A novel paradigm for heart failure with preserved ejection fraction

Valorisation

Socio-economic Relevance

HF is the most prominent cause of hospitalisation globally, with 3.6 million newly diagnosed patients annually[1], and its prevalence is expected to increase by 46% in 2030[323]. More than half of these HF patients suffer from HFpEF and this number is expected to rise even further due to the ageing population and increased survival of patients with non-cardiac comorbidities[324]. HFpEF prognosis is poor with a severely impaired quality of life and high hospital readmission and mortality rate[20,21], resulting in soaring long-term cost are due to increasing emergency rehospitalisations[22]. While significant advancements have been made in the treatment of HFrEF, to date no specific efficient treatments are available for HFpEF due to incomplete pathophysiological understanding, patient population heterogeneity, and inadequate diagnosis[23,24].

Our results are a first step forward in improved therapy for HFpEF patients by a) better understanding of anaesthesia in **diagnosis**, b) **elucidating the understanding of the pathophysiology**, b) and c) identifying novel **prevention/treatment strategies** using a rodent model mimicking human HFpEF.

Echocardiography is the preferred method for diagnosis of patients with suspected HFpEF patients animal models mimicking human HFpEF. In Chapter 3, we show that the **type of anaesthetic** can **influence** the **diagnosis** of **diastolic dysfunction** in a HFpEF-diseased rodent model. Anaesthetic usage during echocardiography acquisition to assess HFpEF progression in animal models is essential. Furthermore, as the prevalence of HFpEF and the number of surgical procedures increases dramatically with ageing, perioperative echocardiography-mediated diagnosis of diastolic dysfunction requiring anaesthetics increases proportionally[301]. This underlines that **well-considered evaluation of anaesthetics** during **echocardiographical**

diagnosis of diastolic dysfunction is required both in **patients** and **pre-clinical animal models**.

Chapter 4 shows for the first time that cardiac microvascular regression is an early event in the development of HFpEF, occurring before the onset of diastolic dysfunction**.** These new insights underline that the **microvascular paradigm originally proposed by Paulus et al.** should be **revised,** and further research should be executed regarding the role of microvascular regression in HFpEF. **Diagnosis of microvascular regression** by usage of **advanced imaging techniques** (e.g. MRI, optical coherence angiography, Glycocheck etc; Horizon2020, E.A.V. Jones) will allow us to **earlier diagnose** HFpEF in suspected patients. Furthermore, we show that cardiac microvascular regression is associated with a reduced coverage of cells that stabilise the small blood vessels, also called pericytes. **Prevention of pericyte loss** in the heart of susceptible patients could **prevent disease progression** to HFpEF.

Chapter 5 shows that linagliptin significantly reduces cardiometabolic risk-induced left ventricular stiffness by reducing titin cleavage and hypophosphorylation. This is the first study showing the importance of titin cleavage in diastolic dysfunction, indicating that the microvascular paradigm originally proposed by Paulus et al. should be revised. Reducing left ventricular stiffness by **linagliptin** might be a potential **prevention and treatment strategy for HFpEF**. Currently, Boehringer investigates linagliptin as a treatment for HFpEF in clinical trials.

Target Groups, Products, Activities, and Future Directives

First of all, the effect of anaesthesia on diastolic dysfunction diagnosis are poorly known. In Chapter 3, we create more awareness for the effect of anaesthesia on diastolic function assessment. Furthermore, the pathophysiology underlying HFpEF is currently poorly

understood. Most research focusses on established HFpEF, while early stages are poorly investigated. In Chapter 4, we provide new insights in the development of HFpEF, using a rodent model mimicking human early, intermediate, and established HFpEF. It crucially underlines that the microvascular hypothesis for HFpEF development needs to be revised, thereby stimulating the **scientific community** to further investigate early stages of HFpEF. Lastly, in Chapter 5 we show the importance of drug repurposing in HFpEF prevention. In order to reach the scientific community, we have published our observations in peer-reviewed scientific journals and discussed the data at several national and international congresses.

Especially **patients suffering from a cluster of non-cardiac comorbidities** and **elderly**, **predominantly female subjects**, have an increased risk of developing HFpEF. As the number of surgical procedures dramatically increases with ageing, caution should be taken when diastolic dysfunction is assessed during perioperative echocardiography using anaesthesia. Furthermore, assessment of microvascular regression in these high-risk patients could provide an early diagnosis strategy. Currently, the diagnostic potential of microvascular regression is investigated by Prof. E.A.V. Jones (Horizon2020 project) aiming to non-invasively diagnose HFpEF patients at an early stage. If these susceptible patients represent with an increased microvascular regression, pericyte-targeted therapies, preventing microvascular regression, in combination with linagliptin, reducing left ventricular stiffness, could prevent the progression towards HFpEF. In established HFpEF patients, linagliptin and pericyte-targeted therapies might prevent deterioration of the disease. In order to explain our findings to the general public and patients, I presented our research at the Pint of Science festival Belgium in 2019 and joined the organization to improve science communication to the general public.

The involvement of microvascular regression is increasingly becoming more apparent in various **other cardiovascular (e.g. HFrEF), renal (e.g. chronic kidney disease), retinal (e.g. diabetic retinopathy), and neurological diseases (e.g. vascular cognitive impairment,**

dementia), while underlying causal triggers of microvascular regression and the resultant molecular pathways are poorly understood. The Horizon2020 grant aims to identify molecular mechanisms (reduced pericyte coverage) underlying microvascular regression and to assess whether microvascular regression could be used as a non-invasive diagnostic marker for vascular cognitive impairment. Thus, this thesis provides far-reaching insides in microvascular regression development beyond HFpEF and the cardiology community. Furthermore, patients with diabetic cardiomyopathy, hypertensive cardiomyopathy, hypertrophic cardiomyopathy, aortic stenosis, and dilated cardiomyopathy show an increased left ventricular stiffness[183,325-327], however linagliptin's potential benefit on left ventricular stiffness in these cardiovascular diseases has never investigated. This thesis could therefore provide potential prevention strategies for other cardiovascular diseases.