Shortening of Action Potential Duration with Increased Work in Contracting Rabbit Hearts

Kara Garrott*, Sarah Kuzmiak-Glancy*, Anastasia Wengrowski*, Hanyu Zhang+, Jack Rogers+, Matthew Kay*

*The George Washington University, School of Engineering and Applied Science, Biomedical Engineering

+The University of Alabama at Birmingham, School of Engineering, Biomedical Engineering

GW Department of Biomedical Engineering

Hypothesis

- In excised, contracting, crystalloid perfused hearts, the greater workload in LV working hearts will result in:
  - Shorter APDs during normal sinus rhythm (NSR) & pacing
  - Faster APD shortening during deoxygenation
- The K_{ATP} channel blocker, glibenclamide, will attenuate APD shortening during deoxygenation.

Background

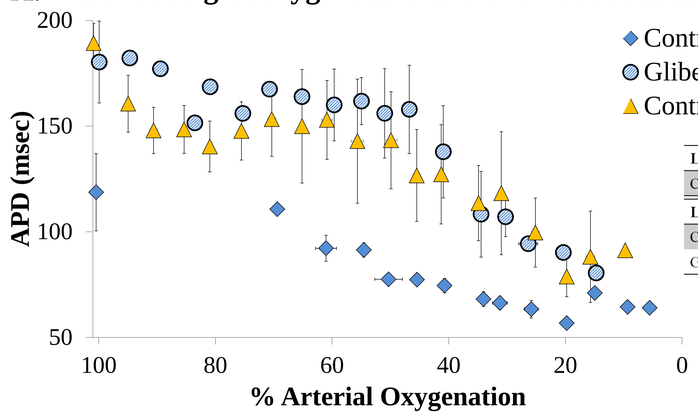
- Hypoxic or ischemic tissue that results from coronary blockage in CHD does not receive oxygen or fuels to maintain normal cardiac function.
- K_{ATP} channels open when [ADP]/[ATP] increases, increasing the outward K+ current and shortening APD.
- Understanding the link between the metabolic and electrical states of the heart provides crucial knowledge in prevention of heart disease.
- Ratiometric optical mapping of fully loaded hearts is a novel method to study electrical activity while replicating *in vivo* energy consumption.

Methods

- Rabbit hearts perfused with oxygenated KH solution were cannulated in two preparations, alternatively:
  1. unloaded Langendorff 2. fully-loaded left working heart (LWH)
- Epicardial APs were measured using optical mapping of Di-4-ANEPPS, a voltage sensitive fluorescent dye.
- Aortic pressure, left atrial preload, epicardial electrograms, LA flow rate, coronary flow rate, and media O_2 saturation in and out of the heart were measured.
- Hearts were gradually deoxygenated by switching from $95\%O_2/5\%CO_2$ gas in KH to N_2 gas in KH.
- A range of workloads were studied by pacing at the following cycle lengths (CLs): 330, 220, and 170 msec.
- APDs were calculated at 100% repolarization by using the time points of the maximum 1st and 2nd derivatives.

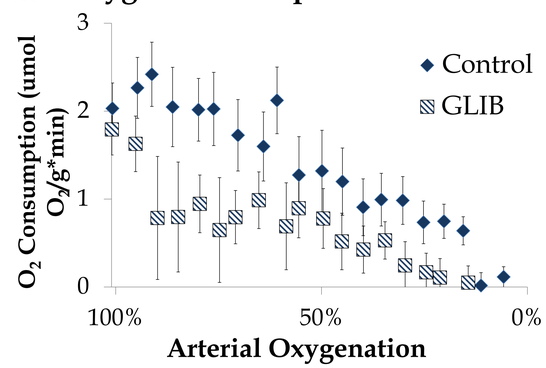
Results

A. APD during Deoxygenation: Effect of Glibenclamide

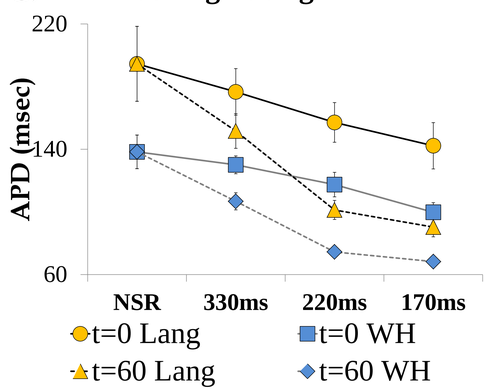


Langendorff	100% O_2	50% O_2	25% O_2
Control	189 ± 21	143 ± 46	99 ± 37
LWH	**100% O_2**	**50% O_2**	**25% O_2**
Control	119 ± 32	78 ± 2.7	63 ± 7.2
Glibenclamide	180 ± 27	156 ± 30	94 ± 0.5

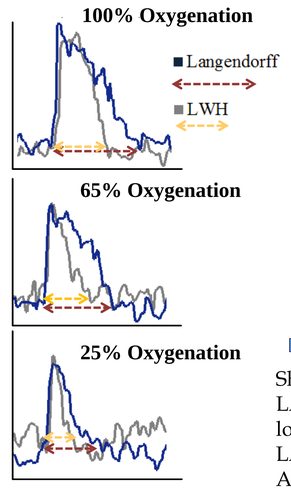
B. Oxygen Consumption



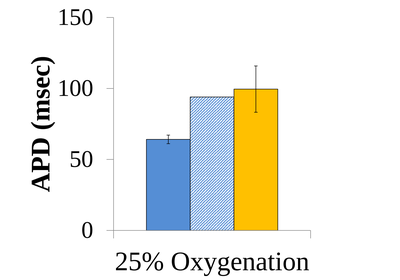
C. APD during Pacing



A.) Shortening of APD with decreasing oxygenation. LWH APD decreases faster and to a greater extent than Langendorff APD. Glibenclamide restores LWH APD to LANG values, as seen in the graph and table.
B.) Glibenclamide causes a decrease in myocardial oxygen consumption due to its vasoconstrictive effect.
C.) Drop in APD that occurs at faster pacing rates. APD is additionally shortened in the working heart compared to the Langendorff preparation.

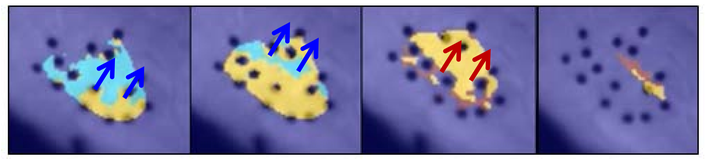


APD at 25% Oxygenation



Shortening in LWH was more severe than LANG during deoxygenation. APD was lower at 25% oxygenation in LWH versus LANG; however, glibenclamide recovered APDs to values close to LANG.

AP Propagation



Propagation of AP across epicardial surface during pacing. The depolarization (blue), plateau phase (yellow), and repolarization (red) propagating across the epicardium are clearly demonstrated.

Conclusion

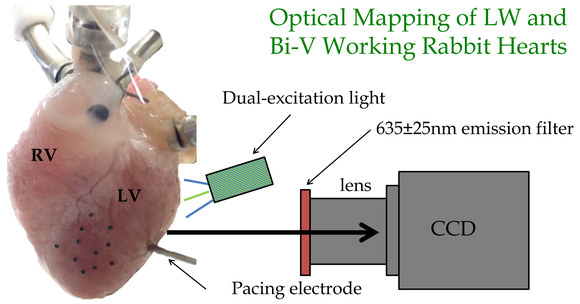
- Optical mapping with motion tracking and ratiometry provides electrophysiological assessments during high workloads.
- K_{ATP} channels are activated more readily in LWH vs. Langendorff.
- K_{ATP} channel opening is attenuated in Langendorff perfused hearts.
- Conducting excised heart studies that more closely mimic physiologic workload is vital.

Experimental Setup

Excitation ratiometry with motion correction:

- 450nm (royal blue) and 505nm (cyan) LEDs excite epicardium
- Excitation illumination rapidly cycled between the 2 colors
- Emission light filtered before images are collected by CCD camera
- Blue light results in upright APs, cyan light results in inverted APs. Ratiometry (blue/cyan) assists in removing motion artifact.

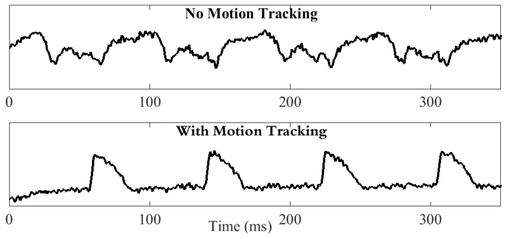
Optical Mapping of LW and Bi-V Working Rabbit Hearts



Motion Correction Algorithm

Motion correction algorithm:

- 2-dimensional Gaussian fitting
- Delauney triangulation and interpolation



Acknowledgements

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References

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