Supplementary Figures:

Figure S1: Heart rate and LV systolic pressure in Mdm2/p53 KO mice after βAR stimulation. A) Heart rate of anesthetized WT (n=13) and Mdm2/p53-KO (n=17) mice after increasing doses of isoproterenol. B) LV systolic pressure of the corresponding mice. Error bars indicate average ± SEM. * $p<0.05$, two-way ANOVA, Bonferroni posttest.

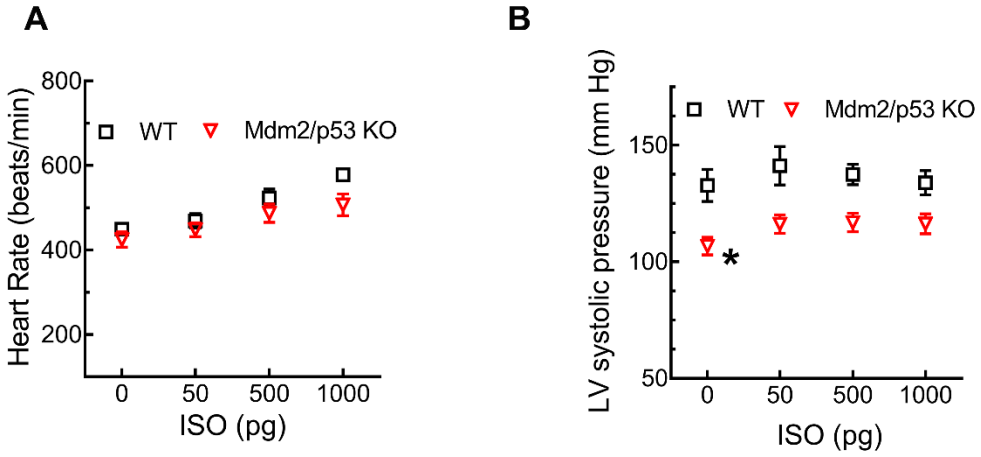

Figure S2: AAV9-Mdm2 gene delivery rescues βAR-induced cardiac responsiveness. A) Lysates prepared from LV's of Mdm2/p53 KO mice injected with either AAV9-GFP or AAV9-Mdm2 were serially immunoblotted for Mdm2, and GAPDH. Hemodynamic parameters measured in anesthetized mice are shown in panels. **B)** maximal first derivative of LV pressure * $p<0.05$, ** $p<0.01$, Two-way ANOVA. **C)** minimal first derivative of LV pressure * $p<0.05$. B and C, n=8 (AAV9-GFP) and n=20 (AAV9-Mdm2). **D**) Comparison of dP/dt_{max} induced by 1000 pg ISO infusion in WT (n=3) and Mdm2/p53 KO (AAV9-GFP, n=8 and AAV9-Mdm2, n=20).

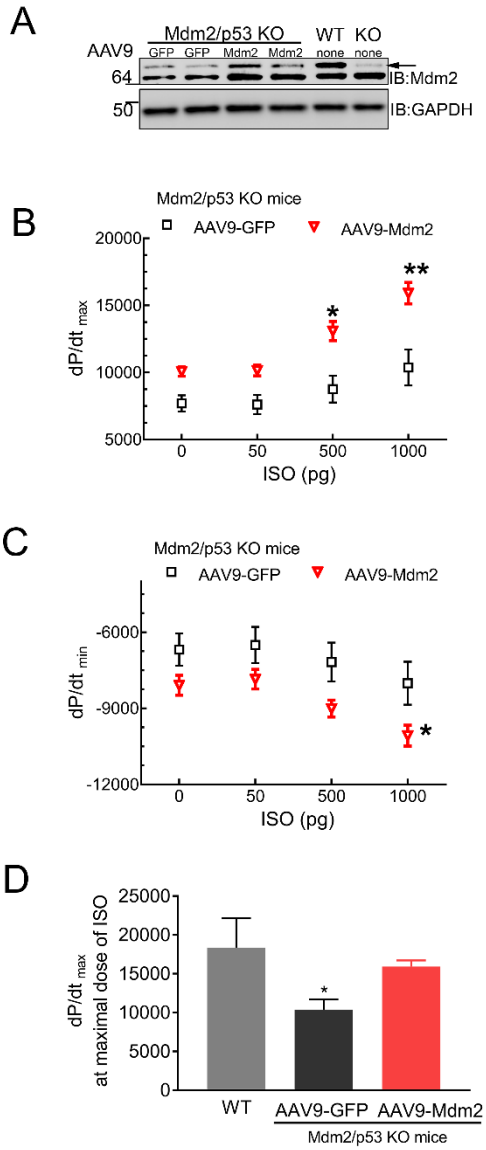

Figure S3: βAR subtypes in WT and Mdm2/p53 KO mice LVs. A) Competitive displacement of the non-selective antagonist radioligand [^{125}I](−)-iodocyanopindolol ([^{125}I]CYP) from βARs in ventricular membranes isolated from WT and Mdm2/p53 KO hearts using the subtype-selective antagonist ICI-118551. Data were fit to a two-site competitive binding model wherein the fractions of high and low affinity sites correspond to proportions of β_2AR and β_1AR, respectively. B) βAR subtypes in LV of WT and Mdm2/p53 KO mice measured by using the subtype-selective βAR antagonist CGP20712A. Non-specific binding was defined by the non-selective antagonist propranolol. Experiments were performed in duplicate. n = 3 for WT and Mdm2/p53 KO. Error bars indicate average ± SEM.

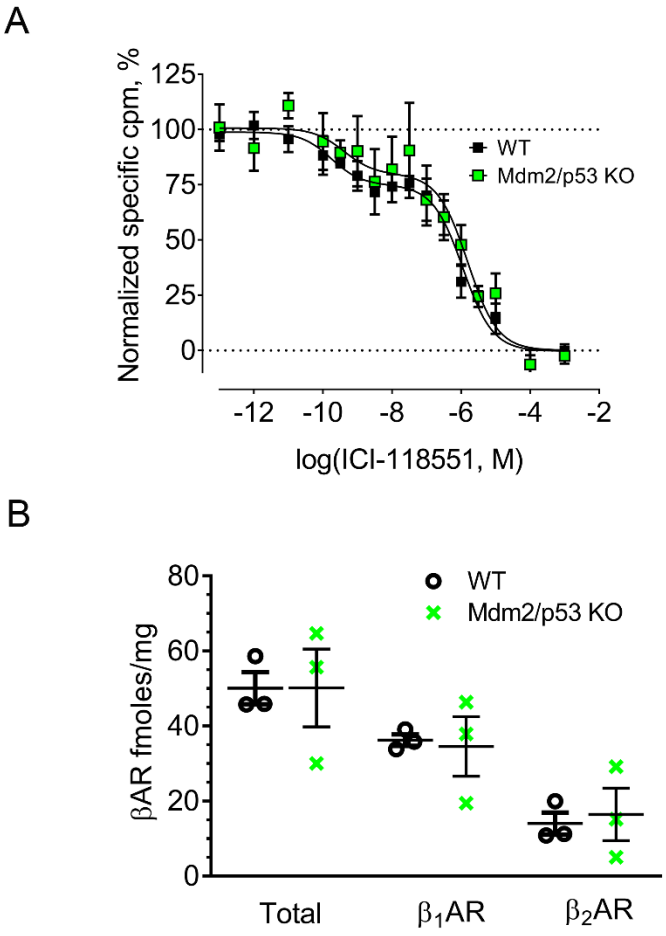

Figure S4: Analyses of PKAα and phospholamban expression in WT and Mdm2/p53 KO mice. Heart lysates prepared from WT and Mdm2/p53 KO mice were immunoblotted for PKAα catalytic subunit (A), and phospholamban, PLN (C). In each case, the membrane was reprobed for GAPDH. The PKAα/GAPDH and PLN/GAPDH ratio in each group are summarized as bar graphs. (WT, n=5; KO, n=6).

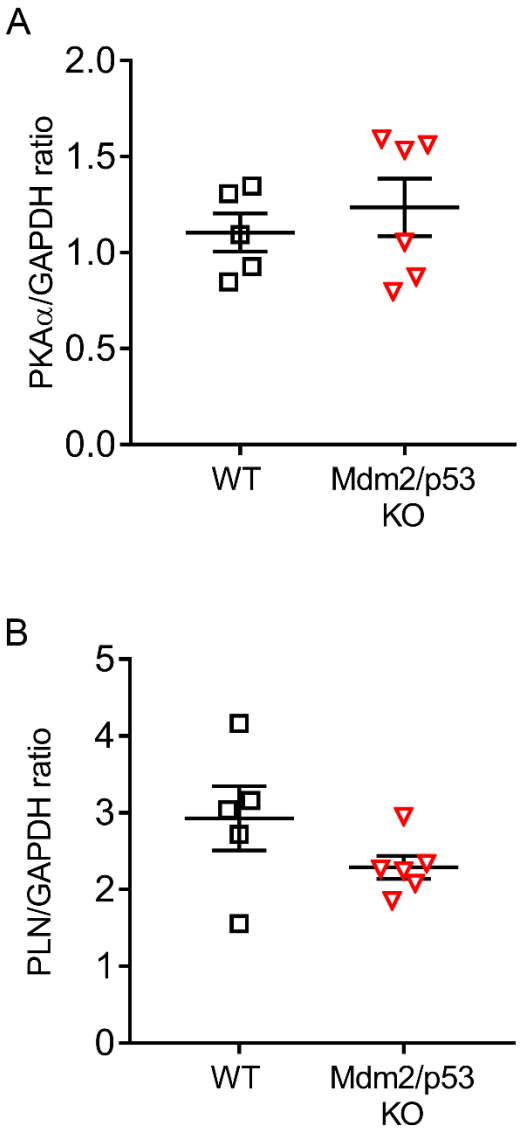

Table S1. Load Independent Hemodynamic Measures

	Wild Type	Mdm2/p53 KO
	N = 5	N = 7
	Compliance Parameters	
EDPVR (Linear) Slope	0.1 ± 0.0	0.4 ± 0.2
EDPVR (Linear) Intercept	1.8 ± 3.0	-2.9 ± 6.3
EDPVR (Quadratic) β coefficient	0.1 ± 0.0	0.1 ± 0.0
EDPVR (Quadratic) α coefficient	2.1 ± 2.4	0.8 ± 0.4
	Contractility Parameters	
ESPVR (Linear) Slope	6.2 ± 1.4	5.1 ± 2.2
ESPVR (Linear) Intercept	-5.1 ± 4.3	-5.7 ± 5.2
ESPVR (Quadratic) a	-0.4 ± 0.4	-0.3 ± 0.3
ESPVR (Quadratic) V_0	-0.7 ± 2.7	-0.6 ± 3.4
ESPVR (Quadratic) E'max	13.2 ± 5.1	10.6 ± 5.2
PRSW Slope	69.4 ± 18.4	49.7 ± 19.9
PRSW Intercept	4.6 ± 5.7	1.2 ± 7.2
dP/dtmax vs EDV slope	308.7 ± 69.4	268.1 ± 50.7
dP/dtmax vs EDV intercept	-1.1 ± 3.3	0.1 ± 4.2
Emax	8.0 ± 2.2	6.8 ± 3.0

Values are expressed as mean ± SD. Parameters of LV compliance (linear and quadratic derived EDPVR) and LV contractility (linear and quadratic derived ESPVR, PRSW, dP/dtmax vs EDV and Emax); Statistical comparisons made with Student's t-test. EDPVR=End Diastolic Pressure Volume Relationship; ESPVR=End Systolic Pressure Volume Relationship; a= coefficient of curvilinearity; Vo=Volume intercept; E'max= maximum slope of quadratic ESPVR; PRSW= Preload Recruitable Stroke Work; Emax=maximal elastance.

Table S2. Tamoxifen treatment: census after 1week TAM

Mouse Genotype	Total mice	Sex	Treatment	Mice survived	Mice dead	% mortality
Mdm2$^{fl/fl}$ MCM	12	Males	vehicle	11	1	9%
Mdm2$^{fl/fl}$ MCM	20	Males	TAM	5	15	75%
Mdm2$^{fl/fl}$ MCM	8	Females	TAM	4	4	50%
Mdm2$^{fl/fl}$	7	Males	TAM	7	0	0%
MCM	20	Males	TAM	20	0	0%
Mdm2 $^{fl/+}$ MCM	16	Males	vehicle	16	0	0%
Mdm2 $^{fl/+}$ MCM	16	Males	TAM	16	0	0%