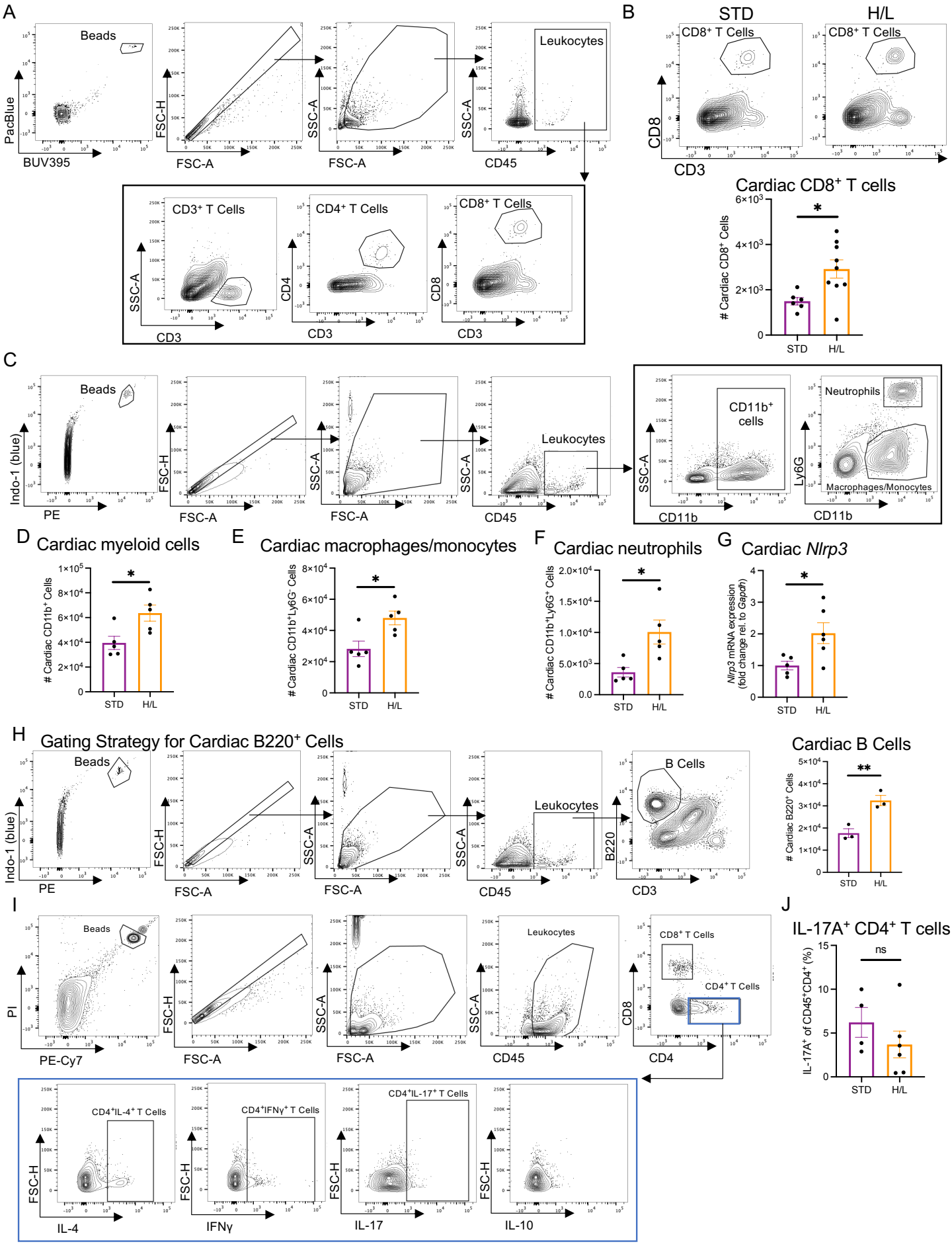
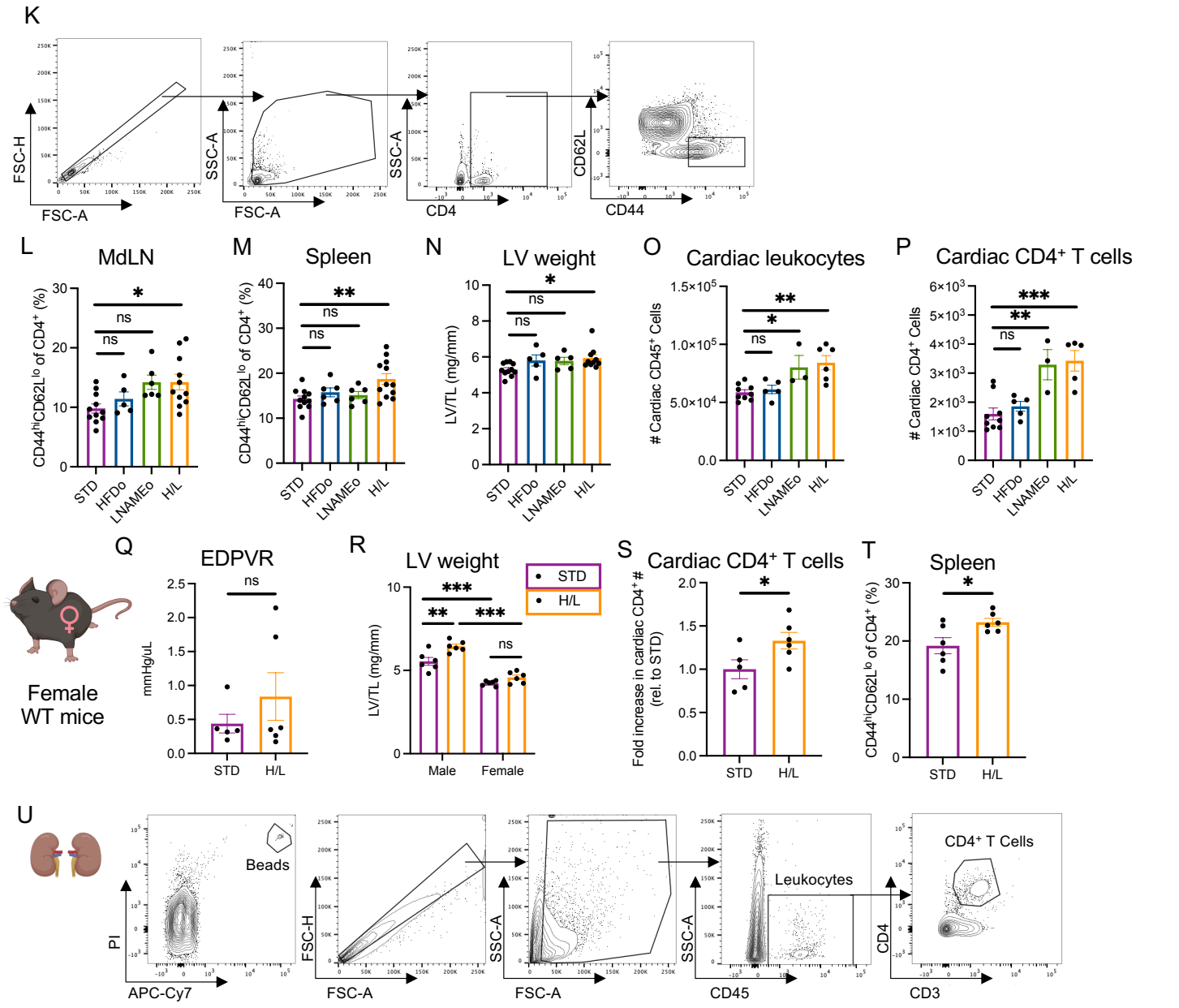
**Supplementary Figure 1**

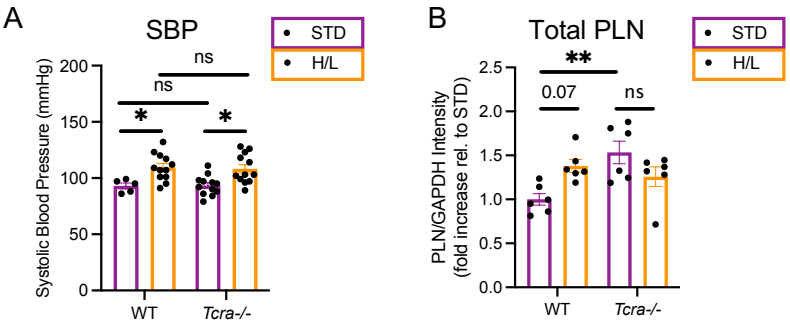


**Supplementary Figure 1 continued**



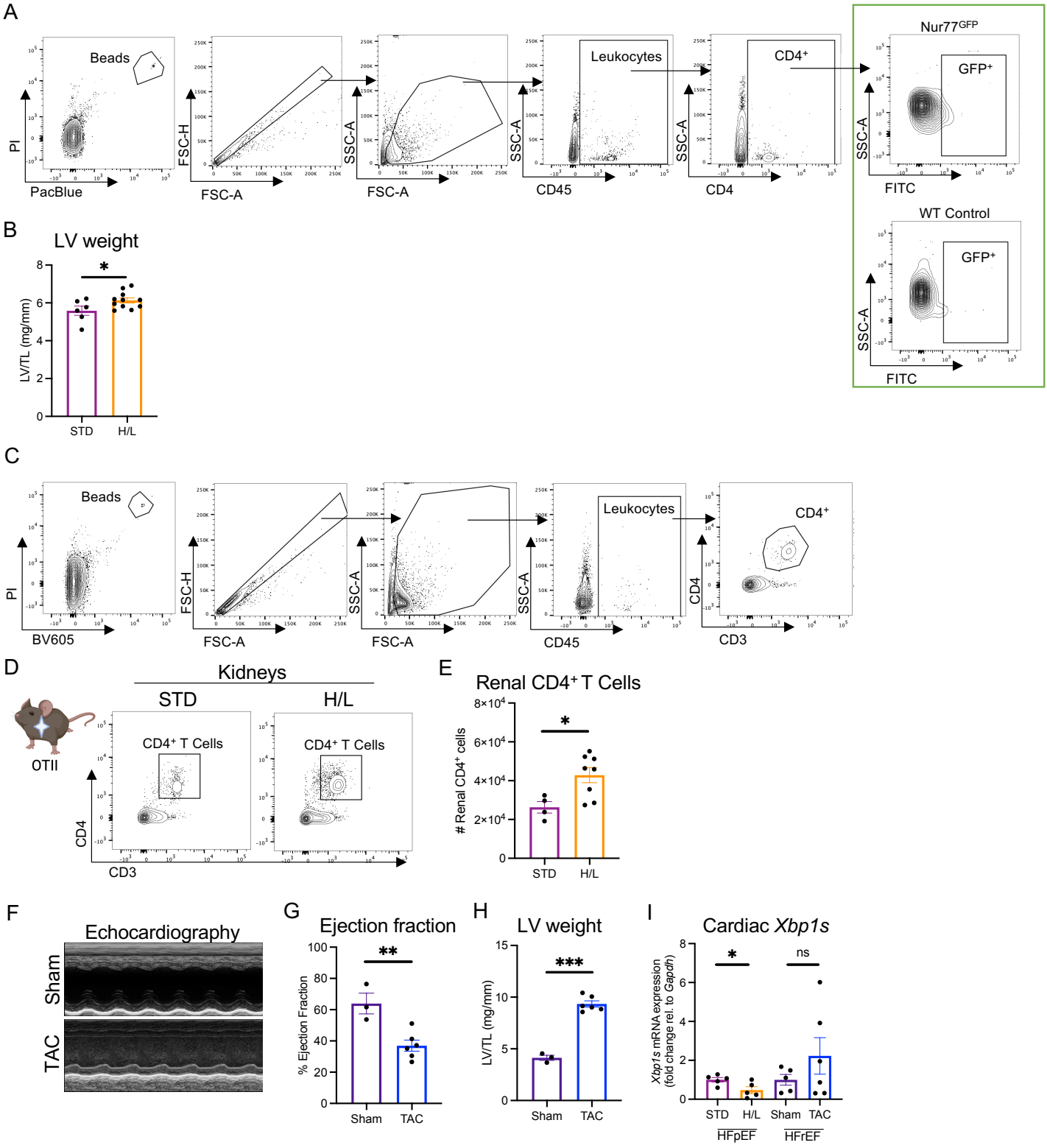
**Supplemental Figure 1: Gating strategies for leukocyte characterization by flow cytometry, and characterizing inflammation in female mice and single diet controls.** WT mice were fed H/L or STD for 5 weeks. Lymphocytes (A) were measured by flow cytometry, and $CD48^+$ T cell infiltration was visualized in LV (B). Leukocytes (C), $CD45^+CD11b^+$ cells (D), $CD45^+CD11b^+Ly6G^-$ cells (E), and $CD45^+CD11b^+Ly6G^+$ cells (F) in LV of mice were measured directly by flow cytometry. Cardiac gene expression of *Nlrp3* was measured by qPCR (G). $CD45^+B220^+$ cells in LV of mice were measured directly by flow cytometry (H). LV $CD45^+CD4^+$ cells expressing IL-4, IFN$\gamma$, IL-10, and IL-17 (I-J) were analyzed by flow cytometry. $CD4^+CD44^{hi}CD62L^{lo}$ effector T cells were measured in mediastinal lymph nodes and spleen (K) by flow cytometry. WT mice fed HFD only (HFDo), L-NAME only (LNAMEo), H/L, or STD chow for 5 weeks were analyzed for lymphoid expansion of $CD4^+CD44^{hi}CD62L^{lo}$ effector T cells (L-M). LV hypertrophy was measured (normalizing LV weight to tibia length, LV/TL, N), and cardiac $CD45^+$ cells (O) and $CD45^+CD3^+CD4^+$ cells (P) were analyzed directly in LV by flow cytometry. Female mice were fed H/L or STD for 5 weeks and invasive hemodynamic analysis were used to characterize end diastolic pressure volume relationship (EDPVR, Q). Normalized LV weight was used to measure hypertrophy (LV/TL, R), and cardiac $CD4^+$ cells (S) and splenic effector $CD4^+$ cells (T) were measured by flow cytometry. In male WT mice (U), renal $CD45^+$ cells and $CD4^+$ cells were measured by flow cytometry. n=4-12. B-J, W, S-T: unpaired t test. L-P: one-way ANOVA with Tukey's multiple comparisons test. R: two-way ANOVA with Sidak's multiple comparisons test. L-M: HFDo, LNAMEo data are shown compared to STD, H/L data from Figure 1. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

**Supplementary Figure 2**

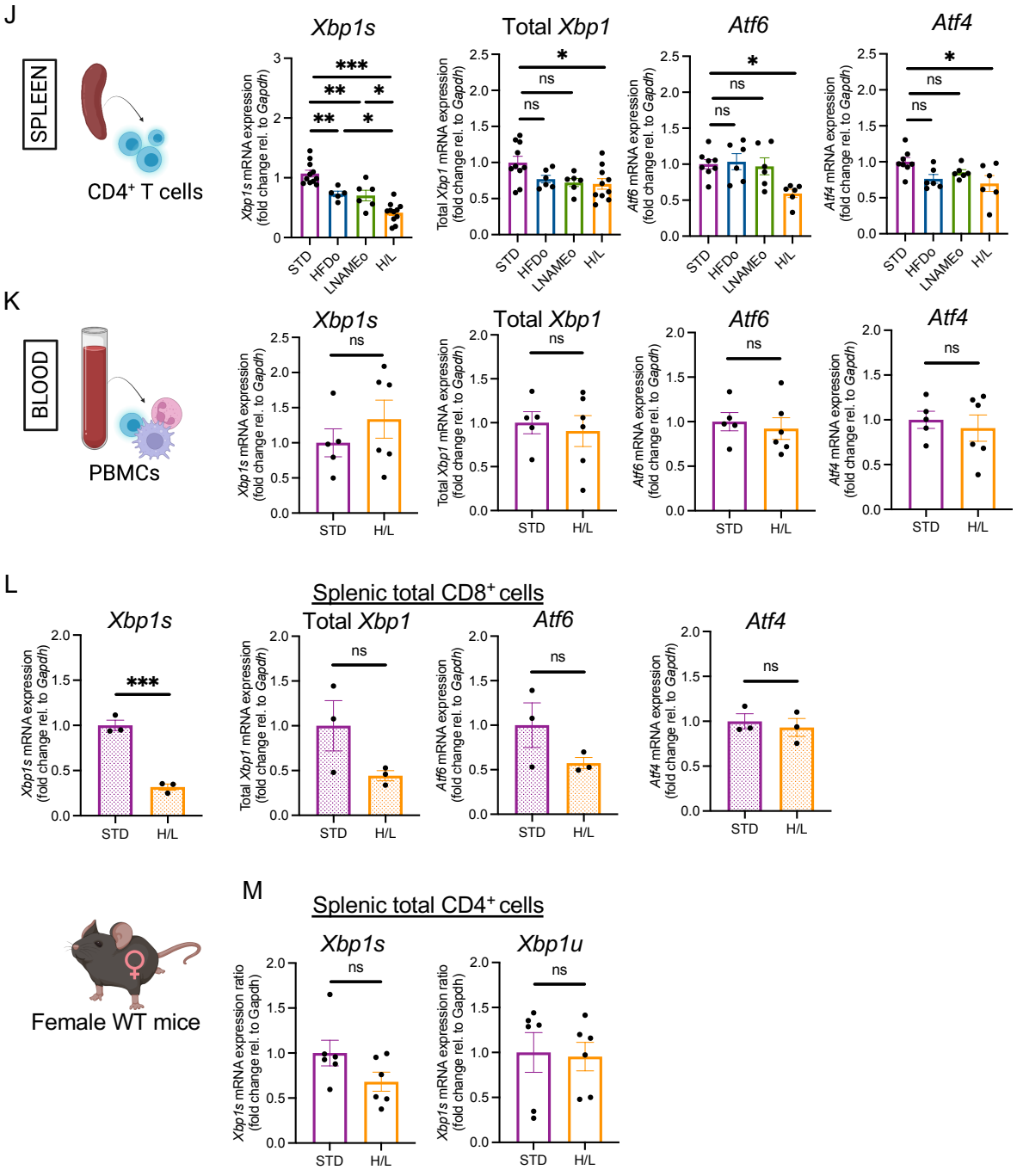


**Supplemental Figure 2: Comparison of WT vs *Tcra-/-* fed HFD/L-NAME or STD diet.** WT and T cell deficient (*Tcra-/-*) mice were fed STD or H/L for 5 weeks and systolic blood pressure (SBP, A) was measured by invasive hemodynamic analysis. Total phospholamban (PLN) protein expression was assessed in left ventricle (LV) samples by Western blot (B). n=6-12. Two-way ANOVA with Sidak's multiple comparisons test. *p≤0.05, **p≤0.01.

**Supplementary Figure 3**

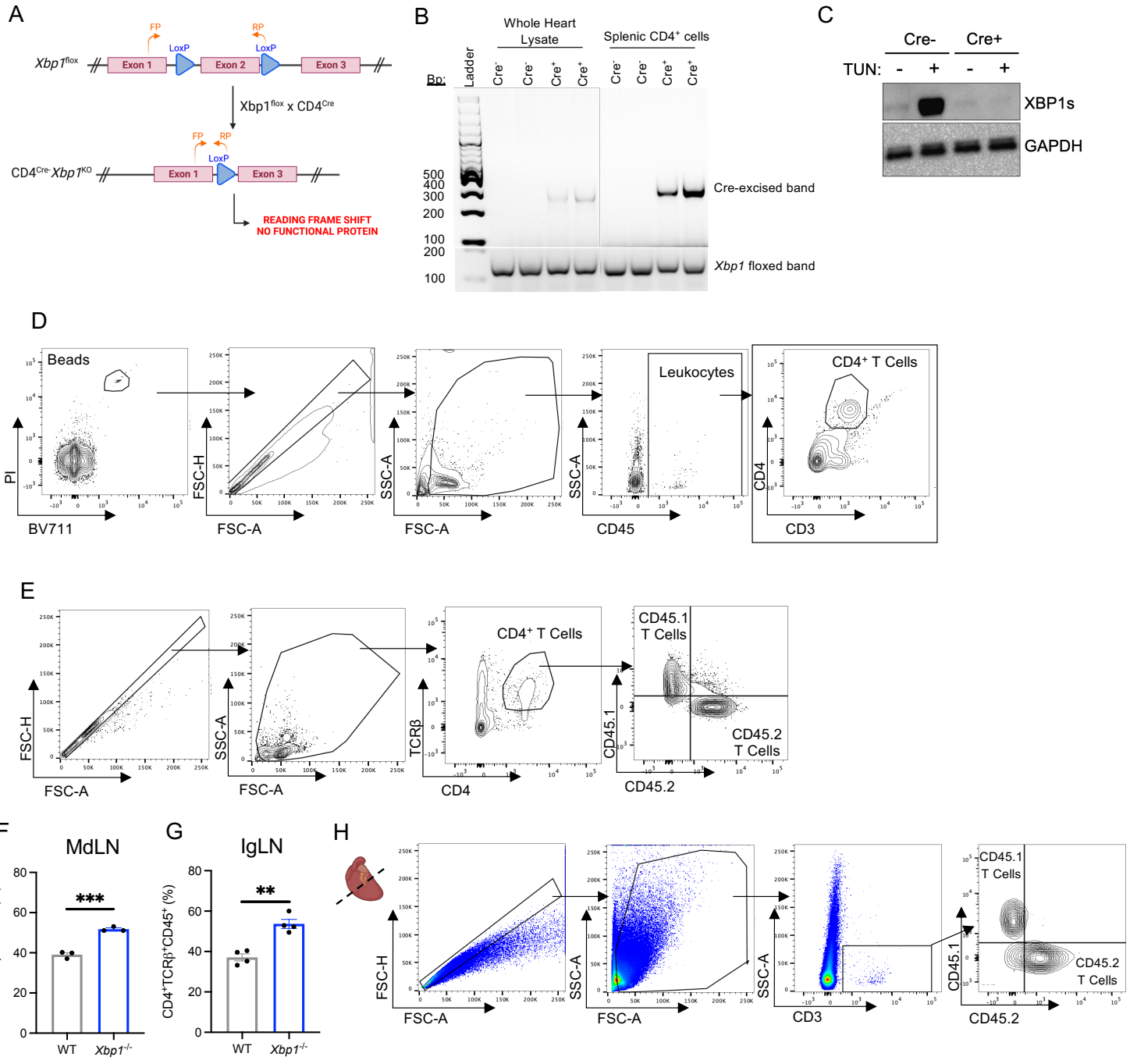


**Supplementary Figure 3 continued**



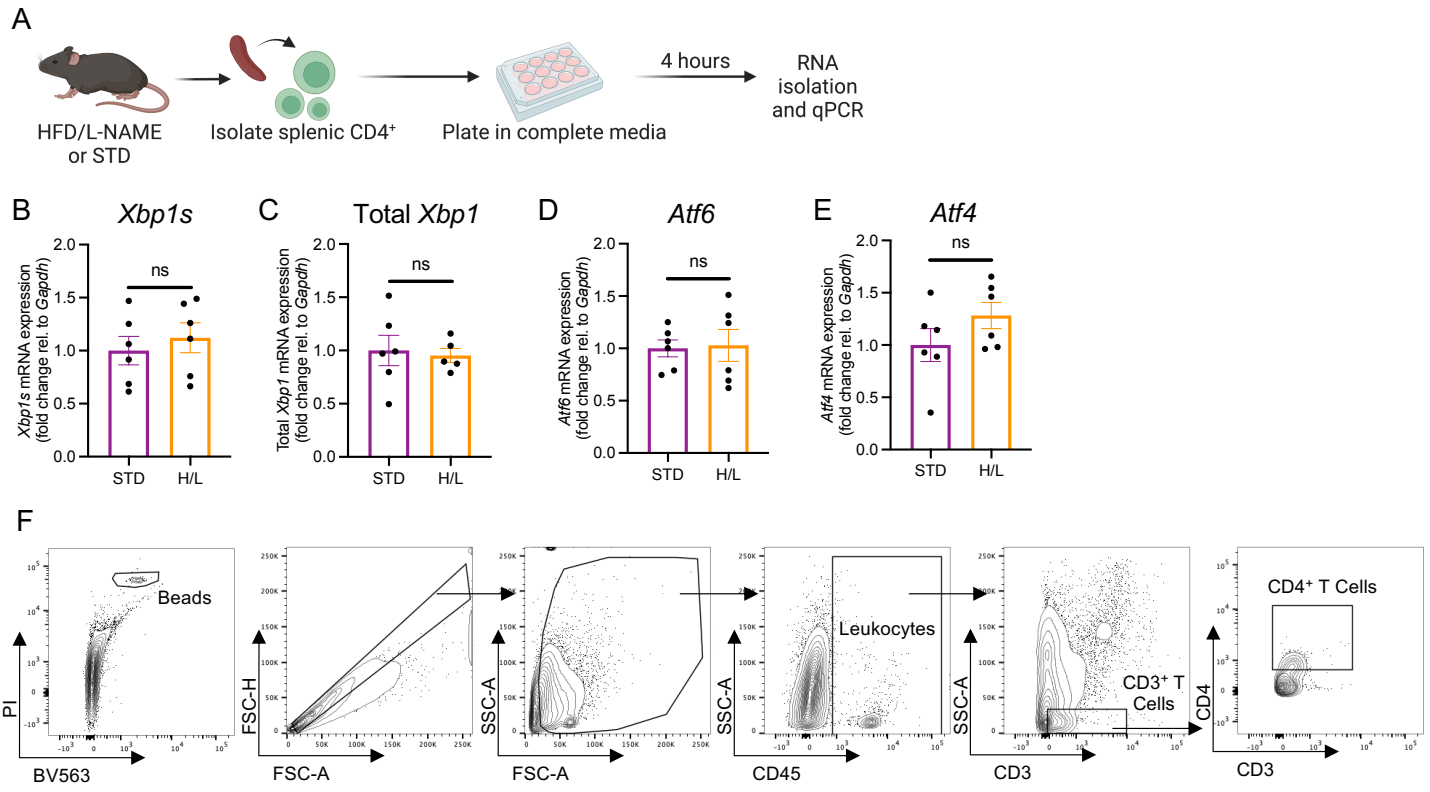
**Supplemental Figure 3: Gating strategies for Nur77$^{GFP}$ and OTII mice and leukocyte UPR expression.** $CD45^+CD4^+GFP^+$ cells were measured in LV of Nur77$^{GFP}$ mice 5 weeks after H/L, STD, or TAC surgery by flow cytometry, using a WT mouse as a negative control for gating (A). Left ventricular hypertrophy was measured in Nur77$^{GFP}$ mice by normalizing LV weight to tibial length (LV/TL, B). $CD45^+CD3^+CD4^+$ cells in LV (C) or in kidneys (D-E) of OTII mice were directly measured by flow cytometry. WT mice underwent TAC or sham surgery, and 5 weeks later, ejection fraction was assessed by echocardiography (F-G) and LV weight was measured (normalized to tibia length, LV/TL, H). Cardiac LV expression of *Xbp1s* was measured by qPCR from mice fed H/L or STD, or receiving TAC or sham surgery, for 5 weeks (I). WT mice were fed HFD only (HFDo), L-NAME only (LNAMEo), H/L, or STD for 5 weeks, then splenic $CD4^+$ T cells were isolated to measure *Xbp1s*, total *Xbp1*, *Atf6*, and *Atf4* expression by qPCR (J). In WT mice fed H/L or STD for 5 weeks, the circulating leukocyte population in blood (K) and splenic $CD8^+$ T cell population (L) were analyzed for expression of *Xbp1s*, total *Xbp1*, *Atf6*, and *Atf4* by qPCR. Splenic $CD4^+$ T cells were isolated from female WT mice fed H/L or STD for 5 weeks, and expression of *Xbp1s* and total *Xbp1* were analyzed by qPCR (M). n=3-11. K-L: each replicate is n=2 mice pooled. B, E-H, K-M: unpaired t test. I: HF groups (H/L or TAC) are compared against their respective controls (STD and sham, respectively) in unpaired t test. J: one way ANOVA with Tukey's multiple comparisons test, and HFDo, LNAMEo groups are shown compared to STD, H/L groups in Figure 3. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

## Supplementary Figure 4



**Supplemental Figure 4: Genotyping CD4$^{Cre}$-*Xbp1*$^{flox}$ mice and gating strategies for cardiac and lymphoid leukocyte populations.** CD4$^{Cre}$-*Xbp1*$^{flox}$ mice were generated by breeding *Xbp1*$^{flox}$ and CD4$^{Cre}$ mice, generating progeny with nonfunctional XBP1 protein (A). Cre excision in splenic CD4$^+$ T cells was present in Cre$^+$ mice, and absent in Cre$^-$ mice (B). Splenic CD4$^+$ T cells were isolated from CD4$^{Cre}$-*Xbp1*$^{flox}$ (T-X*bp1*$^{KO}$) and CD4$^{WT}$-*Xbp1*$^{flox}$ (T-X*bp1*$^{WT}$) mice and expanded into T cell blasts in the presence of $\alpha$CD3/$\alpha$CD28. Cells were either left untreated or treated with tunicamycin (TUN) for 6 hours, then collected for analysis of XBP1s expression by Western blotting (C). Cardiac CD45$^+$CD3$^+$CD4$^+$ T cells were analyzed in LV of T-X*bp1*$^{KO}$ or T-X*bp1*$^{WT}$ mice directly using flow cytometry (D). CD45.2$^+$CD4$^+$Tcr$\beta^+$Xbp1$^{-/-}$ and CD45.1$^+$CD4$^+$Tcr$\beta^+$WT T cells were co-transferred into T cell deficient (*Tcra-/-*) recipients fed H/L for 3 weeks, then respective populations of T cells were directly measured in lymphoid organs using flow cytometry (E). Relative proportions of each cell type were characterized in mediastinal lymph nodes (MdLN, F), and inguinal lymph nodes (IgLN, G) of recipient *Tcra-/-* mice by flow cytometry. Relative proportions of CD3$^+$CD45.1$^+$ and CD3$^+$CD45.2$^+$ cells were measured in left ventricles of *Tcra-/-* mice (H). n=3-4. Unpaired t test. **$p \leq 0.01$, ***$p \leq 0.001$

**Supplementary Figure 5**



**Supplemental Figure 5: UPR recovery in vitro and in vivo.** Splenic $CD4^+$ T cells were isolated from WT mice fed H/L or STD for 5 weeks, plated in complete media for 4 hours in 37°C, then measured for gene expression of *Xbp1s,* total *Xbp1*, Atf6 and *Atf4* by qPCR (A-E). Cardiac $CD45^+CD3^+CD4^+$ T cells were directly measured by flow cytometry in WT mice were fed STD or H/L, or H/L for 5 weeks then reverted to STD for 2 weeks (H/L->S) prior to analysis. n=5-6. Unpaired t test.

## Supplemental Tables

**Supplementary Table 1: Characterization of left ventricular function of female WT mice by echocardiography or pressure volume loops after 5 week treatment with STD or H/L**

| | Ejection Fraction (%) | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) | Systolic Blood Pressure (mm Hg) | dP/dt min (mmHg/s) | dP/dt max (mmHg/s) | EDPVR | ESPVR | PRSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WT STD** | 59.23 ± 2.048 | 30.76 ± 1.418 | 0.793 ± 0.029 | 3.518 ± 0.046 | 2.437 ± 0.067 | 1.174 ± 0.037 | 478.3 ± 12.2 | 95.4 ± 1.66 | -6142 ± 437.2 | 6759 ± 333.1 | 0.439 ± 0.138 | 2.489 ± 0.357 | 38.73 ± 6.363 |
| **WT H/L** | 62.25 ± 1.216 | 32.64 ± 0.806 | 0.925 ± 0.068 | 3.319 ± 0.074* | 2.237 ± 0.068 | 1.295 ± 0.048 | 492.3 ± 13.26 | 120 ± 2.817*** | -7048 ± 620.9 | 7377 ± 730.1 | 0.837 ± 0.351 | 2.674 ± 0.511 | 39.47 ± 8.692 |

Values are means ± SEM. n=7 for echocardiography; n=7-9 for pressure volume loops. Unpaired t-test. *** ≤ 0.001 comparing STD vs H/L

**Supplementary Table 2: Characterization of left ventricular function of WT or *Tcra-/-* mice by echocardiography or pressure volume loops after 5 week treatment with STD or H/L**

| | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) | dP/dt min (mmHg/s) | dP/dt max (mmHg/s) | ESPVR | PRSW |
|---|---|---|---|---|---|---|---|---|---|---|
| **WT STD** | 36.831 ± 3.020 | 0.822 ± 0.061 | 3.592 ± 0.13 | 2.29 ± 0.166 | 0.768 ± 0.39 | 473.111 ± 17.501 | -8172.2 ± 497.635 | 8878 ± 551.957 | 2.508 ± 0.302 | 59.618 ± 8.555 |
| **WT H/L** | 35.266 ± 1.749 | 0.976 ± 0.047 | 3.578 ± 0.1 | 2.331 ± 0.121 | 0.854 ± 0.028 | 520.667 ± 10.761$^{*}$ | -8964.9 ± 562.069 | 8880.9 ± 441.473 | 5.343 ± 1.699 | 51.915 ± 5.105 |
| ***Tcra-/-* STD** | 35.880 ± 1.444 | 0.852 ± 0.046 | 3.86 ± 0.117 | 2.483 ± 0.119 | 0.806 ± 0.027 | 496.778 ± 11.351 | -5523.2 ± 232.392$^{\$\$}$ | 6190.8 ± 293.030$^{\$\$}$ | 2.713 ± 0.589 | 47.458 ± 6.893 |
| ***Tcra-/-* H/L** | 33.534 ± 1.595 | 0.925 ± 0.04 | 3.544 ± 0.091 | 2.364 ± 0.107 | 0.854 ± 0.022 | 488.7 ± 8.234 | -8458.44 ± 359.889 | 8622.889 ± 420.918 | 1.597 ± 0.207 | 52.726 ± 6.001 |

Values are means ± SEM. n=9-12 for echocardiography; n=5-10 for pressure volume loops. Two-way ANOVA with Tukey's multiple comparisons test. $^{*} \leq 0.05$ comparing WT STD vs H/L; $^{\$\$} \leq 0.01$ comparing WT vs *Tcra-/-* STD

**Supplementary Table 3: Characterization of left ventricular function of OTII mice by echocardiography or pressure volume loops after 5 week treatment with STD or H/L**

| | Ejection Fraction (%) | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) | Systolic Blood Pressure (mm Hg) | dP/dt min (mmHg/s) | dP/dt max (mmHg/s) | EDPVR | ESPVR | PRSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **OTII STD** | 62.60 ± 1.402 | 33.33 ± 0.978 | 0.8090 ± 0.038 | 3.884 ± .07338 | 2.592 ± 0.2104 | 0.6859 ± .05153 | 442.3 ± 42.31 | 97.14 ± 2.849 | -6850 ± 447.2 | 7322 ± 576.2 | 0.427 ± 0.164 | 2.722 ± 0.43 | 42.13 ± 6.575 |
| **OTII H/L** | 66.41 ± 2.037 | 36.11 ± 1.636 | 0.9237 ± 0.1378 | 3.665 ± 0.0668* | 2.345 ± 0.2338 | 0.8344 ± 0.03616* | 495.6 ± 51.68* | 113.9 ± 2.201*** | -8094 ± 303.6* | 7895 ± 334.8 | 0.371 ± 0.132 | 2.501 ± 0.4371 | 50.57 ± 5.849 |

Values are means ± SEM. n=7 for echocardiography; n=7-9 for pressure volume loops. Unpaired t-test. * ≤ 0.05, *** ≤ 0.001 comparing STD vs H/L

**Supplementary Table 4: Characterization of left ventricular function of WT mice by echocardiography 5 weeks after TAC or sham surgery**

| | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) |
|---|---|---|---|---|---|---|
| **WT Sham** | 34.28 ± 5.016 | 0.8529 ± 0.088 | 3.252 ± 0.1696 | 2.141 ± 0.3881 | 0.7008 ± 0.0323 | 488.3 ± 59.5 |
| **WT TAC** | 17.80 ± 1.941** | 1.086 ± 0.058* | 4.409 ± 0.0936*** | 3.63 ± 0.3586*** | 0.9833 ± 0.0548* | 520.8 ± 49.49 |

Values are means ± SEM. n=3-6 for echocardiography. Unpaired t-test. * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001 comparing sham vs TAC.

**Supplementary Table 5: Characterization of left ventricular function of T-*Xbp1*$^{WT}$ and T-*Xbp1*$^{KO}$ mice by echocardiography or pressure volume loops after 5 week treatment with STD or H/L**

| | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) | dP/dt min (mmHg/s) | dP/dt max (mmHg/s) | ESPVR | PRSW |
|---|---|---|---|---|---|---|---|---|---|---|
| T-*Xbp1*$^{WT}$ H/L | 29.63 ± 1.217 | 0.946 ± 0.0534 | 3.76 ± 0.1118 | 2.645 ± 0.1536 | 0.9080 ± 0.061 | 526.3 ± 34.11 | -8412 ± 812.0 | 8554 ± 492.3 | 1.126 ± 0.524 | 42.65 ± 5.707 |
| T-*Xbp1*$^{KO}$ H/L | 34.55 ± 1.931 | 1.060 ± 0.1067 | 3.557 ± 0.1050 | 2.330 ± 0.2337 | 1.059 ± 0.0579 | 508.8 ± 37.85 | -7414 ± 276.1 | 7307 ± 172.2* | 0.7312 ± 0.2380 | 48.18 ± 9.814 |

Values are means ± SEM. n=4 for echocardiography; n=4-6 for pressure volume loops. Unpaired t-test. * ≤ 0.05 comparing *Xbp1*$^{WT}$ vs *Xbp1*$^{KO}$

**Supplementary Table 6: Characterization of left ventricular function of WT mice by echocardiography or pressure volume loops after treatment with STD, H/L, or H/L then STD for 2 weeks (2 STD) or 3 weeks (3 STD).**

| | Ejection Fraction (%) | Fractional Shortening (%) | Anterior Wall Thickness (mm) | Internal Diastolic Diameter (mm) | Internal Systolic Diameter (mm) | Posterior Wall Thickness (mm) | Heart Rate (bpm) | dP/dt min (mmHg/s) | dP/dt max (mmHg/s) | ESPVR | PRSW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **WT STD** | 63.71 ± 1.675 | 34.10 ± 1.160 | 0.9438 ± 0.043 | 3.822 ± 0.1462 | 2.525 ± 0.3251 | 0.7998 ± 0.007 | 498.5 ± 16.23 | -7743 ± 596.5 | 7671 ± 450.7 | 1.820 ± 0.2144 | 34.52 ± 6.813 |
| **WT H/L** | 63.45 ± 2.883 | 33.80 ± 2.037 | 0.9304 ± 0.077 | 3.472 ± 0.142 | 2.306 ± 0.3539 | 0.8369 ± 0.0203 | 482.5 ± 10.23 | -7406 ± 249.8 | 8122 ± 116.3 | 9.353 ± 3.344 | 43.28 ± 5.316 |
| **WT H/L -> 2 STD** | 59.74 ± 2.861 | 32.07 ± 2.443 | 0.8820 ± 0.066 | 3.728 ± 0.092 | 2.556 ± 0.214 | 0.8142 ± 0.0238 | 474.5 ± 20.02 | -5403 ± 340.3$^{\$}$ | 5928 ± 345.5$^{\$}$ | 5.662 ± 2.917 | 33.96 ± 11.83 |
| **WT H/L -> 3 STD** | 60.04 ± 2.130 | 31.55 ± 1.397 | 0.898 ± 0.057 | 3.877 ± 0.105 | 2.659 ± 0.116 | 0.924 ± 0.061 | 524.2 ± 8.94$^{\%\%,\ \wedge\wedge\wedge}$ | -7805 ± 686.7$^{\wedge}$ | 8867 ± 687.5$^{\wedge\wedge}$ | 1.961 ± 0.5288 | 43.7 ± 9.448 |

Values are means ± SEM. n=6 for echocardiography; n=5-6 for pressure volume loops. One-way ANOVA with Tukey's multiple comparisons test. $^{\$} \leq 0.05$ comparing H/L vs H/L->2STD; $^{\%\%} \leq 0.01$ comparing H/L vs H/L->3STD; $^{\wedge} \leq 0.05$, $^{\wedge\wedge} \leq 0.01$, $^{\wedge\wedge\wedge} \leq 0.001$ comparing H/L->2STD vs H/L->3STD.

**Supplementary Table 7: Antibodies used for flow cytometry**

| Target | Clone | Biolegend Catalog # |
|---|---|---|
| CD45.2 | 104 | 109841 |
| CD3 | 145-2C11 | 100330 |
| CD4 | GK1.5 | 100412 |
| CD8 | 53-6.7 | 100738 |
| CD11b | M1/70 | 101230 |
| Ly6G | 1A8 | 127628 |
| IL-4 | 11B11 | 504109 |
| IFNγ | XMG1.2 | 505809 |
| IL-17 | TC11-18H10.1 | 506904 |
| IL-10 | JES5-16E3 | 505022 |
| CD44 | IM7 | 103012 |
| CD62L | MEL-14 | 161204 |
| CD45.1 | A20 | 110708 |
| TCRβ | H57-597 | 109220 |
| CD69 | H1.2F3 | 104506 |

**Supplementary Table 8: Primer sequences used for qPCR**

| Gene | Forward (5' – 3') | Reverse (5' – 3') |
|---|---|---|
| *Xbp1s* | GGTCTGCTGAGTCCGCAGCAGG | GAAAGGGAGGCTGGTAAGGAAC |
| Total *Xbp1* | GACAGAGAGTCAAACTAACGTGG | GTCCAGCAGGCAAGAAGGT |
| *Atf6* | AGAAAGCCCGCATTCTCCAG | ACTCCCAGAATTCCTACTGATGC |
| *Atf4* | ATGGCCGGCTATGGATGAT | CGAAGTCAAACTCTTTCAGATCCATT |
| *Nlrp3* | ATTACCCGCCCGAGAAAGG | CATGAGTGTGGCTAGATCCAAG |
| *Gapdh* | TGGCAAAGTGGAGATTGTTGCC | AAGATGGTGATGGGCTTCCCG |
| *Xbp1* (splicing assay) | ACACGCTTGGGAATGGACAC | CCATGGGAAGATGTTCTGGG |
| *18s* (splicing assay) | AAACGGCTACCACATCCAAG | CCTCCAATGGATCCTCGTTA |

**Supplementary Table 9: Antibodies used for Western blot**

| Target | Catalog # |
|---|---|
| Phospho-IRE1α (Ser724) | Novus NB100-2323 |
| IRE1α | Cell Signaling 3294T |
| Phospho-PERK (Thr980) | Cell Signaling 3179S |
| PERK | Cell Signaling 3192S |
| Phospho-EIF2α | Cell Signaling 9721 |
| EIF2α | Cell Signaling 9722 |
| ATF6 | Cell Signaling 65880 |
| ATP2A2/SERCA2 | Cell Signaling 4388 |
| Phospho-Phospholamban (Ser16/Thr17) | Cell Signaling 8496 |
| Phospholamban | Cell Signaling 14562 |
| GAPDH | Cell Signaling 2118S |