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Studies by positron emission tomography

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The doubters said ”Man can not fly”.
The doers said “Maybe, but we’ll try”.
And finally soared in the morning glow
while non-believers watched from below.
- Bruce Lee -

ABSTRACT

Marja Heiskanen

Right ventricular metabolic responses to high-intensity interval and moderate-intensity continuous training: studies by positron emission tomography

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Background: High-intensity interval training (HIIT) has gained interest as an effective alternative for the traditional moderate-intensity continuous training (MICT) to improve physical fitness and whole-body health, but its effect on the right ventricle (RV) is unknown. The aim of this thesis was to study the effects of HIIT and MICT on RV metabolism and function both in healthy men and in subjects with type 2 diabetes mellitus (T2DM) or prediabetes.

Methods: In total, 28 healthy and untrained men and 26 untrained men and women with T2DM or prediabetes were randomized into HIIT and MICT groups. Subjects performed six supervised cycle ergometer sessions within two weeks (HIIT session: 4-6 x 30 s all-out cycling / 4 min recovery, MICT session: 40-60 min cycling at 60% VO_{2peak}). RV glucose and free fatty acid uptake were studied by positron emission tomography. RV structure and function were determined by cardiac magnetic resonance.

Results: In healthy men, both HIIT and MICT decreased RV glucose uptake while RV fatty acid uptake remained unchanged. Further, both exercise modes increased RV volumes and mildly decreased its ejection fraction. In diabetic subjects, RV glucose and free fatty acid uptake remained unaltered. Only MICT increased RV end-diastolic volume and RV mass, whereas both HIIT and MICT increased RV end-systolic volume and decreased RV ejection fraction.

Conclusions: Two weeks of HIIT and MICT induce similar changes in RV of the healthy men regardless of markedly lower volume of HIIT. For a diabetic heart, MICT may be more beneficial as it improves RV dimensions more than HIIT.

Keywords: right ventricle, metabolism, high-intensity interval training, exercise, positron emission tomography, type 2 diabetes mellitus

TIIVISTELMÄ

Marja Heiskanen

Kovatehoisen intervalliharjoittelun ja keskitehoisen kestävyysharjoittelun vaikutukset oikean kammion aineenvaihduntaan: tutkimuksia positroniemissio-tomografialla

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Tausta: Kovatehoinen intervalliharjoittelu (*high-intensity interval training,* HIIT) on osoittautunut tehokkaaksi vaihtoehdoksi kohottaa kuntoa perinteisen keskitehoisen kestävyysharjoittelun (*moderate-intensity continuous training,* MICT) sijaan, mutta sen vaikutuksia sydämen oikeaan kammioon ei tunneta. Tutkimuksen tavoitteena oli selvittää, miten HIIT ja MICT vaikuttavat oikean kammion aineenvaihduntaan ja toimintaan terveillä miehillä sekä tyypin 2 diabeetikoilla tai esidiabeetikoilla.

Menetelmät: Yhteensä 28 liikuntaa harrastamatonta tervettä miestä sekä 26 tyypin 2 diabetesta tai esidiabetesta sairastavaa miestä tai naista satunnaistettiin HIIT ja MICT ryhmiin. Molemmat ryhmät pyöräilivät kuntopyörällä kuusi harjoituskertaa kahden viikon aikana (HIIT-sessio: 4-6 x 30 s maksimaalista vetoa 4 min palautuksilla, MICT-sessio: 40-60 min pyöräilyä teholla 60% VO_{2peak}). Oikean kammion glukoosin ja rasvahappojen käyttöä tutkittiin positroniemissiotomografialla ja rakenteellisia ja toiminnallisia muutoksia magneettikuvauksella.

Tulokset: Terveillä miehillä molemmat liikuntamuodot laskivat oikean kammion glukoosinkäyttöä, mutta rasvahappojen käyttö ei muuttunut. Lisäksi sekä HIIT että MICT suurensivat oikean kammion tilavuutta sekä pienensivät hieman ejektiofraktiota. Diabeetikoiden oikean kammion glukoosin ja rasvahappojen käyttö ei muuttunut. Vain MICT suurensi diabeetikoiden oikean kammion loppu-diastolista tilavuutta ja kasvatti oikean kammion massaa. Molemmat liikuntamuodot suurensivat oikean kammion loppu-systolista tilavuutta ja pienensivät ejektiofraktiota.

Johtopäätökset: Kaksi viikkoa kumpaa tahansa liikuntamuotoa aiheuttaa samanlaisia vaikutuksia terveiden miesten oikeassa kammiossa HIIT-harjoittelun huomattavasti pienemmästä määrästä riippumatta. Diabeetikoiden sydämen kannalta MICT näyttäisi kuitenkin olevan tehokkaampi harjoittelumuoto, sillä se lisää oikean kammio tilavuutta ja massaa enemmän kuin HIIT.

Avainsanat: oikea kammio, aineenvaihdunta, kovatehoinen intervalliharjoittelu, liikunta, positroniemissiotomografia, tyypin 2 diabetes

CONTENTS

ABBREVIATIONS

acetyl-CoA	Acetyl coenzyme A
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate kinase
ATP	Adenosine triphosphate
BMI	Body mass index
CaMK	Calcium-calmodulin kinase
CD36	Cluster of differentiation 36
CMR	Cardiac magnetic resonance
CO	Cardiac output
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
FFA	Free fatty acid
FFAU	Free fatty acid uptake
FTHA	14(*R*,*S*)-[^{18}F]fluoro-6-thia-heptadecanoic acid
GLUT	Glucose transporter
GU	Glucose uptake
HbA_{1c}	Hemoglobin A_{1c}
HIIT	High-intensity interval training
HR	Heart rate
LV	Left ventricle/ventricular
MET	Metabolic equivalent of task
MICT	Moderate-intensity continuous training
M-value	Whole-body insulin-stimulated glucose uptake
NADH	Nicotinamide adenine dinucleotide
OGTT	Oral glucose tolerance test
PAH	Pulmonary artery hypertension
PET	Positron emission tomography
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator-1α
RPE	Rating of perceived exertion
RV	Right ventricle/ventricular
SPECT	Single-photon emission computed tomography
SV	Stroke volume
T2DM	Type 2 diabetes mellitus
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
VOI	Volume of interest

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to the text by the corresponding Roman numerals, I – III.

I. Heiskanen Marja A., Leskinen Tuija, Eskelinen Jari-Joonas, Heinonen Ilkka H.A., Löyttyniemi Eliisa, Virtanen Kirsi, Pärkkä Jussi J., Hannukainen Jarna C., Kalliokoski Kari K. 2015. Different predictors of right and left ventricular metabolism in healthy middle-aged men. *Frontiers in Physiology, Clinical and Translational Physiology* 6, 389.

II. Heiskanen Marja A., Leskinen Tuija, Heinonen Ilkka H.A., Löyttyniemi Eliisa, Eskelinen Jari-Joonas, Virtanen Kirsi, Hannukainen Jarna C., Kalliokoski Kari K. 2016. Right ventricular metabolic adaptations to high-intensity interval and moderate-intensity continuous training in healthy middle-aged men. *American Journal of Physiology, Heart and Circulatory Physiology* 311(1), H667-75.

III. Heiskanen Marja A., Sjöros Tanja J., Heinonen Ilkka H.A., Löyttyniemi Eliisa, Koivumäki Mikko, Motiani Kumail K., Eskelinen Jari-Joonas, Virtanen Kirsi A., Knuuti Juhani, Hannukainen Jarna C., Kalliokoski Kari K. High-intensity interval training decreases left-ventricular glucose uptake compared to moderate-intensity continuous training in subjects with type 2 diabetes or prediabetes. *Submitted*.

1 INTRODUCTION

”Positive health requires a knowledge of man’s primary constitution … There must also be exercise of which the effects must likewise be known … If there is any deficiency in … exercise the body will fall sick”. This is what Hippocrates stated more than two millennia ago (Blair and Morris, 2009). Today, it is well known that regular exercise confers beneficial effects to the heart and the entire body and protects against premature cardiovascular death (Kemi and Wisløff, 2010; Weston et al., 2014). Despite of this knowledge, the amount of exercising decreases and the amount of sitting increases for the majority of population in the modern society, leading to obesity and lifestyle-induced diseases, which could often be avoided or at least alleviated with regular exercise (Blair and Morris, 2009; Weston et al., 2014). Since our sedentary lifestyle poses a major threat to the health of individuals as well as to the public health, new means to encourage and enable people to increase their physical activity are needed.

It is well known that traditional moderate-intensity continuous training (MICT), such as jogging or cycling, induces many beneficial effects to the body, particularly to the systemic circulation and the heart. These exercise-induced changes improve the pumping capacity of the heart, which is closely related to the maximal oxygen uptake, VO_{2max} (Kemi and Wisløff, 2010). In fact, VO_{2max} is a strong predictor of mortality, and improving cardiorespiratory fitness seems to be an even more important factor than body mass index in reducing all-cause mortality (Laukkanen et al., 2001; Rehn et al., 2013; Weston et al., 2014). In line with this, the current guidelines for health-enhancing physical activity recommend at least 150 minutes of MICT or 75 minutes of vigorous-intensity training per week (Garber et al., 2011). However, only few adults meet these criteria, commonly citing lack of time as a barrier (Trost et al., 2002). Therefore, high-intensity interval training (HIIT) has gained a lot of interest as a more time-efficient method of exercise for modern, busy people. Indeed, many recent studies have shown that the changes traditionally associated with high-volume MICT can be achieved by considerably smaller volumes of HIIT (Gibala and McGee, 2008; Jelleyman et al., 2015; Milanović et al., 2015; Weston et al., 2014).

HIIT generally refers to alternating short bursts of high-intensity exercise, often performed in "all-out" effort, with light-intensity recovery periods between bouts. Protocols vary from 10-second sprints to 4-minute intervals, having different warm-ups, cool-downs and durations of active or passive recovery between the intervals (Gibala and McGee, 2008; Metcalfe et al., 2012; Weston et al., 2014). The exercise itself can be anything from running and cycling to functional training such as CrossFit performed at high intensity (Heinrich et al., 2014; Kemi and Wisløff, 2010). Recent meta-analyses have shown that HIIT is not only tolerated but even seems to be superior to moderate-intensity training in improving cardiovascular fitness even in patients with lifestyle-induced cardiometabolic diseases (Jelleyman et al., 2015; Weston et al., 2014). HIIT has also been shown to be effective in preventing or controlling type 2 diabetes as it can improve patient's insulin sensitivity and glycemic control (Babraj et al., 2009; Jelleyman et al., 2015; Little et al., 2011). Hence, HIIT is not only for well-trained athletes.

Exercise-induced hypertrophy of the left ventricle, so called athlete's heart, is generally associated with excellent health outcomes (D'Andrea et al., 2002; Fagard, 2003; Pluim et al., 2000). However, the role of the right ventricle during exercise training has remained unclear. In 1980s it was observed that, not left ventricular function, but right ventricular function and mean pulmonary artery pressure at rest correlated with exercise capacity in patients with chronic left ventricular failure (Baker et al., 1984; Franciosa et al., 1985). These results indicated that the right ventricle may be an important determinant of exercise capacity at least in one patient group. Interestingly, recent studies have further suggested that the right ventricle of the heart can be even more important when considering the effects of exercise on the function of the heart muscle (Elliott and La Gerche, 2015). Surprisingly, intense, prolonged endurance training may have acute adverse effects on the right ventricular function while the left ventricular function remains relatively unaltered (Claessen et al., 2014; La Gerche et al., 2011, 2012; Trivax et al., 2010). Although still unclear, a potential explanation for this observation is much greater increase in the work load of the right ventricle compared to the left ventricular work load during prolonged exercise session (La Gerche et al., 2011; Trivax et al., 2010).

The right ventricle has traditionally been considered as a "passive bystander" as it has to pump blood against a much lower pressure in order to pump cardiac output through the pulmonary vasculature providing merely the pulmonary circulation, but recent studies have indicated its central role in disease states, especially in pulmonary hypertension (Haddad et al., 2008a; Voelkel et al., 2006). Impairment of the right ventricular function may also be a component of the diabetic cardiomyopathy (Tadic et al., 2015; Widya et al., 2013). The underappreciation of the RV as a player in cardiovascular disease may at least in part be due to the fact that assessment of right ventricular anatomy and function has been challenging with traditional imaging methods because of its complex shape and difficult position immediately behind the sternum. However, modern imaging

modalities, such as cardiac magnetic resonance imaging (CMR) and positron emission tomography (PET), enable evaluation of the right ventricle anatomy, function and metabolism non-invasively (Greyson, 2011; Ramani et al., 2010).

Although there are some studies concerning structural adaptations of the right ventricle to endurance exercise training, adaptations of right ventricular metabolism are completely unknown (Heinonen et al., 2014). Hafstad and colleagues showed using an animal model that only HIIT, but not MICT, altered cardiac metabolism in healthy mice (Hafstad et al., 2011), whereas in diet-induced obese mice both HIIT and MICT increased glucose metabolism and normalized mitochondrial capacity (Hafstad et al., 2013). Further studies regarding the significance of exercise intensity on the human heart are important, as it has been suggested that high-intensity training could improve cardiac metabolism and hence alleviate the energetic abnormalities of the failing heart (Murray, 2011).

The aim of this study was first to examine the characteristics of right ventricular metabolism in healthy men using PET (study I). Then, the effects of HIIT and MICT on the right ventricular metabolism and function were studied in the healthy middle-aged men (study II) as well as in middle-aged subjects with type 2 diabetes mellitus or prediabetes (study III). The results of these studies provide knowledge on basic metabolism of the less-known cardiac chamber and its early adaptations to the exercise training.

2 REVIEW OF THE LITERATURE

2.1 Exercise and cardiorespiratory fitness

Physical activity generally refers to any bodily movement which is produced by skeletal muscles with larger energy requirement than resting energy expenditure, whereas exercise is intentional physical activity that aims at improving health and fitness (Garber et al., 2011). The effects of increased physical activity and adequate exercise are well known, including both physical and mental benefits: it lowers blood pressure, improves lipoprotein profile, increases insulin sensitivity, reduces and controls body weight, preserves bone mass, reduces the risk of falling and even prevents or improves mild and moderate depression. In general, regular exercise improves the quality of life and protects against many diseases, especially lifestyle-induced diseases like cardiovascular diseases, type 2 diabetes mellitus (T2DM), and obesity. (Blair and Morris, 2009; Garber et al., 2011; Rehn et al., 2013).

Although the health benefits of regular exercise are well known, sedentary behaviour continues to increase (Blair and Morris, 2009). Sedentary behaviour involves activity with little or no movement with energy requirement close to the resting energy expenditure (Garber et al., 2011). As the most commonly cited reasons for physical inactivity is the lack of time (Trost et al., 2002), many studies have addressed the question “How much physical activity is needed?” (Garber et al., 2011). Many studies have supported the dose-response curve between physical activity levels and health benefits, implying that greater benefits are achieved by greater levels of exercising (Garber et al., 2011; Rehn et al., 2013). However, even a small amount of increased physical activity, starting at about one half of the volume of the current recommendation, has a major beneficial impact on reducing the mortality when compared to totally sedentary behavior (Blair and Morris, 2009; Garber et al., 2011).

From the medical point of view, health-enhancing exercise is often categorized into strength and endurance training, both recommended in moderate intensity. However, from the aspect of the sport science, it is known that the mode, frequency, duration and intensity of the exercise affect the outcome of the training (Wisløff et al., 2009). The key terms related to training volume and intensity are summarized in Table 1.

TABLE 1. Terms and concepts concerning training volume and intensity (modified from Powell *et al.* 2011).

Term	**Definition**
Duration	The length of time an activity is continued.
Frequency	The number of times an activity is performed within a specified time period, or sessions per week.
Intensity (absolute)	The rate of energy expenditure required to perform an activity; the physiologic capabilities of the person are not considered.
Intensity (relative)	Describes the ease or difficulty with which an activity is performed and is proportional to person's current maximal capacity.
Metabolic equivalent (MET)	A measure of energy expenditure. One MET is the energy expenditure while sitting at rest. Conventionally, 1 MET equals to oxygen uptake of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$.
Volume	The total amount of activity accumulated over a specified period of time, usually within a week. Typically expressed as kcal/week, MET-min/week, min/week or km/week.

Exercise intensity refers to the energy required to perform physical activity and it can be measured using several absolute and relative methods. Absolute intensity, such as metabolic equivalent (MET), means the absolute energy needed to perform a certain action, whereas relative intensity is proportional to person's maximal capacity, such as maximal heart rate or maximal oxygen uptake (Garber et al., 2011; Powell et al., 2011). Summary of commonly used classification of training intensities is shown in Table 2.

TABLE 2. Classification of exercise intensity for cardiorespiratory exercise (modified from Garber et al., 2011).

Intensity	%HR_{max}	%VO_{2max}	Perceived Exertion (RPE)	METs
Very light	< 57	< 37	< Very light (RPE < 9)	< 2
Light	57-63	37-45	Very light to fairly light (RPE 9-11)	2.0-2.9
Moderate	64-76	46-63	Fairly light to somewhat hard (RPE 12-13)	3.0-5.9
Vigorous	77-95	64-90	Somewhat hard to very hard (RPE 14-17)	6.0-8.7
Near-maximal to maximal	≥ 96	≥ 91	≥ Very hard (RPE ≥ 18)	≥ 8.8

%HR_{max}: percent of maximal heart rate, %VO_{2max}: percent of maximal oxygen uptake, RPE: ratings of perceived exertion (scale 6-20), METs: metabolic equivalent of the task.

Many studies have suggested that the exercise intensity may play a central role when determining the physiological responses to exercise training, implying that the higher the intensity, the greater the cardiovascular benefits (Garber et al., 2011; Kemi and Wisløff, 2010; Rehn et al., 2013; Wisløff et al., 2009). It has been suggested, that the overload principle of training is applicable to the exercise intensity: no improvement in VO_{2max} or in other physiological parameters can occur if the training intensity does not exceed specific threshold intensity which depends on the person's fitness level (Garber et al., 2011; Kemi and Wisløff, 2010). However, a recent meta-analysis has challenged the relationship between exercise intensity and improvement in VO_{2max} by reporting that exercise intensity did not affect the training-induced improvements in VO_{2max} in young healthy subjects (Scribbans et al., 2016). On the other hand, Scribbans and colleagues further pointed out that similar adaptations can be achieved by low-volume HIIT compared to high-volume MICT. The improvement in VO_{2max} is important, as VO_{2max} seems to be the most important prognostic of cardiovascular disease and morbidity (Weston et al., 2014; Wisløff et al., 2009). It has further been shown that chronic aerobic training improves the contractile capacity of cardiac muscle cells and the magnitude of the improvement is proportional to the exercise intensity (Wisløff et al., 2009). For instance, exercise training at 70% of maximal heart rate did not alter functional parameters of the heart (such as cardiac dilation, stroke volume, ejection fraction), whereas training at 95% of maximal heart rate induced marked improvements to these parameters in elderly subjects with stable post infarction heart failure (Kemi and Wisløff, 2010; Wisløff et al., 2007).

Exercise volume is the amount of physical activity that is accumulated during a specific period of time, typically within a week. The volume is the composition of duration, frequency and intensity (Powell et al., 2011). In research, the volume is often expressed as kilocalories per week or MET-minutes per week, the latter describing the product of number of METs associated with physical activities performed and the time spent in exercise. However, this description is difficult to use as an exercise guideline in common practice. Therefore, exercise volume is typically prescribed as minutes per week. For example, energy expenditure of 1000 $kcal \cdot wk^{-1}$ corresponds to moderate-intensity exercising for 150 min within a week. (Garber et al., 2011).

The current recommendations by The American College of Sports Medicine (ACSM) for health-enhancing physical activity for adults are listed in Table 3 (Garber et al., 2011). Based on these recommendations, the UKK institute has established the Finnish version for health-enhancing physical activity. The recommendation for cardiorespiratory fitness is divided into different options in terms of intensity of the exercise, and some or all of the moderate-intensity training can be replaced by vigorous exercises. Further, it has been suggested that sufficient level of HIIT should be incorporated to a population-based intervention (Rehn et al., 2013).

TABLE 3. ACSM recommendations on physical activity for health, 18-64 years old.

Cardiorespiratory exercise	$\geq$ 30 $min \cdot d^{-1}$ on at least 5 days a week for a total of $\geq$ 150 $min \cdot wk^{-1}$ at moderate intensity OR $\geq$ 20 $min \cdot d^{-1}$ on at least 3 days a week for a total of $\geq$ 75 $min \cdot wk^{-1}$ at vigorous intensity OR Combination of moderate- and vigorous-intensity exercise to achieve a total energy expenditure of $\geq$ 500-1000 $MET \cdot min \cdot wk^{-1}$
Resistance exercise	2-3 days a week for each of the major muscle groups
Other	2-3 days a week exercises involving balance, agility, coordination and flexibility

2.1.1 Moderate-intensity continuous training (MICT)

Moderate-intensity continuous training (MICT) refers to traditional endurance training at a constant intensity throughout a continuous training session without rest intervals, such as brisk walking, jogging or cycling. Typical training program consists of running or cycling at 60-70% of VO_{2max} for 45-60 minutes per session (Scribbans et al., 2016).

Traditionally, health benefits are considered to be achieved through strength and endurance training at moderate intensities (Wisløff et al., 2009). Indeed, regular endurance training is well known to contribute to cardiac hypertrophy, a phenomenon called "athlete's heart" (D'Andrea et al., 2002; Fagard, 2003; Pluim et al., 2000). Currently, aerobic moderate-intensity training has a central role in recommended treatment and prevention of cardiometabolic diseases (Weston et al., 2014). In line with this, the current recommendations for health-enhancing physical activity emphasize the role of MICT.

When an untrained person commits to MICT, beneficial adaptations to skeletal muscles, such as increased number of mitochondria and enhanced respiratory capacity of muscle fibers, take place rapidly (Laursen, 2010). Long-term MICT raises the intramuscular calcium concentration, which in turn activates the calcium-calmodulin kinase (CaMK) signaling pathway and its downstream target, the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a "master switch" leading eventually to mitochondrial biogenesis, increased fat oxidation potential and enhanced glucose transport capacity in the skeletal muscle (Laursen, 2010). Regular exercise training remodels the myocardial structure by inducing hypertrophy and renewal of cardiac muscle cells (Ellison et al., 2012). Further, regular MICT induces adaptations to the coronary circulation, such as increased oxygen supply and extraction in the myocardium as well as the coronary blood flow and transport capacity (Ellison et al., 2012). All of these factors contribute to the improvement of cardiorespiratory fitness, hence reducing the risk of cardiovascular diseases and premature death significantly (Garber et al., 2011; Powell et al., 2011). However, not all individuals can improve their cardiorespiratory fitness and VO_{2max} by MICT (Bouchard and Rankinen, 2001). Further, MICT requires time, but the lack of time remains the major hindrance in engaging the exercise (Trost et al., 2002). On the other hand, for inactive or obese persons MICT is often easier to start with as compared to HIIT and is recommended in order to enhance exercise adoption and adherence (De Feo, 2013; Garber et al., 2011).

When considering endurance athletes, many of them train about 75% of their training using long-duration sessions at intensities below their first ventilatory threshold (corresponding to aerobic threshold), although in competitions much higher intensities are needed. The improvements achieved through MICT in elite endurance athletes are not much studied, possibly because of the large training volume and time needed for enhanced performance. Few studies indicate improvement in the running speed at lactate threshold. It is also speculated that MICT may be needed in order to achieve optimal body composition or to facilitate the adaptations that occur in high-intensity training. (Laursen, 2010).

2.1.2 High-intensity interval training (HIIT)

The concept of high-intensity interval training (HIIT) has existed since early 1900s, and periods of HIIT have been a typical part of athletes' training program for enhancement of performance (Gibala and Jones, 2013; Laursen, 2010). However, as the general population has become increasingly physically inactive, commonly citing lack of time as the main barrier for exercise training, HIIT has gained a lot of interest as an alternative and more time-efficient method of exercise also among common population. Today, numbers of studies and meta-analyses have elucidated the effect of HIIT in sedentary healthy subjects as well as in subjects with lifestyle-induced diseases.

There is no single definition for HIIT. Generally, HIIT refers to repeated, short bursts of exercise often performed with an "all-out" effort or intensity close to VO_{2max} with recovery periods of light intensity between bouts (Gibala and McGee, 2008; Weston et al., 2014). The terminology used varies from study to study. Firstly, terms HIT (high-intensity training) and HIIT (high-intensity interval training) are both widely used interchangeably, and both of them refer to the interval-based training. Secondly, the intensities used in HIIT vary from aerobic interval training (AIT) of 80-100% maximal heart rate to supramaximal >100% VO_{2max} efforts (Weston et al., 2014). Recently, a standardization of the terminology has been proposed, stating that HIIT should stand for protocols between 80-100% of the maximal heart rate, whereas term "sprint interval training" (SIT) should be used for "all-out" supramaximal efforts (Gibala et al., 2014). For clarity, the term HIIT is used throughout this thesis for high-intensity interval training, covering aerobic interval training as well as sprint interval training.

As there are myriads of studies on HIIT, there are also numerous different HIIT protocols. Perhaps one of the reasons why HIIT is not yet included into the recommendations on physical activity for health is the complexity related to prescribing HIIT. Indeed, there are up to nine variables to manipulate, including work interval intensity and duration, recovery interval intensity and duration, exercise modality, number of repetitions within a series, number of series, and finally recovery time between series and the intensity of work load during recovery (Buchheit and Laursen, 2013). Three examples of HIIT protocols are summarized in Table 4. The common protocol used in research is the Wingate test, which is a 30-second cycling effort using supramaximal workload (Burgomaster et al., 2005; Gibala et al., 2006). Since this exercise protocol is extremely demanding, the same research group has more recently developed a more practical and safe model with 60-second bouts at intensities of 90% of maximal heart rate (Gibala et al., 2012). When considering HIIT for persons with or at risk of cardiovascular diseases or T2DM, even longer intervals up to 4 minutes have been recommended (Cassidy et al., 2017; Weston et al., 2014). These, and many more,

different protocols used reflect the fact that the optimal protocol is yet unknown, and it is probably highly individual (Weston et al., 2014).

TABLE 4. Examples of different HIIT protocols.

	Burgomaster *et al*. 2005, Gibala *et al*. 2006	Gibala *et al*. 2012	Weston *et al*. 2014 (recommendation based on meta-analysis of several HIIT studies)
Duration*	~ 20 min	20 min	25 min
Modality	cycle ergometer	cycle ergometer	Treadmill, cycle ergometer
Intensity	supra-maximal "all-out" effort	90% HRmax	85-95% HRmax
Interval times	4-6 x 30 s intervals 4 min recovery	10 x 60 s intervals 60 s recovery	4 x 4 min intervals 3 min recovery

% HRmax: percent of maximal heart rate. *Duration refers to the total duration of the interval training without warm-up and cool-down.

Previously, it has generally been believed that HIIT has only a mild effect on oxidative energy metabolism and endurance capacity (Gibala and McGee, 2008). However, numerous studies have recently shown that HIIT induces the same effects as MICT, such as increased VO_{2max}, activity of mitochondrial enzymes and oxidative capacity of the skeletal muscles (Gibala and McGee, 2008; Gibala et al., 2012; Laursen, 2010). Although HIIT appears to lead to similar improvements and physiological remodelling compared to traditional endurance training, the underlying molecular pathways seem to be different. As discussed in chapter 2.1.1., MICT induces adaptations to calcium concentration, activating the CaMK signalling pathway. Instead, during HIIT, high-energy adenosine triphosphate (ATP) is converted into adenosine monophosphate (AMP), raising the AMP-concentration in the skeletal muscle, which activates the adenosine monophosphate kinase (AMPK) signalling pathway (Chen et al., 2000). The AMPK pathway in turn activates the PGC-1α mRNA, the same transcriptional coactivator activated also by the CaMK pathway (Laursen, 2010). PGC-1α regulates mitochondrial biogenesis along with other adaptations leading to increased capacity to generate ATP aerobically. Thus, from a molecular point of view, HIIT and MICT seem to lead to the same goal but follow different roads, at least when regarding the skeletal muscle (Gibala and McGee, 2008; Gibala et al., 2012; Laursen, 2010).

2.1.3 Exercise training as a treatment for lifestyle-induced diseases

The treatment paradigm of cardiovascular diseases and cardiac patients has undergone major changes over time: in 1950s, all physical activity was banned as it was believed that the cardiac load should be minimal during the healing process (Weston et al., 2014). Today, it is well known that aerobic exercise plays a major role both in the treatment and prevention of cardiovascular diseases (Ellison et al., 2012; Weston et al., 2014). However, many studies have indicated that HIIT is not only safe and tolerable, but has superior effects on patients with cardiovascular diseases when compared to MICT (Gibala et al., 2012; Rehn et al., 2013; Weston et al., 2014). The experimental animal models have suggested that a failing human cardiac muscle may undergo exercise-induced adaptations if the training intensity is high enough (Kemi and Wisløff, 2010). In line with this, it has been shown that pathological remodeling of the myocardium was reversed only after HIIT (Rehn et al., 2013). Gibala and colleagues speculated that short bursts of HIIT could induce major cellular and peripheral vascular stress while saving the heart, allowing much higher training intensity than otherwise possible (Gibala et al., 2012). However, the "all-out" 30 s Wingate protocol may be too demanding and risky for patients with heart failure and the 60 s or 4 min interval models at approximately 90% of maximal heart rate may be more favorable protocols (Gibala et al., 2012; Weston et al., 2014).

Obesity and T2DM are increasingly common in modern society (Rehn et al., 2013) and constitute important risk factors for development and progression of cardiovascular disease. In overnourished obese persons, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones and other factors which contribute to the development of insulin resistance, failure of insulin to sufficiently control blood glucose after a meal (Kahn et al., 2006). T2DM develops when insulin resistance is accompanied by dysfunction of pancreatic islet β-cells, which are the cells that release insulin. (Kahn et al., 2006; Nolan et al., 2011). Decreased insulin secretion affects insulin action in several tissues, resulting in reduced glucose uptake in skeletal muscles, increased glucose production in liver, and increased lipolysis in adipose tissue (Stumvoll et al., 2005). Hence, in T2DM, both circulating fatty acids and blood glucose levels are increased (Stumvoll et al., 2005). As the skeletal muscle is the major tissue involved in glucose uptake after a meal, enhancing the transport of glucose into the muscle improves insulin sensitivity (Babraj et al., 2009). Similarly to insulin, exercise training increases glucose uptake in skeletal muscles (Goodyear and Kahn, 1998). Accordingly, it has been well established that exercise training can lower a biomarker of three-month average plasma glucose concentration, hemoglobin A_{1c} (HbA_{1c}), in subjects with T2DM (Boulé et al., 2001; Umpierre et al., 2011). More recently, many studies have investigated whether HIIT can be used to promote metabolic health in T2DM. According to a recent meta-analysis, HIIT does not induce marked changes in glycemic control (Cassidy et al., 2017). However, based on another meta-analysis, HIIT effectively improves measures

of insulin sensitivity as well as VO_{2max} compared to MICT and non-exercising control group in subjects with T2DM or metabolic syndrome (Jelleyman et al., 2015). It appears that HIIT increases the content of GLUT4, a protein transporting glucose to muscle cells, which contributes to improved glycemic control in patients with T2DM (Babraj et al., 2009; Cassidy et al., 2017; Gibala et al., 2012; Little et al., 2011). Further, while the mitochondrial content, function and biogenesis is reduced in patients with T2DM, the enhancing effects of HIIT on mitochondrial capacity may partly explain the efficacy of HIIT in treating the disease (Cassidy et al., 2017; Little et al., 2011). Taken together, it seems that HIIT can bring about similar enhancements in metabolic health and cardiorespiratory fitness as MICT in patients with T2DM.

Given the demanding nature of many HIIT protocols, there have been questions whether HIIT can be safely applied in different patient populations. The acute cardiac responses to HIIT are not yet fully understood. The number of adverse effects due to HIIT is reported to be low in several meta-analyses regarding the usability of HIIT in patients with lifestyle-induced cardiometabolic diseases (Cassidy et al., 2017; Jelleyman et al., 2015; Weston et al., 2014). Rognmo and colleagues conducted a large study regarding the cardiovascular events during organized HIIT and MICT among 4846 patients with coronary heart disease (Rognmo et al., 2012). They found one fatal cardiac arrest during total of 129 456 hours of MICT and two non-fatal cardiac arrests during total of 46 364 hours of HIIT, and no myocardial infarctions were reported (Rognmo et al., 2012). However, a more recent meta-analysis in patients with cardiometabolic diseases reported higher rate of adverse events during HIIT; 13 adverse responses were reported among 156 clinically stable patients, but the result may have been biased by the fact that only those HIIT studies reporting adverse events were included in the meta-analysis (Levinger et al., 2015). It appears that the risk of adverse cardiac event during HIIT is low compared to the health benefits gained by exercise. However, as the precise cardiac effects of HIIT still remain unknown, it may be wise to start exercise training with MICT and then proceed to supervised HIIT in patients with cardiometabolic diseases. In accordance, it has been suggested that HIIT should be avoided in those patients with severe or unstable state of cardiometabolic disease (Weston et al., 2014).

In addition to safety of HIIT, another potential issue concerning the applicability of HIIT as a therapeutic method to treat lifestyle-induced diseases is the home-based adherence to HIIT. The American College of Sports Medicine has recommended MICT to increase adherence in novice exercisers (Garber et al., 2011). However, the exercise adherence after the traditional 12-week-long cardiac rehabilitation program has been reported to be low (Dolansky et al., 2010). Heinrich and colleagues reported that those obese adults assigned to eight weeks of high-intensity functional training planned to continue exercising more than those participants assigned to MICT and resistance training (Heinrich et al., 2014). A study investigating exercise adherence after one year following 12 weeks of home-based or hospital-based HIIT cardiac rehabilitation program reported

that in both groups majority of participants (> 90%) met the recommendations of physical activity (Aamot et al., 2016). After one year, the home-based group even showed a trend towards increased physical activity compared to hospital-based groups (Aamot et al., 2016). Hence, it appears that home-based HIIT may be a working strategy to prevent and alleviate lifestyle-induced diseases.

2.2 Heart – the driving force of the cardiovascular system

The heart is responsible for pumping oxygenated blood into the body and deoxygenated blood to the lungs through the circulatory system. The heart is composed of the four cardiac chambers, left atrium, left ventricle (LV), right atrium, and right ventricle (RV) as illustrated in Figure 1. LV and RV are separated by the interventricular septum. Deoxygenated blood returns to the heart through the superior and inferior vena cava and enters the right atrium, from which blood enters to RV through the tricuspid valve. RV propels the blood to the pulmonary artery through the pulmonary semilunar valve, where it travels to the lungs for gas exchange, releasing carbon dioxide and absorbing oxygen. Oxygenated blood then enters the pulmonary veins and arrives to the left atrium. From there, blood enters the LV through the mitral valve, and LV then pumps the blood through the aortic valve to the aorta, and finally to the different organs and tissues of the body. Hence, RV is responsible for the pulmonary circulation and LV for the systemic circulation. (Berne and Levy, 1997).

The heart pumps blood in rhythmic contractions (the sinus rhythm). The rhythm is generated by specialized pacemaker cells in the sinoatrial node. The action potential is eventually conducted to cardiomyocytes that initiate their contraction in the specific order, allowing blood to be pumped forward. The cardiac cycle refers to the events occurring within one complete heartbeat, involving five major stages during which blood pressure is increased and decreased in the atria and the ventricles. Briefly, in the first phase called the diastole, the heart is relaxed with the pulmonary and aortic valves closed and the tricuspid and mitral valves open, allowing the ventricles to start filling. In the second stage, the atria contract and blood flows into the ventricles. The third stage is the isovolumic contraction phase, which begins the ventricular systole, in which all the valves are closed and the ventricles are contracted without change in the volume. In the fourth stage, the pulmonary and aortic valves open, the ventricles contract and proportion of blood is ejected into the aorta and the pulmonary artery while some blood remains in the ventricles. Finally, in the fifth stage, all the valves are closed and the ventricles begin their isovolumetric relaxation. The main events during the cardiac cycle are illustrated in Figure 2. (Berne and Levy, 1997).

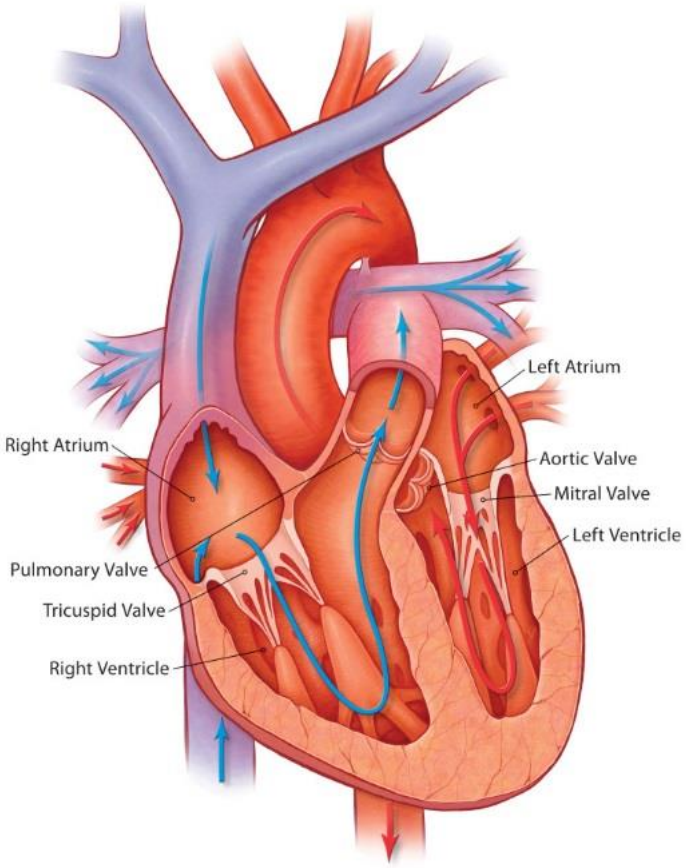

FIGURE 1. Anatomy of the human heart demonstrating the four chambers (left and right atria, and left and right ventricles) and the four main valves (mitral, tricuspid, aortic, and pulmonary). Reprinted with permission from (Forrest, 2012).

End-diastolic volume (EDV) denotes the volume of blood in the ventricle at the end of the filling phase just before the systole, whereas end-systolic volume (ESV) is the blood volume within the ventricle at the end of the contracting phase, as illustrated in Figure 2. EDV is closely related to the preload, the initial stretching of the cardiomyocytes prior to contraction. According to the Frank-Starling mechanism, increase in EDV increases the preload, which in turn increases the force of the contraction and hence the amount of blood ejected from the ventricle during the systole. EDV is affected by the venous blood pressure and the rate of venous return. ESV, in turn, is a parameter describing cardiac emptying. It is affected by contractility of the heart as well as by the afterload. The afterload describes the pressure that the ventricle must reach in order to eject blood, and it is basically the aortic pressure for LV and the pulmonary artery pressure for RV. Hence, impairments in contractile function or increase in the afterload hinders emptying of the ventricle and therefore increases ESV. (Berne and Levy, 1997).

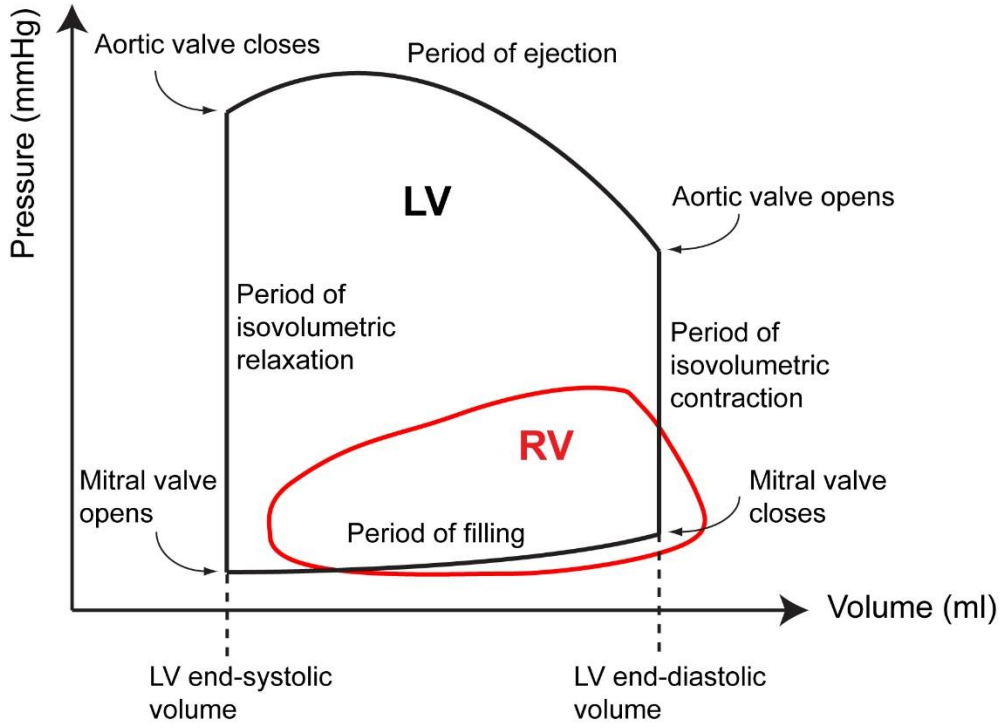

FIGURE 2. Schematic representation of the pressure-volume loop of the cardiac cycle for the left ventricle (LV; black curve) and for the right ventricle (RV; red curve). For clarity, the main events during the cardiac cycle are illustrated for the left ventricle only. The corresponding events involving opening and closing of the tricuspid and pulmonary valves occur in the right ventricle. The area enclosed by the pressure-volume loop represents the ventricular stroke work. While the LV and RV stroke volumes are equal, the RV stroke work is approximately one fourth of the LV stroke work.

Stroke volume (SV) describes the amount of blood that is pumped from the ventricle within one heartbeat. Cardiac output (CO) refers to the amount of blood that is pumped within a unit of time, typically within a minute. Therefore, CO is calculated as the product of SV and heart rate (HR). Finally, ejection fraction (EF) describes the proportion of blood that is ejected from the ventricle during the systole. Functional parameters SV, CO, and EF can therefore be calculated using the following equations:

$$SV = EDV - ESV$$
$$CO = SV \cdot HR$$
$$EF = \frac{SV}{EDV} \cdot 100\%$$

As RV and LV are connected in series, stroke volumes and cardiac outputs of the healthy heart are effectively the same for both ventricles. However, the stroke work of the RV is approximately only one fourth of the stroke work of the LV (Vitarelli and Terzano, 2010), as illustrated in Figure 2 and discussed in more detail in chapter 2.4.1.

2.3 Myocardial metabolism – fuelling cardiac contraction

Cardiac contraction is strongly tied to myocardial metabolism, because without sufficient fuel the heart is not able to pump the blood into the circulation. As the heart muscle must work constantly to meet the circulatory demands, its energy requirement is enormous. The daily adenosine triphosphate (ATP) turnover is more than 6 kg, but the heart has very limited energy reserves. Therefore, the heart must generate ATP at a high rate using an optimal energy substrate and oxygen supply in different physiological and pathophysiological conditions. (Lopaschuk and Dhalla, 2014).

2.3.1 Omnivorous heart utilizes different substrates to generate energy

The heart is an omnivore that is able to derive energy using various carbon substrates, including free fatty acids (FFAs), glucose, lactate, pyruvate, ketone bodies, and amino acids. In order to rapidly generate large amounts of ATP, cardiac myocytes have a high volume density of mitochondria. In normal resting conditions, majority (> 95%) of the ATP is produced by oxidative phosphorylation and the remaining proportion through glycolysis (Lopaschuk and Kelly, 2008; Stanley et al., 2005). Healthy heart at resting state derives approximately 60-90% of its energy from fatty acid oxidation and remaining 10-40% from carbohydrates, primarily from glucose and lactate (Bing et al., 1953; Stanley et al., 2005; van der Vusse et al., 2000). Fatty acids are broken down through the beta-oxidation pathway and turned into acetyl-CoA. Glucose is metabolized through the glycolytic pathway into pyruvate. Pyruvate is also derived by oxidising lactate. The obtained pyruvate is converted to acetyl-CoA. Acetyl-CoA obtained from fatty acids and carbohydrates fuels the tricarboxcylic acid cycle within mitochondria, which produces high-energy nicotinamide adenine dinucleotide (NADH). The energy of NADH is converted to ATP through the electron-transfer chain and finally in the oxidative phosphorylation. (Stanley et al., 2005).

In a healthy heart, myocardial metabolism is highly plastic and the heart can rapidly switch between different energy substrates as a response to changes in metabolic environment. Overview of the metabolic network is presented in Figure 3. The fetal heart relies on carbohydrates as a fuel (Ascuitto and Ross-Ascuitto, 1996). After birth and increased oxygen availability, there is a rapid change to fatty acid oxidation, which

becomes the major energy source (Onay-Besikci, 2006). During fasting conditions, as well as in obesity or T2DM, role of fatty acids becomes even more pronounced (Lopaschuk et al., 2010). In the fed state, plasma glucose and insulin increase, decreasing fatty acid utilization and increasing glucose utilization (Lopaschuk et al., 2010). During intense exercise, myocardial lactate utilization increases due to increased lactate production of the skeletal muscles (Kaijser and Berglund, 1992). Finally, the contribution of ketone bodies and amino acids to overall myocardial oxidative metabolism is small, and they are used as a fuel in prolonged fasting, ketogenic diet or starving (Kolwicz et al., 2013).

Alterations in substrate use can be acute responses to short-term alterations in physiological environment, or chronic responses caused for example by a disease (discussed in more detail in the next section), aging and sex (Peterson and Gropler, 2010). Selection between different energy substrates is complex, and it is regulated by factors such as plasma substrate concentrations, hormone concentrations, coronary flow, cardiac work, and nutritional status (Peterson and Gropler, 2010; Stanley et al., 2005). Furthermore, metabolic plasticity is controlled at multiple levels. Long-term adaptations reflect alterations in gene expression by transcriptional regulation and post-translational modification of key proteins involved in metabolic pathways, whereas short-term responses are controlled by allosteric regulation by substrates and their metabolites (Kolwicz et al., 2013; Peterson and Gropler, 2010). In the healthy heart, there is an efficient interplay between energy substrates so that the metabolism of one substrate inhibits the pathway of another substrate (Peterson and Gropler, 2010). For instance, the fatty acid oxidation pathway is stimulated by adiponectin and fatty acids, and inhibited by glucose and lactate. Correspondingly, glycolysis and glucose oxidation pathways are stimulated by factors such as insulin and epinephrine and inhibited by fatty acids. In addition, several proteins are involved in stimulation and inhibition of each pathway (Kolwicz et al., 2013). Regulation of fatty acid metabolism is thoroughly reviewed by Lopaschuk and colleagues (Lopaschuk et al., 2010) and factors affecting myocardial glucose metabolism are described in detail by Depre and colleagues (Depre et al., 1999).

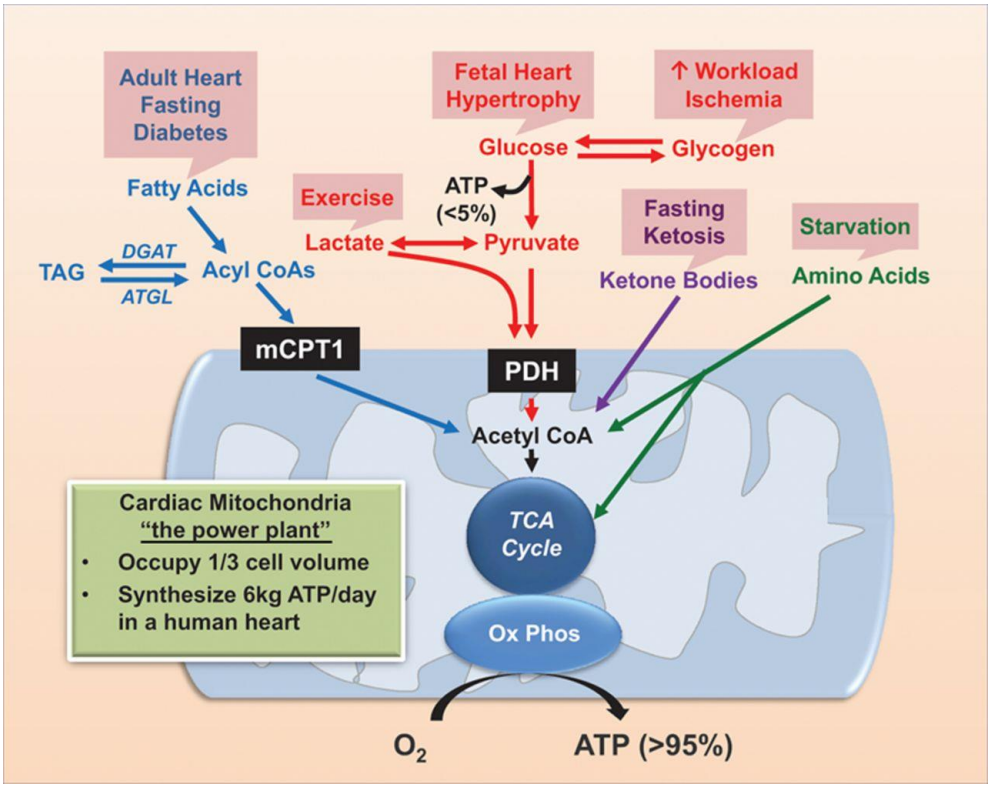

FIGURE 3. Overview of the metabolic network in the cardiomyocyte. The energy-yielding substrates (fatty acids, glucose, ketones, and amino acids), via specific catabolic pathways, converge on acetyl-CoA production with subsequent entry into the tricarboxylic acid (TCA) cycle. The final step of energy transfer is accomplished through oxidative phosphorylation (Ox Phos), supplying >95% of ATP consumed by the heart. The boxes (in pink) above each metabolic pathway indicate the pathological and physiological condition in which the specific substrate becomes a predominant contributor to metabolism. ATGL indicates adipose triglyceride lipase; DGAT, diacylglycerol acyltransferase; mCPT1, muscle form of carnitine-palmitoyl transferase-1; PDH, pyruvate dehydrogenase; TAG, triacylglycerol; and TCA, tricarboxcylic acid. Reprinted with permission from (Kolwicz et al., 2013).

2.3.2 Effects of pathological and physiological hypertrophy on myocardial metabolism

When faced with pathological hypertrophy caused by a disease, myocardial metabolism becomes altered and flexibility in its substrate utilization is reduced. Impairments in substrate metabolism are believed to contribute to contractile dysfunction, potentially leading to heart failure (Ashrafian et al., 2007; Stanley et al., 2005). On the other hand,

positive, physiological hypertrophy caused by exercise training may also affect myocardial metabolism.

Mechanical overload. Hypertension, coronary artery disease, ischemia, and myocardial infarction lead to mechanical overload, which precedes the development of a heart failure (Van Bilsen et al., 2009; Kolwicz et al., 2013). Following long-term pressure and volume overload, as well as regional damages in the heart muscle, oxygen supply to the heart and mitochondrial substrate oxidation are reduced (Van Bilsen et al., 2009). As a consequence, the capacity of the heart to generate sufficient amounts of ATP to maintain cardiac output is compromised. The failing heart has been presented as an engine out of fuel (Neubauer, 2007), underlining the significance of changes in myocardial metabolism in the heart failure.

It is well documented that pathological hypertrophy due to a mechanical overload is associated with the reappearance of the fetal metabolic profile, showing increased carbohydrate metabolism and decreased fatty acid utilization as illustrated in Figure 4 (Razeghi et al., 2001; Sack et al., 1996). Similarly, the right ventricular glucose metabolism is increased in patients with pulmonary artery hypertension or heart failure (Can et al., 2011; Lundgrin et al., 2013; Mielniczuk et al., 2011; Oikawa et al., 2005). The reason for metabolic shift towards glucose remains unclear. One explanation is based on the fact that oxidation of fatty acids requires 12% more oxygen per unit of ATP generated compared to glucose, making oxidation of glucose more favorable especially in an ischemic heart where oxygen supply is limited (Scolletta and Biagioli, 2010). Other explanations may be impaired fatty acid oxidation secondary to mitochondrial derangements, changes in the activities of proteins responsible for mitochondrial entry of glucose-derived acetyl units and of fatty acids, or reduction of the genes involved in fatty acid handling (Van Bilsen et al., 2009). Nevertheless, the net result is increased glucose metabolism, which is associated with accelerated glycolysis (Depre et al., 1999; Kolwicz and Tian, 2011). Despite the increased rate of glycolysis, there appears to be no change in glucose oxidation, whereas there has been documented increased activity of lactate dehydrogenase, which is responsible for conversion of pyruvate to lactate (Kolwicz and Tian, 2011). Hence, in pathological hypertrophy, increased glucose metabolism seems to be related to increased portion of lactate-yielding glycolysis. However, as the heart failure advances, insulin resistance develops in the myocardium and even the glucose metabolism gradually decreases (Neubauer, 2007), leading to energy deprivation and worsening of the heart failure (Figure 4).

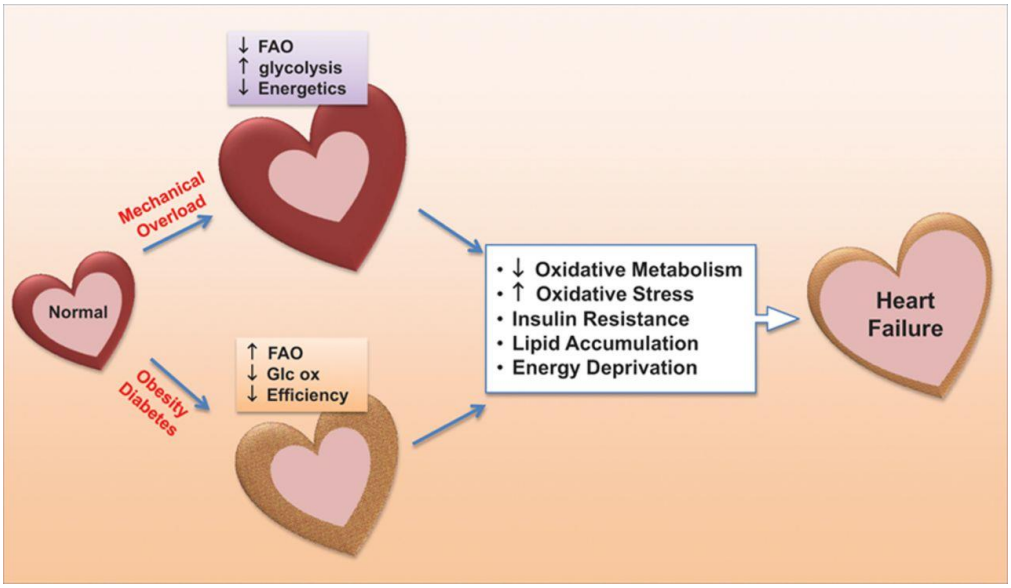

FIGURE 4. Metabolic remodelling and the development of heart failure. Pathological hypertrophy in response to mechanical overload, for example, hypertension, valvular disease, or post-myocardial infarction, is accompanied by metabolic remodelling characterized by decreases in fatty acid oxidation (FAO) and increases in glycolysis. This fetal-like metabolic profile decreases the capacity for ATP synthesis, consistent with the energy starvation model. In contrast, the elevated supply of substrates in the heart of obese individuals and those with diabetes mellitus leads to an upregulation of FAO with a concomitant decrease in glucose oxidation (Glc ox). This lipid overload condition impairs cardiac efficiency. Regardless of the precipitating factor, the persistent metabolic derangements elicit commonalities of decreased oxidative metabolism, increased oxidative stress, insulin resistance, lipid accumulation, and energy deprivation, all contributing to the progression of heart failure. Reprinted with permission from (Kolwicz et al., 2013).

Type 2 diabetes mellitus and obesity. Cardiac dysfunction and pathological hypertrophy, so called diabetic cardiomyopathy, have increasingly been documented in individuals with T2DM or obesity. The metabolic profile of the diabetic cardiomyopathy differs from that caused by a mechanical overload, as the diabetic heart is characterized by increased fatty acid uptake (Peterson et al., 2004; Rijzewijk et al., 2009) and decreased glucose oxidation (Figure 4) (Rijzewijk et al., 2009; Voipio-Pulkki et al., 1993). A unique feature of the cardiac metabolism in obesity and T2DM is that substrate supply exceeds the need of ATP synthesis. A diet rich in fatty acids increases circulating FFAs. This increases sarcolemmal CD36 abundance, a membrane protein responsible for facilitating fatty acid movement into the cardiac cell. In a healthy heart, glucose transporters (GLUT4 and GLUT1) and CD36 exist at the sarcolemma about equally. However, in obesity and T2DM, CD36 is permanently relocated to the sarcolemma as a

response to increased plasma FFA concentration, replacing glucose transporters. As a consequence, fatty acids and their metabolites begin to accumulate within the cardiac cells, contributing to the insulin resistance and dysfunction of the heart (Lopaschuk and Dhalla, 2014). While the heart of a diabetic or obese person relies almost completely on fatty acids, oxygen consumption increases because oxidizing fatty acids requires more oxygen than oxidizing carbohydrates. In addition, it has been suggested that fatty acids waste ATP and oxygen by removing those long-chain fatty acids out of the mitochondria, which are formed from excess intramitochondrial fatty acyl-CoA (Stanley et al., 2005). Hence, a metabolic shift towards fatty acids reduces cardiac mechanical efficiency (Stanley et al., 2005). Diabetic cardiomyopathy progresses from an early development of diastolic dysfunction (Boyer et al., 2004) to increased left ventricular mass and thickness (Devereux et al., 2000) and systolic dysfunction, potentially leading to a heart failure (Ashrafian et al., 2007).

Exercise training. Contractile performance of the heart at a given myocardial oxygen consumption is greater when the heart is oxidizing more glucose and lactate and less fatty acids (Stanley et al., 2005). Furthermore, oxidation of lactate becomes predominant during intense exercise when the skeletal muscle lactate production increases (Kaijser and Berglund, 1992). In concordance, myocardial glucose uptake has been reported to increase only up to moderate-intensity training, whereas at higher exercise intensity glucose uptake returned to that of resting state and lactate oxidation most likely became the major energy substrate (Kemppainen et al., 2002).

It is well known that regular exercise training leads to physiological hypertrophy of the heart. Nevertheless, effects of long-term exercise training on myocardial metabolism have been studied sparsely. A cross-sectional study has reported decreased left ventricular glucose uptake in athletes compared to untrained controls (Nuutila et al., 1994; Takala et al., 1999). However, there have been no changes in fatty acid uptake between subjects of different fitness levels (Hannukainen et al., 2007; Takala et al., 1999; Turpeinen et al., 1996). The decreased myocardial glucose uptake correlated negatively with the left ventricular mass, and appeared to be associated with reduced myocardial work in athletes, possibly because of physiological hypertrophy or the use of alternative substrates (Nuutila et al., 1994; Takala et al., 1999).

2.4 Right ventricle of the heart

For a long time, the right ventricle (RV) has been an understudied cardiac chamber. The concept of RV being "unnecessary" has most likely stemmed from the animal studies conducted in 1940s, which showed that removal or replacement of the RV free wall is tolerated without a reduction in the cardiac output (Haddad et al., 2008b; Sheehan and

Redington, 2008). However, recent studies have shown that RV dysfunction has a central role in prognosis and outcomes for variety of cardiovascular diseases (Haddad et al., 2008a; Voelkel et al., 2006). RV has gained attention also in the field of exercise physiology. For instance, a recent meta-analysis regarding the cardiac adaptations to endurance training has suggested that we may have been overlooking the more important side of the heart (Elliott and La Gerche, 2015).

2.4.1 Anatomy and physiology

The task of both ventricles is to pump blood forward in the circulation. In the normal mammalian heart, RV is connected in series with LV and therefore both ventricles have on average the same stroke volume. However, RV and LV are different in various ways. Differences between the two cardiac chambers are partly explained by different embryologic origins. RV is derived from the anterior heart field, whereas LV as well as both atria are derived from the primary heart field (Zaffran et al., 2004). Fetal RV and LV free wall thickness and force development are equal as the pulmonary artery and the aorta are connected through the ductus arteriosus, and flow through the pulmonary vasculature is impeded by the high resistance. When the lungs expand after birth, the pulmonary pressure decreases and RV undergoes significant changes including regression of RV hypertrophy and structural remodelling (Haddad et al., 2008b).

Normally, RV is located immediately behind the sternum and therefore it is the most anteriorly situated cardiac chamber. While the LV has ellipsoidal shape, the shape of the RV is complex and difficult to model. RV is curved over the LV, and when seen from the cross-section, the cavity of RV appears like a crescent. The shape of the RV is influenced by the position of the interventricular septum. Under normal conditions, the septum is concave towards the LV during the whole cardiac cycle. RV can be divided into three parts: the inlet region composed of the tricuspid valve apparatus, the trabeculated apical myocardium, and the RV outflow tract. The wall of the RV is only 3-5 mm thick. The apical part of the RV is heavily trabeculated. In contrast, LV trabeculations are fine, and hence the trabeculations allows the distinction of morphological LV and RV. Both ventricles are composed of multiple layers of cardiac myocytes, forming a complex three dimensional network. RV wall is mainly composed of superficial and deep muscle layers. The superficial layer are arranged circumferentially, whereas the deep layer is oriented longitudinally from base to apex. Therefore, RV contracts longitudinally in a "peristaltic" pattern. This is in contrast to the LV, in which there is also a middle layer arranged in circumferential pattern, which provide the main driving force of the LV by radial contractions. (Haddad et al., 2008b; Ho and Nihoyannopoulos, 2006; Vitarelli and Terzano, 2010).

The RV is coupled with the low-pressure pulmonary vascular system with low vascular resistance compared to the systemic circulation. Therefore, under normal conditions, right-sided pressures are significantly lower than those of the left side. Since RV systolic pressure rapidly exceeds the pressure of the pulmonary artery, RV isometric contraction time is shorter than in LV. Although the stroke volumes of both ventricles are the same, RV requires only one fourth of the stroke work compared to LV due to low pulmonary pressure. In addition, since the ventricular mass of the RV is about one quarter of the LV mass, its oxygen requirement is also lower. However, RV contraction is largely dependent on its loading condition. RV can handle volume overload much better than pressure overload. RV is shown to be sensitive to changes in afterload, and increase in the pulmonary artery pressure may result in RV dilation. In addition, the influence of mechanical work by breathing affects RV beat-by-beat and breath-by-breath hemodynamics. Breathing creates small changes in mean airway pressure, which is reflected by changes in RV stroke volume. This further highlights the significance of the afterload on RV contractile performance. (Haddad et al., 2008b; Ramani et al., 2010; Sheehan and Redington, 2008; Vitarelli and Terzano, 2010).

2.4.2 Involvement of the right ventricle in cardiac diseases

The RV is affected by numerous pathological processes and also contributes to many diseases, as reviewed for example by Haddad and colleagues as well as by Voelkel and colleagues (Haddad et al., 2008a; Voelkel et al., 2006). Exercise training may acutely increase the pulmonary artery pressure, and in highly trained athletes the exercise-induced changes may overlap with pathological conditions (D'Andrea et al., 2015). Therefore, effects of pulmonary artery hypertension on RV is discussed in more detail. In addition, alterations of RV in the context of diabetic cardiomyopathy are covered.

Pulmonary artery hypertension. One of the major causes of RV dysfunction is pulmonary artery hypertension (PAH). The mean pulmonary artery pressure of the healthy pulmonary circulation ranges between 9-20 mmHg (Ryan and Archer, 2014), and the normal heart is not able to respond to acute pressure overload with mean pulmonary artery pressure exceeding 40 mmHg (Chin et al., 2005). However, PAH often develops gradually, and RV initially adapts to increase in pulmonary pressure by RV dilation and hypertrophy. Therefore, the range in mean pulmonary artery pressure can be as high as 57-61 mmHg in patients with PAH (Ryan and Archer, 2014).Within physiological limits, RV dilation increases RV preload and improves RV contractile function via the Frank-Starling mechanism. However, further increase in RV volume compresses the LV and can compromise the global ventricular function, highlighting the significance of the ventricular interdependence (Haddad et al., 2008a; Voelkel et al., 2006). Several studies in patients with PAH have shown increased RV glucose uptake and decreased RV function (Can et al., 2011; Lundgrin et al., 2013; Oikawa et al., 2005;

Yang et al., 2014). While some patients with PAH can cope with severe pulmonary hypertension for prolonged periods of time, others experience rapid decompensation and death (Chin et al., 2005), underscoring the fatality of increased afterload of the RV.

Type 2 diabetes mellitus. T2DM is strong risk factor for cardiovascular morbidity and mortality, and it increases the risk of developing heart failure even without co-existence of coronary artery disease or hypertension (Garcia et al., 1974; Kannel and Mc Gee, 1979; Nieminen et al., 2006). While it is known that diabetic cardiomyopathy causes LV diastolic, and in more severe form also systolic, dysfunction and LV hypertrophy (Ashrafian et al., 2007; Boyer et al., 2004; Devereux et al., 2000), its impact on RV is studied much less. Previous studies have reported RV diastolic dysfunction (Kosmala et al., 2004; Tadic et al., 2015; Widya et al., 2013) as well as decreased RV end-systolic volume (Tadic et al., 2015; Widya et al., 2013) in subjects with T2DM compared to healthy controls. The results regarding the effect of T2DM on RV ejection fraction are differing, reporting no change (Tadic et al., 2015) or decreased RV ejection fraction (Movahed and Milne, 2007). There appears to be no previous studies concerning the changes in RV mass in subjects with T2DM. Finally, as discussed in detail in section 2.3.2, T2DM alters the myocardial metabolism, but the results are derived from LV measurements. The effect of the disease on RV metabolism has previously been addressed only in Zucker diabetic fatty rats, in which both LV and RV glucose utilization was decreased compared to healthy rats (Van den Brom et al., 2010). However, it remains unclear whether T2DM exerts its detrimental effects on both ventricles uniformly, or whether the RV dysfunction is merely a consequence of LV dysfunction.

2.4.3 Right ventricular adaptations and structural remodelling to exercise

The term "athlete's heart" is often cited in reference to the left ventricular adaptations to long-term, intensive training, including increased left ventricular chamber size, wall thickness, and mass (D'Andrea et al., 2002; Pluim et al., 2000). However, right ventricular adaptations to exercise training are less known. While previous studies have reported balanced hypertrophy of the both ventricles as a response to exercise training (Luijkx et al., 2012; Scharf et al., 2010; Scharhag et al., 2002; Spence et al., 2013), other studies have reported acute RV dysfunction following intense endurance exercise, such as running a marathon (Claessen et al., 2014; La Gerche et al., 2011, 2012; Mousavi et al., 2009; Trivax et al., 2010). A recent meta-analysis has further suggested that intense endurance exercise may lead to reduction of RV function while LV function remains unaffected (Elliott and La Gerche, 2015). As intensive exercise training may predispose a small number of athletes to atrial and ventricular arrhythmias, physiological changes have to be distinguished from those caused by pathological processes (D'Andrea et al., 2015). While RV may be particularly important when considering intensive endurance training, the role of RV during short-term HIIT is unknown and it may be different

compared to ultra-endurance exercise. Therefore, exercise-induced changes in RV structure, function, and metabolism need to be studied in more detail.

Several cross-sectional cardiac magnetic resonance (CMR) imaging studies have consistently reported increased RV volumes, RV mass, and RV stroke volume in endurance-athletes compared with age- and sex-matched controls (La Gerche et al., 2011; Luijkx et al., 2012; Prakken et al., 2010; Scharf et al., 2010; Scharhag et al., 2002). However, the studies disagree whether exercise-induced RV and LV hypertrophy is balanced with preserved LV to RV volume and mass ratio (Luijkx et al., 2012; Scharf et al., 2010; Scharhag et al., 2002) or whether remodeling of RV is greater than that of LV (La Gerche et al., 2011). The effect of long-term exercise training on RV ejection fraction (EF) is also less clear. Some studies have reported no difference between athletes and controls (Scharf et al., 2010; Scharhag et al., 2002), while others have shown small decrease in RVEF in athletes compared to controls (La Gerche et al., 2011; Prakken et al., 2010). The RV dimensions and RVEF of the elite athletes may relatively often fall outside the normal ranges of the healthy individuals (Prakken et al., 2010; Scharf et al., 2010), highlighting the fact that the distinction between athlete's heart and RV pathology can occasionally be difficult. Moreover, cross-sectional studies comparing elite athletes and non-athletes may partly reflect the genetic characteristics of a talented athlete rather than solely the results of prolonged exercise training (Douglas, 2004).

Only a few research groups have investigated RV changes occurring in previously untrained healthy subjects once they engage in exercise training (Arbab-Zadeh et al., 2014; Spence et al., 2013; Vogelsang et al., 2008). The results of these longitudinal studies are summarized in Table 5. All studies consistently reported increased RV end-diastolic volume and RV mass. Further, these parameters were progressively increased in response to one year of intensive endurance training, and cardiac mass even reached close to the same level as that of elite endurance athletes (Arbab-Zadeh et al., 2014). The effect of exercise on RV stroke volume has shown different results (Table 5), while RV ejection fraction has consistently remained unchanged by training. All the studies summarized in Table 5 reported balanced hypertrophy in both RV and LV. Moreover, the cardiac changes were accompanied with increased VO_{2max} (Arbab-Zadeh et al., 2014; Vogelsang et al., 2008). Hence, it can be concluded that exercise training of previously untrained subjects leads to positive, physiological hypertrophy in both ventricles, as well as to better exercise capacity.

TABLE 5. Summary of longitudinal studies regarding right ventricular changes in response to exercise training in previously untrained subjects.

Study	Exercise regimen	Duration	RV EDV	RV ESV	RV SV	RV mass	RV EF
Vogelsang et al., 2008	Rowing	8 weeks	↑	↔	↑	↑	↔
Spence et al., 2013	Endurance OR strength training *	6 months	↑	↔	↔	↑	↔
Arbab-Zadeh et al., 2014	Endurance sport **	1 year	↑	−	↑	↑	−

* Endurance training consisted of progressively overloaded program of walking/jogging/running, whereas strength training consisted of Olympic weightlifting with assistance exercise.
** Progressive endurance training including walking/jogging/running, cycling, and swimming designed to enable all subjects to compete in a marathon at the end of the 12-month period.
↑ Parameter is increased after training; ↔ parameter is unaltered by training; − parameter is not reported; RVEDV, RV end-diastolic volume; RVESV, RV end-systolic volume; RVSV, RV stroke volume; RVEF, RV ejection fraction.

Although exercise training is generally associated with excellent health outcomes and usually appears to lead to balanced hypertrophy in both ventricles, some studies have reported disproportionate load on the RV, at least during the exercise (Claessen et al., 2014; La Gerche et al., 2012; Trivax et al., 2010). During exercise, cardiac output increases many-fold to meet the oxygen demand of the working muscles. However, the workload of RV may increase up to 3.6- to 5.2-fold, whereas the same exercise results in a 2.1- to 2.8-fold increase in LV workload (Douglas et al., 1990). This may explain why intense prolonged exercise seems to be associated with RV dysfunction while LV function is relatively unaffected (Elliott and La Gerche, 2015). While the cause of RV dysfunction following endurance exercise remains unclear, a likely explanation is the significant increase in the pulmonary artery pressure. During exercise, the pulmonary artery systolic pressure has been reported to increase 166% compared to only 36% increase in the systolic blood pressure, and the increase was larger in athletes compared to controls, reaching pulmonary artery systolic pressure of 61.1 mmHg (La Gerche et al., 2011).

The disproportionate increases in the right- and left-sided pressures stem from the differences in the physiology of the pulmonary and systemic circulation. At rest, LV faces a great arterial load due to the resistance of the systemic circulation with large vascular territories, whereas RV is faced with the low-resistance pulmonary vasculature with vessels of short length. The circulatory system responds to exercise by decreasing resistance and increasing its compliance. However, as the pulmonary vasculature has already very low resistance, it has limited capacity for further decrease compared to significant reduction in the systemic vascular resistance. Hence, the increase of pressure in the pulmonary circulation is greater compared to the left-sided systemic pressure,

increasing the afterload and thus workload of the RV. Moreover, as the RV mass is only about one quarter of the mass of LV, the substantial increase in the pulmonary pressure during exercise may put a significant burden on the RV. While it appears that healthy RV can meet the increased work demand for a short time, during prolonged exercise the RV may become prone to cardiac fatigue. (D'Andrea et al., 2015).

Finally, it has been reported that vigorous exercise may increase the risk of sudden cardiac death in adults as well as in adolescent and young adult athletes (Corrado et al., 2006). These feared incidences have raised a question, whether so-called "exercise-induced cardiomyopathy" exists or not. Interestingly, it may be that RV is the "Achilles' heel" of the endurance athlete. According to a recent meta-analysis, abnormal RV function is observed in endurance athletes after intense exercise, but usually it is transient and reversible (Elliott and La Gerche, 2015). However, cumulative bouts of intense exercise training may promote arrhythmias in some highly-trained athletes (Ector et al., 2007; La Gerche et al., 2015; Heidbüchel et al., 2003). It has been thought that sudden cardiac death during intense exercise, such as a marathon, is due to already existing abnormalities of the heart (cardiomyopathy, premature coronary artery disease, congenital coronary anomalies), and sport acts as a trigger of cardiac arrest (Corrado et al., 2006). However, as RV is shown to be vulnerable to intense exercise, a question has emerged whether repeated bouts of exercise can predispose an athlete to arrhythmias even without underlying cardiac abnormalities (D'Andrea et al., 2015). Nevertheless, for majority of people exercise is an effective way to prevent cardiovascular diseases (Corrado et al., 2006). Whether HIIT can have a negative effect on the RV is unknown.

2.4.4 Methods to measure right ventricular structure, function and metabolism in humans

Assessment of the right ventricular function is challenging due to its complex geometry, thin free wall, heavy trabeculations, and its sensitivity to loading conditions (D'Andrea et al., 2015; Ramani et al., 2010). Therefore, there is no single widely accepted method or index to evaluate RV function, and results of different studies may vary depending on the technique and analyses methods used. While an invasive right heart catheterization is a gold standard for hemodynamic assessment (Greyson, 2011), advances in multimodal imaging approaches provide non-invasive methodology to determine many RV parameters. Measurement methods can be roughly classified into those intended to measure *i*. pulmonary hemodynamics, *ii*. regional RV myocardial motion, *iii*. RV volume and ejection fraction, and *iv*. RV myocardial perfusion and metabolism. The most common methods to determine RV parameters are summarized in Table 6.

TABLE 6. Summary of the different methods to determine RV parameters.

Method	RV parameters recommended to measure with the method	Strengths	Limitations
Right heart catheterization	• Pulmonary artery pressure (GS) • Pulmonary vascular resistance (GS) • Cardiac output (GS)	• Accurate	• Invasive
Echocardio-graphy	• Contractile function • Volume (with 3D imaging) • Estimation of pulmonary artery pressure	• Non-invasive • Low cost • Portable • Rapid to perform	• Potentially inaccurate
CMR	• Volume, ejection fraction, mass (GS) • Contractile function (with tissue tagging) • Estimation of pulmonary artery pressure (with phase-contrast velocity mapping)	• Non-invasive • Resolution • Reproducibility	• Expensive • Long scan time • Breath holds • Contraindications
PET	• Metabolism • Perfusion	• Non-invasive • Quantitative	• Exposure to radiation • Expensive • Not widely available • Poor visibility of RV

CMR, cardiac magnetic resonance; PET, positron emission tomography; GS, gold standard.

Right heart catheterization. In this technique, a catheter is inserted into the right ventricle via femoral vein or via radial artery and forearm vein (Callan and Clark, 2016). The method is a gold standard for quantifying pulmonary artery pressures, pulmonary vascular resistance, and RV cardiac output (Callan and Clark, 2016; Greyson, 2011). Right heart catheterization is used in clinical practice to diagnose pulmonary artery hypertension, as this is the only method that can reliably measure pulmonary hemodynamic parameters (Rosenkranz and Preston, 2015). Even though the risks involved in this invasive operation are small, non-invasive imaging approaches are used in practice as a first step to avoid unnecessary catheterizations (Rosenkranz and Preston, 2015). The invasive nature of the procedure also limits its usability in the field of exercise physiology, and estimates of pulmonary hemodynamics are usually derived using non-invasive imaging.

Echocardiography. Transthoracic echocardiography is a non-invasive technique based on ultrasound, which echoes back from the tissue in a specific degree depending on the tissue. The obtained echoes are represented as a sonogram, the image of the heart. Echocardiography can be applied in two and three dimensions, and with Doppler technology it is possible to measure blood flow. Echocardiography is often used as a first step in medical examination, because it is portable, widely available, relatively low cost,

and rapidly performed. While the two-dimensional echocardiography is limited by inaccuracies stemming from geometric assumptions regarding the RV shape, the three-dimensional technology allows better accuracy of RV dimensions. Although the measurement of RV anatomy may not be the strongest side of the echocardiography, it is an excellent technique to assess RV myocardial motion and strain. In addition, it provides relatively accurate alternative for invasive right heart catheterization when examining pulmonary hemodynamics. (Greyson, 2011; Ramani et al., 2010).

Cardiac magnetic resonance (CMR). CMR is a non-invasive imaging method based on nuclear magnetic resonance. It is the gold standard for assessing RV volume, ejection fraction, and mass, providing both accurate and reproducible measurements (Grothues et al., 2004). It provides excellent spatial resolution, and novel CMR applications also allow the calculation of hemodynamic parameters (Ramani et al., 2010). Despite the high-quality resolution images, the comparison of the RV indexes between different studies are limited due to differences in contour tracing protocols, which have been tried to be standardized (Prakken et al., 2008). From a practical point of view, use of CMR is limited because of its high cost, long scan times, and potential incompatibility with pacemakers or ferromagnetic objects within the body. Also, accurate image acquisition requires breath holds during the scan, which may be difficult especially for patients with a cardiopulmonary disease (Ramani et al., 2010).

Nuclear imaging (SPECT/PET). Nuclear imaging involves the delivery of a radioactive tracer into the body, and its accumulation within a tissue can be quantified by non-invasive imaging. The two most commonly used nuclear imaging modalities are single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Basically, the difference between SPECT and PET is that a tracer used in SPECT emits gamma radiation which is measured directly, whereas a tracer used in PET emits positrons. The positrons annihilate with electrons, causing two photons (gamma radiation) to be emitted in opposite directions. Hence, PET provides better spatial resolution than SPECT. Nuclear imaging, especially PET, provides a way to study myocardial metabolism, as tracers used can be prepared to resemble those used naturally as energy substrates for cardiac contractions (glucose and fatty acid derivatives). Therefore, PET allows quantitative measurement of substrate uptake within the myocardium. With the radiolabeled water, PET also enables studying of myocardial perfusion. The downsides of nuclear imaging techniques include exposure to radioactive radiation as well as being very expensive; a radionuclide must first be produced in a high cost cyclotron, followed by complicated on-site chemical synthesis in order to produce the tracer, and finally the imaging procedure itself.

While PET is not limited by the complex anatomy of RV, low tracer uptake compared to LV may lead to poor image quality, making it challenging to evaluate RV metabolism

(Gargiulo et al., 2015). For this reason, RV glucose uptake has been previously measured only in the context of diseases such as pulmonary artery hypertension and heart failure, in which increased glucose uptake due to disease leads to higher tracer counts (Lundgrin et al., 2013; Mielniczuk et al., 2011; Oikawa et al., 2005; Yang et al., 2014). Based on the studies on diseased populations, it has been speculated that nuclear imaging of RV metabolism could provide complementary information about RV adaptations to exercise training (D'Andrea et al., 2015; Gargiulo et al., 2015).

2.5 Summary of the literature review

HIIT has recently gained a lot of interest both in research and in general media as a more time-efficient exercise method compared to traditional MICT. Many studies have shown that HIIT can lead to similar, or even better, improvements in cardiorespiratory fitness and insulin sensitivity compared to MICT both in healthy sedentary subjects as well in patients with lifestyle-induced cardiometabolic diseases (Jelleyman et al., 2015; Milanović et al., 2015; Weston et al., 2014). However, the effects of HIIT on the heart muscle are less known. When considering the right ventricle, even its baseline metabolic characteristics in healthy subjects are largely unknown, and there are no previous human studies regarding the effects of exercise on the right ventricular metabolism. On the other hand, some of the recent studies in the field of exercise physiology have indicated that it is the right ventricle that may become dysfunctional during the exercise while the left ventricle remains relatively unaffected (Claessen et al., 2014; Elliott and La Gerche, 2015; La Gerche et al., 2011, 2012; Trivax et al., 2010), underlining the importance of the right ventricle.

Cardiovascular diseases, obesity, and type 2 diabetes are becoming increasingly common in the modern society. Such diseases are associated with maladaptation of the myocardial metabolism, which can lead to contractile dysfunction and potentially to heart failure (Lopaschuk and Dhalla, 2014; Stanley et al., 2005). Recently, it has been demonstrated that also the right ventricle has a central role in the context of these diseases (Haddad et al., 2008a; Widya et al., 2013; Voelkel et al., 2006). However, it has been suggested that exercise training can alleviate the metabolic disturbances of the heart (Hafstad et al., 2015). Exercise-induced changes in myocardial metabolism can be studied quantitatively using PET.

3 OBJECTIVES OF THE STUDY

While the left ventricle is studied extensively, the right ventricle and especially its metabolism has remained understudied, even though RV is recognized important both from the clinical and exercise physiological points of views (Elliott and La Gerche, 2015; Haddad et al., 2008a; Voelkel et al., 2006). On the other hand, evidence suggest that even the baseline right ventricular metabolism and function may differ from those of the LV (Walker and Buttrick, 2009; Zaffran et al., 2004). Although the efficacy of HIIT to induce similar improvements in cardiorespiratory fitness as MICT is demonstrated in many studies (Jelleyman et al., 2015; Milanović et al., 2015; Weston et al., 2014), the effects of the two training modes on the right ventricular metabolism and function are unclear.

Specifically, the aims of the current thesis were:

1) To examine which factors affect the RV glucose and fat metabolism in healthy men and do they differ from the factors affecting the LV metabolism (I).

2) To study the exercise-induced adaptations of the RV metabolism and function in healthy men following two weeks of HIIT and MICT (II).

3) To study the exercise-induced adaptations of the RV metabolism and function in subjects with type 2 diabetes mellitus or prediabetes following two weeks of HIIT and MICT (III).

4) To compare whether the exercise-induced adaptations are different in healthy and diabetic subjects (unpublished data).

4 STUDY DESIGN AND SUBJECTS

4.1 Study design

This study was a part of the larger research effort titled "The Effects of Short-Term High-Intensity Interval Training on Tissue Glucose and Fat Metabolism in Healthy Subjects and in Patients with Type 2 Diabetes" (NCT01344928). The study was conducted in two phases. The first phase of the measurements was carried out between March 2011 and February 2013, in which subjects were healthy, middle-aged, and untrained men. In the second phase, the measurements carried out between February 2013 and October 2015, the subjects were middle-aged men and women with type 2 diabetes or pre-diabetes. In both phases, the study was conducted as a parallel-group randomized controlled trial with 1:1 allocation ratio for HIIT and MICT training interventions. The study was conducted according to Declaration of Helsinki, and the study protocol was approved by the ethical committee of the Hospital District of Southwest Finland, Turku (decision 95/180/2010 §228). The health status of the subjects was determined by a thorough physical examination during the screening. The purpose, nature, and the potential risks were verbally and literally explained to the subjects before they gave their informed consent to participate to the study.

The measurements and the training interventions were carried out at the Turku PET Centre, Turku, Finland, except for the VO_{2peak} test and the determination of body composition, which were measured at the Paavo Nurmi Centre, University of Turku, Turku, Finland. The study flow is illustrated in Figure 5. Pre-training oral glucose tolerance test (OGTT) was performed during the screening day, followed by the VO_{2peak} test on the same or one of the next few days. At least a week later, pre-intervention PET and CMR measurements were performed in two consecutive days, both starting in the morning approximately at 8 am. The first measurement day started with CMR to measure RV structural and functional parameters, and was followed by ^{18}F-FTHA-PET to measure RV free fatty acid uptake. The second measurement day started with the euglycemic hyperinsulinemic clamp and during the steady state ^{18}F-FDG-PET study was

performed to measure insulin-stimulated RV glucose uptake. Subjects were required to have fasted for at least ten hours before the screening day and both pre-intervention measurement days. In addition, they were instructed to abstain from caffeinated drinks and to avoid exhausting exercise 48 h prior to the measurements. After the screening and both measurement days, the subjects were randomly allocated either into the HIIT or MICT group.

All the measurements were repeated after the two-week-long training interventions starting on the second day (approximately 48 h) after the last training session. The post-training measurements were started with CMR and ^{18}F-FTHA-PET, followed on the third day by euglycemic hyperinsulinemic clamp and ^{18}F-FDG- PET, and completed on the fourth day with OGTT and VO_{2peak} tests.

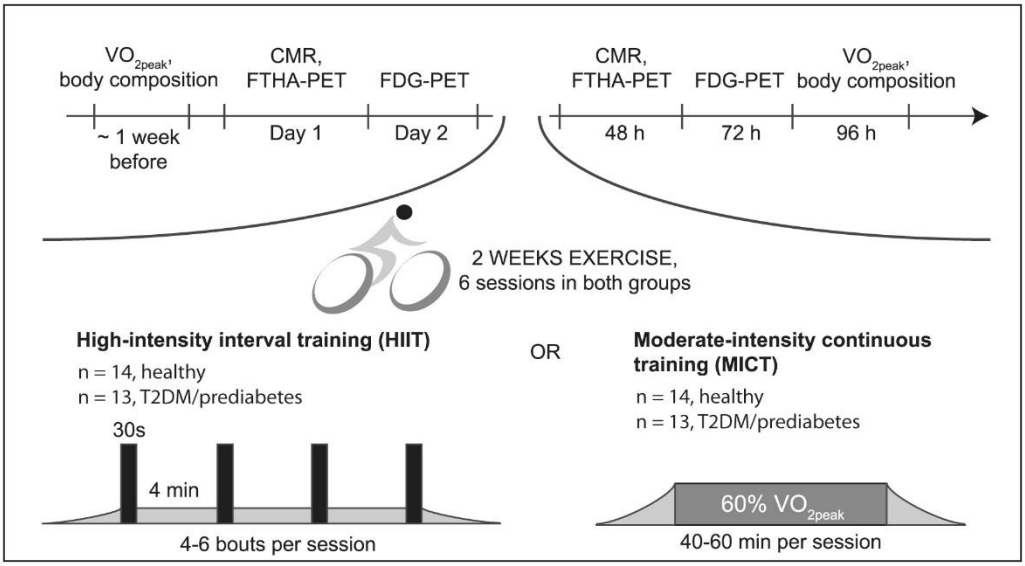

FIGURE 5. Study design. VO_{2peak}, peak oxygen uptake; CMR, cardiac magnetic resonance; FTHA-PET, positron emission tomography for RV fat metabolism; FDG-PET, positron emission tomography for RV glucose metabolism; T2DM, type 2 diabetes mellitus. Modified from sub-study II.

4.2 Subjects and their recruitment

Study participants were recruited via newspaper advertisements, electronic and traditional bulletin boards, and personal contacts. The inclusion criteria for the healthy subjects were male sex, age 40-55 years, body mass index 18.5-30 kg·m^2, normal glycemic control verified by OGTT, and no exercise on regular basis ($VO_{2peak} \leq 40$

$ml \cdot kg^{-1} \cdot min^{-1}$). For subjects with impaired glucose tolerance, the inclusion criteria were the same, except: male or female sex, body mass index 18.5-35 $kg \cdot m^2$, and impaired glucose tolerance according to the criteria of American Diabetes Association (American Diabetes Association, 2015). A candidate was excluded if he or she had a condition which could potentially endanger subject's health during the study or interfere with the interpretation of the results: high blood pressure (>140/90 mmHg in healthy subjects and >160/100 mmHg in T2DM or prediabetic subjects), chronic disease or medical defect requiring medical treatment (other than impaired glucose tolerance in T2DM or prediabetic subjects), presence of ferromagnetic objects that would make magnetic resonance imaging contraindicated, eating disorders, use of steroids, narcotics, tobacco, or other substrates, and heavy use of alcohol. Characteristics of the study subjects are presented in Table 7.

TABLE 7. Study subjects.

	Study I and II	**Study III**
Health status	healthy	T2DM or prediabetes
Number of subjects (men/women)	28/0	16/10
Age (years)	48 ± 5	49 ± 4
Body mass (kg)	84 ± 9	92 ± 13
Height (cm)	179 ± 4	173 ± 8
BMI ($kg \cdot m^2$)	26.1 ± 2.4	30.7 ± 2.8
Body fat (%)	22.6 ± 4.2	33.4 ± 7.5
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	34.2 ± 4.1	27.2 ± 4.6

T2DM, type 2 diabetes mellitus; BMI, body mass index; VO_{2peak}, peak oxygen uptake.

4.3 Training interventions

Both training groups had six exercise sessions in total within two weeks, with at least one recovery day between subsequent sessions. Notably, the total training time in the HIIT group was only 15 minutes (135 min including the recovery periods between the bouts) whereas in the MICT group the total time engaged in training was 300 minutes. Each session was performed in supervised laboratory conditions at the Turku PET Centre.

4.3.1 High-intensity interval training (HIIT) protocol

The HIIT protocol used in this thesis was based on the study originally described by Burgomaster and colleagues which showed that only 15 minutes of HIIT during two

weeks markedly improved skeletal muscle oxidative potential and endurance capacity (Burgomaster et al., 2005). The same protocol was also applied by Gibala and colleagues in a study where they showed that 15 minutes of HIIT brought about remarkably similar enhancements in exercise capacity and skeletal muscle adaptations as 10.5 hours of MICT during two weeks, even though the exercise volume of HIIT was only about 10% to that of MICT (Gibala et al., 2012).

One HIIT session consisted of 4-6 bouts of all-out cycling for 30 seconds with 4 minutes of recovery between the bouts during which subjects were allowed to remain still or do unloaded cycling (Monark Ergomedic 894E; Monark, Vansbro, Sweden). The number of bouts was initially four, and it increased to five and six after every other training session. The subjects were familiarized with HIIT during the screening phase (2 x 30 s bouts). Every bout started with the 5-second acceleration to maximum cadence without any resistance. Once achieving full speed, sudden increase of load was applied and maximal cycling was continued for 30 s. For the healthy men, the load was 7.5% of whole body weight in kg, while for the subjects with T2DM or prediabetes the load was 10% of fat free mass in kg.

Energy consumption was calculated for each subject over all six training sessions. The calculation was based on the average intensity over the bouts, time spent on bouts (15 min in total), and estimated efficiency of 20% in cycling. Time spent on recovery periods between the bouts, warm-up, and cool-down were not included in the calculation.

4.3.2 Moderate-intensity continuous training (MICT) protocol

The MICT protocol was based on the current recommendations for the health-enhancing physical activity to meet the requirement of 150 minutes of moderate-intensity exercise on average per week. The MICT group performed continuous aerobic cycling at moderate intensity (60% of VO_{2peak}) for 40-60 min in a session with electrically-braked cycle ergometer (Tunturi E85; Tunturi Fitness, Almere, The Netherlands). The duration of the cycling was initially 40 min, and the time increased to 50 min and further to 60 min after every other training session. The calculation of energy consumption was based on the average intensity (60% of VO_{2peak} intensity), total time spent on training (300 min), and estimated efficiency of 20% in cycling.

5 METHODS

5.1 Measuring myocardial metabolism – positron emission tomography (PET)

PET is a nuclear imaging technique that produces high-resolution images of physiological function, such as metabolic processes, of human tissues noninvasively. PET is based on delivering trace amount of positron-emitting pharmaceutical radioactive isotope into the living tissue, which interacts with the body through metabolic processes. Therefore, the radioisotope enables the interactions to be followed, mapped and measured quantitatively. The fundamental principles of PET imaging are illustrated in Figure 6. Within the tissue, the radioisotope emits a positron, which interacts with an electron of the tissue. The collision of these two particles results in annihilation, in which the masses of the particles are transformed into energy in the form of two photons that are emitted in the opposite directions. The two photons are simultaneously, or within a certain time window, detected by the ring of scintillation detectors of the PET scanner. Detection of such coincident photons indicates that the annihilation occurred in a line between the two detectors. In reality, a number of annihilations are occurring within the tissue, and the information on pairs of coincident photons is stored in matrices on the computer. Then, an image reconstruction algorithm is applied to recover the underlying radioactivity distribution from all angular and linear positions within the plane that was scanned. Hence, PET image shows indirectly the location and concentration of the tracer as a function of time. (Rudroff et al., 2015; Townsend, 2004).

Radioisotopes used in PET are normal physiological molecules or their analogs which are labeled with a positron emitting radionuclide. The most typical radionuclides, with their half-lives in parentheses, include oxygen-15 (2.03 minutes), nitrogen-13 (9.96 minutes), carbon-11 (20.4 minutes) and fluorine-18 (109.8 minutes) (Townsend, 2004). Currently, the most widely used PET tracer is radiolabeled fluorinated analogue of glucose, 2-deoxy-2-[$^{F}18$]fluoro-D-glucose (FDG), which was used also in this thesis to study the myocardial glucose metabolism. When injected to the body, FDG is

transported into the cells in the same way as the normal glucose. Once within the cell, FDG is phosphorylated, preventing its admittance out of the cell. Phosphorylated FDG is not metabolized further, and hence it remains trapped within the cell, allowing the quantification of accumulated tracer within a specific tissue, such as the heart muscle. (Rudroff et al., 2015).

Another radiotracer used in this thesis is also based on fluorine-18. Myocardial free fatty acid uptake was measured using 14(*R,S*)-[^{F}18]fluoro-6-thia-heptadecanoic acid (FTHA), which is a long-chain fatty acid analog and hence, a substrate for the fatty acid metabolism (DeGrado et al., 1991). Within the heart muscle, majority of FTHA enters mitochondria and the β-oxidation pathway (Takala et al., 2002). Therefore, myocardial free fatty acid β-oxidation can be studied using FTHA as a tracer.

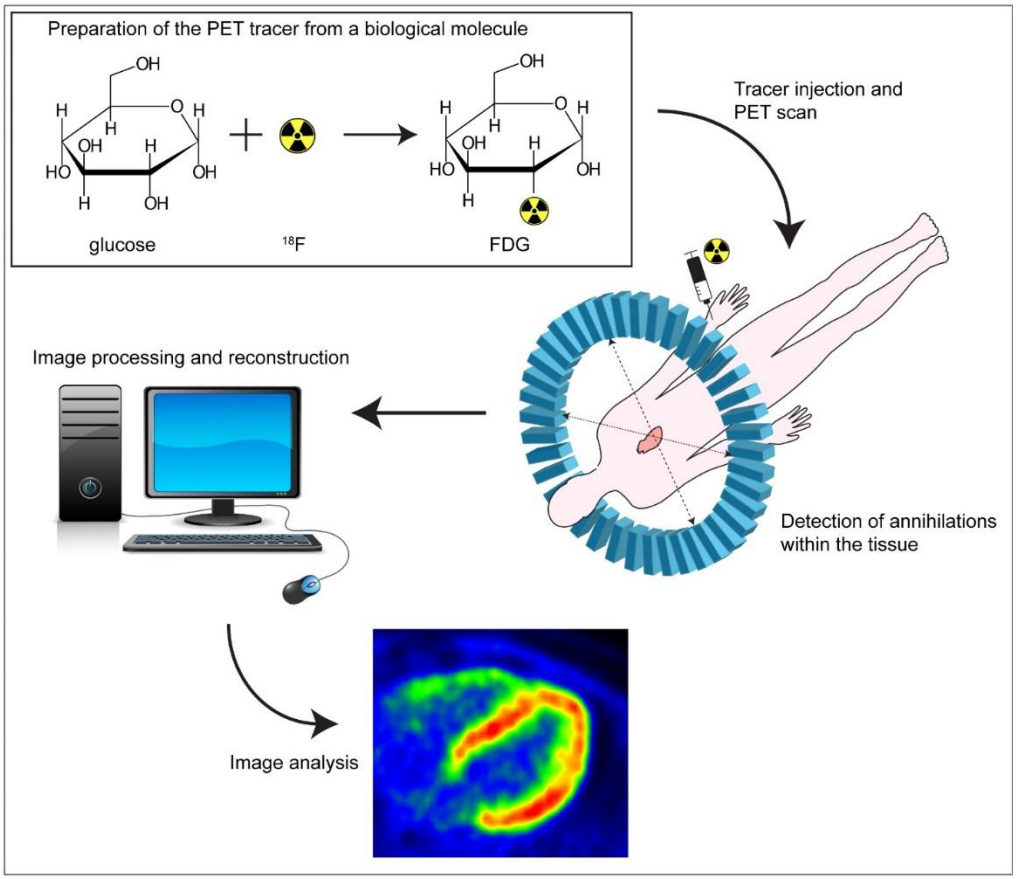

FIGURE 6. Basic principles and procedures for PET imaging.

5.1.1 PET image acquisition

Before the PET experiments, the antecubital veins from both arms were cannulated. One catheter was used for the administration of the PET tracers (FDG or FTHA) and other infusions (glucose-insulin clamp during the FDG-PET study), and the other one for blood sampling during the PET studies which were used to determine the input function. The arm used for blood sampling was heated with an electrically powered cushion for the whole duration of the study to "arterialize" the venous blood. The subject was positioned into the PET scanner in a supine position with the thoracic region in the scanning area of the gantry. The PET imaging was performed with GE Advance PET/CT scanner (General Electric Medical System, Milwaukee,WI, USA).

Free fatty acid uptake (FFAU) was determined using 14(*R,S*)-[^{F}18]fluoro-6-thia-heptadecanoic acid (FTHA) as a tracer. The production of FTHA followed the procedure described by (DeGrado et al., 1991; Mäki et al., 1998). Once the tracer [155 (SD 9) MBq] was injected into the vein, the scanning was started immediately and continued for 40 min in 4 x 15 s, 6 x 20 s, 2 x 60 s, 2 x 150 s, and 6 x 300 s time frames. Blood samples for plasma radioactivity determination (Wizard 1480 3; Wallac, Turku, Finland) and calculation of input function were collected at 4, 5, 7.5, 10, 20, 30, and 40 minutes after the injection of the tracer. In addition, the activities of the LV chamber during the first three minutes (corresponding to the first 10 frames) were used to determine the early part of the input function. As FTHA is metabolized (Takala et al., 2002), another blood samples were collected at time points 5, 10, 20, 30 40, and 50 minutes after the tracer injection. From these samples, metabolites of FTHA were analysed and they were later used to correct the input function to obtain the pure plasma FTHA input function.

On a separate day, insulin-stimulated glucose uptake (GU) was measured using 2-deoxy-2-[^{F}18]fluoro-D-glucose (FDG) as the tracer, which was produced according to (Hamacher et al., 1986). The tracer [157 (SD10) MBq] was injected into the vein and the scanning was performed in similar time frames as the FTHA-PET study. GU was measured during euglycemic hyperinsulinemic clamp (explained in detail in section 5.3.1) at fasted state, which allows better PET image quality and quantification of GU by myocardium (Knuuti et al., 1992). FDG was injected 90 (SD 16) minutes after the start of the euglycemic hyperinsulinemic clamp when the subject had reached the stable glucose concentration of 5 mmol·l^{-1} (±0.5). Except for the clamp, the FDG-PET study was conducted similarly to the FTHA-PET study. As FDG is not metabolized (Rudroff et al., 2015), no additional blood samples were needed for metabolite correction. Glucose concentrations were measured at every five minutes and the whole period was used for the calculations of the final GU values.

5.1.2 PET image analysis

All obtained PET image raw files were corrected for attenuation, dead time, and decay. Images were reconstructed using 3D-OSEM procedure and analysed using Carimas software (version 2.9, www.turkupetcentre.fi/carimas). In FDG-PET images, volumes of interests (VOIs) were drawn manually to the entire RV free wall in transaxial planes (Figure 7).

As the healthy normal RV free wall is approximately only 3-5 mm thick (Vitarelli and Terzano, 2010), the VOI in each transaxial slice was drawn as a line rather than an area (pixel size in the transaxial slice was 2.73 x 2.73 mm). In FTHA-PET images, the tracer uptake of the liver is high, and the liver may interfere with the lower border of the RV. To avoid the spillover due to the liver, VOIs were drawn in the sagittal view to the entire RV free wall except for the lower border of the RV.

Once the VOIs were defined manually, the tissue time activity curves were extracted from the dynamic PET data. Plasma time activity curve, used as the input function, was obtained from the activities of the LV chamber during the first three minutes and measured radioactivity readouts during the PET scan (4 to 40 minutes from the start of the scan). Fractional tracer uptake was calculated from tissue and plasma activity curves by using graphical analysis (Patlak et al., 1983). The rate of GU and FFAU per volume unit was calculated by multiplying the fractional tracer uptake rate with the plasma glucose and FFA concentration during the scanning, respectively. Lumped constant was assumed to be 1.00 for both FDG and FTHA. Finally, the rates of GU and FFAU were multiplied by the myocardial density, 1.03 g/ml, and 100 to get the uptake rates per 100 grams of myocardium ($\mu mol \cdot min^{-1} \cdot 100g^{-1}$).

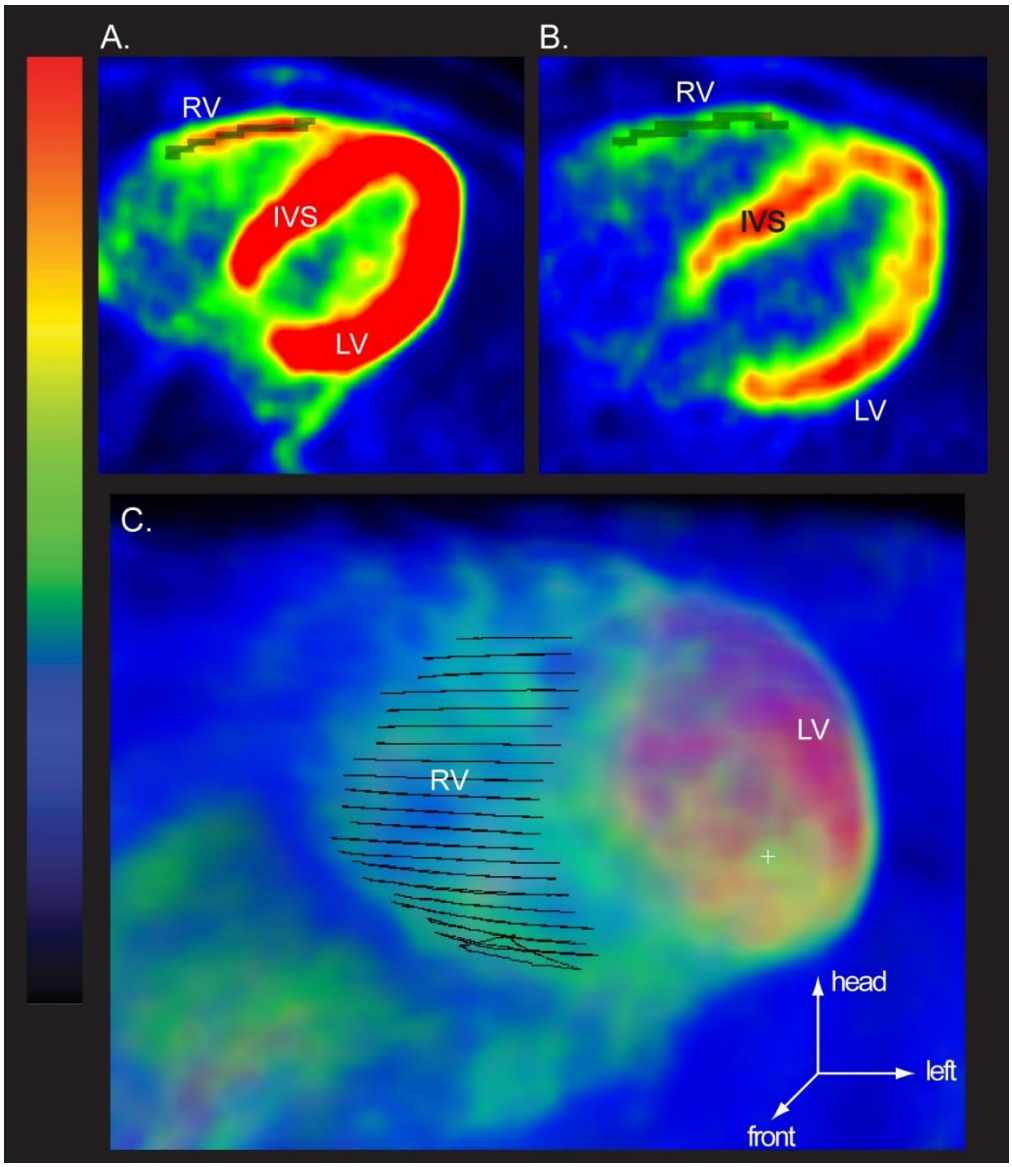

FIGURE 7. Example of the FDG-PET images and volumes of interests (VOIs) for the determination of RV glucose uptake of a representative subject in the HIIT group. VOIs (shown as darker areas) were drawn to the RV free wall in the transaxial view of FDG-PET images so that the thickness of each VOI was only 1–2 voxels, corresponding to the thin-walled RV. One slice before the training is shown in (A), and after the training in (B). The 3D view of the postexercise FDG- PET image is shown in (C) to illustrate that the VOIs cover the entire RV free wall. The images are scaled to the same color scale, with red color depicting the highest tracer counts. IVS, interventricular septum. From sub-study II.

5.2 Determining right ventricular structure and function – cardiac magnetic resonance (CMR)

Cardiac magnetic resonance (CMR) imaging is a noninvasive imaging technique, which enables to study structure and function of the heart. CMR is based on the nuclear magnetic resonance, a physical phenomenon in which atomic nuclei subjected to an external magnetic field absorb and re-emit electromagnetic radiation. The emitted energy is at a specific resonance frequency, which is dependent on the strength of the applied external magnetic field as well as on the magnetic properties of the isotope of the atom. Importantly, the emitted energy of the same isotope is slightly altered in different chemical and physical environments, which forms the basis of differentiating different tissues of the body. Most CMR applications use ^{1}H nuclei, which are naturally abundant in the human body, especially in water and fat. By applying magnetic fields and radiofrequency pulses, the ^{1}H nuclei within a subject absorb and re-emit energy, which is detected by the imaging apparatus and transformed into images. Hence, CMR does not involve use of ionizing radiation and is therefore considered safe procedure, unless contraindications, such as ferromagnetic objects within the body, are found. (Guy and Ffytche, 2005).

While a real-time CMR is possible, functional assessment of the heart is typically made using ECG gating to acquire images at each state of the cardiac cycle over several heartbeats. The technique provides an excellent way to discriminate between blood and heart muscle. Generally, blood appears bright and myocardium darker grey in CMR images. (Guy and Ffytche, 2005).

5.2.1 CMR image acquisition

RV dimensions and function were assessed by CMR using Philips 1.5T Gyroscan Intera CV Nova Dual MR scanner (Philips Medical Systems, Best, The Netherlands). With the subject in supine position, cardiac long axis and short axis planes were planned from localizer images. The images over the entire cardiac cycle were obtained with cardiac cine sequencing: steady-state free-precession cine image series were acquired with balanced turbo field echo pulse sequence to have a stack of 10-14 parallel slices in the short axis plane and four slices in the four-chamber plane. The repetition time was 3.4 ms, time to echo 1.7 ms, flip angle 60º, acquisition matrix 192 x 192, reconstruction matrix 256 x 256, field of view 320 - 360 nm, slice thickness 6 mm without gap between slices, phases per cardiac cycle 25, and two slices per breath-hold, resulting to breath holds of 10 - 18 s.

5.2.2 CMR image analysis

CMR image analysis was performed with Philips Extended MR WorkPlace version 2.6.3.5 (Philips Medical Systems, Best, The Netherlands). The short axis cine images were visually inspected to identify the end-systolic and end-diastolic phases with the smallest and the largest RV ventricular cavities, respectively. Endocardial contours were traced manually on each slice in both end-systole and end-diastole according to the established procedure to overcome the difficulties faced when tracing the most basal two slices in RV (Prakken et al., 2008). Briefly, endocardial contour was drawn on the most basal end-diastolic slice only if the trabeculations stayed visible for at least three following phases (Figure 8), whereas in the most basal end-systolic slice the visible RV contour was always traced. The trabeculations were excluded from the endocardial contours and included into the blood volume. For determination of the RV mass, epicardial contours were drawn in the end-diastolic slices so that epicardial contour overlapped with the endocardial contour at the valve planes and at the septum. Therefore, RV mass corresponds to the RV free wall mass and does not include the interventricular septum (Figure 8). Once the endo- and epicardial contours were defined, end-diastolic volume (EDV), end-systolic volume (ESV), and mass, along with the functional parameters including ejection fraction (EF) and stroke volume (SV) were automatically calculated by the image analysis software. Cardiac output (CO) was calculated as the product of SV and heart rate at rest.

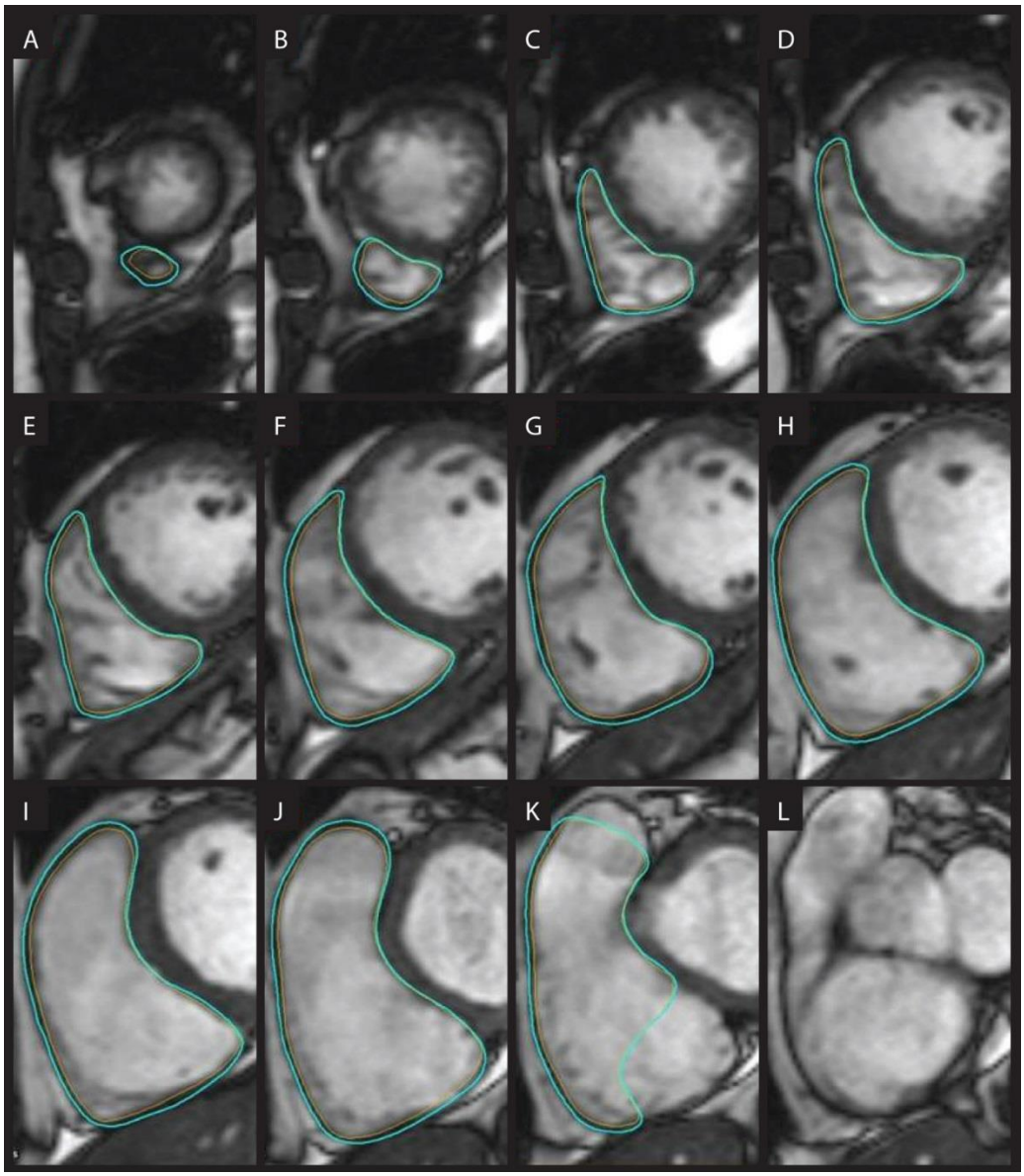

FIGURE 8. An example of tracing the endocontours (orange) and epicontours (light blue) on the RV end-diastolic CMR images from the most apical slice (A) through slices (B–J) to the most basal slice (K). At the most basal slice (K), the pulmonary valve plane and the tricuspid valve plane are excluded according to the instructions by Prakken et al. (2008). As the trabeculations next to the tricuspid valve plane in slice (L) was not visible for the required three phases (figures not shown), no contours were traced to the slice (L) anymore. From sub-study I.

5.3 Other measurements

5.3.1 Whole-body insulin-stimulated glucose uptake (M-value)

Whole-body insulin-stimulated glucose uptake (M-value) is considered to be the most definitive measure of insulin sensitivity in humans (DeFronzo et al., 1979). Both the M-value and FDG-PET scan was measured during the insulin clamp, which was performed according to the original description by DeFronzo et al. (1979) after the subjects had fasted for at least 10 hours. A primed-constant insulin (Actrapid 100U · ml^{-1},NovoNordisk, Bagsvaerd, Denmark) infusion was started with the rate of 40mU per m^2 of body surface area in minute during the first four minutes. Then, the infusion rate was reduced to 20mU per m^2 in minute for the time interval 4–7 min. After 7 minutes, the infusion rate was further reduced to 10mU per m^2 in minute for the rest of the clamp. Exogenous glucose infusion was started 4 minutes after the start of the insulin infusion with a rate of [subjects weight (kg)·0.1]$g \cdot h^{-1}$. At the 10-minute time point, glucose infusion was doubled and after that further adjusted according to blood glucose concentration aiming at the steady level of 5 $mmol \cdot l^{-1}$. Arterialized venous blood samples were collected before the clamp and every 5 minutes during the first 30 minutes of the clamp to determine the glucose concentration for adjusting the glucose infusion rate. After 30 minutes, blood samples were taken at every 10 minutes and modification to the infusion rate were made when necessary. M-value was calculated from the glucose values obtained in the steady state.

5.3.2 Oral glucose tolerance test (OGTT)

The subjects were required to have fasted at least 10 hours before a 2-hour OGTT. The subjects drank a 330-ml solution containing 75 g of glucose (Nutrical, Nutricia Medical, Turku, Finland). Blood samples were collected before the drinking of the solution and at 15, 30, 60, 90, and 120 min after drinking. The glucose and insulin concentrations in the blood were obtained from the samples.

5.3.3 Peak oxygen uptake (VO_{2peak})

Maximal exercise tests were performed at the Paavo Nurmi Centre, University of Turku, on a bicycle ergometer (Ergoline 800s; VIASYS Healthcare, Germany). The test started at 50 W and the load was increased at every two minutes until exhaustion. The subjects were asked to abstain from eating and drinking for two hours before the test. The test was performed for each subject during the screening and four days after the last HIIT or

MICT training session at approximately the same time of the day. Ventilation and gas exchange was measured (Jaeger Oxycon Pro; VIASYS Healthcare) and reported as the mean value per minute. The peak respiratory exchange ratio was ≥ 1.15, and peak lactate concentration, measured from capillary samples obtained immediately and one minute after exhaustion (YSI 2300 Stat Plus; YSI Incorporated Life Sciences, Yellow Springs, OH) was ≥ 7.4 $mmol \cdot l^{-1}$ for all the tests. The highest one-minute mean value of oxygen consumption was defined as VO_{2peak}.

5.3.4 Body composition

Body composition was measured by the bioimpedance monitor (InBody 720, Mega Electronics Ltd., Kuopio, Finland) at the Paavo Nurmi Centre, University of Turku. Weight and height of the subjects were measured by standard procedures.

5.4 Statistical analyses

Sample size was determined for the entire study (NCT01344928) based on its primary outcome, skeletal muscle glucose uptake. For healthy subjects, a total of 24 subjects (12 in each group) were calculated to give > 90% power of detecting a 20% unit difference in insulin-stimulated glucose uptake in quadriceps femoris (estimated increase in HIIT 40% vs. estimated increase in MICT 20%, SD 15) with a level of significance at 5%. For diabetic subjects, a total of 20 subjects (10 in each group) were calculated to give corresponding statistical power (estimated increase in HIIT 60% vs. estimated increase in MICT 30%, SD 20). To allow drop-outs and technical problems in image acquisition, the number of recruited subjects in each group was 14 for healthy subjects and 13 for subjects with T2DM or prediabetes. As there were no previous studies regarding the effects of exercise training on RV metabolism which was the primary outcome of this thesis, the sample size calculated for the entire study was used.

There were some missing data values. In the healthy subjects, one participant from each group dropped out during the training intervention because of personal reasons (HIIT) and exercise-induced hip pain (MICT). In the subjects with T2DM or prediabetes, two subjects from the HIIT group discontinued the trial, one due to claustrophobic feelings in CMR during the pre-intervention scan and one due to migraine during the first HIIT session. Three subjects from the MICT group dropped out because of personal reasons. In addition, some of the PET and CMR scans were unsuccessful due to technical problems (technical problem in insulin clamp, in tracer production, or in PET and CMR scan) or physiological problems (transient drop in blood pressure during the PET scan, mild fever, subject had forgotten to fast, claustrophobic feelings during CMR scan). The

numbers of completed PET and CMR measurements in each study (I-III) are listed in Table 8.

TABLE 8. Number of subjects with successful PET and CMR measurements in each study I-III.

	Study I (n = 28)	**Study II (**n = 28)				**Study III** (n = 26)			
		HIIT		MICT		HIIT		MICT	
		pre	post	pre	post	pre	post	pre	post
RVGU	25	13	12	12	11	10	9	13	10
RVFFAU	24	12	10	12	7	12	8	13	9
CMR	27	14	13	13	13	12	11	13	10

Study I: healthy subjects at baseline, Study II; healthy subjects before and after two weeks of HIIT or MICT, Study III: subjects with T2DM or prediabetes before and after two weeks of HIIT or MICT, RVGU: right ventricular glucose uptake measured during FDG-PET scan, RVFFAU: right ventricular free fatty acid uptake measured during FTHA-PET scan, CMR: cardiac magnetic resonance imaging.

Statistical analyses were performed using R version 3.1.3, the R Foundation for Statistical Computing (http://www.R-project.org/) and SAS System, version 9.3 for Windows (SAS Institute, Cary, NC). Normal distribution of the variables was tested by Shapiro-Wilk test and evaluated visually. Logarithmic transformations were performed when appropriate. The results are presented as mean and 95% confidence interval unless stated otherwise. Correlations (r) are reported as Pearson's product-moment correlation coefficients or Spearman's rank correlation for non-normally distributed variables. The level of statistical significance for all tests was set at $p < 0.05$.

In the sub-study I, the dataset regarding the healthy subjects was visualized using a heatmap, which was produced using the heatmap.2 function in the "gplots" R-package with the manhattan distance function and the Ward's method for the agglomeration of the clusters. All parameters were centered to zero mean and scaled to unit variance. Rows (variables) and columns (individual subjects) were allowed to be reordered. Hence, similar variables and individual profiles are shown close to each other. Further, the metabolic parameters (RVGU, RVFFAU, LVGU, LVFFAU) were modelled using the lasso regression, which is a regression method designed to model datasets involving large number of variables compared to the number of observations (Tibshirani, 1996). Briefly, lasso minimizes the sum of squared errors as in normal linear regression, but in addition it introduces a penalty term for the absolute value of sum of regression coefficients. Because of the penalty term, most of the variables are reduced to zero. Therefore, lasso simultaneously performs predictor selection and builds a regression model. Lasso modelling was performed using the function glmnet in the "glmnet" R-

package with the parameter alpha set to 1. Full details of the lasso method and its implementation are described in (I).

To examine the training effects of HIIT and MICT, statistical analyses were performed using a hierarchical mixed linear model (II, III). The compound symmetry covariance structure was used, including one within-factor (training; before and after intervention), one between-factor (group; HIIT and MICT) and the interaction term (training × group). For the subjects with T2DM or prediabetes, gender and diagnostic group (T2DM/prediabetes) were included as factors in all analyses. In addition, glucose uptake is influenced by plasma FFA concentration (Knuuti et al., 1995), and therefore plasma FFA concentration was used as a covariate when analysing the glucose uptake. For comparison between the healthy and the diabetic subjects (unpublished results, Figure 11), a hierarchical mixed linear model including training, group, DM (healthy/diabetic), and all their interaction terms were used, as well as gender as a factor. The analyses were carried out using intention-to-treat approach and included all the randomized subjects. Missing data points were accounted for by restricted maximum likelihood estimation within the linear mixed models.

6 RESULTS

This chapter presents the main results of the thesis. More details are found in the original research papers (I-III). Although the primary focus of the thesis is on the right ventricle, corresponding results for the left ventricle are shown for reference. The LV results for the healthy subjects have been originally reported by Eskelinen and colleagues (Eskelinen et al., 2016) and for the diabetic subjects in the sub-study III.

6.1 Predictors of right and left ventricular metabolism in healthy middle-aged men (I)

Characteristics of the RV and LV metabolism in the healthy men at the baseline were investigated using three analyses methods, namely visualization by a heatmap, pairwise correlations between the variables, and lasso regression.

Individual values. In order to get the visual overview of the baseline dataset of the healthy subjects, a heatmap including whole-body parameters as well as LV and RV cardiac parameters was plotted (Figure 9). Parameters (rows) and subjects (columns) with similar values are grouped together. For instance, RVGU and LVGU as well as RVFFAU and LVFFAU are closely related, as expected. Cardiac structural and functional parameters form their own cluster. Interestingly, EF is more related to the cardiac metabolism than cardiac structure and even so that LVEF is more tightly related to FFAU and RVEF to GU of both ventricles. M-value, VO_{2peak}, and age are related together, and associate with the cluster of the cardiac metabolism. As expected, body weight, BMI, and fat percent are closely related, and they associate with the cardiac dimensions rather than the cardiac metabolism.

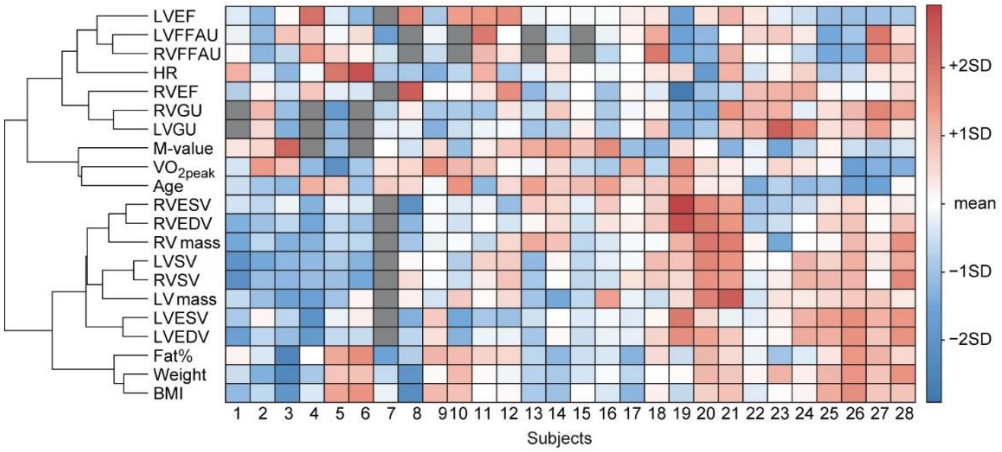

FIGURE 9. A visual presentation of the dataset where each matrix element describes a value for a respective variable (columns) and subject (rows). Each variable is scaled to zero mean and unit variance. Hence, elements with light colors indicate values close to mean of the given variable, whereas values larger than mean are presented as red and values smaller than mean as blue matrix elements. The tree on the left side of the matrix describes how variables are related to each other according to the cluster analysis. The shorter the branches are, the stronger the association between the variables is. For example, RVSV and LVSV are tightly related, as expected. On the other hand, VO2peak, age, and M-value are clustered together but since the branches are longer, the association is not that strong. Dark gray matrix elements indicate missing values. From sub-study I.

Pairwise correlations for GU and FFAU. RVGU correlated negatively with age ($r = -0.43$, $p = 0.034$), whereas RVFFAU correlated positively with resting HR ($r = 0.44$, $p = 0.031$) and LVEF ($r = 0.49$, $p = 0.018$) and negatively with VO_{2peak} ($r = -0.44$, $p = 0.030$), M-value ($r = -0.43$, $p = 0.045$), and LVESV ($r = -0.42$, $p = 0.046$). LVGU was negatively correlated with age ($r = -0.54$, $p = 0.005$) and M-value ($r = -0.59$, $p = 0.002$) and positively with RVEF ($r = 0.49$, $p = 0.015$). As expected, correlations between LVGU and RVGU as well as LVFFAU and RVFFAU were high ($r = 0.74$, $p < 0.001$ for GU and $r = 0.76$, $p < 0.001$ for FFAU). The only statistically significant correlation for LVFFAU was with RVESV ($r = -0.43$, $p = 0.039$).

Lasso regression results. Myocardial metabolism (RVGU, LVGU, RVFFAU, and LVFFAU) was modelled using a lasso regression model. The variables included in each model were age, BMI, fat percent, resting HR, VO_{2peak}, and M-value along with EF, SV, ESV, EDV and mass of both ventricles. The obtained lasso regression equations are presented in Table 9. Considering glucose metabolism, age and RVEF were significant factors in both ventricles, with younger age and higher RVEF related to higher GU. For RVGU, RVSV was also a significant predictor, whereas M-value was a negative predictor of LVGU. In fatty acid metabolism, LVEF affected FFAU of both ventricles.

In addition, RVFFAU was explained by resting HR, VO_{2peak} and M-value while LVFFAU was related to RVESV.

TABLE 9. Lasso regression models for GU and FFAU of both ventricles. From sub-study I.

lasso regression model	n	RMSE
RVGU = 14.0 - 0.079 · age + 0.025 · RVEF + 0.007 · RVSV	24	3.24
LVGU = 80.4 - 0.757 · age - 0.305 · M-value + 0.241 · RVEF	24	9.78
RVFFAU = -1.20 + 0.036 · LVEF + 0.019 · HR - 0.012 · VO_{2peak} - 0.003 · M-value	21	0.36
LVFFAU = 4.65 + 0.022 · LVEF - 0.398 · log(RVESV)	21	1.27

n, number of subjects used in the model; RMSE, root-mean-square error of the residuals.

Based on the three different analyses methods, the main findings regarding the baseline RV and LV metabolism in the healthy men are illustrated in Figure 10.

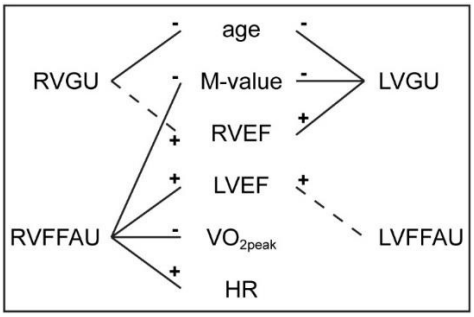

FIGURE 10. The key findings on the baseline RV and LV metabolism in the healthy men. Solid lines indicate associations that were confirmed by both lasso regression model and statistically significant pairwise correlation. Dashed lines present associations which were confirmed by lasso regression but pairwise correlations were not statistically significant. The associations summarized here were also supported by the heatmap. The signs indicate positive (+) and negative (−) associations. From sub-study I.

6.2 Effects of HIIT and MICT on the right ventricular metabolism in healthy middle-aged men (II)

Subject characteristics. The exercise groups were well matched at the baseline (Table 10). Body mass, BMI, resting heart rate, and blood pressure remained unchanged after the training intervention. However, fat percent, VO_{2peak} and M-value were improved after both training modes, indicating that only two weeks of exercise leads to health-enhancing changes in previously untrained subjects. Calculated energy consumption

over all the training sessions was 403 (365, 442) kcal for the HIIT group and 2680 (2474, 2886) kcal for the MICT group ($p < 0.001$ between the groups) (Eskelinen et al., 2015).

TABLE 10. Characteristics of the healthy subjects and their training adaptations to HIIT and MICT. Modified from sub-study II.

	HIIT		**MICT**		
	pre	**post**	**pre**	**post**	
n	14	13	14	13	
Age, years	47 (45, 50)		48 (45, 51)		
Height, cm	180 (177, 182)		179 (176, 181)		
Body weight, kg	83.1 (78.2, 88)	82.6 (77.7, 87.4)	84.1 (79.2, 89.1)	84.1 (79.3, 88.9)	
BMI, $kg \cdot m^{-2}$	25.9 (24.5, 27.2)	25.7 (24.3, 27)	26.4 (25, 27.7)	26.4 (25, 27.7)	
Fat, %	22.2 (19.8, 24.6)	21.2 (18.8, 23.6)	22.9 (20.5, 25.3)	22.1 (19.7, 24.5)	***
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$	34.7 (32.4, 37.1)	36.7 (34.1, 39.3)	33.7 (31.4, 35.9)	34.7 (32.2, 37.2)	***
M-value, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	38.2 (30.1, 46.4)	42.8 (34.5, 51.0)	31.9 (23.1, 40.7)	34.2 (25.4, 43.1)	*
HR_{rest}, beats/min	59 (55, 62)	59 (55, 63)	63 (60, 67)	62 (58, 66)	
BP_{syst}, mm Hg	123 (119, 127)	126 (121, 130)	128 (124, 131)	132 (128,136)	†
BP_{diast}, mm Hg	77 (74, 80)	77 (73, 80)	78 (75, 81)	81 (77, 84)	

Age and height present mean (95% CI) and all other values are model-based means (95% CI). BMI, body mass index; VO_{2peak}, peak oxygen uptake; M-value, whole-body insulin-stimulated glucose uptake, HR_{rest}, heart rate at rest; BP_{syst}, systolic blood pressure; BP_{diast}, diastolic blood pressure.

* $p \leq 0.05$ for the training effect

*** $p \leq 0.001$ for the training effect

† $p \leq 0.05$ for the group effect

RV metabolism. RVGU decreased by -2.6 $\mu mol \cdot 100g^{-1} \cdot min^{-1}$ (95% CI from -4.3 to -0.8 $\mu mol \cdot 100g^{-1} \cdot min^{-1}$) after HIIT and by -1.6 $\mu mol \cdot 100g^{-1} \cdot min^{-1}$ (95% CI from -3.3 to 0.1 $\mu mol \cdot 100g^{-1} \cdot min^{-1}$) after MICT. However, the change was not different between the groups ($p = 0.42$ for training*group interaction) (Table 11). Adjusting for plasma FFA during the scan did not affect the results.

TABLE 11. Right ventricular metabolic, structural, and functional adaptations in healthy subjects. Modified from sub-study II.

	HIIT		MICT		
	pre	**post**	**pre**	**post**	
RVGU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	11.6 (9.8, 13.4)	9.0 (7.2, 10.9)	12.8 (10.9, 14.8)	11.2 (9.2, 13.2)	**
$RVGU_{FFA\text{-}adj}$, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	11.6 (9.8, 13.5)	9.1 (7.2, 11.0)	12.8 (10.9, 14.7)	11.0 (8.8, 13.2)	**
RVFFAU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	1.5 (1.3, 1.8)	1.5 (1.2, 1.8)	2.0 (1.7, 2.3)	1.9 (1.5, 2.3)	†
RV mass, g	31 (29, 34)	32 (29, 34)	32 (30, 35)	32 (30, 35)	
RV mass/BSA, g/m^2	15.4 (14.4, 16.4)	15.7 (14.8, 16.7)	16.0 (15.0, 17.0)	16.0 (15.0, 17.0)	
RVEDV, ml	196 (183, 210)	205 (192, 220)	187 (175, 200)	194 (181, 208)	**
RVEDV/BSA, ml/m^2	97 (92, 103)	102 (96, 108)	92 (87, 97)	96 (91, 101)	**
RVESV, ml	92 (82, 102)	98 (88, 109)	88 (79, 98)	95 (85, 105)	**
RVESV/BSA, ml/m^2	45 (41, 50)	49 (44, 54)	43 (39, 48)	47 (43, 52)	**
RVSV, ml	104 (98, 109)	107 (101, 112)	99 (94, 105)	99 (93, 105)	
RVSV/BSA, ml/m^2	51 (49, 53)	53 (51, 55)	49 (47, 51)	49 (47, 51)	†
RVCO, $l \cdot min^{-1}$	6.0 (5.6, 6.5)	6.3 (5.8, 6.7)	6.3 (5.9, 6.8)	6.2 (5.7, 6.6)	
RVCO/BSA, $l \cdot min^{-1}/m^2$	3.0 (2.8, 3.2)	3.1 (2.9, 3.3)	3.1 (2.9, 3.3)	3.0 (2.9, 3.2)	
RVEF, %	53 (50, 55)	52 (49, 54)	53 (50, 55)	51 (49, 54)	*

Values present model-based means (95% CI). RVGU, RV glucose uptake; $RVGU_{FFA\text{-}adj}$, RV glucose uptake adjusted for plasma FFA concentration; RVFFAU, RV free fatty acid uptake; RVEDV, RV end-diastolic volume; BSA, body surface area; RVESV, RV end-systolic volume; RVSV, RV stroke volume; RVCO, RV cardiac output; RVEF, RV ejection fraction.

* $p \leq 0.05$ for the training effect

** $p \leq 0.01$ for the training effect

† $p \leq 0.05$ for the group effect

RVFFAU was different between the groups ($p = 0.020$ for group effect) and it remained unchanged after the training (Table 11). The changes in RVGU or RVFFAU did not correlate with the changes in RV dimensions or functional parameters, age, or any of the whole-body parameters such as VO_{2peak} or M-value. Plasma glucose, FFA, and insulin concentrations during the FDG-PET and FTHA-PET studies did not change after the training (see exact values in the sub-study II).

RV dimensions and function. Results derived from CMR are presented in Table 11. RVEDV and RVESV increased similarly after both training modes (p = 0.002 and 0.005 for training effect, respectively). The changes corresponded to +5 and +7% increase after HIIT and +4 and +8% after MICT. RVEF mildly decreased after training (p = 0.034 for training effect). RV mass and RVSV remained unchanged. The results were similar when adjusting for body-surface area, except that BSA-normalized RVSV became statistically different between the groups (Table 11). No statistically significant correlations were found between the changes in RV parameters and any of the whole-body parameters.

Changes in LV parameters. The observed changes in RV metabolism, structure, and function were accompanied with similar changes in the corresponding LV parameters (Table 12).

TABLE 12**.** Left ventricular metabolic, structural and functional adaptations in healthy subjects. Modified from (Eskelinen et al., 2016).

	HIIT		**MICT**		
	pre	**post**	**pre**	**post**	
LVGU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	47 (39, 54)	36 (28, 44)	46 (39, 54)	44 (36, 52)	**
$LVGU_{FFA-adj}$, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	47 (40, 54)	36 (29, 44)	46 (39, 54)	43 (34, 52)	*
LVFFAU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	3.9 (3.2, 4.7)	3.7 (2.8, 4.9)	4.5 (3.8, 5.3)	4.2 (3.2, 5.2)	
LV mass, g	125 (116, 135)	125 (115, 134)	118 (109, 128)	119 (110, 129)	
LVEDV, ml	168 (157, 179)	175 (164, 186)	157 (146, 168)	162 (151, 173)	**
LVESV, ml	61 (54, 67)	67 (60, 74)	55 (49, 62)	59 (52, 65)	**
LVSV, ml	107 (101, 114)	108 (102, 114)	102 (96, 108)	104 (97, 110)	
LVCO, $l \cdot min^{-1}$	6.3 (5.8, 6.7)	6.4 (5.9, 6.9)	6.5 (6.0, 7.0)	6.4 (5.9, 6.9)	
LVEF, %	64 (62, 66)	62 (60, 64)	65 (63, 67)	64 (62, 66)	*

Values present model-based means (95% CI). LVGU, LV glucose uptake; $LVGU_{FFA-adj}$, LV glucose uptake adjusted for plasma FFA concentration; LVFFAU, LV free fatty acid uptake; LVEDV, LV end-diastolic volume; BSA, body surface area; LVESV, LV end-systolic volume; LVSV, LV stroke volume; LVCO, LV cardiac output; LVEF, LV ejection fraction.

* $p \leq 0.05$ for the training effect

** $p \leq 0.01$ for the training effect

6.3 Effects of HIIT and MICT on the right ventricular metabolism in subjects with type 2 diabetes or pre-diabetes (III)

Subject characteristics. Based on the whole-body parameters, the training groups were well matched (Table 13). Body mass, BMI, and fat free mass did not change after two-week-long exercise intervention, whereas fat percent was mildly decreased ($p = 0.018$ for training effect). Fasting glucose and 2 h glucose remained unchanged while HbA_{1c} decreased ($p = 0.002$ for training effect). M-value was improved by both training modes ($p = 0.001$). VO_{2peak} changed differently after HIIT and MICT ($p = 0.050$ for group*training interaction), and only HIIT improved it ($p = 0.013$ for training effect in HIIT). Resting heart rate, as well as diastolic and systolic blood pressures were decreased after both training modes ($p \leq 0.010$ for training effect, all). Calculated energy consumption over all the training sessions was 341 (286, 396) kcal for the HIIT group and 2502 (2068, 2936) kcal for the MICT group ($p < 0.001$ between the groups).

RV metabolism. RVGU remained unchanged after the training (Table 14). Although HIIT seemed to lower RVGU and MICT to increase it, the difference between the training modes was not statistically significant ($p = 0.16$ for group*training interaction, Table 14). When plasma FFA concentration during the scan was used as a covariate, it was significantly associated with RVGU ($\beta = -53$, $p = 0.003$). However, the difference between HIIT and MICT still remained insignificant ($p = 0.13$ for group*training interaction). RVFFAU remained also unchanged after training (Table 14).

The glucose and plasma FFA concentrations during both PET measurements were similar between the groups and did not change after the intervention (see exact values in the sub-study III). The insulin levels during the FFAU measurements (fasting condition) decreased after training ($p=0.002$, training) without difference between the groups ($p=0.99$, group*training).

TABLE 13. Characteristics of the subjects with T2DM or prediabetes and their training adaptations to HIIT and MICT. Modified from sub-study III.

	HIIT		MICT		
	pre	**post**	**pre**	**post**	
men/women, *n*	9/4	7/4	7/6	6/4	
T2DM/prediabetes, *n*	11/2	10/1	6/7	4/6	
Glucose lowering medication, *n*					
Metformin	7		4		
DPP-4 inhibitors	4		1		
Sulfonylurea	1		0		
Antihypertensives	5		6		
Statins	4		3		
Affective medication	0		3		
Menopausal hormone therapy	1		2		
Age, years	49 (47, 51)		49 (46, 51)		
Height, cm	173 (168, 179)		172 (167, 176)		
Weight, kg	88.9 (80.6, 97.2)	88.4 (80.1, 96.7)	91.5 (84.5, 98.6)	91.1 (84.0, 98.1)	
BMI	30.5 (28.5, 32.5)	30.3 (28.4, 32.3)	31.0 (29.4, 32.7)	30.8 (29.2, 32.5)	
Fat, %	34.8 (31.4, 38.5)	33.8 (30.5, 37.5)	33.8 (30.8, 36.9)	32.9 (30.0, 36.0)	*
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$	25.7 (23.2, 28.2)	27.0 (24.6, 29.5)	27.0 (24.9, 29.2)	26.9 (24.6, 29.1)	‡
M-value, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	20.6 (13.4, 27.7)	25.7 (18.4, 33.0)	15.7 (9.7, 21.6)	19.7 (13.6, 25.8)	***
HR_{rest}, beats/min	73 (68, 78)	70 (65, 75)	69 (64, 73)	64 (59, 68)	**
BP_{syst}, mm Hg	135 (129, 142)	133 (126, 140)	146 (141, 152)	139 (133, 145)	†**
BP_{diast}, mm Hg	86 (81, 90)	82 (77, 87)	89 (85, 93)	82 (77, 86)	**
HbA_{1c}, %	5.7 (5.4, 6.0)	5.5 (5.2, 5.8)	5.8 (5.5, 6.0)	5.6 (5.3, 5.9)	*
Fasting glucose, mmol/l	7.1 (6.5, 7.7)	7.0 (6.4, 7.6)	6.8 (6.3, 7.3)	7.0 (6.4, 7.5)	
OGTT 2h glucose, mmol/l	10.4 (8.6, 12.3)	9.1 (7.2, 11.1)	10.5 (8.9, 12.1)	10.3 (8.6, 12.0)	

The results are presented as means (95% CI) for age and height. For all other parameters the results are presented as model-based means (95% CI). BMI, body mass index; VO_{2peak}, peak oxygen uptake; M-value, whole-body insulin-stimulated glucose uptake, HR_{rest}, heart rate at rest; BP_{syst}, systolic blood pressure; BP_{diast}, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; OGTT, oral glucose tolerance test.

* $p \leq 0.05$ for the training effect ** $p \leq 0.01$ for the training effect
*** $p \leq 0.001$ for the training effect † $p \leq 0.05$ for the group effect
‡ $p \leq 0.05$ for the group × training interaction

RV dimensions and function. RVEDV changed differently after HIIT and MICT (p=0.022 group*training, Table 14), increasing only after MICT by 15 ml (95% CI 4 ml to 25 ml, p=0.001 for training effect in MICT). Similarly, RV mass increased only after MICT by 1.8 g (95% CI 0.2 g to 3.4 g, p=0.036 group*training, p=0.005 for training effect in MICT). RVESV increased (p = 0.020 for training effect), while RVEF mildly reduced (p = 0.046 for training effect) by both training modes. All of the results persisted when normalizing for the body surface area (BSA). BSA normalization underscored the fact that the hearts were bigger in the MICT group (Table 14).

Changes in LV parameters. The changes observed in the RV parameters were quite closely mirrored by similar changes in LV parameters (Table 15). There were two key differences between RV and LV responses. Firstly, HIIT decreased LVGU adjusted for plasma FFA concentration compared to MICT (p = 0.030 for group*training interaction). Secondly, LVEDV and LV mass increased similarly by both training modes (Table 15).

TABLE 14. Right ventricular metabolic, structural and functional adaptations in subjects with T2DM or prediabetes. Modified from sub-study III.

	HIIT		MICT		
	pre	**post**	**pre**	**post**	
RVGU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	11.0 (7.9, 14.1)	10.4 (7.3, 13.6)	7.5 (5.1, 9.8)	8.9 (6.4, 11.3)	
$RVGU_{FFA\text{-}adj}$, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	10.5 (7.6, 13.4)	9.4 (6.4, 12.4)	8.0 (5.7, 10.2)	8.7 (6.4, 11.0)	
RVFFAU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	2.0 (1.6, 2.4)	2.2 (1.8, 2.6)	2.2 (1.9, 2.5)	2.1 (1.7, 2.4)	
RV mass, g	24.8 (21.8, 27.8)	24.8 (21.8, 27.8)	27.5 (25, 30)	29.3 (26.7, 31.8)	*‡
RV mass/BSA, g/m^2	12.3 (11.4, 13.2)	12.3 (11.4, 13.3)	13.4 (12.7, 14.2)	14.3 (13.5, 15.1)	†*‡
RVEDV, ml	145 (126, 165)	147 (128, 167)	167 (151, 184)	182 (165, 199)	†**‡
RVEDV/BSA, ml/m^2	72 (66, 78)	74 (67, 80)	82 (76, 87)	89 (83, 95)	††**‡
RVESV, ml	59 (46, 72)	61 (48, 74)	69 (58, 79)	79 (68, 90)	*
RVESV/BSA, ml/m^2	29 (24, 34)	31 (25, 36)	33 (29, 38)	39 (34, 43)	*
RVSV, ml	86 (76, 97)	86 (75, 97)	99 (90, 108)	103 (93, 112)	
RVSV/BSA, ml/m^2	43 (39, 47)	43 (39, 47)	48 (45, 51)	50 (47, 53)	†
RVCO, $l \cdot min^{-1}$	6.2 (5.6, 6.9)	5.9 (5.3, 6.6)	6.7 (6.2, 7.3)	6.4 (5.8, 7.1)	
RVCO/BSA, $l \cdot min^{-1}/m^2$	3.1 (2.8, 3.4)	3.0 (2.7, 3.3)	3.2 (2.9, 3.4)	3.2 (2.9, 3.5)	
RVEF, %	60 (56, 64)	58 (54, 63)	60 (56, 63)	57 (53, 61)	*

Values present model-based means (95% CI). RVGU, RV glucose uptake; $RVGU_{FFA\text{-}adj}$, RV glucose uptake adjusted for plasma FFA concentration; RVFFAU, RV free fatty acid uptake; RVEDV, RV end-diastolic volume; BSA, body surface area; RVESV, RV end-systolic volume; RVSV, RV stroke volume; RVCO, RV cardiac output; RVEF, RV ejection fraction.

* $p \leq 0.05$ for the training effect
** $p \leq 0.01$ for the training effect
† $p \leq 0.05$ for the group effect
†† $p \leq 0.01$ for the group effect
‡ $p \leq 0.05$ for the group × training interaction

TABLE 15. Left ventricular metabolic, structural and functional adaptations in subjects with T2DM or prediabetes. Modified from sub-study III.

	HIIT		MICT		
	pre	**post**	**pre**	**post**	
LVGU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	41 (34, 48)	37 (29, 45)	37 (31, 43)	42 (35, 48)	
$LVGU_{FFA\text{-}adj}$, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	42 (35, 48)	36 (29, 43)	37 (32, 43)	41 (35, 47)	‡
LVFFAU, $\mu mol \cdot 100g^{-1} \cdot min^{-1}$	5.4 (4.4, 6.4)	5.7 (4.5, 6.8)	5.4 (4.6, 6.3)	5.2 (4.2, 6.2)	
LV mass, g	100 (86, 113)	101 (87, 115)	120 (109, 132)	122 (111, 134)	†*
LVEDV, ml	135 (115, 155)	140 (120, 160)	156 (139, 173)	166 (149, 183)	***
LVESV, ml	48 (36, 60)	53 (41, 65)	56 (46, 66)	62 (51, 72)	*
LVSV, ml	87 (75, 98)	86 (75, 98)	100 (90, 109)	104 (94, 114)	†
LVCO, $l \cdot min^{-1}$	6.3 (5.6, 7.0)	6.0 (5.2, 6.7)	6.8 (6.2, 7.4)	6.6 (5.9, 7.2)	
LVEF, %	65 (62, 69)	63 (59, 67)	64 (61, 68)	63 (60, 67)	

Values present model-based means (95% CI). LVGU, LV glucose uptake; $LVGU_{FFA\text{-}adj}$, LV glucose uptake adjusted for plasma FFA concentration; LVFFAU, LV free fatty acid uptake; LVEDV, LV end-diastolic volume; BSA, body surface area; LVESV, LV end-systolic volume; LVSV, LV stroke volume; LVCO, LV cardiac output; LVEF, LV ejection fraction.

* $p \leq 0.05$ for the training effect
*** $p \leq 0.001$ for the training effect
† $p \leq 0.05$ for the group effect
‡ $p \leq 0.05$ for the group × training interaction

6.4 Comparison of the healthy and diabetic subjects

Training responses of the healthy and the diabetic subjects were compared using a three-way hierarchical mixed linear model. The results for all the subjects are illustrated in Figure 11. As the gender of the subject may affect responses in some of the RV parameters, the comparison was also performed for male subjects only, and those results are reported below as well.

Comparison of RV metabolism. RVGU was significantly lower in the diabetic subjects compared to the healthy subjects at the baseline ($p = 0.029$). The healthy and the diabetic subjects responded differently to the training ($p = 0.023$ for DM*training interaction) so that RVGU was decreased by training only in the healthy subjects. After the training, there was no longer difference between the healthy and the diabetic subjects ($p = 0.62$). The inferences were similar when considering only the male subjects.

When considering RVFFAU, the overall difference between the healthy and the diabetic subjects tended to be statistically significant so that the diabetic subjects had higher RVFFAU ($p = 0.054$ for DM main effect). The response to the training was not different in the healthy and the diabetic subjects ($p = 0.72$ for DM*training interaction). When considering the male subjects only, the difference between the healthy and the diabetic subjects still tended to be statistically significant ($p = 0.064$).

Comparison of RV dimensions and function. BSA-normalized RV mass, RVEDV, and RVESV were smaller in the diabetic subjects at the baseline ($p < 0.001$, all). RVESV responded similarly to the training both in the healthy and the diabetic subjects ($p = 0.38$ for DM*training interaction), and RVESV continued to be smaller in the diabetic subjects after the training ($p = 0.005$). However, the responses in RVEDV and RV mass to HIIT and MICT were different in the diabetic and the healthy subjects ($p = 0.049$ and $p = 0.055$ for DM*group*training interaction in RVEDV and RV mass, respectively). BSA-normalized RVEDV and RV mass were improved only by MICT in the diabetic subjects. After the training, there was no longer difference between the healthy subjects and the diabetic subjects in MICT group ($p = 0.26$ and $p = 0.27$ for RVEDV and RV mass, respectively). The diabetic subjects in HIIT group continued to have smaller RVEDV and RV mass after the training compared to the healthy subjects ($p < 0.001$ for both RVEDV and RV mass). The results were similar when considering only the male subjects.

RV ejection fraction tended to be larger in the diabetic subjects compared to the healthy subjects at the baseline ($p = 0.066$). Although the training decreased RVEF similarly in both population groups ($p = 0.52$ for DM*training interaction), RVEF decreased slightly more in the diabetic subjects, and after the training there was no longer difference between the healthy and the diabetic subjects ($p = 0.17$). When considering only the male subjects, there was no difference in RVEF at the baseline ($p = 0.10$) nor after the training ($p = 0.11$).

BSA-normalized RV stroke volume was lower in the diabetic subjects at the baseline ($p = 0.003$). HIIT and MICT had statistically significantly different effect on RVSV in the healthy and the diabetic subjects ($p = 0.016$ for DM*group*training interaction). HIIT seemed to mildly increase RVSV in the healthy subject while MICT did not have effect on it. The opposite was observed for the diabetic subjects, in which MICT slightly increased RVSV while it remained unaltered by HIIT. Similar result was obtained when regarding only the male subjects. Finally, BSA-normalized RV cardiac output was similar in the diabetic and healthy subjects at the baseline ($p = 0.37$), and it remained unaltered by the training in both subject groups. The result was the same when considering only the male subjects.

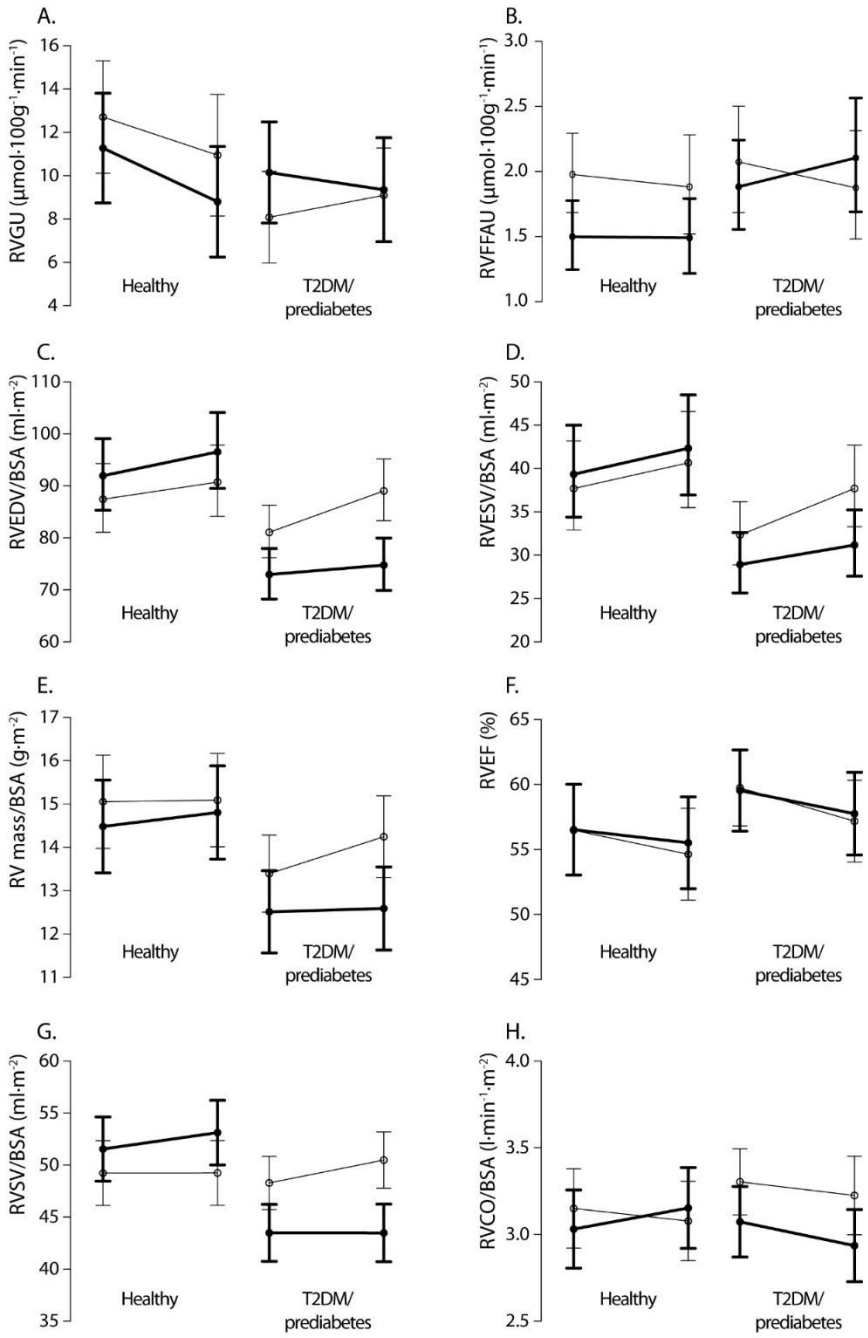

FIGURE 11. Comparison of the healthy and the diabetic subjects before and after the training. (A) RVGU adjusted for plasma FFA, (B) RVFFAU, (C) BSA-normalized RVEDV, (D) BSA-normalized RVESV, (E) BSA-normalized RV mass, (F) RVEF, (G) BSA-normalized RVSV, and (H) BSA-normalized RVCO. Bold lines with closed circle present HIIT and thin lines with open circles MICT.

7 DISCUSSION

The main findings of the thesis were:

1) RV glucose uptake was predicted by age and RVEF in healthy middle-aged men. RV free fatty acid uptake was predicted by VO_{2peak}, resting heart rate, and M-value, which can be all considered as parameters describing physical fitness and health. There were two main differences between RV and LV metabolism: only LVGU was inversely related to the whole-body glucose uptake, whereas only RVFFAU was associated with the exercise capacity and resting heart rate. Therefore, this study shows that results on LV metabolism may not be directly applicable to RV metabolism, which underlines the need for further studies designed on RV (I).

2) Only two weeks of either HIIT or MICT decreased similarly RVGU in healthy middle-aged men while RV fat metabolism remained unaltered. RV volumes increased and RVEF decreased after both training modes, but RV mass and RVSV did not change. Hence, alterations of RVGU, RV volumes and RVEF seem to take place rapidly when previously untrained subjects engage in exercise training, and these adaptations seem to precede possible exercise-induced hypertrophy of RV (II).

3) In subjects with T2DM or prediabetes, two weeks of HIIT or MICT did not have statistically significant effect on RVGU nor RVFFAU. However, RVEDV and RV mass increased only after MICT, whereas both training modes increased RVESV and mildly decreased RVEF. RVSV did not change. It appears that MICT may be more effective than HIIT in subjects with T2DM or prediabetes in improving RV diastolic function and mass (III).

4) At the baseline, diabetic subjects had lower RVGU compared to healthy men. This result shows for the first time in humans that T2DM alters not only LV but also RV metabolism. After two weeks of exercise training, the difference between diabetic and healthy subjects diminished due to reduced RVGU of the healthy subjects. The result raises a question whether exercise-induced reduction in the myocardial glucose utilization is good for the heart or not.

7.1 Differences in right and left ventricular metabolism in healthy men at the baseline (I)

The strongest predictor of the baseline RVGU was age, suggesting that RVGU decreases with increased age among middle-aged healthy men. Similar result was obtained also for LVGU. Association between age and glucose metabolism has previously been studied only regarding the LVGU with varying results. Some studies reported no correlation between age and LVGU (De Groot et al., 2005; Jeong et al., 2013), while other studies reported decreased LVGU in older subjects (Israel et al., 2007), or even increased LVGU in older subjects (Kates et al., 2003). Animal studies have been equally diverging, showing different age-related changes in the myocardial glucose transporter isoform 4 (Cartee, 1993; Martineau et al., 1999; Ozaki et al., 1996). The discrepancies in the results may be explained by differences in study protocols (whether the imaging is performed during insulin clamp or at fasted state), in quantitative analyses, in subjects' health status, and in the age ranges of the subjects. Regardless, the negative association between glucose uptake and age in the present study supports the previous statement by Peterson and Gropler: the age of the subject should be taken into account when measuring myocardial glucose metabolism (Peterson and Gropler, 2010). However, when measuring the changes in RVGU after two weeks of exercise training (sub-studies II and III), age had no effect on the changes in RVGU. Finally, although age had similar effect on both RVGU and LVGU, whole-body glucose uptake (M-value) was negatively correlated only with LVGU, indicating that the characteristics of the glucose utilization of the two ventricles differ from each other.

In healthy men, baseline RVFFAU correlated negatively with VO_{2peak} and M-value and positively with resting heart rate. Interestingly, the result suggests that better physical fitness is associated only with RVFFAU, as such associations were not found for LVFFAU. Previous studies have also found no associations between LV fatty acid utilization and physical fitness levels (Hannukainen et al., 2007; Takala et al., 1999; Turpeinen et al., 1996). The association between RVFFAU and physical fitness appears interesting in the light of the recent studies, which have indicated that RV may actually be more important than LV during the exercise, and RV is the ventricle which is acutely compromised during a strenuous exercise most likely due to the relatively greater increase in the RV work load (Elliott and La Gerche, 2015; La Gerche et al., 2011, 2012; Trivax et al., 2010). The present study further suggests that RV, including its metabolism, may unexpectedly play a major role on the exercise capacity. However, after engaging in a two-week-long exercise training, the changes in VO_{2peak} and resting heart rate no longer correlated with the changes in RVFFAU (sub-studies II and III), which probably is explained by rapid increase in VO_{2peak} as a response to exercise.

Ejection fraction was associated with the metabolism of both ventricles. Interestingly, RVEF was more closely associated with GU of both ventricles, whereas LVEF related more tightly with FFAU of both ventricles. All the associations were positive, implying that increased RVEF in related to increased myocardial glucose uptake whereas increased LVEF relates to increased myocardial free fatty acid utilization. This interesting finding was supported by all the three analysis methods used in the study (clustering within heatmap, pairwise correlations, and lasso regression models). The observation supports the existence of the ventricular interdependence, which has previously been observed in patients with the left heart failure whose RVEF is shown to be a stronger predictor of survival than LVEF (De Groote et al., 1998; Di Salvo et al., 1995; Zornoff et al., 2002). In the present study, increased RVEF was associated with increased RVGU in the healthy subjects, whereas in patients with heart failure or pulmonary hypertension increased RVGU has been reported to relate to decreased RVEF or corresponding parameters obtained by echocardiography (Can et al., 2011; Lundgrin et al., 2013; Mielniczuk et al., 2011; Yang et al., 2014). The difference between health and disease may reflect different downstream metabolism. In the healthy heart, majority of glucose is oxidized to ATP, but in pulmonary artery hypertension increased glucose uptake is related to increased production of lactate (Ryan et al., 2015).

Characteristics of the baseline metabolism in healthy men were determined based on a relatively small number of subjects (n = 28). Although lasso regression is able to model even datasets with larger number of variables than the number of observations, the regression coefficients obtained in this study should be interpreted with caution. Ideally, separate validation dataset would have been optimal. Also, as pairwise correlations were calculated over multiple pairs of variables, it is possible that some of the findings may be by change as a result of multiple testing. On the other hand, the three analyses methods (visualization by heatmap, pairwise correlations, and lasso regression) supported each other. However, the findings should be confirmed with a larger independent dataset.

To conclude, the main finding of the publication (I) is that while RV and LV metabolism have shared characteristics, they are affected also by unique factors. Therefore, previous results on LV metabolism may not be readily applicable to RV metabolism, and further studies designed specifically on RV are needed in order to better understand the less-studied cardiac chamber.

7.2 Effects of HIIT and MICT on RV glucose uptake

7.2.1 Both exercise modes decrease RVGU in healthy subjects (II)

RVGU decreased -22% by HIIT and -12% by MICT in the healthy middle-aged men. Although the reduction was larger in magnitude after HIIT, the difference between the groups was not statistically significant. Similar result was obtained in LVGU for the same subjects (Eskelinen et al., 2016). The finding regarding decreased RVGU is also in line with a previous cross-sectional study, where insulin-stimulated LVGU was 33% lower in endurance athletes compared to untrained subjects (Nuutila et al., 1994). Interestingly, while exercise training increased whole-body insulin-stimulated glucose uptake in the present study, as well as in previous studies (Nuutila et al., 1994; Reichkendler et al., 2013; Takala et al., 1999), it had an opposite effect on myocardial glucose uptake, both in RV and LV.

The reason for exercise-induced decrease in myocardial glucose utilization remains unclear. Similar observation was found in mice after long-term spontaneous exercise (Monleon et al., 2014), where possible explanations included training-induced bradycardia or increased fatty acid oxidation. In the present study in the healthy humans, resting heart rate remained unaltered after the two-week-long training intervention. RVFFAU remained also unaltered, suggesting that there was no change in the fatty acid oxidation. However, RVGU and RVFFAU were measured under different metabolic environment, namely RVGU during euglycemic hyperinsulinemic clamp and RVFFAU in fasted state. Hence, the measurements of the two separate PET studies are not directly comparable. Myocardial glucose uptake is heavily dependent on the plasma FFA concentration (Knuuti et al., 1995; Nuutila et al., 1992), which were similar during the FDG-PET study before and after the exercise intervention, supporting the assumption that there was no change in the fatty acid oxidation during the measurement of RVGU.

Although increased FFA oxidation does not seem to explain the decreased RVGU in the healthy subjects of the present study, the observed decrease in RVGU may nevertheless be attributed to switch in substrate utilization. Lactate is the third important fuel for the heart. Heart is capable of utilizing lactate as a fuel especially during strenuous exercise when the plasma lactate concentration is heavily increased (Kaijser and Berglund, 1992), but lactate may contribute to myocardial energy metabolism also in the resting state. Previous studies have shown higher plasma lactate concentration in endurance athletes compared to sedentary subjects under insulin-stimulated conditions (Takala et al., 1999). Therefore, it is possible that two weeks of exercise training stimulated the lactate utilization in previously untrained subjects, even more by demanding all-out HIIT protocol, which may explain the reduced RVGU after training. Unfortunately,

myocardial lactate uptake was not measured in the presents study to confirm this hypothesis.

Lastly, decrease of RVGU may be due to exercise-induced reduction in the RV work load and the heart muscle becoming more economical. Previously, LVGU has been shown to correlate negatively with LV mass and positively with LV rate-pressure product which estimates LV work (Nuutila et al., 1994; Takala et al., 1999). However, in the present study, RV mass remained unchanged and no correlation was found between RVGU and RV mass. Because determination of the RV workload requires invasive procedures, it was not measured in the study.

7.2.2 Exercise training does not alter RVGU in diabetic subjects (III)

In subjects with T2DM or prediabetes, HIIT reduced RVGU adjusted for plasma FFA concentration by -10% and MICT increase it by +10%, but the difference between the training protocols was not statistically significant due to a large variation between the subjects. For comparison, HIIT reduced LVGU by -14% and MICT increased it by +9% and the difference between HIIT and MICT was statistically significant. As the percentage changes were fairly similar in RVGU and LVGU, it appears that the number of subjects may have been too small to detect statistically significant changes between HIIT and MICT in RVGU, in which variance between the subjects was relatively larger compared to LVGU.

There are no previous studies comparing the effects of HIIT and MICT on myocardial glucose metabolism in T2DM in humans. In diet-induced obese mice, both exercise intensities increased the rate of myocardial glucose oxidation (Hafstad et al., 2013). Thus, it seems that HIIT has an opposite effect in human T2DM or prediabetic subjects compared to animal model of obesity, although FDG-PET used in the present study measures only glucose uptake by the cardiac cells and not the proportion of glucose entering oxidative metabolism.

The opposite effects of HIIT and MICT on RVGU in the diabetic subjects may reflect differences in substrate selection. For instance, blood lactate at rest and during insulin clamp has been shown to be higher in T2DM patients compared to healthy subjects (Del Prato et al., 1993). In diabetic rats, seven weeks of endurance training increased the expression of MCT1 within the heart, which is a protein responsible for increasing myocardial lactate uptake (Nikooie et al., 2013). Therefore, it may be that intense all-out HIIT stimulated the lactate uptake more than MICT and contributed to reduced RVGU after HIIT.

7.2.3 Exercise-induced decrease in glucose uptake – good or bad?

In healthy subjects, both HIIT and MICT decreased RVGU. Similar result was obtained for LVGU (Eskelinen et al., 2016). Although the difference between the training modes was not statistically significant, the decrease after HIIT was greater in magnitude compared to MICT. In subjects with T2DM or prediabetes, RVGU seemed to decrease after HIIT and increase after MICT, and in LVGU this trend was even stronger and reached statistical significance (sub-study III). However, it remains unclear whether the decreased glucose uptake is a positive or negative adaptation to exercise training.

Firstly, exercise-induced reduction in RVGU seems to be a positive adaptation when compared to diseases such as pulmonary artery hypertension and heart failure, in which RVGU is increased most probably because of increased workload of RV due to a disease (Can et al., 2011; Lundgrin et al., 2013; Mielniczuk et al., 2011; Oikawa et al., 2005; Yang et al., 2014). In fact, measurement of myocardial metabolism may provide complementary information to CMR results when determining whether training-induced myocardial changes in athletes are healthy or not. Generally, exercise training leads to excellent health, regarding both the whole body and the heart. However, a minority of highly trained athletes may suffer from an "exercise-induced cardiomyopathy" (D'Andrea et al., 2015). Interestingly, the exercise-induced pathophysiological changes seem to point to RV function, which becomes compromised especially in some endurance athletes (Elliott and La Gerche, 2015; La Gerche et al., 2012; Trivax et al., 2010). Since exercise training induces similar functional changes in RV as the pulmonary artery hypertension, including increased pulmonary artery systolic pressure (D'Andrea et al., 2011) and decreased RVEF (Prakken et al., 2010), it may be difficult to judge whether the exercise-induced changes especially in RV are physiological or pathophysiological. This thesis suggests that exercise training leads to reduced RVGU, as an opposite for increased RVGU in patients with pulmonary artery hypertension. Therefore, as speculated in a recent review (D'Andrea et al., 2015), nuclear imaging may indeed have the potential to differentiate between healthy and unhealthy RV adaptations in athletes. For instance, FDG-PET during euglycemic hyperinsulinemic clamp could be used in clinical settings instead of taking biopsy of those athletes with the most pretest probability of identifying pathology. Thus, when compared to pulmonary artery hypertension or heart failure, reduced RVGU after training seems to be a positive change.

On the other hand, reduced glucose uptake after exercise training leads to similar level of myocardial glucose metabolism as in T2DM. In the presents study, the baseline RVGU was lower in the T2DM and prediabetic subjects compared to the healthy men, but after the training intervention there was no longer difference between these population groups due to reduced RVGU of the healthy subjects. Previous studies on LV

have reported decreased LVGU in T2DM compared to healthy controls (Rijzewijk et al., 2009; Voipio-Pulkki et al., 1993), while decreased RVGU has previously been reported only in Zucker diabetic fatty rats (Van den Brom et al., 2010). On the other hand, a previous study has shown decreased LVGU in athletes compared to untrained subjects (Nuutila et al., 1994). Even though both T2DM and exercise training reduce myocardial glucose uptake, the underlying mechanisms are most likely different. Exercise leads to physiological hypertrophy and the heart muscle may become more economical. On the other hand, decreased glucose uptake observed in T2DM may be due to decreased number of sarcolemmal glucose transporters (GLUT4 and GLUT1) in diabetic cardiac cells (Le Douairon Lahaye et al., 2014).

However, the most interesting question is whether the potential decrease of glucose uptake after HIIT compared to MICT in diabetic subjects is good or bad. In RVGU, the difference between HIIT and MICT was not statistically significant, but it was more pronounced in LVGU. As glucose uptake of the diabetic subjects is already reduced at the baseline as shown in the present study as well as in the previous studies (Rijzewijk et al., 2009; Voipio-Pulkki et al., 1993), it intuitively seems that it cannot be good if it is further decreased by HIIT. On the other hand, several whole-body parameters, such as whole-body glucose uptake, HbA_{1c}, resting heart rate, and blood pressure were improved similarly by HIIT and MICT in the diabetic subjects of the present study. Even more interestingly, VO_{2peak}, the most common parameter describing cardiovascular fitness, improved only after HIIT in the diabetic subjects. In this light, HIIT brings about many health-enhancing changes. Therefore, longer exercise interventions with larger number of subjects are needed to clarify the mechanisms related to exercise-induced reduction in glucose uptake and to determine whether decreased glucose uptake after HIIT is only an acute response to demanding all-out exercise, or will it continue to be decreased after longer periods of HIIT and what its clinical significance is.

7.3 Effects of HIIT and MICT on RV free fatty acid uptake (II, III)

RVFFAU remained unchanged after both training modes in the healthy subjects. However, some of the FTHA-PET measurements were unsuccessful, which may have reduced the power to detect changes after the training interventions. Nevertheless, the result is in line with previous studies on LV, where no difference was observed in LVFFAU in subjects with different fitness levels (Hannukainen et al., 2007; Takala et al., 1999; Turpeinen et al., 1996). Further, the fatty acid β-oxidation index seemed to vary from a subject to subject, which was not explained by parameters such as VO_{2peak} or size of the heart (Turpeinen et al., 1996). In the healthy subjects of the present study, there was a statistically significant difference in RVFFAU between HIIT and MICT groups at the baseline, although VO_{2peak}, heart rate, or size of the RV were not different between the groups. Thus, it seems that random variation also affects RVFFAU.

With regards to the diabetic subjects, RVFFAU remained also unchanged after both HIIT and MICT. RVFFAU tended to be higher in the diabetic subjects compared to the healthy subjects at the baseline. In diet-induced obese mice, both HIIT and MICT decreased myocardial triglyceride content (Hafstad et al., 2013), but it was unaltered in human T2DM subjects after exercise training (Jonker et al., 2013; Schrauwen-Hinderling et al., 2011). When considering medical treatment of T2DM, pioglitazone also had no effect on LVFFAU even though the drug improved both LVEDV and LVSV (Van Der Meer et al., 2009). It is believed that continuously elevated free fatty acid utilization associated with impaired glucose tolerance causes myocardial damage and contractile dysfunction (Peterson et al., 2004; Rodrigues et al., 1998). However, it appears that cardiac function may be improved, at least to some extent, without requiring significant decrease of myocardial fatty acid utilization.

7.4 Changes in RV dimensions and function (II, III)

Changes in RV dimensions and function were determined by CMR. In the healthy subjects, both training modes increased RV end-diastolic and end-systolic volumes, whereas RV ejection fraction mildly reduced. In the diabetic subjects, RVESV increased and RVEF decreased similarly after both HIIT and MICT. Interestingly, only MICT increased RVEDV in the diabetic subjects and even so that the RVEDV normalized for body-surface area no longer differed from that of the healthy subjects after the training intervention.

Increased RV volumes after two weeks of training are most probably due to increased blood plasma volume, which is shown to take place rapidly when starting exercise training (Green et al., 1984). Observed increase in RVEDV is in line with previous longitudinal CMR studies, but the previous studies reported no changes in RVESV or RVEF after training (Arbab-Zadeh et al., 2014; Spence et al., 2013; Vogelsang et al., 2008). However, findings of the present study are in line with cross-sectional CMR studies, where RV volumes of endurance athletes were increased and RVEF was decreased compared to nonathletes (La Gerche et al., 2011; Prakken et al., 2010). The largest changes were observed in high-dynamic high-static sports such as cycling and rowing (Luijkx et al., 2012). It appears that reduced RVEF is a physiological response to exercise-induced RV dilation, and it may be that more optimal pumping capacity is achieved by higher RVEDV at the cost of mildly reduced RVEF (D'Andrea et al., 2015). However, markedly lower RVEF is associated also with heart failure and pulmonary artery hypertension (Mielniczuk et al., 2011; Movahed and Milne, 2007; Oikawa et al., 2005; Yang et al., 2014). This is especially problematic in elite athletes, in which it may be difficult to separate exercise-induced physiological adaptations from pathological hypertrophic cardiomyopathy (D'Andrea et al., 2015; Elliott and La Gerche, 2015; Luijkx et al., 2013). As discussed in section 7.2.3, this study shows that measurement of

RVGU under insulin clamp could provide complementary information to CMR to separate these two conditions as previously speculated (D'Andrea et al., 2015; Gargiulo et al., 2015).

In the healthy subjects, two weeks of exercise training did not affect RV mass. However, in the diabetic subjects, RV mass was increased only after MICT, and the RV mass normalized for the body-surface area reached the same level with the healthy subjects. It is surprising that only two weeks of MICT induces statistically significant increase in RV free wall mass, as it has been previously stated that it takes more than three hours of leisure-time exercise in a week for prolonged period to increase LV mass (Fagard, 2003). More recent studies have shown 12% increases in LV and RV masses after eight weeks of rowing in untrained obese subjects (Vogelsang et al., 2008), and 12% increase in LV mass after 12 weeks of HIIT on cycle ergometer in T2DM subjects (Cassidy et al., 2016). The discrepancy may be explained by technical advancements and increased sensitivity of the imaging technology, especially in CMR, which allows detection of smaller changes in cardiac structure. Also, as the people with T2DM or at risk of developing the disease are typically less physically active than the general population (Morrato et al., 2007), it may be that only two weeks of MICT is enough to induce an increase in RV mass. On the other hand, it is known that pathological hypertrophy of LV is related to T2DM (Dawson et al., 2005; Frey et al., 2004). With regards to RV, T2DM decreases RVEDV (Tadic et al., 2015; Widya et al., 2013). In the present study, MICT increased both RVEDV as well as RV mass, and therefore it is likely that the small increase in cardiac mass is a sign of physiological hypertrophy rather than of a pathological process.

Finally, RV stroke volume remained unchanged both in the healthy subjects as well as in the subjects with T2DM or prediabetes. In diabetic or obese subjects, eight weeks of rowing and 12 weeks of cycling increased RVSV (Cassidy et al., 2016; Vogelsang et al., 2008). However, in healthy subjects six months of endurance or resistance training did not affect RVSV (Spence et al., 2013). In another study, one year of intensive endurance training increased RVSV (Arbab-Zadeh et al., 2014). Taken together, it appears that RV volumes along with RVEF respond rapidly to exercise training, and this study shows that only two weeks of exercise is sufficient to induce changes in these parameters. However, RV mass may require more exercise at least in healthy subjects, while increase in RV stroke volume, as well as in cardiac output, takes longer training period to occur.

7.5 Strengths and limitations

The major strength of the thesis is the use of positron emission tomography, which enables quantitative measurement of myocardial metabolism. The present study is novel, since this is the first time when RV metabolism is studied both in healthy subjects as

well as in subjects with T2DM or prediabetes. Previous studies on RVGU have involved patients with pulmonary artery hypertension or heart failure, whose glucose metabolism, and hence the tracer count in the FDG-PET scan, is increased as a response to their disease. However, this thesis shows that when RV metabolism is determined in the condition with the highest substrate uptake (insulin clamp for RVGU and fasted state for RVFFAU), RV free wall is clearly visualized. Hence, RV metabolism can be measured, for instance, in the context of exercise physiology, and it is not restricted only to patients with increased RVGU and higher tracer count statistics.

The secondary outcomes of the thesis, namely structural and functional parameters of RV, were measured using CMR, which is regarded as the gold standard for cardiac structural assessment (Grothues et al., 2004). Furthermore, RV contours were traced following the established guidelines (Prakken et al., 2008), making it easier to compare the results of this study to other CMR studies. All the exercise interventions were performed in supervised laboratory conditions without variation between subjects in their implementation. Finally, as the healthy subjects performed the similar protocol as the subjects with T2DM or prediabetes, the responses to exercise can be compared between these two populations.

The study is not without limitations. The number of subjects was relatively small to begin with, and unfortunately there were also some unsuccessful PET measurements as well as drop-outs. Especially FTHA-PET scans suffered from technical difficulties both in the healthy and the diabetic subjects due to problems in the tracer production. Therefore, the observation that RVFFAU did not change after the training may be because of too small number of subjects completing the FTHA-PET study successfully. In the healthy subjects, RVGU seemed to decrease consistently in both HIIT and MICT groups, but the difference between the groups was not statistically significant even though the decrease was larger after HIIT (-22%) compared to MICT (-12%). In the diabetic subjects, changes of RVGU remained statistically insignificant, even though LVGU decreased statistically significantly by HIIT compared to MICT. Similar study with a larger number of subjects could shed more light to the questions whether the effects of HIIT and MICT on RVGU are truly similar in healthy subjects and what is the response of diabetic subjects to HIIT and MICT. However, large PET studies are difficult to carry out, as PET studies are expensive and involve the use of ionizing radiation. Moreover, the infrastructure required for PET studies are sparsely available and clinical assessments of patients are often scanned within the same facilities, which also poses a limitation to the number of subjects that can be studied within a reasonable course of time. For these reasons, number of subjects involved in human PET studies are usually relatively small.

While the PET studies were limited by the unsuccessful measurements, the CMR studies regarding structural and functional changes were successful almost for every subject who

completed the training protocol. RVEDV and RVESV appeared to increase consistently while RVEF decreased in most of the subjects. Hence, it seems that only two weeks of exercise training can result in cardiac remodeling in previously untrained subjects.

The subjects with T2DM and prediabetes included both men and women, but the number of each was too small to address possible sex-related differences, which are shown to affect both heart's metabolic and functional responses to diabetic therapies (Lyons et al., 2013) as well as VO_{2peak} (Bagley et al., 2016). Another limitation in the diabetic subjects is somewhat uneven proportion of T2DM and prediabetic subjects in the HIIT and MICT groups. Gender and diagnostic group (T2DM/prediabetes) were taken into account as factors in the statistical analyzes to minimize the effects of these confounding variables. In addition, the diabetic subjects had different medications which could have affected the results. For example, metformin is a common medication for T2DM and it was used by seven T2DM subjects in the HIIT group and four T2DM subjects in the MICT group. Metformin has been shown to reduce metabolic rate of glucose uptake in T2DM patients (Van Der Meer et al., 2009), and therefore it is possible that the different medication of the subjects interfered with the training responses. Oral hypoglycaemic medications were interrupted for two days before the pre- and post-measurement PET scans, but it was not ethical or even clinically possible to prohibit the use of the prescribed drugs for the duration of the entire study. On the other hand, the study population reflects the real-life situation, where T2DM or prediabetic patients typically have different medications for glucose intolerance, as well as for often co-existing hypertension and hyperlipidemia.

Comparison of the training responses between the middle-aged healthy and diabetic subjects is limited by the fact that the healthy subjects were all men but the diabetic subjects included both men and women. Therefore, it cannot be definitely concluded which differences are due to T2DM or prediabetes and which differences are masked by the effect of different sex. Ideally, these groups should have been age- and sex-matched. The initial purpose of the study was to recruit men only in both population groups, but due to difficulties encountered in recruiting male diabetic subjects, women were also included in order to complete the study in a reasonable course of time.

RVGU and RVFFAU were measured in different metabolic conditions, RVGU during the insulin clamp and RVFFAU in the fasted state. Therefore, the results of these two PET studies are not directly comparable. In addition, lactate uptake was not measured at all in the present study, although it is the third important substrate for the myocardial metabolism. Hence, the relative changes in each substrate as a response to the training cannot be deduced based on this study. In addition, RV workload was not measured in this study. Therefore, it remains unclear whether changes in RV metabolism are related to changes in RV workload after training.

The results on RV metabolism as well as on RV structure and function are derived from PET and CMR image analyses, respectively. In general, results of such analyses may depend on the observer, as the analyses are based on visual inspection of the images and manual determination of the regions of interests. In healthy subjects, RVGU was analyzed by two independent observers. The interobserver Pearson's correlation was 0.97 for the baseline RVGU and 0.97 for the training-induced differences in RVGU. Good reproducibility was also supported by the Bland-Altman plots (see study II for details). Furthermore, as the same person (writer of this thesis) analyzed all the PET and CMR images for both healthy and diabetic subjects, the observations should reflect actual physiological changes. In CMR image analysis, tracing of the endocardial contour in the most basal RV slices during diastole was challenging due to the tricuspid and pulmonary valves. Also, because of the thin wall and heavy trabeculation in the RV, it was somewhat difficult to distinguish the epicardial border needed to determine RV mass. However, endo- and epicardial borders were traced by adopting a standardized contour tracing protocol, which has shown to result in a good reproducibility (Prakken et al., 2008). The obtained RV parameters of the healthy men were in good agreement with a previous CMR study following the same contour tracing protocol (Spence et al., 2013).

8 MAIN FINDINGS AND CONCLUSIONS

The results of the current thesis showed that the baseline glucose utilization of both ventricles was lower in older subjects among healthy middle-aged men. Myocardial metabolism was associated with ejection fraction and even so that RV ejection fraction was more tightly associated with glucose uptake and LV ejection fraction to free fatty acid uptake of both ventricles. The result underlines the significance of the ventricular interdependence. The main difference in the baseline metabolism between the two ventricles were that the whole-body insulin-stimulated glucose uptake was related only to LV glucose uptake, whereas maximal exercise capacity and resting heart rate were associated only with RV free fatty acid uptake. To conclude, while RV and LV metabolism have shared characteristics, they also have differences. Therefore, further studies designed specifically on less-known RV are needed.

In the healthy middle-aged men, both high-intensity interval training and more traditional moderate-intensity continuous training exerted similar effects on RV metabolism and function. Remarkably, only two weeks of exercise training in previously untrained men decreased RV glucose uptake, increased RV volumes, and mildly reduced RV ejection fraction. These changes appear to precede possible exercise-induced hypertrophy of the right ventricle. Moreover, both training modes also improved peak oxygen uptake, a parameter describing cardiorespiratory fitness.

Type 2 diabetes is associated with decreased myocardial glucose uptake and increased free fatty acid uptake (Lopaschuk and Dhalla, 2014). In accordance, the diabetic subjects of this study had lower RV glucose uptake compared to the healthy men. Surprisingly, HIIT seemed to further decrease RV glucose uptake compared to MICT in diabetic subjects, but the difference was not statistically significant. Furthermore, only MICT increased RV end-diastolic volume and RV mass. Therefore, the results suggest that HIIT may be less beneficial for a diabetic heart than MICT when considering exercise for diabetic subjects, even though only HIIT improved the exercise capacity.

The purpose of the present study was to investigate the initial responses to short-term HIIT and MICT in previously untrained healthy and diabetic subjects. Responses to prolonged training remain unclear and warrant further studies. For instance, none of the observed changes in the healthy subjects were different after HIIT and MICT. It may be that, for previously untrained subjects, both forms of exercise induce rapid responses in glucose metabolism as well as in RV volumes and ejection fraction. Longer training interventions are needed to study, whether long-term cardiac adaptations are different after HIIT and MICT, or do their effects overlap as seems to happen in skeletal muscle metabolic adaptations (Laursen, 2010). As for diabetic subjects, longer exercise interventions are necessary to determine whether glucose uptake continues to remain decreased after HIIT, or is the change in metabolism that intuitively appears maladaptive rather than adaptive, only an acute response to demanding all-out exercise. Further studies investigating the mechanisms behind the altered RV metabolism as a response to exercise training in healthy and diabetic subjects, as well as in athletes with various training backgrounds, are needed to determine whether the exercise-induced changes are physiological or pathophysiological. The sample size in future studies should be larger compared to this thesis to better accommodate drop-outs and technical problems which occasionally occur in delicate PET measurements.

Based on the current thesis, it is proposed that in healthy subjects HIIT and MICT bring about similar changes in the cardiac function and metabolism, as well as in whole-body health. Although it appears that especially MICT improves right ventricular function and may therefore be more beneficial than HIIT for a diabetic heart, both exercise modes improved similarly several parameters of whole-body health, such as insulin sensitivity, HbA_{1c}, resting heart rate, and blood pressure in the diabetic subjects. It is remarkable that only 15 minutes of exercise performed in "all-out" manner within two weeks induces significant changes both in the heart as well as in whole-body health, even though the exercise volume is considerably less than is recommended in the current recommendations for health-enhancing physical activity.

To conclude, the more time-efficient high-intensity interval training appears to be a good alternative for the traditional moderate-intensity endurance training, and both HIIT and MICT can be used as health-enhancing exercise training according to individual preferences. However, as there are still unanswered questions regarding HIIT, for those individuals with more severe T2DM or cardiovascular disease it may be wiser to start exercise training by MICT.

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