

SECTION 4 : MUSCLE CONTRACTION AND MOTION IN ANIMALS

Roop Mallik

## LECTURE 10 : HEARTBEATS

BSBE – IIT Bombay

Resources :-

Guyton and Hall, Textbook of Medical Physiology

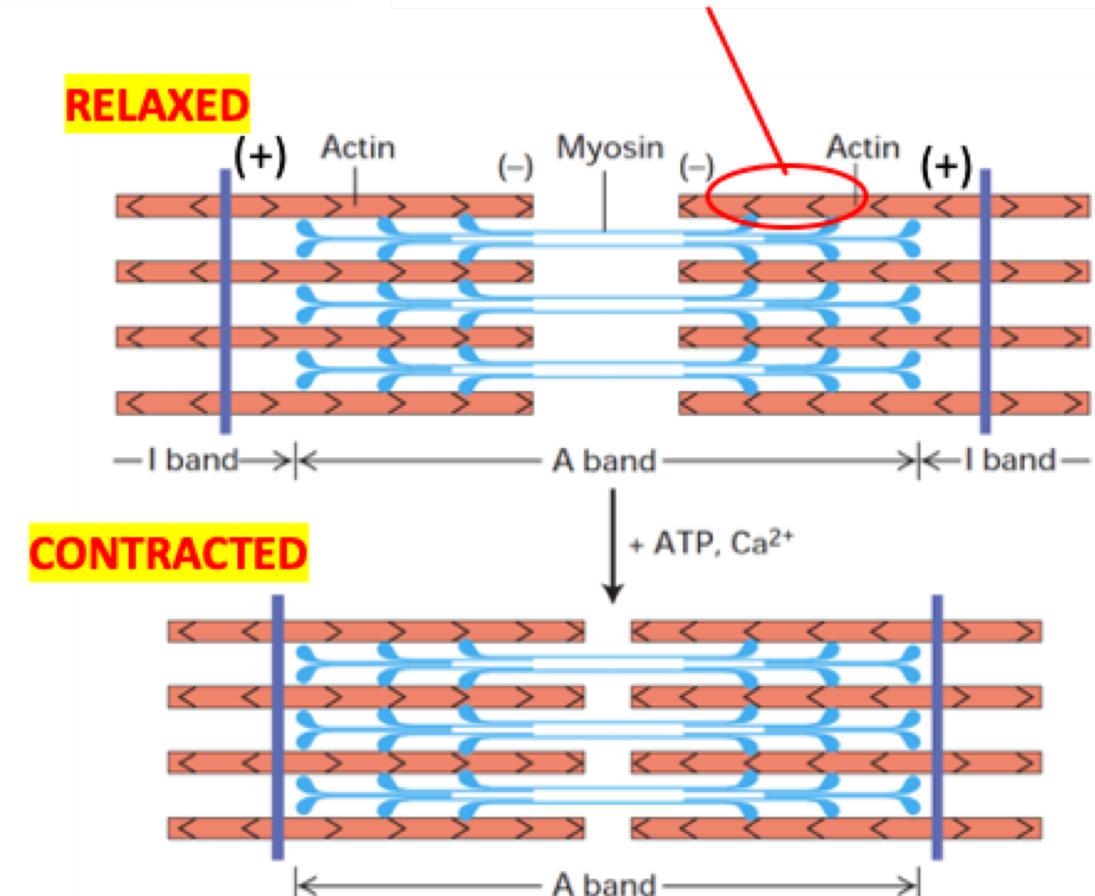
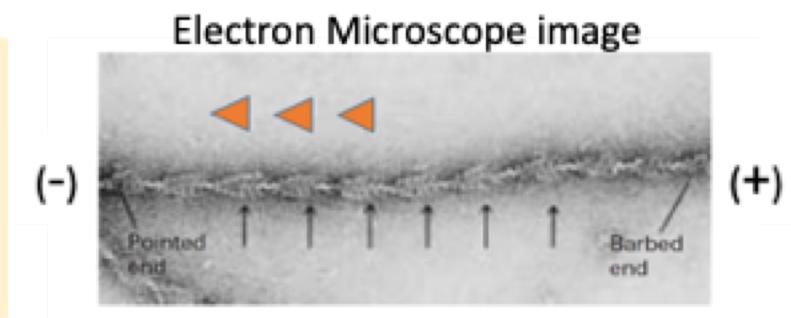
Lodish, Molecular Cell Biology

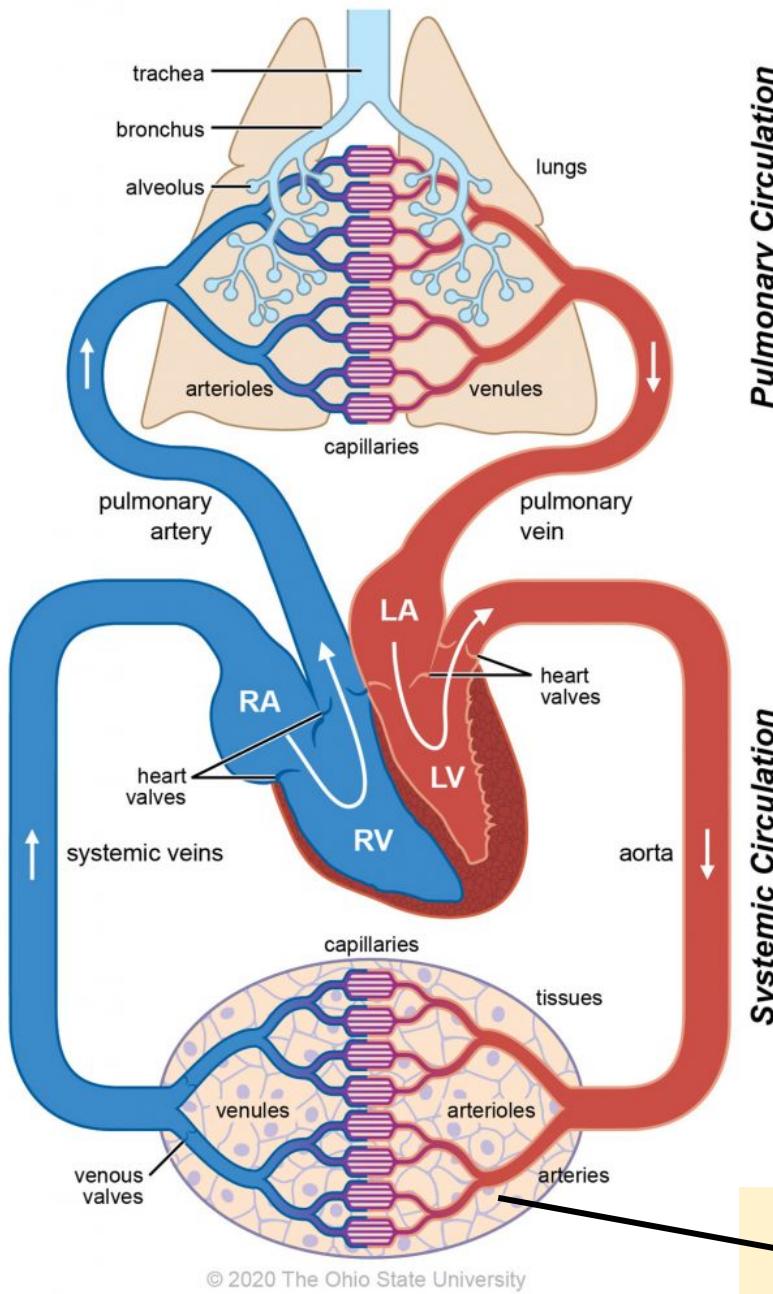
[iBiology Talks by Jim Spudich](#)

# Recall - Muscle Contraction

- Muscle Cell is packed with repeating Sarcomeres (region between two Z-disks)
- Sarcomere contains two inter-digitating structures
  - Thick filaments, containing myosin
  - Thin filaments, containing F-actin
- F-actin within Sarcomere is **Bipolar**  
(Plus end towards Z disk on each side)
- Nerve Impulse at Motor Neuron increases  $\text{Ca}^{2+}$  in muscle cell
  - Certain proteins (Tropomyosin) that otherwise block Actin-binding site of Myosin now release those sites
  - Myosin can then bind Actin and hydrolyses ATP to generate Force and move
- Myosin in each half of a Sarcomere moves towards the +end of Actin (the Z-disk)
  - Actin filaments come closer in the middle
  - Therefore the Z disks come closer
  - Causes Contraction of Sarcomere (upto 70% of its resting length) → Contraction of Muscle

Polarity of actin.  
"Arrows" are pointing to the –end (pointed end) of F-actin





# The Heart as a Pump

Oxygenated blood from Lungs → Heart

→ Pressurize → Send to Body

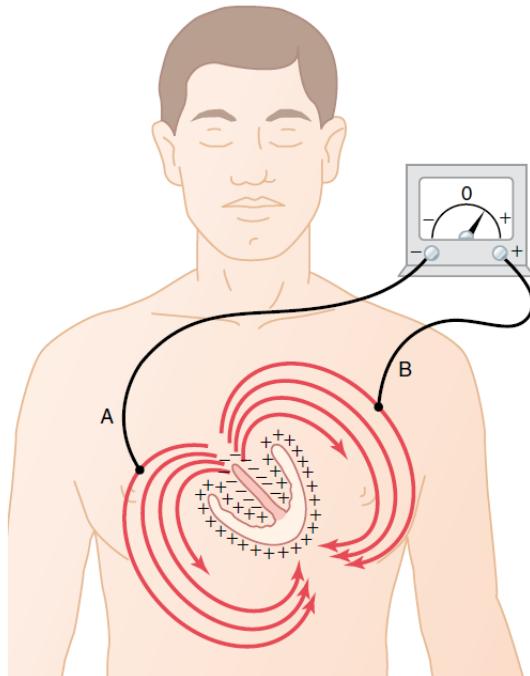
Deoxygenated blood from body → Heart

→ Pressurize → Send to Lungs

1. The heart is not one, but TWO Pumps
2. **RIGHT** pump and **LEFT** pump
3. No blood flow between Left and Right sides inside heart
4. Each pump has an Atrium and a Ventricle (RV,RA,LV,LA)
5. Blood passes through the heart twice in each circuit
6. Pressure in each pump can be controlled independently
7. Arteries Carry **blood from** the heart (High pressure)
8. Veins Carry **blood to** the heart (Less pressure)

Rest of the body  
(where blood supplies oxygen)

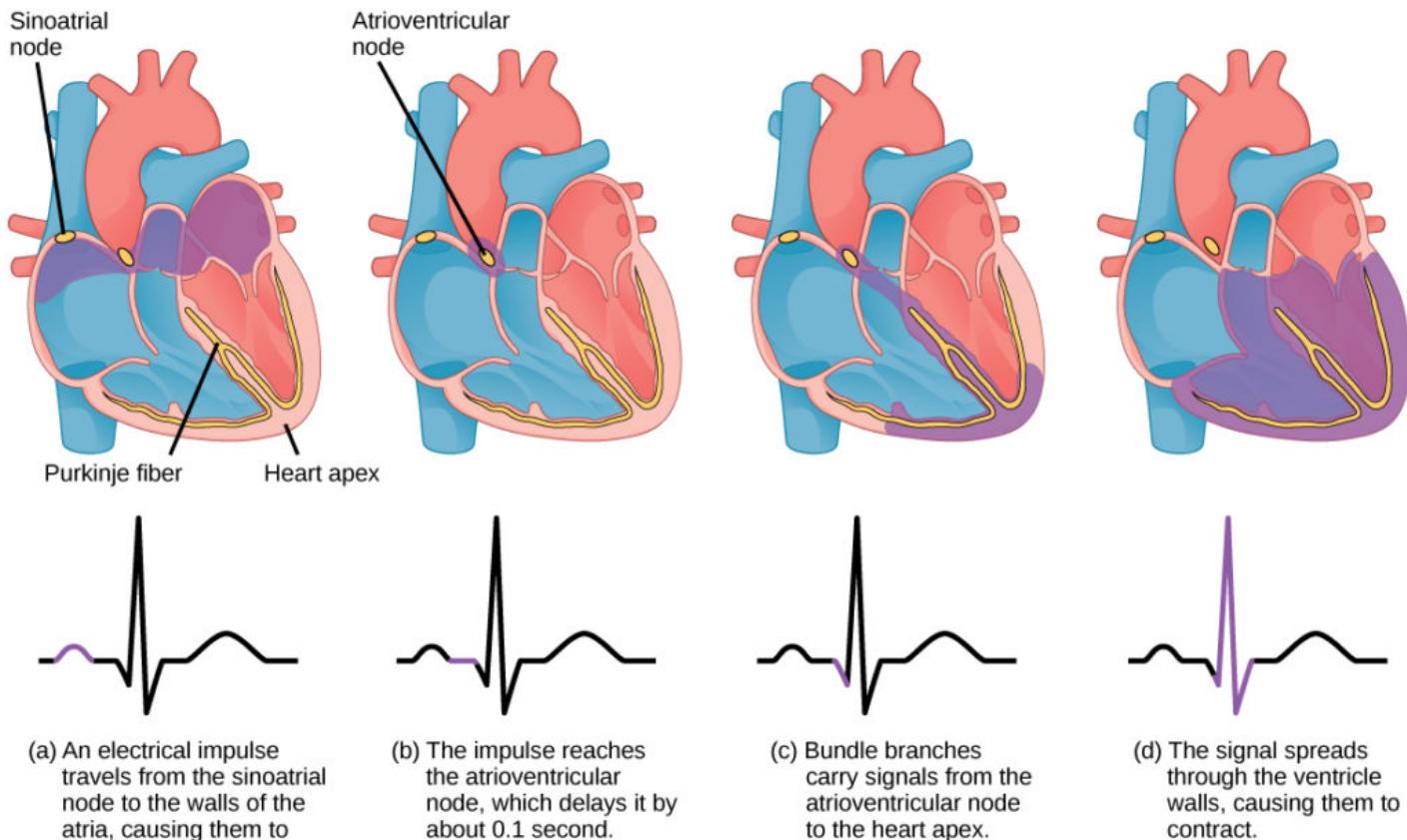
## The Electrocardiogram (ECG)



Recording of Electrical Currents in the heart that spread to the Skin surface

Reveals the Cardiac Cycle:- a pattern of Neuronal activation that in turn causes the muscles in different regions of the heart to Contract and Relax

## The Cardiac Cycle – 72 beats/min = 100,000 times/day. 0.83 sec/beat



Signal is initiated at the Sinoatrial Node – the pacemaker of the heart

Signal then (a) spreads to the atria causing them to contract. Signal is delayed (b) at the atrioventricular node before it is passed on to the (c) heart apex. The delay allows the atria to relax before the (d) ventricles contract.

In summary, an Electro-mechanical Cycle causes Rhythmic beating

<https://www.visiblebody.com/blog/decoding-the-heart-what-is-an-ecg>

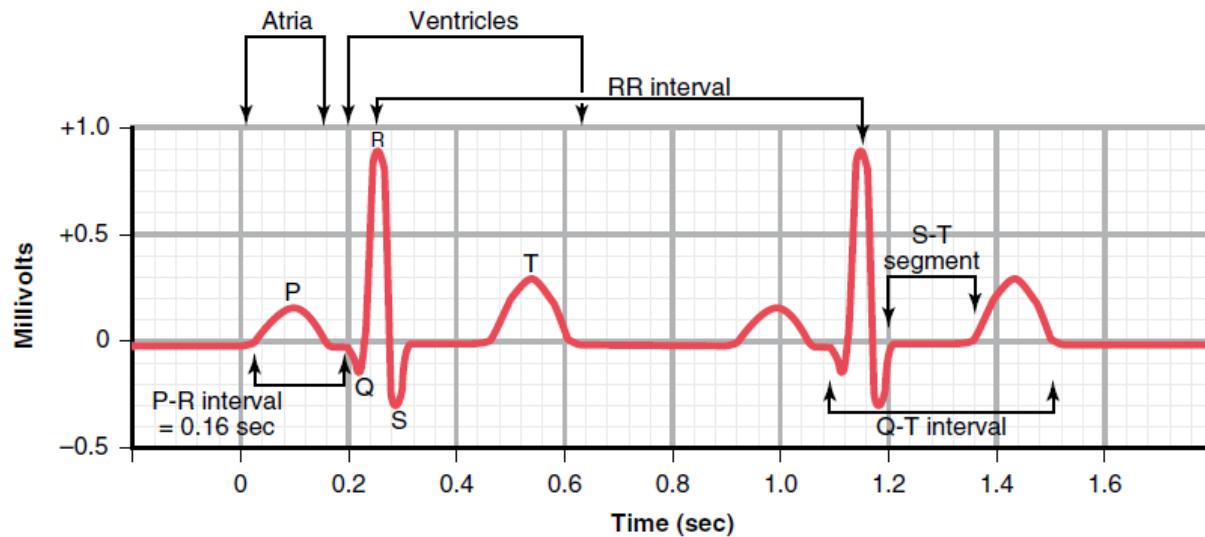
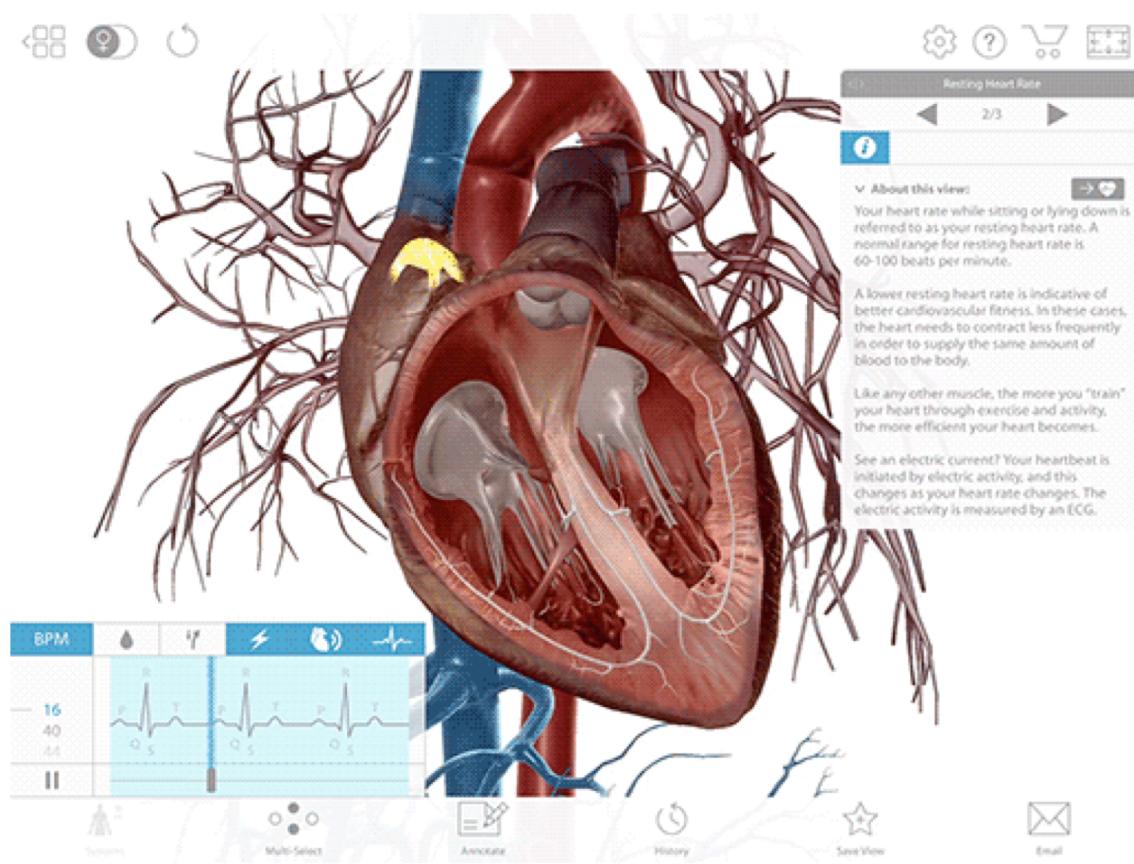
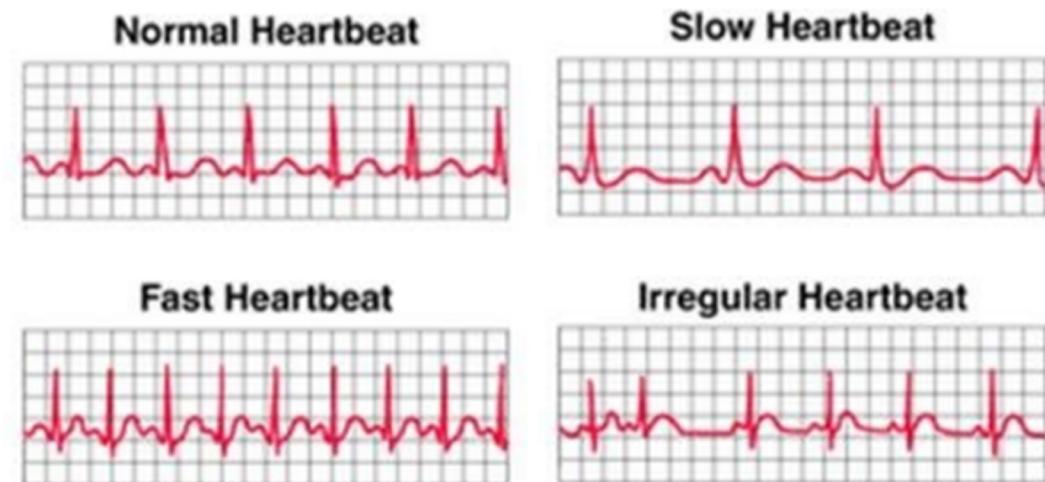
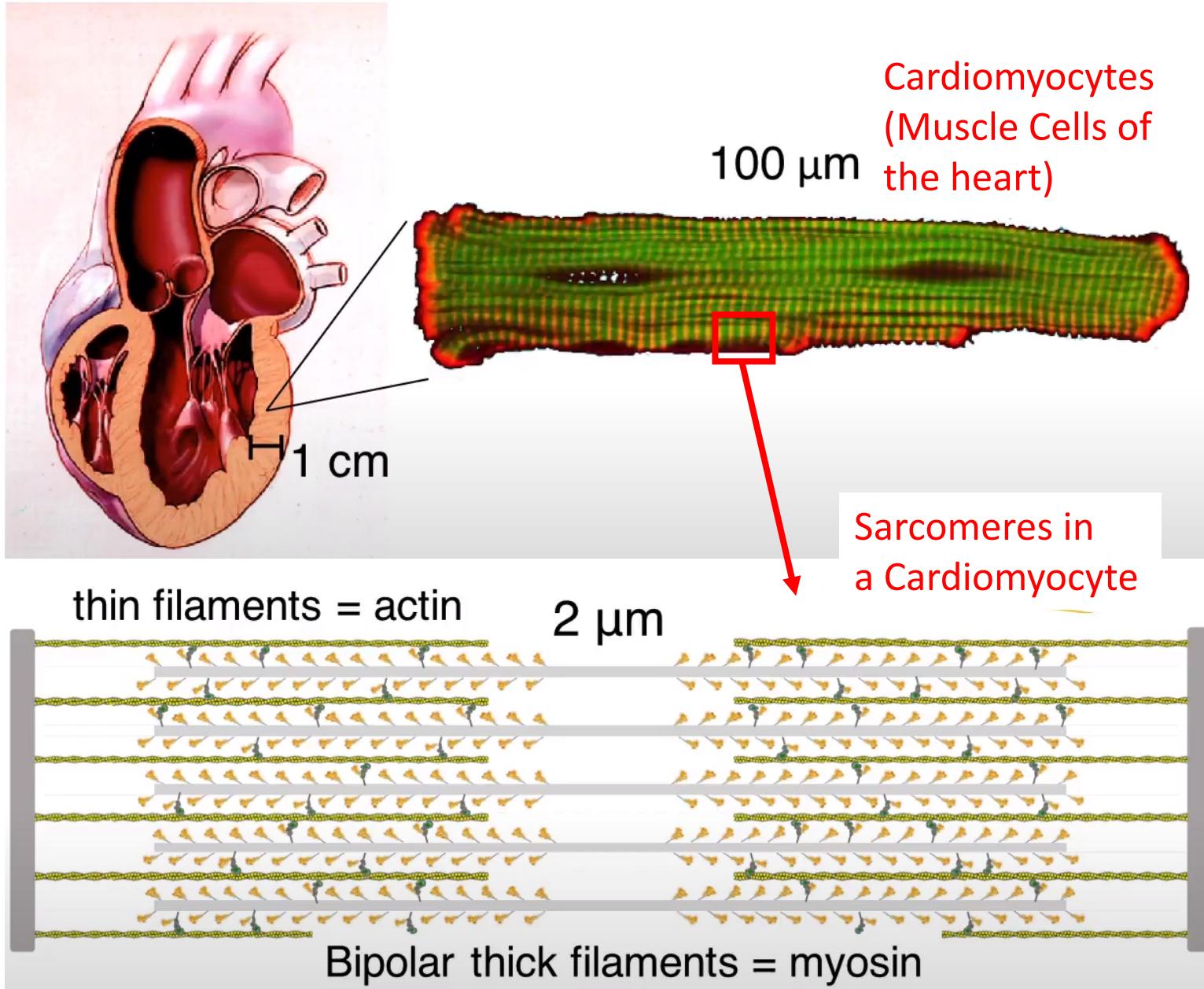


Figure 11-1 Normal electrocardiogram.

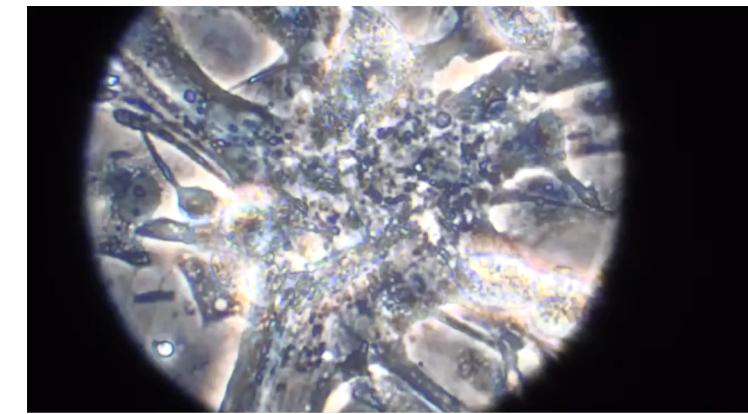


# CARDIOMYOPATHIES



Heart can beat by itself.  
Continues beating for a while  
even if nerves to the heart are cut

Cardiomyocytes continue to beat  
on a petridish !!



Much can be learnt about  
heart disorders by  
understanding Motion  
(Contraction) at the Cellular  
Level

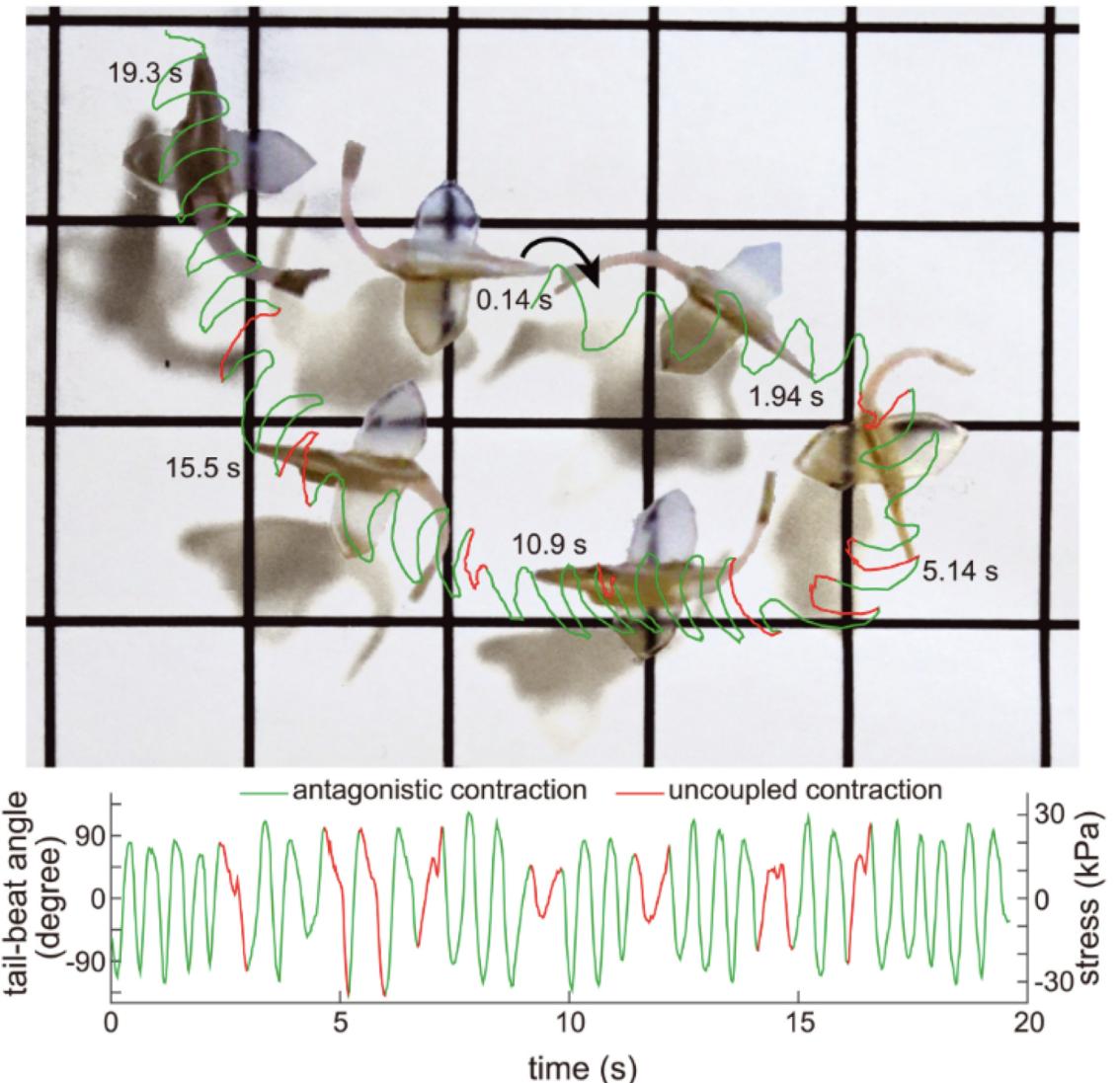
# DIGRESSION ...

## An autonomously swimming biohybrid fish designed with human cardiac biophysics

[LINK TO PAPER](#)

“We recreated reciprocal contraction and relaxation in a muscular bilayer construct where each contraction occurs automatically as a response to the stretching of an antagonistic muscle pair.....

The biohybrid fish equipped with intrinsic control strategies demonstrated self-sustained body-caudal fin swimming, highlighting the role of feedback mechanisms in muscular pumps such as the heart and muscles.”



Thus far >400 mutations in sarcomeric proteins have been associated with cardiomyopathy.  
(e.g. Myosin heavy chain, Cardiac actin, Tropomyosin and Troponin)

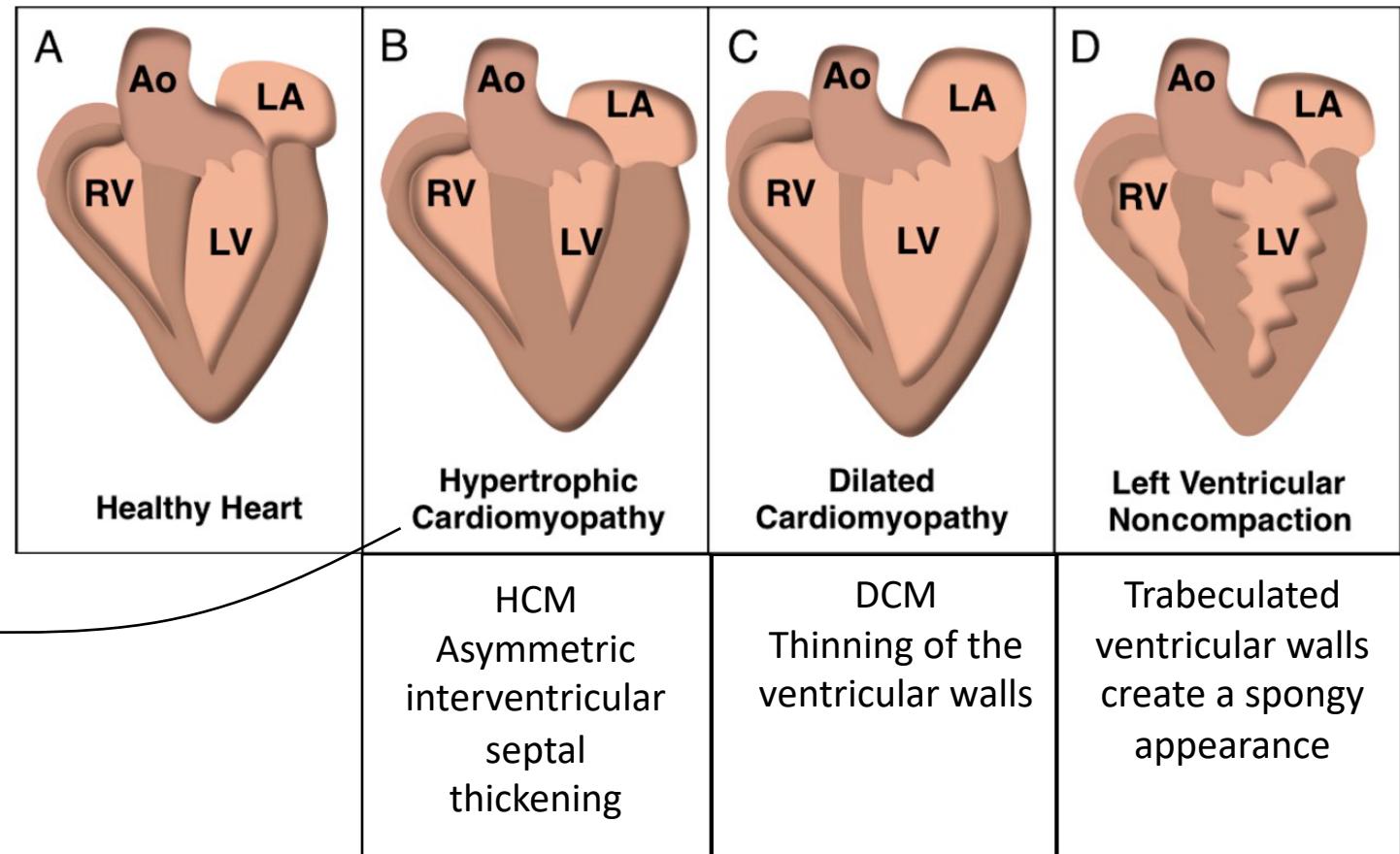
[Cellular mechanisms of cardiomyopathy – JCB 2011](#)

Acquired cardiomyopathies :- Stress, diabetes, smoking, alcohol etc.  
(Will not discuss further)

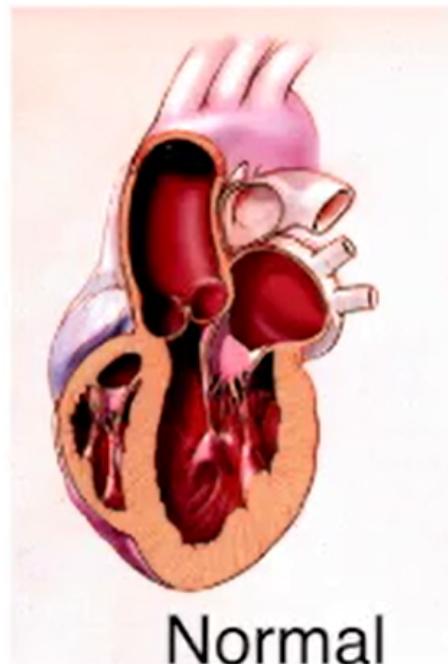
## Inherited Cardiomyopathies (Genetic)

HCM :-

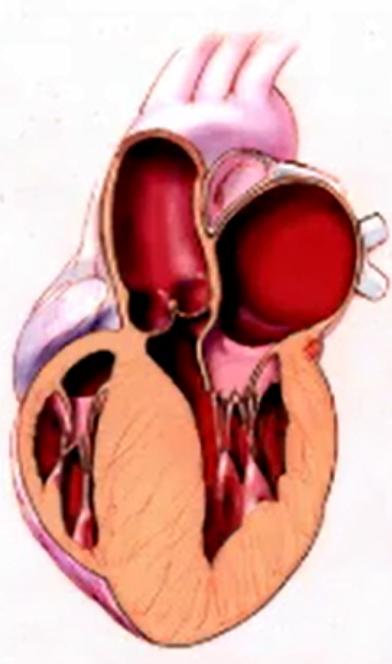
- Inherited in an autosomal-dominant pattern. 1 in 500 individuals.
- Most mutations are in the Myosin Motor domain



# Hypertrophic cardiomyopathy (HCM) affects 1 out of 500 people



Normal



HCM

the most common form of monogenic inherited heart disease

Results in a **hyper-contractile heart**, hypertrophy, fibrosis and sudden death

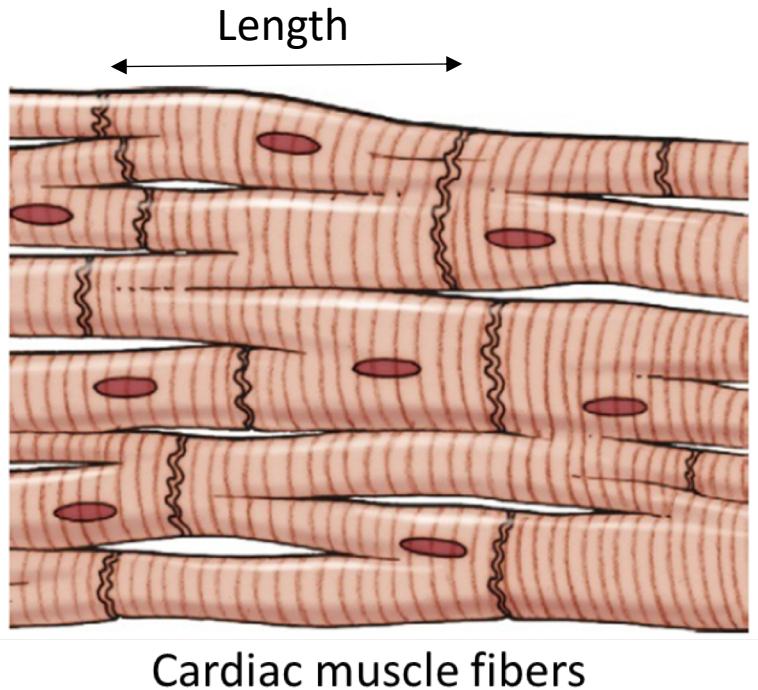
Most common cause of sudden cardiac death in individuals < 35 years old

## HCM – Hypertrophic Cardiomyopathy

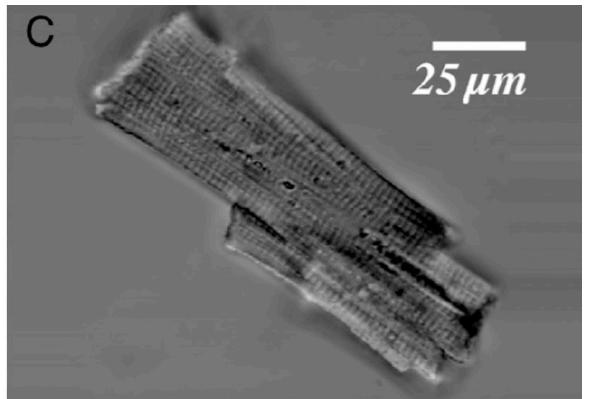
Ventricular cardiomyocytes increase in size by the addition of Sarcomeres. This is actually a Compensatory Mechanism to produce more force.

This increases the thickness of the heart walls, but reduces interior dimensions of the ventricular chambers

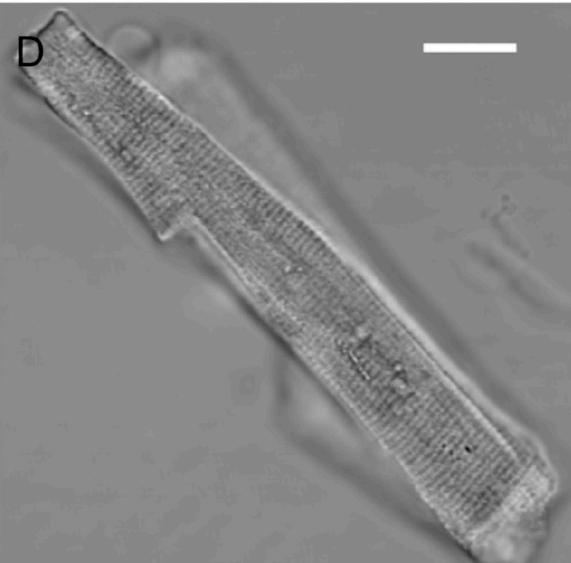
After a while, it disturbs the aspect ratio (Length to Width ratio) of Cardiomyocytes and affects force production



Cardiac muscle fibers



Healthy Cardiomyocyte



HCM Cardiomyocyte  
→ Increased Length  
and decreased width

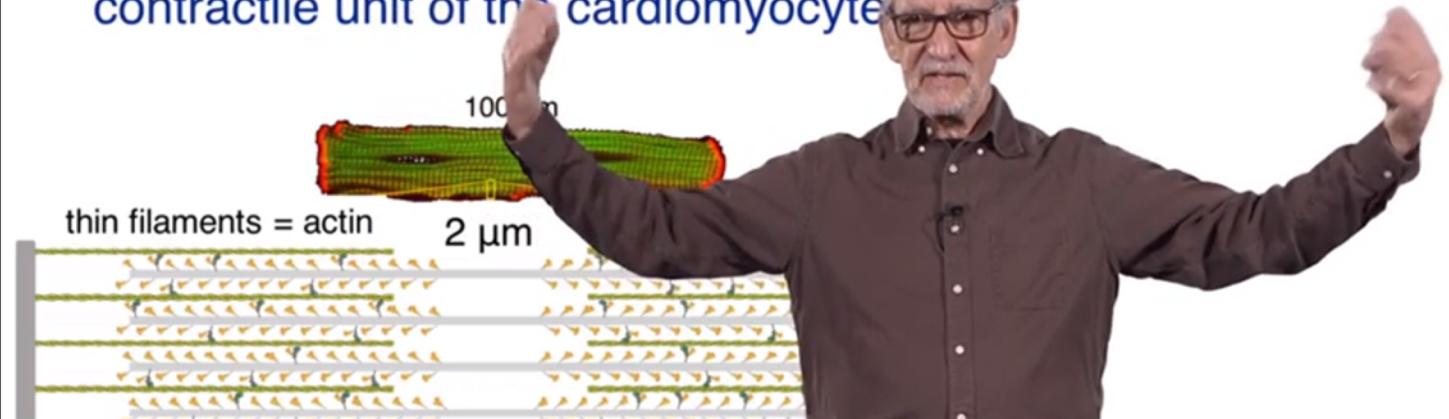
# HCM – Hypertrophic Cardiomyopathy

[iBiology talk by Jim Spudich](#)

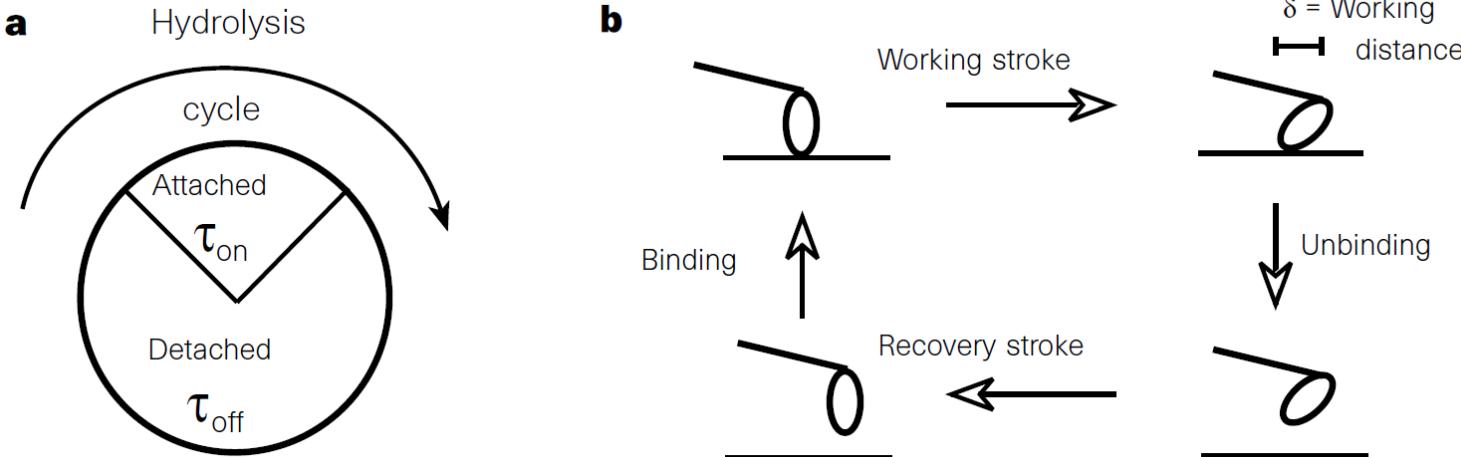
Recall Molecular Property of Motors

$$\text{Duty Ratio} = \frac{\tau_{\text{on}}}{\tau_{\text{on}} + \tau_{\text{off}}} = \frac{\tau_{\text{on}}}{\tau_{\text{total}}}$$

The cardiac sarcomere is the contractile unit of the cardiomyocyte



Jim Spudich demonstrating the action of Myosin in a Sarcomere



[Howard, Nature 1997](#)

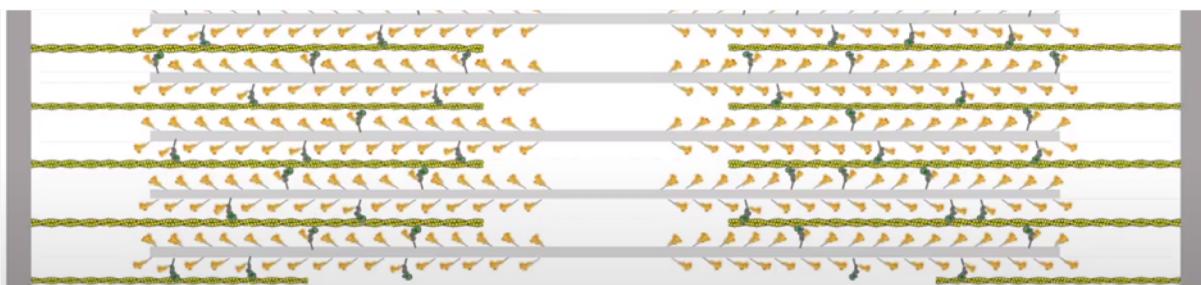
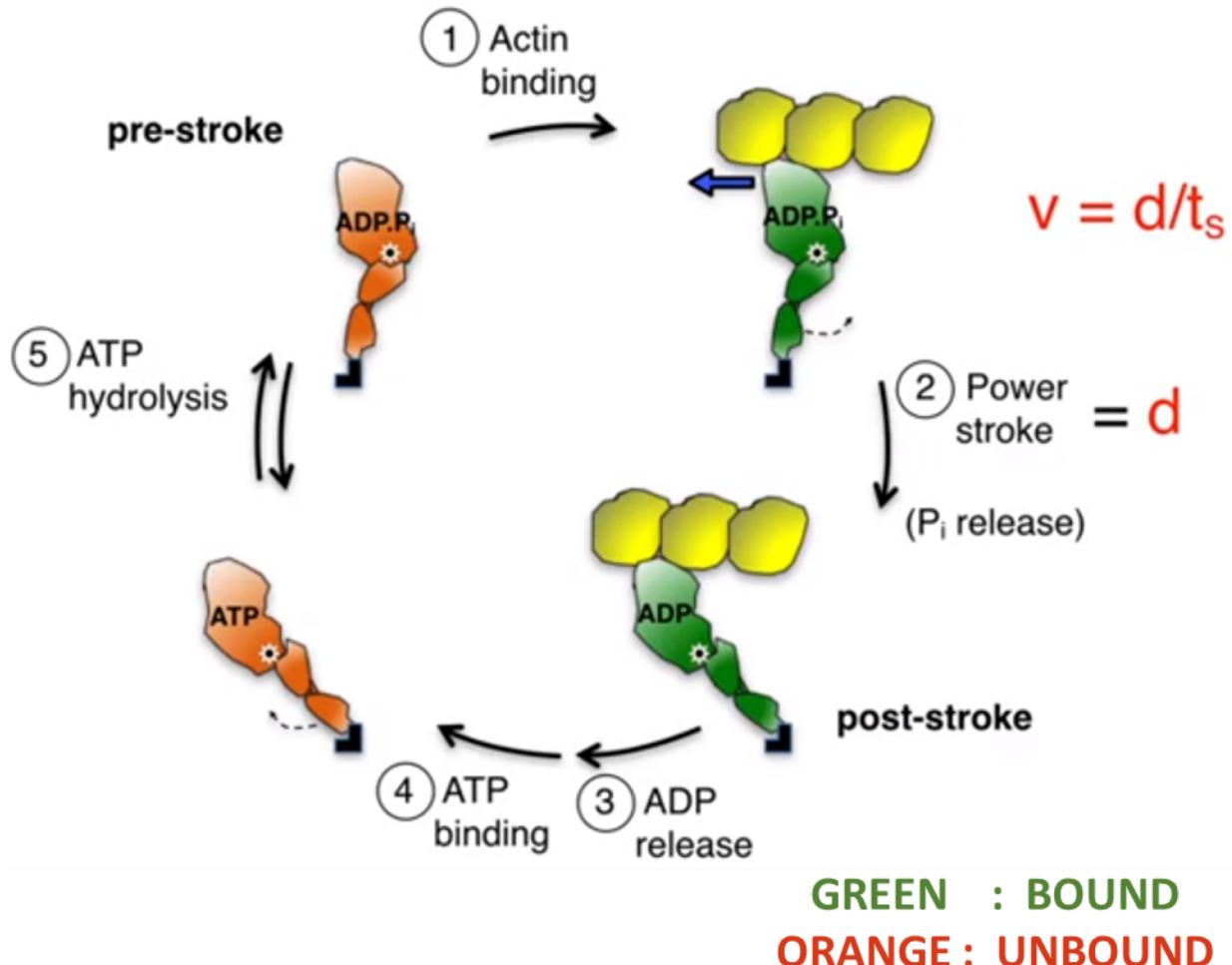
Cardiac Myosin Duty ratio = 20%

So, ~20% of Myosin heads in a Sarcomere are bound at a time. 80% are unbound

Cardiac duty ratio =  $t_s/t_c = \sim 0.2$

Can some Cardiomyopathies be caused by mutations in Myosin that change its duty ratio?

## Velocity of contraction is related to $d/t_s$

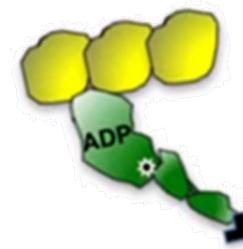


$$v = d/t_s$$

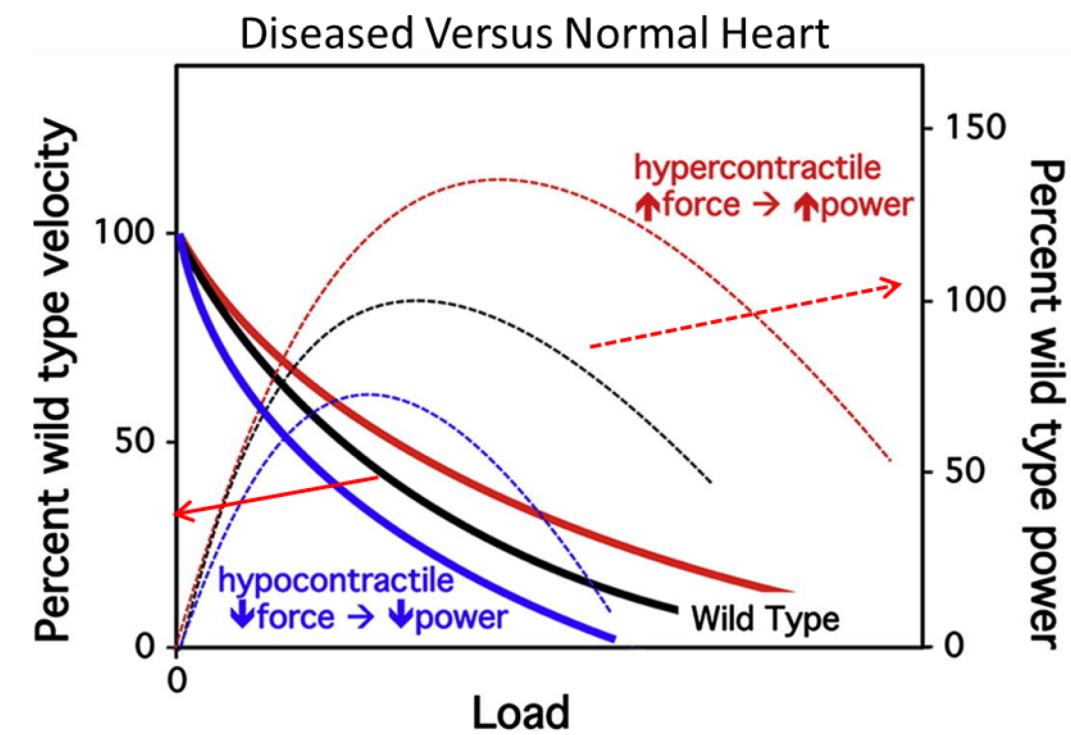
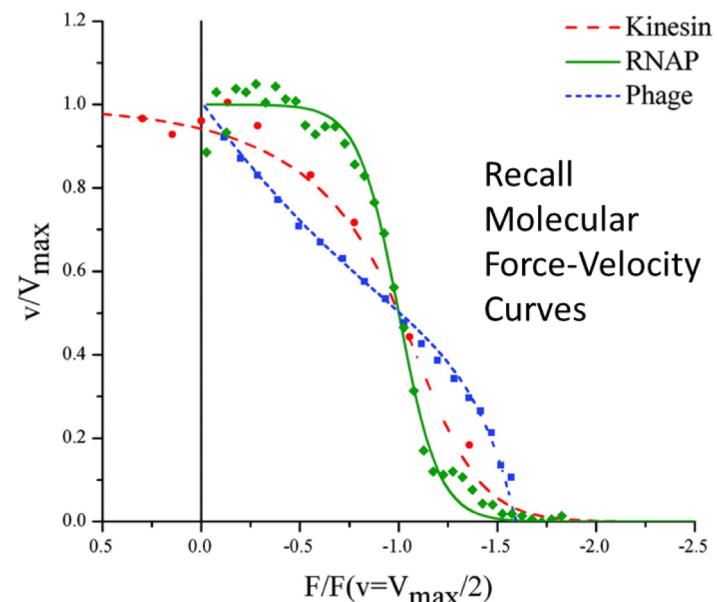
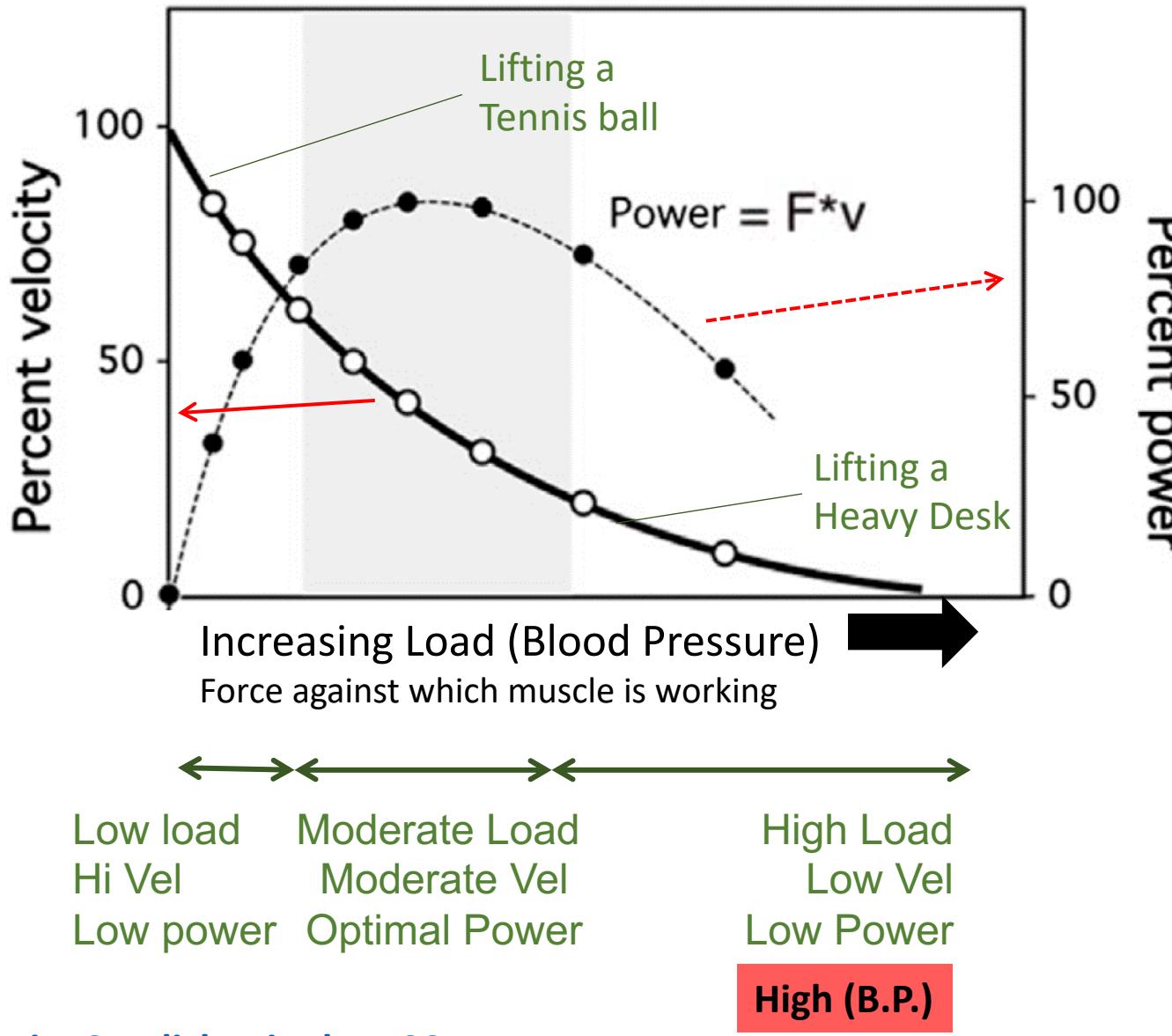
$d$  = Distance travelled in powerstroke ( $\sim 10$  nm)

$t_s$  = Time spent bound to actin  
or  $\tau_{on}$

i.e. in  
Green  
state

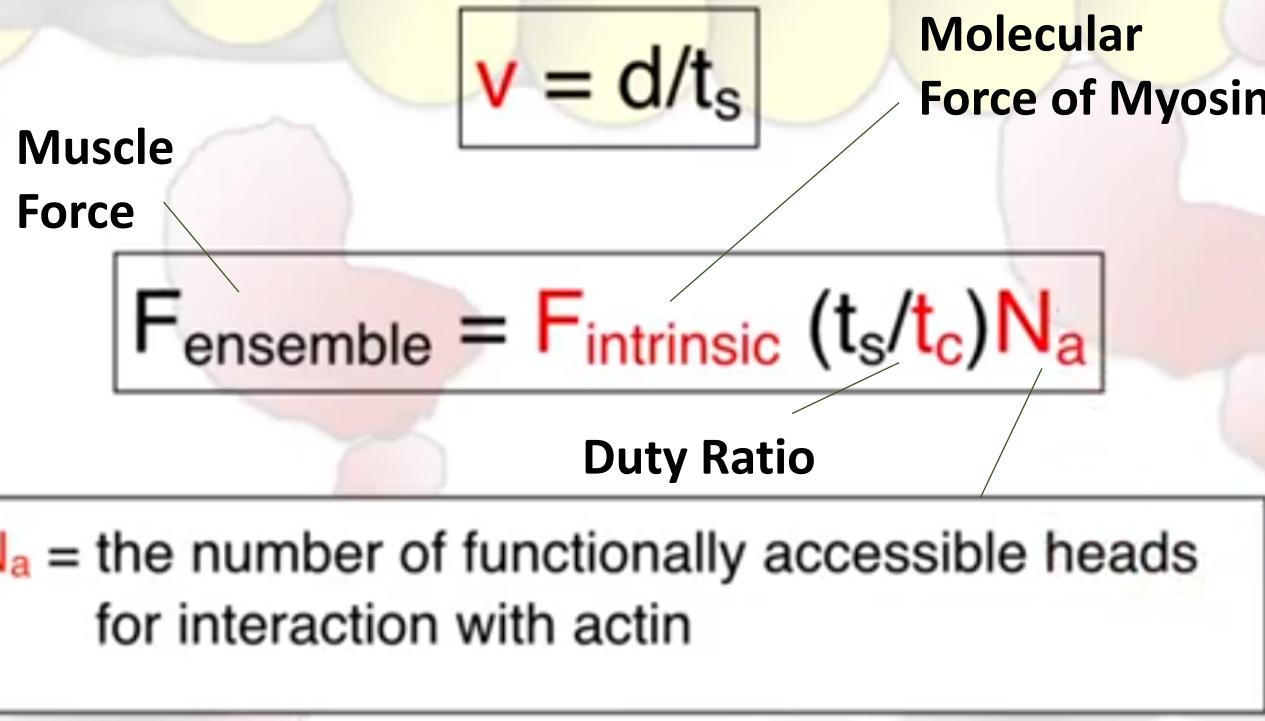


The force-velocity curve describes the power output by the heart

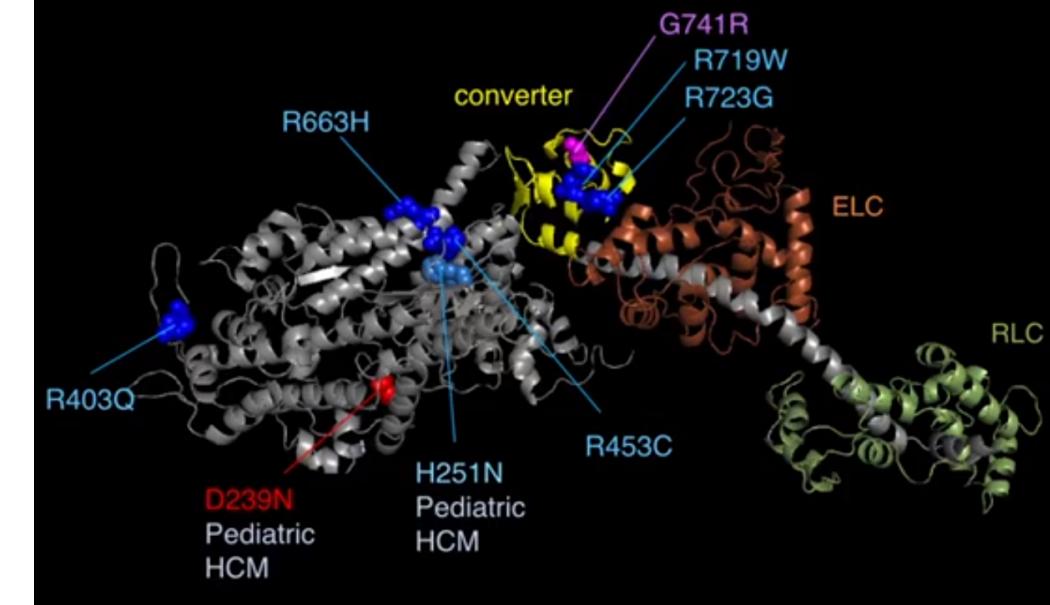


# Human $\beta$ -cardiac myosin

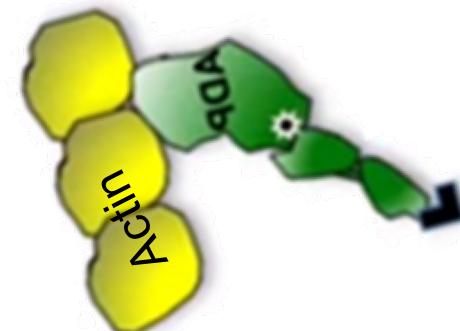
## 4 key parameters determine power output



Eight human  $\beta$ -cardiac myosin HCM mutants

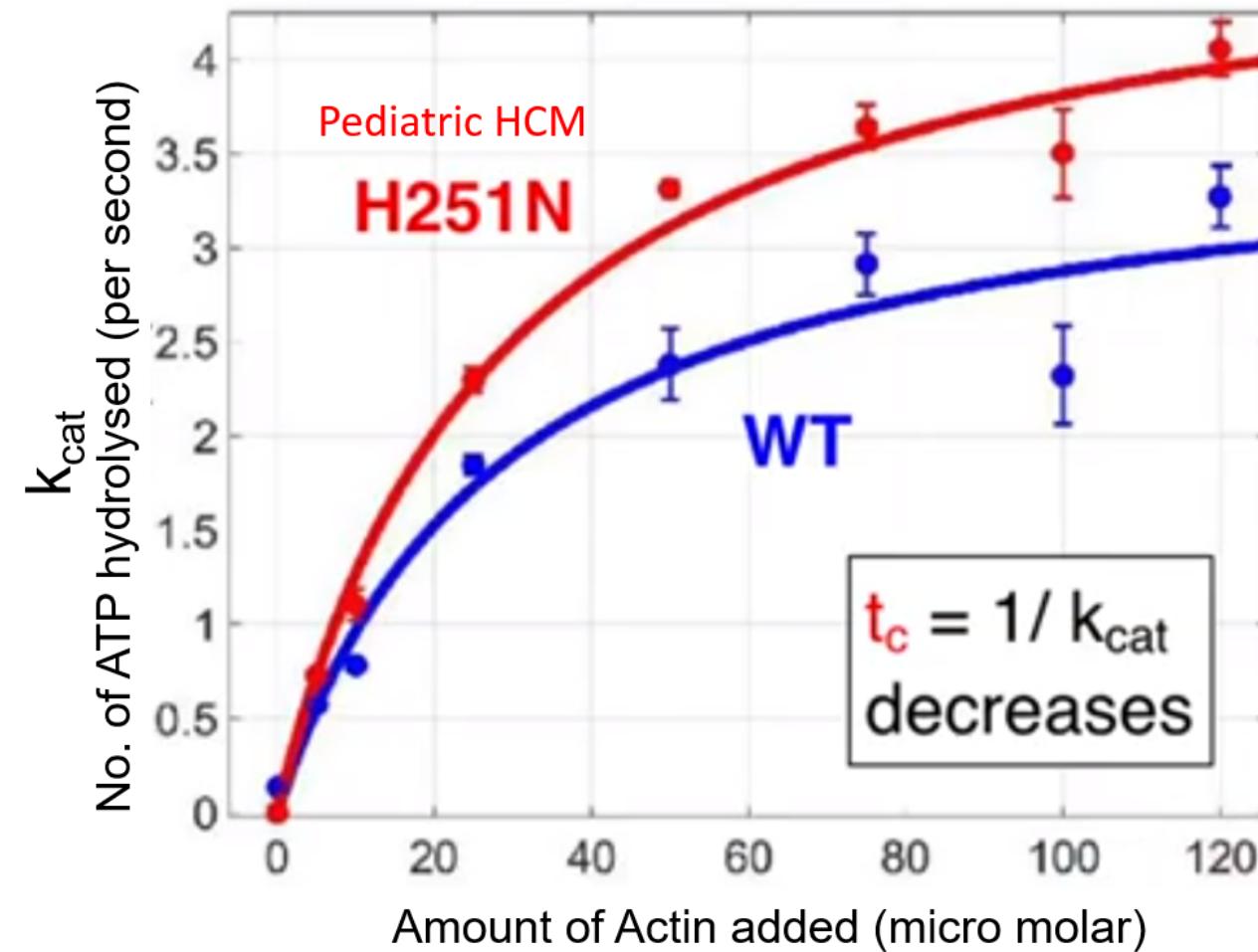


Orientation Matched to structure above



Pediatric HCM : Severe, children die young  
Others : Adult Onset (less severe)

## What does the Mutation do ?



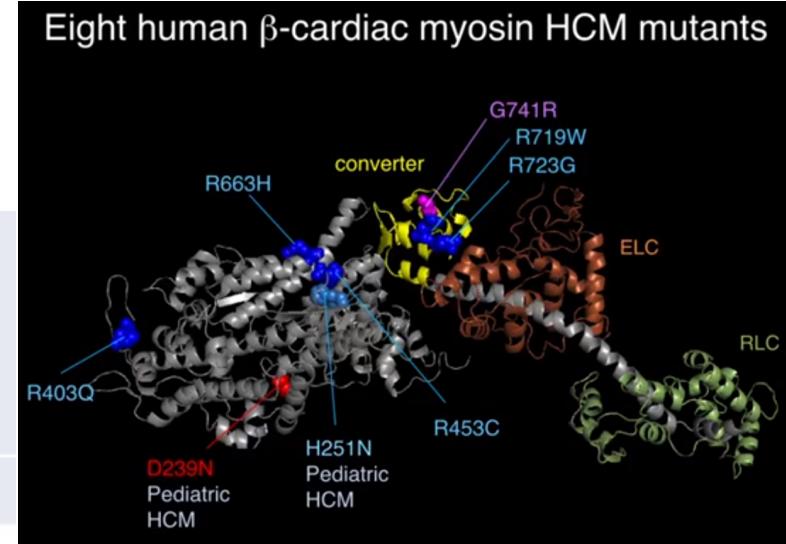
- H251N mutant hydrolyses ATP faster
  - Therefore Cycle-time ( $t_c$ ) is reduced
  - Therefore the Muscle Force is higher
- $F_{ensemble} = F_{intrinsic} (t_s/t_c) N_a$
- Such a heart is generating force for a larger fraction of time (hypercontractile) and can therefore “wear out”

Myosin + ATP + Actin → Incubate  
→ Will produce ADP and Phosphate  
→ Measure using colour reaction

# Changes in force, velocity and ATPase do not generally explain the clinical hyper-contractility phenotype in adult onset HCM

HCM mutation	Intrinsic force ( $F_{intrinsic}$ )	Velocity (v)	ATPase ( $k_{cat}$ )
<b>Fraction of wild type</b>			
R403Q	<b>0.8 ± 0.1</b>	<b>1.2 ± 0.1</b>	<b>1.3 ± 0.1</b>
R453C	<b>1.5 ± 0.1</b>	<b>0.8 ± 0.1</b>	<b>0.7 ± 0.1</b>
R663H	<b>1.0 ± 0.1</b>	<b>1.0 ± 0.1</b>	<b>1.0 ± 0.1</b>
R719W	<b>0.8 ± 0.1</b>	<b>1.2 ± 0.1</b>	<b>1.0 ± 0.1</b>
R723G	<b>0.8 ± 0.1</b>	<b>1.1 ± 0.1</b>	<b>1.0 ± 0.1</b>
G741R	<b>1.0 ± 0.1</b>	<b>1.0 ± 0.1</b>	<b>1.0 ± 0.1</b>

Pediatric HCM mutation	Intrinsic force ( $F_{intrinsic}$ )	Velocity (v)	ATPase ( $k_{cat}$ )
D239N	<b>1.4 ± 0.1</b>	<b>1.9 ± 0.1</b>	<b>1.5 ± 0.1</b>
H251N	<b>1.3 ± 0.1</b>	<b>1.4 ± 0.1</b>	<b>1.4 ± 0.1</b>



## ADULT ONSET MUTATIONS

No clear pattern  
But, patients are Hypercontractile

So, what is going on here ?

## PEDIATRIC MUTATIONS

Faster and Stronger Motors  
(i.e. In "Overdrive")  
Hypercontractile heart expected

What if  $N_a$  is higher for the adult Onset mutations ?  
That would have the same effect (Hypercontractility)

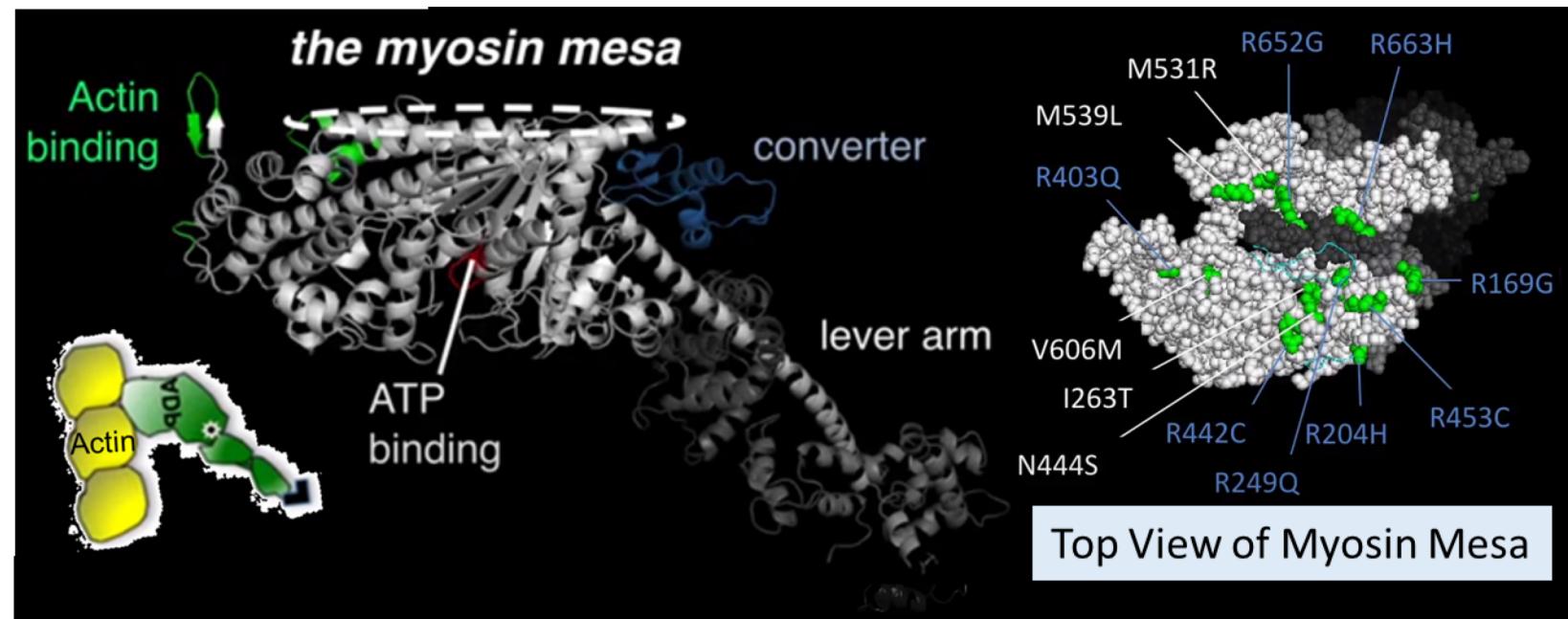
The Mesa hypothesis...



What he found next :-

AA residues in the Mesa highly conserved across species →  
“Mesa” has important functions  
(variations are not tolerated)

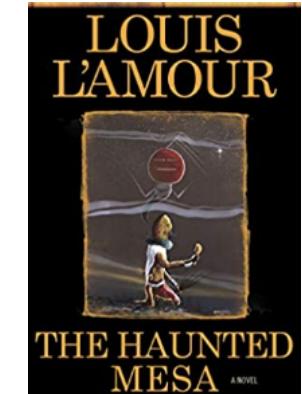
Many mutations relevant to  
hypercontractility are in the  
Mesa !!



$$F_{\text{ensemble}} = F_{\text{intrinsic}} (t_s/t_c) N_a$$

Wife asks him not to think  
about Myosin for 1 night

Gives him a book to read

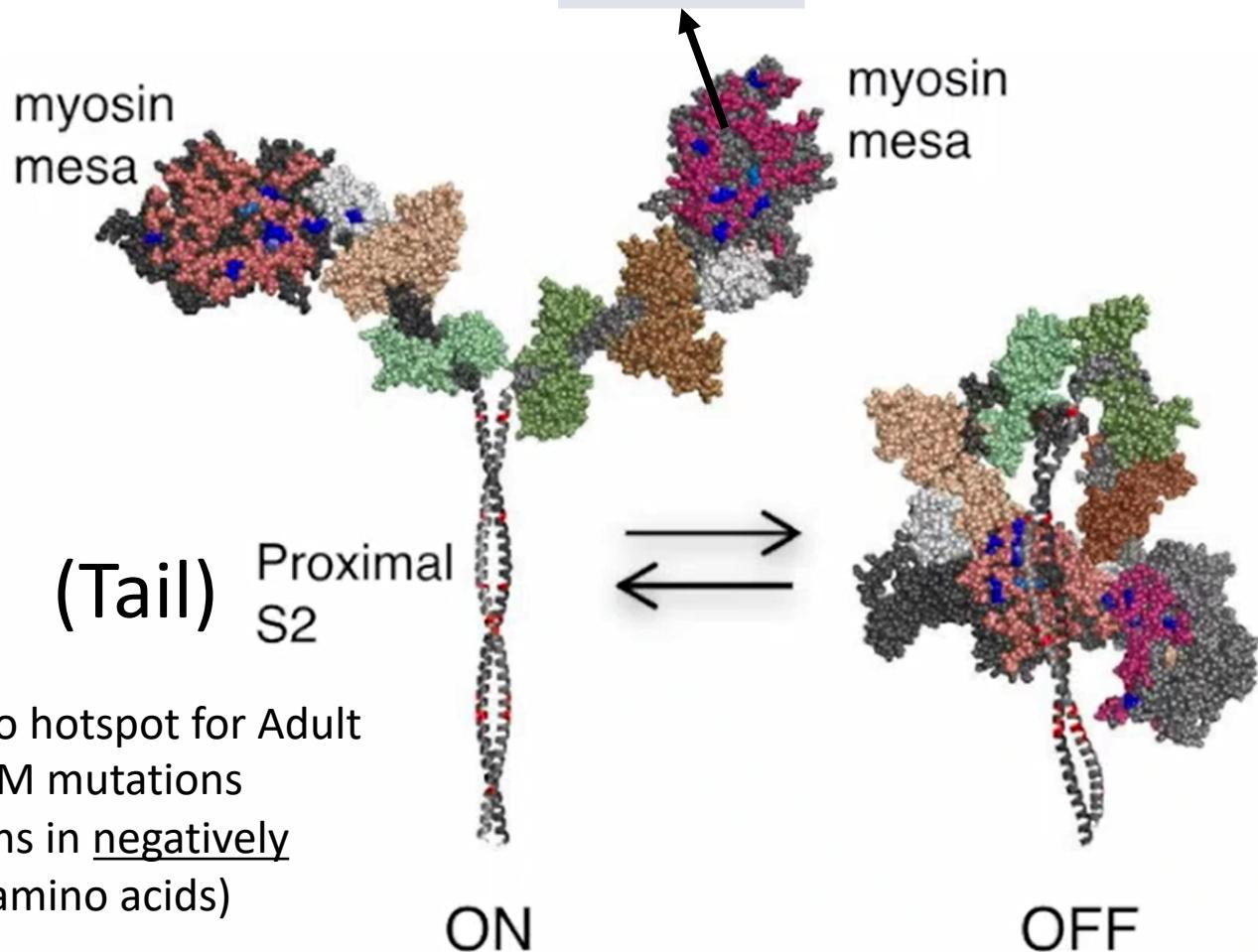


Jim then dreams that Myosin  
has a Mesa !!

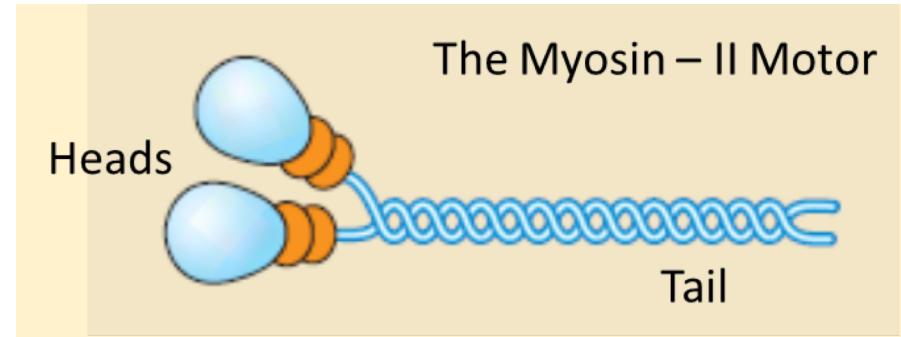
# ON/OFF states of Cardiac Myosin

R403Q  
R453C  
R663H  
R719W  
R723G  
G741R

**Mesa** :- Hotspot for Adult onset HCM mutations  
(Mutations in positively charged amino acid Arginine)



**Tail** :- Also hotspot for Adult onset HCM mutations  
(Mutations in negatively charged amino acids)



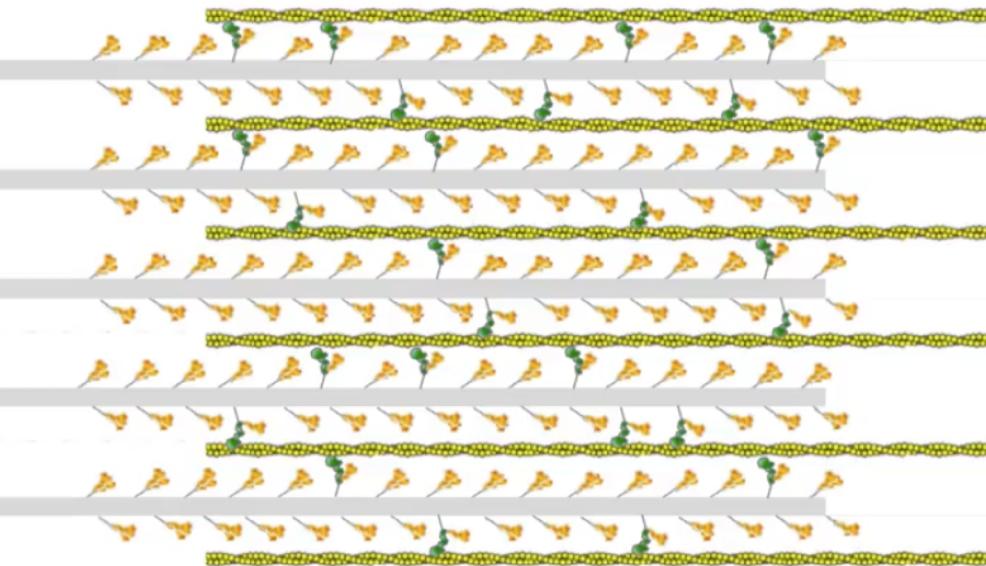
## Hypothesis

Normal heart:- Many Myosins kept in OFF state by Head-Tail interactions

HCM heart :- Mutations in Mesa or Tail cause the same effect → Tail cannot interact with Mesa → Myosin is biased towards ON state → Hypercontractile

## TAKE HOME MESSAGE

The half-sarcomere  
drawn to scale



$N_a$   
increases  
←  
Hyper-  
contractile  
heart

$$F_{\text{ensemble}} = F_{\text{intrinsic}} \left( t_s / t_c \right) N_a$$



This is what we used to think  
Earlier about Cardiac Muscle

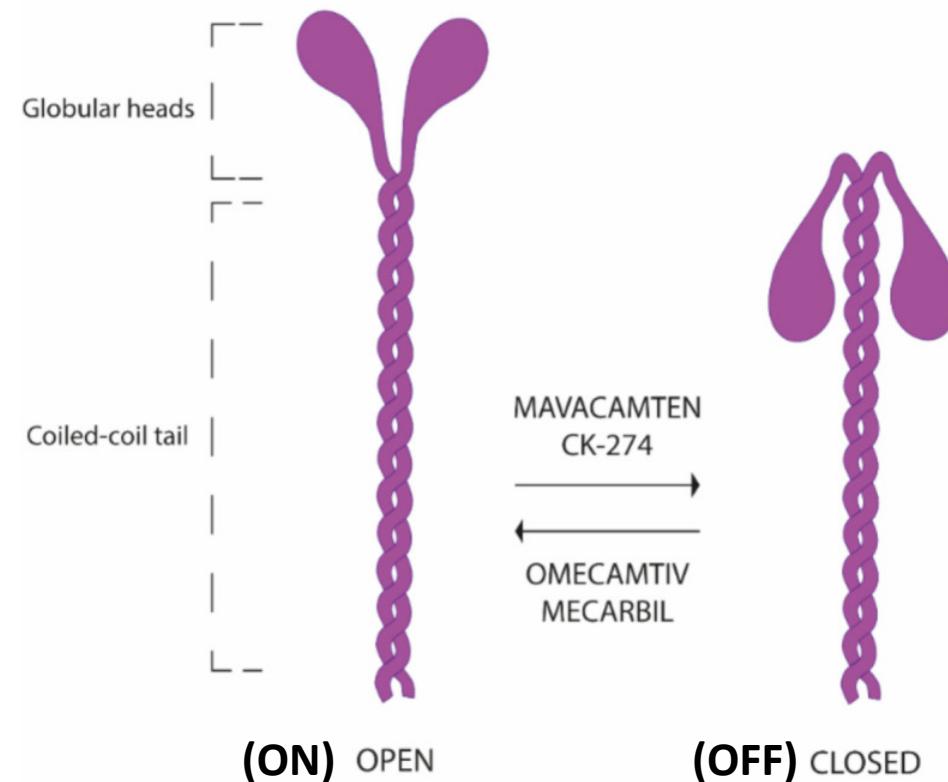
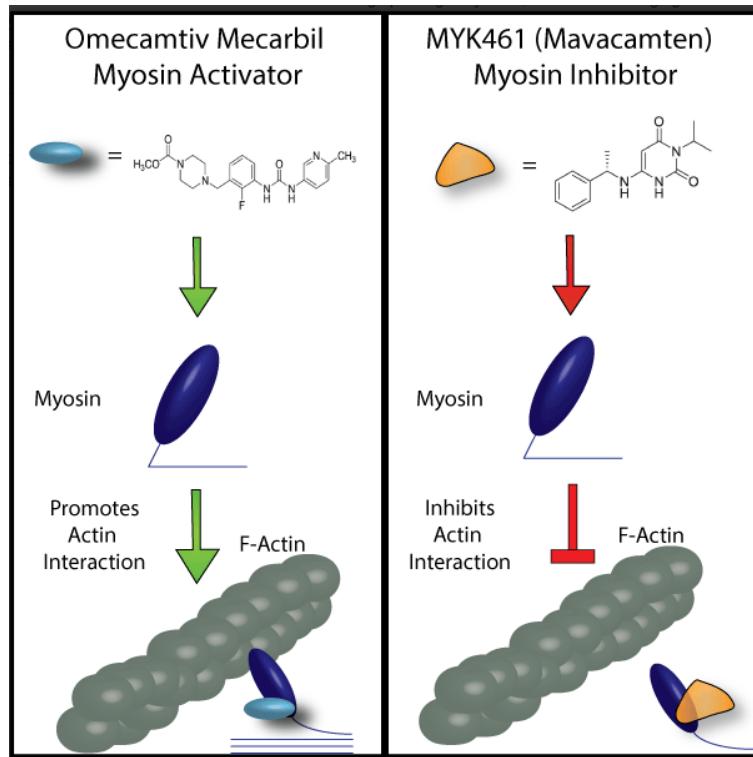
This is what Jim Spudich believes is  
actually true



Indicates that Myosin is OFF

[Home](#) > [A Tale of Two Myosin-Targeting Cardiac Drugs: A Rationale for Sarcomere Mechanistic Investigation](#)

## A Tale Of Two Myosin-Targeting Cardiac Drugs: A Rationale For Sarcomere Mechanistic Investigation



Mavacamten submitted for FDA approval (Mar 2021)

For more, read ...

[Emerging Medical Treatment for Hypertrophic Cardiomyopathy](#)