	Gender (male)	Age	BMI	LVEF (%)	Heart Weight (g)	LVEDD (cm)	Creatinine (mg/dL)	Diabetes	Hypertension	Heart devices
Non-failing	38%	57±2	29.6±2	62.8±3.5	361±30	3.9±0.1	1±0.2	0	50%	0
Non-failing hypertrophy	56%	58±2	28.3±2	60±4.7	487±39*	3.8±0.1	1.3±0.1	0	50%	22%
Failing heart	69%	58±2	25.8±1	14±1*#	504±31*	6.9±0.3*#	1.2±0.1	0	50%	88%

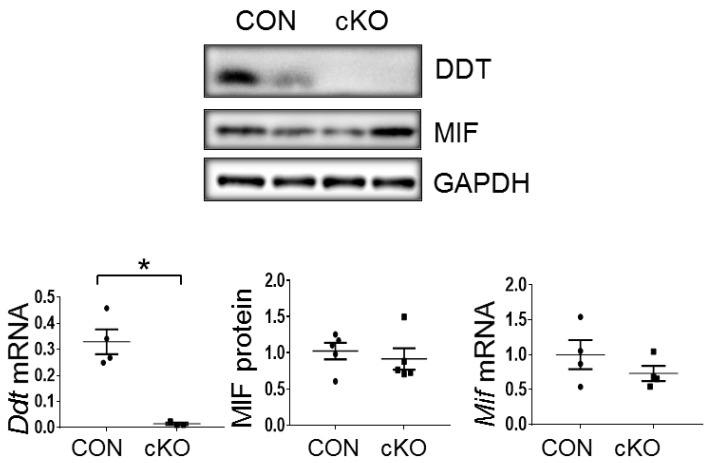
Supplementary table 1. Demographic and clinic features of patient groups. BMI: body mass index, LVEF: Left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter. Heart devices include implantable cardioverter defibrillators and pacemakers. Data are mean ± SEM, n=8 for the non-failing heart and non-failing hypertrophy heart; n=16 for the failing heart group. Significance determined by 2-tailed student's t test. *$p<0.05$ compare with non-failure group, #$p<0.05$ compare with non-failure hypertrophy group.

		CON sham	cKO sham	CON TAC	cKO TAC
Heart Rate (beats/min)	pre-TAC	439.7±8.6	445.8±21.4	419.4±9.6	420.6±8.7
	1 day	404.4±7	402.5±10.5	443.6±14.7	451.7±23.9
	2 weeks	447.7±4.4	439.5±15.9	472.2±18	533.6±15.7
	4 weeks	440.5±14.3	450.1±11.5	504±25.1	494.4±13.6
	6 weeks	440±13.8	470.5±12.7	511.1±25	548.8±11.1
Stroke Volume (uL)	pre-TAC	38.3±2.2	40.6±3.2	43.5±2.2	41.7±1.6
	1 day	34.7±1.4	39.1±2.4	32.1±2.4	34.8±2.3
	2 weeks	34.5±1.7	44.9±1	44±1.6	33.6±4.2*
	4 weeks	39.2±1.5	40.6±0.6	40.3±1.2	28.8±4*
	6 weeks	39.7±4.1	42.3±4.1	39.2±2.4	25.2±3.8*
Fractional Shortening (%)	pre-TAC	28.6±0.9	32.3±3	28.8±1.4	28.8±2
	1 day	25.2±0.7	27.9±2.1	25.8±1.9	24.8±1.9
	2 weeks	24.8±0.7	33.2±1.8	29.9±1.5	22.5±3.6*
	4 weeks	29.2±1.4	28.5±3.5	25.9±1.5	15.4±2.9*
	6 weeks	31.8±3.5	28.7±4.1	23.8±1.8	11.8±2.8*

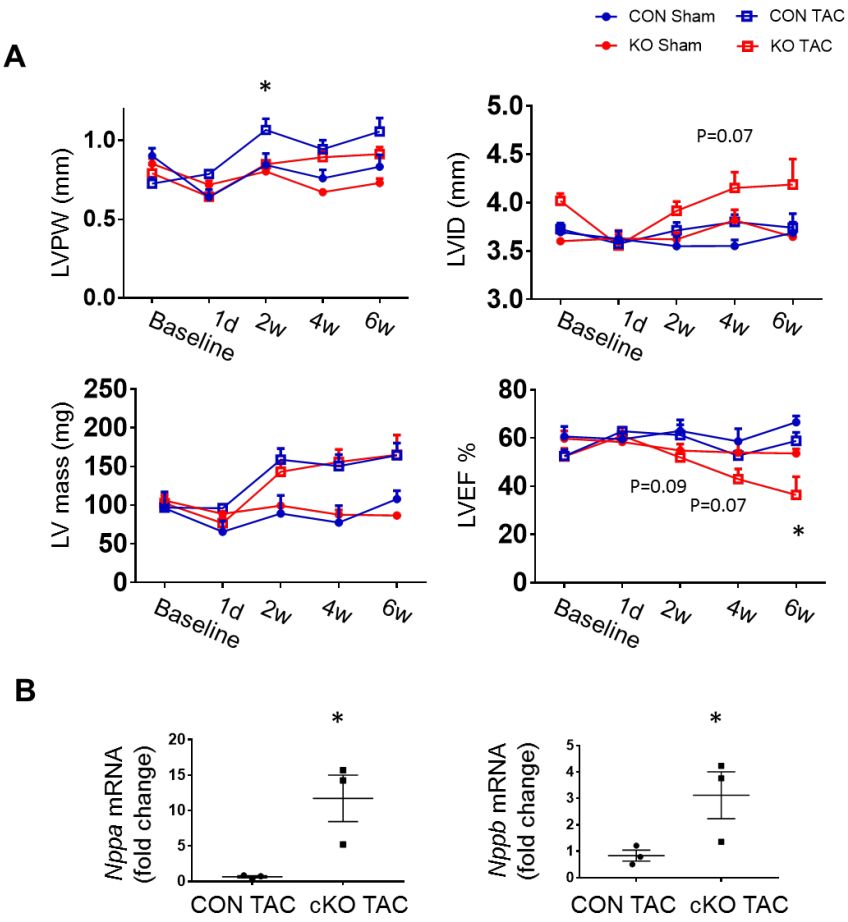
Supplementary table 2. Effects of transverse aortic constriction (TAC) on additional echocardiography measurements in cardiomyocyte specific D-dopachrome tautomerase (DDT) knockout (cKO) mice and its control (CON) mice. Echocardiographic results obtained 1 day prior to TAC or sham surgery, and 1 day, 2 weeks, 4 weeks, 6 weeks after surgeries. Two-way ANOVA testing was used for statistical analysis. *$p<0.05$ compare with CON TAC group. N=9 mice per group.

		CON sham	cKO sham	CON TAC	cKO TAC
1 week surgery male	BW (g)	24.9±0.5	25.4±1	23.7±1.7	23.6±0.8
	LW (wet) (g)	0.14±0.007	0.13±0.005	0.13±0.008	0.13±0.007
	LW (dry) (g)	0.03±0.001	0.03±0.002	0.03±0.002	0.03±0.002
	LW (wet)/BW	0.006±0.0003	0.005±0.0001	0.006±0.0002	0.006±0.0003
	LW (wet)/LW (dry)	4.6±0.1	4.3±0.2	4.5±0.1	4.4±0.1
7 week surgery male	BW (g)	27.7±0.5	30±1.6	28.6±1.1	26.3±1.5
	LW (wet) (g)	0.14±0.003	0.14±0.011	0.14±0.008	0.31±0.061*
	LW (dry) (g)	0.03±0.003	0.03±0.002	0.03±0.002	0.06±0.012*
	LW (wet)/BW	0.005±0.0001	0.005±0.0002	0.005±0.0003	0.012±0.0025*
	LW (wet)/LW (dry)	4.3±0.3	4.6±0.2	4.2±0.1	4.8±0.1*
7 weeks surgery female	BW (g)	20.6±0.5	20.7±0.3	22±0.7	21.6±0.5
	LW (wet) (g)	0.14±0.005	0.12±0.004	0.14±0.004	0.21±0.046
	LW (dry) (g)	0.03±0.001	0.02±0.001	0.03±0.001	0.04±0.009
	LW (wet)/BW	0.007±0.0001	0.006±0.0002	0.006±0.0001	0.01±0.0021
	LW (wet)/LW (dry)	4.4±0.1	5.3±0.4	4.8±0.1	5.1±0.1

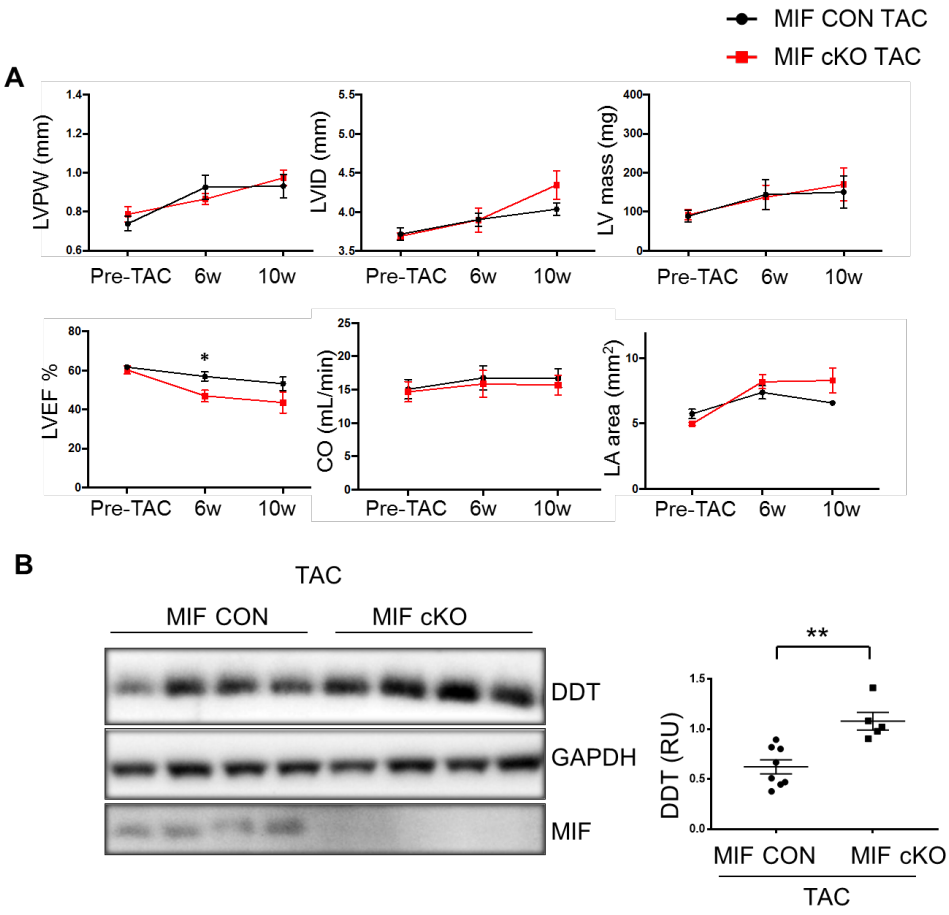
Supplementary table 3. Effects of transverse aortic constriction (TAC) on body weight (BW), wet lung weight (LW), dry LW, and the ratios of wet LW/BW and wet LW/dry LW in cardiomyocyte specific D-dopachrome tautomerase (DDT) knockout (cKO) mice and its control (CON) mice. Two-way ANOVA testing was used for statistical analysis.* $p<0.05$ compare with CON TAC group. N=9 mice per group.



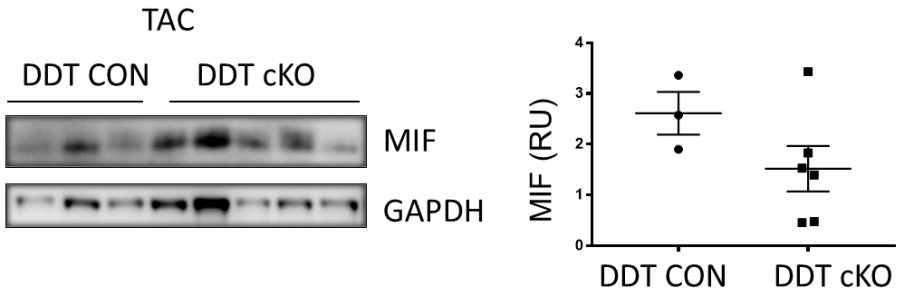
Supplementary figure 1. D-dopachrome tautomerase (DDT) and macrophage migration inhibitory factor (MIF) expressions in cardiomyocyte specific DDT knockout (cKO) mice and littermate control (CON) mice. Upper panel: Immunoblots showing left ventricular tissue homogenate DDT, MIF and GAPDH content in CON and cKO mice. Lower panel: quantification of MIF protein level and *Ddt/Mif* mRNA expression levels. Data are mean ± SEM, n=4-5 mice per group. Significance determined by 2-tailed student's t test. *p<0.05 as indicated by brackets.



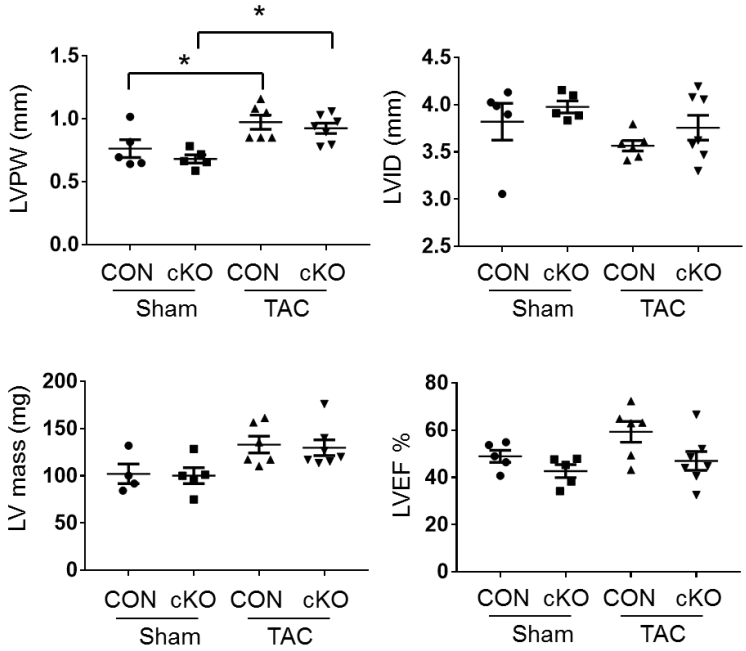
Supplementary figure 2. Effects of cardiomyocyte D-dopachrome tautomerase (DDT) deletion on the transition from hypertrophy to heart failure after pressure overload in female mice. (A) Echocardiographic results in cardiomyocyte specific DDT knockout (cKO) mice and littermate control (CON) mice. LVPW: left ventricular posterior wall thickness; LVID: left ventricular inner diameter; LVEF: left ventricular ejection fraction. Data are mean ± SEM, n=6 per group. There was no group difference by two-way ANOVA testing between control (CON) mice and DDT knockout (cKO) mice after transverse aortic constriction (TAC). *p<0.05 compared with CON TAC group by using Tukey's multiple comparisons test. (B) Heart failure biomarkers in female CON and DDT cKO mice after pressure overload: the content of mRNA transcripts for atrial natriuretic peptide (*Nppa*) and brain natriuretic peptide (*Nppb*) relative to ribosomal protein L32 (*Rpl32*) in the left ventricle 7 weeks after TAC surgery. Significance determined by 2-tailed student's t test. Data are mean ± SEM, n=3 mice per group. *p<0.05 compare to CON TAC.



Supplementary figure 3. Effects of cardiomyocyte macrophage migration inhibitory factor (MIF) deletion after pressure overload. (A) Echocardiographic results in cardiomyocyte specific MIF knockout (cKO) mice and littermate control (CON) mice. MIF cKO and CON mice were imaged 1 day prior to transverse aortic constriction (TAC) or sham surgery, and 6, 10 weeks after surgery. LVPW: left ventricular posterior wall thickness; LVID: left ventricular inner diameter; LVEF: left ventricular ejection fraction; CO: cardiac output. Data are mean ± SEM, n=8 for CON and n=6 for cKO group, There was no group difference by two-way ANOVA testing between control (CON) mice and MIF knockout (cKO) mice after transverse aortic constriction (TAC). **p<0.05 compared with CON TAC group by using Tukey's multiple comparisons test. (B) DDT expression in left ventricular tissue from MIF CON and cKO mice 10 weeks after pressure overload. Data are mean ± SEM, n=6-8 mice per group. Significance determined by 2-tailed student's t test. **p<0.01 compare with MIF CON.

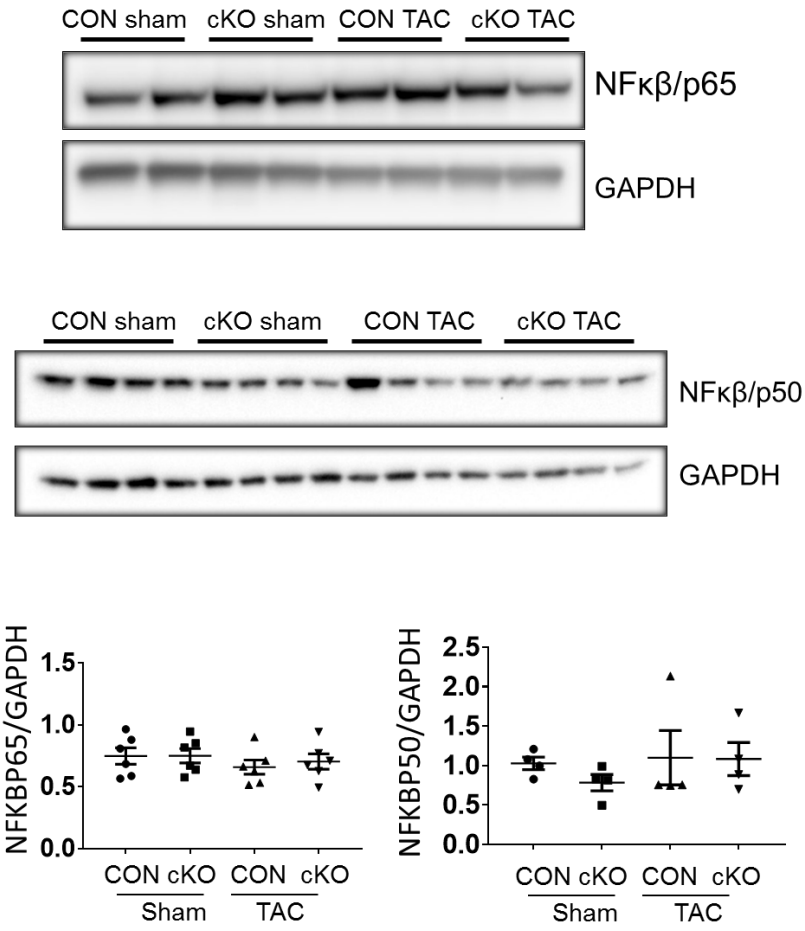


Supplementary figure 4. MIF expression in control (CON) mice and cardiomyocyte specific D-dopachrome tautomerase (DDT) knockout (cKO) mice 7 weeks after transverse aortic constriction (TAC). Data are mean ± SEM, n=3-5 mice per group. 2-tailed student's t test was used for statistical comparison.

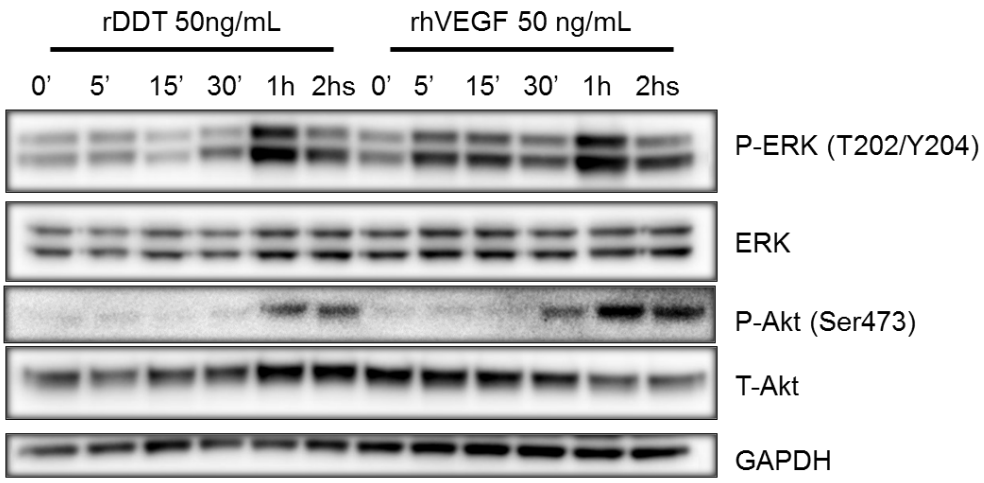


Supplementary figure 5. Echocardiographic results in cardiomyocyte specific DDT knockout (cKO) mice and littermate control (CON) mice 1 week after transverse aortic constriction (TAC) or sham surgery. LVPW: left ventricular posterior wall thickness; LVID: left ventricular inner diameter; LVEF: left ventricular ejection fraction. Data are mean ± SEM, n=5-7 per group. Significance determined by one-way ANOVA with Tukey's multiple comparisons test. *$p<0.05$ as indicated by brackets

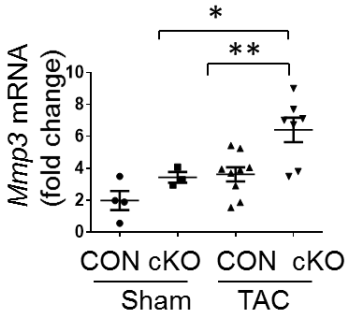
Cytoplasm



Supplementary figure 6. Immunoblots showing NFκβ (p65 and p50) content in the cytoplasmic extract of LV tissue 1 week after transverse aortic constriction (TAC) or sham surgery. CON: control mice; cKO: cardiomyocyte specific D-dopachrome tautomerase (DDT) knockout mice. Data are mean ± SEM, n=5-7 mice per group. One-way ANOVA with Tukey's multiple comparisons test was used for statistical comparisons.



Supplementary figure 7. Immunoblots comparing Akt and ERK phosphorylation in HUVECs after treatment with recombinant D-dopachrome tautomerase (rDDT) and recombinant human VEGF (rhVEGF) both at a concentration of 50 ng/mL.



Supplementary figure 8. Content of mRNA transcripts for *Mmp3*, 7 weeks after transverse aortic constriction (TAC) or sham surgery. CON: control mice; cKO: cardiomyocyte specific D-dopachrome tautomerase (DDT) knockout mice. Data are mean ± SEM, n=4-9. Significance determined by one-way ANOVA with Tukey's multiple comparisons test. *p<0.05, **p<0.01 indicated by brackets.

	Gender (male)	Age	LVEF (%)	BMI
Control	28%	58±0.9	N/A	31±0.7
HFpEF	60%	68±2*	61±1	37.7±2*
HFrEF	90%	62±1#	28±1#	34.4±1

Supplementary table 4. Demographic and clinical features of healthy control (con, n=43), heart failure with preserved ejection fraction (HFpEF, n=41), and heart failure with reduced ejection fraction (HFrEF, n=99) patients. BMI: body mass index, LVEF: Left ventricular ejection fraction. Data are mean ± SEM, significance determined by one-way ANOVA with Tukey's multiple comparisons test.*$p<0.05$ compare with control group, #$p<0.05$ compare with HFpEF group.