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Sex-related differences in the outcome of congestive heart failure: study on rats treated with ACEi alone or combined with soluble epoxide hydrolase inhibitor

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Introduction: In search for new therapeutic measures of congestive heart failure (CHF) attention focused on the role of epoxyeicosatrienoic acids (EETs), cytochrome P450-dependent epoxygenase pathway metabolites of arachidonic acid, with antihypertensive and organ-protective actions. The EETs are rapidly broken-down by soluble epoxide hydrolase (sEH). Blocking sEH and increasing tissue EETs bioavailability had antihypertensive and cardio- and renoprotective effects. The studies of the biological mechanisms underlying the sex-related differences in the CHF and in the responses to new pharmacological measures are missing. The rat model in which CHF is induced by volume overload by creation of the aortocaval fistula (ACF) is recommended for preclinical studies by American Heart Association. It has been noticed that the hypertensive rat transgenic for the mouse Ren-2 renin gene (TGR) presents a unique angiotensin II-dependent model of hypertension. We found that male ACF TGR displayed tissue deficiency of EETs, and increasing intrarenal EETs levels by pharmacological blockade of sEH attenuated the progression of CHF in male ACF TGR. However, we did not examine if this effect occurs also in female ACF TGR.

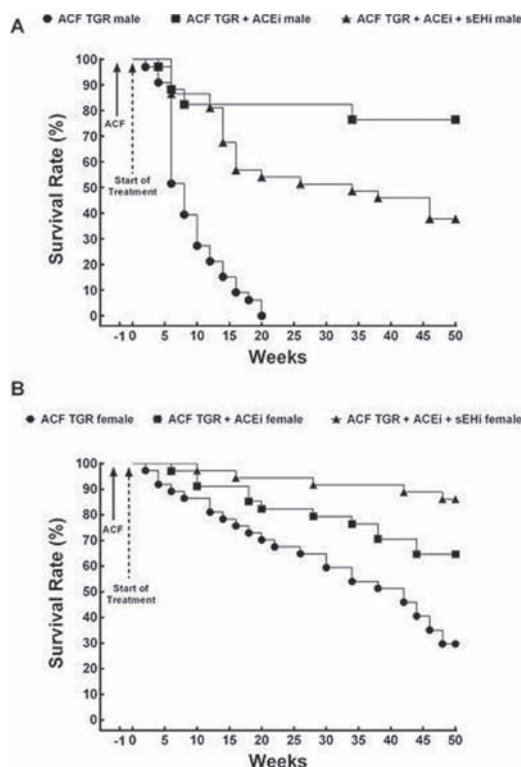
Purpose: The aim was to establish if sex-related differences, if present, are demonstrable with standard treatment with ACEi alone and with the combined treatment with ACEi and sEH.

Methods: Male and female TGR rats were randomly assigned either to ACF procedure or to sham-operation. One week after the procedure rats

were divided into the 8 experimental groups (sham-operated male TGR + placebo, ACF male TGR + placebo, ACF male TGR + ACEi, ACF male TGR + ACEi + sEH, sham-operated female TGR + placebo, ACF female TGR + placebo, ACF female TGR + ACEi, ACF female TGR + ACEi + sEH). C-AUCB was used as an sEH and trandolapril as ACEi, both in drinking water in doses previously tested. The follow-up period was 50 weeks and the primary end-point was death from any cause.

Results: All sham-operated male and female TGR survived until the end of experiment. All untreated male ACF TGR animals died by week 20. In contrast, untreated female ACF survived in the rate of 32%. The treatment with ACEi improved survival rate similarly in male as well as female ACF TGR (74% and 65%). The combined treatment with ACEi and sEH worsened the survival in male ACF TGR as compared with ACF TGR + ACEi (38%). In contrast, the combined treatment with ACEi and sEH in female ACF TGR significantly improved the course and the final survival rate (84%) as compared with female ACF TGR + ACEi alone.

Conclusions: The study suggests that in CHF individuals in whom hypertension and increased RAS activity run in parallel, the patients' sex is the co-determinant of CHF progression. In particular it can influence the effectiveness of the therapeutic measures applied to slow it down. Therefore, in pre- and clinical studies the sex-related differences should be seriously considered.



Picture 1