Supplemental Information

Antibodies used for western blotting

Antibody	Provider	Dilution
pVEGFR2	Cell Signalling	1:500
VEGFR2	Sigma Chemicals	1:1000
pAKt/Akt	Cell Signalling	1:1000
Pim-1	Santa Cruz Biotechnology	1:500
pBad/Bad	Cell Signalling	1:1000
Cleaved Caspase-3	Cell Signalling	1:1000
p-p38MAPK/p38MAPK	Cell Signalling	1:1000

Antibodies used for Immunohistochemistry

Antibody	Provider	Dilution
Biotinylated Isolectin-B4	Invitrogen	1:100
α-smooth muscle actin	Sigma Chemicals	1:400
8-OHDG	Nikken Seil	1:50

Legends to Supplemental Figures

Supplemental Fig. 1: Experimental protocol of the study

*STZ injected at a dose of 40 mg/kg/day/ip for 5 consecutive days. **10 animals that did not develop DM were excluded from the study. #MI was induced by total occlusion of left anterior descending coronary artery.

Supplemental Fig. 2: Serum glucose concentration

Scatter plots show the serum glucose levels at different time points. **P<0.001 versus non-diabetic mice.

Supplemental Fig. 3: Scrambled siRNA has no effect on cardiomyocyte apoptosis.

Bar graphs show G6PD activity (A) and levels of activated caspase-3/7 (B) in cultured adult cardiomyocytes after treatment with scrambled siRNA. Cardiomyocytes cultured in normal (NG) or high glucose (HG) were transfected with scrambled siRNA (NGScr and HGScr) and subjected to hypoxia with 0.2% O_2 for 18h after treating the cells with BFT (NGBScr and HGBScr) or vehicle (NGVScr or HGVScr). Values are mean ±

standard deviation and expressed as units/min/mg of protein for G6PD activity and relative units (RLU) for caspase 3/7 activity. $^{\S}P<0.01$, $^{\S\S}P<0.001$ and $^{\S\S\S}P<0.0001$ versus NG or HG; $^{*}P<0.01$ and $^{**}P<0.001$ versus vehicle-treated NG (NGV) or HG (HGV); $^{\delta}P<0.01$ versus corresponding treatment between NG or HG cultured cells. Each experiment was repeated four times in triplicate for G6PD and was performed in 6 wells per each condition and repeated 3 times for caspase 3/7 activity.

Supplemental Fig. 4: Physiological measurements in sham-operated animals

(A) Table showing the values of LV end-diastolic pressure (LVEDP), LV end-systolic pressure (LVESP) and maximum and minimum rates of developed pressure (dP/dt) in sham-operated non-diabetic (NDS) and diabetic (DS) animals at 2 weeks post surgery (n= at least 12 in each group).

(B) Representative pressure-volume loops obtained by integrated measurement of LV pressure (Millar catheter) and volume (echocardiography) in sham-operated non-diabetic (NDS) and diabetic (DS) animals at 2 weeks post surgery. Values are mean±standard deviation.

Supplemental Fig. 5: Vascular density in the remote zone

Bar graphs show the capillary (A) and arteriole (B) densities in the remote myocardium at 2 weeks after MI. Each group consisted of 5 mice.

Supplemental Fig. 6: Oxidative stress in the remote zone

Bar graphs show the levels of 8-OHDG in the remote zone at 2 weeks after MI. Each group consisted of 5 mice. $^{*}P<0.01$ versus sham-operated non-diabetic or diabetic mice; $^{\#}P<0.01$ versus vehicle-treated non-diabetic (NDV) or diabetic (DV) mice; $^{\delta}P<0.01$ versus corresponding treatment among diabetic and non-diabetic mice.

Supplemental Fig 7: BFT rescue cardiomyocytes exposed to hypoxia under normal or high glucose.

Bar graphs show the levels of activated caspase-3/7 (A), pVEGFR2 (B), pAkt (C), Akt activity (D), Pim-1(E), pBad (F) and Bcl-2 (G) in cultured adult cardiomyocytes. Cardiomyocytes were cultured in normal (NG) or high glucose (HG) in the presence of benfotiamine (NGB and HGB) or vehicle (NGV and HGV) and subjected to hypoxia with 0.2% O_2 for 18h. Values are expressed as n-fold changes toward NGV for all parameters, except caspase 3/7 which is expressed as relative units (RLU), and are mean

± standard deviation. $^{*}P<0.01$ and $^{**}P<0.001$ versus NGV; $^{\#\#}P<0.001$ versus HGV. Each experiment was repeated four times in triplicate except caspase 3/7 activity, which was performed in 6 wells per each condition and repeated 3 times.

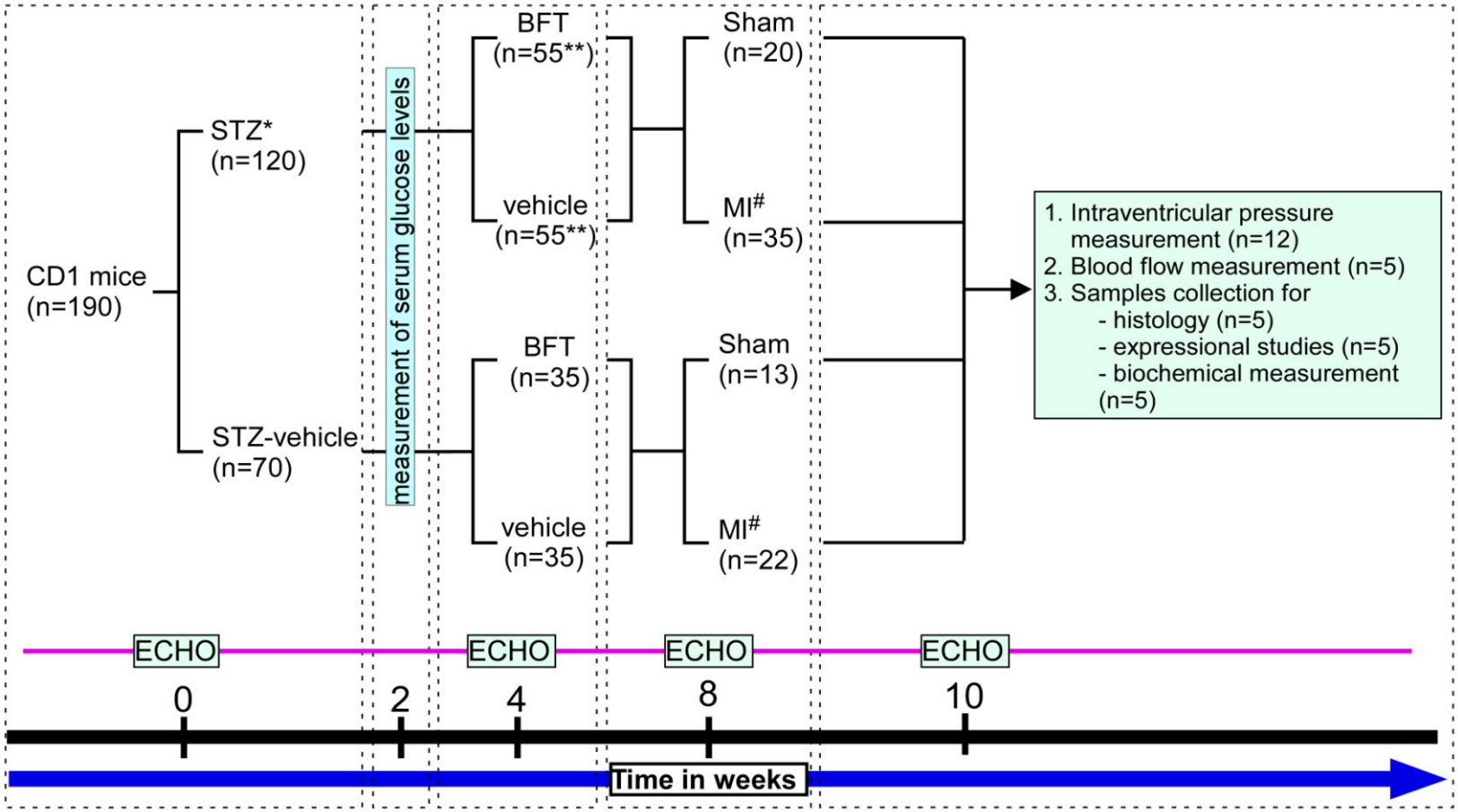
Supplemental Fig 8: BFT stimulates survival signaling in high glucose cultured cells under normoxic conditions

Bar graphs show the levels of activated caspase-3/7 (A), pVEGFR2 (B), pAKt (C), Akt activity (D), Pim-1(E), pBad (F) and Bcl-2 (G) in cultured adult cardiomyocytes. Cardiomyocytes were cultured under normoxic conditions, in normal (NG) or high glucose (HG) in the presence (NG+B and HG+B) or absence of benfotiamine (NG and HG).. Values are expressed as n-fold changes toward NG for all parameters, except caspase 3/7 which is expressed as relative units (RLU), and are mean ± standard deviation. $^{*}P<0.01$ versus NG; $^{\#}P<0.01$ versus HG. Each experiment was repeated four times in triplicate except caspase 3/7 activity, which was performed in 6 wells per each condition and repeated 3 times.

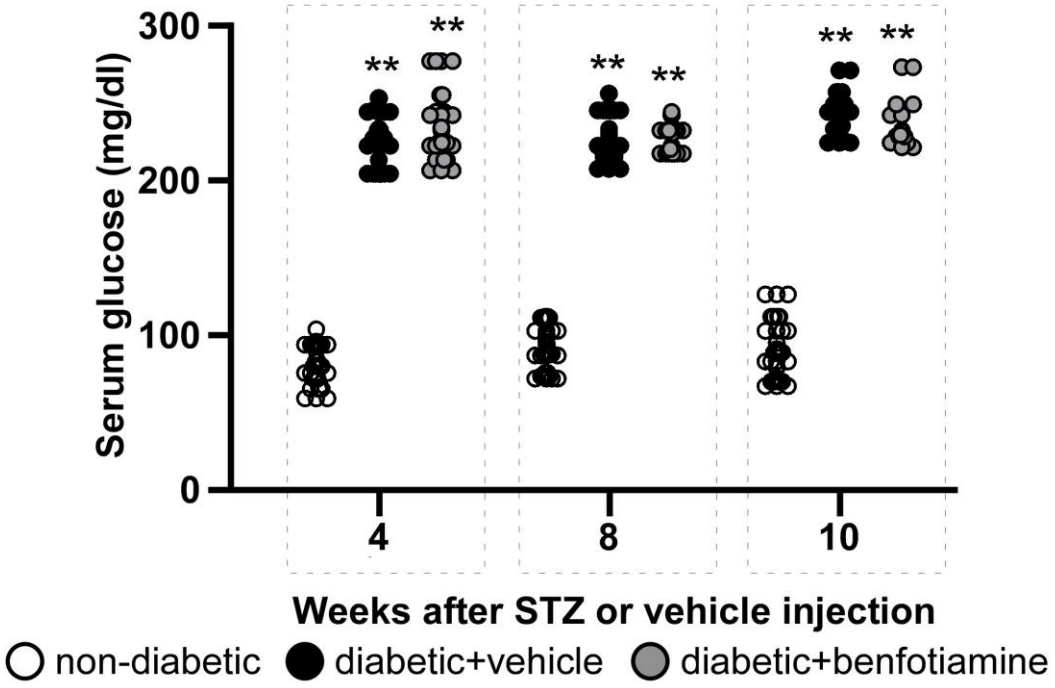
Supplemental Fig 9: Schematic illustration showing the effect of BFT on diabetic heart after MI.

Myocardial ischemia activates a compensatory activation of G6PD. Furthermore, VEGFR2 is induced in ischemic myocardium leading to activation of the prosurvival Akt/Pim1 signaling. This mechanism is dampened by diabetes but restored by BFT. Importantly, silencing G6PD with siRNA and inhibition of Akt activity using *Ad.DN-Akt* attenuated the BFT induced protection.

Supplemental Figure 1

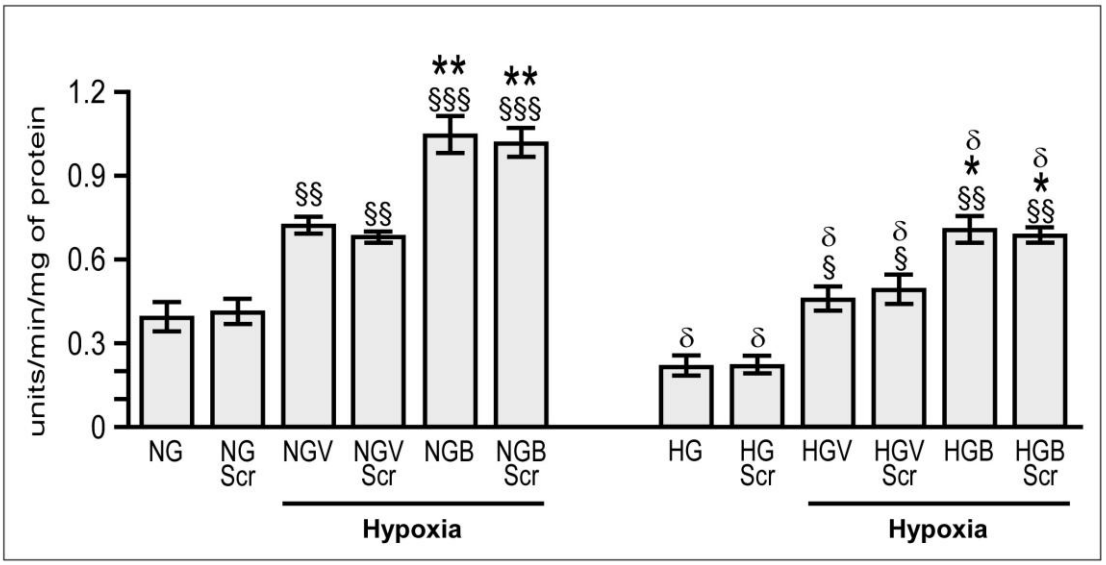


Supplemental Figure 2

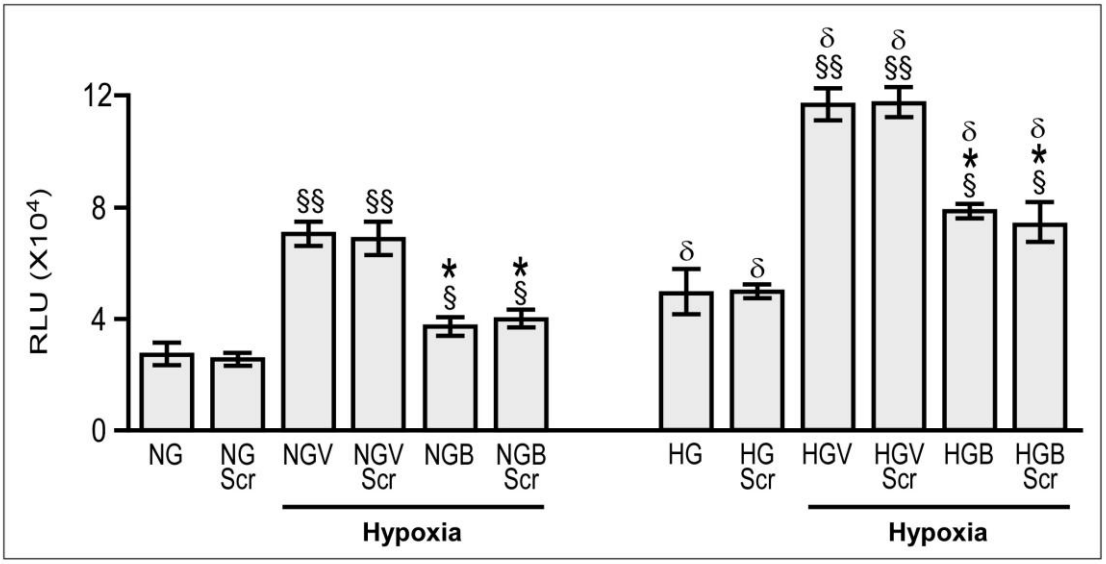


Supplemental Figure 3

A - G6PD activity



B - Caspase 3/7 activity

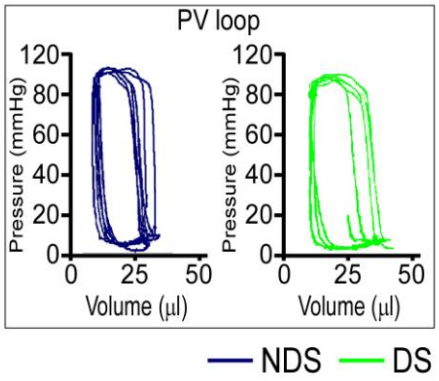


Supplemental Figure 4

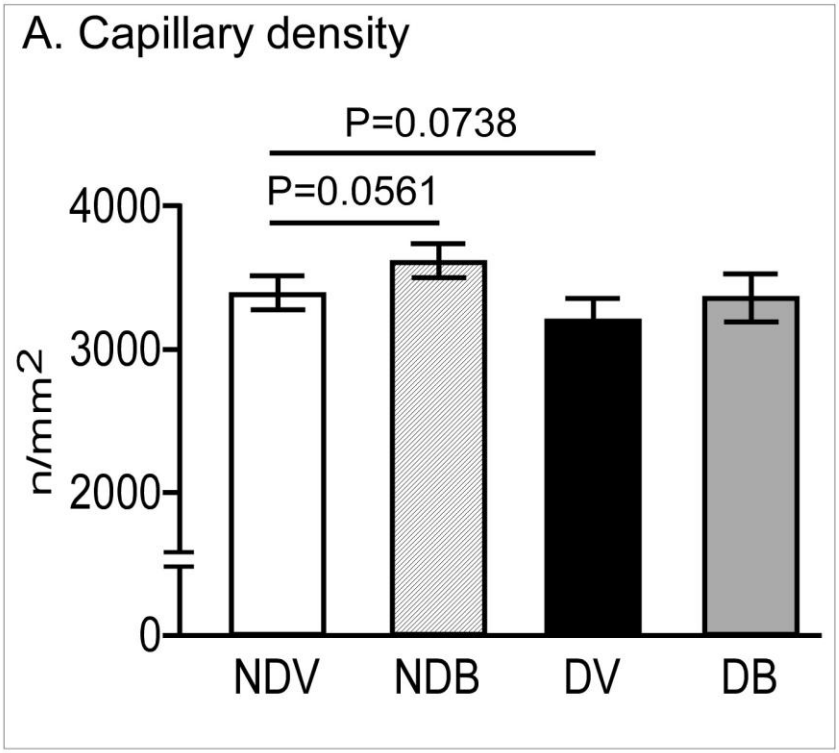
(A)

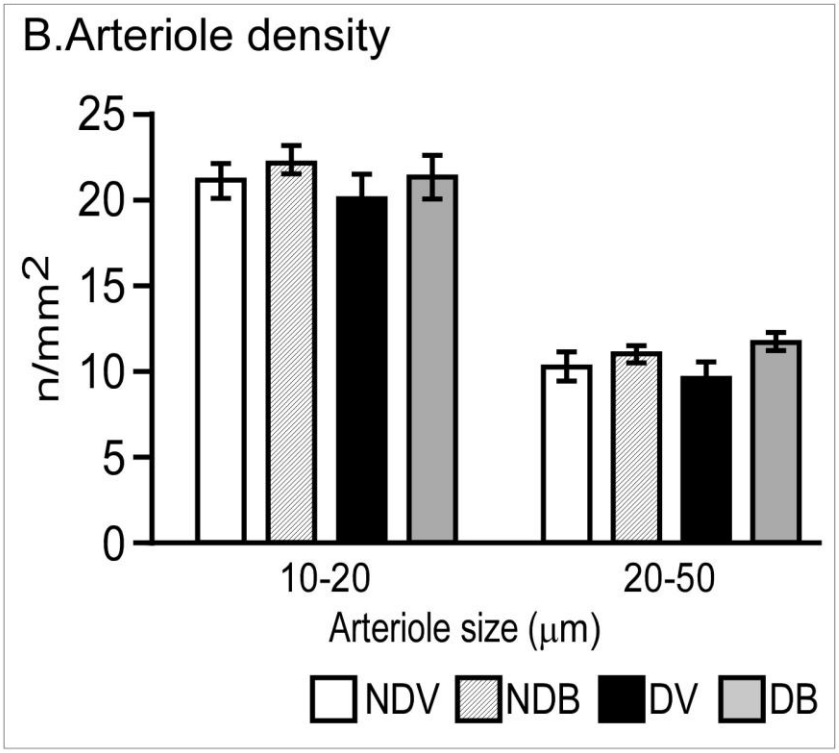
	NDS	DS
LVEDP	2.78±1.31	3.26±1.9
LVESP	101±2.5	93.3±4.1
dP/dt(max)	5893±998	5543±1276
dP/dt(min)	4137±708	3983±878

(B)

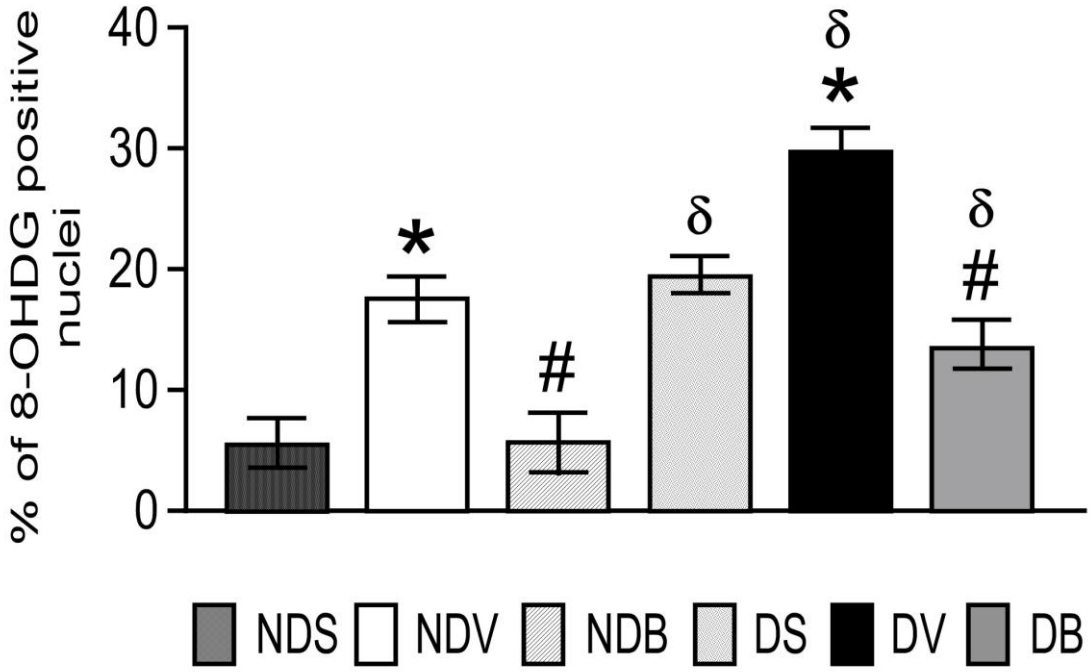


Supplemental Figure 5

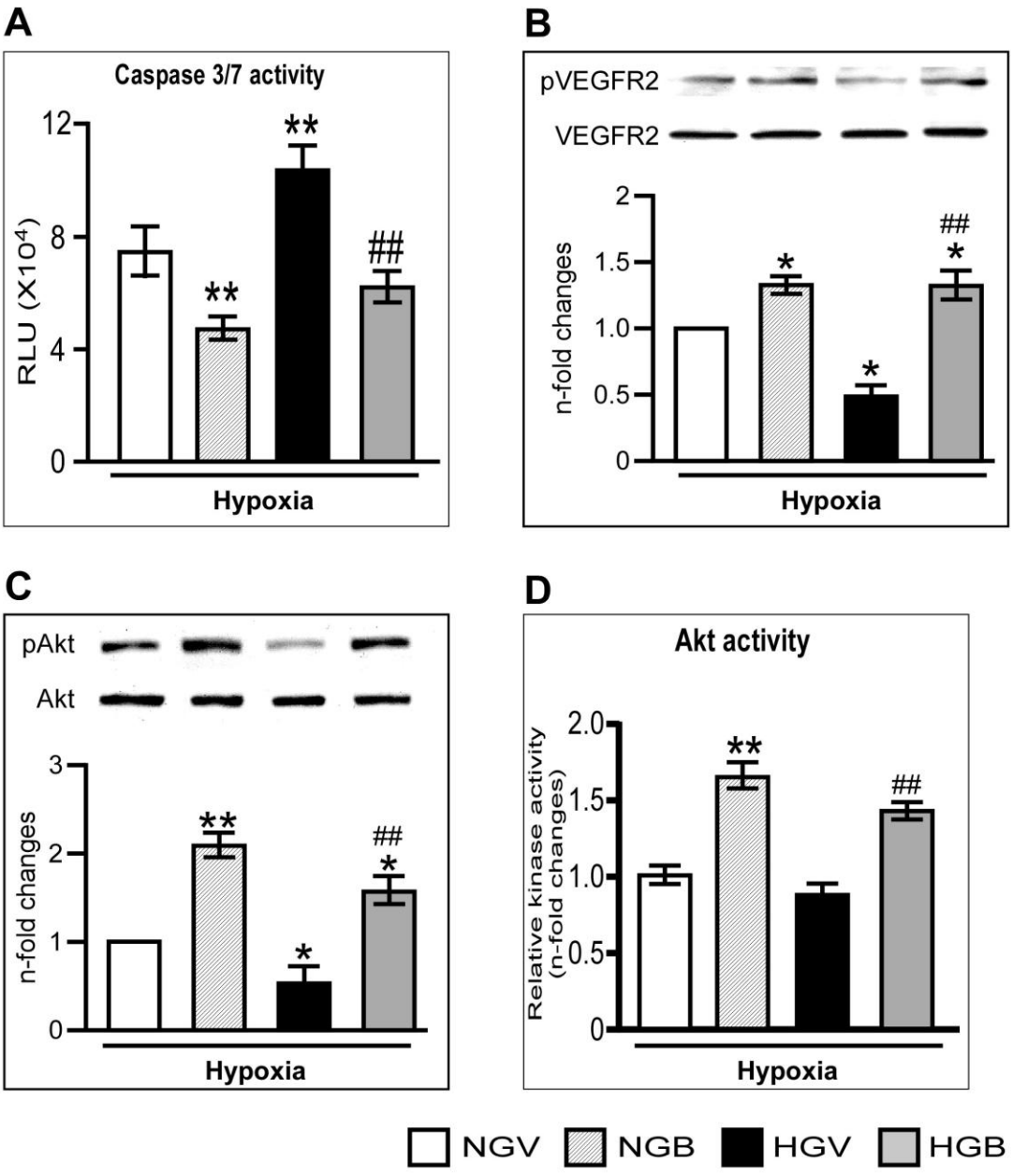




Supplemental Figure 6



Supplemental Figure 7 (i)



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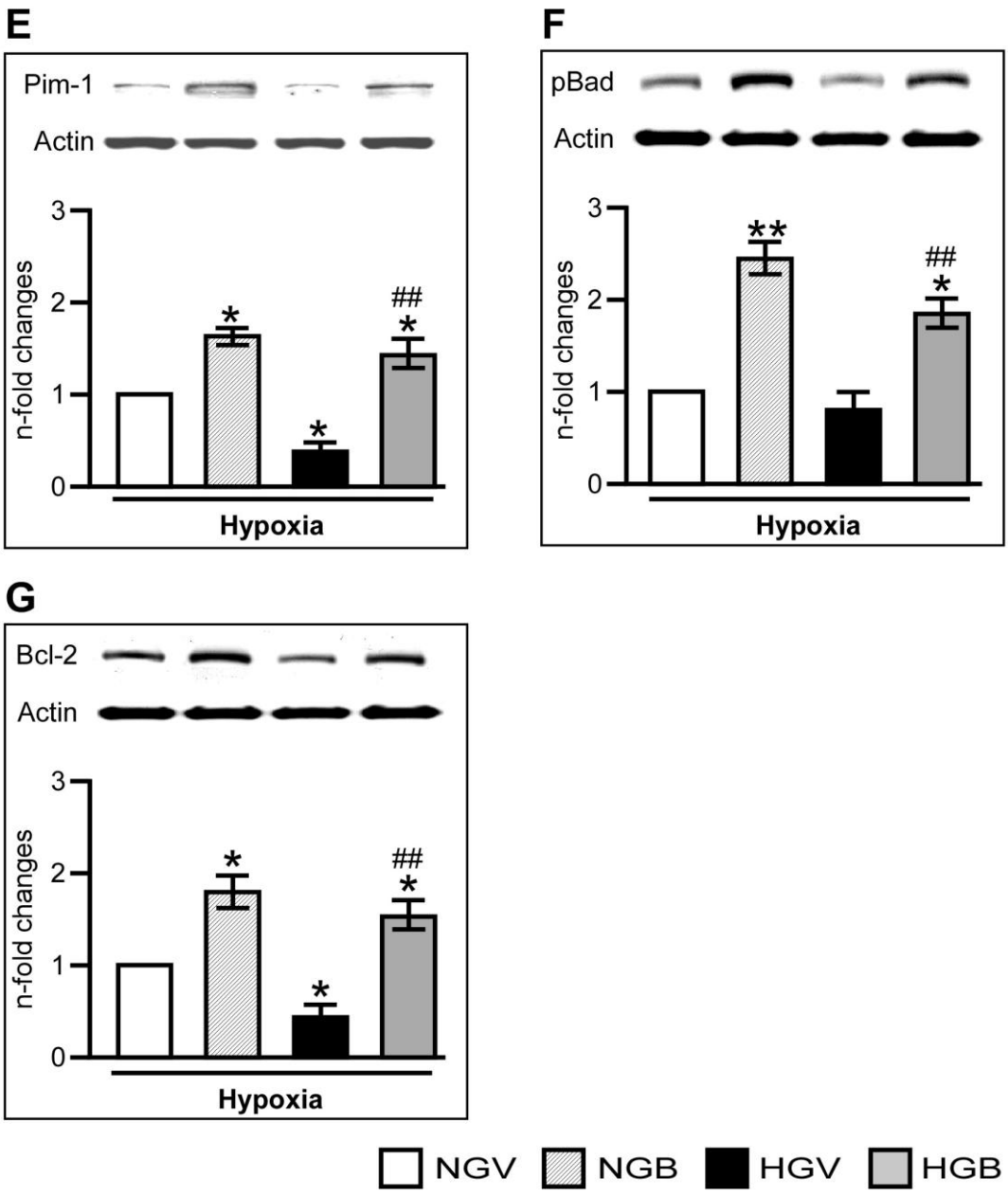
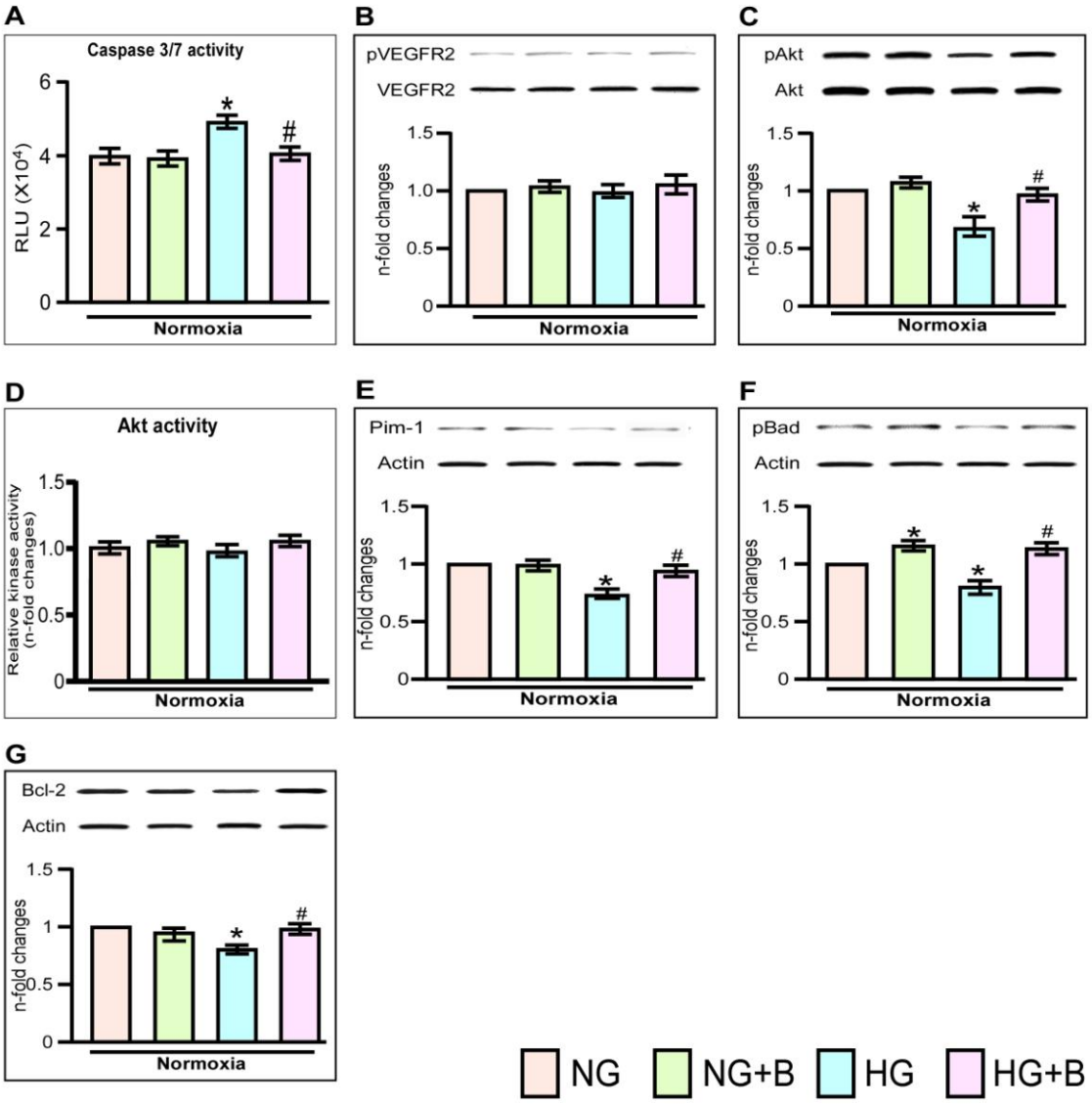


Supplemental Figure 8



Supplemental Figure 9