

GW23-e1018

UP-REGULATING HO-1 IMPROVES POST-INFARCTION HEART FUNCTION OF SPONTANEOUS HYPERTENSIVE RATS VIA ANTI-INFLAMMATION, ANTI-OXIDATION, LOWERING BLOOD GLUCOSE AND IMPROVING ENDOTHELIAL FUNCTION

doi:10.1136/heartjnl-2012-302920a.4

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Objectives Our previous results showed that heme oxygenase 1 (HO-1) is involved in the regulation of endothelial function by the modulation of NOS isoforms and control of oxidative stress. HO-1, in particular, may be well suited as a therapeutic agent for myocardial protection, because the catabolic by-products of heme metabolism, carbon monoxide (CO) and bilirubin, have been reported to exert pleiotropic cytoprotective effects, including inhibition of oxidative stress, inflammation, and apoptosis.

Methods Male spontaneous hypertensive rats (SHR) at 13 weeks (n=40) and age-matched male Wistar rats (n=20) were selected. After basal echocardiography and blood pressure measurement, they were divided into six groups: (1) WT (sham+NS), (2) WT (sham+Copp), (3) SHR(MI+NS), (4) SHR (MI+Copp), (5) SHR (MI+Copp+SnMP), (6) SHR (sham+NS), n=10/group. Sham operation or coronary ligation were performed respectively. The first day after operation, medications were administered among groups: normal saline (NS), or cobalt protoporphyrin (CoPP), an inducer of HO-1, 4.5 mg/kg, or concurrently with tin mesoporphyrin IX dichloride (SnMP), an inhibitor of HO activity, 15 mg/kg, all for 6 weeks, 1/week, intraperitoneally. At 6 weeks, trans-thoracic echocardiography and hemodynamics tests was performed; thereafter, blood was collected for blood biochemistry, NO, PGI₂ testing. One part of isolated hearts were fixed into 10% formalin, paraffin embedded, processed for HE and Masson's trichrome stain. The other part of the hearts were rapidly frozen in liquid nitrogen, stored at -80°C, prepared for western blot analysis of HO-1 expression.

Results

- (1) Blood pressure: Compared with WTs, SHRs exhibited significantly higher blood pressure, including systolic blood pressure (SBP) (212.371±37.309 vs 138.081±13.057, p=0.000), diastolic blood pressure (DBP) (193.545±29.374 vs 115.795±19.305, p=0.000), and mean arterial pressure (MAP) (205.002±40.234 vs 123.223±17.039, p=0.000). Copp treatment significantly lowered SBP, DBP, MAP in SHR(MI+Copp) compared to SHR(MI+NS) (SBP: 154.753±10.591, p=0.000; DBP: 136.900±12.392, p=0.000; MAP: 142.851±11.622, p=0.000).
- (2) Cardiac function: Left ventricular ejection fraction (LVEF) and left ventricular fraction shortening (LVFS) between WTs and SHRs before operation are similar. After coronary ligation operation on SHRs, LVEF and LVFS were significantly decreased in SHR

(MI+NS) group as compared with WT (sham+NS) group. Besides, $+dp/dt_{max}$ and $(-dp/dt_{max})/I/VSP$ were also significantly decreased in SHR (MI+NS) group. Copp treatment could improve LVEF (72.050 ± 2.681 vs 55.967 ± 7.340 , $p=0.000$), LVFS (35.975 ± 2.012 vs 25.500 ± 4.299 , $p=0.000$), $+dp/dt_{max}$ (2591.92 ± 53.85 vs 1375.29 ± 266.13 , $p=0.000$), $(-dp/dt_{max})/I/VSP$ (-17.44 ± 0.32 vs -9.95 ± 0.11 , $p=0.000$) in SHR (MI+Copp), while decrease LVEDD (0.4725 ± 0.0985 vs 0.6411 ± 0.0903 , $p=0.001$) and LVESD (0.3025 ± 0.0675 vs 0.4778 ± 0.0748 , $p=0.000$) as compared with SHR(MI+NS).

- (3) Blood parameters: SHR (MI+NS) group exhibited higher CRP levels, lower NO levels as compared with WT (sham+NS) group, while the levels of TB, Glu, and PGI_2 were similar between two groups. Copp treatment could lower CRP (0.090 ± 0.010 vs 0.142 ± 0.036 , $p=0.020$) and Glu (5.560 ± 1.277 vs 7.620 ± 0.896 , $p=0.001$) levels, and elevate TB (1.673 ± 0.188 vs 1.036 ± 0.426 , $p=0.033$), NO (30.915 ± 5.853 vs 19.483 ± 2.967 , $p=0.001$), PGI_2 (4.361 ± 0.991 vs 1.901 ± 0.801 , $p=0.000$) levels in SHR (MI+Copp) group as compared with SHR(MI+NS).
- (4) Histology: SHR (MI+NS) group exhibited obvious myocardial infarction, LV fibrosis in infarct area; and also showed myocyte hypertrophy, hyperaemia, and chronic inflammation in peri-infarct area. Besides, HW/BW ratio was also significantly higher in SHR (MI+NS) group as compared with WT (sham+NS) group. Copp treatment could significantly diminish infarct area, lower the degree of fibrosis, inhibit myocyte hypertrophy, hyperaemia, and chronic inflammation in peri-infarct area, and decrease the ratio of HW/BW (0.382 ± 0.014 vs 0.472 ± 0.065 , $p=0.001$) compared with SHR (MI+NS).

Western blot: Copp treatment could elevate HO-1 expression ($HO-1/Tubulin$ 1.065 ± 0.061 vs 0.930 ± 0.059 , $p=0.019$) in SHR (MI+Copp) group as compared with SHR (MI+NS) group, while concurrently with SnMP could not only block the up-regulation of HO-1 expression, but also inhibit the accompanied amelioration of blood pressure and cardiac function in SHR with MI.

Conclusions Spontaneous hypertensive rats with myocardial infarction exhibited high blood pressure, impaired systolic and diastolic cardiac function, myocyte hypertrophy, heart dilation, excessive inflammation, and glucose metabolic and endothelial dysfunction. Up-regulation of HO-1 via Copp treatment could lower blood pressure, decrease infarct area, improve post-infarct cardiac function, and inhibit ventricular remodelling in SHR with MI. The relative mechanism might involve inhibiting inflammation, anti-oxidation, improving glucose metabolism and endothelial function.