Effects of SGLT2 Inhibitor Canagliflozin in Chronically Ischemic Myocardium

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Abstract

Background & Aim: Sodium−glucose cotransporter−2 (SGLT2) inhibitors have cardioprotective effects independent of glucose control, as demonstrated in animal models of acute myocardial ischemia and in clinical trials of patients with heart failure. The mechanisms of these effects require further investigation. The purpose of this study is to determine the effects of canagliflozin therapy on myocardial function, perfusion, and microvessel density in a large animal model of chronic myocardial ischemia.

Methods: Yorkshire swine underwent placement of an ameroid constrictor to the left circumflex artery to induce chronic myocardial ischemia. Two weeks later, pigs received either no drug (CON, n=8) or 300mg canagliflozin (CANA) daily (n=8). Treatment continued for five weeks, followed by hemodynamic measurements and harvest. Perfusion, vessel density, and protein expression were measured by microsphere analysis, immunofluorescence, and immunoblotting respectively.

Results: CANA therapy was associated with increased stroke volume ($p=0.007$) and stroke work ($p=0.021$), and decreased left ventricular stiffness ($p=0.007$) compared to CON. The CANA group had improved perfusion to ischemic myocardium at rest ($p=0.036$) and during pacing ($p=0.038$) compared to CON. There were no differences in arteriolar or capillary density between groups ($p>0.05$). In ischemic myocardium of the CANA group, there was increased expression of total AMPK ($p=0.0047$) and p−AMPK ($p=0.038$), decreased expression of p−eNOS ($p=0.028$) with unchanged total eNOS ($p>0.05$), and increased expression of antioxidant SOD2 ($p<0.001$) compared to CON. There were no differences in expression or activation of AKT and ERK1/2 ($p>0.05$).

Conclusion: In the setting of chronic myocardial ischemia, canagliflozin therapy improves myocardial function and perfusion to ischemic territory, without changes in collateralization.

Clinical Implications: These findings suggest that canagliflozin may be a promising therapeutic option in patients with chronic coronary artery disease, even in the absence of diabetes.

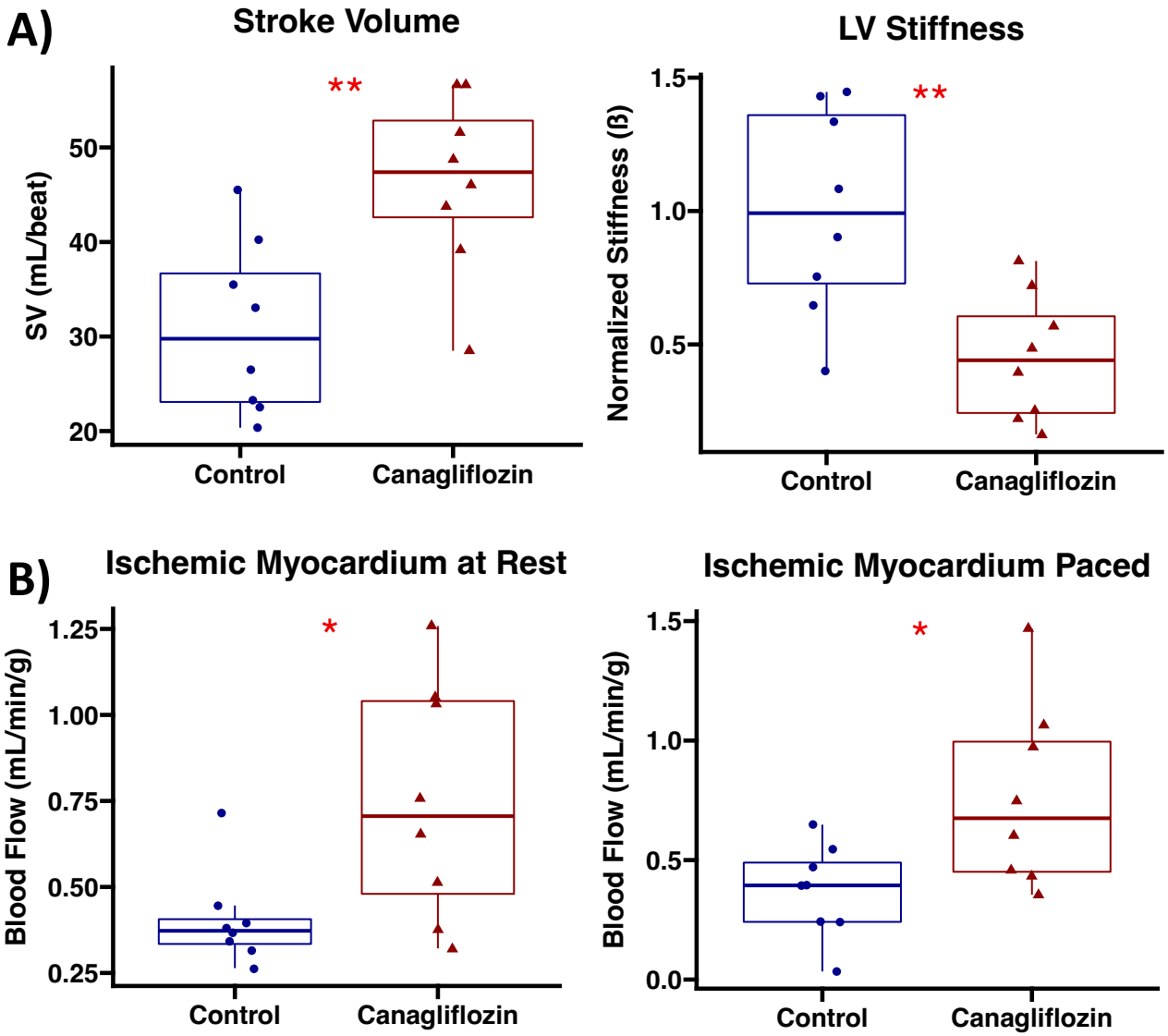

Figure: Effects of canagliflozin therapy on myocardial function and perfusion in the setting of chronic myocardial ischemia. Canagliflozin therapy was associated with improved **A**) hemodynamic parameters, including increased stroke volume (SV) and decreased left ventricular (LV) stiffness, and **B**) perfusion to the ischemic myocardial territory at rest and during pacing to 150 beats per minute, compared to control. LV stiffness coefficient ß derived from end diastolic pressure volume relationship. P values were calculated using Wilcoxon rank sum test. *p<0.05; **p<0.01