

## 7 Summary

*Nadine Ehrenberg: Gender-differences in cardiac extracellular matrix remodeling through voluntary cage wheel running and after myocardial infarction in mice*

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Cardiovascular diseases, especially the myocardial infarction, are the major cause of death in industrialized countries. Incidence and mortality show obvious gender-differences. Until menopause, women rarely have myocardial infarctions and mortality is also low. Postmenopausal however, the risk adapts quite fast and incidence and mortality rise. The protective antiarterosclerotic effect of estrogen is one of the most discussed reasons for this gender-difference, though the exact pathways remain unsolved. The reasons for the higher mortality in males are at least in the mouse model more fatal cardiac adaptations in extracellular matrix remodeling. Male mice show a more pronounced lymphocyte migration and collagen degradation, which is jointly responsible for the higher rate of cardiac rupture. Of great influence are the matrix metalloproteinases (MMP) and their endogenous inhibitors the Tissue inhibitors of matrix metalloproteinases (TIMP), respectively their imbalance. An exaggerated matrix/collagen degradation promotes the risk for ventricular rupture and advances dilatation, while an augmented collagen accumulation increases myocardial stiffness and leads to a restricted pumpfunction.

The protective role of exercise prior to or after myocardial infarction has been described previously. The mechanisms, though, have not been fully understood and it seems as if in women, sport was a better protector against a first myocardial infarction than in men. The present study was done as a foundation for a model investigating the gender-differences in terms of the protective effects a moderate exercise program has on cardiac remodeling after myocardial infarction. The gender-differences concerning this matter have not been investigated in the animal model before. To gain basic knowledge, a model of myocardial infarction and one of voluntary cage wheel running was studied.

In the model of myocardial infarction mortality and left ventricular rupture rate were higher in males. They also showed a more restricted myocardial compliance in diastole, which caused a more severe loss of cardiac pumpfunction. At least in parts the more pronounced fibrosis of the non infarcted areas seems responsible, leading to an augmented cardiac stiffness and greater insufficiency. The higher relative geneexpression of procollagen I and III was only significantly higher in male mice when compared to the sexmatched control group. This was the first study to show that in the mouse-model 14 days post-infarction the relative geneexpression of MMP-9 had returned to baseline and that MMP-2 was still elevated. Apart from MMP-9 and TIMP-4, all other genes were markedly higher after myocardial infarction. The mRNA-expressionlevels of all measured genes after the infarction were almost exactly alike between the two sexes.

The voluntary cage wheel running was chosen as an exercise model, because it is a stressless alternative to commonly used treadmill and swimming models. Besides it is known, that voluntary and involuntary trainingmodels regulate a different set of genes.

In the model of voluntary cage wheel running, female mice showed a higher activity and more pronounced cardiac hypertrophy for every kilometer they ran. A greater hypertrophy reserve is discussed. While the body weight of the female running mice increased mostly over the training period, trained males had a significantly lower body weight and higher heart rate than their sedentary controls. One can proceed from the assumption that this is a symptom of greater stress male mice have shown to suffer during isolated housing. They

react in a characteristically hyperactive way, leading to restlessness and an increased consumption of energy.

The relative expressions of genes involved in extracellular matrix remodeling indicate a sexspecific, training-dependent mRNA-expression especially of procollagen III, MMP-2 and TIMP-1. Of all changes only the higher TIMP-1 Level in males was significant. It seems that exerciseduration and –intensity are too low for these tendencies to reach significance.

Based on this and other data a follow-up study can analyze the gender-differences of the protective role a moderate sportsprogram has on cardiac remodeling after myocardial infarction. Of special interest is if the training reduces or increases the gender-differences in functionloss, mortality, the amount of interstitial collagen and capillarydensity. To analyze the genexpression contributes fundamental knowledge and helps to understand the processes in myocardium after infarction.