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## CELLULAR BIOLOGY AND FUNCTION

### SESSION TITLE: INFLAMMATION IN THE FAILING HEART

# Abstract 18662: Oral Calpain Inhibition Attenuates Inflammation, Hypertrophy and Fibrosis in Distant Myocardium After Transient Coronary Occlusion

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Circulation. 2016;134:A18662

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## Abstract

**Background:** Post-infarction remodeling is an important cause of heart failure and a major medical and social problem. Calpains have been associated with inflammatory responses.

**Objective:** To determine whether delayed oral administration of the calpain inhibitor SNJ-1945 mitigates inflammation, hypertrophy and fibrosis in remote myocardium in response to transient coronary occlusion.

**Methods:** The calpain inhibitor SNJ-1945 was administered orally to male Sprague-Dawley rats that had been subjected to 30 min of coronary artery ligation and for 14 days, starting 24h after reperfusion. Hearts were obtained after 21 days and compared with controls not receiving the drug.

**Results:** At 21 days of reperfusion, calpain-1 and calpain-2, but not calpastatin, protein and mRNA content were increased and correlated with higher calpain activity in control hearts. Oral administration of SNJ-1945 attenuated calpain activation, cardiomyocyte hypertrophy ( $203.0 \pm 13.7 \mu\text{m}^2$  vs.  $291.8 \pm 18.6 \mu\text{m}^2$  cross-sectional area,  $P=0.01$ ) and collagen I deposition ( $4.8 \pm 0.2\%$  vs.  $6.7 \pm 0.3\%$  Picosirius Red stained area,  $P=0.02$ ) in the non-infarcted myocardium, and improved LVEF as determined by echocardiography ( $60.2 \pm 2.3\%$  vs.  $49.3 \pm 2.5\%$ ,  $P=0.02$ ). In isolated myocardial fibroblasts, SNJ-1945 reduced  $\alpha$ -SMA and collagen I synthesis by attenuating TGF- $\beta$ 1 signaling. These results were associated to reduced infiltration of macrophages and expression levels of the proinflammatory markers IL-1 $\beta$  and TNF- $\alpha$  in the ischemic and non-ischemic area at 3 days of reperfusion and attenuated NF- $\kappa$ B and NFAT activation as the result of reduced calpain-dependent degradation of I $\kappa$ B and calcineurin activity respectively.

**Conclusions:** Delayed, oral administration of SNJ-1945 attenuates the inflammatory response, cardiomyocyte hypertrophy, activation of fibroblasts, and deposition of collagen in the non-infarcted myocardium in association to attenuated activation of NF- $\kappa$ B and NFAT. This study proposes pharmacological calpain inhibition as a feasible and effective strategy to limit post-infarction myocardial remodeling.

**Ischemia reperfusion    Remodeling    Fibrosis**

**Inflammation and inflammatory markers    Cardioprotective drugs**

Author Disclosures: **J. Inserte:** None. **M. Poncelas:** None. **D. Aluja:** None. **U. Vilardosa:** None. **L. Ramos:** None. **D. Garcia-Dorado:** None.

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November 11, 2016, Volume 134, Issue Suppl 1





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