Familial hypertrophic cardiomyopathy (FHC) is one of the most frequently hereditary heart diseases and is associated with mutations in many sarcomeric proteins like cardiac Troponin I (cTnI). An early symptom of FHC is an impaired filling of the heart, diastolic dysfunction. In our institute, a transgenic mouse model carrying the FHC-associated mutation ΔK184 was established. Hearts of transgenic mice developed signs of diastolic dysfunction such as slowed down left ventricular pressure decay and enhanced enddiastolic pressure (Blaudeck *et al*., unpublished). At myofibrillar level it was shown that ΔK184 slows down the kinetics of myofibrillar relaxation and Ca^{2+}-controlled switch-off kinetics of troponin (cTn) significantly (Iorga *et al*., 2008) which was suggested to underlay the development of diastolic dysfunction.

We could show that not only ΔK183, but also the FHC-associated mutation R145G slows down switch-off kinetics of incorporated cTn. To test whether a slowed down switch-off kinetics is associated with FHC-linked cTnI-mutations in general, switch-off kinetics of other FHC-associated mutations was analysed in the first part of this study. While R21C slows down switch-off kinetics of incorporated cTn, R162W and G203 have no effect on the switch-off. The switch-on kinetics of incorporated cTn is slowed down by R162W, but not by R21C, R145G, ΔK183 und G203S. Under rigor conditions, where the crossbridges are strongly bound on actin, the retarding effect of R162W is even enhanced, whereas the effects of the other mutations on the switch-off kinetics are similar to those with ATP. The same effect could be shown on isolated cTn, where the retarding effect of R162W is further enhanced compared to incorporated cTn. Furthermore, R21C shows a slowed-down switch-on kinetics under isolated conditions, which is lost by incorporation in the sarcomer. In conclusion a slowed down switch-off kinetics seems not to be a general phenomenon of FHC-linked cTnI-mutations. The results suggest that the localisation of the mutations and the interaction of the specific regions within the cTn seem to play an important role on the effects of the mutations on the switch kinetics of cTn.

A slowed down switch-off kinetics could change the intracellular Ca^{2+}-transients. To determine the effects of FHC-associated cTnI-mutations on the Ca^{2+}-transients, construction of an adeno-associated virus vector (AAV) was the second part of this study. This AAV carries the FHC-associated mutations R21C, R145G, R162W, ΔK183 and G203S, respectively in combination with a heart-specific promotor. In parallel cultivation of cardiomyocytes of the rat was established. Ca^{2+}- transients should be

measured after successful transfection of the cardiomyocytes with the AAV, respectively. This was not possible during the time frame of this study.

The third aim of the study was to determine directly the Ca^{2+}-transients of cardiomyocytes of transgenic $cTnI^{\Delta K184}$-mice by using the Ca^{2+}-indicator Fura-2 AM. Furthermore, it was tested if there is a correlation between the mutation and aging by using mice in the age of 2 month and 2 years. While the rate of fluorescence decay and the fluorescence amplitude are unchanged by the mutation, there is a strong tendency for an enhanced minimal fluorescence with increasing stimulation frequency in transgenic and old mice. The enhanced minimal fluorescence points to an enhanced basal Ca^{2+}-concentration at higher stimulation frequencies. This could promote or enforce diastolic dysfunction at higher frequencies of the heart.

Analysis of the phenotype of the transgenic mouse model ΔK184 showed left atrial hypertrophy and atrial fibrosis (Blaudeck *et al*., unpublished). By ECG a prolonged spread of atrial depolarisation indicated by a prolonged P-wave in an otherwise normal electrocardiogram was obtained. In the forth part of this study contractile parameter of left and right atria of transgenic and non-transgenic mice were studied in the organ bath. Force generation was analysed under standard terms and different stimulating and inhibiting protocols. Left atria of transgenic mice developed less force than their non-transgenic littermates, while for right atria it is the other way round. Time constant of relaxation (τ) is slowed down by the mutation. The influence of sympathicus and parasympathicus was analysed by incubation of right atria with several agonists and antagonists. It was shown that sympathic and parasympathic signal transduction is mainly unchanged by the mutation. Evidence for a changed expression or function of Na^{+}-Ca^{2+}-exchanger was determined by changes in the outer Ca^{2+}-concentration and the use of different stimulation protocols.