

GLYCOGEN AND ATRIAL FIBRILLATION ATRIAL MYOCYTES CONTRACTILITY AS MECHANICAL FACTOR SHIFTING INTRACELLULAR GLYCOGEN AGAINST INTERCALATED DISCS



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ABSTRACT

The purpose of this communication is to introduce in the medical literature an additional factor until now hypothesized action of atrial cells depolarization as factor in intracellular flow of glycogen molecules coalescing against the gap junctions. The demonstrated effect of gap junction blockers on paired cells contractility combined with gap junction's selectivity towards glycogen molecules; and the visualization of contrasting intracellular glycogen images during atrial fibrillation are shown. Published data supporting atrial myocytes contraction as a mechanism in intracellular glycogen molecules migration and its deleterious effects leading into atrial fibrillation (AF) is proposed.

1. INTRODUCTION

In a previous publication in 2014, we show that in atrial myocytes glycogen is heterogeneously distributed in both atria in the normal goat heart; however, in AF the density of glycogen deposits concentrating against the intercalated discs and side to side connections in the left atrial appendage is a critically distinct difference. Impediment of cell to cell conduction **could result** in a non-uniform wavefront of activation, with areas of slowed conduction, predisposing the left atrium to reentrant based atrial fibrillation" [1].

2. MATERIALS AND METHODS

A literature search was conducted relevant to changes in atrial myocytes architecture, with specific emphasis in the effect of myocytes intercellular gap junction blockage, such as from glycogen molecules which has been previously hypothesized as additional factor in the genesis of atrial fibrillation (AF).

3. RESULTS

3.1. ATRIAL DEPOLARIZATION AND GAP JUNCTION BLOCKAGE IN LONGITUDINALLY CONNECTED CELLS

Published data presented now supports the physical force transduction by atrial intracellular depolarization as a primary factor in glycogen molecules accumulating against intercalated discs and causing deleterious effects in cell contractility. The following publication and image were found where a micro device designed for the study of intercellular electromechanical force transduction [2] between atrial myocytes, shows the effect of gap junction blockage on intercellular atrial cell contractility [3], as shown in Exhibit 1 below.

EXHIBIT 1

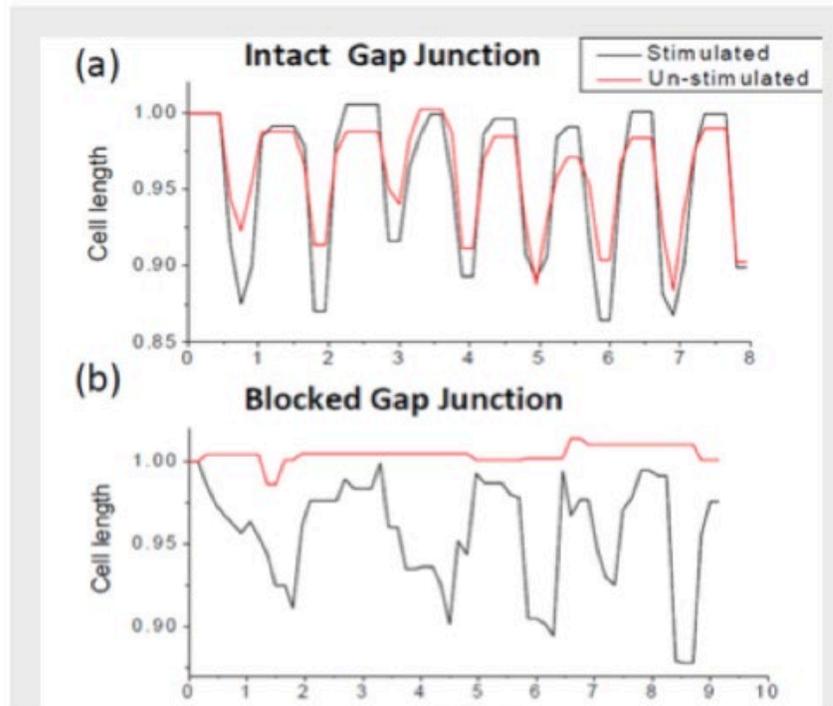


Fig. 7

Contractile performances of two cells in a longitudinally connected cell-cell doublet. (a) before and (b) after a gap junction blocker was applied. (c) Statistics showing the effect of the gap junction blocker on cell contractility.

Above figure reproduced and credit given to: Zhang, X., Wang, Q., Gablaski, B., Zhang, X., Lucchesi, P., & Zhao, Y. (2013). A microdevice for studying intercellular electromechanical transduction in adult cardiac myocytes. *Lab on a chip*, 13(15), 3090–3097. <https://doi.org/10.1039/c3lc50414j>

3.2. UNPUBLISHED IMAGE OF CONTRASTING GLYCOGEN AND GAP JUNCTION BLOCKAGE

The second relevant finding was an unpublished image, albeit used in a university setting Medical Grand Rounds from *in vivo* experiments showing glycogen molecules blocking dog's atrial myocytes in experimentally induced AF.

Tissue biopsy was obtained *in vivo* during induced AF by rapid atrial pacing. The sample then stained using Periodic acid–Schiff (PAS) that is a staining method used to detect polysaccharides such as glycogen.

This image was included in a slide at The University of Oklahoma Medical Grand Rounds in May 2014 entitled “Fact: Atrial Fibrillation is the Most Common Clinical (Sustained) Cardiac Arrhythmia: What are the Factors *Underlying [4] (Exhibits 2,3).

EXHIBIT 2

Fact: Atrial Fibrillation is the Most Common Clinical (Sustained) Cardiac Arrhythmia: What are the factors underlying the fact

Benjamin J. Scherlag, PhD
Abraham A. Embi, MBA/HA
Ling Zhang, MD
Jerry Ritchey, DVM, PhD
Sunny S. Po, MD, PhD

Grand Rounds Presentation Title at University of Oklahoma (May 2014)

EXHIBIT 3

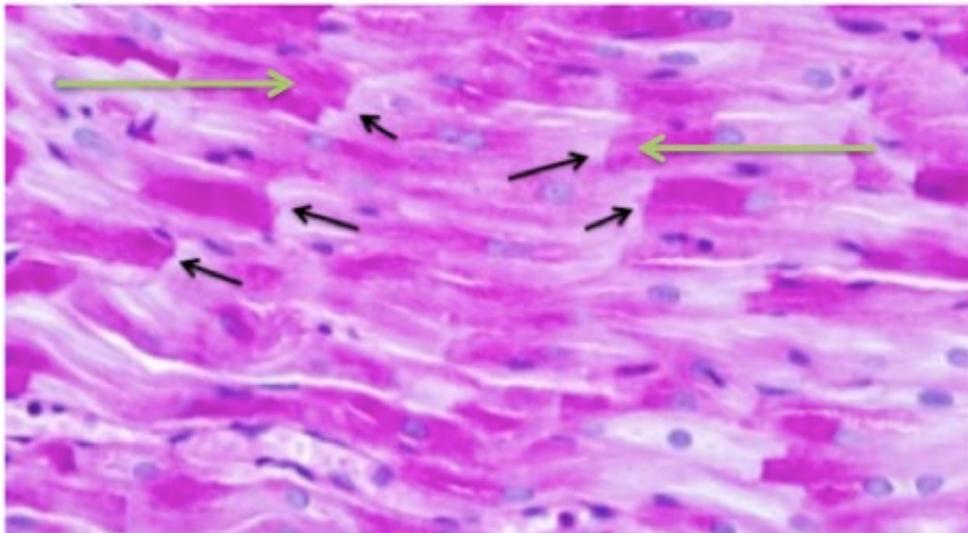


Figure Unpublished image showing glycogen molecules coalescing against intercalated discs during AF.

Tissue sample obtained from the dog Left Atrial Appendage during atrial fibrillation. **Black Arrows:** Pointing at myocytes intercalated discs. Notice the stained glycogen molecules delineating the discs and theorized to be as result of cellular contraction internal forces. This phenomenon is introduced as additional factor affecting intra atrial electrical conduction.

Orange Arrows: Indicating opposite direction of myocytes depolarization or contraction during AF.

Note: Image of tissue obtained, thus remaining unpublished in the medical literature; but presented at Medical Grand Rounds at the University of Oklahoma USA, (May 2014).

3.3. INTRACELLULAR GLYCOGEN AND CENTRIFUGAL FORCES THE MUIR'S EXPERIMENTS (1965)

In a paper published in 1965 non-contractile sheep Purkinje cells were subjected to centrifugal forces prior to fixation as shown in Exhibit 1 below. Only the centrifuged conducting cells show glycogen molecules unable to penetrate and coalescing at the gap junctions (Exhibit 4). In contrast, non-centrifuged control conducting cells show a homogeneous distribution of glycogen.

EXHIBIT 4

PMC full text: [J Anat. 1965 Jan; 99\(Pt 1\): 27-46.](#)
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Figs. 1-2

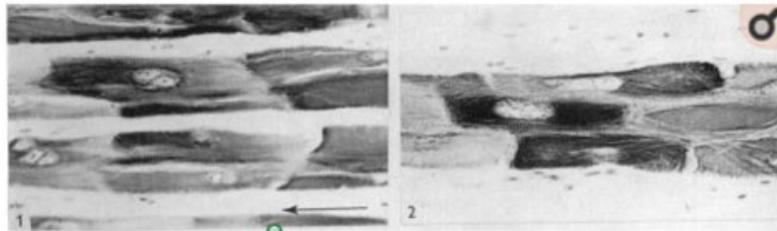


Figure 1: The Purkinje Fibers were subjected to Centrifugal force in the direction of the arrow prior to fixation.

Figure 2: Fibers in this figure are from control specimen.

Heart Sheep: In vitro demonstration of gap junction selectivity towards the glycogen molecules. Figure 1. Purkinje Fibers after centrifugation. Notice the presence of the stained glycogen concentrating against the gap intercellular intercalated discs gap junction. Purkinje cell are reported to have a higher density of pores that the atrial myocytes. Selectivity towards molecular size is clearly demonstrated. (Arrow denotes centrifugal force)

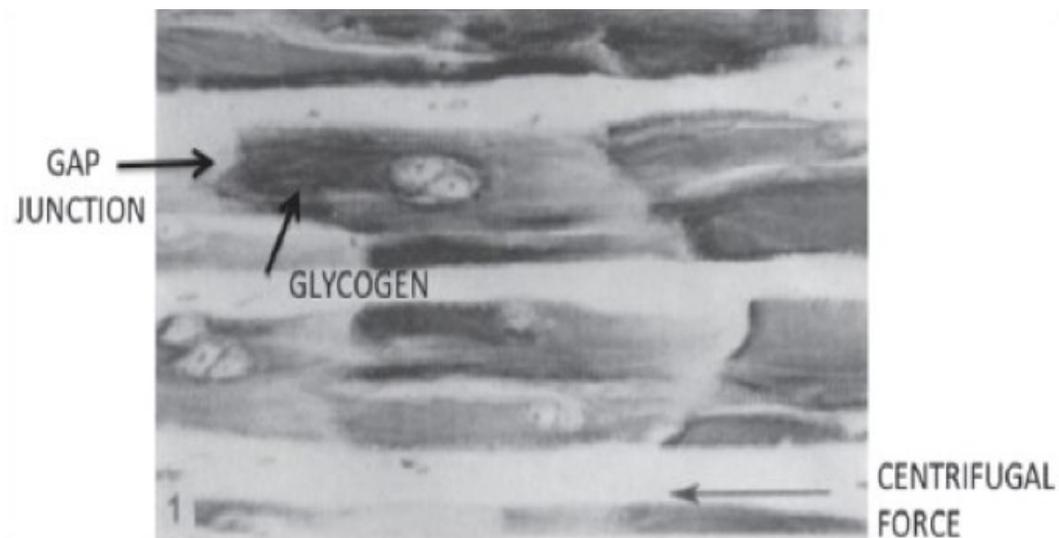


Figure 1: Post Centrifugal Force. Amplified with labels.

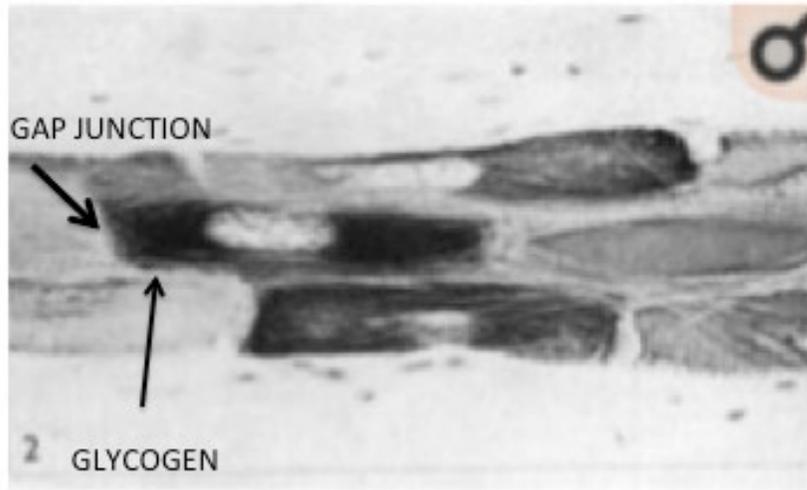


Figure 2: Control experiment. Amplified with labels.

All above Images printed with permission from publisher: Muir AR. Further observations on the cellular structure of cardiac muscle JAnat Lond 1965;99:27-46.

4. DISCUSSION

Atrial Myocytes structural changes in the progression of atrial fibrillation, and the potential role of glycogen and fibrosis as perpetuating factors have been proposed [5]. The data presented in this manuscript supports atrial myocytes contractility as a primary factor in causing glycogen blockage of gap junctions and side by side connections. As concluded by Zangh et al [5].

“The differential in glycogen concentration, in conjunction with other factors, neural and electrophysiological, provide a basis for the greater propensity of the left atrium for paroxysmal AF, at baseline and 48 hours of pacing induced AF. The marked increase in collagen at 8 weeks of pacing provides a substrate for sustained AF. Evidence is presented linking glycogen accumulation and fibrosis as factors in the persistent forms of AF”.

Contractile cells such as atrial or Ventricular myocytes; and constitute 99% of the myocardial tissue, whereas the remainder 1% conducting cells form the heart electrical conducting system, such as Purkinje cells. Relevant to this commentary is that Purkinje cells are much smaller “than the contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons” [7]. In other words, cardiac conducting cells are non-contractile; instead they serve as a conduit to propagate electrical impulses and initiating contractions of the abundant contractile cells.

In this manuscript we are introducing a new insight in the genesis of AF, this being the contractile myocytes as causing intracellular glycogen molecules to coalesce against the intercalated discs and side by side cellular connections. The mechanical intracellular atrial contractility forces exerted on the glycogen molecules is supported by the analogy of centrifugation in the Muir’s experiments. How to counteract the consequences of this phenomenon are in need of further research.

5. CONCLUSIONS

In contractile cardiac cells, such as atrial myocytes, depolarization mechanical transduction is identified as factor for intracellular glycogen molecules blocking intercellular communication.

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CONFLICT OF INTEREST

The author have declared that no competing interests exist.

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