



# Evidence of hypertension and cardiac remodeling found in male TPH2 knockout rats compared to females

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## ABSTRACT

Hypertension (HT) is associated with significant comorbidities including heart failure (HF), the leading cause of death in the US. HT and HF occur more frequently in young men compared to age-matched females. 5-hydroxytryptamine (5-HT) has been implicated in the control of blood pressure. Male rats deficient in tryptophan hydroxylase 2 (TPH2), the rate limiting enzyme in central 5-HT synthesis, are hypertensive at rest; a phenotype that is less severe in females. We sought to determine if 5-HT plays a role in cardiac remodeling. We hypothesized there would be evidence of cardiac remodeling only in male rats lacking TPH2 and that females would be protected. Heart enlargement and increased fibrosis are signs of tissue remodeling indicating the presence of HF. Heart size and left ventricle wall thickness was measured using echocardiogram analysis. Post mortem, tibia lengths (TL) were measured with a digital caliper and hearts were weighed. Evidence of an enlarged heart was determined by comparing heart weight (HW) to TL. Cardiac tissue was collected from the left ventricle. Signs of cardiac tissue remodeling and fibrosis was determined by qPCR. We assessed changes in expression of remodeling proteins such as collagen type I and III, MMP2, MMP9, TIMP1, and TIMP4. Increased expression of collagen is indicative of fibrosis. MMP2 and 9 are enzymes that break down the extracellular matrix; TIMP1 and 4 inhibit MMP enzymes. In preliminary data, we found no significant difference in HW:TL in females (WT 1.85 +/- 0.10, KO 2.12 +/- 0.11), but found significant differences in the males (WT 2.38 +/- 0.11, KO 2.76 +/- 0.04). The KO male HW:TLs were significantly greater ( $P < 0.05$ ) than WT male. This indicates 5-HT is involved in cardiac remodeling in males whereas females are protected.

## BACKGROUND

- HT and HF occur more frequently in young men compared to females.
- Central 5-HT has been implicated in the control of blood pressure.
- Male and female rats deficient in TPH2, the rate limiting enzyme in central 5-HT synthesis, have increased mean arterial pressure (MAP) at rest.

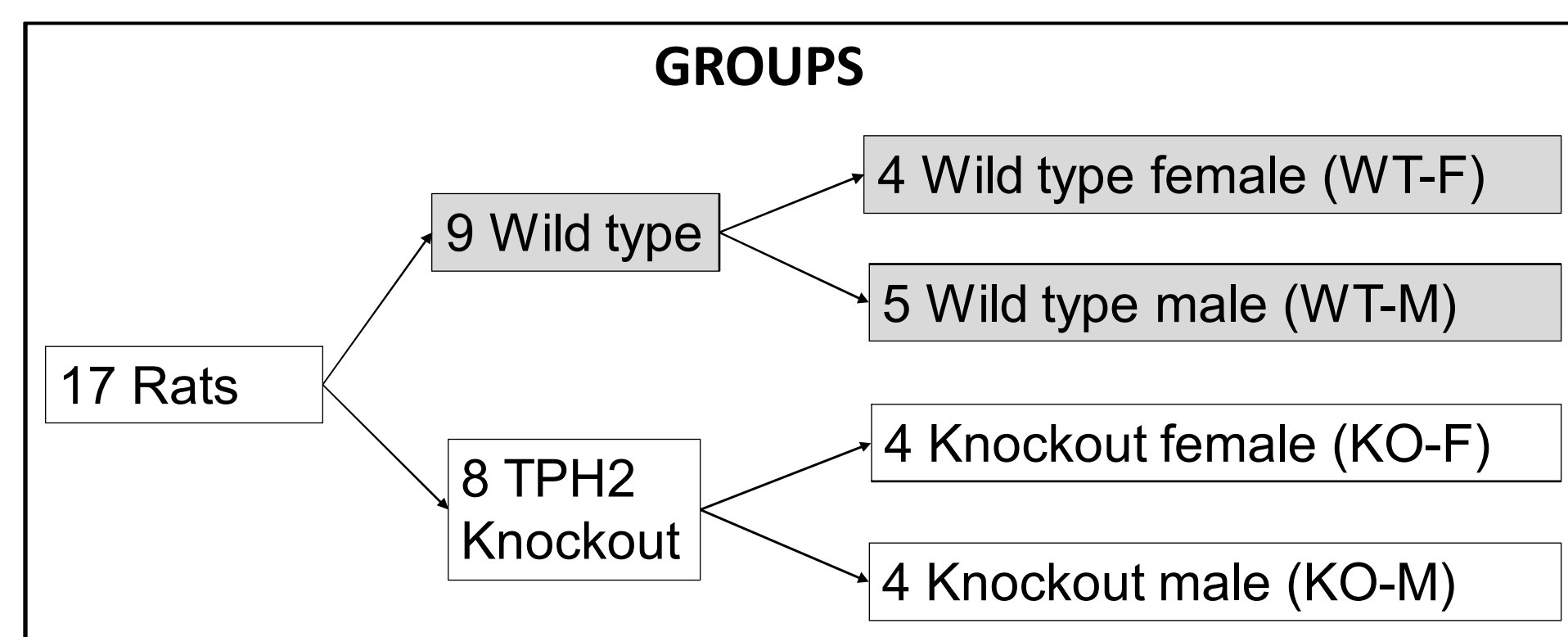
## PURPOSE

- Determine if central 5-HT plays a role in cardiac remodeling.
- Determine if there's a difference in cardiac tissue between male and female TPH2 KO rats.

## HYPOTHESIS

We will find evidence of cardiac remodeling in male rats lacking central 5-HT, but not in females.

## METHODS



- All functional and tissue data was collected at 7-8 months of age.
- Transthoracic echocardiography was performed and analyzed using EchoPac software.
- qPCR was used to determine expression of protein mRNA involved in cardiac tissue remodeling.
- Collagen and protein assays were performed to reveal the respective content in the cardiac tissue.

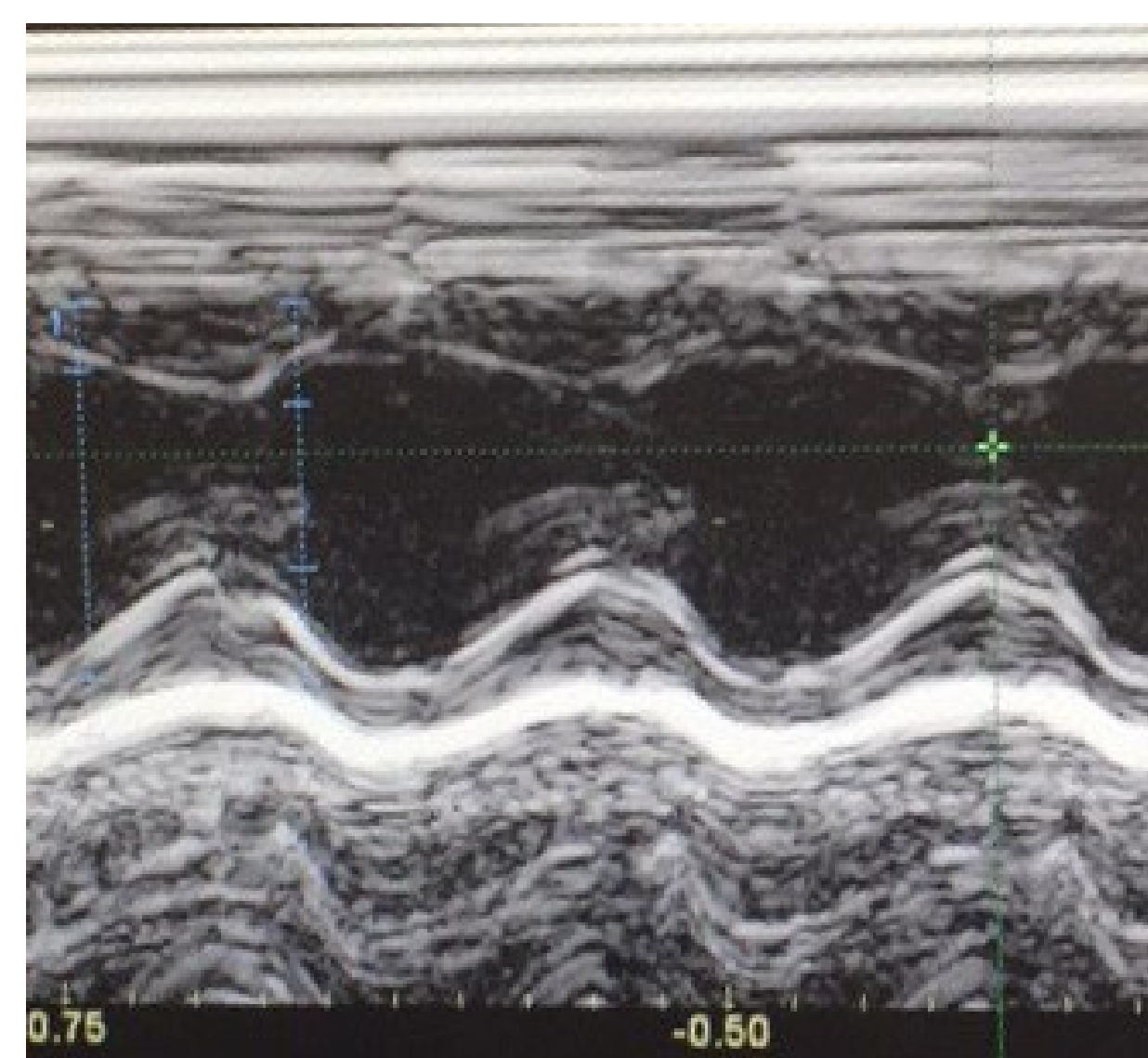


Figure 1. M-mode image of rat transthoracic echocardiogram.

## RESULTS

Table 1. LV function

	WT-F	KO-F	WT-M	KO-M
HR (bpm)	410 ± 14	443 ± 22	431 ± 6	443 ± 11
MAP (mmHg)	111 ± 3	121 ± 5	114 ± 2	125 ± 4
SV (μL)	298 ± 81	320 ± 34	332 ± 70	447 ± 67
FS (%)	48 ± 7	42 ± 5	44 ± 2	40 ± 4
IVRT (ms)	12 ± 1	11 ± 1	13 ± 1	12 ± 1

HR: heart rate, MAP: mean arterial pressure, SV: stroke volume, FS: fractional shortening, IVRT: isovolumic relaxation time. MAP main effect of KO ( $P < 0.05$ ).

## RESULTS

### Physical Characteristics

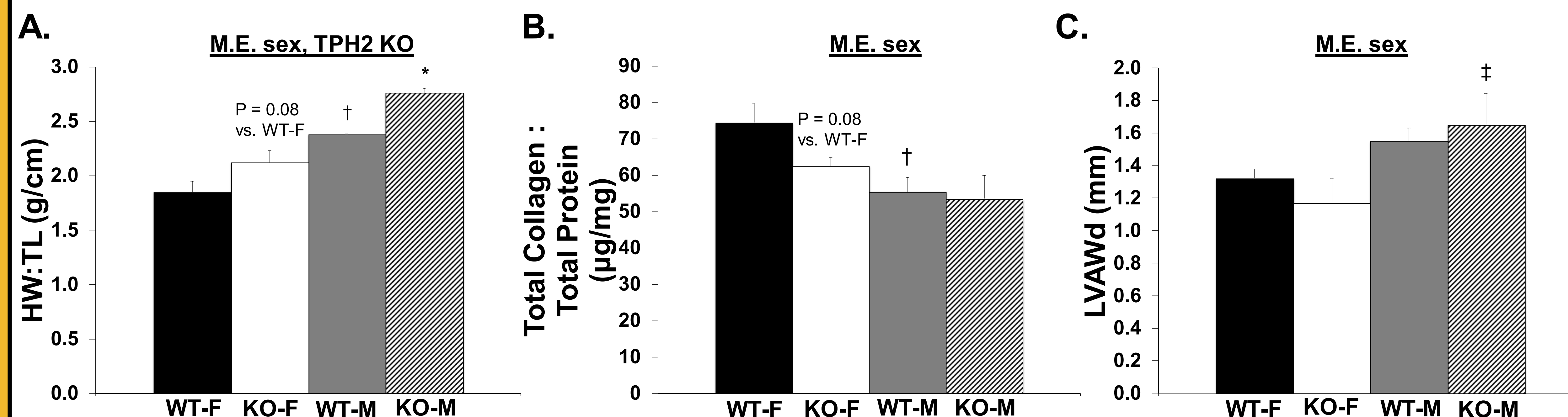


Figure 2. **A**, heart weight (HW) to tibia length (TL) ratio was increased in males and in TPH2 knockouts (main effect of sex and main effect of TPH2 KO,  $P \leq 0.006$ ). **B**, Total collagen to total protein ratio in LV tissue was decreased in males (main effect of sex,  $P < 0.05$ ). **C**, Left ventricular anterior wall thickness during diastole (LVAWd) was increased in males (main effect of sex,  $P = 0.01$ ). \* $P < 0.05$  KO-M vs. WT-M, † $P < 0.05$  WT-M vs. WT-F, ‡KO-M vs. KO-F.

### qPCR

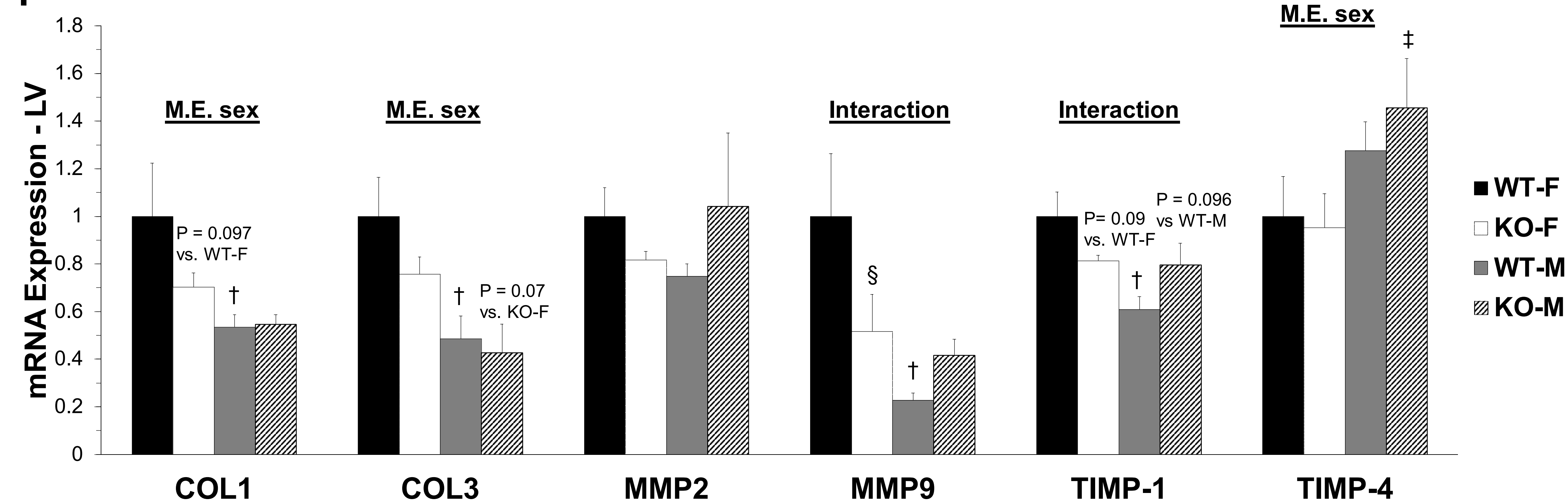


Figure 3. COL1 and COL3 are decreased in males (main effect of sex,  $P < 0.02$ ). No significant differences found in MMP2 protein ( $P > 0.05$ ). MMP9 and TIMP1 were decreased in response to an interaction between sex and TPH2 knockout (sex x TPH2 KO interaction,  $P \leq 0.05$ ). TIMP-4 was increased in males (main effect of sex,  $P = 0.03$ ). † $P < 0.05$  WT-M vs. WT-F, ‡KO-M vs. KO-F, § $P < 0.05$  KO-F vs. WT-F.

## SUMMARY

Central 5-HT and sex both have effects on hemodynamics, HW:TL, and the regulation of extracellular matrix proteins. This implies that cardiac remodeling is influenced by central nervous system 5-HT levels in males and females.