CLOFIBRIC ACID INCREASES CARDIAC CONTRACTILITY

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INTRODUCTION

- Congestive Heart Failure (CHF) results from an inability of the cardiac ventricle to fill with or eject blood sufficiently
- Patients with systolic heart failure are started on Digoxin to improve symptoms and reduce hospitalizations.[1]
- Digoxin's positive inotropic effect stems from its ability to block the NKA pump in cardiac myocytes.
- Peroxisome proliferator-activated receptors (PPARs), such as Clofibrate and Gemfibrozil, are used to treat hypertriglyceridemia.
- Studies have shown PPAR alpha agonists ability to block NKA pump in the kidney.[2]
- We hypothesize that Clofibric acid increases cardiac contractility by blocking the NKA pump.

METHODS

- 12-16 week old wild type and PPAR alpha blocked mice were anesthetized, mouse heart were excised and placed in cardioprotective Ringer's solution that included 2,3-butanedione monoxime (2,3-BDM) for 30 minutes and bubbled under 100% oxygen.
- Muscle strips were excised from the left ventricle.
- The strips were hung vertically and attached to a force transducer between bipolar platinum. stimulating electrodes suspended in a 25-mL glass tissue chambers.
- The strips were rinsed three times in Ringer's to remove the 2,3-BDM. A consistent baseline was obtained for 30 minutes prior to drug administration.
- Muscle strips were paced at 1 Hz and muscle contraction waveforms were measured using Powerlab hardware and LabChart software (AD Instruments).
- After 90 minutes of equilibration, heart strips were tested with 2 and 20 μM of clofibric acid, clofibrate ester, and appropirate vehicle (DMSO and HBSS respectively).

RESULTS

Clofibric Acid increases cardiac contractility in wildtype and PPAR alpha knocknout mice

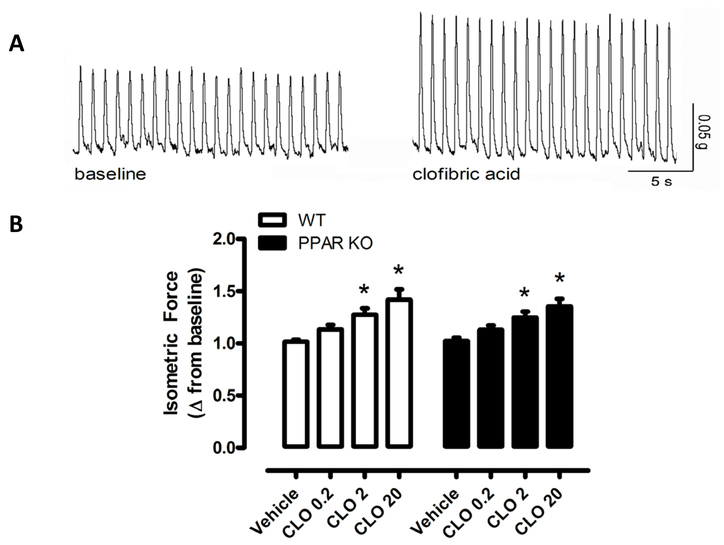

Fig. 1: A) Representative tracings of left ventricular muscle contractions at baseline and 15 min after treatment with clofibric acid (CLO; 20 uM). **B)** Summary data of isometric tension showing a concentration response to clofibric acid from 0.2-20 mM with increased tension when compared to vehicle (n=7-9; $p < 0.05$). *indicates $P<0.05$ from vehicle.

Clofibric Acid mimics the effect of Ouabain on cardiac contractility

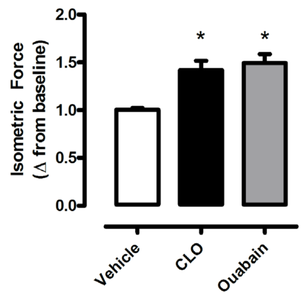

Fig 2: Changes in isometric force after treatment with 1 mM ouabain (n=7) in comparison to 20 mM clofibric acid. *indicates $P<0.05$ from vehicle.

PROPOSED MECHANISM

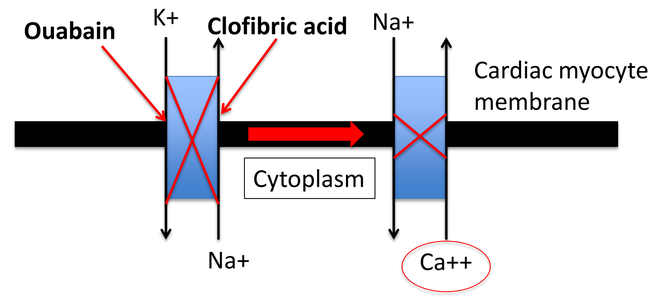

Fig. 3: We hypothesize that Clofibric acid directly inhibits the NKA pump. This inhibition ultimately leads to the reversal of the Na+/Ca++ exchanger, thus increasing intracellular Ca++ and increasing inotrophy.

SUMMARY

- Clofibric acid induced significant changes in cardiac contractility
- Increase in inotrophy was seen within 20 minutes.
- This increase was mediated via a PPA-alpha independent mechanism
- Clofibric acid increases cardiac contraction heights similar to the NKA pump inhibitor, Ouabain
- Currently, PPAR alpha agonists are being used to reduce triglycerides. However, we believe that Clofibrate can be used as a unique drug for heart failure patients to decrease triglyceride levels as well as increase cardiac contractility. These findings provide a novel use for a drug that has already received FDA approval and could improve clinical outcomes and quality of life.

CREDITS/DISCLOSURE/REFERENCES

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