PROJECT DESCRIPTION

Project Title:

GLP 1 Mediated Cardioprotection During Anthracycline Exposure in a Large Animal Physiology Model

Principal Investigator:

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Research Location:

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

Abstract:

Anthracycline chemotherapy is highly effective in cancer treatment, but cumulative exposure produces predictable cardiac injury. The early stages of toxicity involve shifts in oxygen handling, impaired mitochondrial efficiency, and progressive mechanical dysfunction that ultimately progress to heart failure. Therapies that reduce metabolic stress and preserve contractile mechanics may allow greater cumulative dosing without cardiac collapse.

GLP 1 receptor agonists have shown clear cardiovascular benefit in clinical populations. Several groups have reported improved mitochondrial efficiency, improved ATP linked respiration, reduced lipid oxidation and reduced apoptotic signaling with GLP 1 treatment. Retrospective human data also suggest a reduction in heart failure events of roughly fifty percent when GLP 1 therapy is present during anthracycline exposure. These findings indicate that GLP 1 may offset mitochondrial stress, protect the microvasculature, and maintain contractile reserve under toxic load.

This study will quantify cardioprotection using NEOMEDs large animal model. The student will evaluate myocardial oxygen consumption and metabolic efficiency, measure coronary flow reserve, and analyze pressure volume loops for early divergence of contractile mechanics. Results are expected to define an integrated physiological profile that indicates whether GLP 1 slows deterioration or permits higher safe dosing thresholds.

Significance:

Anthracycline toxicity limits the lifetime dose patients are allowed to receive. We believe GLP 1 has the potential to mitigate toxicity and increase lifetime dosing limits. If metabolic efficiency is preserved and coronary reserve remains intact, the heart may tolerate significantly more chemotherapy exposure before failure. Because GLP 1 therapies are widely available and well tolerated, this work has immediate translational value. Any protective phenotype identified in this project could serve as a clinical monitoring target for cardiotoxicity surveillance and for designing future interventional studies.

Goals and Objectives for the Research Project

The overarching goal of this work is to determine whether GLP 1 therapy protects the heart during anthracycline exposure through preservation of metabolic efficiency, coronary reserve, and mechanical performance.

The student will complete the following objectives.

1. Measure myocardial oxygen consumption during treatment exposure and determine whether GLP 1 reduces oxygen cost per unit stroke work.
2. Quantify coronary flow reserve and evaluate whether GLP 1 maintains hyperemic capacity as cumulative drug exposure increases.

3. Process and analyze pressure volume loops to detect the earliest point at which GLP 1 treated hearts maintain contractile function longer than untreated hearts.
4. Optional mechanistic objective, performed only if primary aims are complete. Isolate mitochondria post mortem and measure oxygen consumption rate, respiratory control ratio and ATP linked respiration to establish mechanistic support for observed physiological protection.

Research Methods

All work will be completed in a fully instrumented large animal model. Under general anesthesia, animals will undergo left lateral thoracotomy. Perivascular coronary flow probes will be placed around the left anterior descending and circumflex arteries. Arterial and coronary venous catheters will enable sampling for oxygen content and metabolic substrates. A high fidelity pressure volume catheter may be inserted to allow multi beat characterization of systolic and diastolic mechanics.

Animals will receive serial anthracycline treatments with or without GLP 1 therapy. Data will be collected at and between treatments. This allows direct comparison of metabolic demand, microvascular performance, and contractile function across progressive exposure.

Myocardial oxygen consumption will be calculated from arterial venous gradients and measured coronary flow. Coronary reserve will be assessed by brief LAD occlusion and analysis of peak hyperemia and flow debt repayment. Pressure volume loops will be processed for elastance, preload recruitable stroke work, diastolic stiffness constants and pressure volume area.

If optional mitochondrial analysis is performed, left ventricular tissue will be used to isolate mitochondria and measure oxygen consumption, respiratory control ratio and ATP linked flux using high resolution respirometry.

Methods of Data Analysis

Data will be analyzed using SigmaPlot or GraphPad. Repeated measures ANOVA will be used for longitudinal comparisons. Regression analyses will examine relationships among efficiency, flow reserve and mechanical preservation. Graphs will be constructed to visualize treatment divergence over time and to determine whether GLP 1 delays the onset of dysfunction.

Anticipated Findings

We anticipate that GLP 1 treated hearts will demonstrate lower oxygen cost per unit stroke work, more stable coronary flow reserve during hyperemia, and slower deterioration of pressure volume loop derived contractile indices. Identification of any of these protective responses would provide strong evidence that GLP 1 can reduce anthracycline toxicity and may support revised lifetime dosing limits in future clinical application.

If GLP 1 does not protect across these domains, the result will still be highly informative. The findings will identify the precise stage where toxicity overcomes compensation, which will guide future mechanistic studies and dosing strategies.

This work will produce a high value physiologic dataset that supports the next phase of therapeutic development.

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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