Sex-linked differences in cardiac atrophy after mechanical unloading induced by heterotopic heart transplantation

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IKEM

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Brief Introduction

- **Heart Failure** – syndrome- where the heart is unable to meet proper physiologic tissue requirements
- **Ever increasing incidence**
  - 2% of the world population
  - 10% + of adults over 75
  - Sex related differences
    - Etiology

Heart Transplantation vs. LVAD

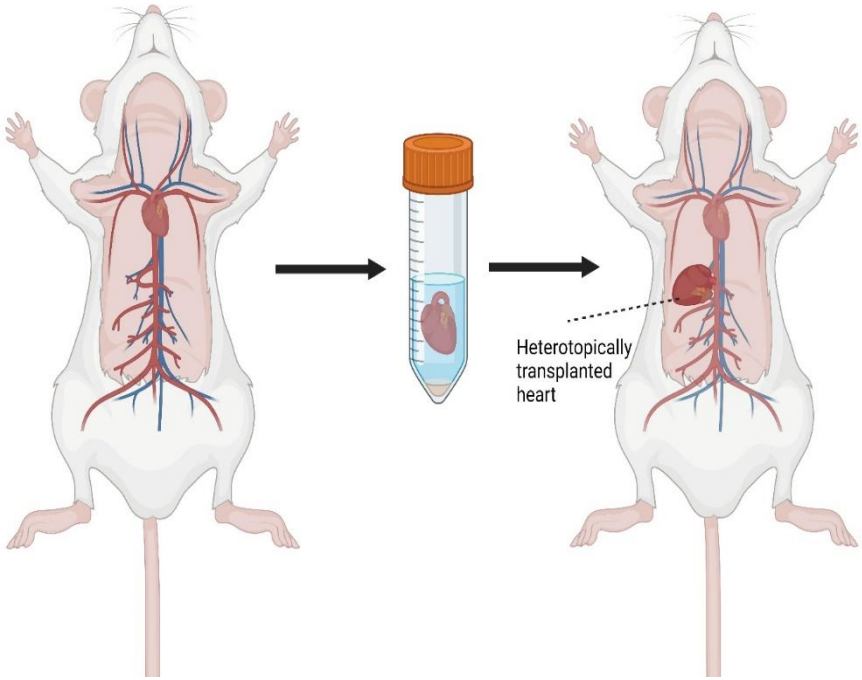
- **Heart transplantation (HT_x)** is still the **GOLD STANDARD** of treatment in Heart Failure
- HT_x is limited due to a **scarcity** of quality organ donors**.**
- **Implantation of left ventricle assist devices (LVAD)** has emerged as an alternative treatment for patients with end-stage HF.
- **Most harmful effect** of long-term LVAD-induced mechanical unloading of the myocardium is **cardiac atrophy**

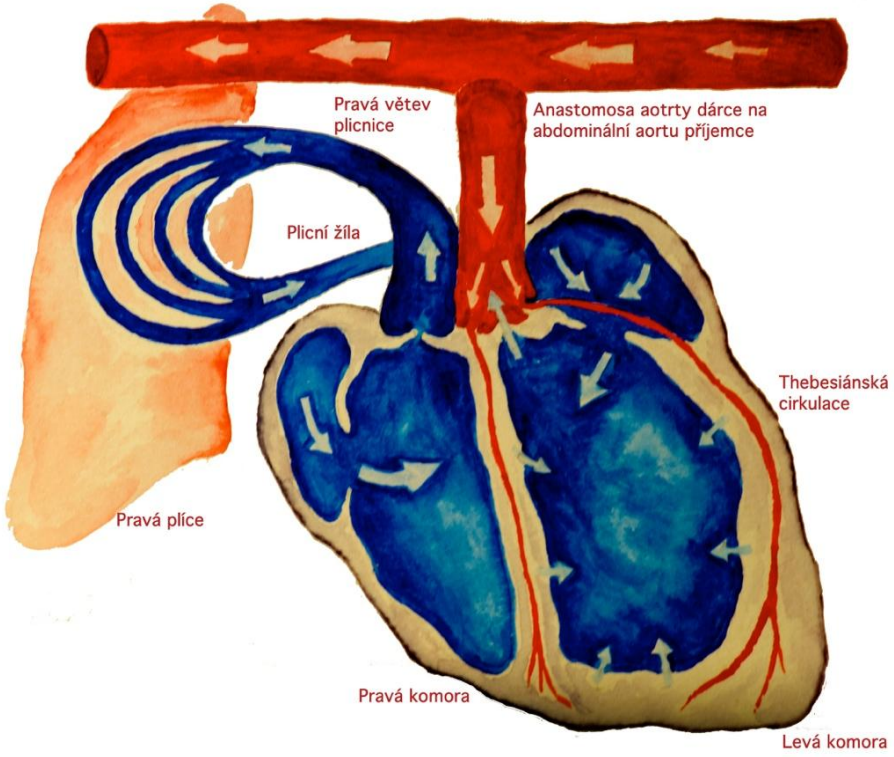
Goal of our Study

- **Limitations of Previous Studies - all previous studies were all performed in male animals only**
- **What degree of sex-related differences are present during the course of cardiac atrophy after heterotopic HT_x**
- **Clinical Extrapolation – differences in treatment ??**

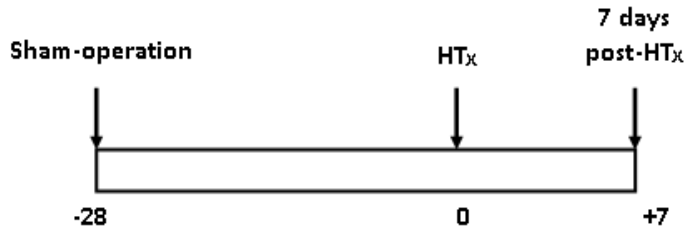
Heterotopic HTx in laboratory Rat

- IKEM
  - **Used by prof. Kolář (preformed approx. 35 years ago)**
  - **MUDr. Martin Pokorný, Ph.D and Ing. Iveta Mrázová (from 2012)**

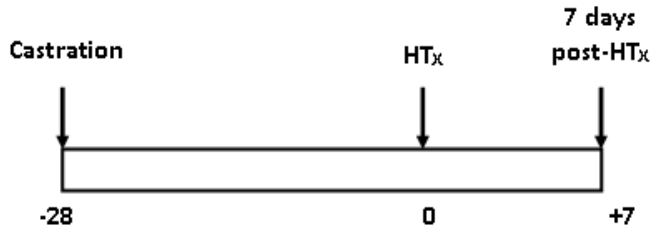




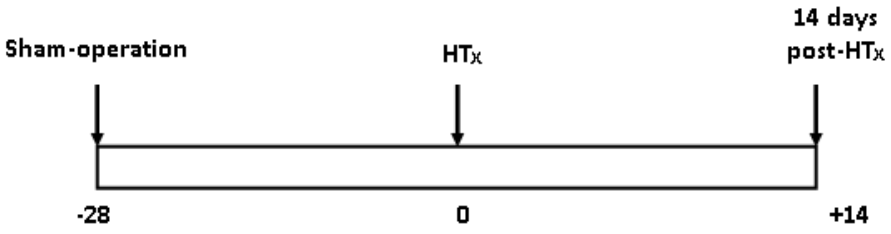
Methods



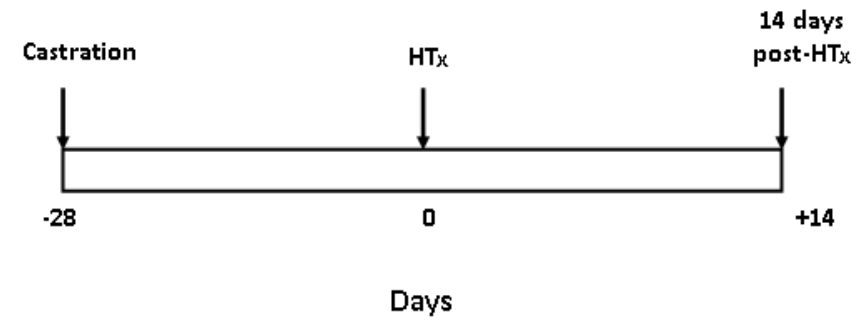
Intact recipient + HT_X of healthy heart



Castrated recipient + HT_X of healthy heart



Intact recipient + HT_X of healthy heart

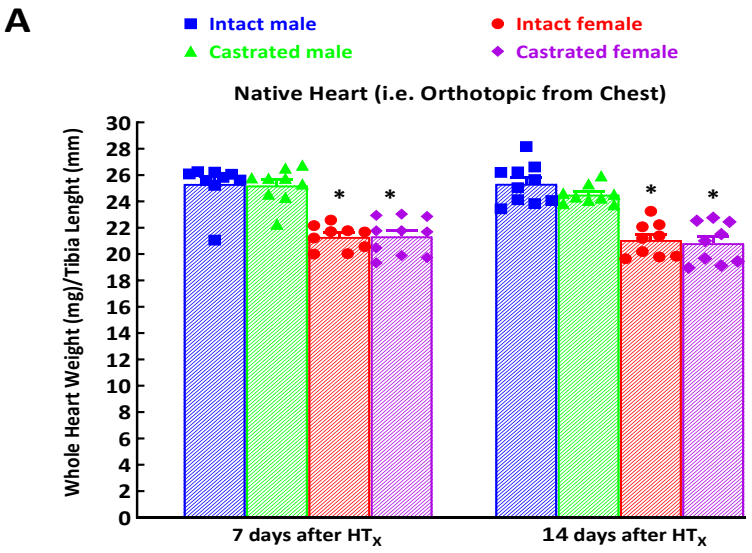


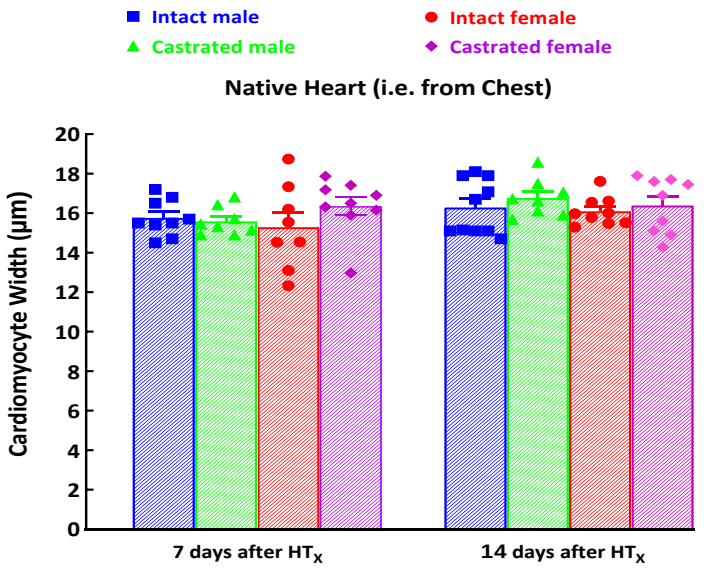
Castrated recipient + HT_X of healthy heart

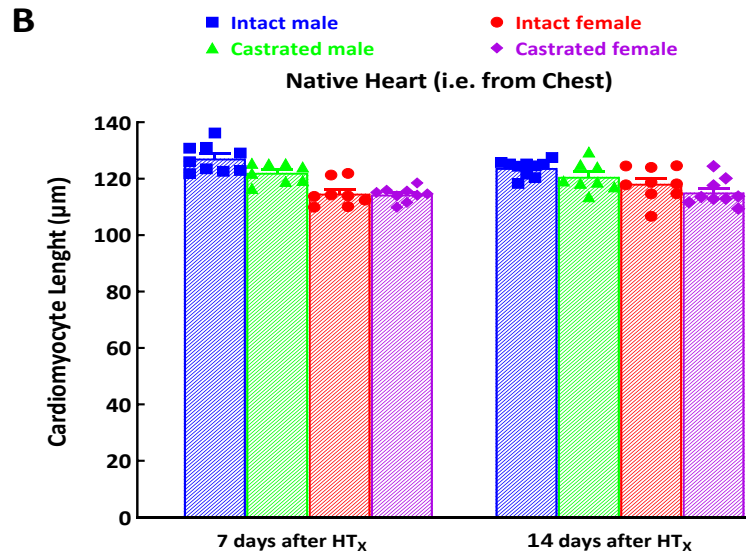
Experimental Groups

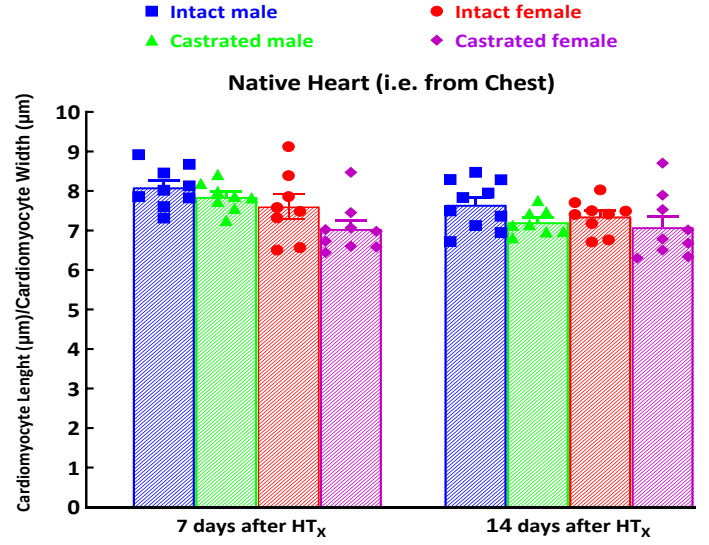
1. **Sham-operated male Lewis rats (recipient) + HT_x of healthy donor´s heart (7 days after HT_x) (n = 9),**
2. **Sham-operated male Lewis rats + HT_x of healthy donor´s heart (14 days) (n = 10),**
3. **Castrated male Lewis rats + HT_x of healthy donor´s heart (7 days) (n = 9),**
4. **Castrated male Lewis rats + HT_x of healthy donor´s heart (14 days) (n = 9),**
5. **Sham-operated female Lewis rats + HT_x of healthy donor´s heart (7 days) (n = 9),**
6. **Sham-operated female Lewis rats + HT_x of healthy donor´s heart (14 days) (n = 9),**
7. **Castrated female Lewis rats + HT_x of healthy donor´s heart (7 days) (n = 10),**
8. **Castrated female Lewis rats + HT_x of healthy donor´s heart (14 days) (n = 9).**

Results

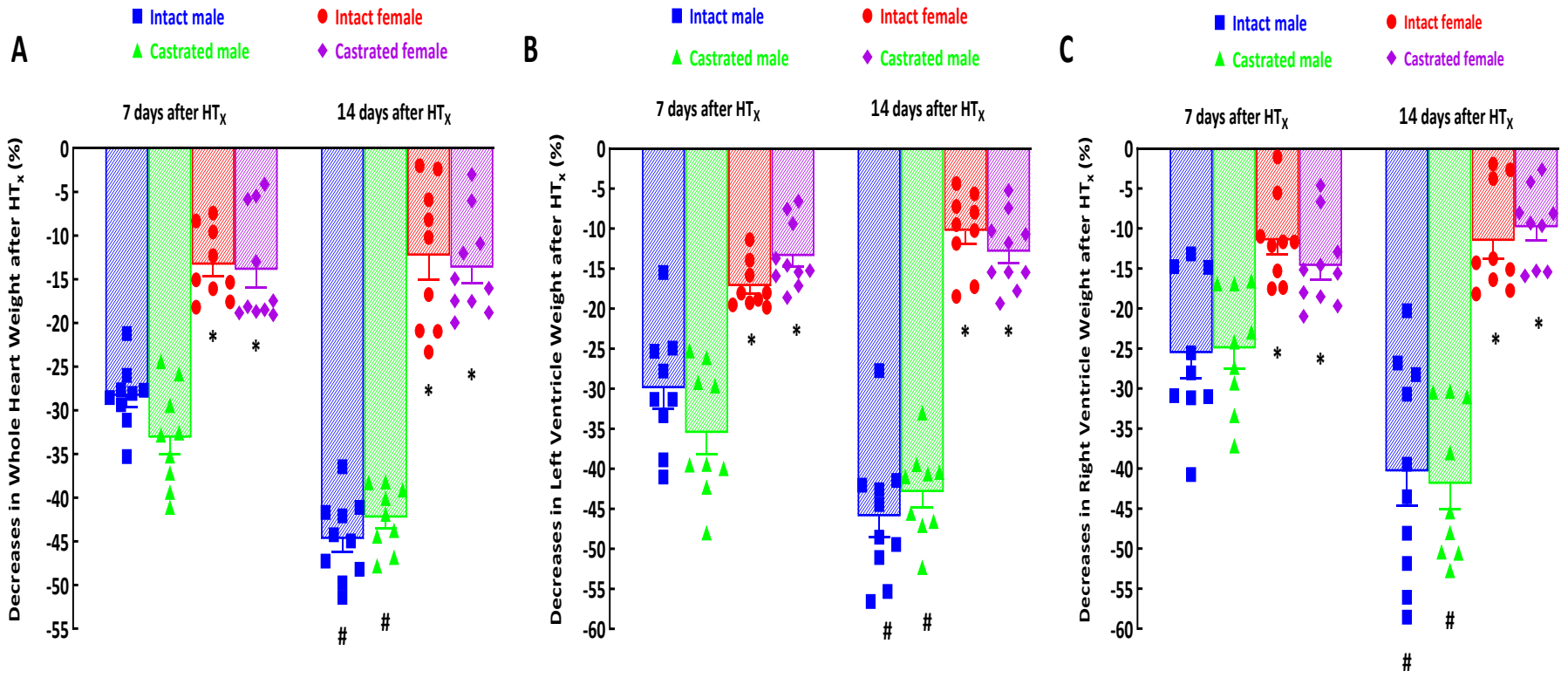

A
Intact male
Intact female
Castrated male
Castrated female
Native Heart (i.e. Orthotopic from Chest)
Whole Heart Weight (mg)/Tibia Lenght (mm)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
*
*
*
*
7 days after HTX
14 days after HTX


C
Intact male
Intact female
Castrated male
Castrated female
Native Heart (i.e. from Chest)
Cardiomyocyte Width (µm)
0
2
4
6
8
10
12
14
16
18
20
7 days after HTX
14 days after HTX

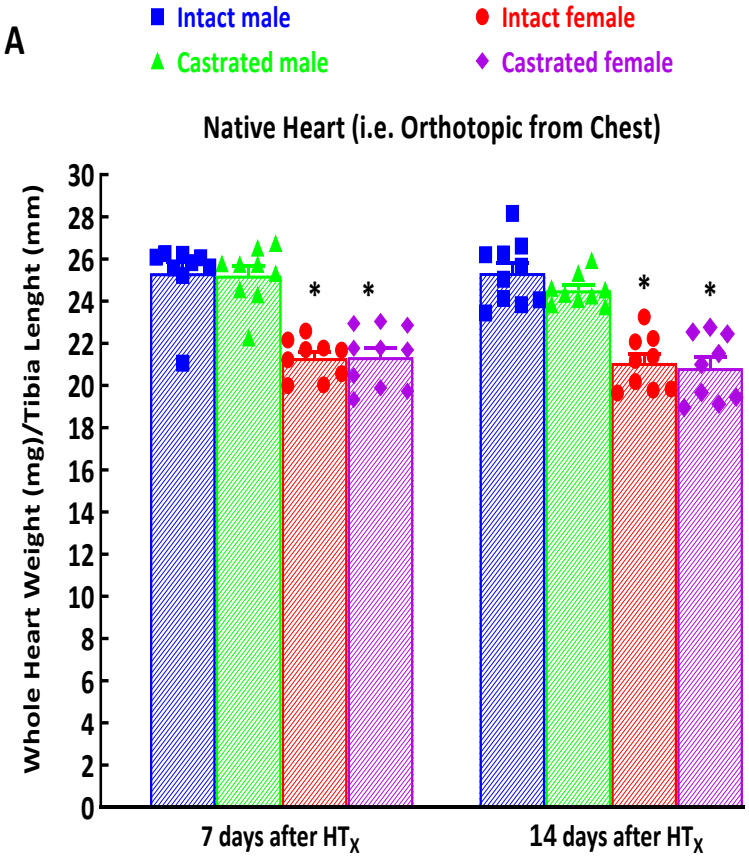

B
Intact male
Intact female
Castrated male
Castrated female
Native Heart (i.e. from Chest)
Cardiomyocyte Lenght (µm)
0
20
40
60
80
100
120
140
7 days after HTX
14 days after HTX

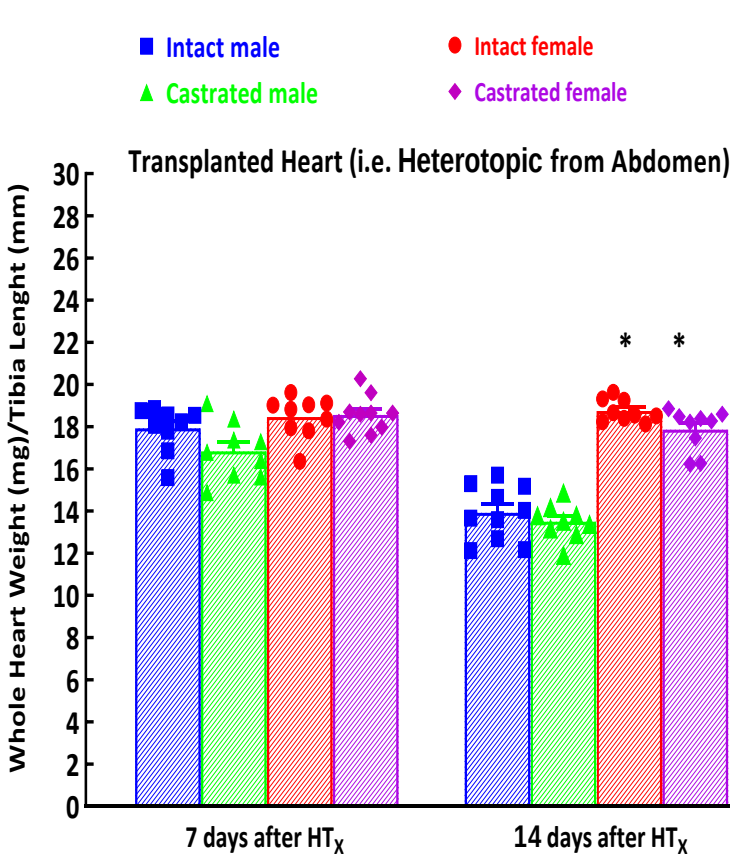

D
Intact male
Intact female
Castrated male
Castrated female
Native Heart (i.e. from Chest)
Cardiomyocyte Lenght (µm)/Cardiomyocyte Width (µm)
0
1
2
3
4
5
6
7
8
9
10
7 days after HTX
14 days after HTX

Results

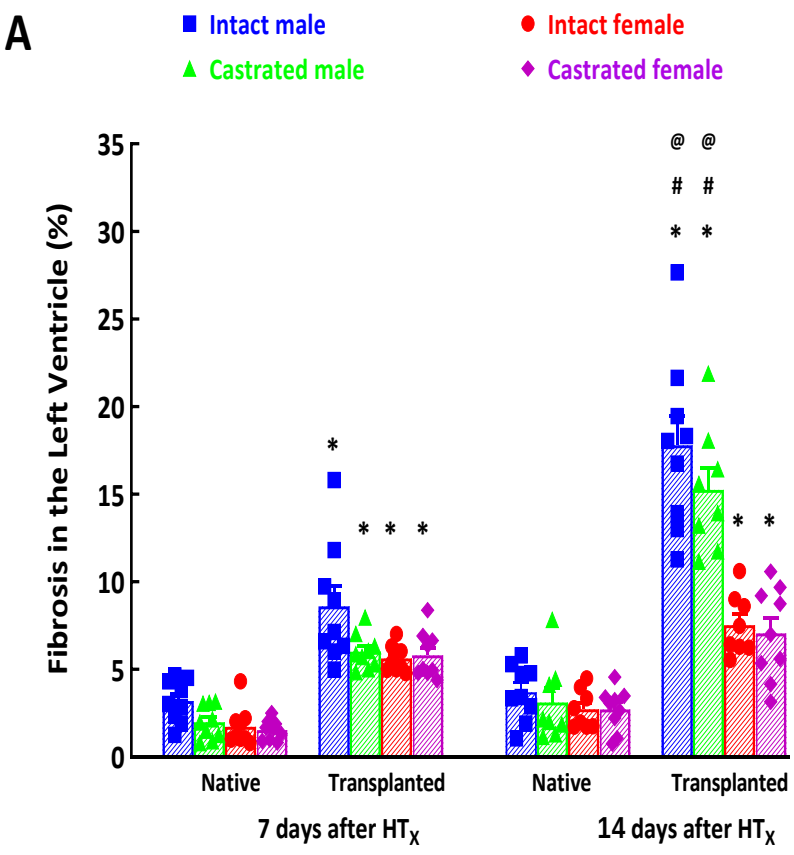

A
B
C
Intact male
Intact female
Castrated male
Castrated female
7 days after HTX
14 days after HTX
Decreases in Whole Heart Weight after HTx (%)
Decreases in Left Ventricle Weight after HTx (%)
Decreases in Right Ventricle Weight after HTx (%)
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
*
#

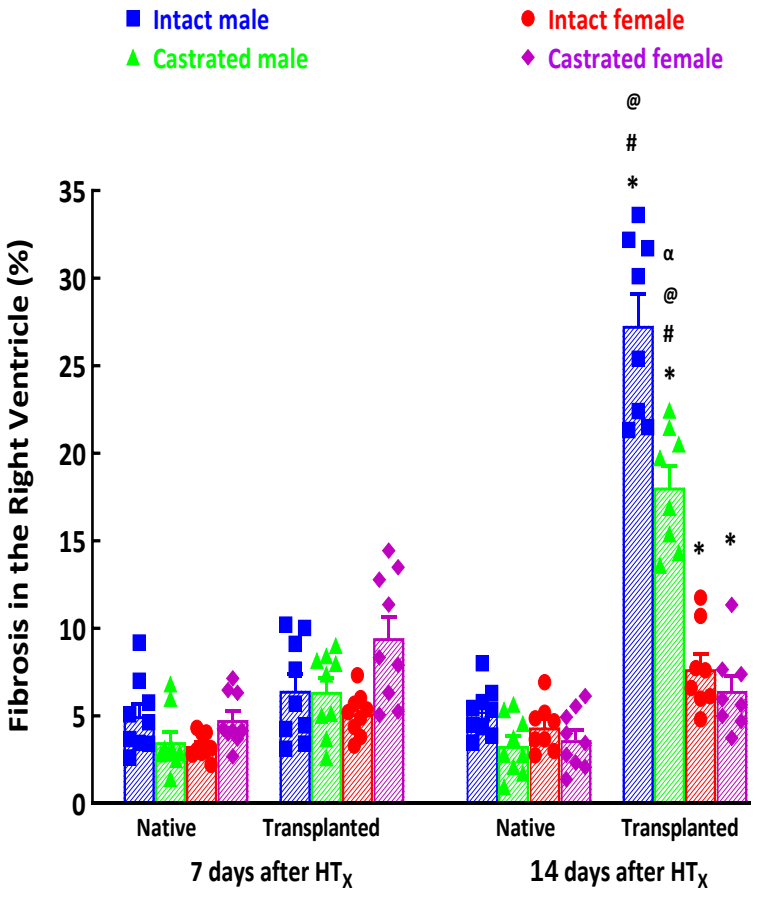
Results


A
Intact male
Intact female
Castrated male
Castrated female
Native Heart (i.e. Orthotopic from Chest)
Whole Heart Weight (mg)/Tibia Lenght (mm)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
*
*
*
*
7 days after HTX
14 days after HTX


B
Intact male
Intact female
Castrated male
Castrated female
Transplanted Heart (i.e. Heterotopic from Abdomen)
Whole Heart Weight (mg)/Tibia Lenght (mm)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
*
*
7 days after HTX
14 days after HTX

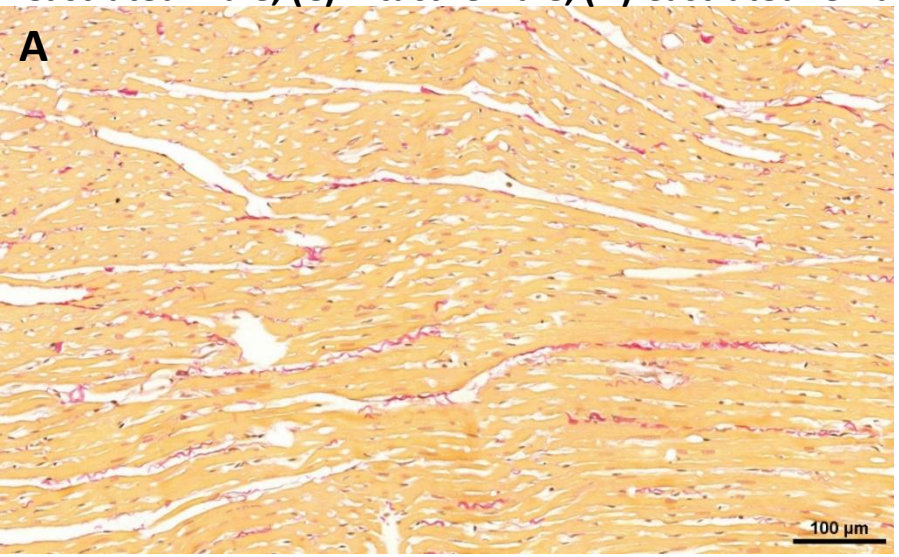
Results

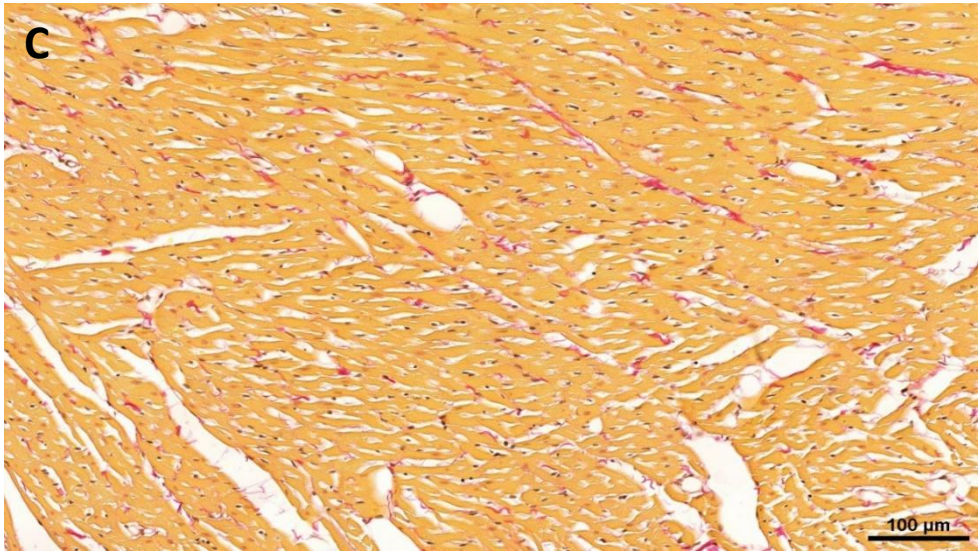

A
Intact male
Castrated male
Intact female
Castrated female
Fibrosis in the Left Ventricle (%)
0
5
10
15
20
25
30
35
Native
Transplanted
Native
Transplanted
7 days after HTX
14 days after HTX

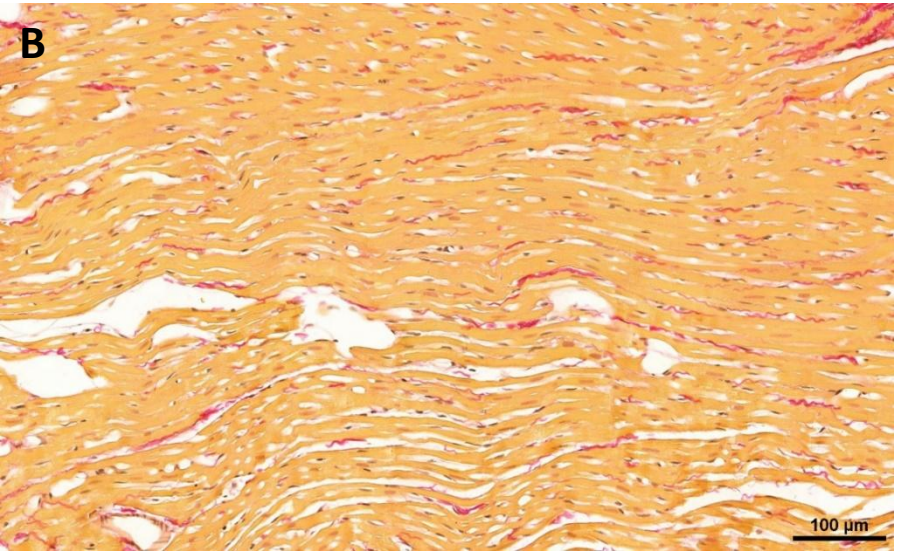

B
Intact male
Castrated male
Intact female
Castrated female
Fibrosis in the Right Ventricle (%)
0
5
10
15
20
25
30
35
Native
Transplanted
Native
Transplanted
7 days after HTX
14 days after HTX

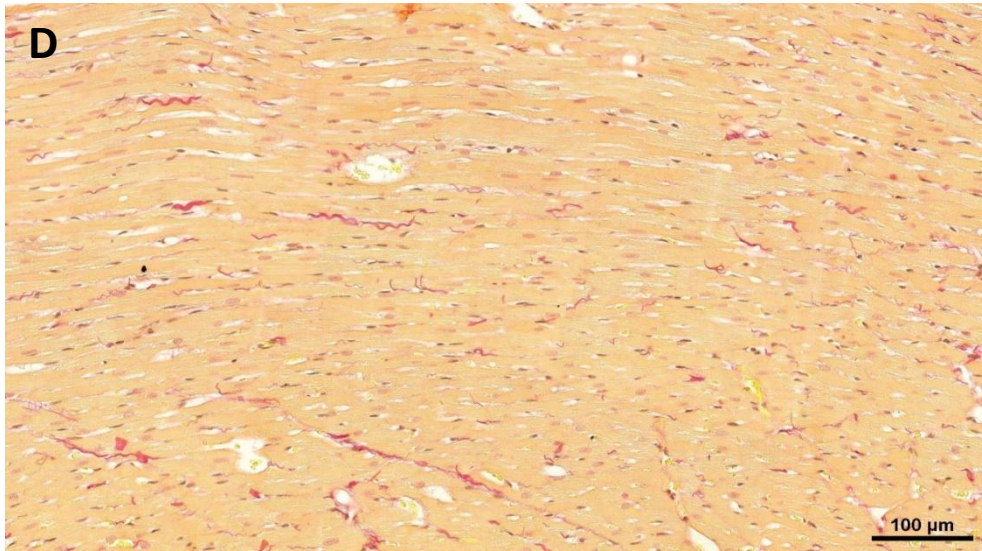
Histologic Findings

LV from the Native Heart 14 days after HHTx. Collagen is red against a pale yellow background. (A) Intact male, (B) Castrated male, (C) Intact female, (D) Castrated female.



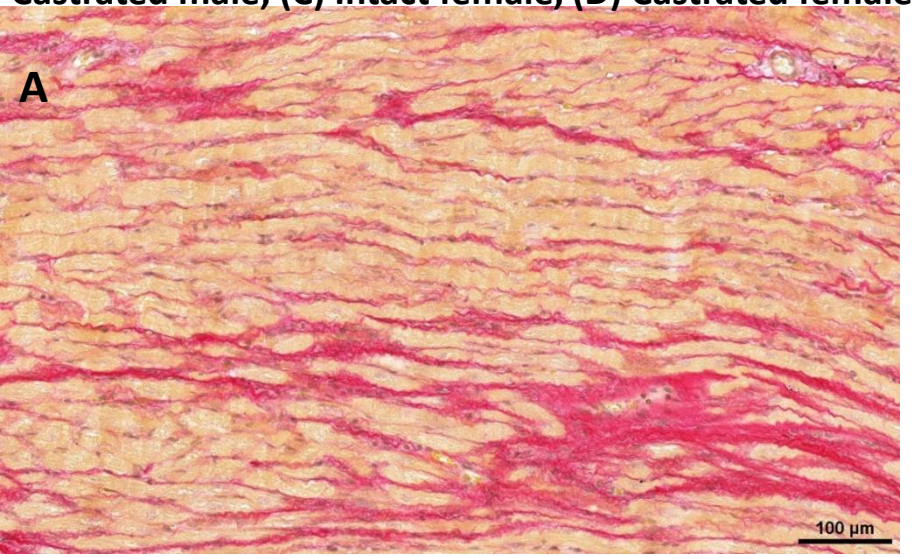


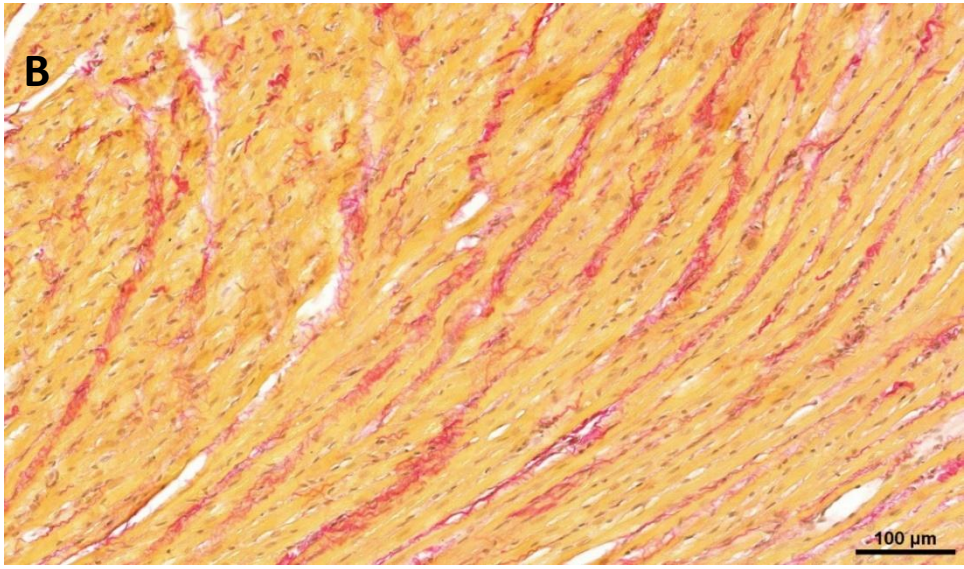


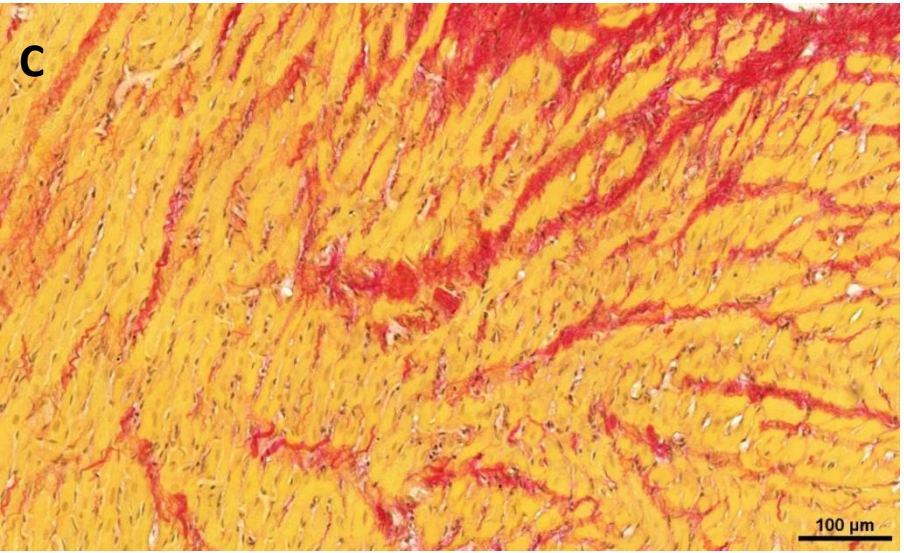


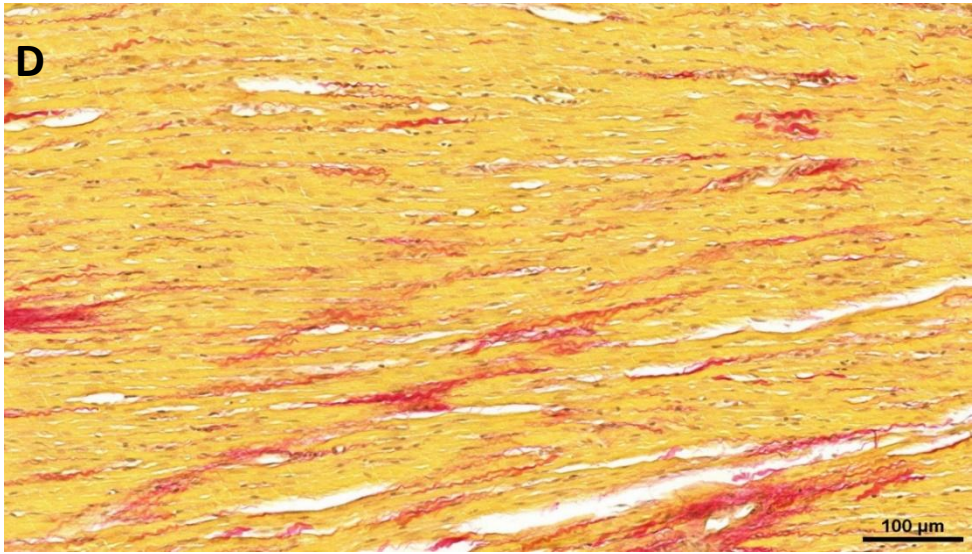
Histologic Findings

LV from the Tx Heart 14 days after HHTx. Collagen is red against a pale yellow background. (A) Intact male, (B) Castrated male, (C) Intact female, (D) Castrated female.









Conclusion

- **Unloading-induced cardiac atrophy and myocardial fibrosis is substantially attenuated in females when compared to male rats**
- **Differences cannot be simply ascribed to the presence of sex steroid hormones.**
- **Cardiac atrophy, the detrimental effect of mechanical unloading by HT_X is reduced in females when compared to male rats.**

Thank you for your attention!