



Effects of sex on skeletal muscle phenotype in heart failure patients

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Patients with heart failure and reduced ejection fraction (HFrEF) demonstrate skeletal muscle defects which limit quality of life and predict mortality (Fulster et al., 2013, von Haehling et al., 2020). Males show a pathological fibre type shift and reduced capillarity that are closely linked to the main symptom of exercise intolerance (Sullivan et al., 1990), but whether females show the same trend is poorly defined. This study aimed to investigate sex-specific differences in the skeletal muscle phenotype of male and female patients with HFrEF.

Immunohistochemical staining for muscle fibre properties and RT-qPCR for genes involved in atrophy were measured in pectoralis major biopsies from male (n=16) and female (n=16) HFrEF patients between 60 and 90 years old. Patients had a left ventricular ejection fraction $\leq 40\%$, NYHA functional class between I and III, and were compared to age-matched controls (male n=17 and female n=16). Two-way ANOVA was performed to assess the interaction between the sex and disease.

There was an interaction between sex and disease on fibre proportions (type I and type IIa) and capillarity ($p < 0.05$). An interaction between sex and disease was found for the pro-growth gene IGF1 ($p < 0.05$), while atrophy-related gene expression was reduced ($p < 0.05$) in females compared to males for MuRF1, MAFbx, ubiquitin, myostatin, autophagy related 7, and LC3.

In conclusion, these preliminary data show that type I fibre proportion and capillarity are increased in females with HFrEF, but decreased in males with HFrEF relative to sex- and age-matched controls, while differences were also found in the expression of genes known to regulate muscle mass. This supports evidence for sexual dimorphism in patients with HFrEF in relation to the skeletal muscle pathology, which may explain clinical differences in symptoms and treatment outcomes observed between sexes.

Fulster, S., Tacke, M., Sandek, A., Ebner, N., Tschope, C., Doehner, W., Anker, S.D. and Von Haehling, S. 2013. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *European Heart Journal*. 34(7), pp.512-519.

von Haehling, S., Garfias Macedo, T., Valentova, M., Anker, M. S., Ebner, N., Bekfani, T., Haarmann, H., Schefold, J. C., Lainscak, M., Cleland, J., Doehner, W., Hasenfuss, G., and Anker, S. D. 2020. Muscle wasting as an independent predictor of survival in patients with chronic heart failure. *Journal of Cachexia, Sarcopenia and Muscle*. 11(5), pp.1242–1249.

Sullivan, M.J., Green, H.J. and Cobb, F.R. 1990. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation*. 81(2), pp.518-527.