4; vehicle 52 ± 11%, prasugrel 27 ± 14%, cinaciguat + dipyridamole 26 ± 16%, triple 11 ± 6%: collagen; vehicle 40 ± 16%, prasugrel 42 ± 10%, cinaciguat + dipyridamole 44 ± 19%, triple 18 ± 11%.

Conclusion Our animal studies suggest that combinations of low doses of cinaciguat, prasugrel and dipyridamole could provide a focused and powerful anti-platelet effect. This could be an effective therapeutic antithrombotic approach with potentially lesser effects at other sGC/PDE sites, particularly the vascular smooth muscle, reducing the incidence of headache and hypotension.

170 PLAKOGLOBIN DEFICIENCY PREDISPOSES TO LEFT ATRIAL ELECTRICAL REMODELING FOLLOWING CHRONIC EXPOSURE TO ANABOLIC STEROIDS

Andrew Holmes*, Fahima Syeda, Samantha Tull, Thomas Wright, Stefan Kuhlmann, Nashitha Kabir, Pushpa Patel, Ting Yu, Davor Pavlovic, Paulus Kirchhof, Larissa Fabritz. *University of Birmingham*; **Presenting Author*

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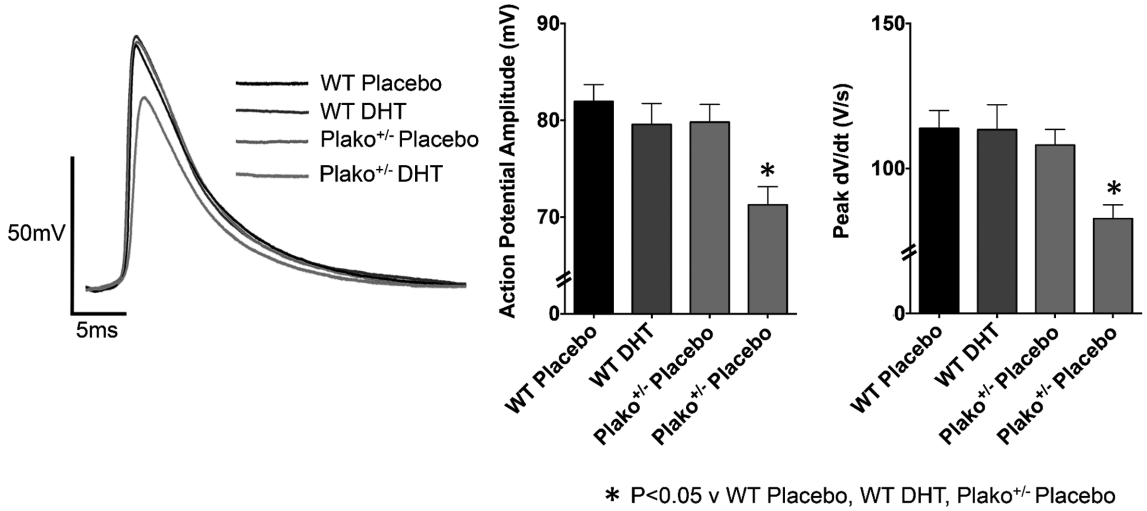
Background The recreational abuse of anabolic steroids is an emerging global health concern and may disrupt cardiac electrophysiology. Every fifth man joining a gym in the UK uses anabolic steroids for performance enhancement. Based on molecular signaling analyses and considering the volume-loading effects of testosterone, individuals with vulnerable desmosomal (cell-cell contact) proteins may be at increased risk of anabolic steroid induced cardiac electrical remodeling. We therefore studied the impact of chronic anabolic steroid exposure on left atrial (LA) electrophysiology in wildtype (WT) and plakoglobin (Plako; or gamma-catenin, a key desmosomal protein) deficient mice using dihydro-testosterone (DHT-a stable derivative of testosterone).

Methods Young adult WT and Plako$^{+/-}$ male mice, bred on 129/sv background were fitted with subcutaneous osmotic mini-pumps containing either DHT (62.5mg/ml) in ethanol, or ethanol alone (Placebo), for 6 weeks. Following treatment, we examined transmembrane action potentials, and generated high spatial resolution activation maps in the Di-4-Anepps loaded LA using the Hamamatsu ORCA flash 4. Significance was taken as $P < 0.05$ v Placebo, one way ANOVA with Bonferroni post hoc analysis. Experiments and analysis were performed blinded to genotype and treatment.

Results DHT minipump exposure lead to supraphysiological DHT plasma levels and increased the ventricular mass:tibial length ratio of both genotypes (WT Placebo 79 ± 2 Plako$^{+/-}$ Placebo 78 ± 2 WT DHT 86 ± 3 Plako$^{+/-}$ DHT 92 ± 3 mg/cm, $P < 0.05$, n = 56 mice total). DHT treatment increased Plako$^{+/-}$ LA mass:tibial length ratio (WT Placebo 2.4 ± 0.1 Plako$^{+/-}$ Placebo 2.3 ± 0.1 WT DHT 2.6 ± 0.2 Plako$^{+/-}$ DHT 3.2 ± 0.2mg/cm, $P < 0.05$, n = 56 mice total) and LA cardiomyocyte fiber size (WT Placebo 0.16 ± 0.01 Plako$^{+/-}$ Placebo 0.14 ± 0.006 WT DHT 0.16 ± 0.004, Plako$^{+/-}$ DHT 0.24 ± 0.04 mm^2, $P < 0.05$ n = 20 LA total).

DHT reduced action potential amplitude in Plako$^{+/-}$ LA, but not WT LA (WT Placebo 82 ± 2 Plako+/- Placebo 80 ± 2 WT DHT 80 ± 2 Plako+/- DHT 71 ± 2mV, $P < 0.05$, n = 65 cells total, n = 22 LA) and peak dV/dt (WT Placebo 114 ± 6 Plako+/- Placebo 108 ± 5 WT DHT 113 ± 9, Plako$^{+/-}$ DHT 82 ± 5 V/s, $P < 0.05$, (see Figure 1). Conduction velocity was significantly attenuated in Plako$^{+/-}$ LA following DHT exposure (WT Placebo 40 ± 0.3 Plako$^{+/-}$ Placebo 40 ± 0.9 WT DHT 37 ± 1.3 Plako$^{+/-}$ DHT 36 ± 1.4 cm/s, $P < 0.05$, n = 29 LA total). Chronic DHT treatment did not alter the action potential duration in either genotype.

Conclusion Reduced cardiac plakoglobin expression increased susceptibility to steroid-induced left atrial hypertrophy, reduced action potential amplitude and lead to significant conduction slowing. These differences are likely to provide an enhanced substrate for atrial arrhythmogenesis. Our results suggest a potentially important interaction between reduced mechanical cell-cell contacts and anabolic steroid use.



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