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Title: Prevention and partial reversal of monocrotaline-induced pulmonary arterial hypertension (PAH) by hsp90 inhibitors

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Body: We tested the hypothesis that the hsp90 inhibitor, 17-AAG might reverse the hemodynamic alterations associated with PAH. PAH was induced in rats by a single injection of monocrotaline (MCT, 60mg/kg, sc). Four weeks later, a subset of these animals began receiving 17-AAG (1mg/kg 3xweekly, ip) for an additional two weeks. Hemodynamics were monitored weekly by high resolution echocardiography. Right ventricular systolic pressure (RVSP) was also measured invasively at 4 and 6 weeks after MCT. Pulmonary acceleration time (PAT) decreased progressively at 4 and 6 weeks after MCT and reached its nadir at 6 weeks. Similarly, cardiac output (CO) and velocity time integral (VTI) decreased progressively at 4 and 6 weeks post MCT and reached their nadir at 6 weeks. 17-AAG reversed the increase in CO and VTI. At 6 weeks post MCT, both values were statistical similar to those prior to MCT. At 6 weeks post MCT, PAT values in rats treated with 17-AAG between weeks 4 and 6, were higher than those in rats receiving MCT alone for 6 weeks, but similar to those in rats receiving MCT alone for 4 weeks. RVSP and the ratio of the right ventricular weight to either the left ventricular + septum weights (RV/LV+S) or to body weight (RV/BW) increased progressively in MCT-treated rats and reached their maximum at 6 weeks after MCT. At 6 weeks post MCT, RVSP, RV/LV+S and RV/BW values in animals treated with 17-AAG between weeks 4 and 6 were lower than those in rats receiving MCT alone for 6 weeks, but similar to those in rats receiving MCT alone for 4 weeks. These findings suggest that hsp90 inhibitors prevent and partly reverse cardiopulmonary hemodynamic changes associated with MCT-induced PAH.