Najah R. Hadi et al., J Comput Sci Syst Biol, 5:1
doi: http://dx.doi.org/10.4172/0974-7230.S1.11

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
Metabolomics & Systems Biology

20-22 February 2012 San Francisco Airport Marriott Waterfront, USA

5-lipoxigenase inhibitor and thyroid hormone analog attenuate global myocardial ischemia reperfusion injury after heterotopic heart transplantation in male rats

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Background: Heart transplantation is a widely accepted therapy for most patients under 65 years of age with advanced heart failure who remain symptomatic with the expectation of high intermediate term mortality, despite optimal heart failure medications.Global myocardial ischemia reperfusion injury after heart transplantation is believed to impair graft function and aggravate both acute and chronic rejection episodes.

Objective: This study was undertaken to assess the possible protective effect of MK-886 (5-lipoxigenase inhibitor) and 3,5-Diiodothyropropionic Acid (DITPA) (thyroid hormone analog) against global myocardial ischemia reperfusion injury after heart transplantation by (using heterotopic heart transplantation model) via interfering with inflammatory pathways.

Materials and Methods: Adult albino rats were randomized into 4 groups (12 rats in each group, 6 donors and 6 recipients) as follow: group I (N=6), sham group, rats underwent the same anesthetic and surgical procedures (for an identicalperiod of time for global myocardial ischemia and reperfusion through transplantation) but with no heterotopic heart transplantation; group II, control group, rats underwent 30 min of global myocardial ischemia followed by 60 min of reperfusion via heterotopic heart transplantation; group III,MK-886 treated group, Donors and recipients rats received MK-886 (0.6 mg/kg) i.p. injection 30 min before transplantation , and the same dose was repeated for recipientsupon reperfusion; group IV,DITPA treated group, Donors and recipients rats pretreated with DITPA(3.75 mg/kg) s.c. for 7days before transplantation.

Results: Compared with sham group, the levels of cardiac TNF-α, IL-1β, ICAM-1 and plasma level of cardiac troponin I (cTnI) were increased in control group (p<0.05). Histologically all rats in control group showed significant cardiac injury (p<0.05).

Both MK-886 and DITPA significantly counteract the increase in the levels of cardiac TNF-α, IL-1β, ICAM-1 and plasma level of (cTnI) (p<0.05). Morphologic analysis showed that both MK-886 and DITPA markedly improved (p<0.05) the severity of cardiac injury in the heterotopically transplanted rats.

Conclusions: The results of this study reveal that both MK-886 and DITPA may ameliorate global ischemia reperfusion injury after heart transplantation via interfering with inflammatory pathway.