Supplementary Figure 1

Fetal gene upregulation by 1-wk TAC is significantly increased in mice lacking RGS2. *ANP*(*Nppa*) /*BNP*(*Nppb*) – A-type and B-type natriuretic peptide; *β-MHC* (*Myh7*) – beta myosin heavy chain. Reduced expression of *SERCA2a* (*Atp2a2a*) was similar in both groups. * p<0.001 versus Sham; † p<0.001 versus TAC-1wk $RGS2^{+/+}$ and Sham; ‡ p<0.01 versus corresponding (within genotype) Sham (n=3-8 for each group).

Supplementary Figure 2A

Invasive hemodynamic data in mice after 48-hrs of TAC. The increase in afterload reflected by peak LV pressure, Ea, and systemic vascular resistance (SVR) was similar in both genotype groups (n=3-7 for each group). Cardiac output and stroke volume change was also similar in both groups. (deleted) None of these parameters yielded a significant interaction term by 2 way ANOVA (TAC×genotype).

Supplementary Figure 2B

Summary echocardiographic data in $RGS2^{+/+}$ mice, and $RGS2^{-/-}$ mice subjected to 48-hr TAC. The latter group was further co-treated with the PLCβ inhibitor U73122, or its inactive analog U73433 as a control. Inhibition of PLCβ prevented early chamber dilation (LV-diastolic diameter: LV-Dd), wall thickening, and reduced fractional shortening (FS) in the $RGS2^{-/-}$ hearts (n=4-9 in each group). * p<0.01 versus Sham for each corresponding genotype.

Supplementary Figure 3

Expression of calcineurin (Cn), phosphorylated CaMKII and ERK1/2 in mice subjected to 6-wk swimming exercise in $RGS2^{+/+}$ and $RGS2^{-/-}$ groups. Unlike with TAC, none of these signaling cascades were stimulated by swimming in either of the genotype groups (n=3-6 in each group).

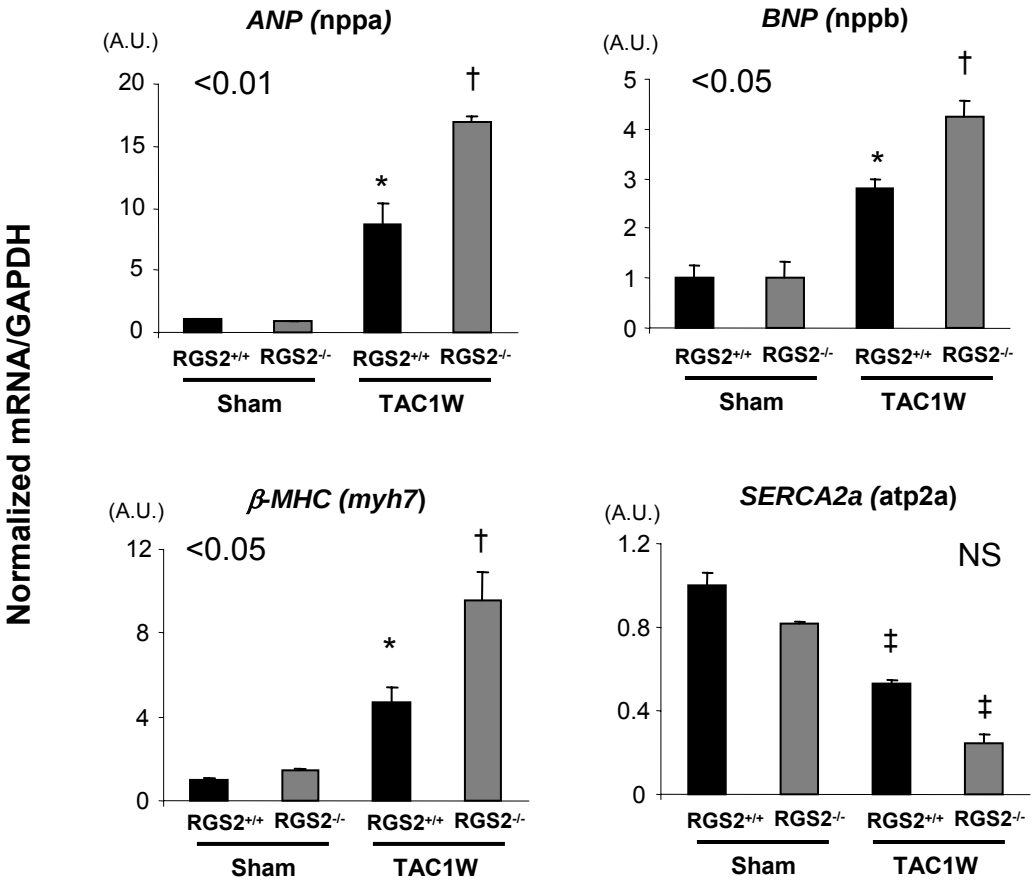
Supplementary Figure 4A

Example of normal PKG1-α distribution in myocyte from $RGS2^{-/-}$ heart showing diffuse localization as observed in control ($RGS2^{+/+}$) cells under rest conditions.

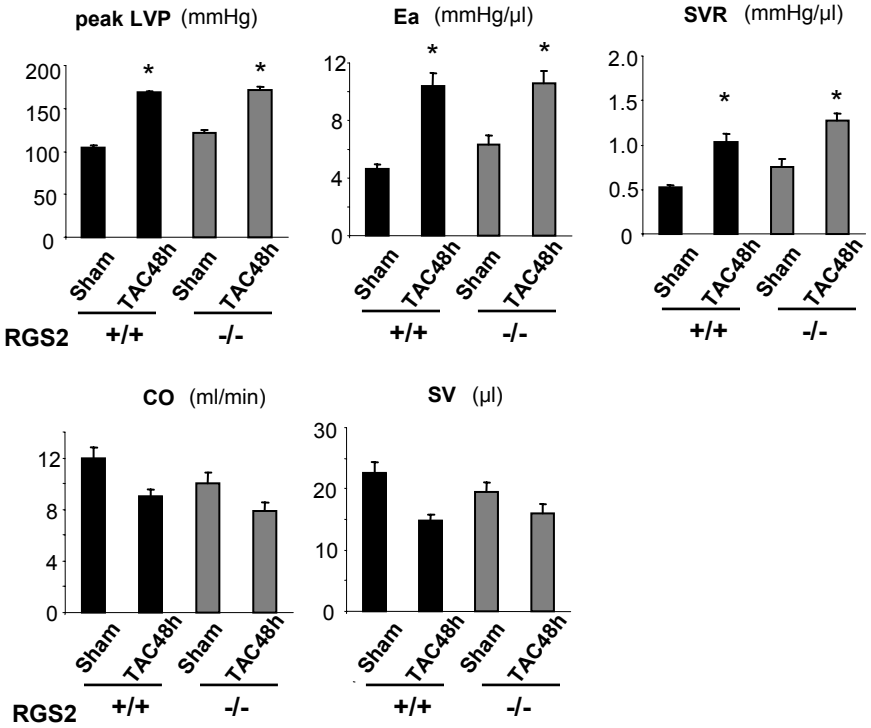
Supplementary Figure 4B.

Ponceau stains of membranes confirming equal protein loading for particulate and soluble fractions for the analysis displayed in Figure 7D.

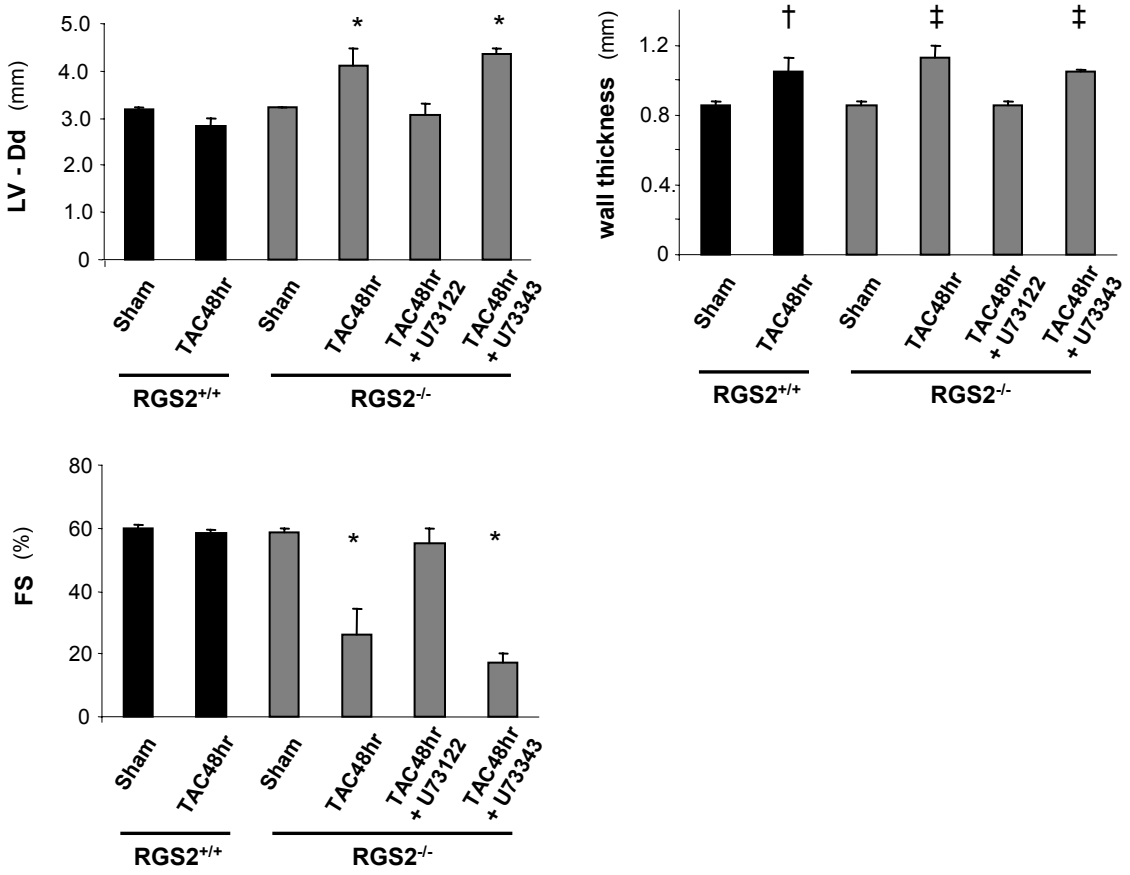
Supplementary Figure 1



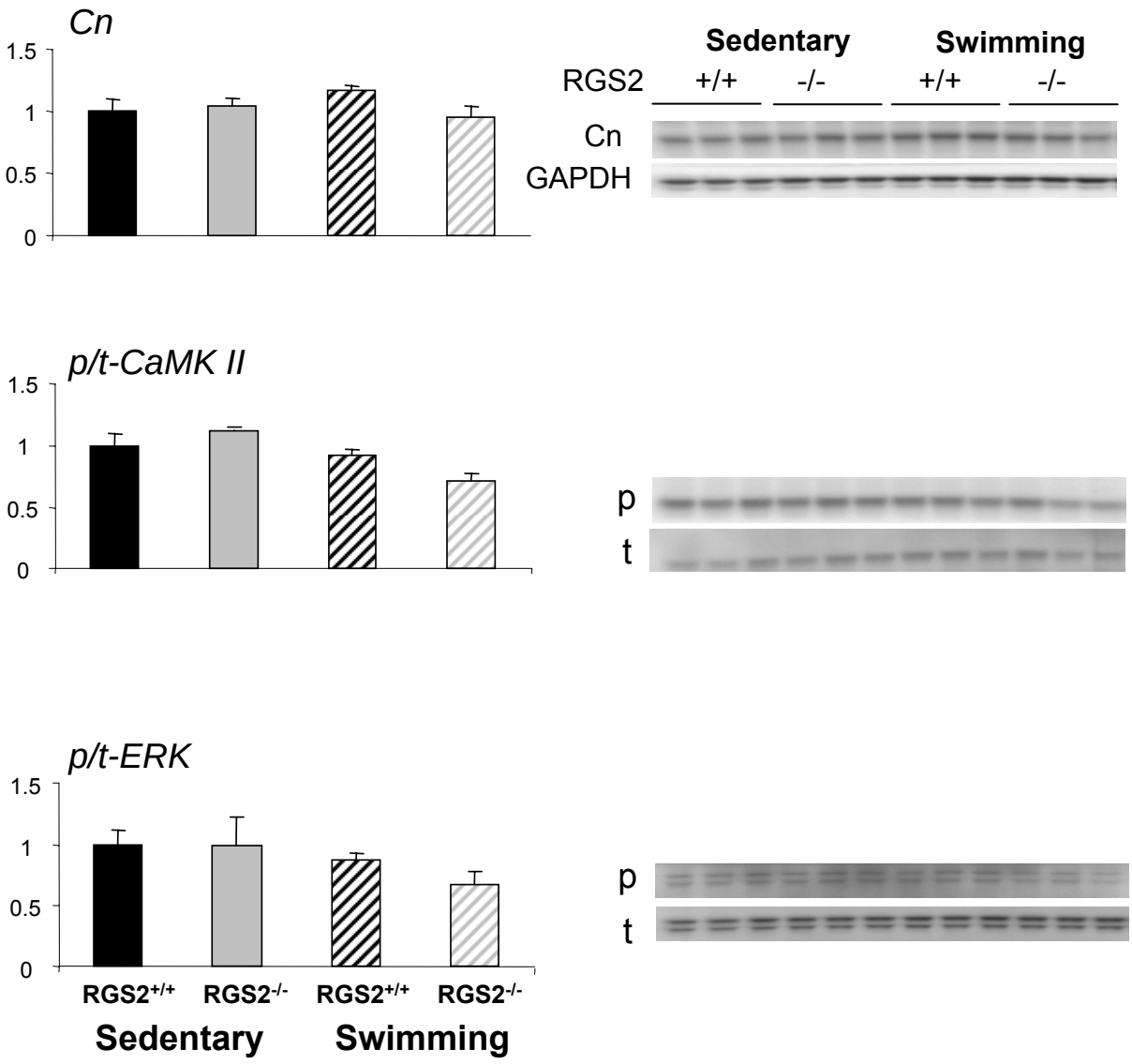
Supplementary Figure 2A



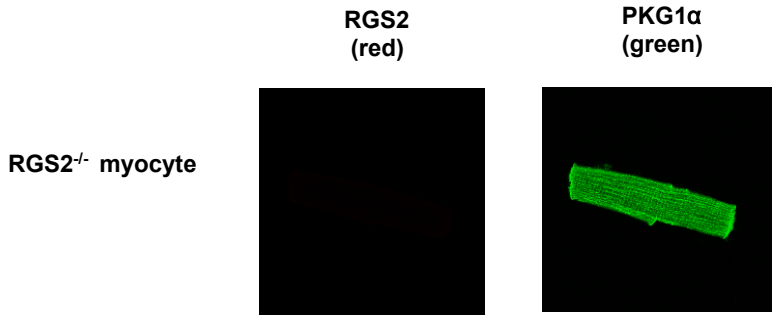
Supplementary Figure 2B



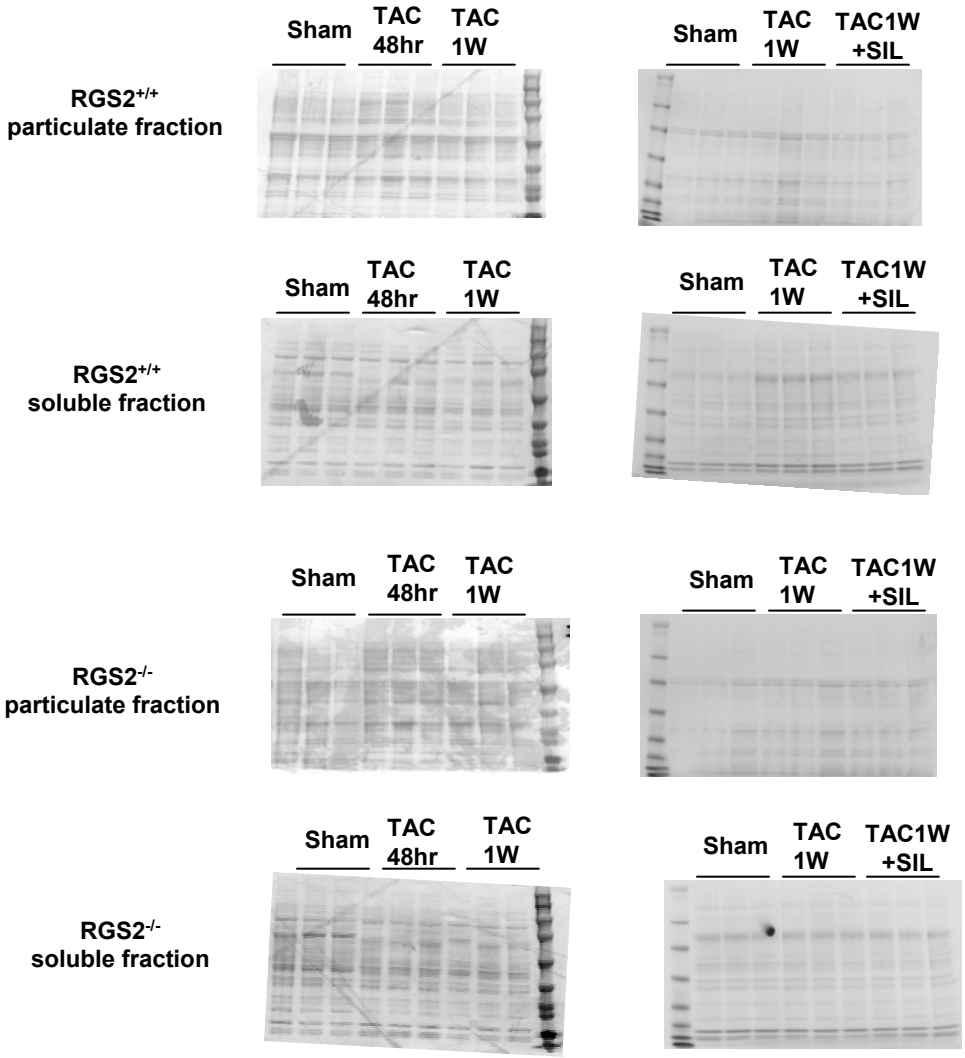
Supplemental Figure 3



Supplementary Figure 4A



Supplementary Figure 4B



Supplementary Table 1 Baseline Characteristics (Body Weight, Heart Weight and Echocardiographic Parameters) in 4-5 month old mice.

Age	4-5 month	
Genotype	$RGS2^{+/+}$ (n = 10)	$RGS2^{-/-}$ (n = 12)
BW (g)	26.2 ± 0.5	25.2 ± 0.5
HW/TL (g/cm)	63.5 ± 1.7	63.5 ± 1.7
LV-Dd (mm)	3.26 ± 0.04	3.22 ± 0.05
LV-Ds (mm)	1.32 ± 0.03	1.30 ± 0.03
WT (mm)	0.84 ± 0.01	0.84 ± 0.01
%FS	59.0 ± 0.6	59.9 ± 0.7
HR (bpm)	672 ± 10	672 ± 10

Data are mean ± SE. p=NS for all between group comparisons ($RGS2^{+/+}$ vs $RGS2^{-/-}$). BW – body weight; HW/TL – heart weight normalized to tibia length; LV-Dd - end-diastolic dimension of left ventricle; LV-Ds - end-systolic dimension of left ventricle; WT - averaged wall thickness of lateral wall and intraventricular septum; %FS - percent fractional shortening calculated as follows: %FS = (LV-Dd – LV-Ds)/ LV-Dd x 100; HR - heart rate.

Supplementary Table 2 Baseline Hemodynamics (age: 4 - 5 month old)

Genotype	$RGS2^{+/+}$ (n = 7)	$RGS2^{-/-}$ (n = 7)
LVP sys (mmHg)	104.7 ± 1.7	120.9 ± 11.1 *
LVP dia (mmHg)	5.4 ± 0.8	5.7 ± 0.7
Ea (mmHg. μl^{-1})	4.6 ± 0.3	6.3 ± 0.7 *
SVR (mmHg. μl^{-1})	0.52 ± 0.04	0.75 ± 0.09 *
SV (µl)	22.5 ± 1.8	19.5 ± 1.6
CO (ml/min)	11.9 ± 0.9	10.0 ± 0.9
EF	0.65 ± 0.04	0.64 ± 0.02
dPdtmx (mmHg.s^{-1})	11732 ± 769	12187 ± 469
dPdt /IP (s^{-1})	187.4 ± 14.7	172.2 ± 6.2
PMXI (mmHg.s^{-1})	30.6 ± 2.2	29.1 ± 1.6
PRSW (mmHg)	80.6 ± 5.6	89.2 ± 5.8
Ees (mmHg.μl^{-1})	5.71 ± 0.96	5.85 ± 0.82
V_{100} (µl)	11.5 ± 1.9	7.9 ± 1.3
dPdtmn (mmHg.s^{-1})	-10422 ± 441	-11226 ± 566
Tau (ms)	7.7 ± 0.5	8.3 ± 0.4
PFR /EDV (s^{-1})	35.7 ± 2.4	32.9 ± 3.5
HR (bpm)	532.3 ± 7.8	513.3 ± 11.1

Data are mean ± SE.

LVP sys - LV end-systolic pressure; LVP dia - LV end-diastolic pressure; Ea - effective arterial elastance - an index of total ventricular afterload; SVR - systemic vascular resistance; SV - LV stroke volume; CO - cardiac output; EF - ejection fraction. Contractile systolic indexes are: dP/dt_{max} - maximal rate of pressure rise; $dP/dt_{mx}/IP$ - dP/dt_{max} normalized to instantaneous developed pressure; PMXI - power index: maximal ventricular power divided by end-diastolic volume; PRSW - preload recruitable stroke work; Ees - end-systolic elastance; V_{100} - end-systolic volume at common end-systolic pressure (= 100mmHg) derived from ESPVR. Diastolic indexes are: Tau - time constant of pressure relaxation; dP/dt_{min} - peak rate of LV pressure decline; PFR/EDV - peak ventricular filling rate normalized to end-diastolic volume. The latter reflects early diastolic properties, i.e. relaxation and passive stiffness during early filling. A higher value reflects improved diastolic function. $^{*}p < 0.05$ vs $RGS2^{+/+}$.

Supplementary Table 3 Baseline Characteristics (Body Weight, Heart Weight and Echocardiographic Parameters) in 10 month old mice.

Age	10 month	
Genotype	$RGS2^{+/+}$ (n = 14)	$RGS2^{-/-}$ (n = 15)
BW (g)	33.3 ± 0.7	31.5 ± 0.5
HW/TL (g/cm)	83.3 ± 3.2	85.4 ± 4.3
LV-Dd (mm)	3.45 ± 0.07	3.51 ± 0.06
LV-Ds (mm)	1.43 ± 0.08	1.35 ± 0.04
WT (mm)	0.94 ± 0.01	0.94 ± 0.02
%FS	58.5 ± 1.6	61.5 ± 0.7
HR (bpm)	643 ± 9	639 ± 10

Data are mean ± SE. p=NS for all between group comparisons ($RGS2^{+/+}$ vs $RGS2^{-/-}$). BW – body weight; HW/TL – heart weight normalized to tibia length; LV-Dd - end-diastolic dimension of left ventricle; LV-Ds - end-systolic dimension of left ventricle; WT - averaged wall thickness of lateral wall and intraventricular septum; %FS - percent fractional shortening calculated as follows: %FS = (LV-Dd – LV-Ds)/ LV-Dd x 100; HR - heart rate.