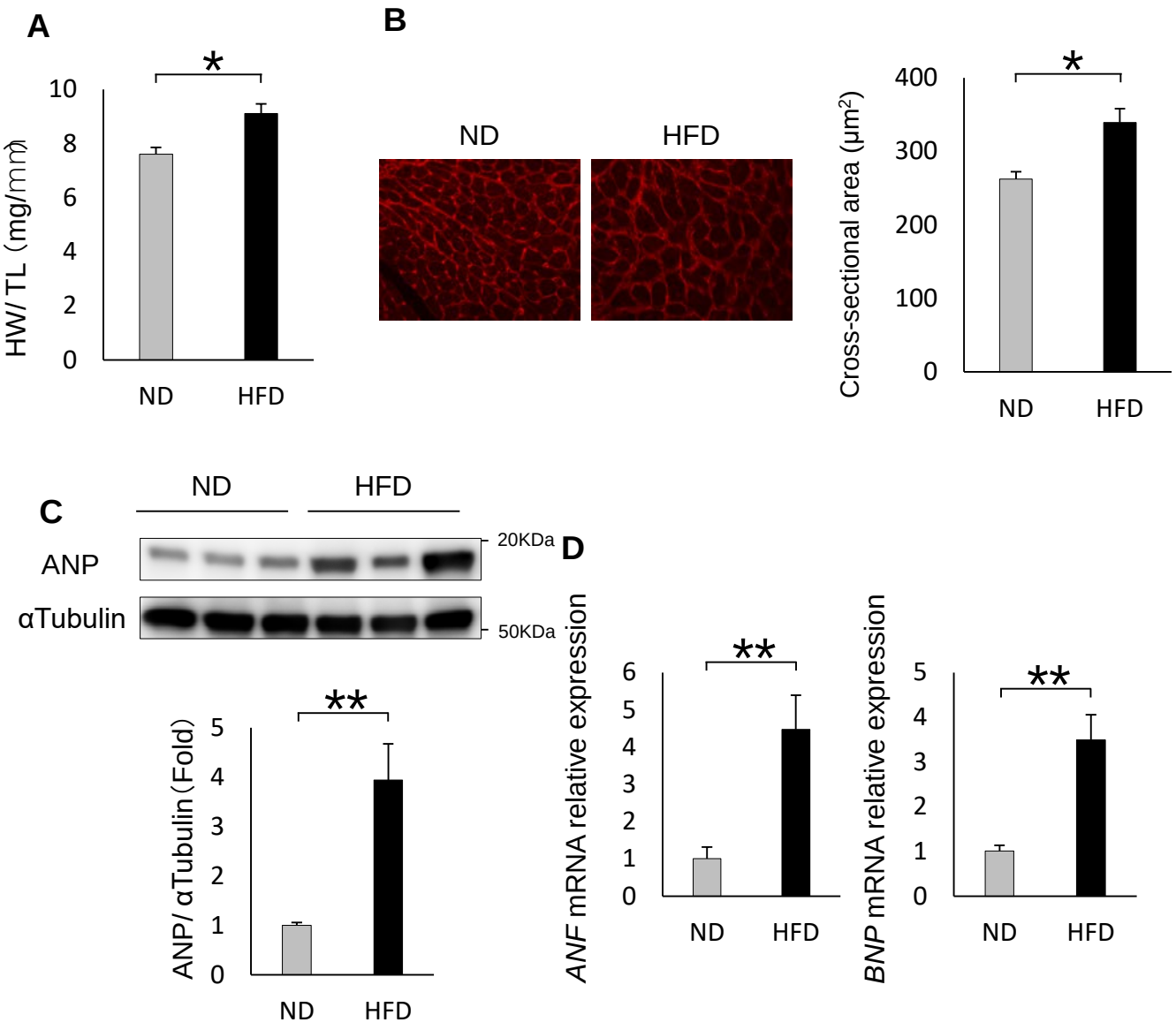
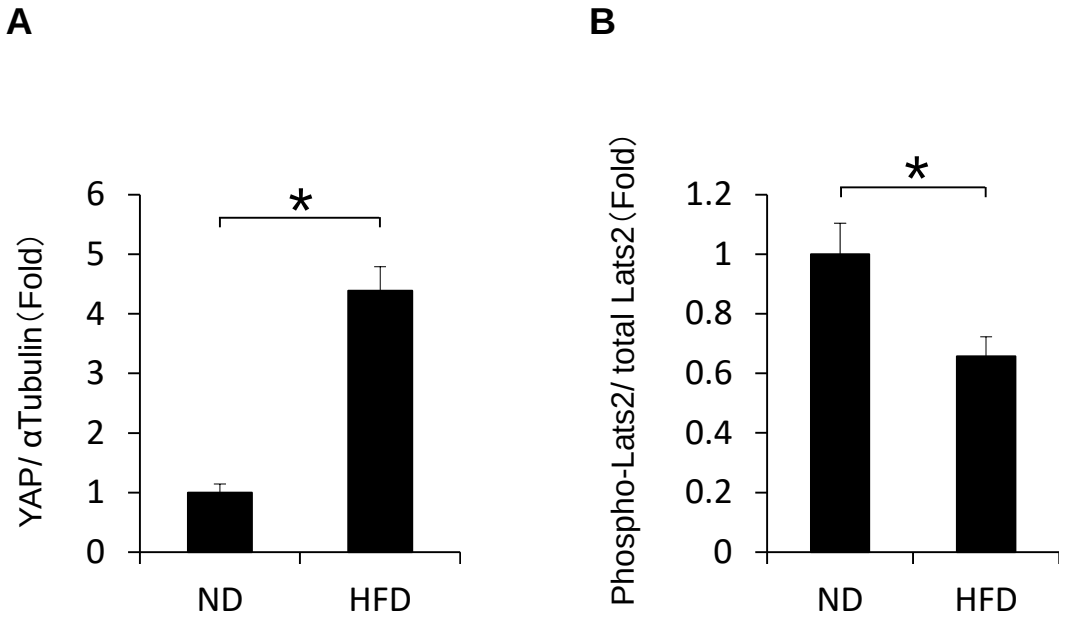
Online Figure 1



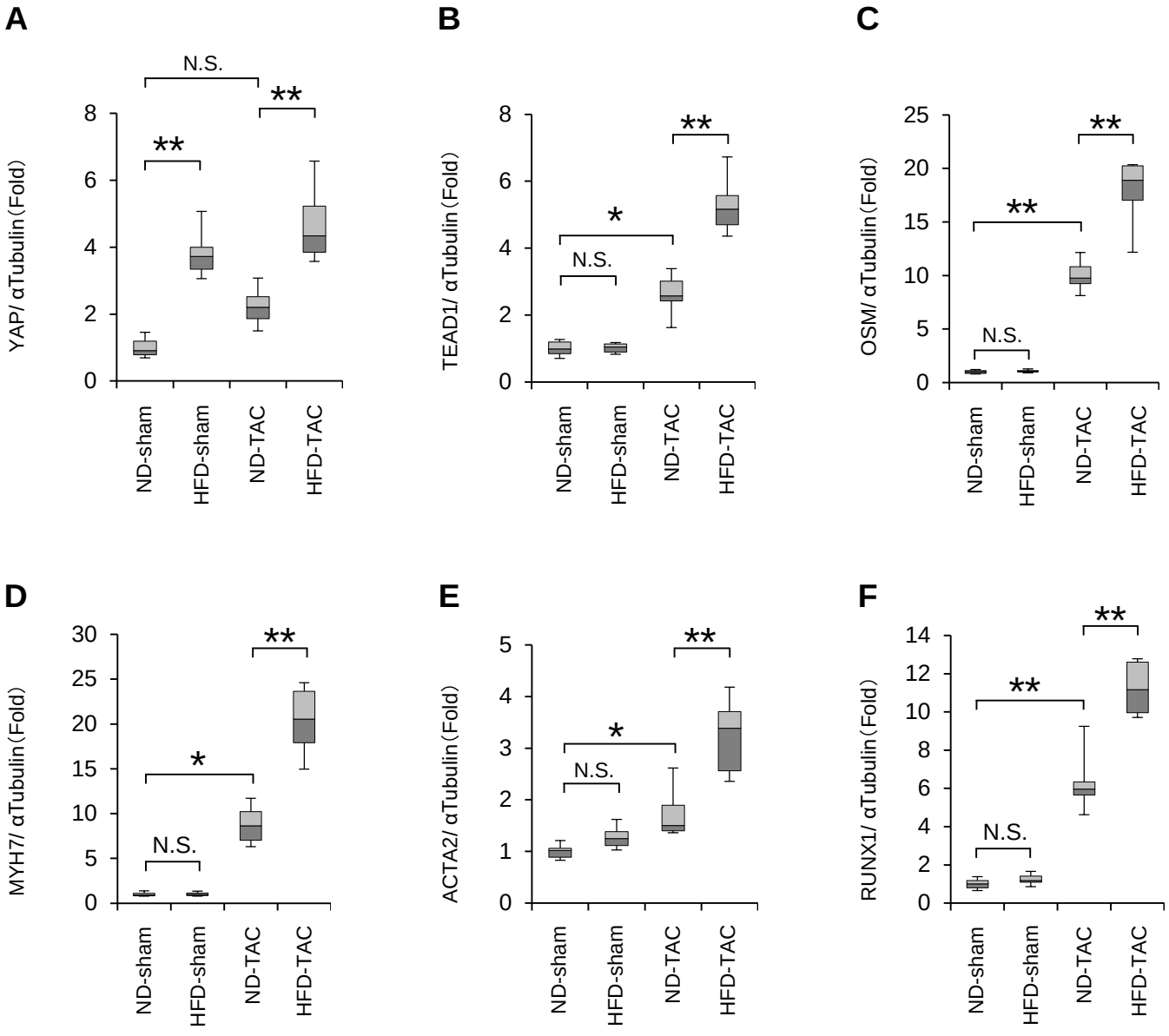
Online Figure 1. HFD induces cardiac hypertrophy in mice
Mice fed with ND or HFD for 8 weeks. (**A**) Heart weight (HW) to tibial length (LV W/ TL) ratio HFD (n=6, each). (**B**) Representative wheat germ agglutinin staining to assess CM cross-sectional area in mice fed with ND or HFD (n=6, each). (**C**) Representative gel pictures and quantitative analysis of ANP and α-tubulin in the heart. (n=6, each). (**D**) Analysis of relative mRNA expression of ANF and BNP in mice fed with ND or HFD (n=6, each). All results are expressed as mean ± SEM. *P<0.05, **P<0.01 by ANOVA.

Online Figure 2



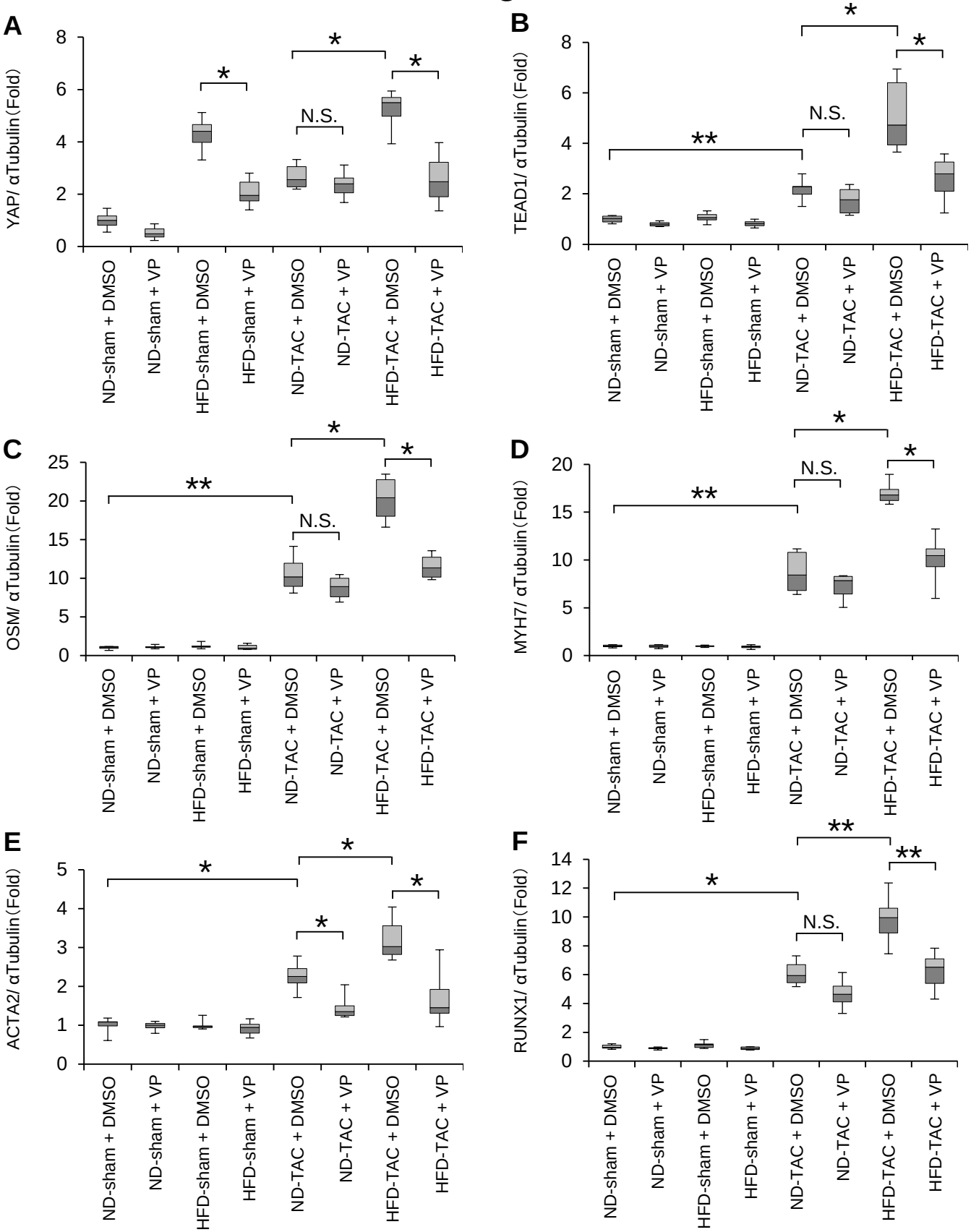
Online Figure 2. HFD induces cardiac activation of YAP and inactivation of Lats2 in mice
Mice fed with ND or HFD for 8 weeks. Quantitative analysis of immunoblot of YAP/ α-tubulin and phosphoLats2/ total Lats2 in the heart. (n=6, each). All results are expressed as mean ± SEM. *P<0.05 by ANOVA.

Online Figure 3



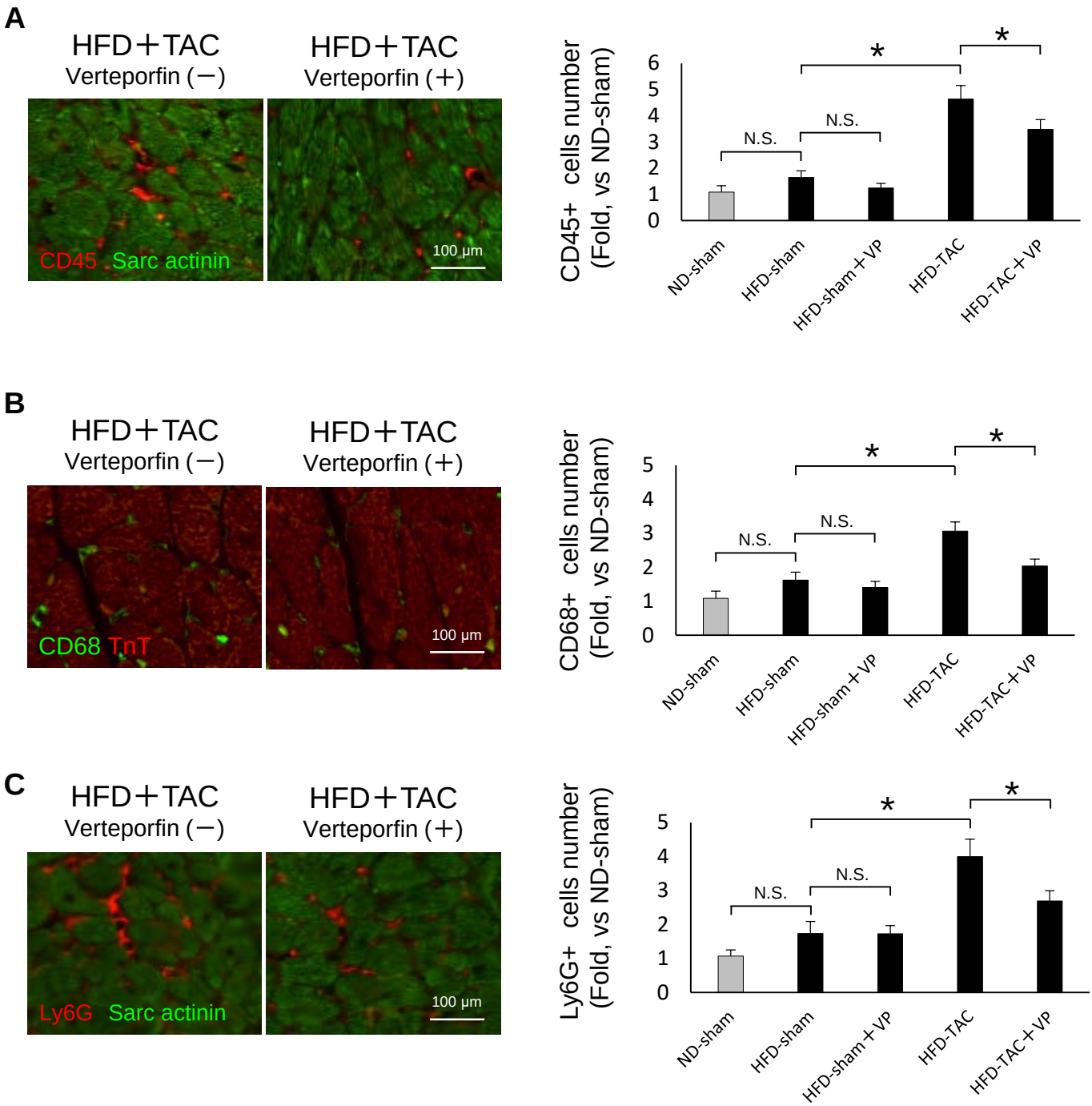
Online Figure 3. The effect of HFD on CM de-differentiation in response to PO
(**A-F**) Quantitative analysis of YAP, TEAD1, OSM, MYH7, ACTA2 and RUNX1 in response to PO after HFD treatment. **P<0.01 by ANOVA. The results are from 6 independent experiments. In box plots, whiskers show minimum and maximum values while bars represent the median and 25th and 75th percentiles.

Online Figure 4



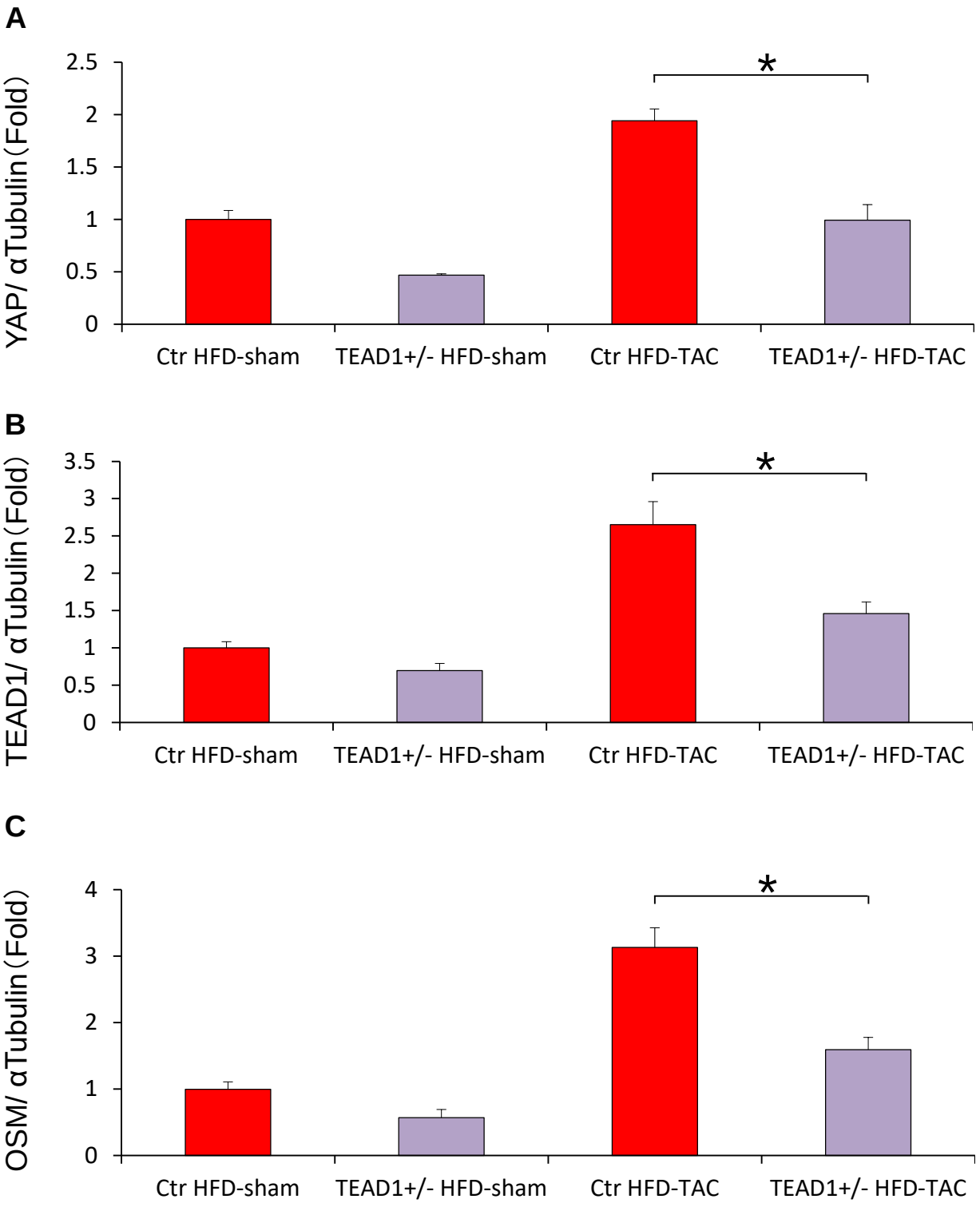
Online Figure 4. CM de-differentiation with or without Verteporfin in response to PO in the presence of HFD (**A-F**) Quantitative analysis of YAP, TEAD1, OSM, MYH7, ACTA2 and RUNX1 in the hearts. **P<0.01 by ANOVA. (n=6,each) In box plots, whiskers show minimum and maximum values while bars represent the median and 25th and 75th percentiles.

Online Figure 5



Online Figure 5. Inflammatory response in the heart during PO in the presence of HFD
(**A**) Representative immunostaining and quantitative analysis of CD45 (CD45, red; Sarc actinin, green; DAPI, blue) in the hearts 4 weeks after operation, with or without Verteporfin（VP）treatment. (n=4, each) (**B**) Representative immunostaining and quantitative analysis of CD68 (CD68, green; TnT, red; DAPI, blue) in the hearts 4 weeks after operation, with or without VP treatment. (n=4, each) (**C**) Representative immunostaining and quantitative analysis of Ly6G (Ly6G, red; Sarc actinin, green; DAPI, blue) in the hearts 4 weeks after operation, with or without VP treatment. (n=4, each) Results are expressed as mean ± SEM. *P<0.05 by ANOVA.

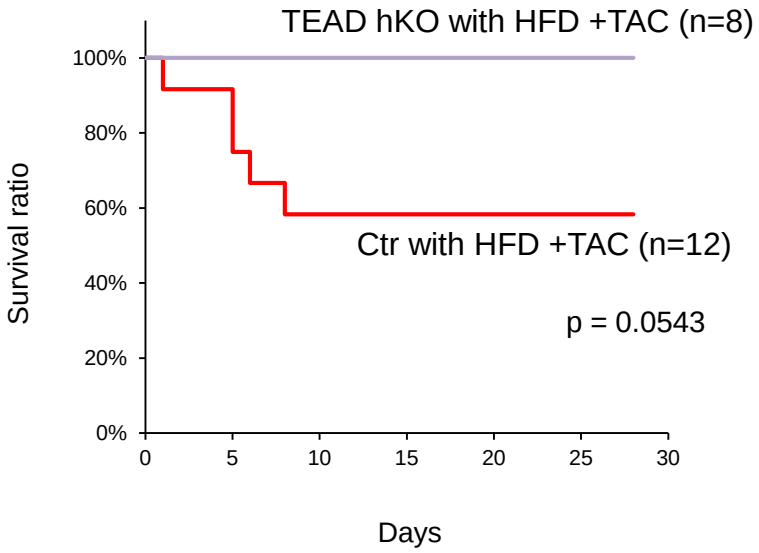
Online Figure 6



Online Figure 6. TEAD1 deletion attenuated the YAP-TEAD1-OSM loop during PO in the presence of HFD

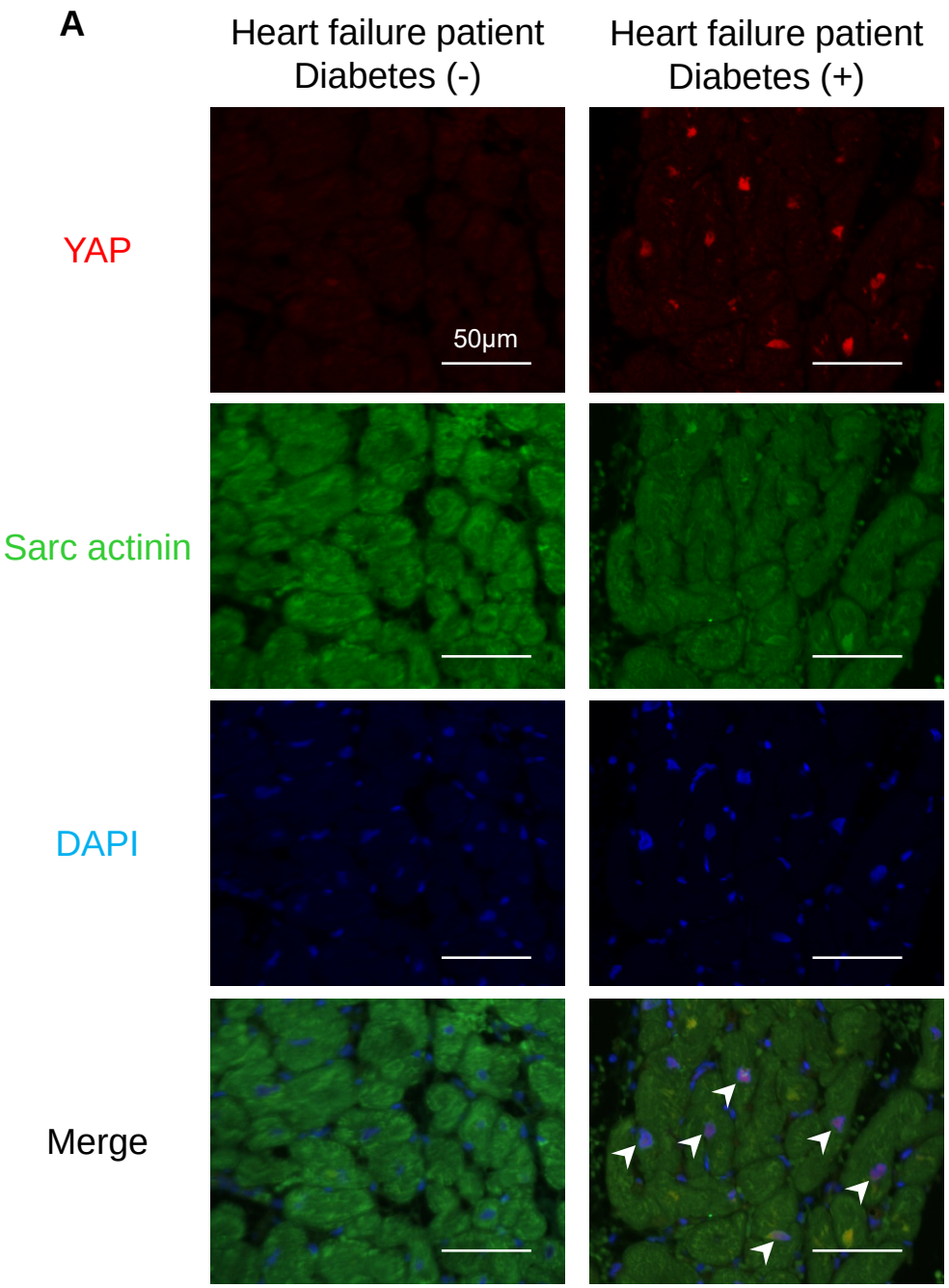
(**A-C**) Quantitative analysis of the immunoblot of the hearts. (n=6,each) All results are expressed as mean ± SEM. *P<0.05, **P<0.01 by ANOVA.

Online Figure 7

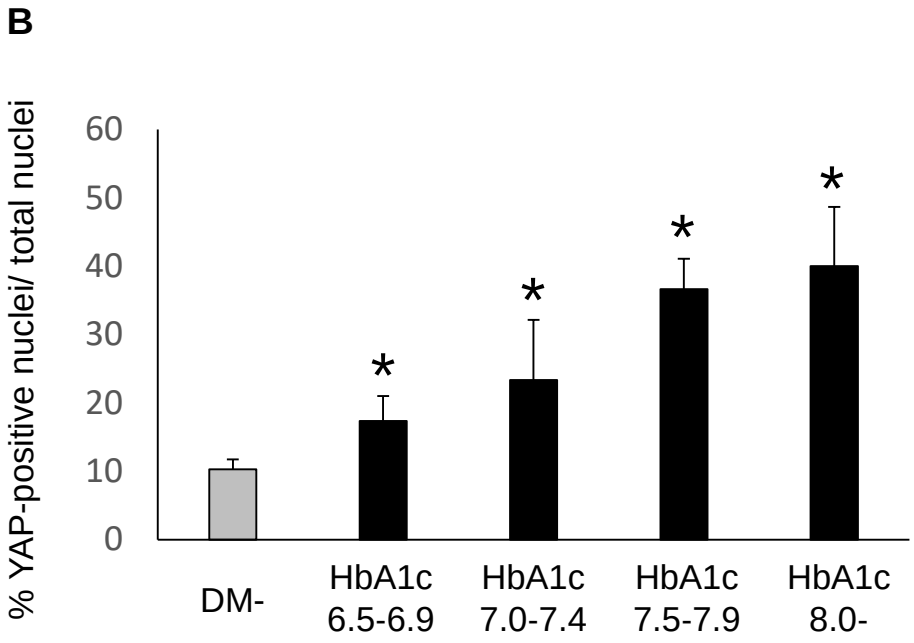


Online Figure 7. TEAD1 deletion attenuates PO-induced cardiac death in the presence of HFD
Kaplan-Meier survival curves after TAC in HFD treated Ctr mice and TEAD1 +/- mice.

Online Figure 8

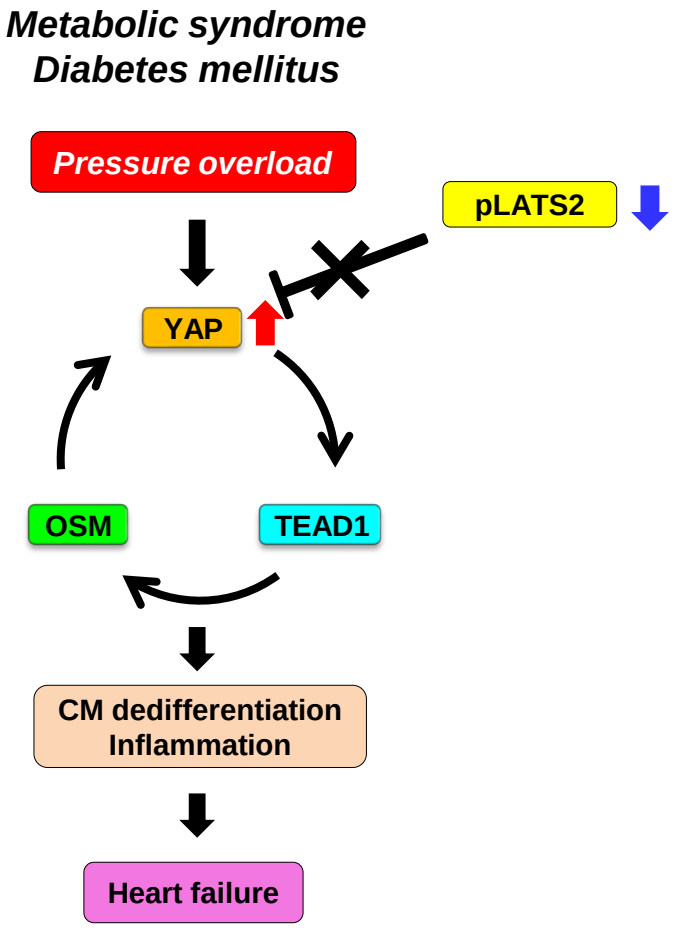


Online Figure 8 - continued-



Online Figure 8. Heart failure patients with diabetes showed YAP activation in CMs
(**A**) Representative double-immunostaining of YAP and Sarcomeric actinin in heart failure patients with and without diabetes (YAP, red; Sarc actinin, green; DAPI, blue). Nuclear YAP accumulation in CMs is indicated by arrow heads. (**B**) Quantitative analysis of YAP immunostaining in heart failure patients with and without diabetes. *P<0.05 versus the patients without diabetes.

Online Figure 9



Online Figure 9. Schematic representation of molecular mechanisms of HFD in response to PO.
PO induces severer cardiac dysfunction accompanied by CM de-differentiation in HFD treated mice through continuous upregulation of YAP. This process is dramatically facilitated by a positive feedback loop consisting of YAP-TEAD1-OSM. We propose that the suppression of YAP-TEAD1 has a novel therapeutic target for the cardiac dysfunction due to CM de-differentiation in metabolic syndrome/ diabetes mellitus with hypertension.

Online Table 1

	ND	HFD
DSEP WT(mm)	0.73 ± 0.03	0.81 ± 0.02
LVEDD(mm)	3.47 ± 0.11	3.54 ± 0.06
DPWT(mm)	0.79 ± 0.03	0.85 ± 0.04
LVESD(mm)	2.0 ± 0.1	2.0 ± 0.1
%FS	42.3 ± 1.4	42.8 ± 1.2
HR (bpm)	494 ± 10	474 ± 22

Online Table 1. Echocardiographic analyses of mice treated with ND or HFD for 8 weeks.
Cardiac function was evaluated with echocardiography (n=6, each). All results are expressed as mean ± SEM.
DSEP WT, diastolic septal wall thickness; **LVEDD**, left ventricular end diastolic dimension; **DPWT**, diastolic posterior wall thickness; **LVESD** left ventricular end systolic dimension; **%FS**, fractional shortening; **HR**, Heart rate.

Online Table 2

	ND	HFD
LVSP (mmHg)	95.3 ± 4.8	94.8 ± 2.4
LVEDP (mmHg)	4.7 ± 0.9	6.2 ± 0.8
+dP/dt (mmHg/s)	7625 ± 381	6958 ± 395
-dP/dt (mmHg/s)	7375 ± 417	6875 ± 346
HR (bpm)	447 ± 10	444 ± 12

Online Table 2. Hemodynamic measurements of mice treated with ND or HFD for 8 weeks. Hemodynamic study was performed with micromanometer catheter (n=6, each). All results are expressed as mean ± SEM.
LVSP, left ventricular systolic pressure; **LVEDP**, left ventricular end diastolic pressure; ***+dP/dt*** **and** ***−dP/dt***, change in pressure over time; **HR**, Heart rate.

Online Table 3

No.	Age	Sex	BMI	DM	Hypertension
1	68y0m	F	21.6	Applicable	under treatment
2	43y4m	F	18.8	N/A	under treatment
3	62y1m	M	21.2	Applicable	under treatment
4	72y7m	M	21.6	Applicable	under treatment
5	40y11m	M	27.9	N/A	N/A
6	66y10m	M	21.5	N/A	under treatment
7	25y3m	M	43.8	Applicable	N/A
8	54y8m	F	28.8	Applicable	under treatment
9	72y8m	M	37.7	N/A	under treatment
10	76y8m	M	16.8	Applicable	under treatment
11	82y4m	M	24.4	N/A	under treatment
12	66y0m	F	25.6	N/A	under treatment
13	46y2m	F	25.0	N/A	N/A
14	72y1m	M	24.3	N/A	under treatment
15	83y1m	F	18.7	Applicable	under treatment
16	71y3m	M	19.3	Applicable	under treatment
17	59y11m	F	21.6	Applicable	under treatment
18	29y10m	M	42.5	N/A	under treatment
19	49y11m	M	30.0	Applicable	under treatment
20	53y8m	F	24.7	N/A	under treatment
21	30y0m	M	26.0	N/A	untreated
22	46y2m	F	40.0	N/A	under treatment
23	49y1m	M	32.2	Applicable	under treatment
24	69y4m	M	25.6	N/A	under treatment
25	52y9m	M	24.1	N/A	under treatment
26	42y10m	F	29.4	Applicable	untreated
27	58y9m	M	24.8	N/A	under treatment
28	66y4m	F	19.1	N/A	under treatment
29	68y5m	M	22.6	N/A	under treatment
30	62y4m	M	23.2	Applicable	under treatment
31	28y9m	F	28.6	Applicable	untreated
32	65y1m	M	23.4	Applicable	under treatment
33	44y5m	M	38.4	Applicable	under treatment
34	65y10m	M	24.9	N/A	under treatment
35	61y8m	F	20.9	N/A	under treatment
36	47y5m	M	41.2	N/A	under treatment

Online Table 3 - continued-

No.	Age	Sex	BMI	DM	Hypertension
37	82y3m	M	24.5	N/A	under treatment
38	73y3m	M	25.0	N/A	under treatment
39	35y1m	M	35.7	N/A	under treatment
40	47y11m	M	34.5	Applicable	under treatment
41	68y3m	F	25.7	Applicable	under treatment
42	73y1m	F	26.6	N/A	under treatment
43	25y8m	M	22.0	N/A	N/A
44	49y0m	F	26.1	N/A	under treatment
45	41y8m	M	29.2	N/A	under treatment
46	57y4m	F	19.4	Applicable	N/A
47	67y0m	F	19.5	N/A	N/A
48	66y7m	M	25.8	N/A	under treatment
49	38y1m	M	24.5	N/A	Untreated
50	43y0m	F	21.2	N/A	N/A
51	56y8m	M	24.6	N/A	under treatment
52	41y1m	M	22.6	N/A	under treatment
53	75y10m	F	20.3	Applicable	under treatment
54	67y1m	F	28.2	N/A	under treatment
55	47y11m	M	18.4	Applicable	under treatment
56	83y3m	F	24.3	Applicable	under treatment
57	57y1m	F	24.8	N/A	under treatment
58	48y5m	F	24.3	N/A	under treatment
59	76y7m	M	26.0	N/A	under treatment
60	49y9m	M	26.5	N/A	under treatment
61	62y1m	F	23.6	N/A	under treatment
62	60y0m	M	16.7	N/A	under treatment
63	62y11m	F	22.9	Applicable	under treatment
64	66y0m	M	23.3	N/A	under treatment
65	68y7m	F	23.5	Applicable	under treatment
66	56y7m	F	20.1	Applicable	under treatment

Online Table 3. The characteristic of patients with heart failure who received myocardial biopsy
Myocardial biopsy specimens were obtained from patients with heart failure for the clinical diagnosis in Tohoku University Hospital. The 66 consecutive observable biopsy specimens were obtained from January 2016 to June 2017. The average Ejection Fraction of heart failure patients was 33.8±7.6 %. Twenty-five patients were diagnosed with DM and their average HbA1c level was 6.98±0.68 %.
BMI; body mass index, DM; diabetes mellitus, M; male, F; female

Online Table 4

	DM- (n=41)	DM+ (n=25)	*P* value
Age (years)	**56.6 ± 14.5**	**59.4 ± 15.0**	**0.42**
Male sex, n (%)	**26 (63.4)**	**12 (48.0)**	**0.22**
Body mass index (kg/m^2)	**25.9 ± 5.8**	**25.1 ± 6.7**	**0.20**
Medical history, n (%)			
Hypertension	**34 (82.9)**	**20 (80.0)**	**0.77**
Untreated Hypertension	**2 (4.9)**	**2 (8.0)**	**0.61**
Dyslipidemia	**30 (73.2)**	**16 (64.0)**	**0.44**
Laboratory data			
LVEF (%)	**33.7 ± 7.0**	**34.1 ± 8.6**	**0.12**
HbA1c (%)	**5.7 ± 0.3**	**7.0 ± 0.7**	**<0.001**
Duration of diabetes (month)		**28.3 ± 20.9**	
Medications, n (%)			
Calcium channel blocker, n (%)	**8 (19.5)**	**4 (12.0)**	**0.72**
ACE inhibitors/ ARB, n (%)	**33 (80.5)**	**19 (76.0)**	**0.67**
Beta blocker, n (%)	**25 (61.0)**	**14 (56.0)**	**0.70**
Oral diabetes medicine, n (%)		**22 (88.0)**	
Insulin injection, n (%)		**2 (8.0)**	

Online Table 4. Characteristics of patients with heart failure who underwent myocardial biopsy
Myocardial biopsy specimens were obtained for clinical diagnosis from patients with heart failure in Tohoku University Hospital. All continuous variables are reported as mean ± SD or n (%). To compare two quantitative variables, t-test and chi-square test was used. ACE : angiotensin-converting enzyme, ARB : angiotensin II receptor blocker