SGLT2 Inhibitor Canagliflozin Modulates Inflammation in Chronically Ischemic Swine Myocardium

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Abstract

Background & Aim: Clinical data from patients treated with sodium−glucose transport protein 2 (SGLT2) inhibitors has shown a reduction in cardiovascular mortality and congestive heart failure symptom burden. However, the biochemical mechanism of SGLT2 inhibitors in the myocardium is poorly understood. Our group has previously shown that SGLT2 inhibitor canagliflozin treatment results in increased cardiac output and myocardial perfusion in a swine model for chronic myocardial ischemia. The current study aims to determine the effects of canagliflozin on inflammation in chronically ischemic myocardium.

Methods: Yorkshire swine underwent placement of an ameroid constrictor on the left circumflex artery to model chronic myocardial ischemia. The pigs recovered for two weeks then were assigned to either no drug (n=8) or 300mg canagliflozin oral daily (n=8) for five weeks. After 5 weeks the pigs were euthanized, and tissues were harvested for analysis. Protein expression was analyzed using immunoblotting. Protein expression was plotted with our previously reported myocardial perfusion data and analyzed for correlations between perfusion and protein expression using Spearman's rank correlation coefficient. Statistical analysis included Mann Whitney U test and t−test as appropriate. Outliers greater than two standard deviations where removed when appropriate.

Results: Canagliflozin treatment was associated with a significant increase in inflammatory markers IL−6, IL−17, IFN−.. and iNOS ($p<0.05$) in ischemic myocardium. There was a trend towards increased expression of the inflammatory markers IL−8 ($p=0.14$) and TNF−a ($p=0.24$) and decreased expression of the anti−inflammatory cytokines IL−10 ($p=0.16$) and IL−4 ($p=0.31$) with canagliflozin treatment. NF..B ($p=0.06$) showed a trend towards decreased expression in the canagliflozin group. There was no significant difference in expression of the proinflammatory markers IL−1, NLRP−3, CD11c, TLR4, HLA−DRA, pNF..B and eNOS ($p>0.40$). There was no statistically significant correlation between myocardial perfusion and protein expression with any of the markers tested.

Conclusion: In chronically ischemic myocardium, canagliflozin results in a significant increase in inflammatory markers IL−6, IL−17, IFN−.., and iNOS. Canagliflozin therapy also results in a trend toward decreased anti−inflammatory cytokines IL−4, and IL−10.

Clinical Implications: It is possible that this relative increase in inflammation plays a role in the increased myocardial perfusion and cardiac output seen with canagliflozin.

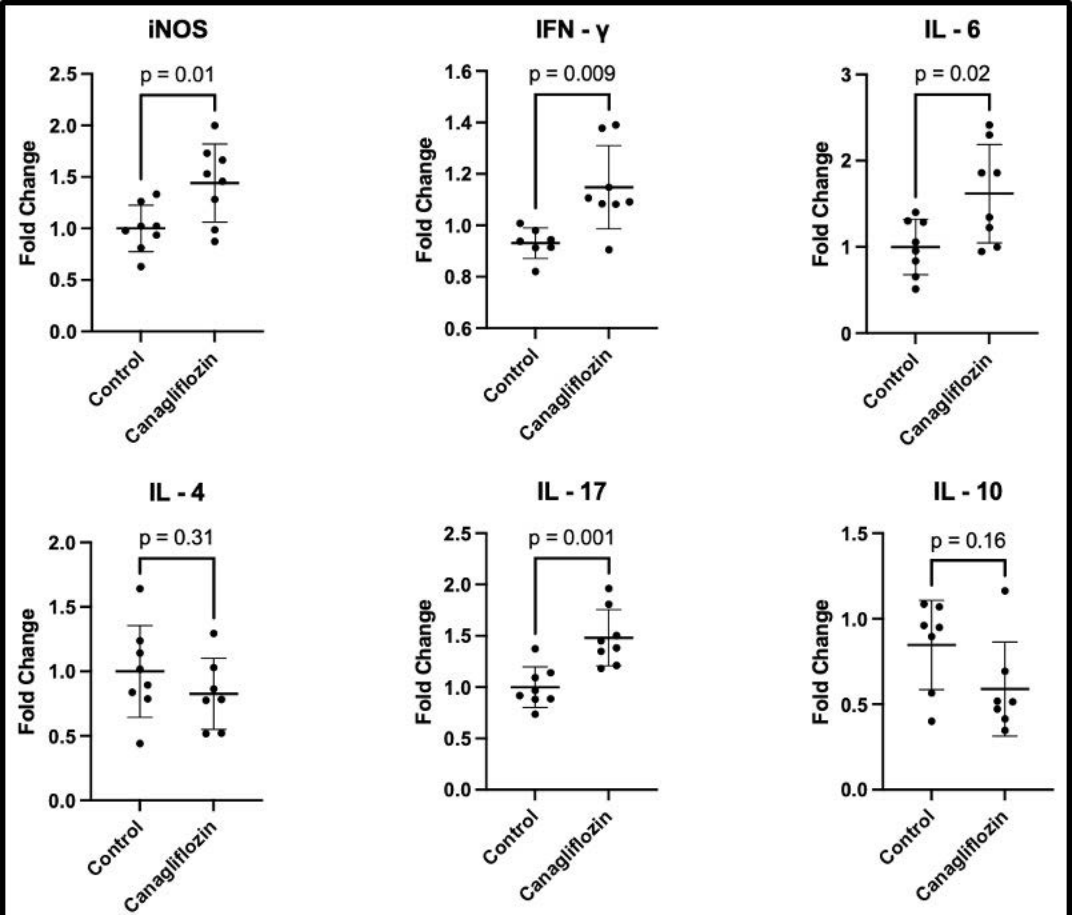

Figure 1: Quantitative analysis of Western blots carried out using ischemic heart tissues from Control (n=8) and Canagliflozin (n=8) treated swine. Data points are fold change compared to average control. Lines represent mean and standard deviation. P-value was calculated using t-test or Mann–Whitney U test based on the results of a Shapiro–Wilk test.