At the heart of the matter

Impact

What is the main aim of the research described in this thesis and what are the most important results and conclusions?

The aim of this thesis is to investigate how cardiac metabolism is changed in prediabetes and how these changes contribute to diastolic dysfunction. Specifically, this thesis focusses on cardiac energy metabolism and cardiac insulin resistance in prediabetes, with special attention for the role of PPARα in regulating cardiac and hepatic metabolism.

Cardiac metabolism is subject of all chapters in this thesis and therefore this gives the reader an indication of where the gaps of our current understanding are, which is valuable for future research. In **chapter 2** the current literature on cardiac fat, lipid and glucose metabolism, and mitochondrial function in the prediabetic heart were reviewed. In prediabetes the increased cardiac fat accumulation is accompanied by an increased FFA uptake and oxidation. Although a vastly decreased glucose uptake, glucose oxidation, and a declined mitochondrial function, have been observed in T2DM, the few studies in prediabetes show conflicting results and the contribution of insulin resistance and mitochondrial inefficiency to the development of cardiac dysfunction remains unclear. It appeared that most studies focus on heart failure and type 2 diabetes mellitus (T2DM), and that the number of studies investigating cardiac metabolism in prediabetes are limited. Even less is known about whether PPARα can influence cardiac metabolism in prediabetes.

The urgency of broadening our knowledge of cardiac metabolism is also shown in **chapter 3**. It shows that even in healthy individuals with a normal cardiac function and without diabetes, an increase in the adipose tissue surrounding the heart (pericardial fat) is associated with a decline in diastolic function, possibly due to a mechanical hindrance. Nonetheless, the changes occur in an overweight, but metabolically rather healthy population and may therefore precede the onset of the metabolic syndrome. The importance of this pericardial fat depot, even in seemingly healthy people, might be underestimated in current literature that mostly focusses on individuals with T2DM.

To gain more insight in cardiac mitochondrial function, we investigated in **chapter 4** whether the cardiac energy status reflects cardiac mitochondrial function, since the ratio of phosphocreatine (PCr) over adenosine triphosphate (ATP) measured by ^{31}P-Magnetic Resonance Spectroscopy (^{31}P-MRS) is a non-invasive surrogate marker of cardiac energy status *in vivo*. However, our results do not support the use of cardiac energy status (PCr/ATP) as a surrogate marker of mitochondrial function in the heart. The dissociation of the two parameters in the present study suggests that mitochondrial function is not the only determinant of cardiac energy status.

While type 2 diabetes is recognized as CVD risk factor and some changes in cardiac metabolism have been reported, the role of metabolic changes in prediabetic heart remain elusive. This is studied in **chapter 5** where we find that cardiac energy status is already reduced in prediabetes. This is an important finding, because although cardiac energy status does not reflect mitochondrial function, it remains an important marker of cardiovascular health.

In **chapter 6** we explore the effects of stimulation of the PPARα pathway in prediabetes. Here, five weeks of treatment with PPARα tended to alter cardiac glucose metabolism and decreased insulin-stimulated glucose uptake in the liver. This is consistent with the expectation that PPARα stimulates fat uptake and oxidation, and through substrate competition inhibits glucose uptake in the liver and possibly in the heart. This is not accompanied by effects on whole body insulin resistance, nor on whole body glucose or fatty acid oxidation rates. Hence, these changes do not seem to be detrimental, despite the stimulatory effect on fat metabolism by the PPARα agonism. New research should be performed to explore the effects of prolonged treatment to see whether the changes in metabolism are permanent in the long term, and more specifically into fat metabolism since we did not study this specifically. It may be the case that through increasing fat oxidative capacity the accumulated fat in the liver is temporary, leading to a higher insulin sensitivity in prediabetes in the end. However, this remains speculative and a new study may lead to novel insights in the PPARα pathway in prediabetic humans.

What is the contribution of the results to science and societal changes?

The prevalence of prediabetes is extremely high worldwide and diastolic dysfunction is frequently present in people with prediabetes. Changes in cardiac metabolism are associated with diastolic dysfunction in type 2 diabetes and quite likely, prediabetic individuals are similarly affected. At present, knowledge about cardiac metabolism in people with prediabetes and the health consequences of disturbed cardiac metabolism are very limited.

The results of the current thesis can guide future research in this area. Firstly, this thesis can help with the choice of suitable methodology. ^{31}P-MRS measures cardiac energy status, which appears to be decreased in prediabetes indicating an increased CVD risk. In addition, a dynamic PET scan measuring glucose uptake during insulin stimulation provided insights upon the PPARα pathway in prediabetes and also highlighted the interplay between fatty acid and glucose metabolism in heart and liver. This study may stimulate future researchers to also use this dynamic PET technique, possibly even with other tracers than a glucose analogue.

In addition, the results of the research described in this thesis contribute to our understanding of human cardiac metabolism in prediabetes and its importance for cardiac function. Future studies can extend the findings presented in this thesis by investigating what effects PPARα agonism may have on the long term and investigate whether diastolic function improves after normalisation of pericardial fat volume. This can give guidance on which pathways are important to influence for the prevention or treatment of cardiac dysfunction in (pre)diabetes. Ultimately, this will contribute to improving prevention of T2DM, reducing health care costs and relieving the pressure on the health care system.

For whom are the results interesting and of relevance?

The results and conclusions presented in this thesis are interesting for other researchers, who can set-up new studies further investigating cardiac metabolic alterations in prediabetes and how these changes contribute to the development of diastolic dysfunction. These studies can make use of the techniques described in this thesis, specifically the dynamic PET-MRI technique during a hyperinsulinemic euglycemic clamp to specifically determine insulin-stimulated fat and glucose uptake and oxidation with different tracers. Ultimately, this knowledge could help in the prevention and treatment of diastolic dysfunction in diabetic

cardiomyopathy. In terms of prevention, this knowledge would be of interest for people with overweight and obesity, as these are at increased risk for prediabetes and diabetes.

Fibrates are known to treat hypertriglyceridemia and thereby reduce health risks in patients at high risk for cardiovascular diseases. Our study does not change the current indication for fibrates and has therefore no consequences for current fibrate users. In this thesis, we studied ciprofibrate as a modulator of PPARα, which has given more insights in the PPARα pathway in prediabetes. The fact that liver glucose uptake decreases and cardiac glucose uptake tends to decrease, demonstrates the effect of stimulating fat oxidation by PPARα. Knowledge from future studies building on our results can lead to more insights in cardiac metabolism, leading to the development of new drugs for the treatment of diastolic dysfunction, thereby reducing the risk for heart failure in diabetes and prediabetes.

Other researchers will be informed about the results described in this thesis through publications in scientific journals and presentations at national and international conferences. Results will also be shared on websites, social media and participant information events, thereby informing the people at risk for the development of diastolic dysfunction due to (pre)diabetes.