**PCSK9 EXPRESSION IN THE ISCHEMIC HEART AND ITS RELATIONSHIP TO INFARCT SIZE AND CARDIAC FUNCTION**
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*Background:* Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a novel therapy to treat hypercholesterolemia and related cardiovascular diseases. We examined if PCSK9 is expressed in the ischemic heart and if so what is its role in the regulation of infarct size and cardiac function during ischemia.

*Methods and Results:* Mice hearts were subjected to left coronary artery (LCA) occlusion. There was intense expression of PCSK9 in the zone bordering the infarct area- in association with marked cardiac contractile dysfunction in the wild-type mice. To assess the role of PCSK9 in the evolution of infarct size and function, we used wild-type mice pretreated with two different PCSK9 inhibitors (Pep2-8 and EGF-A) or mice lacking PCSK9 gene. Both strategies resulted in smaller infarcts and improved cardiac function following LCA ligation. Relationship between myocardial ischemia and PCSK9 expression was examined in cultured primary mouse cardiomyocytes. To determine the role of inflammation which is characteristic of ischemia in PCSK9 release, cardiomyocytes were treated with TNFα which resulted in a robust increase in PCSK9 in a concentration-dependent manner. Further, exposure of cultured cardiomyocytes to hypoxia resulted in prompt PCSK9 expression, which was blocked by HIF-1α siRNA transfection. Hearts of humans with recent infarcts also showed expression of PCSK9 in the border zone- similar to that in the infarcted mouse heart.

*Conclusions:* PCSK9 is upregulated in the ischemic hearts and determines development of infarct size and cardiac function. PCSK9 expression is most likely secondary to inflammation and hypoxia.