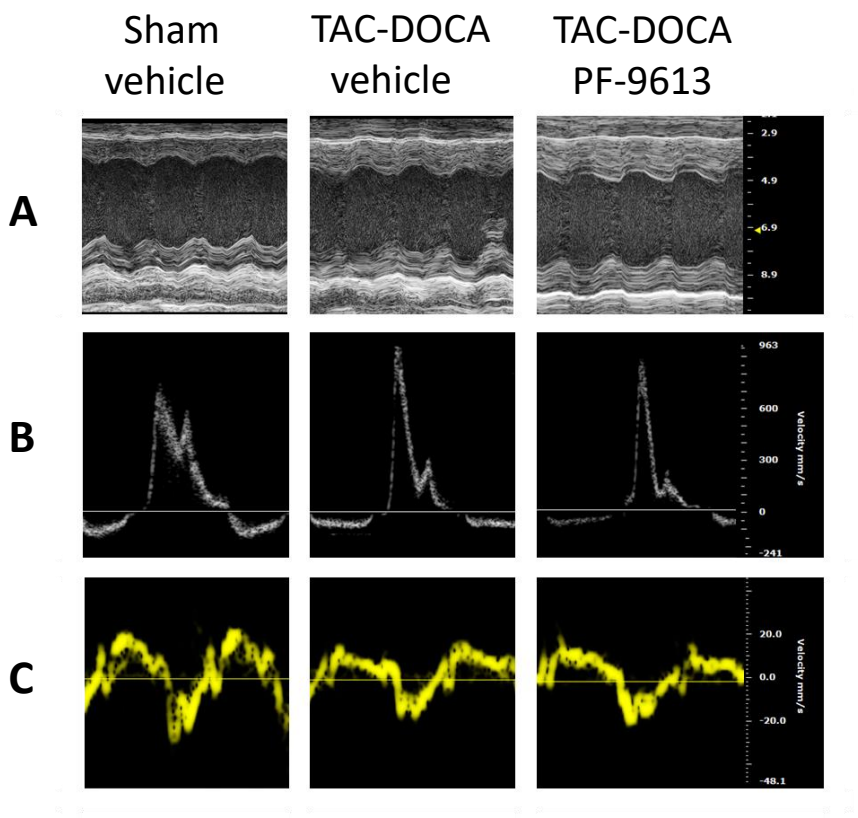
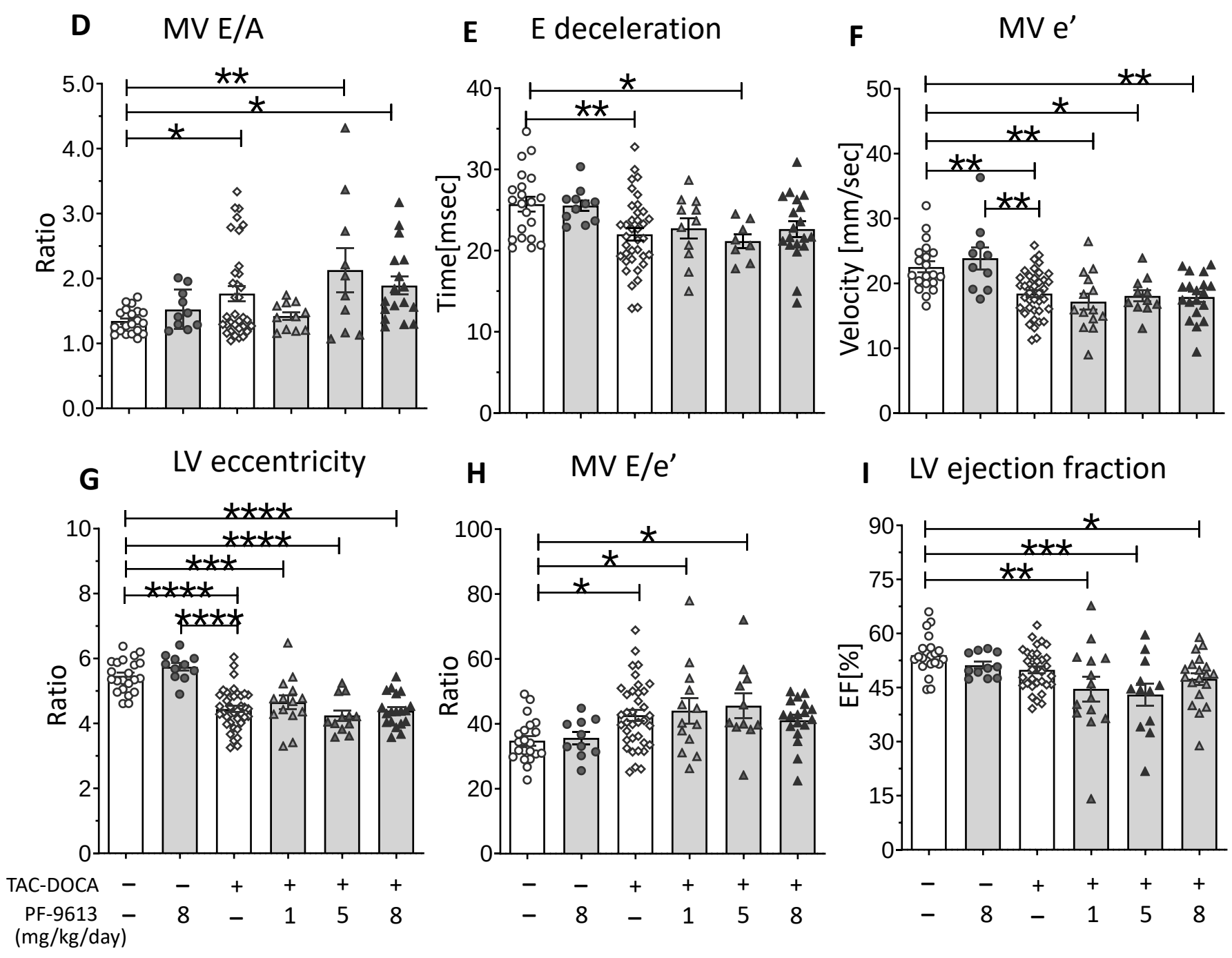


Figure 1. Echocardiography of TAC-DOCA mice. Representative figures of M-Mode **(A)**, mitral inflow pattern**(B)** and mitral annular velocity**(C)**. TAC-DOCA-veh mice exhibit a HFpEF-like condition observed as increased mitral E/A ratio**(D)**, shortened E deceleration time**(E)**, reduced mitral annular e' velocity**(F)**, LV concentric remodeling**(G)**, increased MV E/e' **(H)**, but preserved ejection fraction **(I)**. No difference in diastolic parameter is observed between TAC-DOCA-veh and TAC-DOCA-inh. However there is a significant reduction in LV ejection fraction in all 3 groups of TAC-DOCA-inh **(I)** . (n= 22, 11, 40, 14, 12, 19 mice for sham-vehicle, sham-PF-4449613, TAC-DOCA-vehicle and TAC-DOCA with PF-4449613 at 1mg, 5mg and 8 mg/kg/day respectively) *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001. Two-way ANOVA without repeated measures with a Dunnett test for multiple comparisons of mean of each group with mean of the control group (sham-vehicle or TAC-DOCA-vehicle) was used.



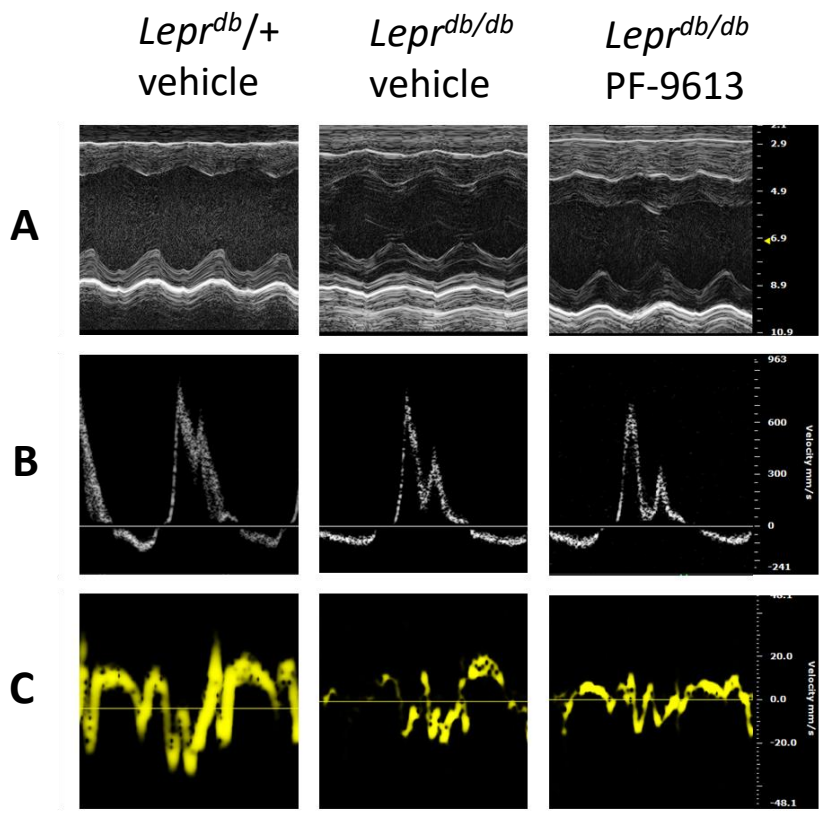
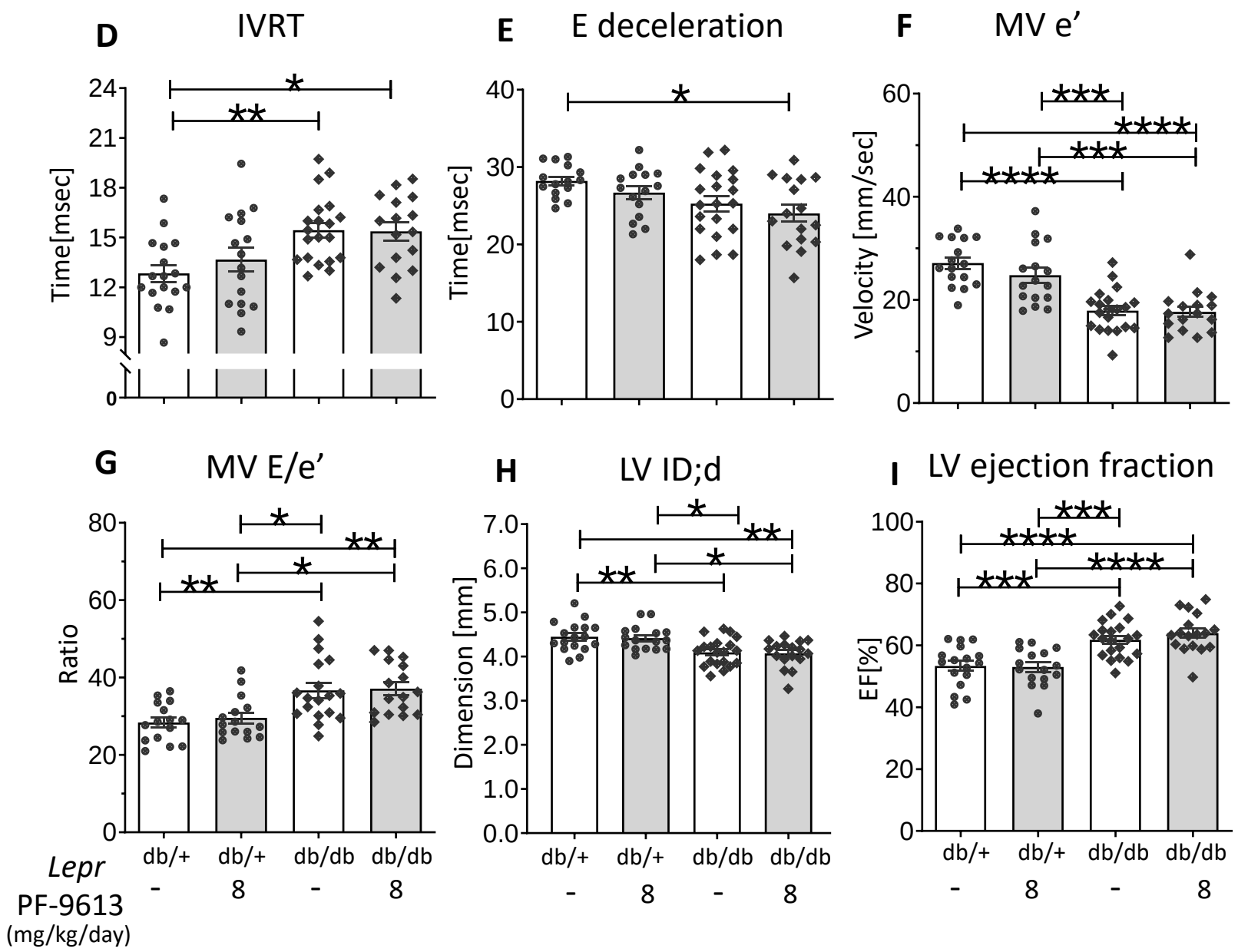


Figure 6. Echocardiography of *Lepr*$^{db/db}$ mice. Representative figures of M-Mode**(A)**, mitral inflow pattern**(B)** and mitral annular velocity**(C)**. *Lepr*$^{db/db}$ mice exhibit diastolic dysfunction observed as prolonged isovolumic relaxation time (IVRT)**(D),** shorten E wave deceleration time**(E)**, reduced mitral annular e' velocity**(F)**, elevated LV diastolic filling pressure (E/e' ratio) **(G),** reduced LV internal dimension in diastole (LV ID;d) **(H)**, but preserved ejection fraction**(I)**. No improvement in diastolic parameters is observed in *Lepr*$^{db/db}$ mice with PDE9a inhibition. (n=17, 16, 20, 17 mice) * p≤0.05 ** p≤0.01 ***p≤0.001 ****p≤0.0001. Two-way ANOVA, without repeated measures with a Tukey test was performed.



Supplemental Table S1. TAC-DOCA mouse model

	Sham Vehicle	Sham PF-9613 8mg/kg/day	TAC-DOCA Vehicle	TAC-DOCA PF-9613 1mg/kg/day	TAC-DOCA PF-9613 5mg/kg/day	TAC-DOCA PF-9613 8mg/kg/day
Age (days)	123.2±1.1	121.3±0.8	121.1±0.8	125.8±1.8†	119.4±0.1	120±0.4
Body Weight (gm)	30.83±0.42	31.08±0.4	29.38±0.29*	31.41±0.36†	30.88±0.60	29.77±0.52
Tibial Length, TL (mm)	17.5±0.05	17.48±0.07	17.34±0.03*	17.25±0.08*	17.55±0.05	17.35±0.06
Echocardiography						
Number of mice	n=22	n=11	n=40	n=14	n=12	n=19
Heart Rate (bpm)	566.3±7.2	581.5±10.8††	533±6.2 **	515.3±10.5 ***	543.2±12.7	537.4±9.7
EF (%)	53.98±1.13	51.2±1.01	49.92±1.0	44.63±3.42**	43.07±3.07***	47.42±1.65*
LV EDV (µL)	75.58±2.59	83.65±2.49	77.86±2.41	80.92±3.71	88.63±4.05*	79.11±2.07
LV stroke volume (µL)	40.29±0.95	42.73±1.31††	37.41±0.63	37.54±1.28	35.97±1.66*	35.21±1.15**
LV diastolic wall strain	0.29±0.01	0.28±0.02	0.23±0.01**	0.22±0.03*	0.21±0.02**	0.23±0.01*
WT;d (mm)	0.75±0.01	0.74±0.02††††	0.95±0.02****	0.92±0.04****	1.03±0.02****	0.93±0.03****
WT;s (mm)	1.07±0.02	1.02±0.03††††	1.23±0.02****	1.18±0.04*	1.31±0.04****	1.22±0.03***
LV MPI	0.46±0.01	0.47±0.02	0.45±0.02	0.44±0.02	0.43±0.02	0.44±0.02
Eccentricity	5.47±0.11	5.74±0.12††††	4.45±0.10****	4.65±0.21***	4.24±0.16****	4.40±0.12****
MV IVRT (msec)	13.19±0.37	13.7±0.54	14.8±0.40	14.99±0.73	14.3±0.77	14.55±0.65
E decel time (ms)	25.72±0.91	25.56±0.65	22.17±0.75**	22.74±1.25	21.16±0.86*	22.66±0.96
MV e' (mm/sec)	22.55±0.85	23.88±1.73††	18.44±0.56**	17.2±1.21**	18.09±0.86*	17.91±0.80**
MV E/A	1.35±0.04	1.52±0.10	1.77±0.12	1.42±0.06	2.13±0.34**	1.89±0.14*
MV E/e´	34.81±1.46	35.67±1.89	42.7±1.70*	44.05±3.87*	45.61±3.79*	41.14±1.66

Supplemental Table S1 (continue)

	Sham Vehicle	Sham PF-9613 8mg/kg/day	TAC-DOCA Vehicle	TAC-DOCA PF-9613 1mg/kg/day	TAC-DOCA PF-9613 5mg/kg/day	TAC-DOCA PF-9613 8mg/kg/day
Pressure-Volume Analysis						
Number of mice	n=22	n=10	n=33	n=14	n=11	n=15
Load Dependent Parameters						
ESP (mmHg)	87.91±1.44	86.96±3.02^{ǂǂǂ}	127.4±2.50****	120.8±5.94****	137.1±2.64****	130.2±4.64****
EDP (mmHg)	3.32±0.48	3.19±0.66	6.23±0.63*	6.28±1.01	8.19±1.31**	8.34±1.22***
dPmax (mmHg/s)	9376±328.6	9170±358.4	8299±195*	7976±285.3**	7886±278.2*	8271±370
dPmin (mmHg/s)	-8109±274.3	-8006±399.4	-8417±228.4	-8032±351.5	-7940±548.7	-8284±460.2
ESV (µl)	31.23±1.90	31.25±2.89	41.32±2.07*	40.45±3.39	60.94±5.03****^{ǂǂǂ}	52.10±5.40****
EDV (µl)	71.25±2.24	70.64±3.02	73.64±2.07	76.09±4.42	91.42±5.02***^{ǂǂ}	83.41±5.27
SV (µl)	40.02±1.08	39.40±0.96	34.66±1.04*	35.64±2.21	30.47±2.01***	31.31±1.88***
CO (mL/min)	21.19±0.71	21.28±0.66^{ǂǂ}	17.01±0.67***	17.32±1.03*	15.34±1.02***	15.99±0.78***
Tau Weiss (ms)	5.75±0.15	5.86±0.22^{ǂ}	7.08±0.21***	6.64±0.20	8.12±0.64****	7.67±0.50****
Ea (mmHg/µl)	2.25±0.07	2.24±0.10^{ǂǂǂ}	4.03±0.19****	3.66±0.35***	4.71±0.35****	4.32±0.31****
VA coupling ratio	0.59±0.05	0.7±0.11	0.82±0.06	0.62±0.07	1.19±0.16****^{ǂ}	1.06±0.12***
Load Independent Parameters						
Ees (mmHg/µl)	4.13±0.31	3.78±0.51	5.46±0.28*	6.38±0.59***	3.98±0.38^{ǂ}	4.49±0.42^{ǂ}
PRSW (mmHg)	92.83±2.01	88.99±3.59^{ǂǂ}	112±3.76**	114.3±5.05**	93.56±7.07^{ǂ}	99.98±6.03
EDPVR (mmHg/µl)	0.020±0.002	0.022±0.004^{ǂǂ}	0.045±0.004****	0.038±0.005*	0.028±0.003^{ǂ}	0.029±0.004^{ǂ}
Tissue Morphometry						
Number of mice	n=26	n=10	n=46	n=14	n=12	n=15
LV/TL (mg/mm)	5.35±0.08	5.56±0.07^{ǂǂǂ}	7.94±0.19****	7.51±0.40****	9.18±0.44****^{ǂǂ}	8.28±0.42****
RV/TL (mg/mm)	1.32±0.03	1.34±0.04	1.31±0.03	1.35±0.04	1.41±0.09	1.40±0.05
Lt ATR/TL(mg/mm)	0.23±0.01	0.24±0.01^{ǂǂ}	0.40±0.02****	0.42±0.041****	0.52±0.06****^{ǂ}	0.48±0.05****
Rt ATR/TL(mg/mm)	0.23±0.01	0.22±0.01	0.26±0.01	0.26±0.02	0.28±0.02	0.29±0.02**
Lung/TL(mg/mm)	8.42±0.17	8.97±0.02	11.2±0.79*	10.06±1.05	N/A	10.02±0.82

Supplemental Table S1. Echocardiography, pressure volume analysis parameters and tissue morphometry of TAC-DOCA mice after 4 weeks of vehicle or PDE9a inhibition. ATR indicates atria; CO, cardiac output; d, diastole; dPmax, maximal rate of pressure change; dPmin, minimal rate of pressure change; Ea, effective arterial elastance; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure-volume relation; EDV, end-diastolic volume; Ees, end-systolic elastance; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; IVRT, isovolumic relaxation time; LA, left atrium; LV, left ventricle; LVID, LV internal dimension; MPI, myocardial performance index; MV, mitral valve; PRSW, preload recruitable stroke work; PV, pressure-volume; RV, right ventricle; S, systole; SV, stroke volume; Tau Weiss, left ventricular relaxation–time constant; TL, tibial length; VA coupling ratio (Ea/Ees),ventricular-arterial coupling ratio; and WT, wall thickness.* $p \leq 0.05$,** $p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$ significant vs. sham vehicle, ŧ $p \leq 0.05$,ŧŧ $p \leq 0.01$, ŧŧŧ$p \leq 0.001$, ŧŧŧŧ $p \leq 0.0001$ significant vs. TAC-DOCA-veh.

Supplemental Table S3. *Lepr^{db}* mouse model

	***Lepr^{db}*/+ Vehicle**	***Lepr^{db}*/+ PF-9613 8 mg/kg/day**	***Lepr$^{db/db}$* Vehicle**	***Lepr$^{db/db}$* PF-9613 8 mg/kg/day**
Age (days)	132.3±2.4	132.4±2.4	131±2.3	132.2±3.0
Body Weight, BW (gm)	35.03±0.40	34.74±0.48	57.48±0.81****^{ŧŧŧŧ}	58.24±1.11****^{ŧŧŧŧ}
Tibial Length, TL (mm)	17.41±0.10	17.38±0.06	16.65±0.12****^{ŧŧŧŧ}	16.46±0.10****^{ŧŧŧŧ}
Echocardiography				
Number of mice	n=17	n=16	n=20	n=17
Heart Rate (bpm)	576.1±6.7	568.9±8.6	509.3±10.2****^{ŧŧŧ}	508.1±11.9****^{ŧŧŧ}
Cardiac output (mL/min)	29.16±1.05	27.7±0.98	23.89±0.70***^{ŧ}	24.01±0.91**^{ŧ}
EF (%)	53.34±1.62	52.98±1.54	61.78±1.28***^{ŧŧŧ}	63.94±1.52****^{ŧŧŧŧ}
LV EDV (µL)	96.38±4.35	93.19±4.05	77±2.98**^{ŧŧ}	74.71±2.73***^{ŧŧ}
LV stroke volume (µL)	49.22±1.41	48.68±1.46	47.06±1.34	47.49±1.66
LV diastolic wall strain	0.26±0.02	0.27±0.02	0.29±0.01	0.31±0.02
WT;d (mm)	0.76±0.02	0.75±0.01	0.72±0.01	0.75±0.02
WT;s (mm)	1.03±0.02	1.03±0.02	1.02±0.02	1.09±0.03
LV MPI	0.46±0.02	0.47±0.02	0.48±0.02	0.47±0.02
Eccentricity	5.96±0.22	5.92±0.11	5.70±0.18	5.54±0.18
MV IVRT (msec)	12.83±0.51	13.67±0.71	15.44±0.45**	15.37±0.54*
E decel time (ms)	28.22±0.54	26.71±0.82	25.27±0.96	24.02±1.09*
MV e' (mm/sec)	27.14±1.12	24.8±1.46	17.93±0.92****^{ŧŧŧ}	17.69±1.01****^{ŧŧŧ}
MV E/A	1.37±0.09	1.41±0.06	1.56±0.13	1.48±0.07
MV E/e´	28.4±1.30	29.57±1.41	36.68±1.92**^{ŧ}	37.14±1.65**^{ŧ}

Supplemental Table S3 (continue)

	Lepr^{db}/+ Vehicle	*Lepr*^{db}/+ PF-9613 8 mg/kg/day	*Lepr*$^{db/db}$ Vehicle	*Lepr*$^{db/db}$ PF-9613 8 mg/kg/day
Pressure-Volume Analysis				
Number of mice	n=9	n=9	n=9	n=8
Load Dependent Parameters				
ESP (mmHg)	90.13±2.38	94.51±2.57	114.42±4.34****†††	108.41±3.42**†
EDP (mmHg)	2.84±0.77	3.32±0.71	10.37±1.86**††	7.90±1.68
dPmax (mmHg/s)	8862±293	9123±447	10,001±891	10,032±432
dPmin (mmHg/s)	-7996±407	-8419±423	-8267±751	-7881±407
ESV (µl)	40.31±2.92	31.13±3.22	41.59±3.41	35.12±3.54
EDV (µl)	85.66±4.43	74.59±3.58	85.09±4.79	76.64±4.58
SV (µl)	45.34±3.10	43.46±1.97	43.5±2.21	41.52±2.73
Tau Weiss (ms)	6.25±0.32	5.93±0.33	9.00±1.08*†	8.14±0.61
Ea (mmHg/µl)	2.09±0.15	2.23±0.11	2.72±0.16*	2.73±0.21*
VA coupling ratio	0.70±0.06	0.60±0.04	1.02±0.12†	1.10±0.15*††
Load Independent Parameters				
Ees (mmHg/µl)	3.11±0.26	3.96±0.46	2.96±0.40	2.66±0.26
PRSW (mmHg)	87.72±3.97	86.18±4.39	86.54±6.36	84.84±4.89
EDPVR (mmHg/µl)	0.019±0.002	0.023±0.004	0.044±0.007**†	0.035±0.005
Tissue Morphometry				
Number of mice	n=9	n=9	n=9	n=9
LV/TL (mg/mm)	6.47±0.20	6.19±0.24	5.81±0.17	5.89±0.12
RV/TL (mg/mm)	1.64±0.10	1.61±0.07	1.44±0.05	1.49±0.06
Lt ATR/TL (mg/mm)	0.29±0.02	0.26±0.01	0.23±0.02	0.23±0.02
Rt ATR/TL (mg/mm)	0.33±0.01	0.28±0.02	0.27±0.03	0.25±0.01*
Lung/TL (mg/mm)	9.30±0.18	9.31±0.23	8.09±0.25**††	8.43±0.19*†

Supplemental Table S3. Echocardiography, pressure volume analysis parameters and tissue morphometry of *Lepr*$^{db/db}$ mice after 4 weeks of vehicle or PF-9613 treatment For abbreviation, please refer to Table S1.* p≤0.05 ** p≤0.01 ***p≤0.001 ****p≤0.0001 significant vs. *Lepr*^{db}/+veh, ŧ p≤0.05,ŧŧ p≤0.01, ŧŧŧp≤0.001, ŧŧŧŧ p≤0.0001 significant vs. *Lepr*^{db}/+ inh.