PROJECT DESCRIPTION

Project Title:

Ischemia Dependent Cardioprotection by SGLT2 Inhibitors Mechanistic and Metabolomic Evaluation in a Large Animal Preparation

Principal Investigator:

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Research Location:

Northeast Ohio Medical University College of Medicine
RGE-300
RGE-308
Comparative Medicine Unit

Abstract:

SGLT2 inhibitors reduce heart failure events across many clinical populations, and this benefit cannot be explained by glucose lowering or canonical endocrine signaling pathways. Our laboratory has established that cardioprotection by SGLT2 inhibitors is strictly dependent on the presence of myocardial ischemia. In a large animal model, we previously demonstrated that the improvement in diastolic relaxation, quantified by the time constant tau, scales with the severity of ischemia. Protection was observed with both canagliflozin and empagliflozin which indicates a class mediated effect rather than a compound specific artifact.

Our group has also developed and published an extracorporeal coronary perfusion preparation in open chest swine that maintains a fully beating, load bearing heart while allowing servo controlled perfusion of the LAD across a wide hemodynamic range. In this model coronary pressure and flow are adjustable from approximately 140 to 40 mmHg and coronary venous sampling provides a direct index of oxygen delivery and extraction. This platform allows controlled induction of ischemia, continuous pressure volume monitoring, measurement of tau, and real time sampling of extracellular fluid from the myocardium.

The purpose of the 2026 student project is to determine whether SGLT2 mediated cardioprotection is driven by direct myocardial drug action or requires systemic signals. We will perform intracoronary infusions of SGLT2 inhibitor into ischemic and non ischemic territories while perfusion is varied across and beyond the autoregulatory range. During each condition we will record pressure volume relations, measure tau, quantify coronary flow, and collect extracellular and coronary venous samples for metabolomic and proteomic analysis in collaboration with Cedars Sinai Medical Center. By integrating physiologic response with biochemical signatures, this work will identify mechanistic pathways responsible for ischemia linked cardioprotection.

Significance:

SGLT2 inhibitors provide robust protection in settings of cardiovascular stress, yet the mechanism remains unresolved. Our data indicate that protection emerges only during ischemia and increases with ischemic intensity. Determining whether this protection arises from direct myocardial effects or through circulating mediators has substantial clinical and scientific value. If a local mechanism dominates, intracoronary or targeted dosing strategies may improve therapy. If protection is mediated through metabolic or humoral pathways, monitoring and modulation of these signals may enhance safety and efficacy. The metabolomic and proteomic dataset generated here will serve as foundational evidence for future R level funding, manuscript publication, and conference presentation.

Goals and Objectives for the Research Project

The primary goal of this project is to define molecular and physiological signatures of SGLT2 mediated cardioprotection under graded ischemia.

The student will complete the following objectives:

1. Reproduce the ischemia dependent relaxation response associated with SGLT2 inhibitors across a more severe ischemic range.
2. Quantify the relationship between ischemia intensity and tau preservation to refine the protection curve.
3. Use intracoronary infusion to test whether drug effect occurs independently of systemic circulation.
4. Collect extracellular and coronary venous fluid samples during each ischemic stage for metabolomic and proteomic analysis.
5. Integrate biochemical signatures with relaxation mechanics to identify mechanistic drivers of protection.

Research Methods

Experiments will be performed in our established swine preparation. Animals will undergo left thoracotomy for instrumentation. The LAD will be cannulated and perfused through an extracorporeal servo controlled pump. Coronary flow will be titrated across and beyond the autoregulatory range to induce graded ischemia. Pressure volume catheters will allow direct measurement of systolic and diastolic mechanics including tau, preload recruitable stroke work, and end diastolic pressure volume relations. Coronary venous blood will be collected from the anterior interventricular vein for oxygen content and metabolite quantification.

SGLT2 inhibitor or vehicle will be infused by intracoronary route into ischemic or normally perfused territories. Myocardial extracellular fluid will be sampled through our interstitial microperfusion system during each perfusion condition. Samples will be frozen, cataloged, and submitted for metabolomic and proteomic analysis. Data acquisition will occur continuously with time alignment between physiology and biochemical sampling.

Methods of Data Analysis

Longitudinal outcomes will be evaluated using repeated measures ANOVA. Tau, oxygen extraction, and flow response will be modeled against ischemia severity. Metabolomic output will be dimensionally reduced to identify treatment specific clusters. Differential metabolite and protein abundance analysis will be used to identify candidate pathways. Integration plots will compare metabolomic signatures to tau preservation to determine which pathways correspond most strongly with cardioprotection.

Anticipated Findings

We expect SGLT2 inhibitors to improve tau at high ischemic severity and to produce metabolomic divergence that tracks with protection. If direct infusion in non ischemic regions does not produce benefit, this will support a requirement for ischemic signaling. If metabolomic signatures predict functional preservation regardless of region, circulating mediators are likely involved. Either outcome will clarify mechanism and inform next phase experimental design.

This work directly advances an active line of research, expands our dataset, and is expected to produce abstract and manuscript level findings within the training interval.

STUDENT FELLOW TRAINING/MENTORING PLAN

Training Plan

All learners will complete required CITI certification and CMU orientation prior to participating in animal work and all procedures will follow approved IACUC protocols. Large animal studies will be performed with direct instruction and supervision from Dr. Goodwill. Students will be encouraged to participate in every stage of the project, including animal preparation, physiological monitoring, sample collection, analytic processing, data interpretation, and final presentation of results.

Cross training will be used to ensure that each learner gains experience in instrument setup, real time acquisition, metabolic and hemodynamic calculations, and visual data analysis. Dr. Goodwill intends to work with students daily to provide guidance, answer questions, and assist with technical and conceptual development. Brief daily check ins will assist with planning, troubleshooting, and maintaining research momentum.

Weekly laboratory meetings will serve as the primary venue for structured discussion and review of ongoing work. Students will also attend the cardiovascular research journal club associated with the research focus area to strengthen their ability to read primary literature and evaluate scientific conclusions. Presentation skills will be developed through staged practice sessions. Each student will present preliminary findings to the laboratory team, revise slides with feedback, and then deliver a refined version to the cardiovascular research group prior to any external symposium or abstract submission.

Data analysis software and computational tools will be available for all trainees. A see one, do one, teach one progression will be used whenever appropriate. Students will observe a workflow first, repeat it independently, and demonstrate competency by guiding another team member through the same process. All figures and analytic results will be reviewed with Dr. Goodwill prior to public presentation.

Finally, students will be encouraged to maintain work life balance. The laboratory values scientific productivity but also believes that mental health supports clarity, creativity, and long term success. Trainees will be encouraged to disconnect at the end of the work day knowing that the research will still be there tomorrow.

Available Resources

- Assorted Surgical Equipment
- ADInstruments Powerlab C with 16 inputs
- Dell XPS Computer for data acquisition
- Grass Amplifier (Multiple)
- Harvard Apparatus Perfusion Servo Controller (2)
- Harvard Apparatus Syringe Pumps (Multiple)
- Harvard Apparatus Transducer Amplifier (8)
- Haake K20 Heated/Cooled Circulating Water Bath
- iWorx Biopotential Amplifier for ECG
- Lifepak 20 Defibrillator with Internal/External Paddles
- Masterflex L/S Peristaltic Pumps (2)
- Stryker 810 Autopsy Saw
- Transonic ADV-550 Admittance Pressure Volume System
- Transonic TS410 Tubing Flow Module (2)
- Transonic TS420 Transit Time Perivascular Flow Module (3)
- Werfen Gem Premier 5000 Blood Gas Analyzer

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