Summary

This aim of this thesis was to define mechanisms that modify cardiomyopathy pathophysiology. The most common cardiomyopathy, hypertrophic cardiomyopathy (HCM) is caused by mutations in genes encoding contractile proteins in the heart. But this causative mechanism is more complex than simply: gene mutation -> phenotype. For instance, the age of onset of disease varies a lot, even in patients with the same mutation. Some mutation carriers do not develop a phenotype at all. Clearly, there is more to HCM than only a mutation. This thesis focused on secondary disease triggers. In part I we focused on β-adrenergic receptor (β-AR) signalling in HCM (chapters 2-4). This pathway is part of the fight-or-flight response of the body and therefore one of the most important regulators of cardiac function. Dysregulation of this pathway is often seen in cardiac disease and we defined its role in HCM. We also studied the effect of exercise in a HCM model (chapter 4). Here we also studied the role of sex on HCM pathophysiology.

In the second part we developed a novel method to study cardiomyocyte function (chapter 5). This method allows us to mimic the pressure-volume loop of the whole heart, at the single cell level. This method was used to study the effect of a RBM20 mutation, associated with dilated cardiomyopathy (DCM). In rodents, this mutation leads to DCM with impaired systolic function, while exercise capacity is increased. We studied active and passive force development in this model to explain these aberrant findings.