mmol/L), AUC 4143 $mmol \cdot L^{-1} \cdot min^{-1}$. Low activity night saw a BG drop of 3.0 mmol/L (range: 11.3±5.3 to 8.3±2.7 mmol/L), AUC 3496 $mmol \cdot L^{-1} \cdot min^{-1}$. Game night saw a BG rise of 0.7 mmol/L (range: 9.3±1.9 to 10.1±3.4 mmol/L), AUC 3563 $mmol \cdot L^{-1} \cdot min^{-1}$.

Figure 7. Continuous Glucose Monitor tracing taken from an individual experiencing nocturnal hypoglycemia following a hockey game, after being in relatively good control before sleep.



This individual had a pre-game meal along with an insulin bolus, 3 hours before their hockey game. Blood glucose plateaued for the duration of the hockey game, after which time the individual tested their glucose and consumed a post-game meal and insulin bolus. Post-game glucometer results indicated false hyperglycemia (BG: 12.9 mmol/L), which resulted in excess insulin being taken. Nocturnal hypoglycemia followed, lasting 230 minutes.

Heart Rate Variability

Thirty-minute post-exercise recordings were complete for 15 individuals (8 T1Ds, 7 controls). Five individuals were not able to supply HRV in exercise recovery due to limitations in equipment availability. This included 2 individuals from the T1-a group and 3 from the Ctrl-a group. As depicted in Figure 8, group analyses revealed that while SDNN, HF, and QTc were greater in the T1-a group than the ctrl-a group, the differences were only slight and not significant (SDNN: 82.62±45.57 vs 59.11±17.80, p=0.22; HF: 43.00±18.58 vs 34.00±15.08 n.u., p=036; QTc: 432.18±8.35 vs 425.66±23.18 ms, p=0.50)

Nocturnal HRV recordings were complete for all individuals. This resulted in 20 nocturnal recordings following the hockey-type laboratory exercise protocol, 20 after the low physical activity day, and 18 after the hockey game day. One individual had prolonged artifact during the night, which resulted in one hour being excluded from analysis. To match the recording length with other study participants, HRV analysis for this individual was extended by one hour.

Of the nocturnal reports, 2nd and 3rd degree atrioventricular (AV) blocks were noted in 2 participants (5%), both whom were non-diabetic. This was in line with the findings of previous research on young elite athletes (99). Additionally, 2 individuals with T1D had EKGs which revealed single ventricular and supraventricular contractions on all three recording nights, while another with T1D revealed abnormal T-wave morphology in three leads, on all three nights. Heart rate pauses lasting greater than 1.9 seconds were noted on 5 participants' EKGs and occurred between 02:00h and 05:00h.

One Ctrl-a individual had a high prevalence of heart pauses, with 15 pauses following the laboratory exercise, 28 pauses after the low physical activity day, and 7 pauses after a hockey game. All individuals with noted abnormalities were referred to their family doctor for follow-up.

Prolonged QTc lasting 5 minutes or more on any one of the study nights was identified in twelve participants (half were from T1-a). Four of the twelve individuals experienced prolonged QTc, lasting more than 10% of the night (3 from T1-a, 1 from Ctrl-a). Of these four individuals, the prolonged QTc was noted following both exercise days for one participant, and following all 3 days for the others. When considering all incidences of prolonged QTc, there was no relationship with BG level. Relationship between nocturnal hypoglycemia and HRV could only be studied in one individual and is shown in figure 9. In this individual, correlation between BG and QTc was -0.573 and significant at the $p<0.0001$ level.

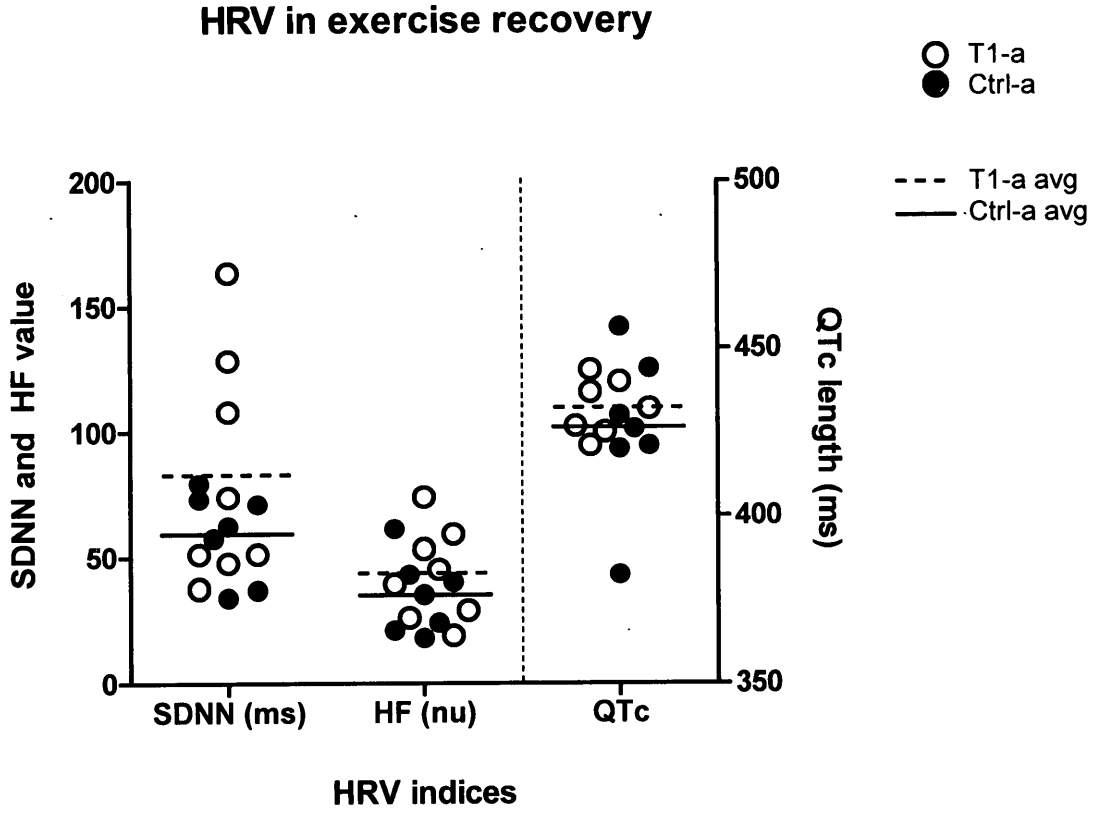
Nocturnal RR length was shorter after exercise took place in the preceding day, indicating that HR had not returned to baseline even hours after exercise had ended. Individuals' means from each night were combined across all participants, as there was no significant difference between T1-a and Ctrl-a RR values. Overall means from each night can be viewed in Figure 10.

Heart rate variability measures did not differ between the T1-a and Ctrl-a groups on any of the nights. There was a trend toward slightly improved nocturnal HRV after a low activity day in both groups, compared to when highly intense exercise took place in the preceding day. The time domain measures SDNN, RMSSD, and pNN50 were all

significantly greater after the low activity day compared to either of the exercise days ($p<0.05$ in all cases). The low activity day also displayed benefits to the HRV profile as seen by the RR and QTc measures. RR length was significantly longer after a low activity day compared to the two exercise days ($p<0.001$), indicating a lower resting heart rate on the low activity night. Slight but significant QTc elongation was evident after the lab exercise compared to the low activity day ($p<0.05$). This trend was also present between the hockey game and low activity night, however it did not reach significance ($p=0.08$).

Individual data and group means for various HRV measures are located in tables 4, 5, and 6. Figure 11 shows graphical representation of average nocturnal SDNN and RMSSD values for each night, and figure 14 shows average QTc length for each night.

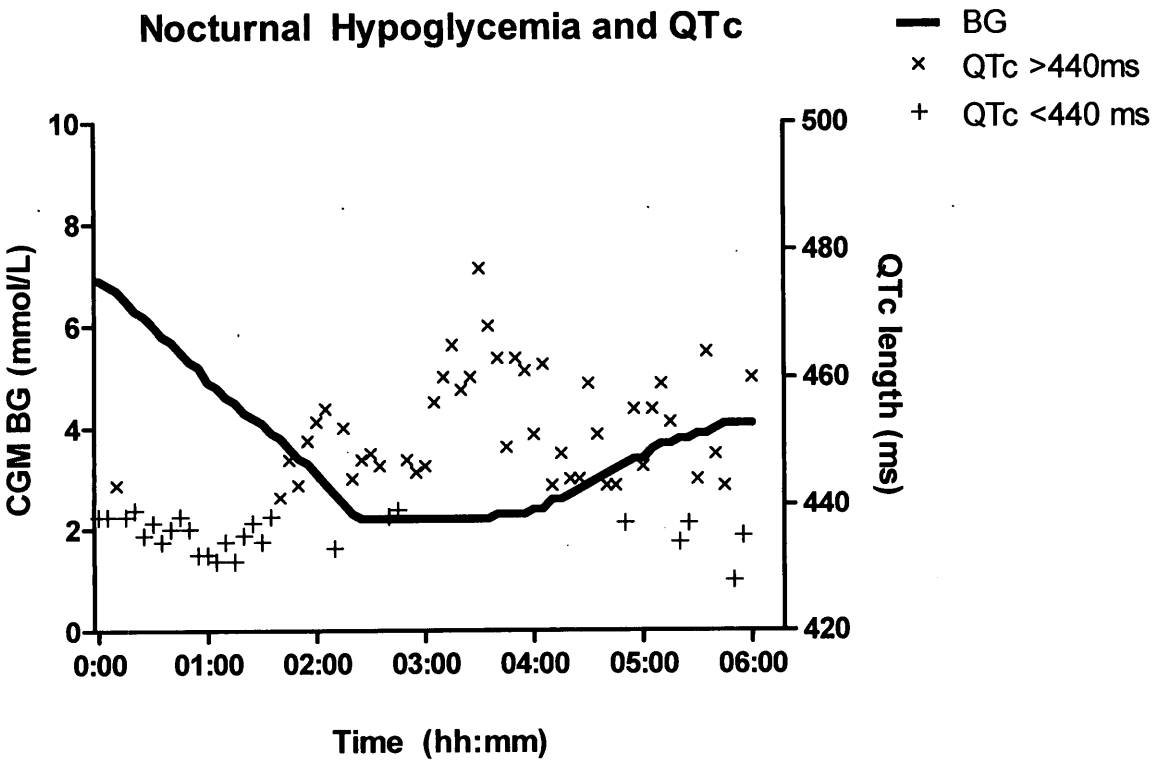
Figure 8. Heart rate variability measures averaged for each individual, over 30 minutes of exercise recovery.



Left y-axis references SDNN and HF plots, right y-axis references QTc plots. "Exercise recovery" took place after the hockey-type lab exercise protocol in the T1-a (open circles) and Ctrl-a (filled circles).

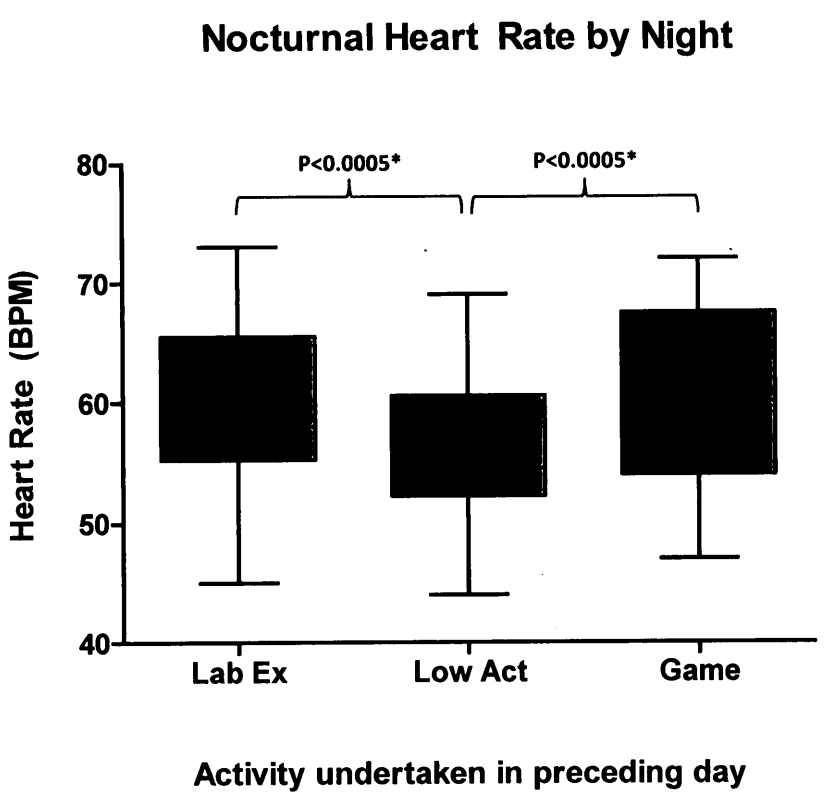
No significant differences were found between T1-a and Ctrl-a HRV in exercise recovery.

Figure 9. 6-hour tracing from a Continuous Glucose Monitor from an individual experiencing nocturnal hypoglycemia (<3.9 mmol/L), and QTc length averaged over 5-minute intervals, plotted on the right Y-axis.



QTc for much of the night preceding the incidental hypoglycemia was within a normal range (<440 ms), as indicated by + symbols. In this individual, only once hypoglycemia sets in, does QTc noticeably lengthen, indicated by X symbols. Correlation between BG and QTc on this night was significant, with an r value of -0.5727 ($p<0.0001$).

Figure 10. Median nocturnal heart rate with boxes to show the 1st and 3rd quartiles, and whiskers showing minimum and maximum values, following the hockey-type lab exercise, low activity, or game in the preceding day.



Nocturnal heart rate from individuals was significantly increased during sleep, after exercise took place in the preceding day ($p<0.0005$). Mean nocturnal HR after lab exercise, low activity, and a hockey game was 60 ± 8, 55 ± 6, and 60 ± 7 bpm, respectively. Values were 7-10 beats higher in females than males on each night ($p<0.05$), and no different between the t1-a and ctrl-a group ($p=0.69$).

Table 4. Individual and group mean RR and corrected QTc values from the 12am-6am period following the hockey-type lab exercise protocol, low activity day, and hockey game.

RR						QTc					
Lab Exercise		Low Activity		Hockey Game		Lab Exercise		Low Activity		Hockey Game	
T1-a	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**
1127.00	882.00	1174.69	912.53	1091.40	867.77	445.36	434.00	437.08	429.70	448.00	434.44
908.63	827.58	975.90	946.48	871.46	846.58	419.46	441.26	414.61	446.85	412.54	437.74
874.00	813.29	863.53	878.58	843.99	828.88	448.00	464.55	441.64	460.58	446.08	454.36
967.21	1286.62	1048.07	1307.82	1003.18	1210.65	421.67	416.51	424.63	410.26	416.60	422.08
992.00	1258.23	1088.92	1311.87	--	--	428.00	377.44	429.88	368.67	--	--
1080.03	1137.00	1138.48	1117.00	1111.89	1056.53	437.19	425.00	438.52	424.00	437.86	431.94
1066.19	1044.30	1127.33	1160.59	1002.09	1045.00	407.91	423.52	407.64	424.63	410.86	426.00
1060.62	935.86	1131.25	966.25	1103.92	891.32	407.30	412.84	406.50	413.03	420.97	422.89
1036.92	1054.25	1032.00	1342.46	960.70	1113.21	409.58	430.61	417.00	401.04	411.42	397.29
960.47	1040.81	1003.03	1024.07	963.39	913.47	434.75	415.95	423.27	403.56	439.17	419.36
1007.3	**1027.99**	**1058.32**	**1096.76**	**994.67**	**974.82**	**425.92**	**424.17**	**424.08**	**418.23**	**427.06**	**427.34**
±80.52	±166.32	±94.03	±177.05	±96.94	±135.24	±15.18	±22.36	±12.65	±25.55	±15.52	±15.51
1017.65 ± 127.62		**1077.54 ±139.38**		**984.75 ± 114.60**		**425.04 ± 18.62**		**421.15 ± 19.85**		**427.20 ± 15.06**	
		P=0.0008*		**P<0.0008***				**P<0.05****		**P=0.08**	

No significant differences existed between T1-a and Ctrl-a groups on any of the nights, when considering 6-hour average RR and QTc lengths. Similarly, no differences were noted in the nocturnal measures following the lab exercise compared to the hockey game.

*When combining the 2 groups and comparing average values based on night, RR was significantly shorter on the two nights where exercise took place in the preceding day, indicating higher mean heart rate ($p<0.0005$ for both T-tests).

**When combining the 2 groups and comparing average values based on night, QTc was significantly longer on the night following the hockey-type lab exercise protocol ($p<0.05$). Despite a greater mean difference between nocturnal QTc following low activity and the hockey game, significance was not reached due to the fewer number of participants ($p=0.08$).

Table 5. Individual and group mean HF/total and triangular index values from the 12am-6am period following the hockey-type lab exercise protocol, low activity day, and hockey game.

HF (n.u.)						Triangular Index					
Lab Exercise		Low Activity		Hockey Game		Lab Exercise		Low Activity		Hockey Game	
T1-a	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**
0.61	0.50	0.64	0.54	0.61	0.52	49.71	19.40	47.28	20.26	53.35	20.61
0.42	0.43	0.25	0.57	0.34	0.48	22.54	22.76	24.59	27.82	18.43	19.24
0.31	0.35	0.35	0.40	0.30	0.39	14.96	21.41	16.86	18.79	13.99	15.59
0.45	0.50	0.55	0.52	0.43	0.36	25.95	35.30	37.43	53.41	32.30	27.28
0.31	0.42	0.33	0.36	--	--	17.93	40.16	19.65	40.76	--	--
0.62	0.22	0.68	0.31	0.70	0.24	58.99	12.22	44.49	10.84	59.86	25.34
0.36	0.23	0.37	0.24	0.31	0.21	32.12	21.36	33.42	22.13	28.56	17.62
0.59	0.45	0.44	0.44	0.49	0.44	51.42	18.12	22.07	26.10	32.37	25.28
0.28	0.60	0.36	0.47	0.25	0.59	22.21	57.75	35.16	27.07	27.01	57.60
0.28	0.44	0.39	0.49	0.39	0.36	33.02	23.37	28.50	49.24	28.64	24.50
0.42	**0.41**	**0.44**	**0.43**	**0.43**	**0.40**	**32.89**	**27.68**	**30.94**	**29.64**	**32.72**	**25.89**
±0.14	±0.12	±0.14	±0.10	±0.15	±0.12	±15.36	±13.42	±10.37	±13.79	±14.93	±12.53
0.42 ± 0.13		**0.43 ± 0.12**		**0.41 ± 0.14**		**30.29 ± 14.29**		**30.29 ± 11.89**		**29.31 ± 13.83**	
		P=0.40	**P=0.07**					**P=0.10**	**P=0.76**		

No significant differences existed between T1-a and Ctrl-a groups on any of the nights, when considering 6-hour-averages of relative HF power and triangular index values. Furthermore, after combining the two groups, no significant differences were observed between nocturnal collections.

Table 6. Individual and group mean SDNN and pNN50 values from the 12am-6am period following the hockey-type lab exercise protocol, low activity day, and hockey game.

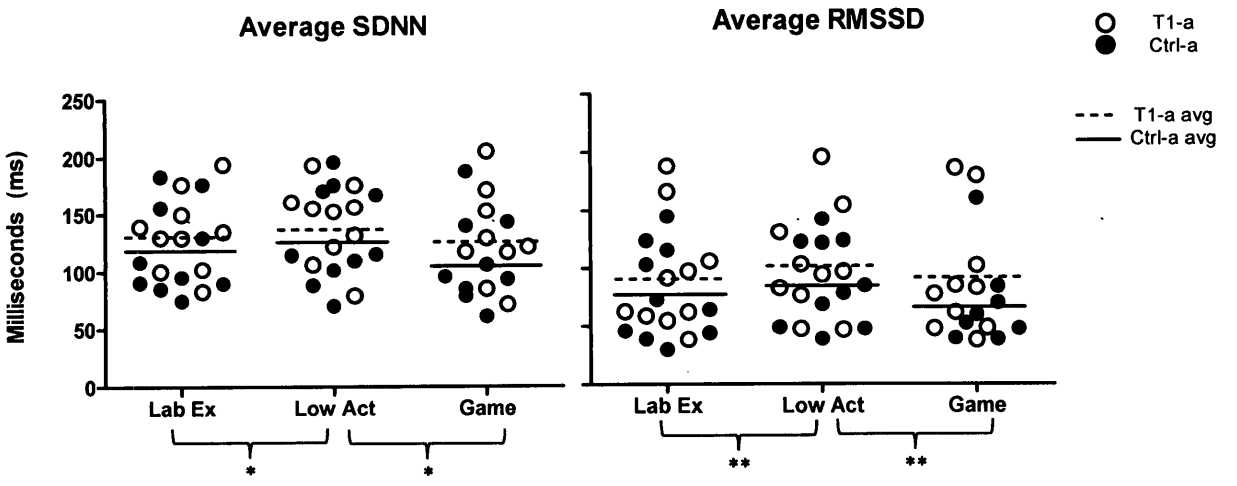
SDNN						pNN50					
Lab Exercise		Low Activity		Hockey Game		Lab Exercise		Low Activity		Hockey Game	
T1-a	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**	**T1-a**	**Ctrl-a**
176.53	85.16	192.98	88.03	171.49	78.68	69.89	32.21	70.27	40.57	70.65	26.92
100.06	89.74	131.66	114.99	85.08	85.23	31.98	15.05	44.82	45.97	1.14	22.05
82.86	74.74	79.08	69.92	71.43	61.23	6.06	14.89	13.12	24.80	5.45	15.11
129.99	176.64	155.41	195.70	152.94	139.87	41.61	63.52	58.94	66.51	41.83	43.41
129.51	155.77	106.24	170.69	--	--	19.89	65.03	10.08	64.30	--	--
193.94	95.31	175.88	101.37	204.99	143.39	69.81	13.74	70.86	11.61	71.90	32.71
138.96	90.64	152.44	114.45	117.51	93.66	54.09	5.70	56.60	22.21	44.98	7.71
149.84	108.43	156.31	109.72	129.06	105.98	52.05	22.42	40.42	28.48	49.74	22.92
102.04	183.42	160.91	167.40	116.93	187.61	31.95	69.78	43.51	58.22	24.08	71.24
134.49	129.77	121.45	175.78	121.46	95.91	27.89	42.05	43.82	52.12	43.90	15.32
133.82 ±34.16	**188.96** ±39.97	**143.24** ±33.91	**130.81** ±42.86	**130.10** ±41.41	**110.17** ±39.50	**40.52** ±20.97	**34.46** ±24.16	**45.24** ±20.81	**41.48** ±19.07	40.96 ±22.65	28.60 ±19.13
126.39 ± 36.98		**137.02 ± 38.15**		**120.14 ± 40.58**		**37.49 ± 22.24**		**43.36 ± 19.52**		**34.78 ± 21.31**	
		P<0.04*		**P<0.04***				**P<0.03****		**P<0.02****	

No significant differences existed between T1-a and Ctrl-a groups on any of the nights, when considering 6-hour average SDNN and pNN50 values. Similarly, no differences were noted in the nocturnal measures following the lab exercise compared to the hockey game.

*After combining the 2 groups and comparing average values based on night, SDNN was significantly lower on the two nights where exercise took place in the preceding day, indicating more favourable HRV on the low activity night ($p<0.04$ for both T-tests).

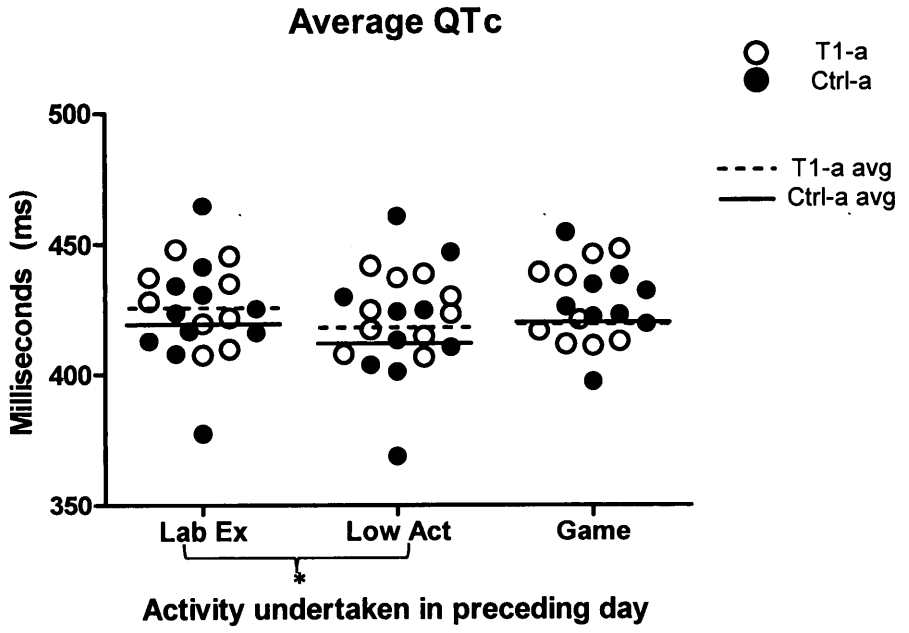
**After combining the 2 groups and comparing average values based on night, pNN50 was significantly higher on the night following a low activity day, indicating more favourable HRV in these elite athletes following a rested day ($p<0.03$ for both T-tests).

Figure 11. 6-hour nocturnal average of SDNN and RMSSD from 00:00-06:00 following the lab exercise, low activity, and hockey game days.



T1-a values are shown by open circles and Ctrl-a values are shown by closed circles. Group means are displayed by lines; broken line represents T1-a, solid line represents Ctrl-a. No significant difference was found between HRV between T1-a and Ctrl-a group. After calculating an overall mean value for each night, nocturnal SDNN and RMSSD were lower after the lab exercise and hockey game, compared to the low activity day (*$p<0.04$ for SDNN and **$p<0.02$ for RMSSD).

Figure 12. Average 12:00-6:00AM corrected QT values from each participant, following each activity, with group means represented.



There was no difference in average nocturnal QTc length between athletes with or without diabetes, indicating that heart contractility is not disadvantaged in this population with type 1 diabetes.

Mean nocturnal QTc was longer after the lab exercise compared to the low activity day (*$p<0.05$), but not between the game and low activity day ($p=0.08$). The lack of significance may be due to the fewer number of individuals who contributed HRV measures after a hockey game.

DISCUSSION 6

Blood Glucose

One of the most challenging aspects of managing T1D is controlling blood glucose. While physical activity participation is recommended for individuals with T1D and T2D, it further complicates the relationship between carbohydrate consumption and insulin injection in order to maintain balanced BG. Although recommendations are made for managing BG with physical activity participation, all physical activity is not the same. Different kinds of physical activity can have profoundly different effects on BG, as is demonstrated in this study.

This study aimed to match work done in the laboratory to that done in a regular hockey game. Nonetheless, BG response for each type of exercise bout was different. While BG tended to decrease with the laboratory exercise, hockey had a seemingly opposite effect. The type of physical activity cannot solely account for this difference since food and insulin were not controlled in this study however it certainly presents a possible explanation. It seems that the psychological excitement and release of adrenalin associated with hockey games causes an increase in BG that is not seen with similar-intensity exercise in a controlled laboratory setting. This is particularly important because guidelines which offer BG management strategies are typically based on studies with exercise occurring in a laboratory setting, rather than in the field. In order to accurately guide individuals with T1D in their glucose regulation during sports, efforts should be made to include studies performed in the field when designing activity-specific guidelines.

IHE has been implicated in preventing the decreases in BG that are seen with steady-state, moderate-intensity exercise (83). Our study demonstrated a similar absolute BG decrease of 2-3 mmol/L. Compared to the laboratory physical activity, similar high intensity bouts were experienced with hockey play, yet most individuals experienced a rise in BG from the start to the end of their game. One individual experienced a drastic drop in BG with the hockey game which skewed the data and made the mean increase less drastic. It is important to note that this individual went into their hockey game at a BG of 17.4 mmol/L and took an insulin bolus to correct for their high BG. This resulted in their BG falling to a more appropriate level of 11.2 mmol/L after their hockey game. An additional individual started their hockey game at a BG of 22.1 mmol/L and saw their levels drop to 20.88 mmol/L. While this countered the general trend of BG increasing with hockey, it is natural and healthy to see a drop in BG at such hyperglycemic states. As such, this individual contributed to the number of individuals who did not see a BG rise with hockey, and also made the mean increase less drastic.

Nocturnal BG was high in many participants, after all nights. The greatest prevalence of nocturnal hyperglycemia occurred following the hockey-type laboratory physical activity session. The drop in BG that many experienced from the laboratory exercise bout may have led to over-consumption of carbohydrate in the evening hours, and subsequent hyperglycemia with sleep. On the other hand, the low physical activity day and game day resulted in nocturnal BG values that were closest to the euglycemic range. While a seemingly positive effect of a low activity day, this was negated by the large 3 mM drop that occurred from midnight to 6:00 AM. Previous literature (100)

specifies that overnight BG change should be no more than 1.7 mM. The hockey game night was associated with the smallest change in BG, which may be a result of the work that individuals in this study have put into understanding their BG levels with hockey.

While a lot of personal experimentation goes into perfecting BG management with sport in elite athletes, the poorer BG management after the non-hockey days suggest that BG trend familiarity may be activity-specific. For example, young hockey players with T1D may work so hard at optimizing BG levels with hockey games that management is improved with that specific activity, but that activity alone. As demonstrated by AUC measurements and total BG change overnight, nocturnal BG management was improved following a hockey game, but not after similar IHE occurred in a controlled setting, or after a day in which no exercise took place.

Unfortunately, one individual experienced a prolonged hypoglycemic episode following their hockey game (Figure 7). Upon further analysis of the CGM, it appeared that the individual's BG was coming down after their pre-game meal and insulin bolus, at which point their hockey game caused their BG to plateau for its duration. Following the hockey game, this individual's glucometer suggested that their BG had increased 5 mM (to 12.9 mM) with the hockey game, and thus they took a correctional bolus to for the apparent hyperglycemia. Retrospective CGM analysis revealed a BG of 8 mmol/L; a euglycemic level which would not have provoked an insulin bolus. Hockey players with T1D are accustomed to experiencing BG rises with hockey, and it was likely because of this familiar trend that the individual in this case did not question the accuracy of their meter. The false glucometer high may have been caused by remnants of glucose on the finger that their lancet pricked – a common error when taking glucometer readings.

While efforts are made to ensure safe and accurate glucometer readings are performed, it is important that individuals with T1D be mindful of the consequences of erroneous glucometer readings. Particularly with BG measurements made around the time of physical activity, duplicate readings may be ideal.

Following the correction with a bolus of insulin, BG values decreased and led to the nocturnal hypoglycemic episode. Fortunately the hypoglycemia resolved itself, but with its relationship to DIB, that is not always the case. In one review (71), the participation in exercise combined with over-insulinization before bed was documented in several cases of DIB. This brings our attention to the importance of ensuring that the correct amount of carbohydrate and insulin is consumed following strenuous physical activities such as a hockey game, in order to reduce nocturnal hypoglycemia.

While this research was conducted on hockey players with T1D, it can be generalized to other sports. Similar sports that include intermittent high-intensity exercise in adrenalin-rising games would be expected to bring about similar trends in BG. Examples may include lacrosse, soccer, and basketball. It is interesting to note however, that the rises in BG are not commonly reported in hockey practices. As such, it is important to engage in careful BG monitoring with practices and games, to establish effective regimens. If similar rises in BG are confirmed by other studies, T1D guidelines may be modified to recommend the consumption of fewer pre-game carbohydrates, and to consume water during their games rather than sports beverages which contain glucose. In order to prevent nocturnal hypoglycemia, rises in BG that occur with games should be treated with patience. Patients should be aware that BG may naturally

decrease following the IHE, as glycogen stores are replaced. If hyperglycemia persists, corrective insulin can be taken in small amounts so that hypoglycemia does not ensue.

Heart Rate Variability

T1D and ANS dysfunction are two health ailments that are certainly related, though this complex relationship is one which needs to be further elucidated. Previous research has been inconclusive as to the first onset of sub-clinical ANS disturbances in youth with T1D. The impact of age, blood pressure, physical activity level, and BG control on HRV in T1D is highly debated. However, puberty seems to be a critical period for the development of impaired ANS function. This study demonstrated that even after the onset of puberty, hindrances were not noted in highly-active, highly-trained youth with T1D. This suggests that being physically fit may confer cardioprotective effects which delay the onset of ANS dysfunction in individuals with T1D.

It was interesting to note the high prevalence of prolonged QTc (>450 ms in boys, >460 ms in girls), occurring in 60% of the study participants. Contrary to other studies, prolonged QTc presented itself throughout the BG spectrum and was not more prevalent during hypoglycemia. While the onset of hypoglycemia did bring about prolonged QTc in one individual following their hockey game, prolonged QTc was similarly noted on another night in this individual, despite maintaining stable BG control between 7.9 and 9.4 mmol/L. An additional individual had prolonged QTc on all three nights without experiencing any hypoglycemia. On one evening, this particular

individual's BG was cycling from values as high as 12.9 to as low as 6.2 mmol/L, however they never fell within the hypo-or excessively hyperglycemic ranges.

QTc lengthening was also not biased toward those with T1D compared to those without. While the incidence of long QTc was just as high after a low physical activity day as a day where intense exercise took place, prolonged QTc has been linked to low potassium as a result of intense exercise. Therefore this study may emphasize the importance of electrolyte replacement post-exercise, particularly in those with T1D whose diagnosis puts them at increased risk for nocturnal sudden death. This may not reduce QTc lengthening after low physical activity days, but it could positively impact HRV profile (in particular QTc) after intense exercise, thereby reducing risk of sudden death.

This study highlighted the fact that HRV is not reduced in young elite athletes with T1D, compared to their non-diabetic teammates. While many studies suggest that reduced HRV can be noted at the onset of T1D diagnosis, many of them fail to mention the physical activity status of the participants. This study offers a more optimistic view for these individuals, if they are highly active or become highly trained athletes. Despite the positive impact chronic exercise seems to have on HRV of athletes with T1D, it is interesting to note that most optimal HRV profiles were noted in all athletes after the low-activity day. This may very likely be a result of over-training in elite athletes, which results in reduced HRV due to fatigue (101). This research (101) suggested that HRV should be studied in high-level athletes in order to determine when the athlete is experiencing fatigue and should reduce training, or when the athlete is well-rested and can take on more rigorous training. In light of this, the slightly improved HRV that the

present study observed after a low active day may be a result of the rest day which allowed their bodies to rest and recover. Nonetheless, it seems most accurate to conclude that a single bout of intense physical activity does not acutely reduce HRV in elite athletes with T1D, who do not possess disturbances in the autonomic nervous system.

LIMITATIONS & FUTURE DIRECTIONS 7

The specific population targeted by this study prevented a large sample from being recruited and assessed. As a result, even though there were trends of increased HRV indices in those with T1D compared to those without, the findings were not significant due to the large variability between individuals. It would be advantageous to include more individuals in this study, and have a 50% intake of females, matched on menstrual cycle phase. It will also be meaningful to complete assessment and analysis of age- and sex- matched non-active individuals with T1D.

Despite selecting a nocturnal period during sleep to assess HRV because of the risk of DIB in T1D, this introduced several possible confounds. For one, the signal was non-stationary, as the participants may have been moving around in their sleep. This could have led to less-clear and therefore false reports of various spectral frequency bands. Sleep stages and breathing rate were not accounted for, which can also introduce confounds. Because the monitors were set up at home by participants or their parents, the EKG configuration was not set up identically for all participants. This may have resulted in false differences in TP, and power measures which were not comparable from different Holter recordings. If the situation allowed, it would be ideal to have the participants visit a sleep laboratory for HRV analysis following each day. This would allow a trained individual to set up the EKG on each participant, and to control for movement during sleep. A sleep laboratory would also allow for the use of a 12-lead EKG set up on the Holter monitor, instead of the 5-lead set up that was used by this study. 12-lead set ups allow for a more thorough picture of heart rate activity to be

formulated, therefore most QTc analyses are conducted exclusively on data from 12 or more leads. In this study, a simpler 5-lead set up was used to promote simplicity of Holter monitor set up for participants, and comfort while sleeping. While many studies on healthy individuals suggest that sleep is characterized by an increase in HF power which is less obvious in those with T1D, this study did not assess HRV at rest, before sleep. If this study were repeated, it would be ideal to monitor HRV in an evening period while lying in bed, with paced breathing.

As a result of losing at least partial CGM data for 2 individuals, nocturnal hypoglycemia may have been missed. Furthermore, prolonged QTc could not be correlated to BG values in these participants. It would have been ideal to re-do the study on the individuals who lost their CGM values, so that analyses could be completed.

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Appendix A: Recruitment Poster

YORK UNIVERSITÉ UNIVERSITY

Looking for Hockey Players Aged 13-21 with Type 1 Diabetes to Participate in a Study

Do you have trouble managing your glucose levels during or after games?

Are you interested in learning more about how hockey influences your body?

In an area of many unknowns, we want to help.

What we're studying: 1) glucose levels during and after hockey games
2) post-exercise heart rate variability

What is required: Must visit an exercise lab at York University on 2 occasions

- ☆ Participants will be fitted with a glucose monitor (Medtronic iPro2) and Polar heart rate monitor to wear for 1 week, including 1 hockey game
- ☆ Lab Visit 1: maximum aerobic threshold test (VO2 max) on a treadmill
- ☆ Lab Visit 2: 60-minute exercise bout on a stationary bike
- ☆ Must wear a non-invasive Holter monitor on 3 nights to assess the effect of hockey & hockey-type activity on glucose levels and heart rate variability.

If interested, please contact Lisa at lmiadov@yorku.ca, 416-736-2100 ext 22324

lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca lmiadov@yorku.ca

YORK UNIVERSITÉ UNIVERSITY redefine THE POSSIBLE

Appendix B: Par-Q

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	1. **Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2. **Do you feel pain in your chest when you do physical activity?**
☐	☐	3. **In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4. **Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5. **Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6. **Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7. **Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better.
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing the questionnaire, should consult their doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT _____ WITNESS _____
or GUARDIAN (for participants under the age of majority)

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

Appendix C: Consent Forms

Minor Assent Form

Study Name: Assessing the impact of intermittent high-intensity exercise on subsequent glucose management and autonomic function in elite-level youth athletes with type 1 diabetes

Researchers: Dr. Michael Riddell, Dr. Veronica Jamnik
mriddell@yorku.ca, ronij@yorku.ca, 416-736-2100 ext 22324
Lisa Miadovnik, MSc Candidate, Kinesiology & Health Science, York University,
lmiadov@yorku.ca

Purpose of the Research: This will be the first study completed and published on type 1 diabetic hockey players. Because of the unique glycemic response reported in hockey players, we want to see how this type of exercise impacts later glucose management. We also want to see how hockey-type exercise impacts overnight autonomic function. Autonomic function refers to how the nervous system functions and can be measured by looking at heart rate variability. A Holter monitor is used to assess heart rate variability, which is basically the variation in the time interval between heartbeats. Since a healthy nervous system constantly changes how it stimulates the heart, a healthy person will have high heart rate variability. Our overall goal is to determine the effects that hockey and hockey-type exercise have on your blood sugar management and heart rate variability afterwards. We also want to see if blood sugar levels impact heart rate variability. This research will be presented to graduate students and professors at a seminar held at York University. We also aim to have it published in an academic journal, and presented at various professional conferences on diabetes.

What You Will Be Asked to Do in the Research: This study will require 2 trips to the Human Performance Laboratory at York University. All participants will complete an initial fitness assessment in the laboratory which will take roughly 1.5 hours. This assessment will include measurement of height, weight, skinfolds/body fat, and 2 maximal exertion cardiorespiratory tests. On this visit, each participant will be required to complete a 30-second Wingate anaerobic cycling test, and a 15-20 minute aerobic (VO_2 max) test performed on a motorized treadmill.

Participants will also be required to visit the lab on a 2nd occasion which will last 2.5-3 hours. During this visit, the participants will complete an exercise protocol on a cycle ergometer which mimics the work done by the legs during a hockey game. This protocol will involve 45 minutes of intermittent cycling, which will take place over a 60 minute time frame (to simulate a game). Participants will wear a polar heart rate strap, and a Fitmate ™ VO_2 device which will continuously measure the amount of oxygen you're using – or how hard you're working. Following the completion of this protocol, all equipment will be removed and a Holter Monitor ™ will be placed on the participant. This monitor will be worn for 30 minutes in exercise recovery, while lying down in a dark, quiet room.

The Holter Monitor ™ is a small electronic device, worn on the hip. Connected to it are 5 wires with gel pads that are stuck to the front of the chest cavity. These gel pads pick up electrical activity of the heart, and transmit the information to the monitor, where the information is recorded. This monitor is to be worn on 3 occasions, from 12:00 AM or earlier, until 6:00 AM or later. One occasion will be after completing the lab exercise protocol as mentioned above. A second occasion will be after a hockey game, and a third occasion will be after a low-activity day. Individuals will be asked to record the activities they partake in on each of these 3 days. It is important that minimal physical activity is performed on the low-activity day.

All of the above requirements apply to both participants with diabetes, and their control (non-diabetic) participants. All procedures listed above are non-invasive.

Participants with diabetes will have the additional requirement of wearing a Medtronic iPro2, blinded continuous glucose monitor (CGM), for the 3 days when they assess their nocturnal heart rate variability. Scheduling will be designed so that all 3 data collection nights (ie after the hockey game, after the lab exercise protocol, and after the low-activity day) occur within a 5-day span. While wearing the CGM, participants will also be asked to manually check their blood sugar using their own glucose monitoring device at least once every 9 hours, and record all carbohydrate consumption and insulin administrations on the provided sheets.

Risks and Discomforts: Because this strenuous exercise is known to induce hyperglycemia during exercise, participants may suffer post-exercise hypoglycemia afterward. Participants will receive coaching on how to reduce the incidence of hypoglycemia by exercise specialists such as Dr. Riddell - for example, reduce onboard insulin to zero during exercise, restrict insulin after exercise, and monitor blood glucose levels closely after exercise so that if levels start to drop, glucose can be consumed. Participants are also exposed to the typical risk of injury that is associated with exercise, including fatigue, lightheadedness, loss of consciousness, abnormal blood pressure, chest discomfort, leg gramps, nausea, and in rare cases, heart rhythm disturbances or heart attacks. Because all participants are elite athletes who are accustomed to intense exericse, the likelihood of experiencing the above side effects are quite small. Additionally, exercise will be supervised by qualified professionals to limit the risks to the participants, and a consent form will be read and signed by the dependent's parent or guardian prior to initiating the study. PAR-Q+ and if necessary, ePAR-medX evaluations will also be completed prior to exercise to insure participants are all eligible to partake in exercise, and understand the associated risks.

Benefits of the Research and Benefits to You: You will have the opportunity to participate in unique fitness testing procedures that are common to many elite and national-level athletes. You will also have access to your CGM data upon study completion, to observe the impact of hockey on your blood sugar management.

Voluntary Participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence the nature of the relationship you may have with the researchers or study staff, or the nature of your relationship with York University either now, or in the future.

Withdrawal from the Study: You can stop participating in the study at any time, for any reason, if you so decide. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, York University, or any other group associated with this project. If you choose to withdraw from the study, all associated data collected will be immediately destroyed if you choose.

Confidentiality: All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research. Data will be collected via hand-written notes, and converted into electronic documents where possible. All collected information will be coded to preserve your anonymity. Your data will be safely stored in a password-protected computer in a locked facility and only research staff will have access to this information. Confidentiality will be provided to the fullest extent possible by law. Collected data will be kept for a maximum of 5 years, after which time it will be destroyed.

Questions About the Research? If you have questions about the research in general or about your role in the study, please feel free to contact Lisa Miadovnik or the Graduate Supervisor - Dr. Michael Riddell either by telephone (listed above) or by e-mail (mriddell@yorku.ca). This research has received approval by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:
I_____, consent to participate in "Assessing the impact of intermittent high-intensity exercise on subsequent glucose management and autonomic function in elite-level youth with type 1 diabetes" conducted by Lisa Miadovnik, Supervised by Dr. Michael Riddell & Dr. Veronica Jamnik. I have understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature_____ **Date**_____
Participant

Signature_____ **Date**_____
Principal Investigator

Parental Consent Form

Study Name: Assessing the impact of intermittent high-intensity exercise on subsequent glucose management and autonomic function in elite-level youth athletes with type 1 diabetes

Researchers: Dr. Michael Riddell, Dr. Veronica Jamnik
mriddell@yorku.ca, ronij@yorku.ca, 416-736-2100 ext 22324
Lisa Miadovnik, MSc Candidate, Kinesiology & Health Science, York University,
lmiadov@yorku.ca

Purpose of the Research: This research aims to be the first-ever study completed and published on type 1 diabetic hockey players. Given the unique glycemic response reported in hockey players, we aim to assess the impact of this type of exercise on subsequent glucose management. We also aim to assess the acute effects of hockey-type exercise on nocturnal autonomic function. Autonomic function refers to how the nervous system functions and can be measured by looking at heart rate variability. A Holter monitor is used to assess heart rate variability, which is basically the variation in the time interval between heartbeats. Since a healthy nervous system constantly changes how it stimulates the heart, a healthy person will have high heart rate variability. Our overall purpose is to determine the nocturnal effects of hockey and hockey-type exercise on blood sugar management and heart rate variability, and to determine whether the two markers are correlated. This research will be presented to peers at a graduate seminar held at York University. We also aim to have it published in a scholarly journal, and presented at various professional conferences on diabetes. All participants will remain anonymous.

What You Will Be Asked to Do in the Research: This study will require 2 trips to the Human Performance Laboratory at York University. All participants will require an initial fitness assessment in the laboratory which will take roughly 1.5 hours. This assessment will include measurement of height, weight, skinfolds/body fat, and 2 maximal exertion cardiorespiratory tests. On this visit, each participant will be required to complete a 30-second Wingate anaerobic cycling test, and a 15-20 minute aerobic (VO_2 max) test performed on a motorized treadmill.

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Participants with diabetes will have the additional requirement of wearing a Medtronic iPro2, blinded continuous glucose monitor (CGM), for the 3 days when they assess their nocturnal heart rate variability. As such, scheduling will be designed such that all 3 data collection nights (ie after the hockey game, after the lab exercise protocol, and after the low-activity day) occur within a 5-day span. While wearing the CGM, participants will also be asked to manually check their blood sugar using their own glucose monitoring device at least once every 9 hours, and record all carbohydrate consumption and insulin administrations on the provided sheets.
Risks and Discomforts: Because exercise of this intensity is known to induce hyperglycemia during exercise, participants may suffer post-exercise hypoglycemia afterward. Participants will receive coaching on how to reduce the incidence of hypoglycemia by exercise specialists such as Dr. Riddell - for example, reduce onboard insulin to

zero during exercise, restrict insulin after exercise, and monitor blood glucose levels closely after exercise so that if levels start to drop, glucose can be consumed. Participants are also exposed to the typical risk of injury that is associated with exercise, including fatigue, episodes of transient lightheadedness, loss of consciousness, abnormal blood pressure, chest discomfort, leg gramps, nausea, and in rare cases, heart rhythm disturbances or heart attacks. Because all participants are elite athletes who are accustomed to intense exericse, the likelihood of experiencing the above side effects are quite small. Additionally, exercise will be supervised by qualified professionals to reduce potential risks to the participants, and a consent form will be read and signed by the dependent's parent or guardian prior to initiating the study. PAR-Q+ and if necessary, ePAR-medX evaluations will also be completed prior to exercise to insure participants are all eligible to partake in exercise, and understand the associated risks.

Benefits of the Research and Benefits to You: Participants will have the opportunity to experience unique fitness testing procedures that are common to many elite and national-level athletes. They will also have access to their CGM data upon study completion, to observe the impact of hockey on their blood sugar management. This information will be available as a result of their participation in this study.

Voluntary Participation: Participation in the study is completely voluntary and individuals may choose to stop participating at any time. The decision not to volunteer will not influence the nature of the ongoing relationship you may have with the researchers or study staff, or the nature of your relationship with York University either now, or in the future.

Withdrawal from the Study: You or your dependent can stop participating in the study at any time, for any reason, if you so decide. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, York University, or any other group associated with this project. In the event you withdraw from the study, all associated data collected will be immediately destroyed if you choose.

Confidentiality: All information supplied during the research will be held in confidence and unless consent is specifically indicated, names will not appear in any report or publication of the research. Data will be collected via hand-written notes, and converted into electronic documents where possible. All collected information will be coded to preserve your anonymity. Data will be safely stored in a password-protected computer in a locked facility and only research staff will have access to this information. Confidentiality will be provided to the fullest extent possible by law. Collected data will be kept for a maximum of 5 years, after which time it will be destroyed.

Questions About the Research? If you have questions about the research in general or about your role in the study, please feel free to contact Lisa Miadovnik or the Graduate Supervisor - Dr. Michael Riddell either by telephone (listed above) or by e-mail (mriddell@yorku.ca). This research has received approval by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:

I_____, provide my consent for my dependent to participate in "Assessing the impact of intermittent high-intensity exercise on subsequent glucose management and autonomic function in elite-level youth with type 1 diabetes" conducted by Lisa Miadovnik, Supervised by Dr. Michael Riddell & Dr. Veronica Jamnik. I have understood the nature of this project and wish my dependent to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature_____ **Date**_____
Participant

Signature_____ **Date**_____
Principal Investigator

Informed Consent Form

Study Name: Assessing the impact of intermittent high-intensity exercise on subsequent glucose management and autonomic function in elite-level youth athletes with type 1 diabetes

Researchers: Dr. Michael Riddell, Dr. Veronica Jamnik
mriddell@yorku.ca, ronij@yorku.ca, 416-736-2100 ext 22324
Lisa Miadovnik, MSc Candidate, Kinesiology & Health Science, York University,
lmiadov@yorku.ca

Purpose of the Research: This research aims to be the first-ever study completed and published on type 1 diabetic hockey players. Given the unique glycemic response reported in hockey players, we aim to assess the impact of this type of exercise on subsequent glucose management. We also aim to assess the acute effects of hockey-type exercise on nocturnal autonomic function. Autonomic function refers to how the nervous system functions and can be measured by looking at heart rate variability. A Holter monitor is used to assess heart rate variability, which is basically the variation in the time interval between heartbeats. Since a healthy nervous system constantly changes how it stimulates the heart, a healthy person will have high heart rate variability. Our overall purpose is to determine the nocturnal effects of hockey and hockey-type exercise on blood sugar management and heart rate variability, and to determine whether the two markers are correlated. This research will be presented to peers at a graduate seminar held at York University. We also aim to have it published in a scholarly journal, and presented at various professional conferences on diabetes. All participants will remain anonymous.

What You Will Be Asked to Do in the Research: This study will require 2 trips to the Human Performance Laboratory at York University. All participants will require an initial fitness assessment in the laboratory which will take roughly 1.5 hours. This assessment will include measurement of height, weight, skinfolds/body fat, and 2 maximal exertion cardiorespiratory tests. On this visit, each participant will be required to complete a 30-second Wingate anaerobic cycling test, and a 15-20 minute aerobic (VO_2 max) test performed on a motorized treadmill.

Participants will also be required to visit the lab on a 2nd occasion which will last 2.5-3 hours. During this visit, the participants will complete an exercise protocol on a cycle ergometer which mimics the work done by the legs during a hockey game. This protocol will involve 45 minutes of intermittent cycling, which will take place over a 60 minute time frame (to simulate a game). Participants will be fitted with a polar heart rate strap, and a Fitmate ™ VO_2 device which will continually assess the volume of oxygen utilized by the exercising individual. Following the completion of this protocol, individuals will be asked to lay down for 30 minutes to assess heart rate variability in recovery. This monitor will be worn for 30 minutes in exercise recovery, while lying down in a dark, quiet room.

The Holter Monitor ™ is a small electronic device, worn on the hip. Connected to it are 5 wires with gel pads that are stuck to the front of the chest cavity. These gel pads pick up electrical activity of the heart, and transmit the information to the monitor, where the information is recorded. This monitor is to be worn on 3 occasions, from 12:00 AM or earlier, until 6:00 AM or later. One occasion will be after completing the lab exercise protocol as mentioned above. A second occasion will be after a hockey game, and a third occasion will be after a low-activity day. Individuals will be asked to record the activities they partake in, on each of these 3 days. It is important that minimal physical activity is performed on the low-activity day.

All of the above requirements apply to both participants with diabetes, and their control (non-diabetic) participants. All procedures listed above are non-invasive.

Participants with diabetes will have the additional requirement of wearing a Medtronic iPro2, blinded continuous glucose monitor (CGM), for the 3 days when they assess their nocturnal heart rate variability. As such, scheduling will be designed such that all 3 data collection nights (ie after the hockey game, after the lab exercise protocol, and after the low-activity day) occur within a 5-day span. While wearing the CGM, participants will also be asked to manually check their blood sugar using their own glucose monitoring device at least once every 9 hours, and record all carbohydrate consumption and insulin administrations on the provided sheets.

Risks and Discomforts: Because exercise of this intensity is known to induce hyperglycemia during exercise, participants may suffer post-exercise hypoglycemia afterward. Participants will receive coaching on how to reduce

the incidence of hypoglycemia by exercise specialists such as Dr. Riddell - for example, reduce onboard insulin to zero during exercise, restrict insulin after exercise, and monitor blood glucose levels closely after exercise so that if levels start to drop, glucose can be consumed. Participants are also exposed to the typical risk of injury that is associated with exercise, including fatigue, episodes of transient lightheadedness, loss of consciousness, abnormal blood pressure, chest discomfort, leg gramps, nausea, and in rare cases, heart rhythm disturbances or heart attacks. Because all participants are elite athletes who are accustomed to intense exericse, the likelihood of experiencing the above side effects are quite small. Additionally, exercise will be supervised by qualified professionals to reduce potential risks to the participants, and a consent form will be read and signed by the dependent's parent or guardian prior to initiating the study. PAR-Q+ and if necessary, ePAR-medX evaluations will also be completed prior to exercise to insure participants are all eligible to partake in exercise, and understand the associated risks.

Benefits of the Research and Benefits to You: Participants will have the opportunity to experience unique fitness testing procedures that are common to many elite and national-level athletes. They will also have access to their CGM data upon study completion, to observe the impact of hockey on their blood sugar management. This information will be available as a result of their participation in this study.

Voluntary Participation: Participation in the study is completely voluntary and individuals may choose to stop participating at any time. The decision not to volunteer will not influence the nature of the ongoing relationship you may have with the researchers or study staff, or the nature of your relationship with York University either now, or in the future.

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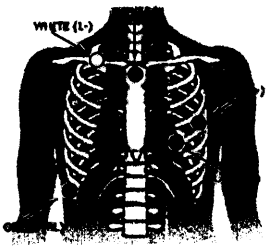
Signature_____ **Date**_____
Participant

Signature_____ **Date**_____
Principal Investigator

Appendix D: Holter Guide

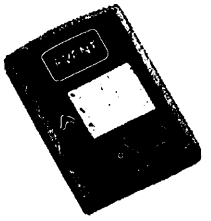
DR200 Hook-Up Guide for Holter

5-Electrode Placement

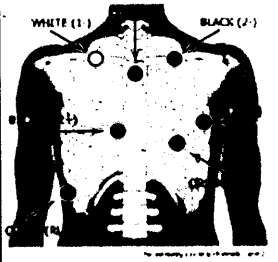


Electrodes

–	+	
RED	BROWN	Ch. 1 CM5
RED	BLACK	Ch. 2 aVF
WHITE	BLACK	Ch. 3 lead II
GREEN (Ground)		



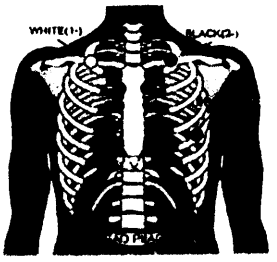
7-Electrode Placement



Electrodes

–	+	
WHITE	RED	Ch. 1 mod V5
BLACK	BROWN	Ch. 2 mod V1
BLUE	ORANGE	Ch. 3 lead III
GREEN (Ground)		

3-Electrode Placement

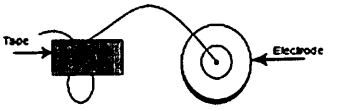


Electrodes

–	+	
BLACK	WHITE	Ch. 1 lead I
BROWN	WHITE	Ch. 2 mod V5
BROWN	BLACK	Ch. 3 mod III

Patient Preparation

- Select area over bone, avoiding muscle areas and breast tissue.
- Clean electrode sites aggressively with alcohol and use a razor to remove hair.
- Abrade electrode sites with a scrub pad or gauze. Allow sites to dry before applying electrodes.
- Firmly snap electrodes to the lead wires.
- Apply electrodes to appropriate sites. Press adhesive border firmly for consistent adhesion.
- To help alleviate tension, loop and tape lead wires down.



NorthEast Monitoring, Inc.

NEMM020 - Rev-E - English - August 2012

DR200 Quick-Start Guide for Holter

TO START RECORDER FOR HOLTER

Step 1 - Insert formatted SD Card and battery into recorder.

Step 2 - Screen will display "DR200/HE" and "NorthEast Monitoring" information." Press ENTER to continue to main menu. Erase memory if prompted to do so.

Step 3 - If desired, adjust Settings by using arrows - ▼and ▲ - to move the cursor and the ENTER button to select. Use arrows to navigate to General Settings menu and to adjust entries. Press ENTER to select and return to menu.

Step 4 - From main menu go to New Patient screen to verify or enter Patient ID. At least one character must be entered for Patient ID.

Step 5 - Use arrows and ENTER to input ID and press EVENT when finished. (Hold down ENTER button to backspace.) Recorder will now start automatically after 10 minutes or by pressing EVENT button for 3 seconds. ECG signal and quality will appear on screen.

Step 6 - To remove card after recording, gently push inward to release. Never pull card out of slot, as it may damage the recorder

***Note:** If screen displays a 15 second countdown, you will need to interrupt by pressing ENTER, ▼, ▲, and EVENT buttons, in that order.

GENERAL SETTINGS:

Contrast - Adjusts LCD screen contrast

Lead Loose - Enables/Disables "Lead Loose" error message

Event Marker - Denotes event location on ECG

Key mode - "Quiet" turns off key beeping. "Delayed" prevents accidental events by requiring patient to hold button down for several seconds to record an event

Rec Type - Switch between Holter, Event or Both recording modes.

Menu Lock - Locks settings on the recorder

To lock recorder enter "217"

To unlock the recorder enter "151"

Language - Choose from multiple languages

Hi Res - Enable/Disable high resolution recording (Holter only.)

Diary - Enable/Disable patient text diaries.

MESSAGES:

LEAD LOOSE – Occurs when the patient is not hooked up or if there is a problem with the hook up. The problem may be with an electrode, a lead, or the cable that connects the leads to the recorder. The message will continue to flash for about 10 seconds after corrected. When corrected, the ECG, then Time-of-day will appear on the screen. If you choose, you can turn this error message off via the main menu.

Battery LOW or FAILURE– Put in new battery before starting recorder.

Erase memory YES/NO - If the SD card has been used for a previous patient, you will need to erase now. If the card should not be erased as it has ECG data that you do not want to lose, you will need to remove it and put in a new formatted SD card.

SD Card errors - **SD Cards must be formatted using your LX Holter software.** Refer to your Operator's Manual for details on SD Card errors and how to format and correct.

NEMM020 - Rev-E - English - August 2012

Appendix E: Activity Log

Participant Name:

Date	Activity, Duration, Intensity
	Hockey/Lab Exercise/Low Activity
	Hockey/Lab Exercise/Low Activity
	Hockey/Lab Exercise/Low Activity

Participant: *(name)*

On the attached sheet, please record activities performed each day. These can include things like walking to school, biking, activities on lunch break, walking around a mall, etc. Include psychological stressors if they apply, especially if they occur near bed time (try to avoid these!). This sheet does not have to be overly specific or completely accurate – just do your best.

Estimate the duration of each activity and rank the intensity from 1-5 (1 being a slow walk, 5 being an intense game or activity).

Please ensure you are "low active" on the low active day – (*include date here).*

If possible, try to match your physical activities during the day on your hockey game day to the physical activities you performed on the day you visited the lab for the biking session (*date*). For example, if you were fairly inactive during the day before coming in for the hockey-type lab exercise, aim for the same on your game day.

Holter Monitor:
Instructions are included in your kit. Ensure the correct wires are attached to the correct gel pads (and not on the opposite side of the body). For the nights you wear the monitor, please aim to sleep from 11pm at the latest, until at least 6am.

If the time on the holter monitor is different from the actual time, please record both times on the attached sheet, when you start the monitor recording.

Record the time you get into bed or the time you think you will fall asleep at.
Record the time you wake up at, and so long as it is past 6am, you can turn off and remove the monitor.

To turn off the monitor, simply pull the battery out.
Throw the battery in the garbage so it is not accidentally reused the following night.
Remove the memory card so it does not get written over during the next use.

Appendix F: Hockey-type laboratory exercise protocol

Name: **Date:** **Period: 1 2 3**

Pre-Weight: **Post-Weight:** **Resistance:**

Shift	On Ice	Play – Whistle – Play	Off Ice	Bench
1	0:00	**20** – 20 – **40**	1:20	
	RPM HR/VO2			
2	3:10	**20** – 30 – **20** – 30 – **15**	5:05	
	RPM HR/VO2			
3	6:00	**30** – 20 – **10**	7:00	
	RPM HR/VO2			
4	10:10	**10** – 20 – **40**	11:20	
	RPM HR/VO2			
5	12:10	**30** – 20 – **20**	13:20	
	RPM HR/VO2			
6	15:40	**10** – 20 – **10**	16:20	
	RPM HR/VO2			
7	17:20	**20** – 40 – **20** – 40 – **20** – 10 – **10**	20:00	
	RPM HR/VO2			

Blood Sugar check!!!

Pre: Period 1 end: Period 2 end: Post:

Appendix G: Additional Recruitment

Because there was no HRV difference between the athletes with T1D compared to those without, we cannot ascertain that our measures worked properly unless we recruit a group of non-active individuals with T1D and see slightly diminished HRV as is supported by the literature. While this was not originally a part of this thesis project, it has been added in hopes of securing a publication once complete.

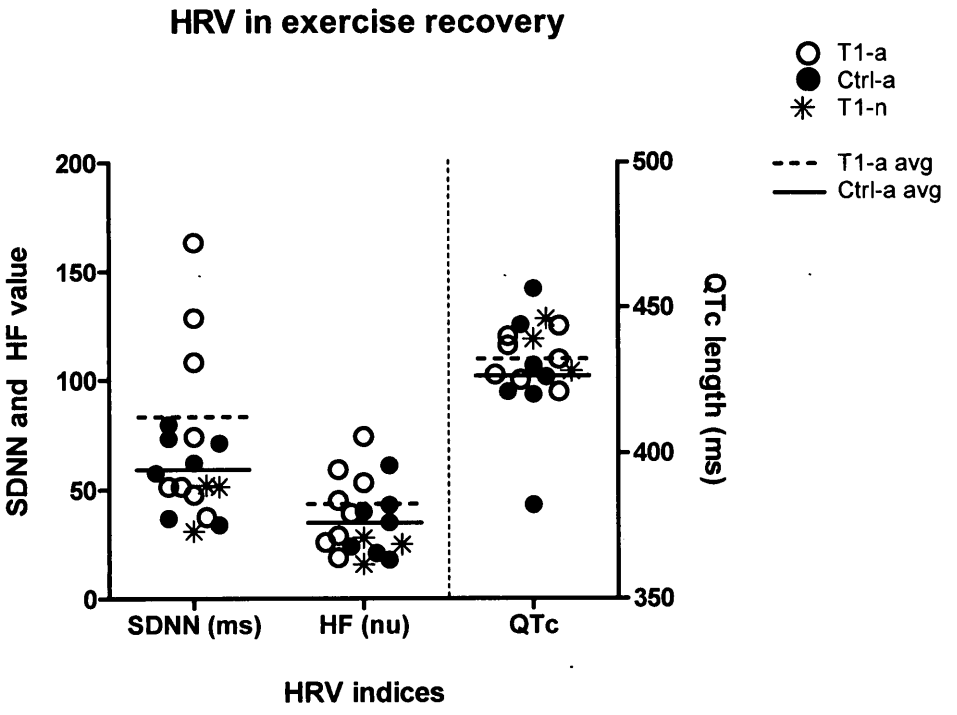
In addition to the participating hockey players with and without T1D, a group of non-athletes with T1D is being recruited ("T1-n"). These individuals are age-matched to the hockey-playing participants, and selected randomly based on being self-described as "inactive." Identical exclusion criteria were followed for this group as for the hockey-playing participants with T1D. For participation in the study, these individuals are required to wear a Medtronic iPro2 blinded CGM and wear a Holter monitor on two nights. The initial visit for these individuals includes insertion of the CGM as well as the collection of the same anthropometric measurements as taken on the hockey playing group. On this initial visit, individuals are required to have a safe and stable BG level of 5-15 mmol/L prior to completing the aerobic fitness assessment. For this group of individuals, aerobic fitness is assessed by a maximal VO_2 test, conducted in the same manner as mentioned previously. No Wingate tests will be conducted on this group.

Following completion of the VO_2 max test, individuals lay supine in a quiet, dark room while wearing the Holter monitor for 30 minutes. These individuals also wear the Holter monitors for the nocturnal collection after their VO_2 max test which was considered an "exercise day," and after a typical low activity day where no exercise was

performed. The HRV recordings after a low activity day in this group were to function as a reference group for the recordings of the elite hockey players.

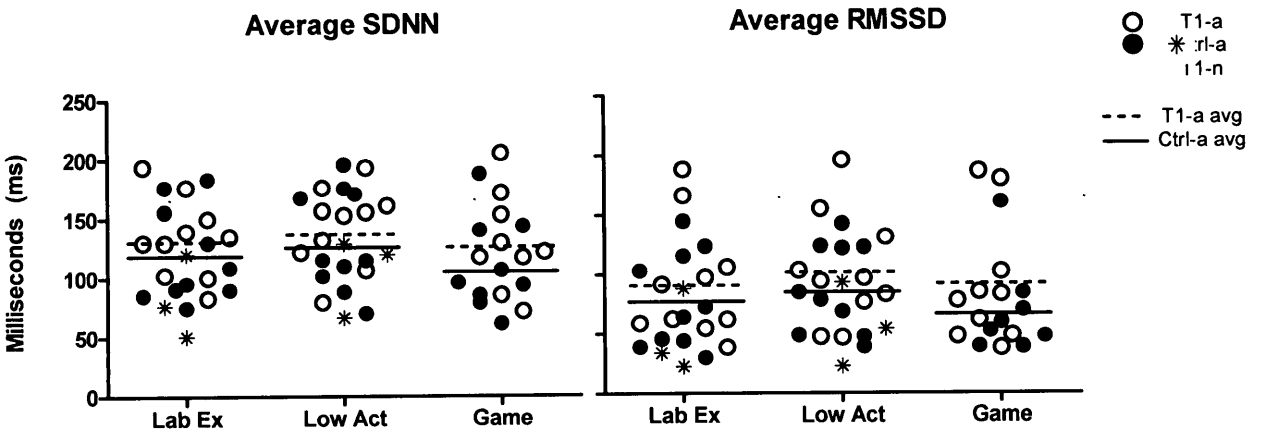
Currently, 3 individuals of this additional group have been included and their data analyzed. This includes one boy and two girls. Mean age was 16 ± 1, mean VO_2max was 38.38 ± 4.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. While these individuals did not complete the same exercise protocol as the hockey players did, their HRV was instead measured following their maximal VO_2 test. This group was also monitored after a typical low-activity day, and wore CGMs for the duration of the study. Their values have been super-imposed onto the earlier figures to show their placement with respect to the two athlete groups.

Heart rate variability measures averaged for each individual, over 30 minutes of exercise recovery, with an emphasis on the non-athlete population (T1-n), represented by asterisks.



Left y-axis references SDNN and HF plots, right y-axis references QTc plots.

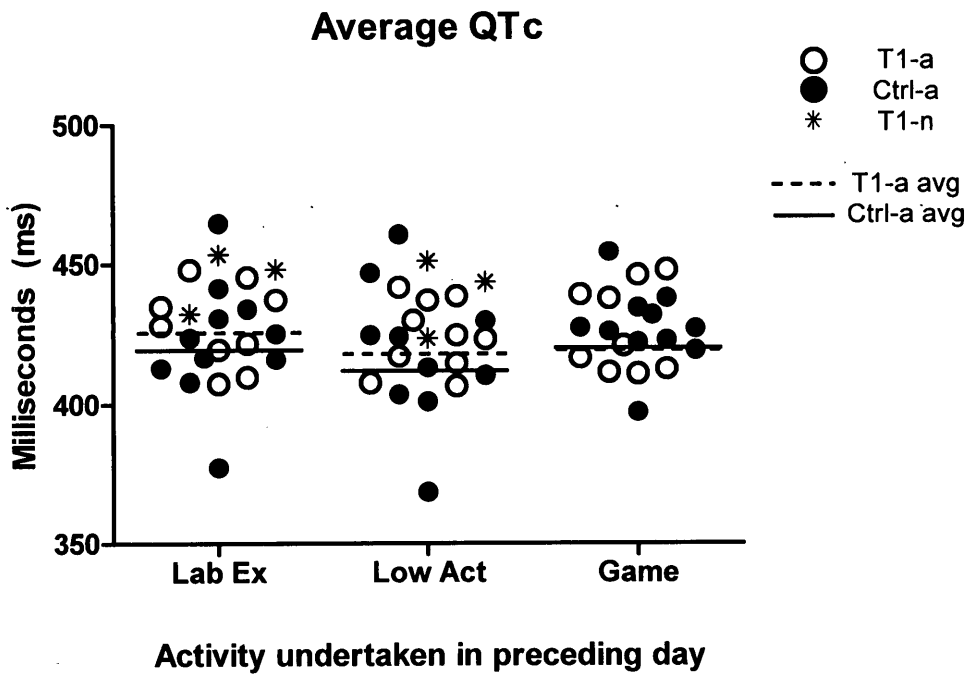
6-hour nocturnal average of SDNN and RMSSD from 00:00-06:00h following the lab exercise, low activity, and hockey game days, with values for the T1-n group added where applicable.



T1-a values are shown by open circles and Ctrl-a values are shown by closed circles. Group means are displayed by lines; broken line represents T1-a, solid line represents Ctrl-a. Values from several tested non-active youth with T1D (T1-n) are included in asterisks. No significant difference was found between HRV between T1-a and Ctrl-a group. After calculating an overall mean value for each night, nocturnal SDNN and RMSSD were lower after the lab exercise and hockey game, compared to the low activity day.

All non-active individuals with T1D (t1-n) had SDNN and RMSSD values that were below the T1-a means, indicating worsened HRV, however more individuals are needed to confirm this apparent trend.

Average 12:00-6:00AM corrected QT values from each participant, following each activity, with group means represented, and T1-n values included



There was no difference in average nocturnal QTc length between athletes with or without diabetes, however there seems to be an increase in QTc length in non-athletes with T1D. More individuals in the T1-n group are needed to confirm this trend.

Mean nocturnal QTc was longer after the lab exercise compared to the low activity day ($p<0.05$), but not between the game and low activity day ($p=0.08$). The lack of significance may be due to the fewer number of individuals who contributed HRV measures after a hockey game.

QTc length seems to be longer in the T1-n group, but this needs to be verified with more participants.

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