Chapter 1
Introduction

Introduction

Heart failure (HF) is a major public health problem with a lifetime risk of almost 1 in 3 to develop this disease.[1,2] HF is the condition where the heart's blood supply does not suffice the body's demands. Despite improved treatment, the mortality rate for HF exceeds that of most malignancies.[3] As the most energy-consuming organ in the body, failing energy metabolism is thought to play an important role in the development of HF.[4] In this thesis, we investigated several aspects of metabolic interventions in HF. In the first part we investigated clinical aspects, including the position of β-blockers that have various metabolic effects. In this part we also describe the effect of coronary artery bypass grafting (CABG) in diabetic patients on HF development. In the second part we investigated the effects of A kinase interacting protein 1 (AKIP1) on cardiac remodelling and metabolism. This potential mitochondrial target for HF treatment was investigated using a transgenic mouse model.

Metabolic interventions after revascularization

Several established therapies also affect cardiac metabolism. We focused on β-blockers, that are known to have several metabolic "side-effects", and it has been suggested that new onset diabetes and dyslipidaemia are possibly related to the use of β-blockers.[5,6] Nevertheless, β-blockers have been recommended as first line therapy for stable coronary artery disease (CAD) for over 5 decades, based on their potent anti-anginal effects and on extrapolation of the prognostic benefits that has been demonstrated after myocardial infarction (MI) and in patients with HF.[7] CAD is a leading cause of morbidity and mortality worldwide and is the main cause of systolic HF.[8] The lifetime risk of developing CAD is 30-50%.[9] While mortality rates are decreasing by continued refinements in the treatment of acute coronary syndromes, innovation in the treatment of stable CAD has been limited. The studies supporting the efficacy of β-blockers in patients with CAD predate the current era of urgent coronary revascularisation and were specifically designed to evaluate their effects on angina. Of note, there is no evidence that β-blockers provide superior angina relief compared to calcium channel antagonists, nitrates or ivabradine. Furthermore, the evidence for the efficacy of β-blockers after revascularization in patients with stable CAD is sparse.[7] Nevertheless, β-blockers are often continued in these patients, even when left ventricular function is preserved and there are no other indications for their continued use.[10] In **chapter 2** we therefore aimed to evaluate whether β-blocker therapy is associated with a reduced incidence of angina or cardiovascular events when continued after revascularization. For this purpose we performed a post-hoc analysis of the IMAGINE (Ischaemia Management with Acupril post bypass Graft via Inhibition of angiotensin coNverting Enzyme) trial database which comprised of low-risk patients with normal cardiac function, randomized to quinapril or placebo early

after elective coronary artery bypass grafting (CABG) surgery for CAD. This trail allowed us to study the low risk subgroup where we do not have evidence to support the routine use of β-blockers after CABG.

In **chapter 3**, we sought to determine whether CABG reduces the propensity to develop HF in diabetic patients with CAD and preserved cardiac function. Patients with diabetes have a two-fold higher lifetime risk to develop HF.[11,12] This is often linked to the propensity of diabetic patients to develop CAD and MI. Diabetic patients are also more prone to HF in the absence of CAD. The underlying mechanism is not completely clarified but is suggested to include increased oxidative stress and glycosylation leading to the activation of detrimental signal transduction pathways (Figure 1).[13] Diabetes is an important risk factor for CAD and the extent of CAD is more severe in diabetic patients. This results in a higher frequency of MI and contributes to the two-fold higher lifetime risk to develop HF in diabetic patients (Figure1). Accordingly, CAD is treated aggressively in diabetic patients and the threshold for choosing CABG surgery over PCI is reduced.[14,15] However, whether CABG also reduces the propensity to develop HF in diabetic patients is unknown.

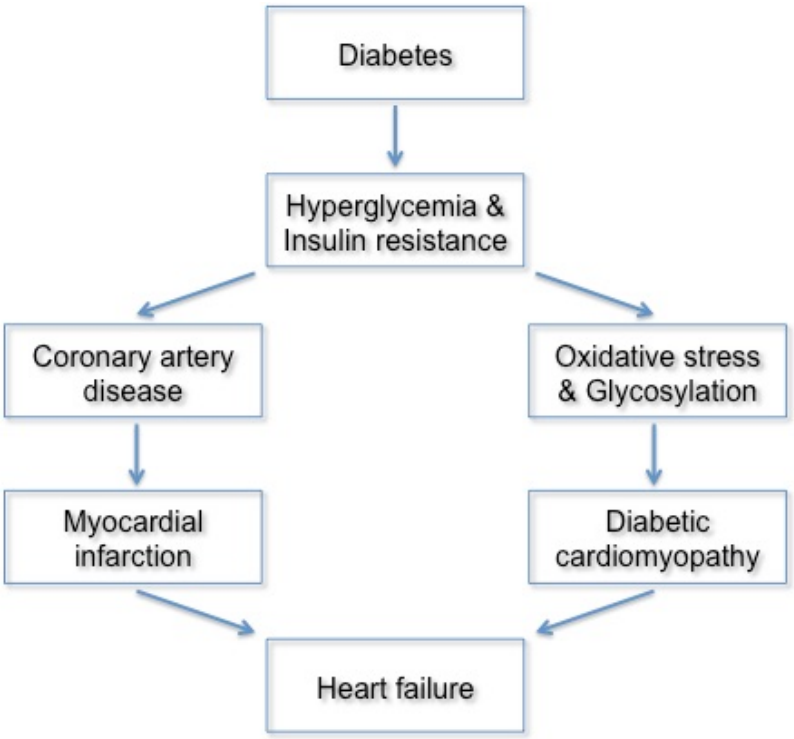

Figure 1 Pathophysiological links between diabetes and heart failure, adjusted from Dei Cas et al.[13]

AKIP1 in cardiac stress

Myocardial hypertrophy is the compensatory cardiac reaction to improve ventricular ejection performance after hemodynamic overload or injury. While initially myocardial hypertrophy reduces wall stress by restoring the ratio

between intracavitary pressure and wall thickness, it eventually decompensates and leads to HF.[16,17] This pathological hypertrophy is accompanied by a gene expression profile that resembles the embryonic heart.[18] Since it would be beneficial to only retain the adaptive aspects of physiological hypertrophy and prevent the deleterious collateral effects, we aim to determine what signaling pathways lead to hypertrophic decompensation. We previously performed genome wide transcription studies in a set of HF and hypertrophy models. We compared gene expression levels in 2 *in vivo* models (hypertension and post-MI) and 3 *in vitro* models in order to control for collateral differences in gene expression that are related to changes in hemodynamics rather than hypertrophic growth. One of the genes consistently upregulated was AKIP1.[19]

AKIP1 is a 21 kDa protein that was first identified as Breast Cancer Associatated gene 3 (BCA3). In the initial studies, AKIP1 was found to be upregulated in several cancer cell lines, to tweak NF-κB and PKA activity,[20,21] and promote the induction of apoptosis.[22,23] In contrast, AKIP1 stimulates neovascularisation and tumor growth in other malignancies.[24,25] Therefore, AKIP1 may have different roles, depending on cell type and clinical condition. We previously performed several gain- and loss of function experiments of AKIP1 in cultured cardiomyocytes and found that AKIP1 promoted physiological growth in these cells.[26] AKT-activation served as a mediator of AKIP1-induced physiological hypertrophy. Furthermore, we found that AKIP1 stimulates mitochondrial respiration while reducing mitochondrial ROS productions, arguably making respiration more efficient.[27] In **chapter 4** we will review in more detail how different aspects of metabolic dysfunction, like decreased energy supply and exacerbation of oxidative stress, lead to deteriorating HF. Another group found that AKIP1 attenuates ischemia / reperfusion (I/R) injury in *ex vivo* perfused hearts.[28] Together, this suggests that AKIP1 has a vital role in both acute and chronic cardiac stress and that interventions targeting AKIP1 could offer a viable strategy to treat patients with heart disease. To investigate this hypothesis, we generated a transgenic mouse line with cardiomyocyte specific overexpression of AKIP1. In **chapter 5 & 6** we describe our studies exploring whether cardiac overexpression of AKIP1 translates into beneficial effects on both acute and chronic cardiac insults *in vivo* and whether it modulates physiological hypertrophy (Figure2).

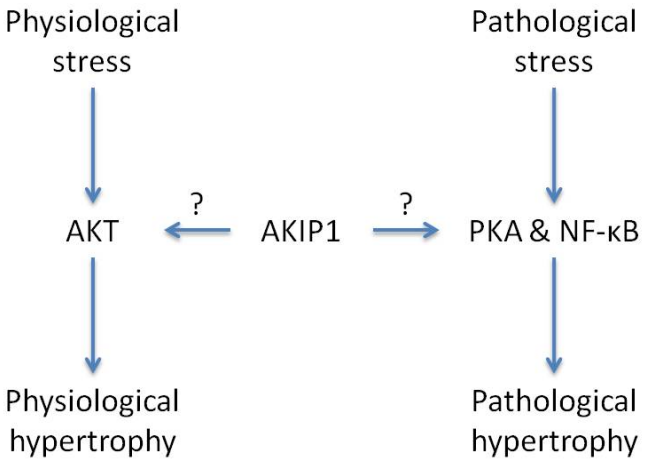

Figure 2 AKIP1 might influence cardiac hypertrophy development in response to different types of cardiac stress.

References

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30-41.
2. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25:1614-1619.
3. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-322.
4. Neubauer S The failing heart - an engine out of fuel. N Engl J Med 2007;356:1140-1151.
5. Bangalore S, Steg G, Deedwania P, et al. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308:1340-139.
6. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J 2012;33:1635-1701.
7. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
8. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur J Heart Fail 2012;14:803-869.
9. Lloyd-Jones DM, Wilson PW, Larson MG, Leip E, Beiser A, D'Agostino RB, Cleeman JI, Levy D. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. Arch Intern Med 2003;163:1966-1972.
10. Rouleau JL, Warnica WJ, Baillot R, et al. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation 2008;117:24-31.
11. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29-34.
12. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komaida M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, Euroheart Survey

Investigators. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-2736.
13. Dei Cas A, Fonarow GC, Gheorghiade M, Butler J. Concomitant diabetes mellitus and heart failure. Curr Probl Cardiol 2015;40:7-43.
14. Authors/Task Force Members, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013;34:3035-3087.
15. Habib RH, Dimitrova KR, Badour SA, Yammine MB, El-Hage-Sleiman AK, Hoffman DM, Geller CM, Schwann TA, Tranbaugh RF.CABG Versus PCI: Greater Benefit in Long-Term Outcomes With Multiple Arterial Bypass Grafting. J Am Coll Cardiol 2015;66:1417-1427.
16. Dorn GW 2nd. The fuzzy logic of physiological cardiac hypertrophy. Hypertension. 2007;49:962-70.
17. Westenbrink BD, Ling H, Divakaruni AS, Gray CB, Zambon AC, Dalton ND, Peterson KL, Gu Y, Matkovich SJ, Murphy AN, Miyamoto S, Dorn GW 2nd, Heller Brown J. Mitochondrial reprogramming induced by CaMKIIδ mediates hypertrophy decompensation. Circ Res 2015;116:e28-39.
18. Bernardo BC1, Weeks KL, Pretorius L, McMullen JR. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. Pharmacol Ther 2010 ;128:191-227.
19. Lu B, Yu H, Zwartbol M, Ruifrok WP, van Gilst WH, de Boer RA, Sillje HH. Identification of hypertrophy- and heart failure-associated genes by combining in vitro and in vivo models. Physiol Genomics 2012;44:443-454.
20. Gao N, Asamitsu K, Hibi Y, Ueno T, Okamoto T. AKIP1 enhances NF-kappaB-dependent gene expression by promoting the nuclear retention and phosphorylation of p65. J Biol Chem 2008;283:7834-7843.
21. Sastri M, Barraclough DM, Carmichael PT, Taylor SS. A-kinase-interacting protein localizes protein kinase A in the nucleus. Proc Natl Acad Sci USA 2005;102:349-354.
22. Leung TH, Ngan HY. Interaction of TAp73 and breast cancer-associated gene 3 enhances the sensitivity of cervical cancer cells in response to irradiation-induced apoptosis. Cancer Res 2010;70:6486-6496.
23. Zimmerman R, Peng DJ, Lanz H, Zhang YH, Danen-Van Oorschot A, Qu S, Backendorf C, Noteborn M. PP2A inactivation is a crucial step in triggering apoptin-induced tumor-selective cell killing. Cell Death Dis 2012;3:e291.
24. Lin C, Song L, Liu A, Gong H, Lin X, Wu J, Li M, Li J. Overexpression of AKIP1 promotes angiogenesis and lymphangiogenesis in human esophageal squamous cell carcinoma. Oncogene 2015;34:384-393.
25. Lin C, Song L, Gong H, Liu A, Lin X, Wu J, Li M, Li J. Nkx2-8 downregulation promotes angiogenesis and activates NF-kappaB in esophageal cancer. Cancer Res 2013;73:3638-3648.
26. Yu H, Tigchelaar W, Lu B, van Gilst WH, de Boer RA, Westenbrink BD, Sillje HH. AKIP1, a cardiac hypertrophy induced protein that stimulates cardiomyocyte growth via the Akt pathway. Int J Mol Sci 2013;14:21378-21393.
27. Yu H, Tigchelaar W, Koonen DP, Patel HH, de Boer RA, van Gilst WH, Westenbrink BD, Sillje HH. AKIP1 expression modulates mitochondrial function in rat neonatal cardiomyocytes. PLoS One 2013;8:e80815.
28. Sastri M, Haushalter KJ, Panneerselvam M, Chang P, Fridolfsson H, Finley JC, Ng D, Schilling JM, Miyanohara A, Day ME, Hakozaki H Petrosyan S, Koller A, King CC, Darshi M, Blumenthal DK, Ali SS, Roth DM, Patel HH, Taylor SS. A kinase interacting protein (AKIP1) is a key regulator of cardiac stress. Proc Natl Acad Sci USA 2013;110:E387-396.

Part 1
Metabolic interventions after revascularization