Metabolic phenotyping of the pressure-overloaded heart

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Valorization
Socio-economic relevance and clinical potential

Heart failure is the leading cause of death worldwide, currently affecting at least 26 million people\(^1\), and continuously increasing in its incidence, prevalence, and economic costs\(^1\). There are many external triggers that can lead to heart failure. Aortic stenosis and systemic arterial hypertension, each resulting in cardiac pressure overload, belong to the most-frequent cardiovascular diseases and major risk factors of heart failure\(^2\). Currently, over 1.13 billion people suffer from hypertension worldwide, a number that has nearly doubled since 1975 and is still on the rise\(^3\). Also the incidence of aortic stenosis, the most serious global valve disease problem, reaches epidemic proportions. With demographic aging of the global population the incidence of pressure overload-induced heart failure is expected to increase even further, thereby stressing the urgent need for effective medical therapy. Currently, there is, however, still no cure for pressure overload-induced heart failure, and unfortunately most available therapies are limited to symptom treatment. Before physical symptoms become apparent, the hearts of heart failure patients often already undergo asymptomatic structural and/or functional abnormalities (left ventricular dysfunction)\(^4\). Early detection and prevention are therefore of high importance. It has been proposed that derangements in cardiac energy substrate metabolism play a key role in the early pathogenesis of pressure overload-induced cardiac hypertrophy and eventually failure. Unravelling the underlying molecular triggers responsible for the occurring changes in substrate metabolism and protein synthesis, as seen in hypertrophying hearts, holds great promise to provide novel therapeutic strategies to prevent or treat the failing heart.

Potential target groups

The focus of this thesis is on the pathophysiology of heart failure as a consequence of pressure overload. The content of this thesis holds relevant information for (1) academic scientists working in various research fields, including cellular biology and function, substrate metabolism, protein synthesis and cardiac (patho)physiology, (2) the pharmaceutical industry working on the development of drugs/therapies against pressure overload (hypertension and aortic stenosis)-induced heart failure, (3)
clinicians/cardiologists, (4) and patients with hypertension and/or aortic stenosis, who are at high risk of developing cardiac complications. Moreover, scientists working on diseases (or patients suffering from diseases), with similar metabolic derangements as observed in the pressure-overloaded heart, such as cancer, could ultimately also benefit from our new discoveries.

To provide our obtained knowledge to the scientific community and beyond, our findings are published in scientific journals relevant to the research field, such as *Cardiovascular Research*, *BBA-Molecular Basis of Disease* and *Journal of Biological Chemistry*. Additionally, the studies described in this thesis were presented at relevant national (2\textsuperscript{nd} Maastricht-Nijmegen Science day, Nijmegen, The Netherlands; CARIM day 2016, Maastricht, The Netherlands; 17\textsuperscript{th} Society for Heart and Vascular Metabolism conference, Amsterdam, The Netherlands) and international (14\textsuperscript{th} Society for Heart and Vascular Metabolism conference, Beijing, China; 17\textsuperscript{th} Dutch-German Joint Meeting of the Molecular Cardiology Working Groups, Göttingen, Germany) scientific meetings/conferences by means of oral and poster presentations.

**Activities and products**

The knowledge acquired in this thesis and the established *in vitro* and *in vivo* models to study pressure overload-induced heart failure, has provided our research group with new expertise and advanced understanding in the underlying molecular mechanisms contributing to the development of pressure overload-induced heart failure, allowing them and other scientists to use these models and this new knowledge to implement in future research.

Additionally, products of great relevance for the society may be the public awareness of heart failure as a growing societal and economic burden. Connecting to cardiovascular foundations such as the Hartstichting and other health care organizations/professionals could make the knowledge described in this thesis better accessible and more useful for the benefit of the society. The main elements of public awareness campaigns by these
organizations, pay attention to signs and the sudden complications associated with heart failure, making the general public aware of heart failure symptoms and appropriate measures to take in case of an incident. Moreover, their patients education programs could help heart failure patients to make informed decisions and fully participate in all aspects of their illness, ultimately saving lives and enabling improved quality of live for patients with heart failure. Sharing information regarding research content and progress with these organizations, will not only allow these organizations to translate our findings to relevant information intelligible for layman, but will also allow foundations to assess whether funding in this particular research fields is needed.

Innovation and future directions

This thesis provides new insights into the metabolic changes during the development of pressure overload-induced heart failure. Continuing and expanding this research is highly essential if we aim to understand and further unravel the complex underlying mechanisms contributing to the development of cardiac hypertrophy and ultimately failure. In this thesis I provide evidence for the important role of changes in substrate metabolism during the development of pressure overload-induced heart failure. This fundamental research forms a first step towards the discovery of new potential therapeutic treatment targets. The facts that metabolic changes seem to precede structural and functional changes in the pressure-overloaded heart, and the fact that metabolic interventions are able to protect cardiomyocytes from contractile dysfunction, provides new target sides for early and late stage metabolic intervention studies. Although we have established a useful in vitro model that closely mimics the main characteristics of pressure overload-induced cardiac hypertrophy, future research will have to confirm our in vitro findings in animal and ultimately human disease models. Despite the projects described in this thesis being mostly of fundamental nature, these findings provide the first “building blocks” for future implementation of metabolic substrate metabolism as a non-invasive diagnostic tool in hypertensive and aortic stenosis patients. In vivo monitoring of substrate metabolism in pressure overload-induced heart failure patients (including determination of the disease
stage) would provide a base for tailored and patient specific treatment. Moreover, future research should focus on screening for new compounds that might be able to restore metabolic abnormalities in the pressure-overloaded heart.

References