The relationship between exercise-induced cardiac Troponin increase and physical workload during prolonged strenuous exercise

North Sea Endurance Exercise Study (NEEDED) 2018

Magnus Bjørkavoll-Bergseth

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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1. Scientific environment

This work is part of the North Sea Endurance Exercise Study (NEEDED) Research Group, led by Professor Stein Ørn, University of Stavanger and Stavanger University Hospital. Board members of this research group are Dr. Tor Melberg, Dr. Øyvind Skadberg, PhD Øyunn Kleiven and Dr. Rolf Bergseth.

Associate members of this research group include Associate Professor Kristin Moberg Aakre, University of Bergen. The project also cooperates with the University of Stavanger, represented by Professors Kjersti Engan, Trygve Eftestøl, Bjørn Auestad, and Tomasz Wiktorski, the University of Oslo, represented by professors Knut Gjesdal and Thor Edvardsen, and the University of Radboum represented by professors Thijs M. H. Eijsvogels.

As a PhD candidate, I have been affiliated with the Department of Clinical Medicine, Faculty of Medicine, University of Bergen. As a doctoral research fellow, I received funding from the Health Authority of Western Norway (HelseVest).

2. Content

3. Acknowledgments

As a former professional cyclist, exercising has been a massive part of my daily routine. Combining medical studies and a cycling career gave me a unique insight into the effects of training on the human body. During my career, I can remember episodes of other cyclists suffering cardiac arrest. This made a massive impact on me, and feeling my heart pounding as I tried to stay in the group going uphill, I sometimes wondered if this lifestyle could be healthy. In 2013, I attended the NEEDED pilot study as a participant. Working then as a general practitioner, I recognised the participants as representative of the population I met daily.

The NEEDED study gave me a unique chance to investigate this further, and as for 2014, I was a part of the team planning and executing the 2014 data collection. Given my experience as a cyclist, I was responsible for collecting and organising files from heart rate monitors. In the first years, work was done on top of my full-time job, but in 2018, I received a PhD scholarship from the Health Authorities from Western Norway, allowing me to pursue a PhD thesis. This led to a new data collection in 2018. Ten years after I started my journey, I have finished my thesis based on these data.

I am incredibly grateful that Stein Ørn wanted me to join his research group. Working with him has allowed me to develop myself as a scientist, human and clinician. Finding a doctor so dedicated to using research in his clinical work is intriguing. Even though he is a busy man, he always finds time (even if it sometimes involves meetings at 20.00 on Sunday evenings) to push the NEEDED project further. My co-supervisor, Kristin Moberg Aakre, has given me valuable feedback to increase my academic work.

Øyvind Skadberg has been responsible for the blood samples from 2013 till this day. On top of his clinical work, he has found a way to collect, organise and quality-check all blood samples ever gathered in the NEEDED project. As a part of the NEEDED research group, he always finds a way to give meaningful and thorough feedback. I

also greatly appreciate other members of the NEEDED research group, Øyunn Kleiven, Christine Bjørkvik Erevik and Tor Melberg. I also need to thank Bjørn Auestad, Trygve Eftestøl, Kjersti Engan and Tomasz Wiktorski at the University of Stavanger for valuable feedback and help in data analysis.

The close collaboration with the North Sea Race is unique for this project. None of our studies could have been done without these people's enthusiasm and a high degree of facilitation— thanks to Siri Ommedal and Aina Andreassen. I am humbled and grateful for all the support and work done by several volunteers using their leisure time to help us collect data. A special thanks to ConocoPhillips and the Fougner Hartmann Family Trust for their financial support in funding equipment for the 2018 study.

NEEDED has been more than a work project; it is a place where I have developed myself as a researcher and a clinician. I will always look back with gratitude on the days of close work with my fellow PhD students. Thank you for meaningful discussions, many hours of data-collection and humorous coffee breaks, Christine, Ida, Vidar and Øyunn. Thank you, Øyunn Kleiven, for your dedication and thoroughness. Your hard work and attention to detail are truly appreciated and have raised the quality of my academic work. My colleagues at Opus Legesenter have shown great patience, allowing me to pursue a PhD thesis while maintaining my job as a general practitioner.

Lastly, my family has given me the courage to proceed and the support needed to manage this task. Recruited to this study by my father, Rolf Bergseth, a part of the NEEDED research group, this has indeed become a family project. My wife, Andrea, has shown more patience than could be expected. Working on a paper outside the tent on camping holidays was more a rule than an exception for some years. Thank you to my kids, Thea Rebekka, Nora Louise, Peter and Øystein, for your love and always giving me perspective on life.

4. Abbreviations

AMI - Acute Myocardial Infarction

ARVC - Arrhythmogenic Right Ventricle Dysplasia

ATP - Adenosine Triphosphate

BPM - Beats per minute

CACS – Coronary artery calcium score

CAD - Coronary Artery Disease

CCTA – Contrast-enhanced coronary CT angiography

CHD - Coronary heart disease

CMR - Cardiac magnetic resonance imaging

CO2 - Carbon Dioxide

CPET - Cardiopulmonary exercise test

CRF – Cardiorespiratory fitness

cTn - Cardiac Troponin

CV - Cardiovascular

CVD - Cardiovascular death

EACVI - European Association of Cardiovascular Imaging

ECG - Electrocardiogram

GPS - Global Positioning System

HF- Heart Failure

HFpEF - Heart failure with preserved ejection fraction

HR - Heart rate

HRV - Heart rate variability

LV - Left ventricular.

METS - Metabolic equivalents of task

MI – Myocardial infarction

MW -Myocardial work

NCD - Non-communicable diseases

NEEDED - North Sea Endurance Race Exercise Study

O2 - Oxygen

PAI - Personal activity intelligence

PO – Power output

RER – Respiratory exchange ratio.

RPP - Rate Pressure Product

RQ - Respiratory Quotient

RV - Right Ventricle

SCA - Sudden cardiac arrest

SCD – Sudden cardiac death

SD - Standard deviation

TnC - Troponin C

TnI - Troponin I

TnT - Troponin T

TPM - Tropomyosin

TUNEL - Terminal deoxynucleotidyl transferase dUTP nick end labelling

VO2 - Oxygen consumption

WHO - World Health Organization

5. List of Publications

Bjørkavoll-Bergseth M, Kleiven Ø, Auestad B, Eftestøl T, Oskal K, Nygård M, Skadberg Ø, Aakre KM, Melberg T, Gjesdal K, Ørn S. Duration of Elevated Heart Rate Is an Important Predictor of Exercise-Induced Troponin Elevation. J Am Heart Assoc. 2020 Feb 18;9(4):e014408. doi: 10.1161/JAHA.119.014408. Epub 2020 Feb 17. PMID: 32065043; PMCID: PMC7070191.

Bjørkavoll-Bergseth M, Erevik CB, Kleiven Ø, Eijsvogels TMH, Skadberg Ø, Frøysa V, Wiktorski T, Auestad B, Edvardsen T, Moberg Aakre K, Ørn S. Determinants of Interindividual Variation in Exercise-Induced Cardiac Troponin I Levels. J Am Heart Assoc. 2021 Sep 7;10(17):e021710. doi: 10.1161/JAHA.121.021710. Epub 2021 Aug 28. PMID: 34459237; PMCID: PMC8649268.

M. Bjorkavoll-Bergseth, C. Erevik, Ø. Kleiven, T. Wiktorski, B. Auestad, Ø. Skadberg, K. M. Aakre[e], T.M.H. Eijsvogels, S. Ørn. Cardiac troponin elevation is associated with physical workload in middle-aged athletes with non-obstructive coronary atherosclerosis. – Submitted –

6. Abstract in English

Background

High levels of cardiac Troponin (cTn) have been linked to increased mortality and a higher chance of undiagnosed coronary artery disease (CAD). This thesis aimed to investigate the link between exercise intensity and cTn levels, the reproducibility of exercise-induced cTn and the difference in cTn release in patients with and without coronary atherosclerosis.

Methods

Data was collected from participants before and at 3 and 24 hours after completing a 91 km mountain bike race, the North Sea Race (2013, 2014 and 2018), and a cardiopulmonary exercise test (CPET) (2018). A contrast-enhanced coronary CT angiography was done after the race. Several measurements of intensity were analysed in relationship to exercise-induced cTn, individual characteristics and the presence of atherosclerosis.

Results

In paper 1, the duration of the race with a heart rate above 150 bpm had the most significant impact in improving the explanatory value (R^2). Paper 2 found a strong correlation between the cTn values from the 2013/14, 2018 race and the CPET. In paper 3, Rate Pressure Product (RPP) and power-to-weight (watt/kg) ratio correlated with cTn levels after the race in participants with atherosclerosis but not those without.

Conclusions

The exercise duration while maintaining a heart rate above 150 bpm is strongly linked to post-exercise cTn levels in our group of participants. The exercise-induced cTn response is unique to each individual and can be replicated. The presence of atherosclerosis changes the association between exercise-induced cTn and the intensity of exercise measured by rate pressure product and power-to-weight ratio.

7. Abstract in Norwegian

Bakgrunn

Høye nivåer av kardial troponin (cTn) er knyttet til økt dødelighet og en høyere sjanse for udiagnostisert koronararteriesykdom (CAD). Denne avhandlingen hadde som mål å undersøke sammenhengen mellom treningsintensitet og cTn-nivåer, reproduserbarheten til treningsindusert cTn, og forskjellen i cTn-utskillelse hos pasienter med og uten koronar aterosklerose.

Metoder

Data ble samlet inn fra deltakere før, 3 timer og 24 timer etter å ha fullført et 91 km terrengsykkelritt, Nordsjørittet (2013, 2014 og 2018), samt en belastningstest (CPET) i 2018. Et CT-angiografi ble utført etter rittet. Flere mål på intensitet ble analysert i forhold til trening-indusert cTn, individuelle egenskaper og tilstedeværelsen av aterosklerose.

Resultater

I artikkel 1 hadde varigheten av ritt med en hjertefrekvens over 150 slag per minutt den mest signifikante effekten på forbedring av forklaringsverdien (R^2). I artikkel 2 ble det funnet en sterk korrelasjon mellom cTn-verdiene fra rittet gjennomført i 2013/14, 2018 og CPET. I artikkel 3 korrelerte produktet av blodtrykk og hjerterate (RPP) og forholdet mellom kraft og kroppsvekt (watt/kg) med cTn-nivåer etter rittet hos deltakere med aterosklerose, men ikke hos de uten.

Konklusjoner

Varigheten av trening med en hjertefrekvens over 150 slag per minutt er sterkt knyttet til cTn-nivåer etter trening i vår deltakergruppe. Den treningsinduserte cTn-responsen er unik for hver enkelt person og er reproduserbar. Tilstedeværelsen av aterosklerose endrer sammenhengen mellom trening-indusert cTn og intensiteten av trening målt ved RPP og watt/kg.

8. Introduction

Regular physical activity is essential for good health and can increase life expectancy[1]. From a public health perspective, physical activity is one of the most beneficial interventions in sedentary populations[2]. Recreational sports events have become increasingly popular as a motivational tool[3]. Still, they also attract middle-aged participants who may face a higher risk of heart problems and death during intense exercise[4,5]. To reduce these risks, it is recommended that individuals over 35 years of age who plan to engage in strenuous exercise undergo pre-participation screening[6,7]. Strenuous exercise requires more than 6 Metabolic equivalents of task (METS), where 1 MET is the resting metabolic rate when awake and sitting quietly, accounting for 3.5 ml oxygen/kg/min. The screening should include an ECG and a maximal exercise test for high-risk participants. However, some countries, such as Norway, still do not adhere to these recommendations due to serious concerns about their accuracy. Even though football players on the international level are subject to yearly cardiac screening, the football player Christian Eriksen on the national team of Denmark suffered cardiac arrest during the opening game of the European Championship 2021. In 2011, Olympic swimmer Alexander Dale Oen died after what was shown to be cardiac arrest due to an occluded coronary artery. Even highly trained and specialised centres fail to detect cardiac disease[8].

Cardiovascular disease is the leading cause of mortality worldwide[9], and a significant number of deaths during physical activity are due to myocardial ischemia in individuals over the age of 35[5,10]. Detecting coronary artery disease (CAD) early is critical, but it is challenging to develop screening protocols[11-13]. CAD is a progressive disease that causes a gradual decline in vessel function, leading to a mismatch between blood supply and oxygen, resulting in "demand" ischemia. In the early stages of CAD, only very high workloads can cause ischemia, which makes it challenging to identify using current methods. Furthermore, prolonged strenuous

exercise significantly impacts myocardial metabolism, which can influence the effects of ischemia in susceptible subjects[5].

Ischemia can be detected through physiological or pharmacological stress tests. These tests are often complex and seldom replicate the metabolic changes seen during prolonged exercise. As such, they have a low cost-benefit, mainly when applied to a low-risk population[14,15]. To find high-risk participants over 35, it is essential to consider new evaluation criterias[16]. These techniques should consider the gradual development of CAD and the impact of metabolic changes during exercise-related ischemia.

Cardiac Troponins (cTn) have become the mainstay in diagnosing myocardial infarction[17]. The distinctive rise and fall pattern typical for myocardial infarction has made the diagnostic work easier, faster, and more reliable[18]. The possibility for a rapid diagnosis or to rule out myocardial infarction as the cause of chest pain has made this biomarker a valuable tool for clinicians[19]. The development of high-sensitive assays has made it possible to detect low levels of cardiac Troponins even in the absence of myocardial infarction. Even without the distinctive rise and fall pattern, elevations of cardiac Troponins in concentrations far below those seen in myocardial infarction have been linked to increased mortality and morbidity[20,21]. Biomarkers (e.g., Troponin) play a vital role in the recent guidelines for the management of non-cardiac surgery, both as a prognostic tool and to detect cardiac damage without symptoms[22]. Troponin is also recommended as a screening tool for early prevention of heart failure in diabetic patients[23] and the cardiac follow-up of oncological patients[24].

The high diagnostic potential and availability make the measurement of cTn a candidate for detecting CAD in asymptomatic individuals participating in strenuous exercise. For over 20 years, cTn has been known to increase after exercise, initially thought to be a harmful effect but now considered a primarily physiological phenomenon[25,26]. Our current knowledge about the potential mechanisms behind

exercise-induced cTn is limited. As there are no defined limits for exercise-induced cTn, it is difficult to determine whether an increase in cTn levels results from a physiological or pathological response. This lack of clarity may lead to unnecessary hospitalisation and evaluations for patients with a benign cTn increase[27]. By better understanding the mechanisms and factors that control exercise-induced cTn, we can distinguish between pathological and physiological cTn-release and potentially use cTn as a diagnostic tool.

Increased cTn after prolonged strenuous exercise has been linked to coronary artery disease[28,29]. In a mass sports event including 1000 participants, several predictors of cTn were evaluated; interestingly, only baseline blood pressure and race duration were significant ($p<0.0001$), but the explanatory value was low[30].

Systolic blood pressure and race time represent two separate physiological variables: total work measured as race time and cardiac work measured as systolic blood pressure. Our leading theory in this thesis is to investigate whether a more direct and continuous measurement of muscular work and measurement of cardiac work using surrogate markers (e.g., blood pressure) can predict physiological cTn increase.

8.1 What are Troponins?

8.1.1 Molecular basis and structure

Troponin is an intracellular protein and consists of three subunits known as Troponin I (TnI), T (TnT), and C (TnC). Cardiac-specific isoforms exist for I and T, named cardiac Troponin I and T (cTnI and cTnT). In cardiomyocytes, they form a complex bound to Tropomyosin (TPM), but some cTn molecules are also loosely bound in the cytosol[31,32]. TPM is together with the actin, part of thin filaments which, together with thick filaments, forms the contractible unit of striated muscle cells (cardiac and skeletal). Each Troponin subunit has specific regulatory functions in the contraction-relaxation of myofilaments. TnI is an inhibitory subunit preventing muscle contraction in the absence of Calcium. TnT is a regulatory subunit, anchoring the Troponin complex to thin filaments, and TnC is the calcium-binding subunit. When an action potential reaches the cardiomyocyte, calcium channels in the sarcoplasmic reticulum open, releasing calcium ions into the sarcoplasm. Calcium binds to TnC, changing the form of the cTn protein complex. This exposes myosin binding sites on the actin filaments, enabling the myosin head to interact with actin, leading to muscle contraction[33].

TnC exists in only one isoform identical in amino acid structure in cardiac and skeletal muscle and is, therefore, not suitable as a diagnostic biomarker. TnT and TnI exist in three different isoforms depending on location in either slow skeletal muscle, fast skeletal muscle, or cardiac muscle cells. Differences between the isoforms are mainly located in the N-terminal extension[34], and the cardiac isoforms differ in amino acid sequence from the skeletal isoform by approximately 40-60%.[33]

The genes encoding TnT are in 1q32 (cardiac), 19q13,4 (slow skeletal muscle), and 11p15.5 (fast skeletal muscle). The molecular weight of cardiac TnT is about 37 kDa[34]. TnI has a molecular weight of approximately 24 kDa, and the genes are found in 1q31,3 (slow skeletal muscle), 11p15,5 (fast skeletal muscle), and 19q13,4 (cardiac muscle)[35]. It is believed that cTnT and cTnI evolved from a TnI-like ancestor gene[35].

8.1.2 Measurement and Clinical Assays

Monoclonal antibodies are used to detect both cTnI and cTnT in blood samples. Both cTnI and cTnT can be affected by various factors such as proteolytic degradation, phosphorylation, heparin, heterophile and human antimouse antibodies, cTn-specific antibodies, and the formation of macro-Troponins[36]. Because cTnI assays use antibodies specific to varying epitopes of circulating cTnI, measurements of cTnI are different between different manufacturers. This makes the standardisation of measurements difficult[37]. The high-sensitive cTnT assay from Roche Diagnostics uses antibodies directed to the central region of cTnT[38]. It has been demonstrated that the Roche high-sensitive cTnT assay has cross-reactivity with skeletal muscle. This can lead to incorrect positive results in skeletal muscle disease or rhabdomyolysis cases. If this is suspected, it is advised to use an alternative cTnI assay for testing[39]. The assay is not affected by physical activity.

8.1.3 Release mechanisms of cTn.

Circulating cTn can be found in the bloodstream through various means; the most common use of cTn release is the diagnosis of necrotic cell death during an acute myocardial infarction (AMI). A sudden increase in calcium levels leads to increased contraction and consumption of ATP, causing necrosis and the release of both cTnI and other cell components. Due to the high levels of calcium found in cardiomyocytes, they are more prone to this Ca2+ paradox or the oxygen paradox[40].

Another way that the myocardium releases molecules is through the creation of cardiomyocyte "blebs", first described in the 1980s. When ATP levels drop, it causes the cells to swell internally, leading to oedema. However, because of the anchoring points for dystrophin in the sarcomeres, blebs are formed instead of swelling, which makes the cell membrane more fragile but keeps it from breaking.[41]. Contractility reoccurs when the tissue is reoxygenated, leading cells to die. This results in contraction band necrosis and the subsequent release of cTn from the damaged cells[42].

Controlled cell death, apoptosis, is a mechanism where the cell, in a controlled manner, “shuts down” in response to different stressors. In opposition to necrosis, apoptosis does not result in cell swelling and rupture of membranes, but rather cell shrinkage and formation of apoptotic bodies that are rapidly engulfed by phagocytic cells[43]. In this situation, cTnI should not be released to the bloodstream since it is expected that all the intracellular content is “eaten” by surrounding cells and immune cells. Nevertheless, in their study from 2017, Weil et al. demonstrate a rise in cTn after a period of ischemia. Using TUNEL labelling, the researchers found markers of apoptosis but no sign of necrosis[44].

Necroptosis is best described as programmed necrosis[45], resulting in cardiomyocyte lyses and the possible leakage of larger intracellular content[42]. In chronically ill patients with and without cardiac disease, cTn is elevated[46]. There is a debate regarding whether this is caused by cell damage or programmed cell death. It is uncertain if cardiac stress can trigger these pathways and result in the release of cTn.

Cardiomyocytes can exchange large molecules across the cytoplasmic membrane without inducing cell death. Cells do not burst if holes are created in their membrane, but due to a Ca2+-dependent cell wound repair system, holes as large as ten μm^2 can be fixed in seconds[42]. Different impairments of the cell wound repair system lead to dystrophies due to accumulated muscle injury caused by contraction[42]. It has been shown that mice with one kind of cell wound impairment (dysferlin) have increased cTn levels further elevated by exercise.[47] If this is the case in humans is not proven, but it has been proven that cardiomyocytes in ischaemic conditions can expel large amounts of intracellular proteins without cell death[48,49] and thus can give an explanation to cTn elevations seen in different clinical settings in the absence of cell death and ischemia.

8.1.4 Degradation and Elimination

Detectable cTn can be bound to structural components of the myocardium or exist in smaller fragments in the cytoplasm[32]. In the cytosol, cTn is degraded by calpase and

μ-calpain, but around 5% of the total cTn content is thought to exist in this loosely bound state that can rapidly be released to the circulation[31]. This early rise is seen in the early stages after an AMI and in situations that represent reversible cell injury due to increased cell membrane permeability[50]. Structural-bound cTn has a stronger linkage and depends on degradation from the cell's myoskeleton to be released and detected. This slow process reflects more extensive cell damage, as seen in irreversible cell damage[31].

After cTn has entered the circulation, it is eliminated via renal clearance and cellular uptake in the liver. Due to high levels of cTn in patients with end-stage kidney disease, renal clearance was considered the main elimination pathway.[51] This is challenged by a recent study where radioactively labelled cTn was injected into the bloodstream of rats. At high concentrations, uptake was most increased in the liver, whereas kidney clearance seemed to dominate at lower concentrations.[52] The initial clearance of cTn has a half-life of approximately 0.5 hours. After AMI, where we typically see high levels of cTn, extra-renal clearance and intracellular degradation dominate, but elimination seems more kidney-dependent at low levels.

8.1.5 Differences in cTn measurements in different clinical settings

When the membrane is damaged, as occurs in necrosis, the release of cTn is immediate. But, because cTn has an absolute affinity to the thin filaments, the release is not as fast as with other cardiac injury biomarkers. This slow washout makes for a delayed and sustained elevation of cTn, especially in large transmural infarctions.[40]

Because Troponin is subject to proteolysis after being released from cardiomyocytes, there is a difference in the size of molecules dependent on the clinical situation. After an MI, Troponin is found as a part of T-I-C complexes, unbound cTnI, and T molecules and fragments of these. For cTnT, 29 kDa and 15-20 kDa are found after a transmural infarction, but following a marathon run, only smaller pieces, 15-20 kDa, are found[53]. The same type of study has yet to be done for cTnI. Assays for cTnI and

cTnT are directed to epitopes in the stable region of cTn, and despite proteolysis, cTnT and I can be measured precisely and specifically.

Differences in release kinetics after exercise and myocardial infarction. Levels of cTn are lower and reach a maximum earlier after exercise than after myocardial infarction. Whereas kinetics after an MI are well described, the kinetics after exercise are only general and based on several observations. The impact of duration, intensity, and exercise mode is not considered due to the heterogeneity in study methods. After a myocardial infarction, concentrations of cTn reach a maximum of 10-12 hours after hospital admission. The peak is achieved earlier after exercise. For cTnT, a peak can be found 3-4 hours after cessation of exercise, whereas cTnI reaches a peak value of 4-6 hours after exercise[54]. cTn values return to normal quicker after exercise compared to myocardial infarction. Whereas concentrations after MI can remain elevated for up to 10 days, post-exercise values usually return to normal after 24-48 hours[54]. Elevated levels 24 hours after exercise have been associated with an increased risk of CAD[55].

8.1.6 Prognostic significance

A strong relationship exists between resting cTn concentrations and the risk of adverse health outcomes[20,46,56]. CTnI might have a stronger association with cardiovascular events and cTnT with all-cause mortality[32]. Recently, cTn has also been established as a biomarker for risk stratification in non-cardiac surgery[57]. CTn serve both as a prognostic marker and can be used to screen for perioperative myocardial infarction[57]. Troponins have also proven to have prognostic potential in patients undergoing cardiac transplant[58], adults with congenital heart disease[59], heart failure[60,61] and infection[62,63], even in patients with cerebral stroke[64]. Still, there is no consensus on how to use cTn as a prognostic marker in chronic diseases[65]. Some researchers advocate that a gender-specific approach on cTn could be used to screen for cardiac disease in women, as these are often underdiagnosed regarding cardiac disease.[66]

8.1.7 Troponins and Exercise

The evolving work in using cardiac Troponins as a prognostic biomarker makes it hard to interpret exercise-induced cTn. If elevated levels of cTn in the general population are linked to a worse prognosis, what about exercise-induced cTn? CTn levels rise after exercise, but as this usually has been described in a healthy cohort with low risk of cardiac disease and without any findings of cardiac damage, this has been considered a merely physiological phenomenon[32]. However, recent reports highlight the possibility that exercise-induced cTn has the potential as a prognostic[29] and diagnostic marker[28,55]. A recent study finds a small but significant reduction of cTnI after a 12-week structured training program in patients with heart failure with reduced ejection fraction.[67] The study participants showed improved functional capacity, indicating a potential use of cTnI as a prognostic follow-up of cardiac patients[67]. A similar finding has been made for cTnT; these data showed that 12 weeks of training reduced cTnT, which was also significantly reduced after 1 year[68]. Several studies have tried establishing predictors of exercise-induced cTn, including age, blood pressure, and training experience. There is an established relationship between the duration and intensity of exercise and post-exercise cTn[69]; this relationship is related to personal characteristics and may be influenced by training status[69]. However, the heterogenicity between studies and findings makes it hard to conclude. Much research is still needed to establish exercise-induced cTn as a diagnostic marker in an exercise setting.

8.2 Exercise

The ability to move and be physically active is one of the ground principles of being a human. There are few areas in science where evidence and consensus are as broad as the benefits of physical activity. Despite this, from a global perspective, over one in four adults and over 80% of adolescents fail to meet the recommended physical activity levels proposed by the World Health Organization (WHO). Exercise is a structured activity designed to develop and preserve physical fitness[70]. Broadly, it can

be divided into endurance, muscle strengthening, bone strength, and balance. A structured exercise program should include all the modalities mentioned above. Current recommendations for adults, as proposed by the WHO, are 150-300 minutes of moderate-intensity activity a week. This should include two days a week of muscle-strengthening activities and three days of multicomponent training for balance and strength.[71]

8.2.1 Basic Exercise Physiology

When we exercise, our muscles use ATP - a high-energy bond - to contract. Energy is released when ATP splits. This allows actin and myosin to interact and cause muscle contraction. ATP can be made from glucose or fatty acids. If enough oxygen is present (aerobic pathway), one glucose molecule can produce 36 ATP molecules. Without oxygen (anaerobic pathway), one glucose molecule can only produce 3 ATP molecules. The beating heart delivers oxygen to the muscles, making it essential for proper muscle function during exercise[72].

During intense exercise, the heart can increase its cardiac output from 5L/min at rest to 25-35L/min. The skeletal muscle requires approximately 84% of this blood volume during exercise. Aerobic glycolysis is the most efficient energy source at the beginning of movement, which couples ATP production with oxygen consumption. As the demand from exercising muscle increases, oxygen transport becomes insufficient, and energy must come from the anaerobic pathway. Above this anaerobic threshold, lactic acid accumulates due to oxygen debt. This oxygen debt is repaid during the recovery phase of exercise. During intense exercise, oxygen uptake eventually reaches a point where it plateaus. This is the maximum amount of oxygen your body can consume during exercise[72]. It is called peak VO_2 and is a crucial factor for optimal performance. Peak VO_2 reflects the combined function of muscle metabolism, the cardiovascular system, and pulmonary ventilation. Any limitations in these systems can result in a decrease in peak oxygen consumption. The Fick equation describes this concept.

$$VO_2 = CO\ x\ C(a-v)O_2$$

A clear understanding of the Fick equation is essential for correctly interpreting cardiovascular exercise test results. During rest, both fat and glucose are broken down to generate ATP. The ratio between the metabolic production of carbon dioxide (CO_2) and the uptake of oxygen (O_2) is called the respiratory exchange ratio (RER). This is calculated by dividing carbon dioxide output (VCO_2) by oxygen uptake (VO_2), with the ratio established by comparing exhaled gases to room air[73]. As demand increases, anaerobic glycolysis of carbohydrates and the accumulation of lactic acid occur. This lactic acid is buffered by bicarbonate and increases the production of CO2 compared to O2, resulting in an RER greater than 1.0. An RER greater than 1.10 or 1.15 indicates an effort well above the ventilatory threshold[72].

Proper ventilation is essential for inhaling oxygen and exhaling carbon dioxide. During physical activity, ventilation can increase from 6 to 100 litres per minute. This increase in ventilation is triggered by chemoreceptors that are sensitive to carbon dioxide and lower pH levels caused by the buildup of lactic acid. More alveoli are utilised during exercise, and capillary blood flow improves, making the gas exchange more effective. Enhancing ventilation-perfusion also helps with circulation by ensuring adequate venous return and filling of the right ventricle. Ventilation and blood oxygen enrichment are not limiting factors to exercise in healthy individuals[72].

8.2.2 Benefits of regular exercise

According to the 2020 guidelines from the WHO, physical activity is beneficial for almost everyone, regardless of gender, age, disabilities, chronic illnesses, or pregnancy[71]. An exception exists for some cardiac diseases. Physical activity is a known way to prevent and manage non-communicable diseases such as cardiovascular disease, cancer, and type 2 diabetes[71]. Individuals who meet the recommended physical activity levels have a reduced risk of premature death by 20-30%. By being more physically active, 7-8% of all cases of CVD, dementia, and depression and approximately 5% of all type 2 diabetes cases could have been

prevented[74]. Physical activity is also beneficial for mental health and cognitive functions[75,76], which can reduce the onset of dementia and maintain overall well-being[71].

8.2.3 Risk associated with regular exercise

There are few valid reasons to discourage individuals from engaging in physical activity. The advantages outweigh the potential disadvantages, as the training is based on the individual's abilities, reducing the risk of overexertion.[71]. Regular exercise boosts strength and endurance by adapting to increased stress levels. Still, it can also temporarily raise the risk of injury and cardiovascular issues. This paradox of exercise is well-known, but despite these risks, consistent physical activity is linked to a reduced risk of mortality.[77]

Most data regarding adverse incidents during exercise is gathered from participants in large-scale sporting events. A medical encounter is usually defined as any issue reported to the medical staff during or up to 24 hours after the event[78]. These problems range from minor to life-threatening events like sudden death or cardiac arrest. Generally, medical encounters are more common in events that last longer and have harsher weather conditions.[78,79]

Many mountain bikers experience overuse injuries, with reports ranging from 45-90%. These injuries are often caused by friction between the body and equipment during exercise[80]. The risk of injury during mountain biking is 16.8 per 1000 hours of exposure, with cross-country biking resulting in 0.4 injuries per 100 hours of riding[80]. Most injuries occur in males between the ages of 20 and 39[81]. Although the numbers are relatively low, the increasing popularity of cycling has led to higher rates of injury, including more severe injuries like spinal cord injuries[82,83]. In a study from Kristiansand, Norway, 69% of patients admitted to the hospital for bicycle trauma had minor or moderate injuries. Of the 224 patients, 22 were classified as severe, with head and neck injuries being the primary cause[84].

Running is increasingly popular, but acute running injuries are rare, usually limited to muscular injuries or skin lesions. The most common running injuries are overuse injuries (80%), where the knee is the predominant site, with an incidence from 7.2% to 50%. Injuries in the lower extremities range from 19.4% to 79.3%[85]. Prior injuries are a risk factor for new injuries[86].

Among Elite Athletes, asthma was found in 16.5% of studies in 9 European countries[87]. Asthma was more prevalent in athletes than in the general population and more common in endurance athletes. One mechanism is thought to be increased mechanical stress of the airways[87].

8.2.4 Training

Exercise training is a structured program of physical activity that aims to improve physical fitness or athletic ability[70]. It involves performing specific exercises and activities that target muscle groups or physical systems. The type and frequency of exercise in a training program vary depending on individual goals and needs. Examples include resistance training, cardiovascular exercise, and flexibility training. Proper exercise training should be personalised to minimise the risk of adverse events. All cardiac patients benefit from training and physical activity, but conflicting evidence exists on the best exercise. While high-intensity training yields the best results in improving fitness, some studies find an increased risk of adverse events with increasing intensity and duration[88].

8.2.5 Competitions

The competitive exercise involves physical challenges that test participants' athletic abilities. These competitions come in various forms, and individuals can compete at their level for higher accomplishments. According to the WHO, competition is a motivational factor that can increase physical activity[71]. The type of exercise and athletic abilities being tested will determine the specific nature of the competition. Competitive training aims to push participants to their limits, allowing them to showcase their physical fitness, endurance, and athletic ability. However, it's

important to note that pushing boundaries can increase the risk of adverse effects, especially for individuals with established heart disease who are at the highest risk of sudden cardiac death (SCD).[89]

8.3 Cardiac response to exercise

8.3.1 Physiological response

When we begin to exercise, our brain triggers movement by activating the vasomotor centre and the sympathetic nervous system. While resting, there is minimal blood flow through muscle capillaries, but as we exercise and oxygen levels decrease, these capillaries quickly open. Adenosine, a vasodilator, is also released at the start of exercise due to the lack of oxygen. Local vasodilators continue to promote vasodilation throughout training, activating the sympathetic nervous system and increasing heart rate and contractility. Systemic circulation releases noradrenaline and adrenaline, which act as vasoconstrictors in all tissues except those overwhelmed by local vasodilators[72]. This diverts blood to the working muscles and can increase blood flow to the muscles by up to 2 litres per minute[72]. Constriction of the muscular venous wall increases systemic venous filling pressure, increasing venous return to the heart and cardiac output.

The cardiac output of the heart increases when both stroke volume and heart rate increase. Intrinsic and extrinsic forces regulate these two factors. Intrinsic forces operate through the Frank-Starling relationship, which involves increased myocardial fibre stretch during diastole, increasing contractile force and stroke volume to match venous return. Extrinsic forces, such as the sympathetic nervous system, can also increase contractile force independently of myocardial fibre tension[72]. If the rise in stroke volume is insufficient, the heart rate will increase through the action of sympathetic nerve fibres on the sinoatrial node. However, higher heart rates can reduce ventricular filling during diastole, leading to a decrease in efficiency.

The heart can adjust to increased demand on the cardiovascular system through repeated exposure, resulting in increased size and performance. This is commonly known as the "athlete's heart," which refers to several changes that improve the heart's ability to deliver oxygen to working muscles[72]. These changes include increased left and right ventricular and left atrial size while maintaining diastolic function. The most significant factor in this remodelling is left ventricular (LV) wall stress, or the force acting against myocardial cells. When preload and/or afterload increase, LV wall thickness must increase to normalise wall stress, as described by the Laplace law;

$$LV\ wall\ stress = (LV\ pressure\ \times radius)(2\ \times LW\ wall\ thickness)$$

Exercise training affects humoral factors and hormones that influence the cardiac myocyte. The physiological adaptation is typically a balanced remodelling where LV cavity size matches the increase in LV mass. Athletes have 50% higher LV end-diastolic volumes compared to untrained individuals[72]. After years of training, the adaptations are usually dynamic and return to normal dimensions observed in the general population.

8.3.2 Too little exercise

The World Health Organization has predicted that if the current level of inactivity remains the same, preventable diseases will result in an annual treatment cost of 27 billion USD between 2020 and 2030[90]. Furthermore, 47% of new non-communicable disease (NCD) cases will be due to hypertension, accounting for 22% of total direct healthcare costs. Failure to engage in recommended physical activity levels increases the risk of developing coronary heart disease (CHD) and diabetes[91]. On a global scale, physical inactivity accounts for 7.6% of all deaths due to cardiovascular disease.[92] Physically inactivity is linked to an increased risk of arterial stiffness[93], and 1.6% of new cases of hypertension and 8.1% of dementia are related to physical inactivity[92]. In older populations, the risk of cardiovascular mortality is reduced with higher doses of physical activity[94], probably because exercise counteracts the natural

age-related reduction in arterial compliance and function[95]. Recent research from Sweden has found that physical inactivity is associated with an increased risk of all-cause mortality and rehospitalisation in patients with heart failure (HF)[96]. A large study from New York finds that patients with HF can increase their cardiorespiratory fitness; this increase is linked to reduced cardiovascular (CV) mortality hospitalisation and is not linked to increased adverse events[97,98]. These improvements are believed to be due to improvements in both cardiac and peripheral noncardiac factors[99]. Noncardiac factors play a higher role in exercise intolerance in patients with heart failure with preserved ejection fraction (HFpEF)[100]. Obese patients have a higher risk of developing HFpEF. Adiposity and peripheral noncardiac factors significantly contribute to reduced cardiorespiratory fitness (CRF)[101], and both can be modified with exercise[102].

There is a clear link between CRF and the lifetime risk of cardiovascular death (CVD). Low CRF levels are associated with a high risk of cardiovascular disease, all-cause mortality, and mortality from various cancers.[103] High CRF counteracts known risk factors of CVD[104], and improving CRF reduces risk, even in patients with a high risk of CVD[105-107]. It even counteracts obesity; it is shown that a higher CRF in obese people is related to a reduced risk of CVD compared to obese people with a low CRF.[101,108] The use of cTn measurement to monitor physical activity is not yet established, but several researchers have found a beneficial relationship between increased physical activity and reduced cTn[109,110]. This relationship is modifiable, with a lower cTn and a higher CRF[111]. The long-term prognosis linked to reduced cTn has not yet been established; hence, using cTn as a prognostic tool to monitor the effect of exercise is not yet possible.[112]

There is a broad consensus that 150 minutes of moderate-intensity activity per week or 75 minutes of high-intensity exercise is beneficial[71,113,114]. However, even small increases in daily activity reduce mortality[115], and adherence to regular activity is beneficial even if one fails to meet recommendations[116]. To improve the public CRF,

a group of scientists in Trondheim has developed a tool called Personal Activity Intelligence (PAI). Unlike other methods, the PAI score uses heart rate to measure activity intensity and combines this with time spent with this heart rate. A weekly PAI score above 100 is associated with a reduced risk of cardiovascular mortality and can be used as a motivational tool[117].

8.3.3 Too much – risks of adverse events

Sudden cardiac events are rare but potentially lethal, especially sudden cardiac arrest—the most feared complication. A study that followed two marathons from 1982 to 2009 found that 14 runners experienced cardiac arrest, which translates to a rate of 2.6 per 100,000[118]. Interestingly, women had a significantly lower incidence rate than men, with only 0.6 per 100,000[118]. Men have a higher risk of SCD than women, even when accounting for higher participation rates among men.[88] An analysis of 26 years of data from the London Marathon revealed a similar incidence rate of 2.2 per 100,000[78]. A study called RACE PARIS analysed more than 1 million people who participated in marathons and found 36 life-threatening events, with the majority (25) being major cardiovascular events. The leading causes of sudden cardiac arrests (SCA) were coronary thrombosis and atherosclerosis, which tended to occur towards the end of the race. However, 89% of those who suffered from cardiac arrest were successfully resuscitated. This highlights the significance of both participants' and bystanders' having proper resuscitation skills.[119,120] A recent publication from Norway finds an incidence of exercise-related SCA as 0.8 per 100.000 person-years vs 7.8 per 100.000 person-years out-of-hospital cardiac arrest and a higher prevalence seen with higher training volumes[121]. As the intensity of physical activity increases, so does the demand on the cardiovascular system. However, due to differences in individual fitness levels, it is not easy to establish universal recommendations for what constitutes excessive intensity. An intensity level of 6 METs is considered vigorous activity. Still, for completely sedentary individuals, even lower intensity levels can place significant stress on the heart.[88] Engaging in intense physical activity can raise the likelihood of experiencing SCD,

with some studies showing a 17-fold increase in risk[122]. However, this risk can be modified. People who regularly exercise have a lower chance of experiencing SCD in the short term than those with the lowest levels of physical activity.[88]. The risk of a sudden cardiac event during physical activity, specifically myocardial infarction (MI), is elevated, but the absolute risk is low. A retrospective multicenter study from fitness facilities reported non-fatal cardiac events in 1 out of 1,124,200 person-hours[88]. Patients with known coronary artery disease in a stable condition and no sign of ischemia can participate in all sports, including competitions[10]. Regular reassessment of the condition and management of risk factors are advised[10].

The heart changes after long-term training, including enlarged cardiac chambers, improved cardiac function, and electrical remodelling. While these adaptations are generally considered positive, some research suggests that excessive and intense exercise may lead to harmful cardiac maladaptation in susceptible individuals[88]. Endurance exercise increases Right Ventricle (RV) dimensions. In individuals vulnerable to the genetic condition Arrhythmogenic Right Ventricle Dysplasia (ARVC), exercise seems to increase the penetrance of ARVC[123]. Patients with cardiovascular disease, whether congenital or acquired, are advised to engage in physical activity, regardless of the severity of their condition. However, the activity must be customised to the patient's abilities. In some cases, patients may be advised against participating in competitive sports and instead encouraged to choose an activity with low to moderate intensity[124,125].

An individualised approach is recommended when prescribing exercise to individuals with cardiac disease. Cardiomyopathy, both hypertrophic[126] and arrhythmogenic[127], is associated with an increased risk of SCD during exercise. Despite the increased risk, these patients should engage in regular moderate physical activity. Symptomatic patients should not engage in competitive exercise[128]. Patients with valvular disease should receive regular monitoring and advice based on their physical findings, even if they are asymptomatic and able to compete[124].

In animal studies, markers of myocardial fibrosis have been increased after high levels of exercise, but this has not been proven in humans[123]. Even though physical exercise reduces the risk of coronary artery disease, amateur athletes have been found to have more atherosclerotic plaques than their sedentary counterparts[129]. A recent study found that high-intensity exercise was linked to the progression of calcification[130]. The authors suggest increased stress induces inflammation via catecholamines, and increased heart rate potentially increases vessel stress[130].

Several arrhythmias are linked to endurance exercise. A study from Sweden examining hospitalisation from arrhythmia in participants in the Nordic Ski Race Vasaloppet found an increased risk of arrhythmia in those who finished five or more times compared to those finishing only one.[131] Among these, atrial fibrillation seems to dominate, confirmed in a similar study from Norway[132].

8.4 Assessment of Exercise Modalities

There are two ways to measure intensity: absolute and relative. Relative intensity is based on a person's capacity. On a scale from 0-10, 0 represents sitting, and 10 represents the highest level of effort possible. Moderate intensity falls within the range of 5-6, while vigorous activity falls within the range of 7-8[113]. Absolute intensity is expressed in MET; 1 MET accounts for 3.5 ml oxygen/kg/min. Moderate activity requires 3.5 – 5.9 METs, and vigorous activity requires > 6 METs[113]. Multiplying METs from the specific activity with the number of minutes spent on this given activity gives METs minutes. An exercise at a given absolute intensity will be higher for a person with a lower aerobic capacity than a more fit person. To effectively plan and evaluate a cardiovascular exercise program, it is crucial to monitor and measure both its intensity and modality[133]. There are several ways to accomplish this task, which will be further explained in the following chapters.

8.4.1 Duration

Physical performance is typically evaluated based on the duration of the exercise. The shorter the duration at a specific distance, the higher the intensity of the exercise. Similarly, a longer duration at a given intensity will require more effort during the exercise. While stopwatches have been traditionally used for measuring duration, modern heart rate monitors have advanced features that allow measuring several metrics, including GPS, for accurately measuring speed, distance, and altitude. However, there is a downside to using GPS monitors as they may stop tracking when movement stops. Most race organisers use transponder timing to get results that are as accurate as possible. Transponders (active or passive) with a unique code are attached to the participants, and their signals are detected by radio receivers along the racecourse. Portable receivers allow for checkpoints and intermediate results along the race.

8.4.2 Heart rate (HR)

As resistance increases, the body must adapt to increasing muscle demand. The heart adapts to this increasing demand by increasing cardiac output. As stroke volume usually reaches a plateau, increases in cardiac output must come from increased heart rate. Hence, a higher heart rate usually equals higher intensity or effort. Heart rate can be measured in several ways. In a laboratory setting, ECG is often used. Modern heart rate monitors are an easier-to-use alternative and provide sufficient accuracy, especially when combined with a worn chest strap.[134] The ability to achieve a higher heart rate is reduced by age; hence, heart rate is often normalised according to calculated estimated heart rate. The most used equation to predict maximum heart rate based on age is (208 – 0.8 x Age), developed by Tanaka et al. based on a meta-analysis of 18 712 subjects[135].

8.4.3 Power

To plan and follow up on exercise activities, measuring the intensity of exercise as precisely as possible is essential[136]. During the last decades, the development of

activity trackers has increased the number of objective measurements, providing more accessible and accurate intensity measurements. Measuring the muscular force generated at the site of movement gives the possibility of accurately measuring current resistance and work produced by the muscles. In this thesis, all measurements have been done on cyclists. A cyclist applies force to the pedals, which are transferred to the wheel, producing movement and speed. According to Newton's third law, increasing resistance, such as headwinds or going uphill, demands higher force generated by the cyclist. When exercising, the heart supplies muscles with oxygenated blood based on the demand from the working muscles. Muscle work is adapted to the participant's resistance to maintain or increase speed (accelerate). The heart responds to this adaption by increasing cardiac output, stroke volume, and heart rate. Both of these reach a plateau where it's not efficient to increase cardiac output anymore. With increasing heart rate, diastolic time is reduced, reducing the filling of the coronary arteries and the ventricle. The body can overcome increasing resistance by switching to anaerobic metabolism. Heart rate measurement provides a picture of the demand on the cardiovascular system but not a view of the actual work or resistance the muscles are facing. Power measures the force the muscles produce to overcome or equalise resistance; there is a delay between the power produced and the heart's adaption to this resistance. Hence, power measurement allows instant intensity feedback with a higher variation than observed in heart rate. Power represents energy output over time and is measured in watts. A power meter computes power output (PO) by measuring strain and movement in either the pedal, pedal arm, or wheel and is proven to be an accurate measurement of power applied[137]. As muscular output reflects the muscular size, higher power is seen in larger humans. The most precise way of measuring power is to normalise power to weight, using watt/kg. Power meters are commonly used in professional cycling to assess and guide training[138].

As intensity increases, so do muscular demands and the force of working muscles. Heart rate during exercise is influenced by current or beginning infections, recovery status, hydration levels, and emotional stress and can give a wrong image of the

intensity level. By measuring the power, we can accurately evaluate the intensity of exercise applied to these participants. Figure 1 shows the differences between power measurement and heart rate measurement. The effort at a given interval during a race was divided by the maximum achieved value during a laboratory test. As illustrated in the figure, there is a low variation in the relative intensity when measuring heart rate but a high variability when measuring power.

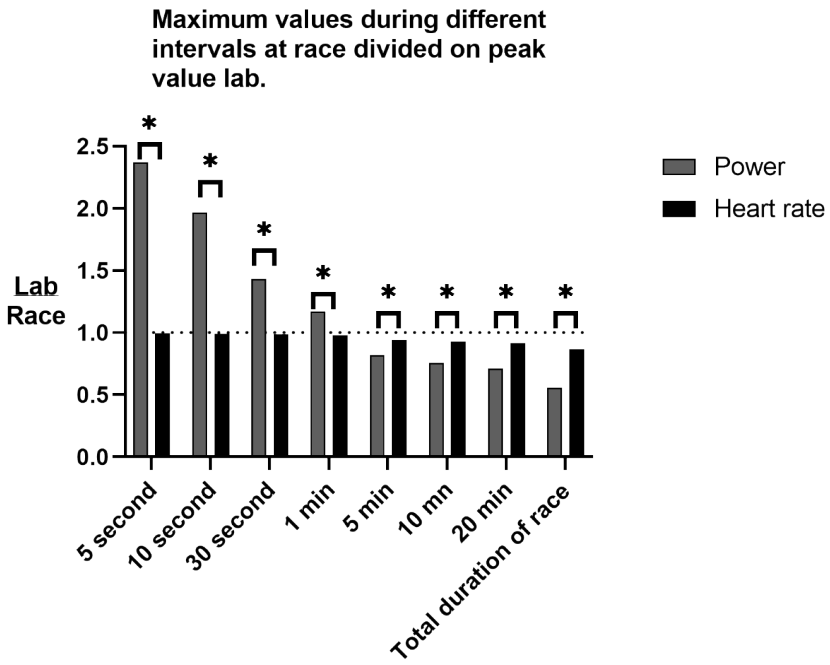

Figure 1: Values of heart rate and power sampled over different durations divided by the maximum achieved value in the laboratory (maximum heart rate and maximum power). Figure based on material from our 2018 data collection, unpublished data.

8.4.4 Speed

Increasing speed is related to increased energy and higher muscular demand in all types of exercise. However, it is possible to maintain a high speed in some sports without increasing energy output. This is particularly so in cycling, where the force of gravitation works in the same direction as the participant when going downhill.

Utilising the slip-stream behind another cyclist can reduce energy output while maintaining a high speed[139]. On the contrary, a strong headwind increases energy output but reduces speed. Speed not seen in context to other measurements is, in other words, not a reliable indicator when assessing energy expenditure in cycling.

8.4.5 Competition results

In all competitions, participants can be evaluated based on their results. One can accurately measure an individual's fitness by ranking participants based on their performance compared to peers. Results can often be filtered based on sex, age, and fitness level. The higher the participation, the more accurate the estimation. Results also inherit the capability of predicting future performance as results at a young age are proven to be the strongest predictor of future results[140].

8.5 Imaging modalities of coronary artery disease.

Several imaging modalities can be used to assess CAD, including functional tests for ischemia and anatomical visualisation for coronary arteries. Functional tests include stress-echocardiography, and cardiac magnetic resonance imaging (CMR) myocardial perfusion scintigraphy. Anatomical assessments include coronary computed tomography angiography (CCTA), invasive coronary angiography, and CMR coronary angiography.

8.5.1 Echocardiography

Cardiac echocardiography is a non-invasive medical test that uses ultrasound to produce images of the heart. Echocardiography can be done bedside or, as in this thesis, in a field office, providing images of cardiac function immediately after exercise. In addition to images of the heart's structures, echocardiography provides excellent pictures of the function and can be used to detect CAD due to abnormal findings in contractility[141]. However, echocardiography has a limited capacity to detect CAD in recreational athletes as part of a routine check-up[142]. Guidelines for assessing and quantifying cardiac chambers are published regularly to improve

uniformity and facilitate communication between practitioners.[143] These guidelines do not provide athlete-specific recommendations.

8.5.2 Cardiac Computed Tomography (CT)

CAD is the main reason for cardiac arrest in athletes > 35 years old. Various imaging modalities can detect occult coronary artery disease, but CT coronary angiography (CCTA) provides direct information about the anatomy, presence, and extent of atherosclerosis[142]. CAC-score or Agatston-score is a score of the calcium burden, ranging from 0 (no coronary calcium), 1-10 (minimal), 11-100 (mild), 101-400 (moderate) and >400 (extensive). Scores > 100 are associated with an increased risk of future CV events.[142] Exercise tests suggesting ischemia may require further evaluation with CT coronary angiography[144]. On CT coronary angiography, veteran athletes may display underlying CAD despite poor correlation with established risk factors[16].

Obstructive CAD apparent on CT is associated with a high risk of MI and death[145]. This also applies to athletes but seems to be reduced by higher CRF and physical activity[146,147]. In addition to this, contrast-enhanced CT angiography (CCTA) provides information about luminal narrowing ranging from moderate (50% luminal narrowing) to severe (>75% luminal narrowing). Both the American Heart Association (AHA) and the European Society of Cardiology recommend the use of coronary artery calcium scoring (CACS) in patients with intermediate to high risk of coronary artery disease (CAD)[12]. If other non-invasive tests, such as exercise testing, fail to provide an answer, computed tomography (CT) angiography is also recommended[148].

There is still debate on how to interpret and act on CAC scores regarding treatment and/or invasive therapy, and future research is needed to implement this procedure as part of a routine check-up[149].

9. Knowledge gaps

Even though cTn is established as a marker of myocardial damage and the prognostic use is currently increasing[20,46], many unanswered questions remain. Exercise-induced cTn is currently debated whether it can be used as a diagnostic marker or if this is just a normal phenomenon[112]. The use of cTn as screening for cardiac disease has yet to be established, and several essential gaps need to be filled to use this as a pre-participation tool.

There is an established link between exercise intensity and exercise-induced cTn. Several different features have been used to prove this relationship, but as for now, it has yet to be established which is the best to use or if there is a difference between the methods. Using heart rate as an example, researchers use absolute and relative HR. Even the relative HR varies among studies, with some using HR in relation to maximum achieved HR, while others use HR as a per cent of estimated maximum heart rate. Other intensity measurements should also be explored, emphasising the difference between cardiac and muscular load. It is possible to use more accurate measurements of muscular load, especially in cycling. There is an established link between blood pressure and exercise-induced cTn, but few studies have explored the relationship between blood pressure during exercise and cTn.

Exercise studies are usually a one-off event. Hence, few studies have investigated the reproducibility of exercise-induced cTn. Is cTn after exercise only linked to different features related to the exercise, or are there individual differences in the release pattern of cTn? There is increasing evidence that atherosclerosis affects exercise-induced cTn, but how this affects the release still needs to be established.

10. Aims

This thesis aims to determine which factors influence exercise-induced cTn elevation in healthy recreational middle-aged athletes and explore how different measurements can improve our understanding of the cTn response.

10.1 Specific aims

- Explore how different heart rate features correlate with exercise-induced cTn and investigate whether a threshold heart rate is related to troponin release (Paper 1).
- Determine how individuality influences personal cTn levels by re-testing the cTn response in the same participants in different exercise settings separated by several years (Paper 2).
- Determine how non-obstructive CAD influences post-exercise cTn elevation using power meters and cardiac workload parameters to measure exercise-induced workload (Paper 3).

11. Materials and methods

The NEEDED study consists of three studies: a pilot study in 2013, the main study in 2014 and a follow-up study in 2018. The NEEDED study is designed to evaluate the significance of exercise-induced cTn in a healthy population both in the short and long term. The NEEDED study uses computed coronary angiography (CCTA) to investigate coronary anatomy.

Paper 1 in this thesis uses material from the NEEDED 2014 study. Papers 2 and 3 use material from the NEEDED 2018 follow-up study on a selected cohort from the 2013 and 2014 populations. All studies involve participation in the North Sea Race, a 91 km mountain bike race; in addition, all participants in the 2018 study were tested in a cardiopulmonary exercise test (CPET) prior to the race.

The 2014 study included 1002 subjects; among these, 177 were selected based on the availability of heart rate monitors. One hundred twenty participants with a negative CT scan from the 2013 or 2014 study were invited to a new study in 2018; among these, 62 responded to the invitation and 59 completed both the CPET test and the Race. See Table 1 and Figure 2.

Table 1: Overview of design, data and conclusion of articles included in this thesis

Article	I	II	III
Design	Observational		
Data Source	NEEDED 2014	NEEDED 2013, 2014, NEEDED 2018	NEEDED 2018
Time of data collection	2014	2013, 2014 and 2018	2018
Numbers included in the analysis	177	59	40
Main laboratory method	Roche Diagnostics, Abbot Diagnostics	Roche Diagnostics, Abbot Diagnostics	Abbot Diagnostics
Main physical effort	North Sea Race	Laboratory test, North Sea Race	Laboratory test, North Sea Race
Measurement of intensity	Data was collected from participants' heart rate monitors.	All participants had identical heart rate monitors in the 2018 study (Garmin Forerunner 935). 40 participants equipped with power meters (Stages) (2018)	All participants had identical heart rate monitors (Garmin Forerunner 935). 40 participants equipped with power meters (Stages)
Imaging	NA	CT Angiography, Echocardiography (2018)	CT angiography
Main Statistical analysis	Spearman Rho, Multiple backward regression,	Spearman Rho, Multiple backward regression, Linear mixed effect.	Spearman Rho, Boot-strap.
Conclusion	Duration with a heart rate above 150 bpm is associated with excessive pos-exercise cTn.	Exercise-induced cTn response is individual and reproducible	The presence of CAD affects the relationship between physical effort and exercise-induced cTn.

11.1 Study organisation, approval, and registration

Professor Stein Ørn, MD, PhD, led the NEEDED study group. The study board included Dr Ørn, Dr Tor Harald Melberg, MD, Ph.D. of the cardiology department, Dr Øyvind Skadberg, MD, Department of Biochemistry, Dr Rolf Bergseth, MD,

Medical officer for the North Sea Race, Torbjørn Aarsland, Research Department, and Jone Selvaag, Department of Biochemistry. The protocol was written by Dr Ørn and Melberg and approved by the board. The study is supported by the Regional Ethics Committee (2013/550REKvest, and 2018/63REKvest) and is registered in clinicaltrials.gov (NCT02166216).

11.2 Study design

The NEEDED study aimed to investigate biochemical changes after strenuous physical exercise. The North Sea Race provided an ideal setting for this study due to its high participation rate, which exceeded 10,000 attendees in 2014. Many local businesses used the race as an activity to increase physical activity among their employees. The racecourse is also manageable for amateur athletes with low cycling experience, which attracted participants with a lower degree of physical fitness than other comparable endurance events.

The North Sea Race is a 91 km race that has followed the same route since its inception in 1998, except for minor changes. The race takes place along the coast of western Norway between Egersund and Sandnes. The race duration varies due to weather conditions, typically lasting 4-5 hours. The race had its highest number of participants in 2011.

The NEEDED study was made possible thanks to close collaboration with the North Sea Race organisation. This organisation has experience dealing with sudden cardiac arrest and myocardial infarction during the race and is committed to ensuring the safety of all participants. Six strategically placed ambulances and six teams on all-terrain vehicles are positioned along the course to assist in areas with limited access. Furthermore, eighty medical personnel are stationed at various points throughout the route, and all personnel (approximately 300) are trained in chest compression and basic first aid, as well as how to communicate via phone or radio with the organising committee or the regional emergency centre[150].

11.3 Population

Recruitment of participants for the study was done through the official website of the North Sea Race, with everyone invited to participate. A pilot study was conducted in 2013, followed by the primary data collection in 2014. In 2018, more targeted research was conducted on a sub-group selected from the participants of the two previous time points. The invitation was closed once enough subjects had signed up, with 169 subjects in 2013 and 1250 subjects in 2014. The study included 97 cyclists in 2013 and 1002 in 2014.[30]

Participants had to be ≥ 16 years of age, reside in Norway, and sign the informed consent to participate. Exclusion criteria were any symptoms or treatment of CV disease, any findings suspect of underlying CV disease on baseline ECG (Q-waves > 3 mm in depth or > 40 ms in duration in two or more leads except III, aVR, and V1), T inversion > 1 mm in depth in two or more leads in V2-6, II, and aVF, or I and aVL), left bundle branch block or atrial or ventricular tachyarrhythmia[150].

In the first paper of this thesis, participants were required to bring and use their own heart rate monitors. Of the 1002 participants, 291 submitted data files from heart rate monitors for further analysis. Only subjects with a complete dataset of HR data and data from blood samples and physical examinations in 2014 were included in the study (n=177).

Selection of participants for CCTA

In the pilot study, participants with cTnI levels above 500 ng/L were chosen for a CCTA; this predetermined cut-off was based on non-published data on elite cyclists. Both participants with a cTn above 500 ng/L in 2013 had CAD, so the number of scans with decreasing cTn levels increased until CAD was no longer detected in 5 consecutive scans (13 scans total)[150]. This led to a cut-off of 201 ng/L for planning CCTA in the 2014 study. The protocol was amended to include a reference group of 40 participants matched for age and sex. CCTA of this group was performed 3-12

months after the race, and participants with coronary artery disease found during the examination were excluded from the analysis[150]. See Figure 2 for a graphical display of the selection.

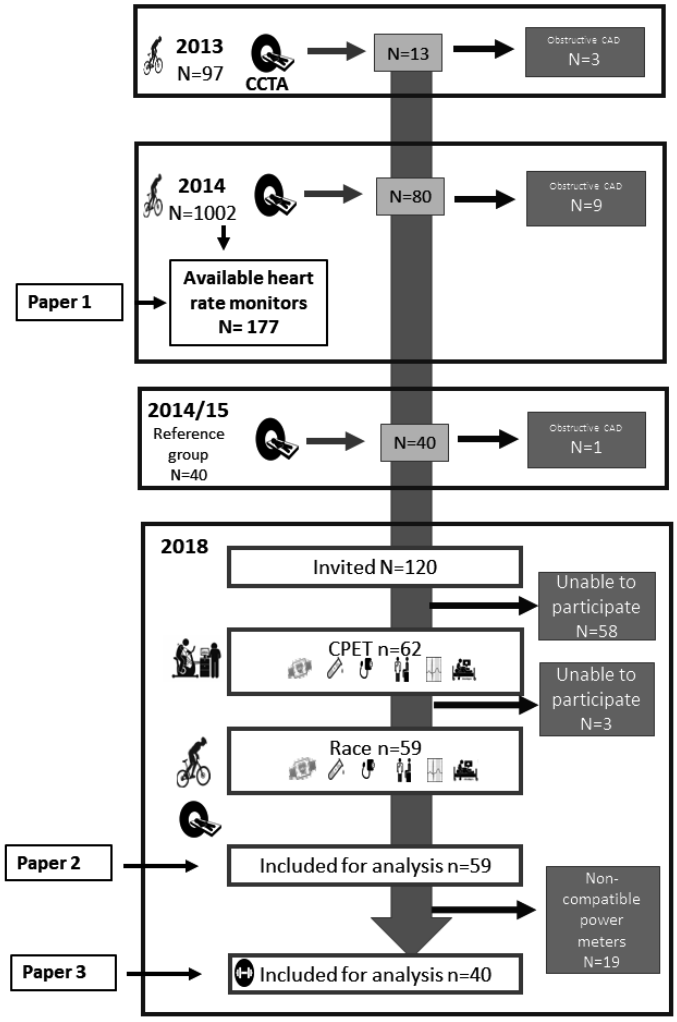

Figure 2: Timeline of the studies included in this thesis and the selection of participants in each paper.

The NEEDED 2018 study was conducted as a follow-up of the NEEDED 2013 pilot study or the NEEDED 2014 study.[30,151] Participants for the 2018 study were invited, among those with a negative CT scan in either 2013 or 2014 or from the reference group (CT scan done in late 2014 or 2015) (T0). In 2018, the recruited study participants had to be eligible for a CPET (T1) 2-3 weeks before a renewed participation in the North Sea Race (T2). A coronary computed tomography angiography (CCTA) was performed following the North Sea Race in 2018 to ensure no one had developed obstructive coronary artery disease.

11.4 Cardiac Troponins

Assays used in this thesis are the high-sensitive cTnI from Abbot and the high-sensitive cTnT from Roche. Both assays have high precision, <10% at the 99th percentile[38], as recommended by guidelines for diagnosing myocardial infarction[17]. Data from a population of middle-aged blood donors was used to obtain the 99th percentile used in this thesis for both the overall and sex-specific 99th percentiles (cTnI overall 26 ng/L, males 28 ng/L, females 22ng/L. cTnT: overall 14 ng/L, males 16 ng/L, females 10 ng/L).[37] Venous blood samples were drawn from the antecubital vein. Cardiac TnI (serum) was analysed within 24 hours at Stavanger University Hospital on an Architect i2000SR using the high-sensitive cTnI STAT assay from Abbott Diagnostics (Abbott Diagnostics, IL, USA). In 2014, Frozen samples were transported on dry ice to Haukeland University Hospital, Bergen, and cTnT was analysed using a high-sensitivity cTnT assay on Cobas e601 (Roche Diagnostics, Switzerland) on first-time thawed serum[150]. The Roche Diagnostics hs-cTnT assay has a limit of blank (LoB) of 3 ng/L, a limit of detection (LoD) of 5 ng/L and in our hands, a CV_A of 10% or lower for concentrations >4.5 ng/L. The 99th percentile URL is 14 ng/L (9.0 ng/L in women and 16.8 ng/L in men)[152]. The high-sensitive cardiac troponin I assay (hs-cTnI STAT) (Architect SR2000i, Abbott Diagnostics, IL, USA) was used to measure troponin I during all three events: T0, T1, and T2. In 2013/14 (T0) and 2018 (T1 and T2), the reported results were a limit of blank 0.9 ng/L and a

Limit of Detection (LoD) of 1.6 ng/L[152]. The cTnI assay had a total Coefficient of Variation (CVa) of 10% at 6 ng/L, 7% at 27 ng/L, and 5% at 140 ng/L. The 99th percentile was 26 ng/L (34 ng/L in men and 16 ng/L in women).[37]

11.5 Heart rate monitors and heart rate processing.

After the 2014 race, HR and GPS data from sports watches were downloaded by participants either on-site, via email, or through a web-based solution provided by Trainingpeaks™. The Department of Electrical Engineering and Computer Science at the University of Stavanger in Norway processed and analysed the data files. Since the watches were from different manufacturers, the data had to be transformed into a consistent format and given unique IDs before being imported into MATLAB for further processing and analysis. HR data was standardised to report one value per second to account for variations in device sampling intervals. Any missing data was filled in using standard interpolation techniques[153]. Data were smoothed before further processing to reduce signal noise. To assure synchronicity between monitor time and actual time and place during the race, results from the official timekeeper were used to generate reproducible reference points in the files.[154]

In 2018, all participants wore the same heart monitor. Heart rate, geo-positioning, speed, and power-output data were registered with a Garmin Forerunner 935 (Garmin, Colorado, US). GPS coordinates, altitude, speed, distances, and absolute heart rate were sampled every second. Heart rate was collected with a compatible Garmin chest strap.

Heart rate features

2014 HR data was analysed for the entire race to determine the mean and maximum heart rate. The time/intensity domain was also examined by calculating the time spent above heart rate thresholds of 140, 150, and 160 bpm throughout the race. The mean heart rates and Time/HR integral (above each HR threshold) were then calculated. The selected HR thresholds were based on previous studies that indicate an increase

in cTn between mean HR of 140 and 160 bpm[155]. Additionally, the time spent with a heart rate above 85%, 90%, and 95% of the maximum achieved heart rate during the race was calculated to provide an overall assessment of the heart rate distribution during maximal effort.

11.6 Power

Total and cardiac work data during the recruitment race (T0) was unavailable except for the time to complete the race. However, we were able to measure power in 2018. The Cyclus 2 electronically braked ergo trainer (RBM Elektronik-Automation; Leipzig, Germany)[156] was used for each participant during the CPET (T1) test. Power was controlled by the Cyclus 2, and data from the test software was used to calculate power during the laboratory test. Forty participants had bikes compatible with a power meter from Stages (Stagespower, Boulder, Colorado. US)[137]. These were fitted to the bikes and connected to the Garmin Forerunner the week before the race. The Stages power meters replace the original crank arm on the left side and have been tested for validity elsewhere[137]. All power meters were calibrated at the start of the race. Participants were blinded for power measurements during the race.

11.7 Blood pressure and RPP.

During the baseline examination and 3 and 24 hours after the race, an automated device was used to measure the participant's resting blood pressure. The rate-pressure-product (RPP) was calculated to estimate cardiac work during exercise[157]. The RPP value was determined as either mean or maximal RPP. Mean RPP was calculated by multiplying the mean systolic blood pressure during exercise by the mean heart rate. Heart rate was taken from the heart rate monitors (Garmin Forerunner 935, Garmin, Olathe, KA, USA) during both the CPET test (T1) and the 2018 race (T2) by all study subjects. Blood pressure was measured automatically during the CPET test (T1) using a Tango M2 Stress test monitor (Suntech Medical

Morrisville, NC, USA). During the 2018 race (T2), blood pressure was measured manually on the right arm with a Heine G5, G7, or XXL LF-T (Heine, Herrsching, Germany) before the start, at the finish line, and four pit-stops at the maximum and minimum anticipated efforts at the top and bottom at the two largest hills of the race after 34, 41, 69, and 76 km.

11.8 Exercise stress test

Participants brought their bikes fitted to a Cyclus 2 (RBM Elektronik-automation; Leipzig, GE) electronically braked ergotrainer[156]. Before the exercise tests, each participant underwent a 10-minute warm-up. The lactate threshold test was a 4-minute steady-state stepwise test that determined the lactate threshold as a lactate value greater than 1.5 mmol/l over the mean value from steps 1 and 2 or an RER greater than 1.0. Lactate was measured in capillary blood from the participant's index finger on the Lactate Scout+ (EKF Diagnostic, Cardiff, GB). Throughout the test, including rest and warm-up, the following variables were recorded: resistance (in watts), blood pressure (in mmHg), VO2 (in ml/min/kg), RER, lactate, and heart rate (in bpm). After the test, participants were allowed a 5-minute cool down by pedalling at no resistance before undergoing the anaerobic capacity test. Pedalling was stopped one minute before the start of the test to allow blood pressure to decrease. Resting blood pressure was measured at the beginning of the test, and maximal blood pressure was taken immediately after the end of the test. At the same time, the participants remained seated on their bikes. The Ramp protocol was used until exhaustion to reach maximum effort between 5 and 10 minutes, and VO2 max was defined as the point where VO2 reached a plateau despite increasing resistance. Peak power and heart rate were the maximum values averaged over the last 30 seconds of this test.

11.9 Echocardiography

The GE Vivid E 95 system, manufactured by Vingmed Horten, was utilised to obtain echocardiography. Three medical doctors acquired images in T1, while six worked on parallel stations in T2 to acquire images immediately after the participants had finished. An offline GE EchoPAC (GE Healthcare) was used for post-processing by a researcher blinded to clinical data and exercise information. Comprehensive imaging protocols were applied with complete coverage of both atria and ventricles, including parasternal and apical views, and appropriate framerates to enable later high-quality post-processing, including speckle tracking and global and regional strain analysis. All parameters were calculated according to the European Association of Cardiovascular Imaging (EACVI) recommendations[143]. The Research Group on myocardial function and cardiac imaging from Oslo University Hospital Rikshospitalet collaborated on the analysis.

11.10 Coronary computed tomography angiography

The Siemens Somatom Definition, Flash Dual Source, was used to obtain coronary calcification and CCTA. Participants whose heart rate exceeded 60 beats per minute were administered atenolol or metoprolol tartrate before the examination. Before the scan, all participants were given 0.8 mg nitroglycerine sublingually. The slice acquisition parameter was 0.6 x 128 mm. CT calcium score scans were conducted with gantry rotation 280 ms, 12 kV, and 80 mAs after a scout scan from under the tracheal bifurcation to the diaphragm. High-pitch or prospectively ECG-triggered protocols were administered, with an injection of Omnipaque 350 mg/ml at a rate of 6 ml/sec followed by 0.9% saline[150]. CCTA was reconstructed with a slice thickness of 0.6 mm medium smooth tissue. Non-obstructive CAD included any atherosclerotic plaque with luminal stenosis less than 50% in any of the three main coronary arteries, a diagonal or marginal branch[150]. Two experienced radiologists independently assessed examinations, blinded to the cTnI and echocardiographic findings.

11.11 Statistical analysis

Continuous variables with a fairly even distribution are reported as the mean ± standard deviation (SD). Continuous variables with a skewed distribution are reported as the median and interquartile range (IQR), reporting the 25th and 75th percentile. The Shapiro-Wilk test was employed to test for normality. Differences between groups were assessed using either the Mann-Whitney U or Student T-test. Bivariate correlations were evaluated with Spearman's rank-order correlation. For categorical variables, a Chi-Square Test was utilised. A Paired Student T test or a Wilcoxon signed-rank test was used when comparing sampling points.

Many statistical tests were conducted as part of the exploring method used in paper 1, resulting in an increased rate of false positives. Therefore, a p-value of less than 0.01 was deemed significant. Multiple linear regression was used to analyse possible links between HR variables and cTn levels. Due to skewed distributions, cTn values were transformed using the natural logarithm. We established a fixed set of parameters for a basic model based on our 2014 study[30]. This model included age, sex, BMI, race duration, SBP, eGFR, LDL, FRS, resting HR, and baseline ln-cTn. We then added different HR features one by one to the model to observe the changes in R^2. These features included mean HR, maximum HR, mean HR as a percentage of estimated maximum HR, time spent with an HR > 140, 150, and 160 bpm, integral of time, HR with an HR > 140, 150, and 160 bpm, integral of time with an HR > 85, 90, and 95% of maximum achieved HR, mean HR above 140, 150, and 160 bpm, and percentage of race time within HR > 140, 150, and 160 bpm. Both backward selection and forward inclusion linear regression models showed similar effects on prediction and significance levels.

In Papers 2 and 3, bivariate associations were studied using Spearman correlation. A two-tailed p-value less than 0.05 was considered to be significant. Paper 2 used a linear mixed effects model with a random intercept to estimate group differences.

Differences were assessed at baseline, +3 hours, and +24 hours. These assessments were made between the T0, T1, and T2 groups.

In paper 2, post-exercise cTnI values at 3- and 24 hours after the CPET test and the race in 2018 were used as dependent values in multiple linear regression with backward elimination. Age, sex, duration of exercise, and systolic blood pressure at baseline were selected a priori. Troponin values were transformed using the natural logarithm due to a skewed distribution. Explanatory variables with a p-value less than 0.05 were included in the models based on the correlation analysis with cTnI as the dependent variable. The same variables were selected for both T1 and T2. Corresponding values from T0 and T1 or T2 were added to investigate whether these variables would influence exercise-induced cTn differently.

In paper 3, Regression analysis was used to estimate the slope coefficients between power output and exercise-induced cTn for both groups in Race and CPET. Due to suspected dependencies, Bootstrap was used to assess differences in the steepness of the regression lines between CPET and Race.

The statistical software programs SPSS version 24 - 26 (IBM Corp, New York, US) and GraphPad Prism 9 (GraphPad Software, San Diego, CA, US) were used for statistical analysis and for generating the graphs.

12. Summary of the results

Paper 1 examines whether the introduction of heart rate variables can increase the predictability of the multivariate analysis from the main 2014 study using a selected cohort of the 2014 population. Papers 2 and 3 are based on the NEEDED 2018 study on a selected cohort from the NEEDED 2013 pilot and the NEEDED 2014 study. Paper 2 examines the impact of exercise intensity and duration on cTn in two groups determined by their earlier cTn response following exercise. Paper 3 seeks to establish how exercise intensity impacts the release of cTn in two different groups based on the presence of atherosclerosis assessed by CCTA.

12.1 Study populations

The baseline characteristics of the 2014 and 2018 cohorts are outlined in Table 2

Table 2: Table legend: Baseline characteristics of the 2014 and 2018 population. Values are reported as mean ± SD, or median (25^{th}-75^{th}) percentile if markedly skewed distributions.

	NEEDED 2014 (n=177)	*NEEDED 2018 (n=59)*
Age (years)	43.9 ± 8.0	50.3 ±9.6
Male Sex n (%)	146 82	46 78
Body mass index (kg/m^2)	25.6 ± 2.7	24.9 (23.3 – 27.1)
Systolic blood pressure (mmHg)	138 ± 15	135 (122 – 146)
Diastolic blood pressure (mmHg)	80 ± 10	81 (74 – 89)
Resting heart rate (bpm)	59 ± 10	60 ±10
Endurance training (years)	11.8 ± 10.6	10 (7 – 21)

12.2 Paper 1:

From the 2014 study, the variables with the highest predictive value were Baseline LncTn, BMI, Age, Sex, race duration, resting HR at baseline, systolic blood pressure at baseline, LDL cholesterol, eGFR, and Framingham Risk Score. By introducing different heart rate variables one by one and following the change in the coefficient of determination ($R^{2)}$ in the established model, we found that the duration of race with a heart rate higher than 150 bpm and the % of race duration with a heart rate > 150 bpm are the two variables that increase R^2 the most. See Table 3.

Table 3: Table legend: This table shows the effects of adding a single extra heart rate (HR) variable to the basic multiple model derived from the main NEEDED 2014 study. Variables included in the basic multiple linear regression model were: Baseline Ln cTn, BMI, age, sex, race duration, resting HR at baseline, systolic blood pressure at baseline, LDL cholesterol, eGFR and Framingham Risk Score. Individual HR variables were added to the basic model to assess the impact of these variables on the coefficient of determination (R^2) and the association with cTn. The strongest models that were significant at all time-points for both cTnT and cTnI, were race-time > 150 bpm and percent of race-time with a heart rate > 150 bpm (highlighted in grey).

Dependent variables	*LncTnI 3h*			*LncTnT 3h*			*LncTnI 24h*			*LncTnT 24h*		
	R^2	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**P**	**R^2**	**B**	**p**
Basic Model	**0.19**			**0.17**			**0.37**			**0.26**		
Mean HR	0.20	0.01	0.18	0.17	0.01	0.29	0.38	0.01	0.48	0.26	0.01	0.22
Mean HR % of estimated max HR	0.20	1.88	0.18	0.17	1.08	0.29	0.38	0.93	0.49	0.26	1.08	0.24
mean HR > 140 bpm	0.20	0.02	0.09	0.18	0.01	0.13	0.38	0.01	0.20	0.28	0.01	0.09
mean HR > 150 bpm	0.19	0.01	0.34	0.17	0.01	0.35	0.38	0.01	0.46	0.27	0.01	0.19
mean HR > 160 bpm	0.19	0.00	0.78	0.17	0.01	0.64	0.37	0.01	0.77	0.27	0.01	0.26
Race time> 140 bpm	0.23	0.36	0.003	0.21	0.26	0.003	0.39	0.26	0.03	0.29	0.20	0.01
Race-time > 150 bpm	**0.24**	**0.25**	**0.001**	**0.21**	**0.16**	**0.002**	**0.40**	**0.19**	**0.009**	**0.29**	**0.13**	**0.01**
Race time> 160 bpm	0.21	0.12	0.06	0.18	0.07	0.12	0.38	0.07	0.25	0.27	0.06	0.14
% race-time >140 bpm	0.23	1.4	0.004	0.22	1.03	0.003	0.39	1.05	0.02	0.29	0.83	0.009
% race-time >150 bpm	**0.24**	**0.97**	**0.001**	**0.21**	**0.63**	**0.003**	**0.40**	**0.77**	**0.006**	**0.30**	**0.52**	**0.007**
% race-time >160 bpm	0.20	0.43	0.07	0.18	0.26	0.13	0.38	0.29	0.20	0.27	0.25	0.11
The integral of time and HR > 140 bpm	0.21	0.005	0.03	0.19	0.00	0.05	0.38	0.00	0.14	0.28	0.00	0.05
Integral of time and HR > 150 bpm	0.20	0.01	0.11	0.18	0.00	0.15	0.37	0.00	0.33	0.27	0.00	0.13
The integral of time and HR > 160 bpm	0.19	0.00	0.49	0.17	0.00	0.51	0.37	0.00	0.81	0.27	0.00	0.34
Time-HR integral > 85% of achieved max HR	0.24	0.02	0.001	0.20	0.01	0.02	0.40	0.02	0.006	0.28	0.006	0.10
Time-HR integral > 90% of achieved max HR	0.24	0.03	0.001	0.20	0.02	0.02	0.41	0.03	0.003	0.28	0.01	0.08
Time-HR integral > 95% of achieved max HR	0.22	0.09	0.008	0.19	0.05	0.06	0.41	0.09	0.004	0.27	0.04	0.10

12.3 Paper 2

Values of cTn at baseline and 3- and 24-hours following exercise in 2014 and 2018 were compared. Race 1 in 2014 had the highest post-exercise cTn values, see Figure 3. Participants with a high cTn response in 2014 were proven to have a similar reaction in 2018. As the CPET test differed in intensity and duration, we could see a different response in cTn following this exercise compared to the races. Figure 4 highlights the consistency in the ranking of cTn values. Figure 5 shows the correlation between individual cTn values between sampling points.

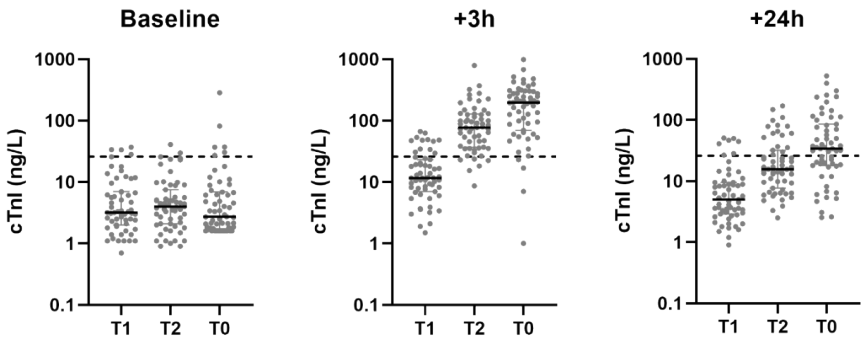

Figure 3: Cardiac Troponin I (cTnI), at baseline, 3 hours and 24 hours after the cardiopulmonary exercise (CPET) test in 2018 (T1), the North Sea Race in 2018 (T2), and the North Sea Race in either 2013 or 2014 (T0). Scale is log10-transformed. Dotted lines indicate the 99th percentile of the high-sensitive cTnI assay (26ng/L).

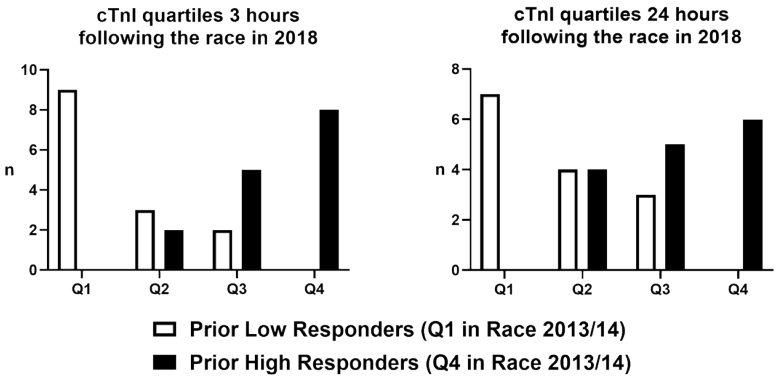

Figure 4 The figure displays the consistency in ranking of cTnI values following the recruitment race (the North Sea Race in either 2013 or 2014) and the 2018 North Sea Race. Low-responders are defined as individuals with a cTnI value within the first quartile (Q1)) of the recruitment race (T0), while High-responders are defined as individuals with a cTnI value within the highest quartile (Q4) of the recruitment race (T0). The graph displays the number of individuals in each of the four quartiles based on the cTnI values achieved in the 2018 race (T2).

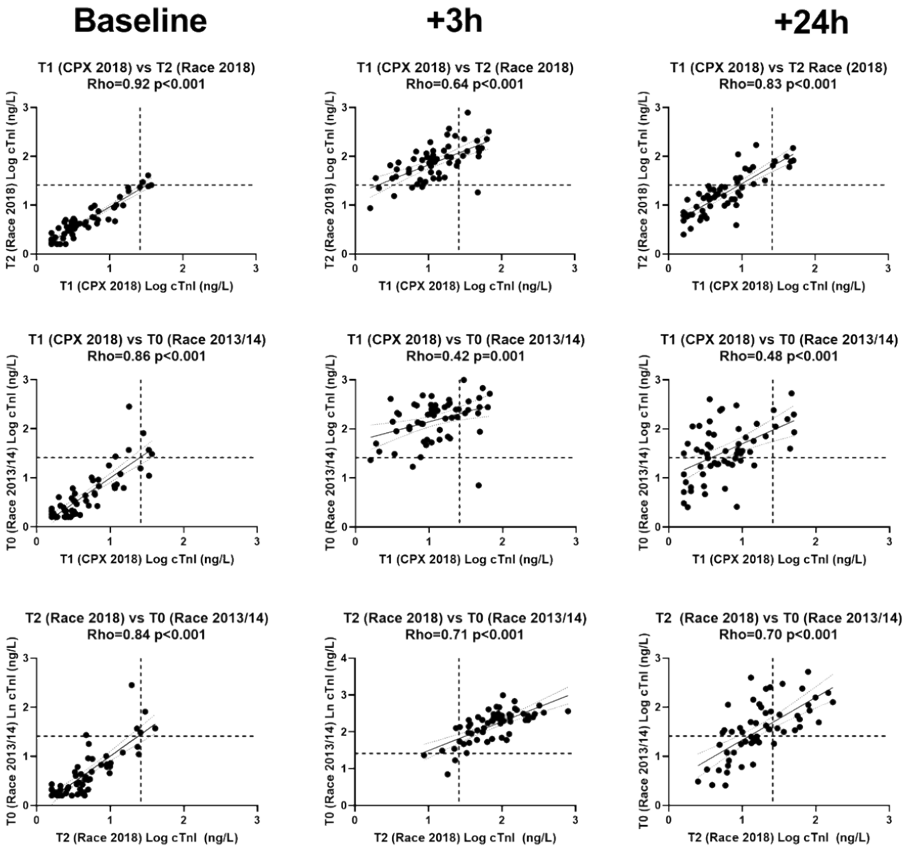

Figure 5: Scatterplot shows individual Troponin I (cTnI) response at baseline, 3 hours, and 24 hours after the cardiopulmonary exercise (CPET) test in 2018 (T1), the 2018 race (T2), and the recruitment race (in either 2013 or 2014) (T0). Spearman bivariate correlations were used to assess the correlations between time points. The dotted lines indicate the 99th percentile of the high-sensitive cTnI assay (26 ng/L).

12.4 Paper 3

In Paper 3, participants were divided into two groups based on the presence of atherosclerosis as defined by CCTA. A subgroup of 40 participants was equipped with power meters to evaluate the impact of muscular work on exercise-induced Troponin. Besides higher age, higher METhrs per week, and higher Hba1c in the

Atherosclerotic group, there were no differences between the two groups regarding cardiac risk factors, baseline characteristics or results from the race. The participants showed a similar cTn profile after the race and the CPET. Still, exercise-induced cTn was correlated to power and RPP in the Atherosclerotic group but not in the group without Atherosclerosis. In the Atherosclerotic group, there were significant differences in the steepness of the regression lines both at 3 hours (CPET: B_1=22.4 (±6.8) vs Race: 111.6 (±34.2), p<0.0001) and at 24 hours (CPET: B_1=7.1 (±6.0) vs Race 28.4 (±10.3), p < 0.001) between CPET and Race data. This highlights the impact of duration on cTnI kinetics, see figure 6.

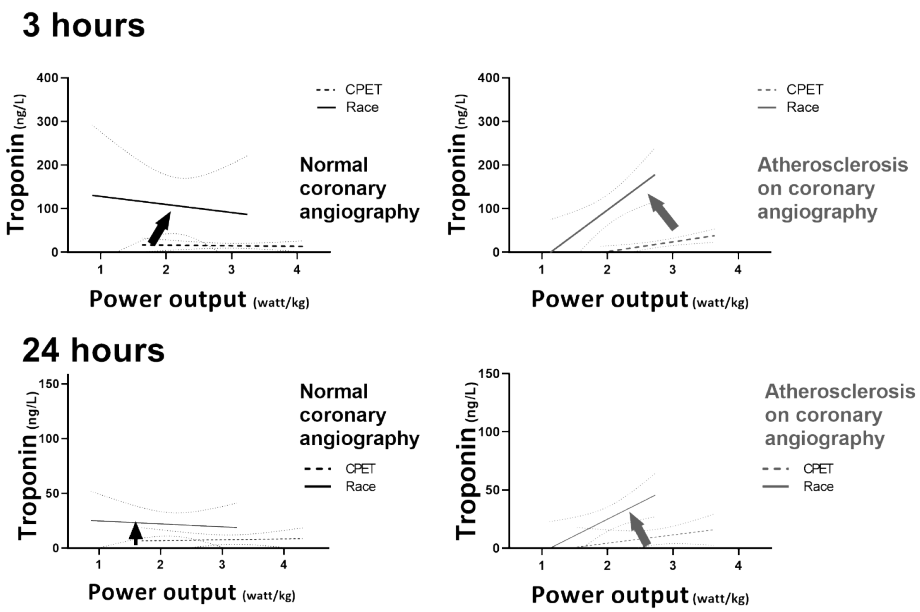

Figure 6: Difference in cTnI kinetics between participants with (red) and without (black) established Atherosclerosis. Dotted lines represent the CPET, while complete lines represent the Race. Significant differences were found in the Atherosclerotic group.

The Atherosclerotic group had a lower average workload (2.73 W/kg) than the Normal group (3.24 W/kg). When comparing individuals with similar workloads, cTnI levels were significantly higher in the Atherosclerotic group at 3 hours (130.0 ng/L compared to 70.1 ng/L, p=0.036), but not at 24 hours (30.0 ng/L compared to 11.6 ng/L, p=0.21).

13. Discussion

The following paragraphs will discuss three main areas where this thesis adds new evidence to existing literature:

1. When assessing the relationship between exercise and cTn, the product of intensity and duration more accurately reflects cardiac workload than measurements of intensity alone. The duration of exercise with a heart rate above 150 bpm is an independent predictor of exercise-induced cTn.
2. Exercise-induced cTn is highly individual and reproducible.
3. The presence of coronary atherosclerosis alters the relationship between the intensity of exercise and exercise-induced cTn.

By using HR as a marker of intensity, we were able to establish the relationship between the duration of exercise intensity and cTn elevation after exercise (Paper 1). This relationship was strengthened when comparing cTn elevations after two activities with different durations, showing increasing cTn with increasing duration ((CPET vs. Race) (Paper 2)).

In addition, Paper 2 shows significant but reproducible differences in the magnitude of the exercise-induced cTnI responses between individuals. This underscores the need to consider workload, sampling timing, and earlier cTnI response when evaluating exercise-induced cTnI. Exercise intensity and duration affect the elevation of cTn in a person-specific manner. Future studies should seek to investigate what this implies and if it is related to enzymatic differences or potential pathological differences.

Paper 3 allowed us to evaluate the impact of one potential pathological difference, the presence of coronary atherosclerosis. This study shows that non-obstructive coronary atherosclerosis influences power output and post-exercise cTnI levels. We examined participants within the same intensity range and found a difference in exercise-induced cTn elevation. There was a strong relationship between power output and the

exercise-induced cTnI response in the cohort of individuals with non-obstructive coronary atherosclerosis; this relationship could not be found in the Normal population despite an overall increase in cTn after both CPET and Race.

When trying to distinguish between a pathological or physiological cTn response, the results of this thesis highlight the significance of accurate measurement of intensity and the duration of this intensity. Additionally, previous exercise-induced cTn response and the presence of Atherosclerosis should be considered.

13.1 Attributes of exercise

The findings from our first paper suggest that the length of time the heart rate remains elevated is an essential determinant of the physiological cTn response. Using an existing model based on results from 1002 participants[30], the highest increase in R^2 came when we added features combining exercise duration and intensity.

13.1.1 Heart rate

This study discovered that the race's duration while maintaining a heart rate above 150 bpm significantly impacted the predictive model based on 1002 participants. More research is needed, but other studies support this finding. In their meta-analysis by Donaldson et al., heart rate during exercise was the most influential factor in cTn elevation (R^2=0.31)[158]. In a study of patients with normal coronary arteries and supraventricular tachycardia, those with high Troponin T had higher heart rates than those with normal levels (191 vs 170 bpm p=0.008). Additionally, there was a significant correlation between the level of troponin and maximum HR (r=0.64, p=0.001)[159]. A similar relationship has been found in a study on marathon runners; elevation of cTn was associated with relative intensity.[160]

Cardiovascular magnetic resonance can detect myocardial oedema; increased extracellular volume has been shown after exercise and is correlated to post-exercise cTnI[50]. This membrane leakage has been proposed as a potential mechanism

explaining exercise-induced cTn—a study by Ghekiere et al., examining 18 cyclists after a 175 km bike race, confirmed this. Exercise-induced cTn correlated to myocardial oedema markers and high-intensity cycling. (HR zone 4 r=0.607, p=0.03)[161].

There is discussion about whether the heart rate or the intensity it represents increases cTn. An intriguing study by Li highlights this. In their cross-over study, cTn after continuous or intermittent exercise is evaluated[162]. Exercise is guided so that the total amount of work is the same between the exercises. Still, intermittent exercise achieves a heart rate of 90% of Vo2 max compared to only 70% in continuous exercise. After exercise, there are minor differences between the two exercise modes, but findings indicate a real difference in cTn after the exercise with the highest heart rate. In their study comparing three different intensities on treadmill running, Ngyuen et al. found a higher cTn after higher intensity[163]. Heart rate in per cent of maximum significantly correlates to cTn, consistent across three different cTn assays[163]. This might suggest that the heart rate could influence the release of cTn. No threshold has been established regarding what heart rate increases cTn. In our study, there seems to be a threshold around 150 bpm, while Stewart et suggest a threshold near 145 bpm[155]. Ghekiere et al. use Heart Rate Zone 4 based on the papers above and confirm these findings; cTn is correlated to cycling in Heart Rate Zone 4[161]. When the heart rate increases, the time for diastole is shortened. This leads to reduced subendocardial filling time, potentially increasing the stress on the myocardium. Whether the release of cTn and other cell components is a protective mechanism remains speculation. In patients with undiagnosed coronary artery disease, this reduced subendocardial filling time could provoke ischemia, potentially explaining some cTn elevation.

13.1.2 Duration

The same study by Ghekiere et al. found an inverse relationship between the duration of cycling and cTnI. This is best explained by the fact that a shorter duration means higher effort and intensity. Our study examined the impact of the time and heart rate

(HR) rather than just the HR alone. We found that the HR increase should be sustained for a specific period, consistent with the findings of a study conducted by Lara et al. This study discovered that cTnT levels increase during longer-running competitions[164]. This finding was also demonstrated in paper 2. In this paper, 59 participants were compared in response to three similar exercises but with different duration and intensities. When examining cTn values after a laboratory test, 43 (40-45) minutes and two bicycle races, 3.6 (3.4-4.0) and 4.2 (3.6-4.6) hours, absolute cTn values were highest after the race with the lowest duration and the suspected highest intensity. The cohort in 2014 was larger and less selected than the 2018 cohort, where the study was designed to evaluate differences between high and low cTn responders. In addition, participants were stopped during the 2018 race, making the race less hard and reducing the intensity. Stops were necessary to measure blood pressure, but these stops might influence our other measurements, explaining why we do not observe the exact relationship between intensity and cTn in the 2018 study vs the 2014 study.

13.1.3 Power

Power measurement is a more precise method to monitor intensity in cycling compared to heart rate (see Figure 1). Unfortunately, the equipment used is expensive and only adaptable to some bikes. Traditionally, power has been used in a laboratory setting to guide resistance and has often been adjusted by a test leader. Power measurement during a race allows for a thorough evaluation of muscular effort and the cardiovascular system's demands. This is especially important in cyclists, where there is a vast difference in the effort, depending on whether you go up or downhill, are catching all the wind, or can hide in the slipstream. We were lucky to use power measurements on 40 participants, but unfortunately, few other studies have done the same, so comparison is difficult. Richardson et al. have extensively measured marathon runners, comparing several running features with post-exercise cTn[160]. In their study, mean heart rate in per cent of heart rate on Vo2 max is correlated to post-exercise cTn, and in a marathon, this is probably a sufficient measurement of intensity.

13.1.4 Blood pressure and RPP

In line with the findings from Kleiven et al., we found an association between exercise-induced cTn elevation and systolic blood pressure in paper 1. A population-based study based on HUNT data has found increased blood pressure related to increased cTn[165], highlighting the relationship between systolic blood pressure and cTn. Resting SBP significantly correlates to SBP in exercise[166] (personal info Knut Gjesdal, unpublished material), and resting SBP probably reflects SBP during exercise, suggesting that the exercise-induced cTn response is exacerbated in subjects likely to have increased cardiac work during exercise. Cardiac work is defined as the product of stroke volume and aortic pressure. Rate Pressure Product (RPP) is the product of heart rate and systolic pressure and is used to estimate myocardial oxygen consumption, reflecting myocardial work[157]. In 2018, the maximum systolic blood pressure correlated with cTnI 24 hours after the lab test, while RPP was significantly correlated to cTnI. RPP was only significant in multiple regression models 3 hours after the lab test. Mohlenkamp et al. found no relationship between cardiac risk factors, e.g. blood pressure, in their study from 2014. Still, they only did baseline blood pressure and no measurements in a field setting[167]. Blood pressure has not been given much attention in investigating exercise-induced cTn[168,169]. Still, some studies have investigated the relationship between exercise-induced hypertension and cTn and found similar findings as ours[170]. In a large survey of Elite Soccer players in Norway, hypertension during preparticipation screening was correlated to higher left ventricular mass[171]. Systolic blood pressure is indicative of cardiac load. Common changes found in athletes are commonly thought to reflect increased volume load, but these findings suggest that changes could also be due to pressure overload in some athletes[171]. A follow-up of the same population investigating hypertension with ambulatory blood measurements indicates increased sympathetic activity in players with hypertension[172]. An experimental study induced hypertension in a swine model using phenylephrine and found an association between cTn, systolic blood pressure, and apoptosis without evidence of ischemia, highlighting the critical effect of blood pressure[173]. There is a need for more investigation of exercise-induced blood pressure

and long-term effects, especially in athletes over 40 years.[174] It is essential for future research to investigate the association between exercise-induced cTn and exercise-induced blood pressure, as both may have a pathological origin and potential predictive value, especially in a long-term perspective.

13.2 Individual factors

Even though exercise intensity and duration can explain some of the exercise-induced, there is a high degree of inter-individual variability[175]. In our study, individual cTn values from corresponding exercises were introduced in multiple regression analysis. By adding these results from both heart rate, blood pressure, or the combination of these were extruded. Baseline and 3-hour post-race cTn measurements were significant predictors of post-exercise Troponin elevation, explaining 65% of the variation. When dividing the group into quartiles based on previous cTn results, none from the highest quartile was found in the lowest quartile in the following results. This indicates that the release and detection of cTn are highly individual. Tian et al. conducted a study that yielded results similar to ours. Although their research took place in a laboratory rather than a field setting like ours, they still found a comparable level of correlation[176]. Aengevaeren et al. examined participants after a long walking march for four consecutive days. They found a reduction in cTn levels in healthy patients and patients with cardiovascular risk factors but not in patients with established CVD[177]. Even though the cTn values declined during the study, the researchers showed a similar between-group response to our findings. Individual properties in the processing of cTn need to be considered when evaluating exercise-induced cTn. From a clinical perspective, a patient with a former elevated cTn without cardiac disease will most possibly react similarly when exposed to a similar workload.

13.3 Atherosclerosis

Earlier studies have found a relationship between obstructive CAD and levels of cTn after 24 h[55], and Aengevaren found higher mortality in participants with elevated cTn after physical exercise[29]. In paper 3, we investigated the relationship between workload and exercise-induced troponin I (cTnI) elevation in individuals with and without atherosclerosis and the impact of workload on the cTnI response in the absence of obstructive coronary artery disease (CAD). The results revealed that workload had a significant relationship with cTnI elevation following strenuous exercise in individuals with non-obstructive CAD but not those without detectable CAD.

A significant correlation between intensity, measured as power or RPP, is first evident when dividing the group based on the presence of coronary atherosclerosis. Highly trained individuals can sustain a high workload despite reaching their maximum levels. This ability puts the heart under more stress than work on moderate intensities. In these individuals, vessels affected by atherosclerosis might affect blood flow so that the cardiac muscle is damaged. This is evident when we compare individuals with and without coronary atherosclerosis within the same work range. Individuals with atherosclerosis have a higher cTn than individuals without. In a recent study by Noaman et al., patients with coronary microvascular disease show increased levels of cTn after exercise in participants with increased microvascular resistance[178]. These patients had known ischemia or myocardial injury and were not comparable to our cohort. Still, similar mechanisms could be responsible for our study's relationship between exercise intensity and cTn.

A higher prevalence of coronary calcification is found in amateur athletes than controls, and higher activity levels indicate a higher degree of calcification. So far, this has not been linked to an increase in risk, and one reason could be that plaque morphology differs between athletes and controls, with athletes showing a more benign plaque composition[147]. The explanation for this increased coronary

calcification in athletes is much debated, and several answers exist, including inflammation, increases in blood pressure and endocrinological changes.[147] Some explanations are similar to those used to explain exercise-induced cTn, and there might be confounding reasons. Longitudinal studies between exercise-induced cTn and the development of Atherosclerosis could highlight this relationship and further increase our knowledge regarding pathological and physiological exercise-induced cTn[32].

This study measured the workload as global work measured with power meters and cardiac work measured with RPP. Atherosclerosis added an impact on the relationship between workload and subsequent cTnI elevation. We also found that cTnI response was only higher in individuals with atherosclerosis exposed to the most increased workloads, indicating a demand/supply mismatch when myocardial energy demand exceeds the oxygen-delivering capacity of the coronary arteries in atherosclerotic individuals. Still, our findings are only indicative since this analysis is based on a small and highly selected population. The results showed a consistent relationship between the exercise-induced cTnI response and power output in individuals with CAD. In contrast, there was only a significant relationship between the cTnI response and RPP following the race. RPP is a surrogate marker of cardiac workload but is more challenging to interpret since participants need to be stopped at selected points to get adequate measurements. Power and heart rate collection are done continuously with a heart rate monitor, giving much smoother data. Power measurement should be seen as a stress marker and will induce cTn at both short and long durations. RPP is a marker of myocardial work and could indicate a more ischemic pathway in long-distance races in selected populations[170]. This suggests that the exercise-induced troponin response needs to be interpreted to the timing of the blood-sample acquisition, workload, and underlying coronary artery disease. The findings have several clinical implications, including individual guidance to physical exercise and the evaluation of therapeutic interventions.

13.4 Methodological considerations

This observational study is designed to explore the effects of strenuous exercise. We have been approved to monitor our participants for 20 years, providing us with valuable insights into the long-term effects of physical activity. In paper 2, we use a cohort design to track participants exhibiting high levels of exercise-induced cTnI to determine whether this is a personal characteristic or merely related to a given exercise. An observational study allows for a detailed exploration and description of the effects of exercise but cannot establish a cause-effect relationship. To do this, a more interventional design would be suited. However, in exercise-induced cTn, there is still much to learn, and several questions remain unanswered. A more explorative design is suited. In subsequent studies, several findings from our NEEDED observational study will be used to generate hypotheses for controlled intervention studies.

Our data are generally of good quality despite the high number of participants, especially in 2014[150]. Trained nurses and health personnel were used to get the results as accurately as possible. Still, with these amounts of data, some errors will occur, both due to human and analytical errors.

In Paper 1, we needed more funding to equip all the participants with the same device. We had to rely on participants to bring their own devices. Of 1002 participants, we could get hold of 291 participants with sports watches, and out of these, 114 had to be excluded due to quality issues. The remaining files were not sampled at the same rate and had to be interpolated for comparable results. The interpolation was done according to mathematical standards, resulting in a master's thesis at the University of Stavanger.[154] The heart rate monitors were from different manufacturers and stored data in various file formats. We believe the data holds an adequate quality for our analysis. Our findings underscore that intensity duration is more important than short episodes of high HR. A sampling time of 1 sec is sufficient. More advanced measurements, such as Heart Rate Variability (HRV),

were impossible due to the lack of beat-to-beat data. Neurohormonal changes can be found in HRV measurements; we cannot exclude a relationship between HRV and the exercise-induced cTn response.

Blood pressure during CPET was taken with the same blood pressure device on all participants with the same study personnel. During the race, blood pressure was taken at four different pitstops. At the top and after the two most prominent hills. The top of the two hills was thought to reflect the maximum effort, and after these two hills, blood pressure most possibly decreased. Due to logistical reasons, we needed to use four different teams to get these measurements, but they all used the same equipment and followed the same procedure. Blood pressure during exercise was only measured once, thought to reflect a peak pressure. Multiple measurements could have increased accuracy but would have acquired more time, probably reducing the pressure since exercise was stopped. All samplings from the exercise test results were weighted equally in calculating mean RPP. We do not know the pressure between sampling points or whether our calculated pressure reflects an actual mean pressure during the race. It seems impossible to get continuous blood pressure measurements from a mountain bike race, and this was the best indication of blood pressure during the test we could get. It would have been difficult to stop the participants at more stations as these would probably give them lower speed and intensity. There are different opinions on whether to stop an exercise test if blood pressure exceeds a certain limit[174,179]. We did not have this kind of limit. All our participants are used to exercising with a high effort, and these results are thought to reflect the same effort they usually place upon themselves. The blood pressure we measure reflects the blood pressure these participants are exposed to during regular activity, such as spinning lessons and amateur racing. The same applies to the CPET test, where participants were encouraged to perform at a maximum level but not forced to overachieve.

The grouping of participants based on the findings of CAD was done after the race. This limits the possibility of bias as both the doctor doing the stress test and the doctors performing echocardiography were blinded to whether this was a patient with atherosclerosis. Based on our findings from 2014, we believed there would be a difference in cTn values based on findings of CAD, but our data does not have the power to find this difference. However, based on bivariate correlations, the elevation of cTn seems to react differently in the two groups. Resting values of cTn are known to have a prognostic capability[180], and there is a small but significant difference between the two groups at baseline before the race. We do not have the activity measurement between the CPET test and the race. Based on personal experience and information from the participants, it is possible to imagine an increased level of activity leading up to the race, potentially creating different cTn profiles between the two groups. Further research using the same equipment but with a controlled load is needed to highlight the difference between participants with CAD and those without.

13.4.1 Study population

The NEEDED 2014 population is based on registration from the web solution from the North Sea Endurance Race; only participants already interested in the race were invited to participate. The study was also promoted as a heart study, which means that participants with an underlying concern or cardiac disease in their families were prone to be more interested in the study.

In our first paper, only participants who owned their heart rate monitors were allowed to participate. Only monitors with the possibility of exporting the heart rate data as a file for further processing were included. This limits the heart rate monitor model to a specific capacity and price range. This gives a highly selected population with an increased risk of selection bias since these participants are more likely to be interested in health and training. Despite this, the population from our first paper resembles the population from the main study regarding gender, age, personal characteristics, and results from the North Sea Race.

The 2018 study included only participants screened with CCTA in either 2013, 2014, or 2015. From the 2013 and 2014 studies, only participants with a high cTn value were selected. The remainder were randomly selected from the 2014 population with cTn values below 200. This selection was made to see whether exercise-induced cTn was a trait specifically for this person or if this could be modified. None of the participants developed a significant obstructive disease in the observation period (2013 – 2018), but progression of CAC was found in 15 participants. This progression was related to age and baseline CAC, not training experience[181]. The study is well-designed to highlight the differences between participants with high or low levels of exercise-induced cTn. Due to the diversity of atherosclerotic disease, concluding when we divide based on CCTA findings is a bit more conflicting. As none of the participants had developed significant stenosis, we split the group in two, even though a more stepwise approach could have been used. This is why even small findings of CAC were reported as atherosclerosis, to keep the term "Normal" as uniform as possible. Since the number of participants is small, the risk of type 2 error increases if we divide the participants into several smaller groups.

13.4.2 Diagnostic methods

Increasing CAC scores are related to increased risk; the absence of atherosclerosis (CAC = 0) gives a meagre chance of future cardiac events.[182] As earlier studies have found a relationship between coronary stenosis, MACE, and elevated exercise-induced cTn levels; there was an expectation that this might apply to participants with atherosclerosis. The term INOCA (ischemia in non-obstructed coronary arteries) has received increased interest in recent years. The term is used on several conditions with suspected or proven ischemia but without findings of obstructed coronary arteries. As CCTA is a merely anatomical examination, we cannot tell whether cTn in our cohort is part of an ischaemic pathway. Future studies should further implement functional tests to investigate the relationship between coronary atherosclerosis and ischemic cTn release.

Echocardiography offers the ability to get a functional assessment of cardiac movement after exercise. Participants were examined with echocardiography without delay directly after CPET and as soon as possible after the Race. Echocardiography after the test should be seen as an exercise stress echocardiogram. There were no differences between groups, neither when dividing based on cTn elevation or Atherosclerosis. All our participants are highly trained and used to exercise during high intensity. Even if cTn should have an ischemic origin, current measurements are inaccurate enough to find these changes. A recent publication on the same cohort using measurements of myocardial work (MW) shows increased myocardial inefficiency after the race compared to the CPET[183]. Still, measurements of strain or ejection fraction fail to find any differences.[183] The use of new techniques may increase the ability to find the origin of exercise-induced cTn.

14. Limitations

Our second study used study subjects from a selected cohort. Since only a subgroup had heart rate monitors, no additional data exist to evaluate exercise intensity from the recruitment race (T0) other than race duration. Hence, it is impossible to accurately compare race intensity differences between the (T0) and the 2018 race (T2). We only followed exercise-induced cTn response for 24 hours. We have previously reported that prolonged release of cTnI might be associated with a pathological cTnI response[55]. The reproducibility of cTn elevation beyond 24 hours should be monitored in other studies.

In our third study, the small sample size reflects a highly selected study population. The present findings should be seen as merely hypothesis-generating. The results are restricted to this population of highly trained amateur athletes, but these middle-aged, well-trained athletes represent a substantial risk group. Several limitations apply to the measurements of RPP. Physical and psychological stressors can impact the findings in a field setting, and the four measurements during the Race are all weighted the same but acquired in different locations (top and bottom of the two most prominent hills). These findings should be taken into consideration in the planning of new studies.

CCTA is only an anatomical examination, and to use this to divide into sub-groups is troublesome. To avoid even smaller groups, we only split them into two, Normal or Atherosclerotic. However, one should expect differences in the atherosclerotic subgroup as the range of CAC scores was from 1 to 372. However, age affects the percentile scoring, and the range in the calcium percentile is smaller, from 40 to 92%, meaning that even though the absolute score is low, they could not have been classified as Normal. Reducing the number in each group increases the risk of Type 2 errors. We already excluded 19 participants due to the lack of power meters, so we used Normal and Atherosclerotic as classifiers.

15. Conclusions

This thesis has explored the relationship between exercise intensity and cardiac troponins. The following conclusions can be made from our findings.

- Duration of exercise with a heart rate over 150 bpm is an independent predictor of exercise-induced cTn, improving the predictability of an existing model based on multivariate analysis. This suggests that exercise-induced cTn elevation is related to both the intensity and duration of this intensity.
- Elevation of cTn after exercise is reproducible and related to individual characteristics. Higher duration was associated with higher cTn, and the highest values of cTn were found after the exercise with the expected highest intensity.
- External load measured by power meters is associated with elevation of cardiac Troponins in patients with coronary artery disease but not in their healthy counterparts.

16. The future role of Troponins in exercise

The use of cardiac Troponins is well established in diagnosing acute myocardial infarction, and recent guidelines take advantage of the high sensitivity assays in the pre-screening and follow-up of patients undergoing non-cardiac surgery. It is intriguing to think of the possibility of doing the same in an athletic population, but this has yet to be established. A recent pilot study examining the use of cardiac troponins after stress-ECG in soccer players fails to find any changes in cTn[184]. A meta-analysis from 2019 from patients undergoing stress-ecg concludes that cTn patterns appear inconsistent and without differences between those with and those without inducible ischemia[185]. The current thesis highlights several aspects that must be addressed before cTn is used as a screening tool. Firstly, as demonstrated in a recent article examining different cTn responses after 60 minutes of treadmill running at different intensities, the intensity and duration of this intensity need to be considered when evaluating post-exercise levels of cTn[163]. Secondly, previous results of cTn should be considered. After an initial screening to exclude underlying coronary atherosclerosis, it should be possible to develop a personal cTn profile, which could be used as a part of a yearly follow-up.

Physical exercise is recommended for all conditions, even for heart disease. When prescribing exercise programs for patients after myocardial disease, cTn can be a screening tool. During early rehabilitation, it's intriguing to picture a possible establishment of a personal cTn profile based on data from heart rate monitors and work measures. In future follow-ups or examinations after new-onset symptoms, deviation from this follow-up could indicate progressing disease. We recommend that future studies combine data from activity trackers and cardiac Troponin levels to establish such algorithms.

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ORIGINAL RESEARCH

Duration of Elevated Heart Rate Is an Important Predictor of Exercise-Induced Troponin Elevation

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Background—The precise mechanisms causing cardiac troponin (cTn) increase after exercise remain to be determined. The aim of this study was to investigate the impact of heart rate (HR) on exercise-induced cTn increase by using sports watch data from a large bicycle competition.

Methods and Results—Participants were recruited from NEEDED (North Sea Race Endurance Exercise Study). All completed a 91-km recreational mountain bike race (North Sea Race). Clinical status, ECG, blood pressure, and blood samples were obtained 24 hours before and 3 and 24 hours after the race. Participants (n=177) were, on average, 44 years old; 31 (18%) were women. Both cTnI and cTnT increased in all individuals, reaching the highest level (of the 3 time points assessed) at 3 hours after the race ($P<0.001$). In multiple regression models, the duration of exercise with an HR >150 beats per minute was a significant predictor of both cTnI and cTnT, at both 3 and 24 hours after exercise. Neither mean HR nor mean HR in percentage of maximum HR was a significant predictor of the cTn response at 3 and 24 hours after exercise.

Conclusions—The duration of elevated HR is an important predictor of physiological exercise-induced cTn elevation.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02166216. **(*J Am Heart Assoc*. 2020;9: e014408. DOI: 10.1161/JAHA.119.014408.)**

Key Words: cardiac troponins • cardiac work • heart rate • physical exercise

Prolonged strenuous physical exercise leads to elevation in circulating cardiac troponin (cTn) levels in healthy subjects.[1] Although increased cTn levels are considered to reflect myocardial damage, the exercise-induced cTn elevation in healthy subjects is considered to be a physiological response.[2] The cause and implications of the activity-mediated cTn response remain to be determined.[3,4]

We recently demonstrated an inverse correlation between race duration and exercise-induced cTn elevation, suggesting that the duration of high-intensity exercise is a significant determinant of the cTn response.[5] Heart rate (HR) is a major marker of exercise intensity.[6] A relationship between HR during exercise and the exercise-induced cTn elevation may therefore be anticipated. However, studies reporting on the relationship between HR and cTn levels have been conflicting: Some studies have found a relationship between HR and cTn levels,[7–10] whereas others have not.[11,12] The relationship between HR and the exercise-induced cTn response therefore remains obscure. Previous studies have been subject to several potential limitations: no study included >100 subjects, and most studies only reported on the relationship between cTn and mean and maximum HR.[9]

The aim of the present study was 3-fold: (1) to describe the relationship between HR and the exercise-induced cTn elevation in a larger population of healthy recreational athletes, (2) to explore the additional value of a comprehensive HR feature analysis for the prediction of the exercise-induced cTn response, and (3) to determine the presence of a potential HR threshold associated with the exercise-induced cTn response.

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Accompanying Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014408

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Clinical Perspective

What Is New?

- The duration of elevated heart rate >150 beats per minute is an independent and important predictor of exercise-induced troponin elevation.
- There may be a heart rate threshold associated with an exercise-induced troponin elevation.

What Are the Clinical Implications?

- Sport watches may be used to monitor exercise intensity and duration in relation to troponin release.
- The clinical role of heart rate threshold values associated with exercise-induced troponin elevation needs to be determined.
- Heart rate threshold of exercise-induced troponin release may potentially represent both training targets and safety margins of training.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Study subjects were recruited among healthy recreational cyclists participating in NEEDED (North Sea Race Endurance Exercise Study) 2014 (NCT 02166216). All study subjects completed the 91-km recreational mountain-bike race, the North Sea Race (Figure 1), in 2014. Participants in whom coronary artery disease was revealed by examinations after the race were excluded from the present analysis. Recruitment, inclusion and exclusion criteria, and data sampling in the main NEEDED 2014 have been described previously.[5] HR data were extracted from personal sport watches used by study subjects during the race (Figure 2). Digital HR data were harmonized, and HR features were calculated. The various HR features were compared with cTn levels acquired before and 3 and 24 hours after the race. All participants signed informed consent before enrollment into the study. The study was conducted according to the Declaration of Helsinki and approved by the Regional Ethics Committee (Regional Etisk komité No. 2013/550).

Sport Watch Data Processing

The sport watch files containing HR and geopositioning data were downloaded after the race, on site, sent by e-mail, or uploaded via a web-based solution delivered by Trainingpeaks (Trainingpeaks.com, CO). Sport watch data files were processed and analyzed at the Department of Electrical Engineering and Computer Science, University of Stavanger, Stavanger, Norway. The HR files did not contain information on the specific sport watch type. We were therefore not able to adjust for the different types of sport watch used.

To minimize the potential differences between different sport watches, we applied stringent measures to harmonize data and to ensure as high-data quality as possible. We excluded all files (n=114; Figure 2) with incomplete data sets, insufficient data sampling frequency, longer periods of missing data, or HR=0 (as described below).

The following file types were excluded because of missing combination of HR and/or geopositioning data: GPX, WKO,

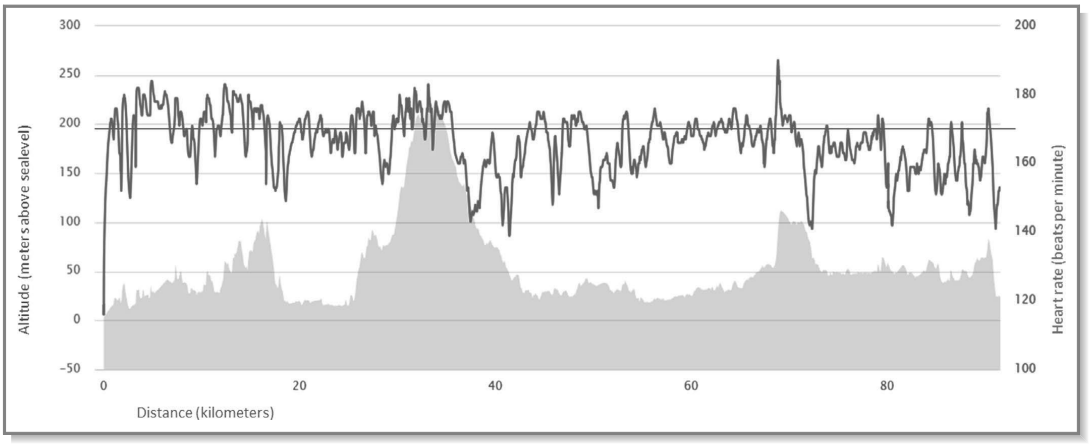

Figure 1. Diagram of heart rate (HR), altitude, and distance at the 91-km North Sea Race. HR is outlined in red, and altitude is in gray. The diagram is a representative presentation of HR from a single study participant, and the horizontal line is the subject's mean HR during the race (168 bpm). Distance (in kilometers) is along the *x* axis. The diagram is exported from the Garmin Connect website (copyright Garmin International, KS, US).

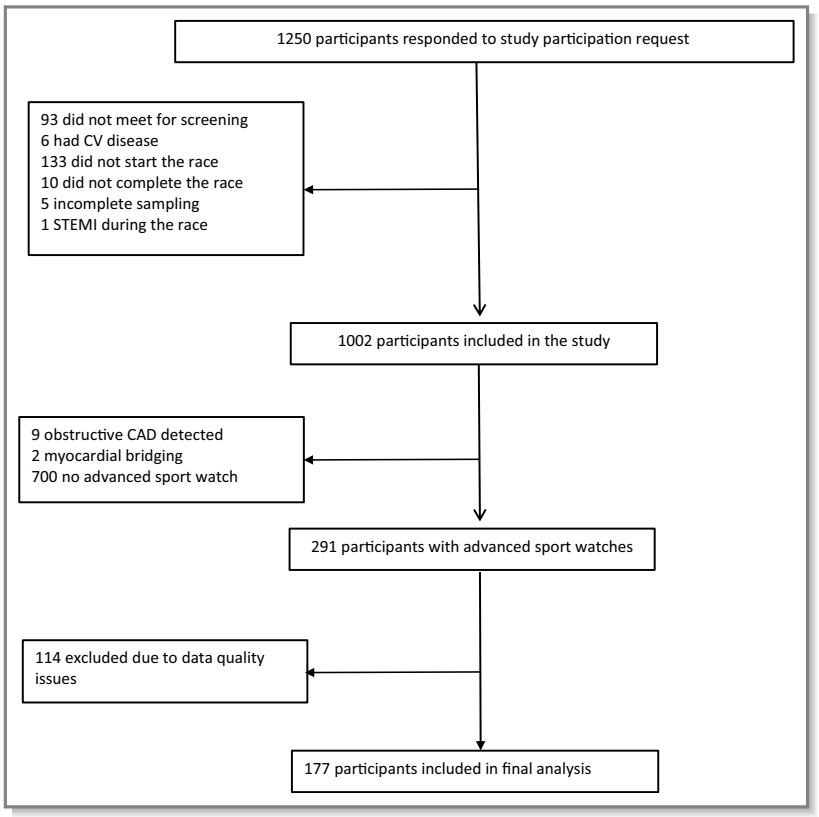

Figure 2. Flowchart depicting the recruitment of the study participants. CAD indicates coronary artery disease; CV, cardiovascular; STEMI, ST-segment–elevation myocardial infarction.

HRM, LSX, and OPL (n=14). The files included in the initial evaluation were CSV files (n=212), FIT (n=38), TCX (n=15), PWX (n=21), and XML (n=4).

These files were given a unique identifier and imported into MATLAB (Mathworks Inc, MA) for further processing. The files were harmonized by accurately defining start/stop of activity. All data were adjusted to a frequency of 1 HR value (beats per minute [bpm]) per 1 second. To correct for missing data, HR per second was interpolated from neighboring HR data. Files that did not allow harmonization of starting/stopping points or contained insufficient data to allow HR interpolation every second were excluded. A total of 177 files were included in the final analysis.

HR Features

HR data were downloaded and analyzed for the whole race, and mean and maximal HR values were calculated. The theoretical age-adjusted HR was estimated using the formula of Tanaka et al.[13] The intensity/time domain was analyzed by calculating the duration of time spent above HR thresholds of 140, 150, and 160 bpm for the complete race. Mean HRs and the time/HR integrals (above each of these HR thresholds) were calculated. The purpose of the variable time-HR integral, HR >×bpm, was to allow an interpretation of the troponin response to the combined effects of the duration and the magnitude of HR elevation above the specified HR limit. The time-HR integral corresponds to the area under the HR curve for all HR values exceeding the given HR threshold. The chosen HR thresholds were based on prior studies that suggest a stepwise increase in cTn between mean HR of 140 and 160 bpm.[14] In addition, the time spent with an HR >85%, >90%, and >95% of the maximal achieved HR during the race was calculated to allow a global assessment of HR distribution close to maximal effort.

Blood Samples

Blood samples were acquired 24 hours before and at 3 and 24 hours after exercise. The decision to sample blood at 3 hours

rather than immediately after exercise was based on the findings from the NEEDED 2013 pilot study that demonstrated better hydration and cTn levels more close to the expected physiological postexercise peak when cTn was sampled at 3 hours after exercise.[15] Venous blood samples were drawn from the antecubital vein. Cardiac TnI (serum) was analyzed within 24 hours at Stavanger University Hospital on an Architect i2000SR using the high-sensitive cTnI STAT assay from Abbott Diagnostics (IL). Frozen samples were transported on dry ice to Haukeland University Hospital, Bergen, Norway; and cTnT was analyzed using a high-sensitivity cTnT assay on Cobas e601 (Roche Diagnostics, Switzerland) on first-time thawed serum. The cTnI assay has a lower limit of detection of 1.6 ng/L, and the 99th percentile of the assay was set at 26 ng/L. The cTnT assay had a limit of blank of 3 ng/L and a 99th percentile of 14 ng/L.[16]

Statistical Analysis

Continuous and fairly symmetrically distributed variables are reported as mean±SD, whereas continuous variables with markedly skewed distributions are reported as median and interquartile range, reporting the 25th and 75th percentiles. The Shapiro-Wilk test was used to test for normality. Mann-Whitney *U* test and Student *t* test were used to test for difference between groups. For changes over all 3 time points, a Friedman test was used for markedly skewed distributions and a repeated-measures ANOVA was used for normally distributed variables. For comparison between 2 time points, Wilcoxon signed rank test was used for variables with markedly skewed distribution and paired Student *t* test was used for normally distributed variables. For bivariate correlations, Spearman's rank-order correlation was used. Because of the considerable number of statistical tests performed and the corresponding increased false-positive rate, a $P<0.01$ was regarded as significant. Multiple linear regression was used to study possible associations between HR variables and cTn levels. Because of markedly skewed distributions, cTn values were ln transformed. In the multiple regression models, we prespecified a fixed set of parameters for a basic model based on our findings from our main study.[5] The following variables were included in this model: age, sex, body mass index, race duration, systolic blood pressure (SBP), estimated glomerular filtration rate, low-density lipoprotein, Framingham Risk Score, resting HR, and baseline ln cTn. Different HR features were then added to the model one by one to see the changes in coefficient of determination (R^2). The following variables were added by this method: mean HR, maximum HR, mean HR in percentage of estimated maximum HR, time spent with an HR >140, >150, and >160 bpm, integral of time and HR with an HR >140, >150, and >160 bpm, integral of time with an HR >85%, >90%, and >95% of maximum achieved HR, mean HR >140, >150, and >160 bpm, and percentage of race time with an HR >140, >150, and >160 bpm. Recent data suggest that training history influences the exercise-induced cTn response.[17] Therefore, in addition to the basic model described in the Introduction, we constructed a new extended basic model that also contained training history expressed as years of endurance training. The following variables were included in the "extended basic model": age, sex, body mass index, race duration, SBP, estimated glomerular filtration rate, low-density lipoprotein, Framingham Risk Score, resting HR, baseline ln-cTn, and years of endurance training. Linear regression models using backward selection and forward inclusion showed similar effects on both the level of prediction and the level of significance. For all statistical analyses, the statistical software programs SPSS, version 24, and R[18] were used.

Results

A total of 177 subjects, 44±8 years of age, 31 (18%) women, were included in this analysis (Figure 2). Baseline values for the included subjects are outlined in Table 1. There was no former history of diabetes mellitus, hypertension, or heart disease among study participants. Mean race duration was 3:23 hours for men and 4:00 hours for women ($P<0.001$). Maximal and mean HR, as well as total time spent above the HR thresholds, are shown in Table 2.

cTn and Clinical Variables

Median cTnI at baseline was 1.9 (1.6–3.3) ng/L, increased to 60.0 (36.0–99.3) ng/L at 3 hours ($P<0.001$) and declined at 24 hours to 10.9 (6.1–22.4) ng/L ($P<0.001$). A similar profile was found for cTnT: baseline, <3.0 (<3.0–3.8) ng/L; 3 hours, 38.3 (25.6–55.2) ng/L ($P<0.001$); and 24 hours, 11.0 (7.2–17.4) ng/L ($P<0.001$) (Figure 3). HR at baseline was 59±10 bpm. At 3 hours after the race, mean resting HR increased to 78±10 bpm ($P<0.001$). Both SBP and diastolic blood pressure were significantly ($P<0.001$) decreased 3 hours after the race, compared with baseline: SBP, 138 (126–148) mm Hg (baseline) versus 129 (120–172) mm Hg (3 hours); and diastolic blood pressure, 80 (74–86) mm Hg (baseline) versus 74 (69–79) mm Hg (3 hours). Blood pressure was lower at 24 hours compared with baseline: SBP, 130 (120–138) mm Hg; and diastolic blood pressure, 73 (68–79) mm Hg ($P<0.001$). There was no change in HR at 24 hours compared with baseline. SBP at baseline was correlated with cTnI and cTnT levels at 24 hours after the race, but not with the peak cTn levels 3 hours after the race. There was no major change in body weight from baseline to 3 and 24 hours after exercise (Table 1).

Table 1. Baseline Variables

Variables	Values (n=177)
Age, y	43.9±8.0
Men, n (%)	142 (82)
Weight, kg	82.2±11.5
BMI, kg/m^2	25.6±2.7
Resting HR at baseline, bpm	59±10
SBP at baseline, mm Hg	138 (126 to 148)
DBP at baseline, mm Hg	80 (74 to 86)
Framingham Risk Score	1 (0 to 2)
Training status and competitive experience	
Endurance training, y	11.8±10.6
METs, minimum, min/wk	3948±2976
No. of endurance competitions in past 5 y	10 (5 to 20)
Biomarkers at baseline	
cTnI, ng/L	1.9 (1.6 to 3.3)
cTnT, ng/L	<3.0 (<3.0 to 3.8)
Total cholesterol, mmol/L	5.1 (4.5 to 5.7)
LDL, mmol/L	3.1±0.83
HDL, mmol/L	1.5 (1.3–1.7)
eGFR, mL/min per 1.73 m^2	93±13
Race data	
Race duration (h:min)	3:33 (3:09–3:54)
Change in body weight from baseline to 3 h, %	0.5 (−0.6 to 1.4)
Change in body weight from baseline to 24 h, %	0.0 (−1.0 to 0.81)

Baseline characteristics and race performance in study subjects (n=177). Values are given as mean±SD or median (25th–75th percentile) if markedly skewed distributions. BMI indicates body mass index; bpm, beats per minute; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; MET, metabolic equivalent; SBP, systolic blood pressure.

Table 2. HR Variables During the Race

HR Variables	Values
Mean HR, bpm	158±11
Maximum HR, bpm	179±11
Mean HR of estimated maximum HR, %	89±6
Maximum HR of estimated maximum HR, %	100 (97–105)
No. of episodes with HR >150 bpm	32 (11–64)
Mean HR >140 bpm, bpm	160 (153–166)
Mean HR >150 bpm, bpm	162 (157–167)
Mean HR >160 bpm, bpm	167 (163–170)
Time-intensity (HR) domain	
Race time with HR >140 bpm, min	200 (175–215)
Race time with HR >150 bpm, min	175 (133–203)
Race time with HR >160 bpm, min	97 (36–166)
% Race time with HR >140 bpm, %	98 (91–100)
% Race time with HR >150 bpm, %	88 (63–97)
% Race time with HR >160 bpm, %	52 (16–80)
Time-HR integral HR >140 bpm, HR h	62.5 (43.8–90.1)
Time-HR integral HR >150 bpm, HR h	30.7 (15.5–55.5)
Time-HR integral HR >160 bpm, HR h	8.9 (2.1–25.0)
Race time >85% of maximum achieved HR, min	183 (159–211)
Race time >90% of maximum achieved HR, min	159 (88–189)
Race time >95% of maximum achieved HR, min	69 (16–138)
Time-HR integral >85% of achieved maximum HR, HR h	43.9 (36.8–52.3)
Time-HR integral >90% of achieved maximum HR, HR h	19.3 (14.6–23.7)
Time-HR integral >95% of achieved maximum HR, HR h	3.7 (2.5–5.4)

HR variables during the race in 177 study subjects. Values are given as mean±SD or median (25th–75th percentile) if markedly skewed distributions. Mean HR >140, >150, and >160 bpm relates to the mean of HR values exceeding the HR threshold in each individual. Table 2 reports the distribution of these individual mean HR values between all study subjects. The distribution of the mean individual HR values was skewed, and these data are therefore presented as medians (25th–75th percentiles). Bpm indicates beats per minute; HR, heart rate.

Exercise-Induced Troponin Response and HR Variables During the Race

Bivariate correlations with cTn and HR variables are outlined in Table 3. At 3 hours after the race, only time spent with HR >150 bpm correlated significantly to both the cTnI (r=0.18; P=0.017) and cTnT (r=0.16; P=0.034) responses. The same relationship could be found with the integral of race-time with HR >150 bpm and the percentage of race-time with an HR >150 bpm. No significant association was found to time spent in HR zones defined as the percentage of maximum HR. The number of episodes with HR >150 bpm did not correlate with cTn levels at any time point.

Multiple Regression Models

The basic model reached approximately the same R^2 in this subgroup analysis as in the main study[5] (3-hour cTnI R^2=0.15 and cTnT R^2=0.16; 24-hour cTnI R^2=0.36 and cTnT R^2=0.28). By adding HR features, the R^2 increased by a maximum of 5 percentage points. Duration of time with an HR of ≥150 bpm was the only explanatory variable showing significant association with both cTnI and cTnT at both 3 and 24 hours. At the same time, between all the candidate variables, this variable produced the relatively largest increase in explained variance in

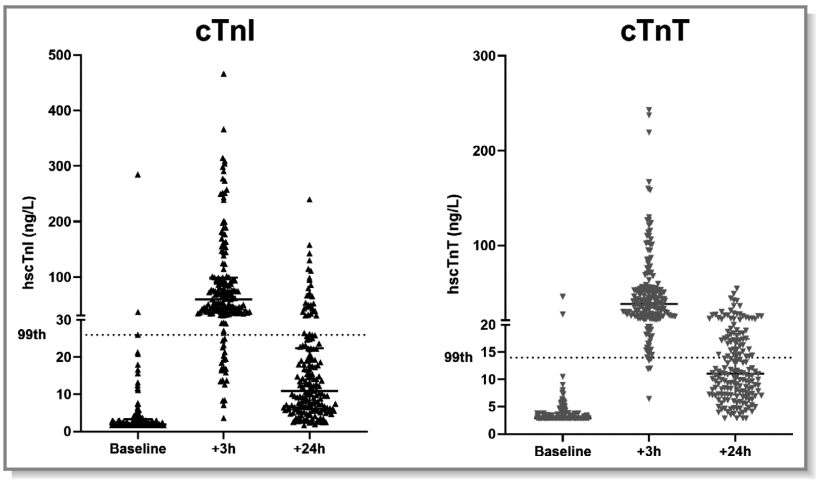

Figure 3. Scatter plot of cardiac troponin (cTn) values at all postrace time points. The *y* axis has been modified to allow a representative display of both high and low numbers in the same figure. The timing of blood sampling is represented by the *x* axis: baseline blood samples were acquired between 24 and 12 hours before the race, whereas blood samples +3 h and +24 h were acquired 3 and 24 hours after the race, respectively. The dotted lines represent the 99th percentile (high-sensitivity cTnT [hscTnT], 14 ng/L; and high-sensitivity cTnI [hscTnI], 26 ng/L). The horizontal black lines represent the median value.

the regression models of cTn elevation (Table 4). The same results could be found when using time >150 bpm in percentage of total race-duration. The extended basic model (including years of endurance training as an additional explanatory variable) increased the R^2 in all subgroups compared with the original basic model derived from the main study. The model increased the R^2 value at 3 hours (cTnI R^2=0.25 and cTnT R^2=0.23) and at 24 hours (cTnI R^2=0.44 and cTnT R^2=0.32). Also in the extended model, the duration of HR of ≥150 bpm was the variable with the highest increase in R^2 that also remained significant for both cTnI and cTnT at both time points: the R^2 increased between 3 and 5 percentage points in the models (Table 5). Full models containing all variables could be found in the supplemental tables: basic model (Table S1), basic model with time >150 bpm (Table S2), basic model with percentage of race duration >150 bpm (Table S3), and extended basic model with time >150 bpm (Table S4).

Discussion

The present study is the largest study to date to investigate the relationship between HR and the exercise-induced cTn response in recreational athletes. The study indicates that the duration of elevated HR is an important determinant of the physiological cTn response. Our findings suggest that there may be a HR threshold defining the lowest exercise intensity needed to generate an exercise-induced troponin response. Pure chronotropic measures, such as mean HR and mean HR in percentage of maximum HR, did not increase the level of prediction of the cTn response. In contrast, features that combined HR with duration of exercise improved the prediction models up to 5 percentage points.

During prolonged high-intensity exercise, there is a cTn elevation in healthy individuals without evidence of myocardial injury.[19] Several mechanisms have been proposed to explain this response, including increased wall tension and ventricular strain caused by volume overload, neurohormonal stimulation, and/or reversible ischemia attributable to increased myocardial energy demands.[1,20] In the main NEEDED 2014, we demonstrated that SBP and race duration were major determinants of the physiological cTn response after exercise.[5] The present study confirms and extends these findings by demonstrating independent effects of the time-intensity domain on the prediction models of the exercise-induced cTn response.

A relationship between HR and cTn elevation is expected. Myocardial perfusion occurs predominantly during diastole. Increased HR shortens diastole with subsequent decrease in subendocardial perfusion, potentially inducing ischemia during exercise. In patients with normal coronary arteries admitted for supraventricular tachycardia, subjects with elevated troponin T had significantly higher HR compared to those with normal levels (191 versus 170 bpm; P=0.008). Furthermore, there was a significant correlation between maximum HR and the level of troponin elevation (r=0.64; P=0.001).[21] A recent meta-analysis by Donaldson et al may indicate a potential link between diastolic function and exercise-induced cTn elevation: In the

Table 3. Bivariate Correlations

	cTnI + 3 h		cTnT + 3 h		cTnI + 24 h		cTnT +24 h	
Variables	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value
Basic variables and race duration								
Age	−0.10	0.20	0.04	0.62	0.08	0.29	0.04	0.59
Resting HR	−0.04	0.57	−0.05	0.54	−0.09	0.22	−0.11	0.14
SBP baseline	0.11	0.14	0.07	0.37	0.22	0.004†	0.17	0.02*
DBP baseline	0.04	0.58	−0.04	0.57	0.18	0.02*	0.07	0.37
Resting HR 3 h after the race	−0.05	0.49	−0.04	0.62	−0.09	0.22	−0.10	0.21
SBP 3 h after the race	0.15	0.04*	0.09	0.26	0.18	0.02*	0.19	0.01*
DBP 3 h after the race	0.09	0.26	0.02	0.84	0.14	0.07	0.03	0.69
BMI	−0.05	0.50	−0.05	0.53	0.06	0.44	0.09	0.26
Weight	−0.02	0.78	0.02	0.84	0.06	0.46	0.18	0.02*
Waist circumference	−0.10	0.18	−0.05	0.52	0.02	0.77	0.15	0.04*
METs, min/wk	0.04	0.64	0.05	0.50	0.05	0.53	0.07	0.36
Years of endurance training	−0.09	0.24	−0.10	0.22	0.05	0.95	−0.03	0.67
Race duration	−0.13	0.10	−0.19	0.01*	−0.09	0.22	−0.22	0.004†
HR variables during the race								
Maximum HR	0.04	0.65	−0.01	0.94	−0.05	0.52	−0.01	0.89
Mean HR	0.13	0.08	0.11	0.14	−0.01	0.91	0.03	0.67
Maximum HR in % of estimated maximum	0.04	0.59	0.01	0.87	0.04	0.63	0.03	0.69
Mean HR in % of estimated maximum HR	0.10	0.21	0.07	0.34	0.09	0.24	0.06	0.38
No. of HR periods >150 bpm	−0.13	0.09	−0.11	0.15	−0.04	0.61	−0.06	0.40
Mean HR >140 bpm	0.16	0.03*	0.13	0.08	0.03	0.75	0.05	0.51
Mean HR >150 bpm	0.13	0.10	0.09	0.23	0.0	1.0	0.02	0.75
Mean HR >160 bpm	0.09	0.22	0.05	0.50	−0.03	0.72	0.01	0.94
Time-intensity (HR) domain								
Race time with HR >140 bpm	0.12	0.12	0.08	0.28	0.04	0.63	−0.03	0.66
Race time with HR >150 bpm	0.18	0.02*	0.16	0.03*	0.06	0.45	0.04	0.59
Race time with HR >160 bpm	0.15	0.05	0.11	0.16	0.00	0.99	0.01	0.90
% Race time with HR >140 bpm	0.18	0.02*	0.18	0.02*	0.06	0.43	0.13	0.10
% Race time with HR >150 bpm	0.19	0.01*	0.18	0.02*	0.06	0.44	0.11	0.15
% Race time with HR >160 bpm	0.18	0.02*	0.14	0.06	0.04	0.60	0.06	0.43
Time-HR integral >140 bpm	0.17	0.03*	0.13	0.08	0.02	0.75	0.04	0.65
Time-HR integral >150 bpm	0.16	0.04*	0.13	0.10	0.01	0.86	0.04	0.64
Time-HR integral >160 bpm	0.13	0.08	0.10	0.20	0.0	0.99	0.03	0.73
Race time >85% of achieved maximum HR	0.07	0.33	0.08	0.29	0.05	0.50	0.05	0.51
Race time >90% of achieved maximum HR	0.02	0.81	0.06	0.44	0.00	1.00	−0.02	0.76
Race time >95% of achieved maximum HR	−0.01	0.94	−0.02	0.78	−0.06	0.45	−0.02	0.79

Continued

Table 3. Continued

Variables	cTnI + 3 h		cTnT + 3 h		cTnI + 24 h		cTnT +24 h	
	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value
Time-HR integral >85% of achieved maximum HR	0.18	0.02*	0.14	0.06	0.08	0.30	0.03	0.71
Time-HR integral >90% of achieved maximum HR	0.22	0.004†	0.19	0.01*	0.11	0.13	0.07	0.35
Time-HR integral >95% of achieved maximum HR	0.19	0.01*	0.16	0.03*	0.11	0.13	0.07	0.36

Bivariate correlations (*P* values based on Spearman's rank test) between troponin (cTnI and cTnT) response and baseline and HR variables in blood samples acquired 3 and 24 hours after the race. BMI indicates body mass index; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DBP, diastolic blood pressure; HR, heart rate; MET, metabolic equivalent; SBP, systolic blood pressure.
*$P<0.05$, †$P<0.01$.

meta-analysis, exercise HR was the strongest predictor of increased cTn levels (R^2=0.31).[22] More important, the analysis found diastolic function to be influenced by exercise HR and cTn release, implying that high-intensity exercise elicits cTn release and reduces left ventricular diastolic function. One may therefore anticipate the exercise-induced cTn elevation to be related to increased HR.[23] However, as demonstrated by the present study, it is the combination of duration and HR, and not solely HR, that relates to the exercise-induced cTn elevation. Hence, to generate a cTn release, HR elevation must persist for a certain period. These findings are in line with the study by Lara et al demonstrating increasing cTnT levels in running competitions of increasing duration.[24] Our findings suggest that there may be an HR threshold required to generate an exercise-

Table 4. Changes After Adding HR Variables to the Basic Multiple Regression Model

Dependent Variables	Ln cTnI 3 h			Ln cTnT 3 h			Ln cTnI 24 h			Ln cTnT 24 h		
	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value
Basic model	0.19	. . .	. . .	0.17	. . .	. . .	0.37	. . .	. . .	0.26	. . .	. . .
Mean HR	0.20	0.01	0.18	0.17	0.01	0.29	0.38	0.01	0.48	0.26	0.01	0.22
Mean HR % of estimated maximum HR	0.20	1.88	0.18	0.17	1.08	0.29	0.38	0.93	0.49	0.26	1.08	0.24
Mean HR >140 bpm	0.20	0.02	0.09	0.18	0.01	0.13	0.38	0.01	0.20	0.28	0.01	0.09
Mean HR >150 bpm	0.19	0.01	0.34	0.17	0.01	0.35	0.38	0.01	0.46	0.27	0.01	0.19
Mean HR >160 bpm	0.19	0.00	0.78	0.17	0.01	0.64	0.37	0.01	0.77	0.27	0.01	0.26
Race time with HR >140 bpm	0.23	0.36	0.003	0.21	0.26	0.003	0.39	0.26	0.03	0.29	0.20	0.01
Race time with HR >150 bpm	**0.24**	**0.25**	**0.001**	**0.21**	**0.16**	**0.002**	**0.40**	**0.19**	**0.009**	**0.29**	**0.13**	**0.01**
Race time with HR >160 bpm	0.21	0.12	0.06	0.18	0.07	0.12	0.38	0.07	0.25	0.27	0.06	0.14
% Race time >140 bpm	0.23	1.41	0.004	0.21	1.03	0.003	0.39	1.05	0.02	0.29	0.83	0.009
% Race time >150 bpm	**0.24**	**0.97**	**0.001**	**0.21**	**0.63**	**0.003**	**0.40**	**0.77**	**0.006**	**0.30**	**0.52**	**0.007**
% Race time >160 bpm	0.20	0.43	0.07	0.18	0.26	0.13	0.38	0.29	0.20	0.27	0.25	0.11
Integral of time and HR >140 bpm	0.21	0.005	0.03	0.19	0.00	0.05	0.38	0.00	0.14	0.28	0.00	0.05
Integral of time and HR >150 bpm	0.20	0.01	0.11	0.18	0.00	0.15	0.38	0.00	0.33	0.27	0.00	0.13
Integral of time and HR >160 bpm	0.19	0.00	0.49	0.17	0.00	0.51	0.37	0.00	0.81	0.27	0.00	0.34
Time-HR integral >85% of achieved maximum HR	0.24	0.02	0.001	0.20	0.01	0.02	0.40	0.02	0.006	0.28	0.006	0.10
Time-HR integral >90% of achieved maximum HR	0.24	0.03	0.001	0.20	0.02	0.02	0.41	0.03	0.003	0.28	0.01	0.08
Time-HR integral >95% of achieved maximum HR	0.22	0.09	0.008	0.19	0.05	0.06	0.41	0.09	0.004	0.27	0.04	0.10

This table shows the effects of adding a single extra HR variable to the basic multiple model derived from the main NEEDED (North Sea Race Endurance Exercise Study) 2014. Variables included in the basic multiple linear regression model were as follows: baseline ln cTnI/cTnT, body mass index, age, sex, race duration, resting HR at baseline, systolic blood pressure at baseline, low-density lipoprotein cholesterol, estimated glomerular filtration rate, and Framingham Risk Score. Individual HR variables were added to the basic model to assess the impact of these variables on the R^2 and the association with cardiac troponin. The strongest models that were significant at all time points for both cTnT and cTnI were race time with HR >150 bpm and percentage of race time with an HR >150 bpm (outlined in bold letters). The full basic model is presented in Table S1. cTnI indicates cardiac troponin I; cTnT, cardiac troponin T; HR, heart rate; R^2, coefficient of determination.

Table 5. Changes After Adding HR Variables to the Extended Basic Model

	Ln cTnI 3 h			Ln cTnT 3 h			Ln cTnI 24 h			Ln cTnT 24 h		
Dependent Variables	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value
Extended basic model	0.25	. . .	. . .	0.23	. . .	. . .	0.44	. . .	. . .	0.32	. . .	. . .
Mean HR	0.26	0.01	0.28	0.23	0.01	0.43	0.44	0.01	0.55	0.33	0.01	0.37
Mean HR % of estimated maximum HR	0.26	1.61	0.28	0.23	0.86	0.42	0.44	0.81	0.56	0.33	0.81	0.39
Mean HR >140 bpm	0.26	0.02	0.13	0.24	0.01	0.19	0.45	0.01	0.17	0.34	0.01	0.13
Mean HR >150 bpm	0.25	0.01	0.40	0.23	0.01	0.40	0.44	0.01	0.39	0.33	0.01	0.21
Mean HR >160 bpm	0.25	0.004	0.78	0.23	0.01	0.60	0.44	0.01	0.63	0.33	0.01	0.22
Race time with HR >140 bpm	0.28	0.35	0.01	0.25	0.23	0.03	0.46	0.27	0.04	0.34	0.18	0.05
Race time with HR >150 bpm	**0.30**	**0.25**	**0.003**	**0.26**	**0.15**	**0.01**	**0.47**	**0.20**	**0.01**	**0.35**	**0.11**	**0.04**
Race time with HR >160 bpm	0.26	0.10	0.15	0.23	0.05	0.27	0.45	0.07	0.28	0.33	0.05	0.30
% Race time with HR >140 bpm	0.28	1.23	0.02	0.25	0.83	0.03	0.45	0.97	0.06	0.34	0.66	0.06
% Race time with HR >150 bpm	0.29	0.90	0.004	0.26	0.55	0.02	0.47	0.75	0.01	0.34	0.42	0.04
% Race time with HR >160 bpm	0.26	0.35	0.17	0.23	0.18	0.31	0.45	0.27	0.25	0.33	0.17	0.28
Integral of time and HR >140 bpm	0.27	0.005	0.06	0.24	0.003	0.11	0.45	0.004	0.11	0.34	0.003	0.09
Integral of time and HR >150 bpm	0.26	0.004	0.18	0.23	0.003	0.25	0.45	0.003	0.26	0.33	0.003	0.18
Integral of time and HR >160 bpm	0.26	0.003	0.57	0.23	0.002	0.59	0.44	0.002	0.63	0.33	0.003	0.32
Time-HR integral >85% of achieved maximum HR	0.29	0.02	0.008	0.24	0.01	0.11	0.46	0.01	0.02	0.33	0.003	0.44
Time-HR integral >90% of achieved maximum HR	0.29	0.03	0.008	0.24	0.01	0.09	0.47	0.02	0.01	0.33	0.01	0.34
Time-HR integral >95% of achieved maximum HR	0.28	0.08	0.02	0.24	0.04	0.11	0.46	0.08	0.02	0.33	0.02	0.28

This table shows the effects of adding a single extra HR variable to the extended basic model. Variables included in the "extended basic model" are as follows: age, sex, body mass index, race duration, systolic blood pressure, low-density lipoprotein cholesterol, estimated glomerular filtration rate, Framingham Risk Score, resting HR, baseline ln cTnI/cTnT, and years of endurance training. The model reaching the highest R^2 and keeping significance was race time with an HR >150 bpm (outlined in bold letters). cTnI indicates cardiac troponin I; cTnT, cardiac troponin T; HR, heart rate; R^2, coefficient of determination.

induced cTn response. This is in line with the small (n=10) mechanistic study by Stewart et al[14] that found a difference in mean HR between subjects with a high (HR, 160±3 bpm) compared with a low (HR, 145±2 bpm) cTnI response. In the study by Stewart et al,[14] the exercise protocols were repeated in the same subjects comparing the same total amount of work, but with increased intensity (and shortened duration). There was a highly significant increase in cTnI levels after the high-intensity compared with the medium-intensity protocol, suggesting that there may be an exercise intensity threshold for inducing an accentuated cTnI response. Only 10 study subjects were examined; the possibility to assess interindividual variations in HR thresholds was therefore limited. The present study was not able to precisely define the HR threshold associated with an exacerbated exercise-induced cTn response. Our data suggest that it may be between 140 and 150 bpm. Future studies need to address these issues further.

The development of myocardial stress and myocardial injury is reflected by several factors influencing myocardial work and myocardial energetics. Weil et al[20] used infusion of phenylepinephrine in pigs to induce an increased HR and SBP with a subsequent increase in cTnI. The cTn elevation occurred without evidence of myocardial injury.[20] These findings suggest that neurohormonal activation during strenuous exercise may be an important determinant of the physiological cTn release. In this context, HR may be a consequence rather than a determinant of factors causing a cTn release. Fourth, in line with the main study, the present analysis found an association between the exercise-induced cTn elevation and SBP. From other studies, we know that resting SBP is significantly correlated to SBP in exercise[25] (Knut Gjesdal, personal communication [Date of communication: May 27, 2019]). Although we were unable to measure SBP during the race, these findings may suggest that the exercise-induced cTn response is exacerbated in subjects likely to have increased cardiac work during exercise.

Limitations

Our study is a prespecified subgroup analysis of the NEEDED 2014 cohort of presumably healthy recreational athletes with

self-owned advanced sport watches. Our analyses are based on recordings from several different sport watch producers that used different data acquisition and storage algorithms. We had to remove data from 114 subjects because of insufficient data quality. The present analysis used conventional methods to harmonize data between the different sport watches, and extrapolated missing data only in files with sufficiently high data density. However, despite challenges related to data acquisition and analysis, our findings are consistent, suggesting that simple chronotropic parameters (mean and maximum HR) are not related to the exercise-induced cTn elevation if they are not linked with the duration of exercise. Our findings underscore that the duration of intensity is more important than short episodes of high HR. Sampling time of 1 HR value (bpm) per 1 second should therefore be sufficient. Beat-to-beat data were not available in the current analysis, and a more comprehensive assessment of HR variability was not possible. We therefore cannot exclude a relationship between HR variability and the exercise-induced cTn response. Because there is a link between HR variability and neurohormonal activation, exploration of beat-to-beat measurements and the exercise-induced cTn response is warranted in future studies.

The present study did not assess individual maximal oxygen uptake or anaerobic threshold. It is therefore not possible to determine the relationship between cTn levels and HR at these biological hallmarks.

Conclusions

The present study shows that the duration of elevated HR is an independent predictor of exercise-induced cTn elevation. The present study does not allow the determination of the minimum duration of exercise required to cause an exacerbated exercise-induced cTn release, and it does not allow the determination of a potential threshold of HR. Future studies should aim to identify both the duration and the HR level associated with an exercise-induced cTn elevation.

Both the present and earlier studies have used HR as a surrogate marker of intensity.[26] No direct measurement of cardiac or total work was performed. Development of new activity trackers and power meters allows more comprehensive measurements of both total work and cardiac work. Future studies should combine these methods to further increase our understanding of the underlying mechanisms of the exercise-induced cTn response.

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Disclosures

The following modest conflicts of interest have been reported by Drs Skadberg and Aakre. Dr Skadberg has received lecture fees from Abbott Diagnostics. Dr Aakre has served on one advisory board for Roche Diagnostics. The remaining authors have no disclosures to report.

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Journal of the American Heart Association

ORIGINAL RESEARCH

Determinants of Interindividual Variation in Exercise-Induced Cardiac Troponin I Levels

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BACKGROUND: Postexercise cardiac troponin levels show considerable interindividual variations. This study aimed to identify the major determinants of this postexercise variation in cardiac troponin I (cTnI) following 3 episodes of prolonged high-intensity endurance exercise.

METHODS AND RESULTS: Study subjects were recruited among prior participants in a study of recreational cyclists completing a 91-km mountain bike race in either 2013 or 2014 (first race). In 2018, study participants completed a cardiopulmonary exercise test 2 to 3 weeks before renewed participation in the same race (second race). Blood was sampled before and at 3 and 24 hours following all exercises. Blood samples were analyzed using the same Abbot high-sensitivity cTnI STAT assay. Fifty-nine individuals (aged 50±9 years, 13 women) without cardiovascular disease were included. Troponin values were lowest before, highest at 3 hours, and declining at 24 hours. The largest cTnI difference was at 3 hours following exercise between the most (first race) (cTnI: 200 [87–300] ng/L) and the least strenuous exercise (cardiopulmonary exercise test) (cTnI: 12 [7–23] ng/L; $P<0.001$). The strongest correlation between troponin values at corresponding times was before exercise ($r=0.92$, $P<0.0001$). The strongest correlations at 3 hours were between the 2 races ($r=0.72$, $P<0.001$) and at 24 hours between the cardiopulmonary exercise test and the second race ($r=0.83$, $P<0.001$). Participants with the highest or lowest cTnI levels showed no differences in race performance or baseline echocardiographic parameters.

CONCLUSIONS: The variation in exercise-induced cTnI elevation is largely determined by a unique individual cTnI response that is dependent on the duration of high-intensity exercise and the timing of cTnI sampling.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02166216.

Key Words: biomarkers ■ exercise physiology ■ troponin

Elevated cardiac troponin (cTn) is a marker of myocardial damage, and high levels are associated with an adverse prognosis in both patients with and without known coronary artery disease.[1,2] It has been known for >3 decades that prolonged strenuous exercise causes an increase in the cTn values in healthy individuals. The exercise-induced cTn elevation in healthy individuals is considered a benign response to exercise.[3] However, recent studies found independent associations between exercise-induced cTn elevation, adverse cardiovascular events, and obstructive coronary artery disease.[4,5] These findings suggest a potential diagnostic role for postexercise cTn assessment. However, no cTn level cutoffs to differentiate a benign from a pathologic cTn elevation have been identified. This is possibly because of the considerable interindividual variations in cTn values, and a limited understanding of the mechanisms causing exercise-induced troponin elevation in healthy individuals. A better understanding of the determinants of the exercise-induced cTn elevation might pave the way for the potential use

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CLINICAL PERSPECTIVE

What Is New?

- The magnitude of exercise-induced troponin elevation is largely determined by a reproducible, unique individual troponin response.
- This individual response is not related to alterations in physical performance or baseline echocardiographic parameters.

What Are the Clinical Implications?

- The individual troponin response needs to be included in the interpretation of individual exercise-induced troponin values.
- These large physiological interindividual variations in the exercise-induced troponin response requires the establishment of individual troponin reference values if the response is to be used for diagnostic purposes.

Nonstandard Abbreviations and Acronyms

CPX	cardiopulmonary exercise test
cTn	cardiac troponin
cTnI	cardiac troponin I
RPP	rate pressure product

of exercise-induced cTn elevation in a diagnostic setting.

Previous studies have identified baseline cTn, exercise intensity, and duration of exercise as predictors of the exercise-induced cTn elevation.[6–9] Recent studies suggest that the duration of elevated heart rate and blood pressure before exercise might be predictors of the exercise-induced cTn response.[10] However, the current prediction models only explain part (<36%) of the physiological cTn variation,[9] underlining the possibility that other individual factors play a more important role. This is the first study to evaluate the individual reproducibility of exercise-induced cTn elevation following physical efforts separated by >4 years. The aim of this study was to identify the major determinants of individual variation in the cTn response to exercise, with a particular focus on the impact of the individual cTn response in relation to workload and timing of cTn sampling following exercise.

METHODS

In 2018, study individuals were recruited from a pool of previous participants in the NEEDED (North Sea Race Endurance Study) in either 2013 or 2014.[9,11] All participants had participated in the 91-km leisure sport mountain bike race (the North Sea Race) in either 2013 or 2014 (T0). In 2018, the recruited study participants were examined by a cardiopulmonary exercise (CPX) test (T1), 2 to 3 weeks before a renewed participation in the North Sea Race (T2). There was a comprehensive measurement of physiological parameters during the 2018 race (T2). Blood was sampled at similar time points (before and at 3 and 24 hours following the race) and analyzed using the same high-sensitivity cardiac troponin I (cTnI) assay at the 2 races (T0 and T2) and the CPX test (T1). Coronary computed tomography angiography was performed following T2 to ensure that no individual had obstructive coronary artery disease. The present study complies with the Declaration of Helsinki, all participants signed informed consent forms before the study, and the regional ethics committee approved the study (REK no. 2013/550 and no. 2018/63). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Subjects and Baseline Measurements

Only healthy subjects without obstructive coronary artery disease on coronary computed tomography angiography in 2013 or 2014 were eligible for the present study.[12] Only data from individuals participating in all 3 exercises were included in the final analysis (Figure 1). All study subjects underwent a thorough examination at inclusion in 2018, including a detailed history, blood investigations, ECG, blood pressure, and

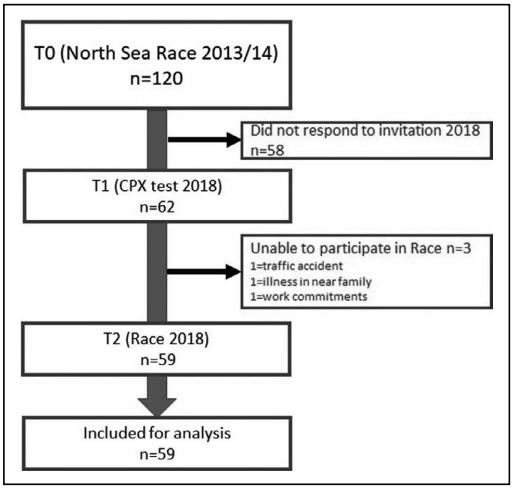

Figure 1. Flowchart of the study.
CPX indicates cardiopulmonary exercise; T0, recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

echocardiographic examination. Twelve-lead ECGs were taken at baseline and at 3 and 24 hours after exercise. Each participant answered questionnaires about symptoms after all exercises at all 3 time points. Noninvasive blood pressure was measured 3 times in a sitting position with an automated blood pressure monitor. The average of the 2 last measurements was used to calculate blood pressure. For an assessment of the amount of daily exercise, the International Activity Questionnaire was used.[13] The data from the International Activity Questionnaire were used to calculate the metabolic equivalent hours per week for each participant.

Estimation of Total and Cardiac Work

Except for the time taken to complete the race, there were no data about the total and cardiac work from the recruitment race (T0). During both the CPX test (T1) and the 2018 race (T2), power meters were used to assess the total work performed. Work during the CPX test (T1) was measured by a Cyclus 2 electronically braked ergo trainer (RBM Elektronik-Automation, Leipzig, Germany).[14] Each participant used their own bikes fitted to the Cyclus2 during the CPX test. Work performed during the 2018 race (T2) (n=40) was measured continuously with Stages power meters (StagesPower, Boulder, CO).[15] The Stages power meters were mounted on the bikes by replacing the original crank arm of the left side with a crank arm with a Stages power sensor. The rate pressure product (RPP) was used to estimate cardiac work during the exercise.[16] RPP was calculated as either mean or maximal RPP. Mean RPP was calculated as mean systolic blood pressure during exercise multiplied by mean heart rate, whereas maximum RPP was calculated as the highest measured systolic blood pressure multiplied by the maximal heart rate. Both during the CPX test (T1) and the 2018 race (T2), heart rate was measured continuously by chest straps and similar heart rate monitors in all the study subjects (Garmin Forerunner 935; Garmin, Olathe, KS). During the CPX test (T1), blood pressure was measured automatically using a Tango M2 Stress test monitor (Suntech Medical, Morrisville, NC). During the 2018 race (T2), blood pressure was measured manually on the right arm with a Heine G5, G7, or XXL LF-T (Heine, Herrsching, Germany) at 4 pit stops at the maximum and minimum anticipated efforts at the top and bottom at the 2 largest hills of the race after 34, 41, 69, and 76 km (Figure S1). A detailed description of the CPX test can be found in Data S1.

Blood Sampling

Blood was sampled at similar time points for all 3 exercises (T0, T1, and T2): the day before (baseline) the exercise and at 3 and 24 hours following the exercise. Blood samples were taken from the antecubital vein in a sitting position after a resting period of >5 minutes. Blood samples were stored at 4 ºC and analyzed within 24 hours of sampling.

Troponin Measurements

The same high-sensitivity cTnI assay (STAT) from Abbott Diagnostics was used for the measurement of troponin during all 3 events: T0, T1, and T2. The assay was analyzed on an Architect SR2000i (Abbott) for all sampling points. In 2013/2014 (T0) and 2018 (T1 and T2), the reported results were at or more than the limit of detection (1.6 ng/L) and limit of blank (0.9 ng/L). The cTnI assay had a total coefficient of variation of 10% at 6 ng/L, 7% at 27 ng/L, and 5% at 140 ng/L. Overall 99th percentile was 26 ng/L (men: 34 ng/L and women: 16 ng/L).[17]

Echocardiographic Assessment

Two GE Vivid E 95 systems (Vingmed, Horten, Norway) were used for the echocardiographic assessment performed at inclusion (T1). Comprehensive imaging protocols were applied, with complete coverage of both atria and ventricles, including parasternal and apical views, and adequate high frame rates to allow high-quality postprocessing, including speckle tracking and both global and regional strain analysis. An experienced medical doctor, blinded to the clinical data and exercise information, performed off-line postprocessing on a GE EchoPAC (GE Healthcare, Horten, Norway). All parameters were calculated according to the recommendations of the European Association of Cardiovascular Imaging.[18]

Statistical Analysis

Normally distributed continuous variables are reported as mean±standard deviation, whereas continuous variables with markedly skewed distributions are reported as the median and interquartile range (25th–75th percentile). The Shapiro-Wilk test was used to test for normality. For changes over time, a paired *t* test or Wilcoxon signed rank test was used as appropriate. Spearman correlation was used to study bivariate associations. A 2-tailed *P* value <0.05 was considered significant. A linear mixed effects model with random intercept was used for estimation of between-group differences. Differences were estimated at each time point (baseline, +3 hours, and +24 hours) among the 3 groups, T0, T1, and T2. Multiple linear regression with a backward elimination was used with postexercise cTnI values at 3 and 24 hours after the CPX test and the race in 2018 as dependent values. Age, sex, duration of exercise, and systolic blood pressure at baseline were selected a priori.[9,19,20] Because of markedly skewed distribution, troponin values were transformed using

a natural logarithm. Based on the correlation analysis with cTnI as the dependent variable, explanatory variables with $P<0.05$ were included in the models. The same variables of effort were selected for both T1 and T2. Corresponding values from T0 and T1 or T2 were added to investigate if these variables would have a different influence on exercise-induced cTn. The statistical software programs SPSS version 26 (IBM, Armonk, NY) and GraphPad Prism 9 (GraphPad Software, San Diego, CA) were used for statistical analysis and generating the graphs.

RESULTS

Data from a total of 59 healthy cyclists (aged 50±9 years, 13 women) were included in the present analysis. There were no major abnormal echocardiographic findings at baseline (Table 1), and there was no obstructive coronary artery disease on coronary computed tomography angiography following T2. None of the participants reported symptoms or had ECG findings suggestive of cardiac disease.

Exercise Characteristics

There were significant differences in exercise workload between the CPX test (T1) and the 2018 race (T2) (Table 2). The exercise workload was higher in the 2018 race (T2) compared with the CPX test (T1); the duration of high-intensity exercise was longer in the race, and the mean heart rate, peak power output, the peak and mean systolic blood pressure, and the peak and mean RPP were all higher in the race (T2). In contrast, there was no difference in maximal heart rate, and the mean power output and mean systolic pressure were lower during T2 compared with T1 (Table 2).

For the recruitment race (T0), the only measurement of exercise intensity was the duration of the race. The duration was shorter ($P<0.001$) in T0 (3.6 [3.4–4.0] hours) than in T2 (4.2 [3.6–4.6] hours), at least partly because of interrupted exercise because of the four 2-minute pit stops to assess the blood pressure. The race course and the weather conditions were the same during T0 and T2, reflected by the same race duration for all participants in the race: mean 4.2 hours in 2018 (n=2650) compared with mean 4.1 hours in 2013/2014 (n=8763).

Exercise-Induced cTnI Profile

The cTnI values had the same profile following all 3 rounds of exercise (T0, T1, and T2): the lowest cTnI levels were at baseline, the highest at 3 hours after exercise, with declining values at 24 hours (Figure 2). The 3-hour exercise-induced cTnI levels were higher after T2 (77 [37–128] ng/L) than after T1 (12 [7–23] ng/L), and were highest after T0 (200 [87–300] ng/L) ($P<0.001$). A similar pattern was seen for the 24-hour values, T1 (5 [3–9] ng/L), T2 (16 [8–32] ng/L), and T0 (34 [18–85] ng/L) ($P<0.001$).

Table 1. Baseline Characteristics and Physical Measurements During the CPX Test and the 2018 Race

Physical Characteristics and Training Status	Value	Minimum–Maximum
Male sex, n (%)	46 (74%)	
Age, y	50.3±9.6	31–77
Body mass index, kg/m^2	24.9 (23.3–27.1)	21.4–33.6
Systolic blood pressure, mm Hg	135 (122–146)	110–175
Diastolic blood pressure, mm Hg	81 (74–89)	61–104
Resting heart rate, bpm	60±10	41–92
Waist circumference, cm	86 (81–93)	72–107
Years of endurance training	10 (7–21)	0–50
Total MET h, MET h/wk	61 (47–102)	15–359
CPX test, T1		
Vo2Max, mL/min per kg	41.3±8.3	24.0–57.1
Power at lactate threshold, W	200±47	80–300
Heart rate lactate threshold, bpm	162±13	134–200
Echocardiographic findings at baseline		
LV measurements		
LV mass index, 2D, g/m^2	87.1±14.2	63.0–129.0
LV septum, mm	10.4±1.1	7.0–13.0
LV volume, 3D, mL/m^2		
Diastole	84.4±18.2	59.7–129.5
Systole	35.3±8.3	19.4–57.4
E/A ratio	1.4±0.4	0.9–2.5
LV ejection fraction, 3D, %	58.3±3.7	51.0–67.0
LV GLS, %	20.2±2.2	15.9–25.5
RV measurements		
RV volume, mL/m^2, 3D		
Diastole	75.3±14.7	51.0–116.0
Systole	40.2±9.8	24.0–69.0
RV 3 segment GLS, %	26.8±3.8	14.4–34.3

Normally distributed values are reported as mean±SD and markedly skewed values are reported as median (25th–75th percentile) unless indicated otherwise. CPX indicates cardiopulmonary exercise; GLS, global longitudinal strain; LV, left ventricle; MET, metabolic equivalent; RV, right ventricle; Vo2Max, maximum oxygen consumption; 2D, two-dimensional; and 3D, three-dimensional

Correlation Between Physical Measurements and Exercise-Induced cTnI Values

There was no correlation between baseline echocardiographic parameters and cTnI levels, and no correlation between cTnI levels and duration of exercise above the heart rate and power thresholds. A summary of the main findings and the basic parameters are presented in Table 2. RPP was found to have a significant correlation with exercise-induced cTnI value at both T1 and T2. Peak systolic pressure was significantly correlated

Table 2. Correlation Between cTnI and Exercise Data in CPX Test 2018 and Race 2018

Exercise Variables	T1, CPX Test 2018	T2, race 2018	*P* Value, T1 vs T2	Correlation T1 cTnI, +3 h, ρ/*P* Value	Correlation T1 cTnI, +24 h, ρ/*P* Value	Correlation T2 cTnI, +3 h, ρ/*P* Value	Correlation T2 cTnI +24 h, ρ/*P* Value
Duration of exercise, min	43 (40–45)	230 (210–245)	*P*<0.001	0.13/0.32	−0.14/0.30	−0.14/0.30	−0.21/0.11
HR peak, bpm	177±12	175±12	NS	0.08/0.56	−0.07/0.61	0.08/0.55	−0.03/0.83
HR mean, bpm	132±12	154±10	*P*<0.001	0.13/0.31	−0.06/0.65	0.16/0.23	0.09/0.51
Power peak, W	301 (242–342)	655 (502–759)	*P*<0.001	0.07/0.56	−0.07/0.61	0.27/0.55	0.20/0.07
Power mean, W	225±51	172±51	*P*<0.001	0.05/0.70	0.14/0.30	0.15/0.37	0.16/0.33
Work total, W×min	8650±1778	40289±7714	*P*<0.001	0.02/0.90	0.10/0.48	0.11/0.51	0.15/0.36
Work/kg total, W×min/kg	107±21	496±65	*P*<0.001	0.06/0.66	0.07/0.60	0.05/0.77	0.07/0.68
SBP peak, mm Hg	201 (181–216)	230 (210–245)	*P*<0.001	0.23/0.09	**0.29/0.003**†	0.21/0.12	0.25/0.06
SBP mean, mm Hg	183±14	166±15	*P*<0.001	0.13/0.33	0.11/0.42	0.20/0.14	0.22/0.09
DBP peak, mm Hg	83 (68–94)	100 (90–110)	*P*<0.001	−0.03/0.78	−0.08/0.57	0.06/0.64	0.09/051
DBP mean, mm Hg	83±9	84±8	NS	−0.11/0.42	−0.17/0.20	0.06/0.64	0.09/0.51
RPP peak, bpm×mm Hg	31594±4822	34416±4173	*P*<0.05	**0.32/0.02***	**0.30/0.03***	**0.26/0.045***	**0.29/0.03***
RPP mean, bpm×mm Hg	26511±2783	25319±2843	*P*<0.05	0.22/0.10	0.09/0.51	**0.27/0.04***	0.24/0.06
Weight reduction, kg	0.4 (0.2–0.6)	1.3 (0.8–1.8)	*P*<0.001	0.01/0.94	−0.01/0.92	0.02/0.88	0.15/0.26
Delta creatinine 3 h, µmol/L	2.7±4.5	11.0±12.7	*P*<0.001	0.17/0.20	0.23/0.09	0.26/0.05	**0.29/0.03***

Comparison is between variables of effort and biochemical variables after the 2 exercises in 2018. Skewed variables reported as median (25th–75th quartile) and normally distributed variables reported as mean±SD. Differences between the sample points were analyzed using the Wilcoxon signed rank or a paired-samples *t* test when appropriate. Work during the race (W) was assessed continuously by power meters in a subset of 40 study subjects. Normally distributed values are reported as mean±SD, and markedly skewed values are reported as median (25th–75th percentile). Bivariate correlation was analyzed with the Spearman rank method. Significant correlations are highlighted in bold letters. CPX indicates cardiopulmonary exercise; cTnI, cardiac troponin I; DBP, diastolic blood pressure; HR, heart rate; NS, not significant; RPP, rate pressure product; SBP, systolic blood pressure; T0, recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

*P<0.05.

†P<0.01.

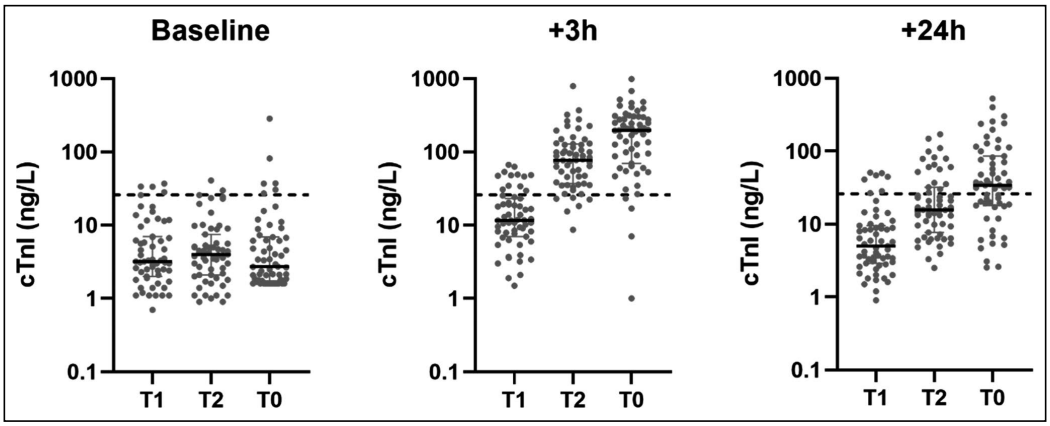

Figure 2. Cardiac troponin I (cTnI), at baseline, 3 h, and 24 h, after the cardiopulmonary exercise test in 2018 (T1), the North Sea Race in 2018 (T2), and the North Sea Race recruitment race in either 2013 or 2014 (T0).
Scale is log10-transformed. Dotted lines indicate the 99th percentile of the high-sensitivity cTnI assay (26 ng/L).

with the exercise-induced cTnI value at 24 hours following the CPX test (r=0.29, P=0.003) and reached borderline significance at 24 hours following the race (T2) (r=0.25, P=0.06).

Low- Versus High-cTnI Responders

Figure 3 displays the consistency in the rankings of cTnI values following the 2 races T0 and T2. Individuals were either classified as low- or high-cTnI responders depending on their cTnI value 3 hours after exercise in the recruitment race (T0). Low responders were defined as individuals with a cTnI level within the first quartile after T0, whereas high responders were defined as individuals with a cTnI level in the highest quartile in T0. There was no difference in the physical performance or echocardiographic parameters after the 2018 race

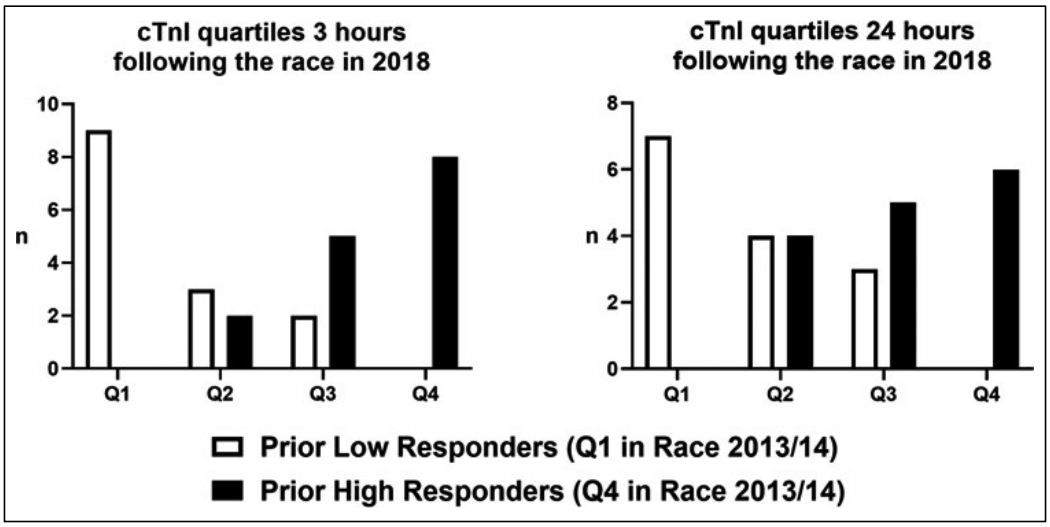

Figure 3. Consistency in ranking of cardiac troponin I (cTnI) values following the recruitment race (the North Sea Race in either 2013 or 2014) and the 2018 North Sea Race.
Low responders are defined as individuals with a cTnI value within the first quartile (Q1) of the recruitment race (T0), whereas high responders are defined as individuals with a cTnI value within the highest quartile (Q4) of the recruitment race (T0). The graph displays the number of individuals in each of the 4 quartiles based on the cTnI values achieved in the 2018 race (T2). T0 indicates recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

between low- and high-cTnI responders. Following the race in 2018, none of the low responders in the recruitment race (T0) were classified as high responders in the second race (T2), and none of the high responders were classified as low responders in the second race (T2).

Correlation Between cTnI Levels at Corresponding Time Points During the 3 Exercises

In the individual subjects, there were strong correlations between cTnI values from the 2 races (T0 and T2) and the CPX test (T1) at all corresponding time points (Figure 4). The strongest correlations between cTnI values were observed at baseline (ie, 24 hours before the exercise). Following exercise, the strongest correlation at 3 hours was between the 2 races (r=0.72, P<0.001) and at 24 hours between the CPX test and the second race (r=0.83, P<0.001). The weakest correlations were between the recruitment race (T0) and the CPX test (T1) at both 3 and 24 hours following exercise.

Linear Mixed Effects

Differences between expected values are presented in Table 3. The largest difference in expected values

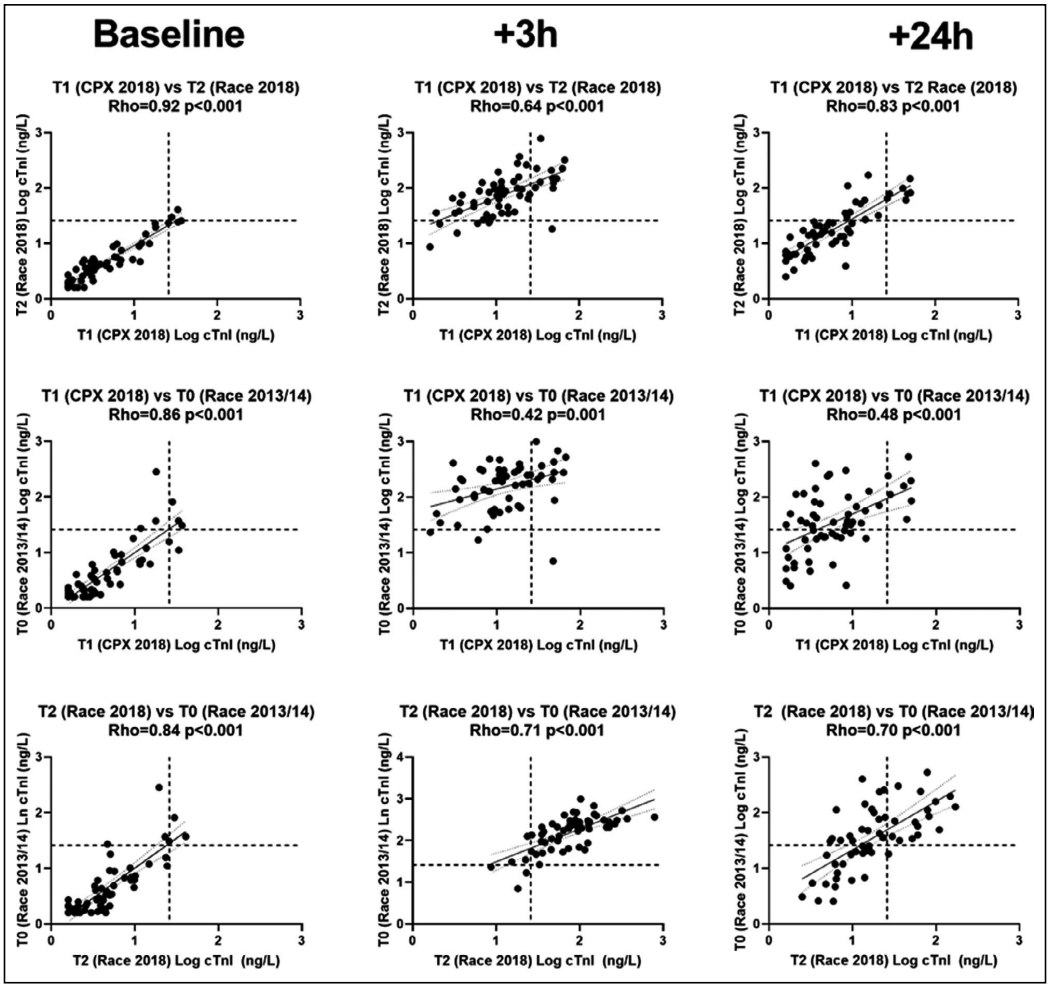

Figure 4. Scatterplot shows individual cardiac troponin I (cTnI) response at baseline, 3 h, and 24 h after the cardiopulmonary exercise (CPX) test in 2018 (T1), the 2018 race (T2), and the recruitment race in either 2013 or 2014 (T0).
Spearman bivariate correlations were used to assess the correlations between time points. Dotted lines indicate the 99th percentile of the high-sensitivity cTnI assay (26 ng/L).

Table 3. Linear Mixed Effects

Comparison Between Groups	Expected Difference	*P* Value	95% CI
Baseline			
T0–T1	5.1	0.18	−2.4 to 12.6
T0–T2	5.4	0.16	−2.1 to 12.9
T1–T2	0.3	0.95	−7.2 to 7.8
3 h after exercise			
T0–T1	199.4	<0.0005	159.9 to 238.9
T0–T2	108.1	<0.0005	68.6 to 147.6
T1–T2	−91.3	<0.0005	−130.8 to −51.8
24 h after exercise			
T0–T1	63.8	<0.00005	43.3 to 84.3
T0–T2	44.3	<0.00005	23.8 to 64.8
T1–T2	−19.5	0.06	−40.0 to 1.0

All 3 exercises (T1, T2, and T0) compared with a random intercept linear mixed-effects model. Expected differences with *P* value and 95% CI at corresponding time points between T0, T1, and T2. T0 indicates recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

were found at 3 hours between T0 and T1. The smallest difference was at baseline between T1 and T2. Differences were highly significant at 3 hours among all groups ($P<0.00005$). At 24 hours, there was a significant difference between T0 and T1 and T0 and T2, but not between T1 and T2.

Multiple Regression Models

Multiple regression models were used to identify the predictors of the postexercise cTnI values after T1 and T2 (Table 4). Following the CPX test (T1), baseline cTnI, maximal RPP, and maximal systolic blood pressure were independent predictors of cTnI elevation at 3 hours. Following the race in 2018 (T2), baseline and cTnI response at identical time points of the race in 2013/2014 (T0) were the strongest predictors of the exercise-induced cTnI levels at both 3 and 24 hours. Duration of the race was an independent predictor of cTnI levels at 24 hours after the race but not at 3 hours.

DISCUSSION

This study demonstrates that the exercise-induced cTnI elevation is specific to each individual and that the individual cTnI level is strongly related to the workload and timing of sampling. These findings underscore that the exercise-induced cTn response needs to be interpreted in relation to the subject-specific response

Table 4. Multiple Regression Analysis

cTnI 3 h After CPX Test (T1), R^2=0.69	Nonstandardized Coefficients		Standardized Coefficients		
	B	SE	β	*t*	*P* Value
Ln cTnI baseline T1	0.53	0.09	0.58	5.97	<0.001
Ln cTnI 3 h T2	0.34	0.10	0.32	3.29	<0.001
Systolic blood pressure maximum	−0.01	0.00	−0.35	−2.12	0.04
Peak RPP	0.00	0.00	0.48	2.94	0.005
Duration of test	−0.03	0.02	−0.18	−2.17	0.03
cTnI 24 h after CPX test (T1) R^2=0.87					
Ln cTnI baseline T1	0.72	0.10	0.73	7.53	<0.001
Ln cTnI 24 h T2	0.21	0.10	0.21	2.14	0.04
Male sex	0.21	0.11	0.10	1.88	0.07
cTnI 3 h after race 2018 (T2) R^2=0.65					
Ln cTnI 3 h T1	0.40	0.08	0.43	5.0	<0.001
Ln cTnI 3 h T0	0.48	0.08	0.54	6.28	<0.001
cTnI 24 h after race 2018 (T2) R^2=0.83					
Ln cTnI baseline T2	0.40	0.15	0.39	2.72	0.009
Ln cTnI 24 h T0	0.20	0.05	0.26	3.66	0.001
Ln cTnI 24 h T1	0.37	0.14	0.37	2.65	0.01
Male sex	−0.26	0.15	−0.12	−1.76	0.08
Duration of the race	−0.18	0.09	−0.13	−2.09	0.04

The table presents the multiple linear regression models using the backward elimination method. The models included predefined variables (age, sex, systolic blood pressure baseline, metabolic equivalent, hours, duration of exercise, cTnI at baseline), variables with a bivariate correlation *P* value <0.05 (Table 2), and the cTnI values at corresponding timepoints at CPX test 2018 (T1), 2018 race (T2), and the recruitment race (T0). CPX indicates cardiopulmonary exercise; cTnI, cardiac troponin I; Ln cTnI, natural logarithm of cardiac troponin I; and RPP, rate pressure product.

to exercise, exercise workload, and timing of sampling following the exercise. These findings have implications for both clinical interpretation and future scientific studies exploring the exercise-induced cTn response. The present findings are particularly important for the differentiation between a physiological and pathological response, emphasizing that knowledge of the prior exercise-induced cTn response and precise information about workload (exercise intensity and duration) are necessary to generate reliable prediction models. These findings underscore the limitations in the interpretation of cTn increase following exercise in a clinical setting, wherein information about prior cTn response and exercise workload are rarely available.

The increase in troponin following exercise has been demonstrated by numerous studies.[3] In line with the previous studies, the present study demonstrates that cTnI levels relate to baseline cTn concentration, exercise intensity, and duration of exercise.[10,21,22] However, the precise relationship between workload and cTn elevation remains obscure. Figure 2 demonstrates the close relationship between troponin response and exercise intensity and duration, with the lowest postexercise cTnI levels following the CPX test (T1), higher following the race in 2018 (T2), and highest following the recruitment race (T0). The difference in cTnI levels following the 2 races (T0 and T2) reflects the higher exercise intensity in the recruitment race (T0) than in the 2018 race (T2). The race duration was shorter in the recruitment race (T0) than in the 2018 race (T2), indicating a longer duration of high-intensity exercise in the recruitment race than in the 2018 race. The primary reason for this difference in race duration relates to the study-related interference during the 2018 race. In 2018, all study individuals were stopped 4 times for blood pressure measurements during the race. Although each pit stop lasted <2 minutes, most riders waited to join other riders coming up from behind. Because there was a ranking of participants in the race, subsequent groups were slower, thereby further reducing the duration of high-intensity exercise. This is underlined by the findings from the linear mixed-effects models. The expected differences in cTnI values increase with increasing exercise intensity and duration; the largest differences were at 3 hours after exercise between the first race, the second race, and the CPX test. These findings underscore the impact of exercise intensity and duration on the cTnI response both at 3 and 24 hours following exercise. Although race duration is a surrogate for the duration of high-intensity exercise, it is a complex parameter that needs careful interpretation. Because there were no accurate measurements of heart rate or work during the first race, it is not possible to evaluate differences in the physical performance in study participants between the recruitment race and the 2018 race (T0 and T2) accurately. Future studies need to incorporate repeated exercise with accurate measurements of workload to allow a better prediction of the relationship between repeated exercise and cTn release.

Both during the CPX test and the 2018 race, there was a univariate correlation between cTnI and peak RPP following exercise. However, in multiple regression models, RPP remained an independent predictor of cTnI elevation only at 3 hours following exercise in the CPX test. When interpreting these results, it should be noted that peak RPP measurements from the 2018 race have a drawback of uncertainty because blood pressure was measured at only 4 time points during the race. The use of more accurate tools, allowing more frequent monitoring of blood pressure during exercise, preferably without the need to interrupt the exercise, might provide better insights into the relationship between increased cardiac workload during exercise and exercise-induced cTn response.

Few studies have used multiple regression models to predict the exercise-induced cTn response.[9,23–25] Several variables have been identified as independent predictors of the cTnI response, including age,[23] duration of exercise,[24] the intensity of exercise,[8,22] changes in creatinine,[26] exercise experience,[27] and systolic blood pressure.[9] However, no study has used information from a previous exercise-induced cTn response in the models. A common finding from the multiple regression models is that the models explain only a small proportion of the total variation in the cTn response to exercise, with an R^2 ranging from 9% to 44%.[23,24] Compared with the previous studies, the present study found multiple regression models with far larger explanatory (R^2) values ranging from 65% to 87%. The model fit after adding information about the previous cTnI value (T0) in the multiple regression models was more evident following the race in 2018 (T2) than following the CPX test (T1). This might, in part, be explained by lesser exercise-induced cTnI elevation following the CPX test than the cTnI elevation following the 2 races (T0 and T2) (Figure 2).

The physiological mechanisms causing troponin release during exercise are largely unknown. It has been proposed that cTn elevation might be because of an increase in preload, causing increased myocardial stretch and integrin-mediated transportation of cTn molecules across the intact myocyte membranes.[28] However, in the present study, no difference in the echocardiographic parameters was observed, and markers of dehydration (creatinine) did not explain the variation in the exercise-induced cTnI response in the multiple regression models. Circulating troponins levels are influenced by posttranslational modifications such as proteolytic degradation, phosphorylation, glycation, and acetylation.[29] Individual differences in these changes might

alter the circulating cTn molecules and influence the detection of cTn molecules by current assays. Notably, a recent study demonstrated the presence of smaller cTnT molecules released in healthy runners after a marathon, compared with larger cTnT molecules released after acute myocardial infarction.[30] This finding suggests that there might be changes in the molecular structure of circulating troponins when comparing exercise with ischemic injury. It remains to be determined whether there are also changes in the molecular structure of cTnI that can explain the large individual differences in the exercise-induced cTnI response.

Strengths and Limitations

The strengths of this study are the extensive data and the measurement of high-sensitivity cTnI at different exercise loads and time points separated by >4 years. Normal echocardiographic findings and the absence of coronary pathology on repeated coronary computed tomography angiography ensured that the cause of cTnI elevation was not related to the abnormal cardiac function or obstructive coronary artery disease. Although the study subjects were well-trained participants from a selected cohort, age, sex, and physical characteristics are representative of an average recreational athlete. The recruitment of well-trained subjects in the present study ensures that exercise-performance was not limited by factors such as muscular capacity or technical skills.

Several limitations apply to the present study. First, this is an observational study with study subjects reflecting a highly selective cohort. Second, as discussed above, there are no additional data except the race duration to evaluate exercise intensity from the recruitment race (T0). Hence, it is not possible to make an accurate comparison of difference in race intensity between the recruitment (T0) and the 2018 race (T2). The exercise-induced cTnI response was only followed for 24 hours. We have previously reported that prolonged release of cTnI might be associated with a pathological cTnI response.[5] It would be of interest to study the reproducibility of the duration of the cTnI elevation beyond 24 hours following exercise.

CONCLUSIONS

The present study shows that there are large but reproducible differences in the magnitude of the exercise-induced cTnI responses among individuals. The exercise-induced cTnI response reflects exercise intensity and duration in a person-specific manner. This finding underscores the need to consider both workload, timing of sampling, and earlier cTnI response when attempting to differentiate physiological from a pathological cTnI response to exercise. These findings have important implications for the interpretation of postexercise cTnI values and for the future design of studies evaluating the exercise-induced cTnI response.

ARTICLE INFORMATION

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Disclosures

Ø.S. has received lecture fees from Abbott Diagnostics. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Figure S1

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Supplemental Material

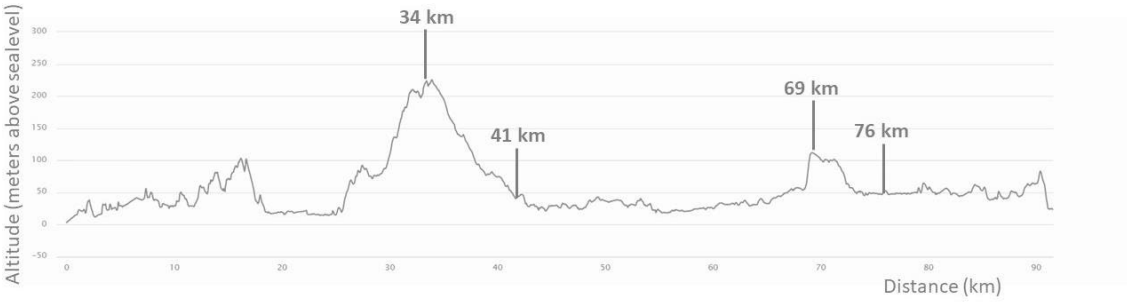
Data S1.

Supplemental Methods

Cardiopulmonary exercise (CPX) test

All study participants were tested on their personal bikes fitted to a Cyclus 2 electronically braked ergotrainer (RBM elektronik-automation; Leipzig, GER)[14]. Each participant performed a 10-minute warm-up before exercise tests, resistance was kept low and was guided by the test-leader. The lactate threshold test was executed as a 4-minute incremental load stepwise test. The workload was based on previous training history and results from warm-up (min 50w – maximum 220w). The workload was increased with fixed individualized (min 15w – maximum 30w) steps every fourth minute. Lactate was measured in capillary blood from the participants' index finger on the Lactate Scout+ (EKF Diagnostic, Cardiff, GB). Gas exchange was measured breath by breath on a Jaeger Vyntus CPX (Carefusion, Hoechberg, GE). Lactate threshold was defined as a lactate value > 1.5 mmol/l above mean value from step 1 and 2 or a RER > 1.0. For each step, including rest and warm-up, the following variables were collected; Work (watt), blood pressure (mmHg), VO_2 (ml/min/kg), RER, Lactate, and heart rate (bpm). Following the stepwise determination of lactate threshold, participants were allowed a maximum of 5-minute cooldown, before performing the VO_{2max} test. The VO_{2max} test was a ramp protocol started at 70-250 (min-max) watts with an increase in the workload of 15-32 (min-max) Watt/min until exhaustion. The VO_{2max} test was performed to reach maximum effort between 5 and 10 minutes. Pre-test blood pressure was obtained at the start of the test and maximal blood pressure was obtained immediately after the end of the test with the participant still seated on the bike. VO_{2max} was defined as the point where VO_2 reached a plateau despite increasing resistance. Peak power and peak heart rate were the maximum value achieved during this test.

Figure S1. Race profile, altitude outlined.



Points of blood pressure measurements marked. Diagram exported from the Garmin Connect website (copyright Garmin International, KS, US).

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