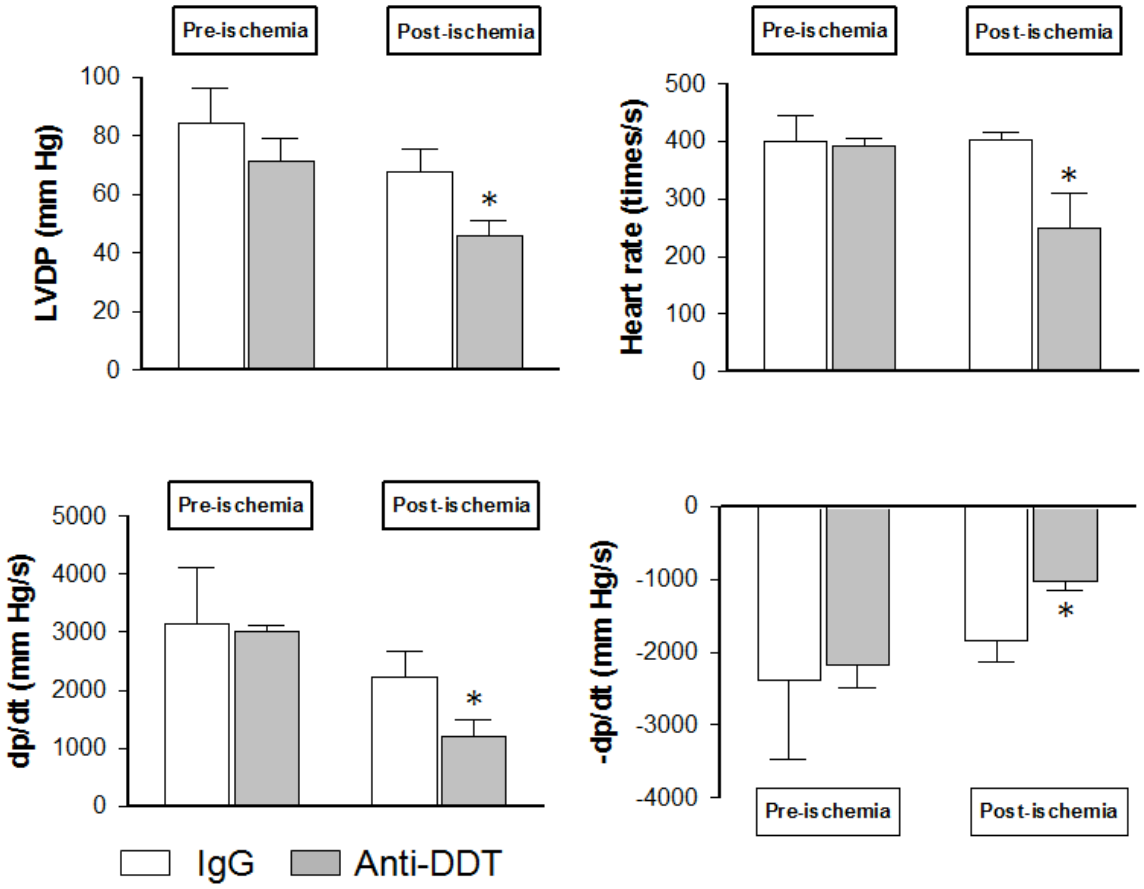
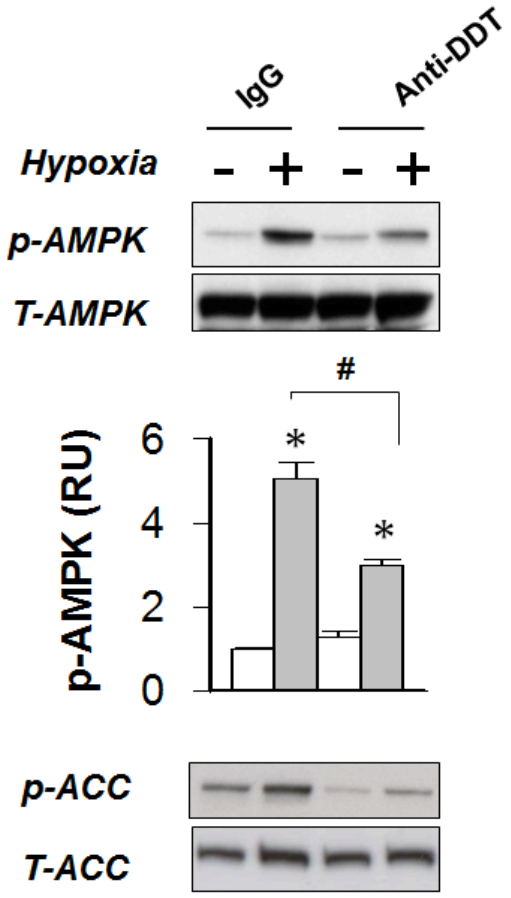
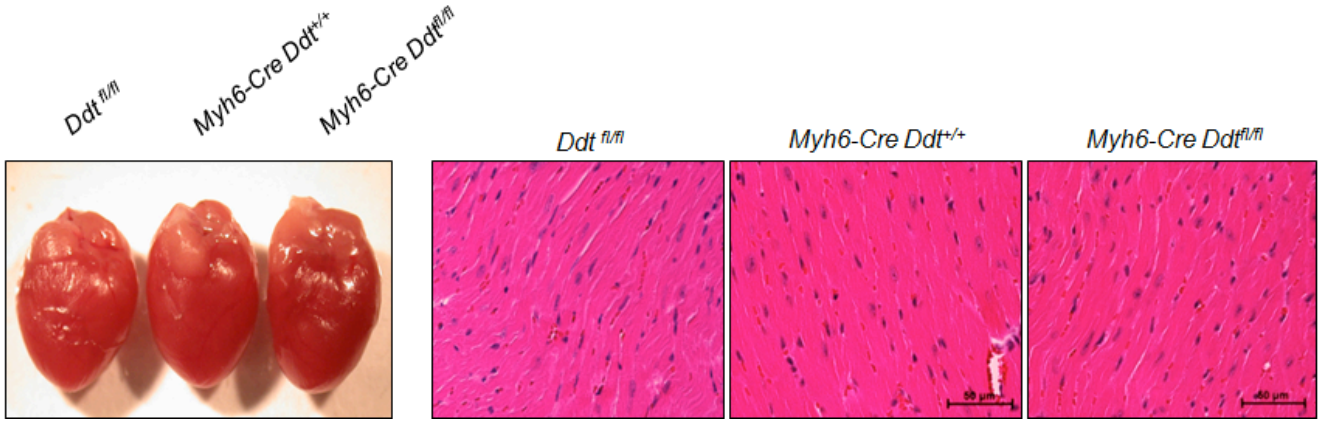
ONLINE SUPPLEMENTAL DATA



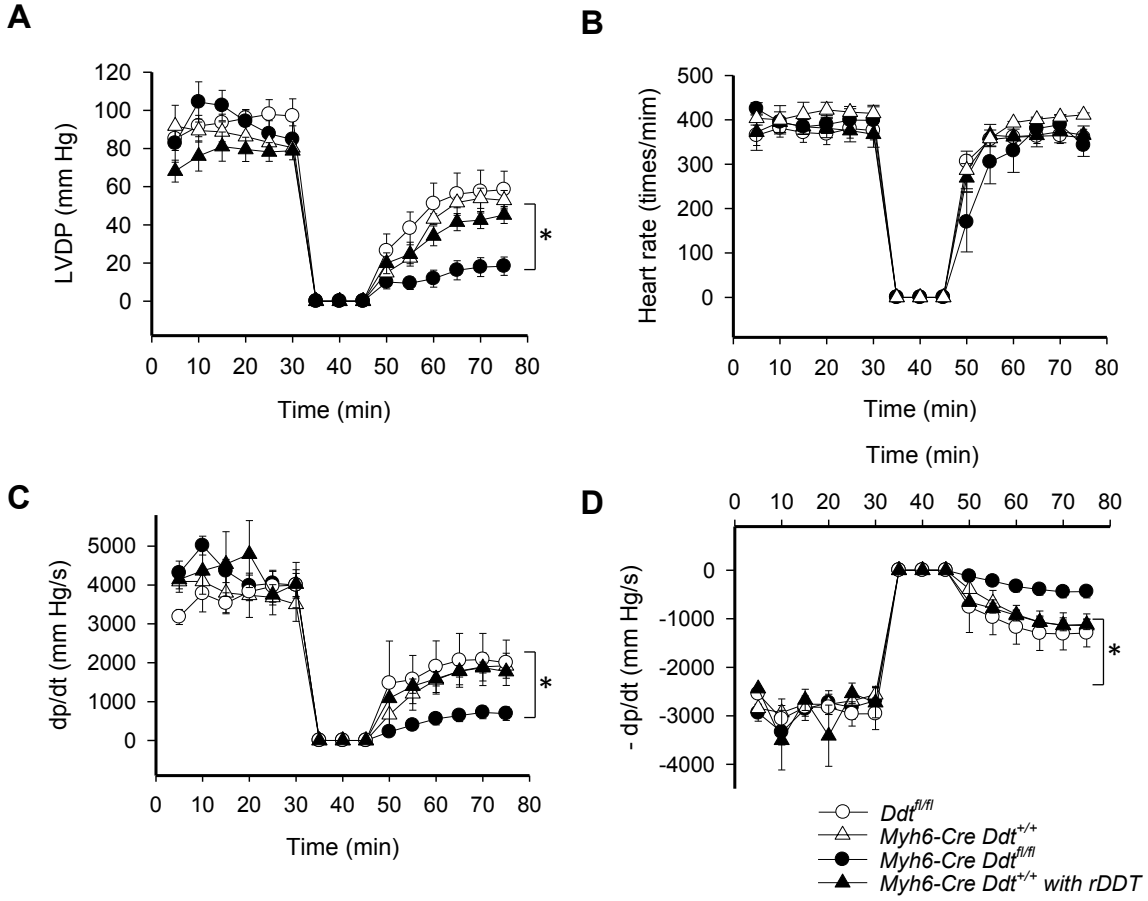
Supplemental Figure 1 *Immuno-neutralization of heart-derived DDT attenuates cardiac function recovery following ischemia-reperfusion.* Isolated mouse hearts were treated with anti-DDT or non-immune control IgG prior to 15 min ischemia and 30 min reperfusion. Left ventricular (LV) developed pressure (LVDP) (**A**), heart rate (HR) (**B**), LV dp/dt (**C**) and LV –dp/dt (**D**) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * $P < 0.05$ comparing ischemic conditions with IgG vs. anti-DDT treatment.



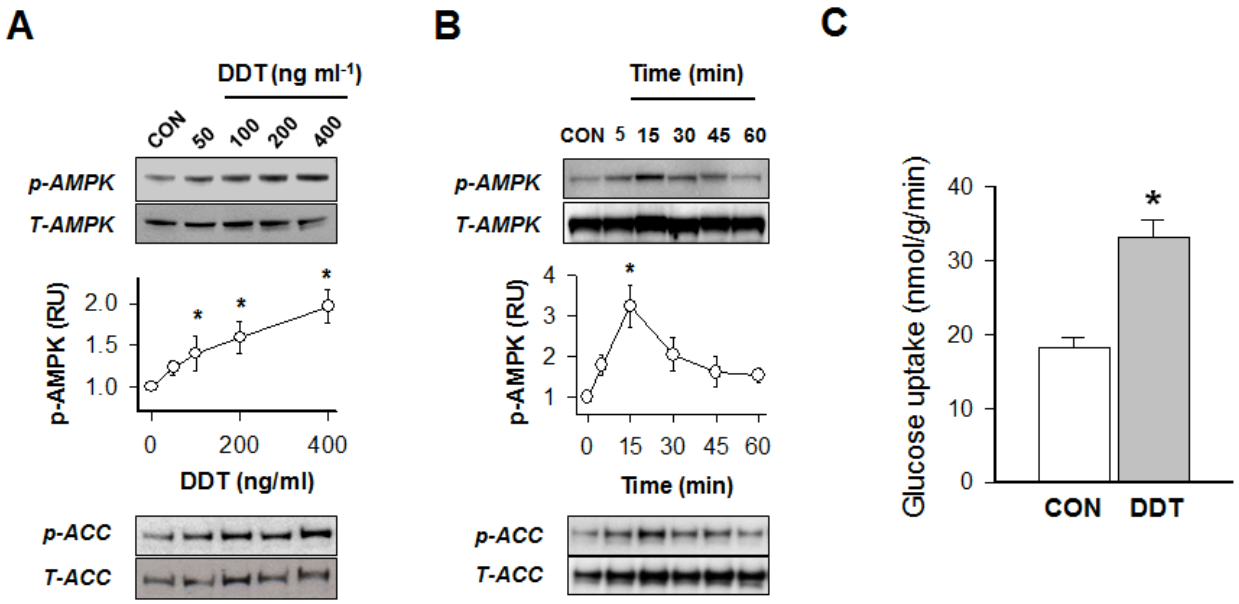
Supplemental Figure 2 *Immuno-neutralization of endogenous secreted DDT inhibits hypoxia-induced AMPK activation in cardiomyocytes.* Adult rat ventricular cardiomyocytes were treated with DDT or non-immune IgG antibody (100 μg/ml) for 30 min and then incubated under aerobic or hypoxic conditions for an additional 30 min. Cell lysates underwent immunoblotting for phospho and total AMPK and ACC. Values are means ± SEM, n=5 per group. * $P < 0.05$ vs. control. $^{\#}P < 0.05$ vs. non-immune IgG with hypoxia.



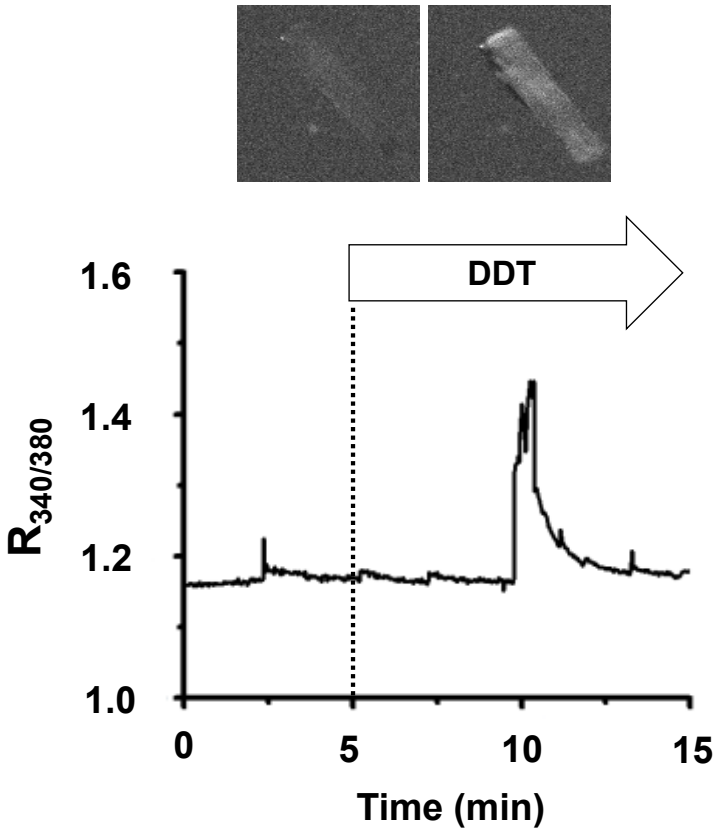
Supplemental Figure 3 *The morphology and histology of DDT cardiac specific knockout hearts. Ex vivo* photographs (left panel) *and* H&E staining of left ventricular sections (right panel) from control *Ddt* floxed (*Ddt*$^{fl/fl}$) and MHC-Cre (*Myh6-Cre Ddt*$^{+/+}$) mice and cardiomyocyte-specific DDT knockout (*Myh6-Cre Ddt*$^{fl/fl}$) mice at 8 weeks of age.



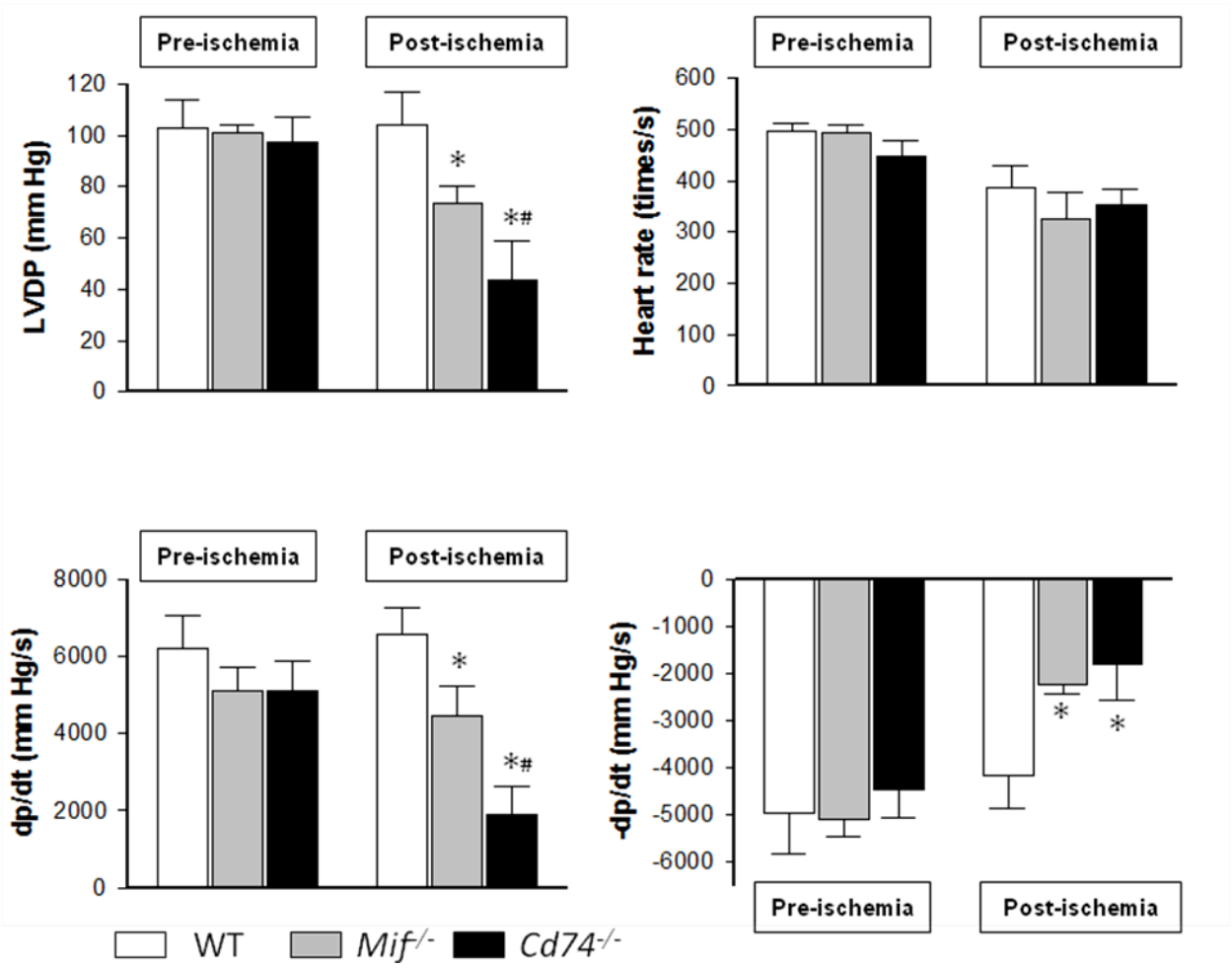
Supplemental Figure 4 *Impaired cardiac contractile function in mouse hearts from DDT cardiomyocyte specific knockout mice following ischemia-reperfusion.* Hearts from control Ddt floxed (*Ddt*$^{fl/fl}$) and MHC-Cre (*Myh6-Cre Ddt*$^{+/+}$) mice, and DDT knockout (*Myh6-Cre Ddt*$^{fl/fl}$) mice were subjected to *ex vivo* ischemia (15 min) and reperfusion (30min). In a separate group, cardiomyocyte-specific DDT knockout hearts were also perfused with buffer containing rDDT (50 ng/ml). Left ventricular developed pressure (LVDP) (**A**), heart rate (HR) (**B**), LV dp/dt (**C**) and LV –dp/dt (**D**) were recorded. Data are means ± SEM, n = 4-6 per group. * $P < 0.05$ vs. DDT knockout.



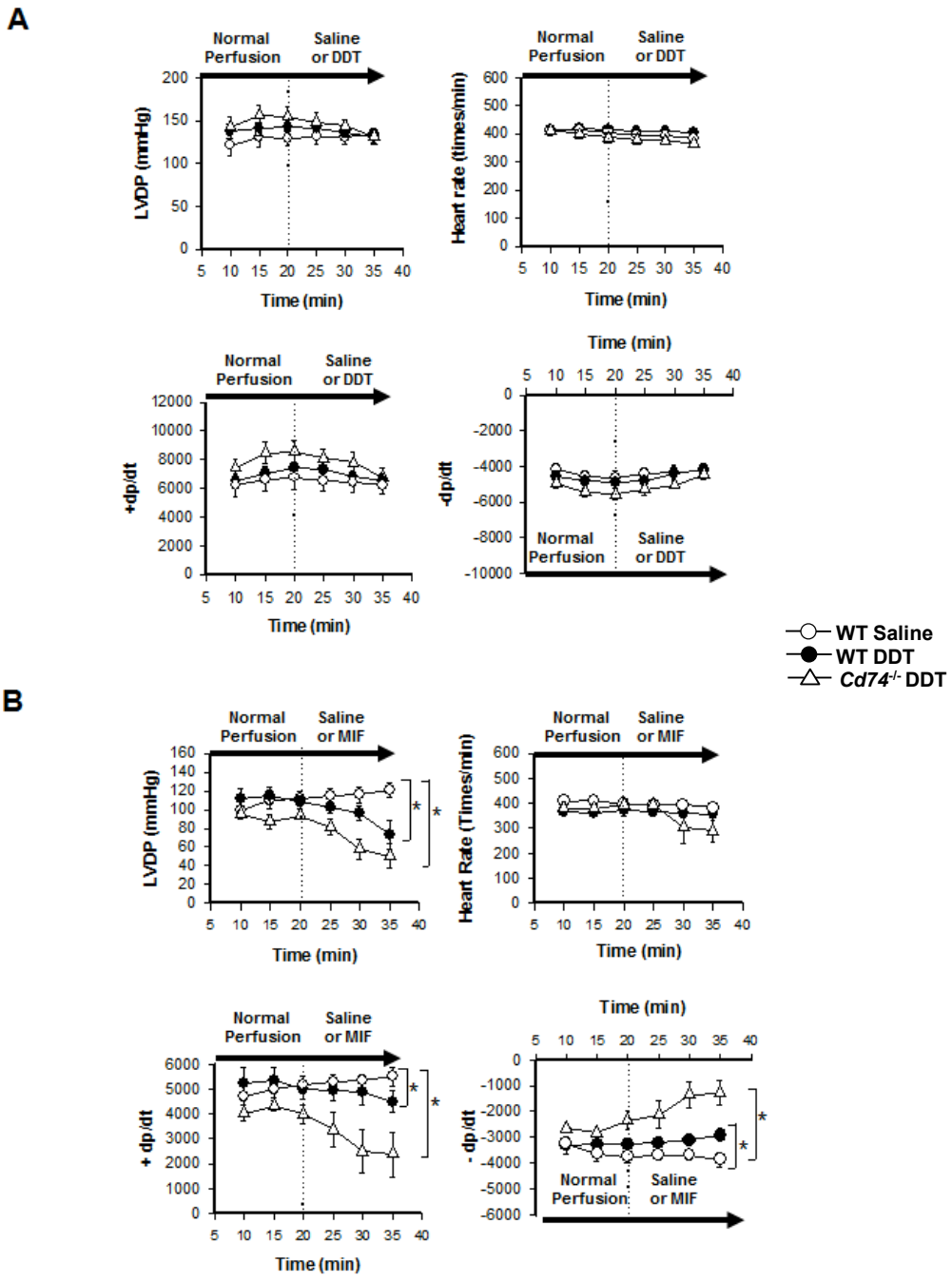
Supplemental Figure 5 *rDDT stimulates AMPK activation and glucose uptake.* (**A**) Excised rat left ventricular papillary muscles were incubated with rDDT (50 to 400 ng/ml) for 15 min. (**B**) Muscles were treated with 400 ng/ml rDDT for 5 to 60 min. Muscle homogenates were then immunoblotted for phospho and total AMPK and ACC. (**C**) Glucose uptake was measured with ^{3}H-2-deoxyglucose in the presence of 5 mM glucose. Values are means ± SEM, n=4 per group, *P < 0.05 vs. control.



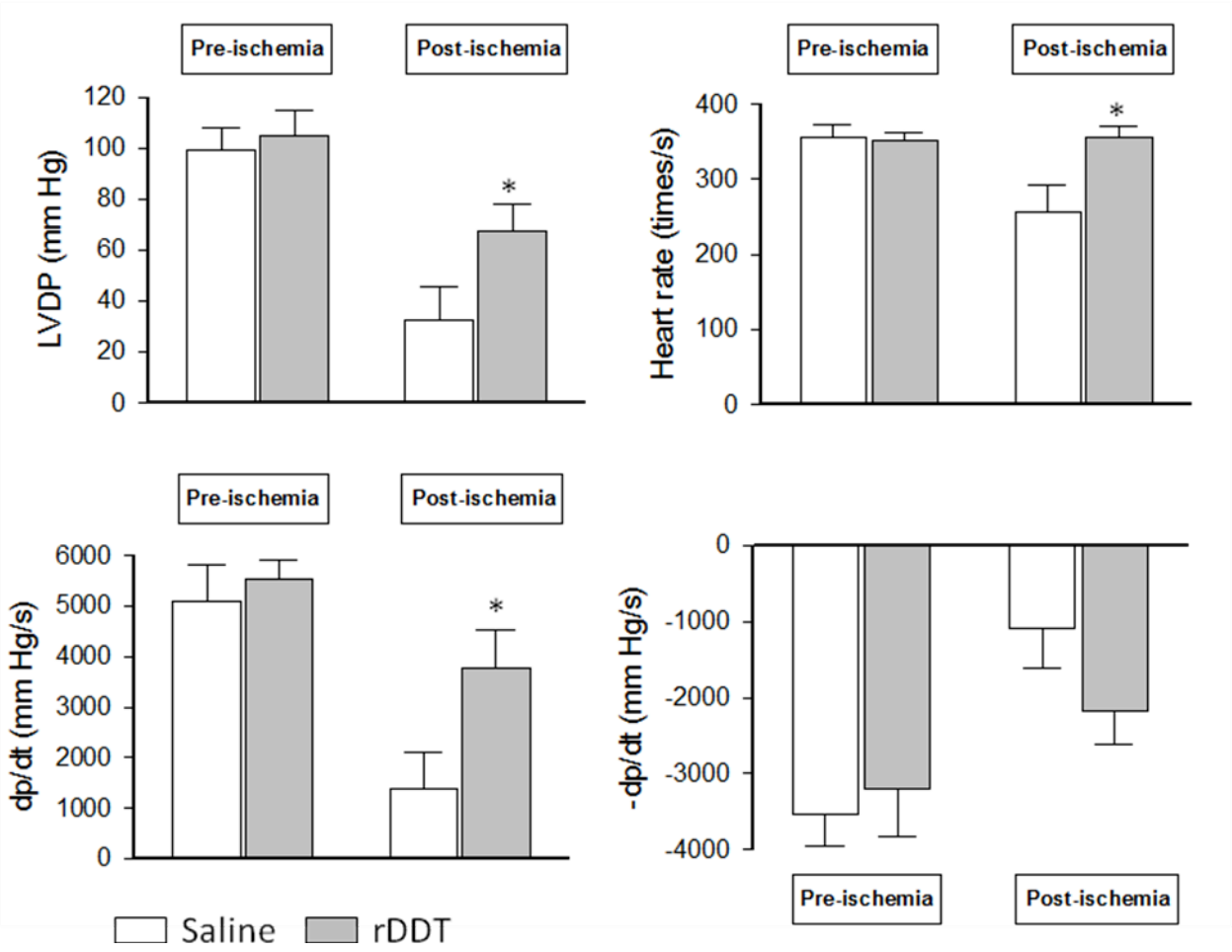
Supplemental Figure 6 *rDDT treatment transiently increases intracellular calcium in unpaced isolated adult rat cardiomyocytes.* Intracellular calcium imaging was performed in rat adult ventricular cardiomyocytes pre-incubated with fura-2-acetoxymethyl ester (2 μM), before (upper left panel) or after (upper right panel) the addition of rDDT (400 ng/ml). The ratio of 340 to 380 nm fluorescence intensity [$R_{(340/380)}$] was quantified as a relative measure of intracellular calcium concentration ($[Ca^{2+}]_i$) (lower panel graph).



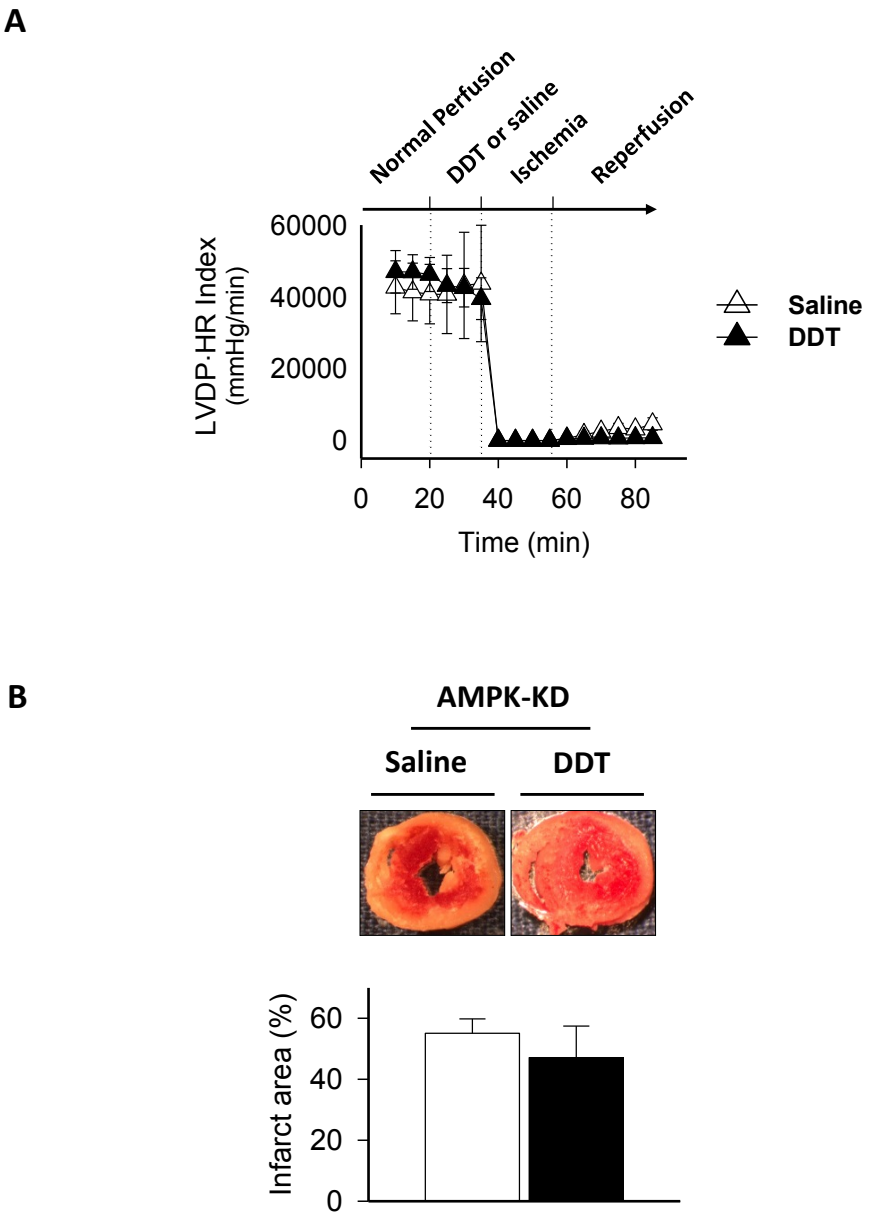
Supplemental Figure 7 *Differential cardiac function recovery after ischemia in Mif*$^{-/-}$ *and Cd74*$^{-/-}$ *hearts.* Hearts from wild type (WT), MIF knockout (*Mif*$^{-/-}$) and CD74 knockout (*Cd74*$^{-/-}$) mice were perfused *ex vivo* at normal flow for 30 min and then subjected to ischemia (15 min) with or without subsequent reperfusion (30 min). Left ventricular developed pressure (LVDP) (**A**), heart rate (HR) (**B**), LV dp/dt (**C**) and LV –dp/dt (**D**) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * $P < 0.05$ vs. WT; # $P < 0.05$ vs. *Mif*$^{-/-}$.



Supplemental Figure 8 *The effects of DDT and MIF on cardiac function in WT and Cd74$^{-/-}$ hearts.* Mouse hearts were perfused with or without 50 ng/ml of rDDT (A) or rMIF for 15 min (B). Data are means ± SEM, n = 4-6 per group. * $P < 0.05$ vs. WT.



Supplemental Figure 9 *DDT pretreatment prior to ischemia improves post-ischemic cardiac function.* Hearts isolated from WT mice were treated with saline (CON) or rDDT (50 ng/ml) for 15 min and then subjected to 20 min global ischemia followed by 30 min reperfusion. Left ventricular developed pressure (LVDP) (**A**), heart rate (HR) (**B**), LV dp/dt (**C**) and LV –dp/dt (**D**) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * $P < 0.05$ vs. WT.



Supplemental Figure 10 *DDT requires AMPK activation to reduce injury during ischemia-reperfusion*. Hearts isolated from AMPK kinase-inactivated "kinase-dead" (KD) mice Tg[*Ckmm-Ampka*^{K45R}) were treated with saline (CON) or rDDT (50 ng/ml) for 15 min and then subjected to 20 min global ischemia followed by 30 min reperfusion. (**A**) Cardiac contractile function was evaluated as the product of LV developed pressure (LVDP) and heart rate (HR). (**B**) Triphenyl tetrazolium chloride vital staining was used to quantify the extent of necrosis (infarct area calculated as a percentage of ventricular area). Data are means ± SEM, n=4-6 per group.