



Otago Spotlight Series
Cardiovascular Disease

Understanding Arrhythmias

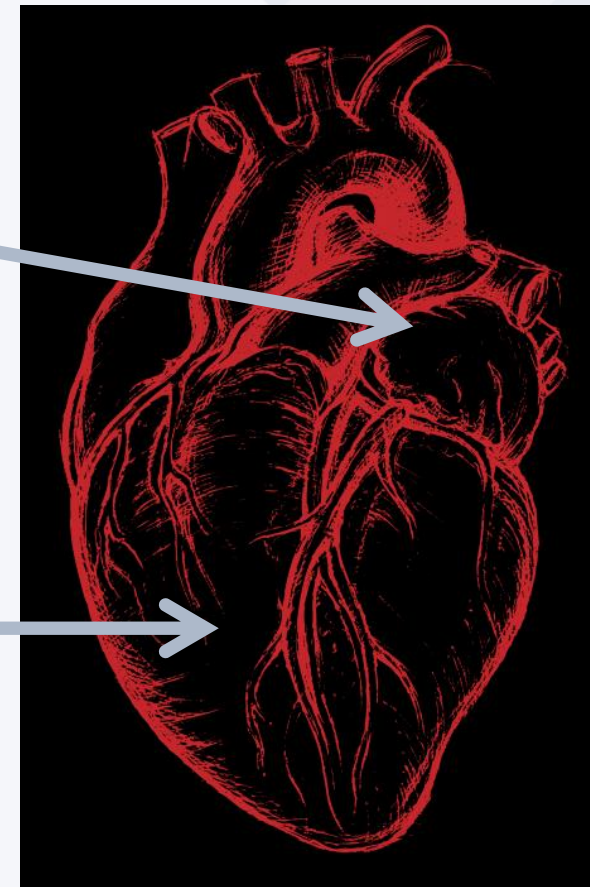
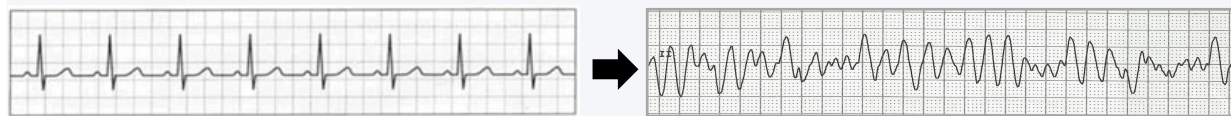
Dr Pete Jones

What are Arrhythmias?

- Altered rhythm of the heart
 - Atrial arrhythmias
 - Atrial flutter
 - Atrial fibrillation



- Ventricular arrhythmias
 - Ventricular tachycardia
 - Ventricular fibrillation



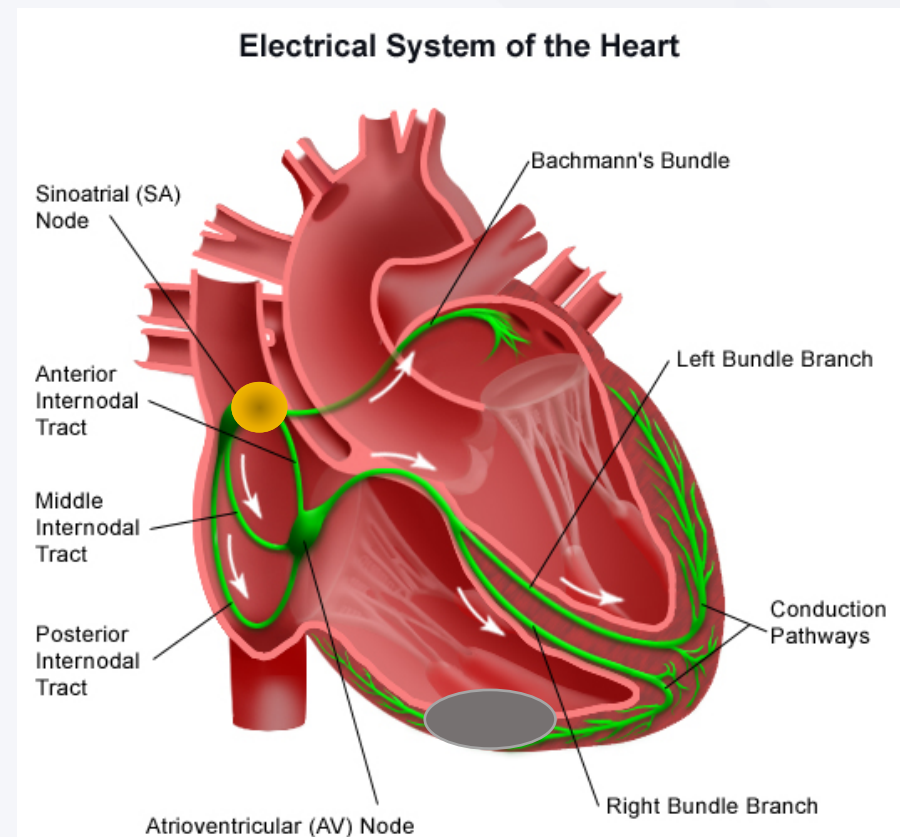


Why Study Them?

- Arrhythmias precipitating cardiac arrest are the most common mechanism of sudden cardiac death
 - Sudden cardiac death is the leading cause of natural death

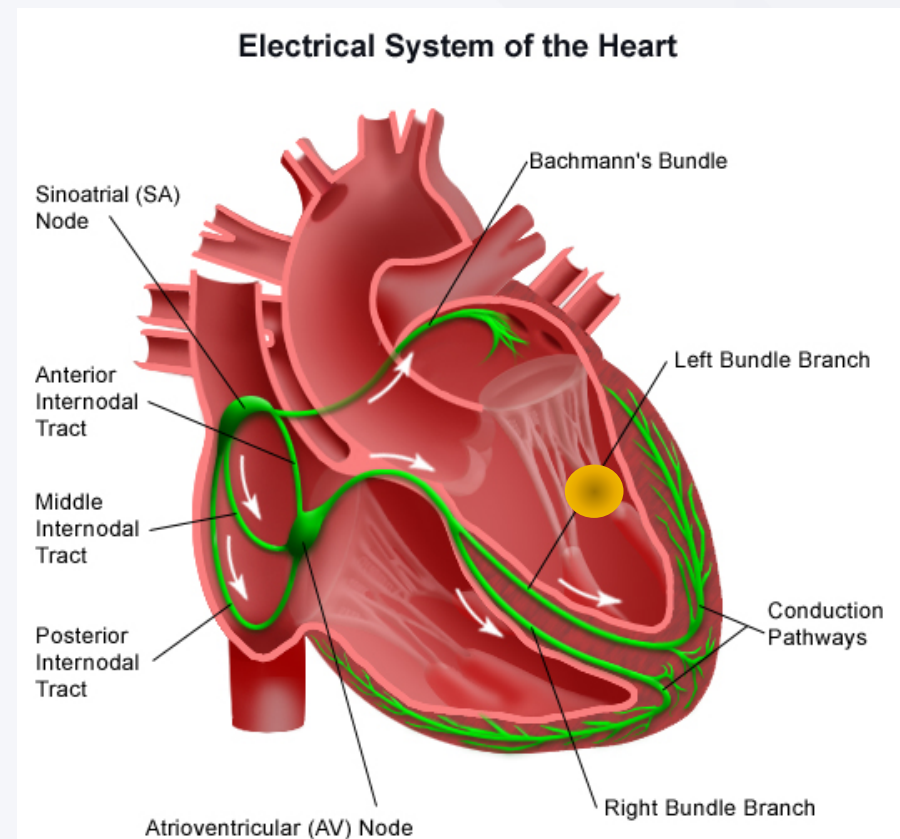
Why do Arrhythmias Occur?

- Structural arrhythmias
 - Due to damage to the heart muscle following a heart attack

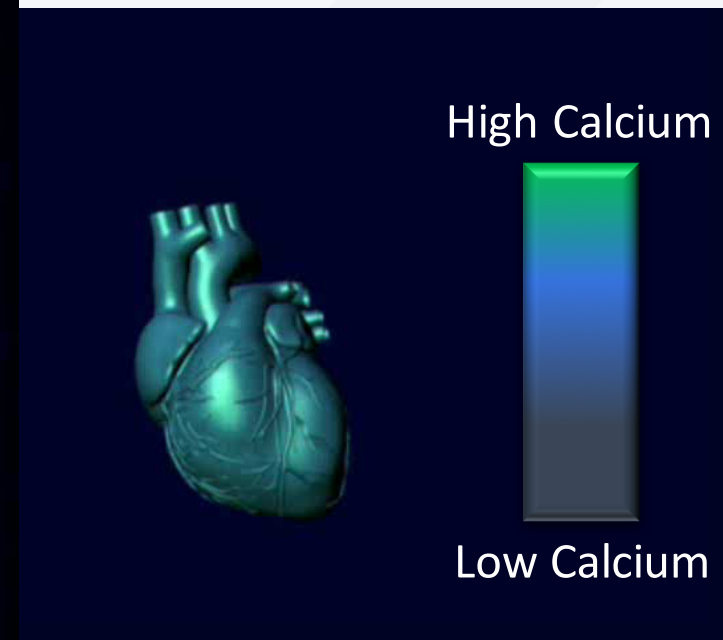
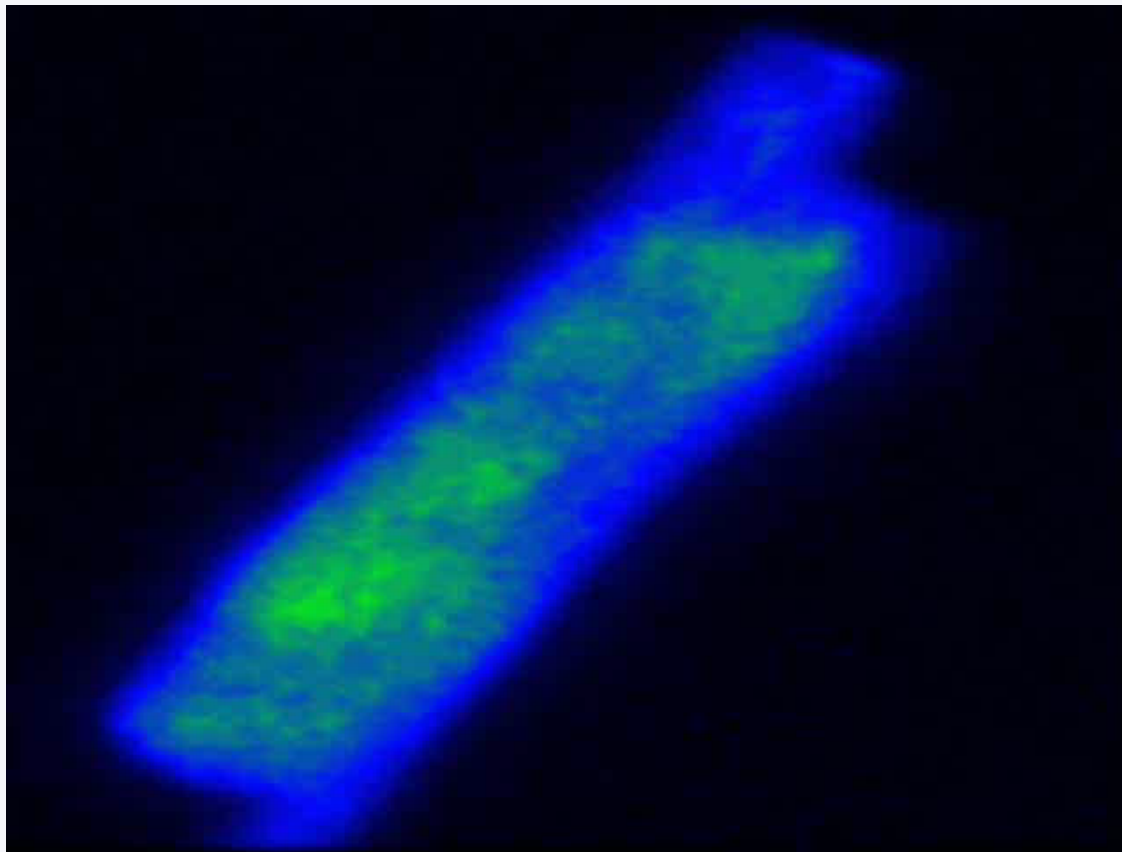


Why do Arrhythmias Occur?

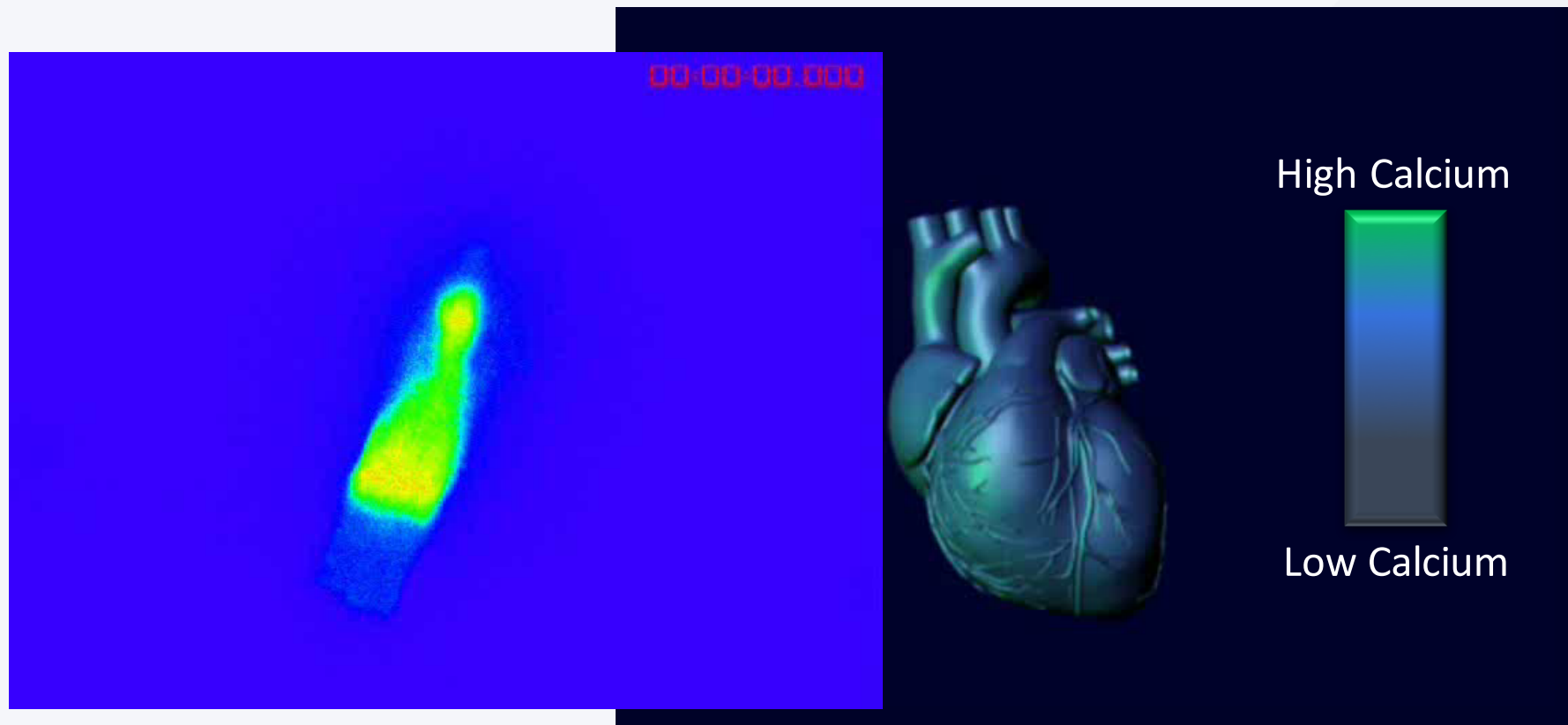
- Non-structural, spontaneous arrhythmias
 - Due to the formation of an ectopic pacemaker



Calcium = Contraction

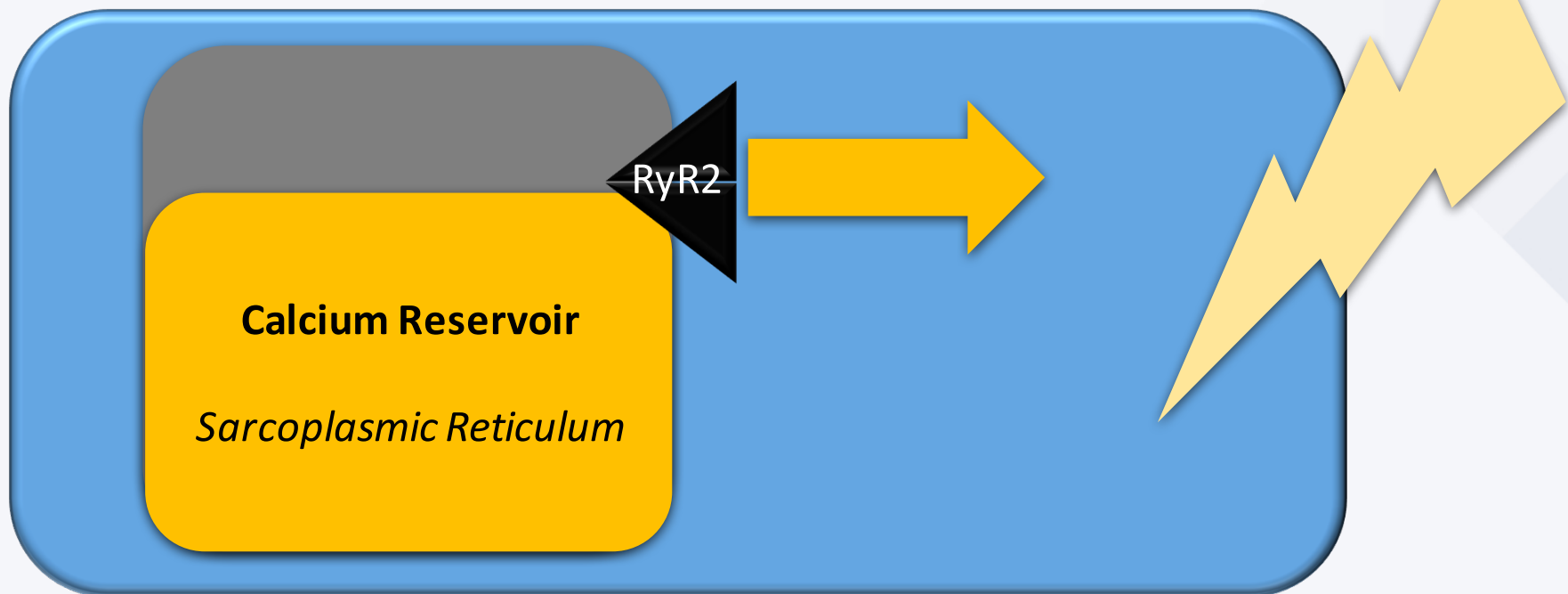


Calcium = Contraction



What causes Spontaneous Calcium Release?

- Most of the calcium required for contraction comes from an internal reservoir the sarcoplasmic reticulum (SR)



What causes Spontaneous Calcium Release?

- In addition to normal stimulation RyR2 can open due to calcium within the SR
- In disease RyR2 becomes too sensitive to calcium
 - This decreases the SR 'threshold' at which it will release calcium

Cell from a
Healthy Heart

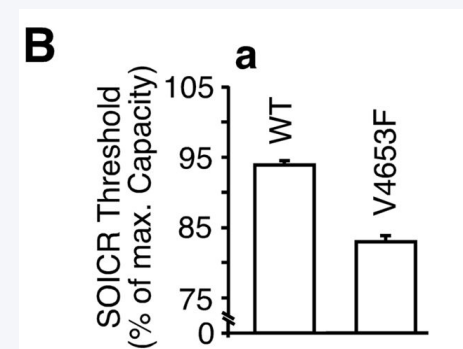
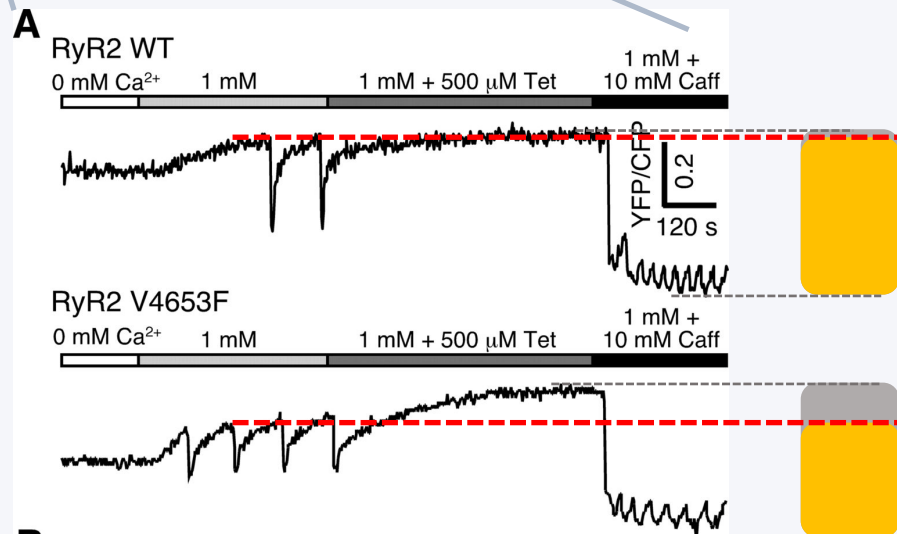
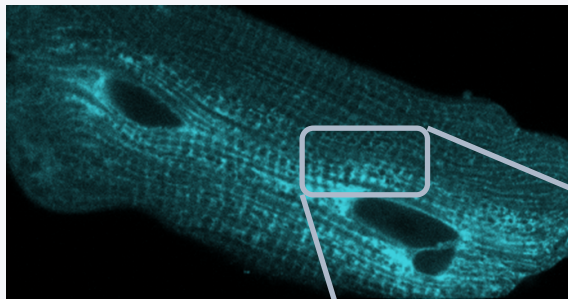


Cell from a
Diseased Heart



How do we know this?

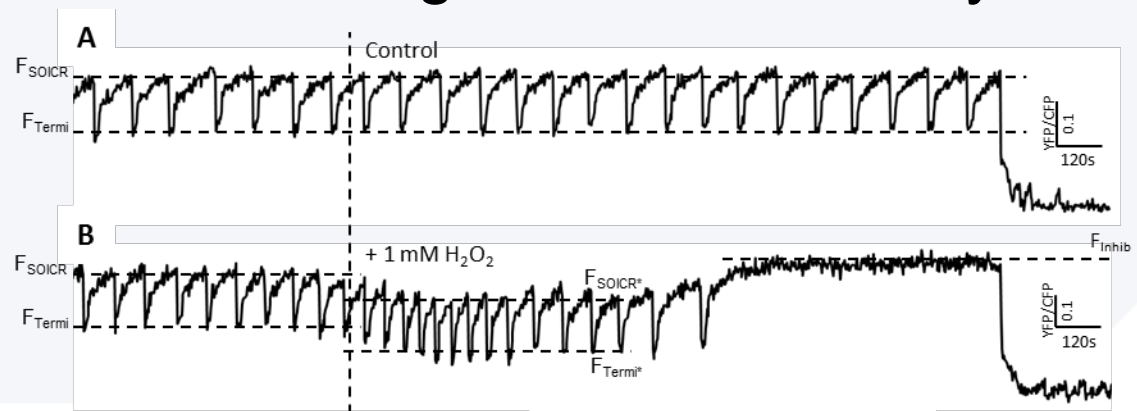
- We can measure calcium inside the SR using calcium sensitive proteins derived from jellyfish



Jones PP *et al.* Biochem. J. 2008

Why Does this Happen to RyR2 During Heart Disease?

- A diseased heart experiences many stressors including:
 - Increased oxidation
 - Increased sympathetic drive
 - Increased nerve activity to the heart
 - Alterations in the amount of certain proteins in cells
- We have found that all of these things can sensitise RyR2 to calcium in the SR



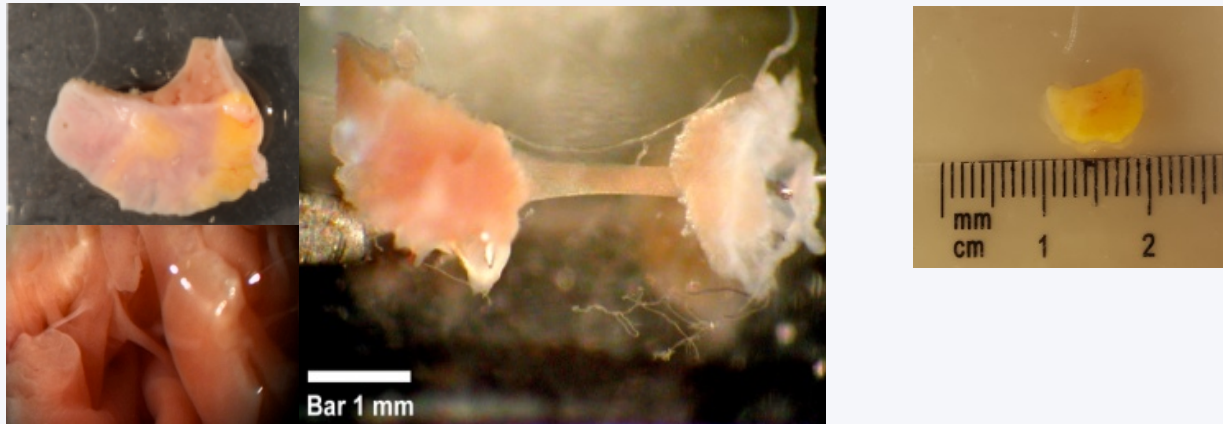


What's next?

- Obesity and diabetic heart disease
 - 1 in 3 in NZ is overweight
- We want to know how increased fat and glucose affect RyR2 function

What's next?

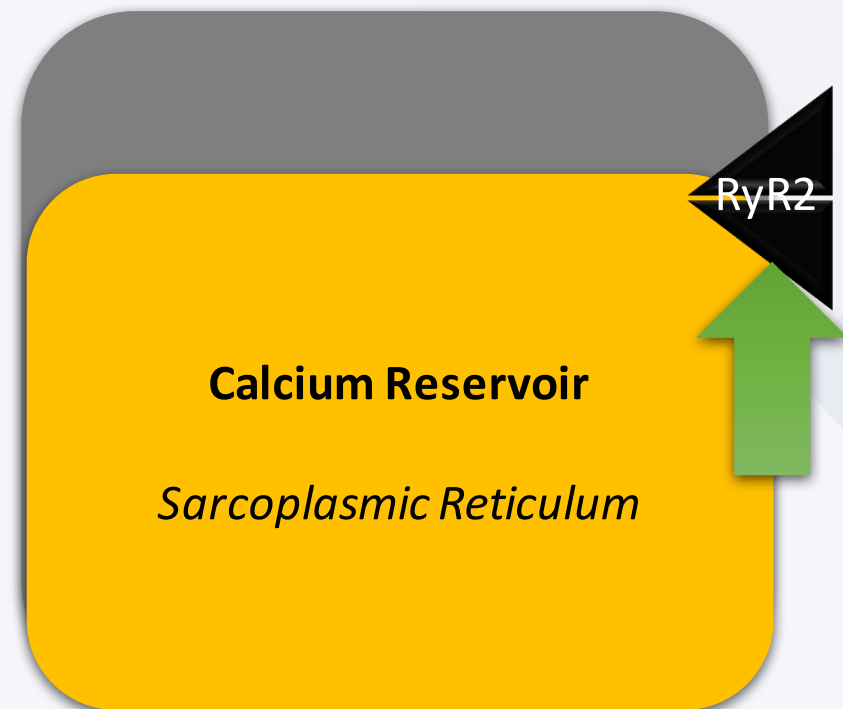
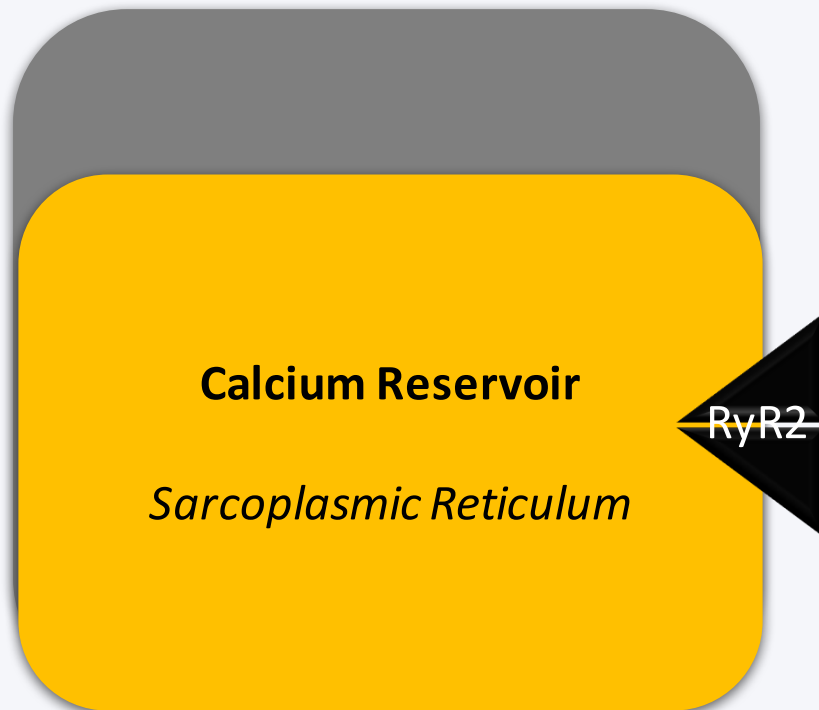
- Because obesity and diabetes are so common we can study them in human tissue
 - Remove tissue and fat during bypass surgery



- We can then test the susceptibility to arrhythmia and compare diabetics to obese and to lean patients
 - We can also look at what happens if we add the fat from an obese patient to the tissue from a lean patient

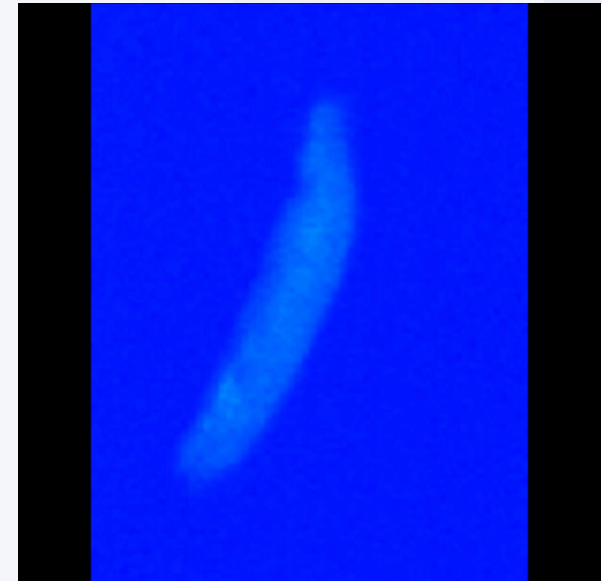
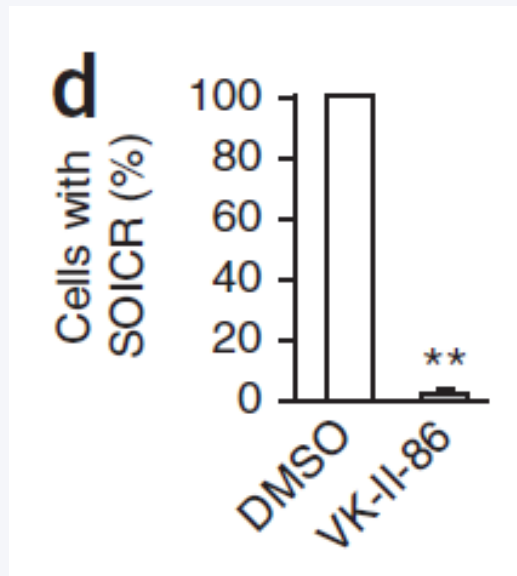
Its Not All Bad News!

- Now we know why RyR2 becomes dysfunctional
can we fix it?



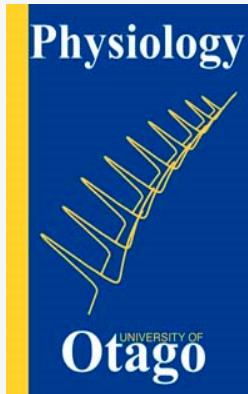
Its Not All Bad News!

- Can we make an inhibitor of RyR2 that is not a β -blocker?





Acknowledgements



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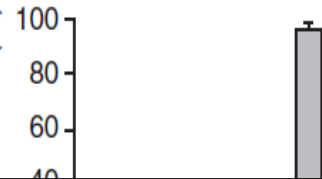
HEARTOTAGO

- Regis Lamberts
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- Marilyn Noye
- Chris Baldi
- Sean Coffey
- Pankaj Saxena
- Ivor Galvin
- Patients at Dunedin Hospital

Its Not All Bad News!

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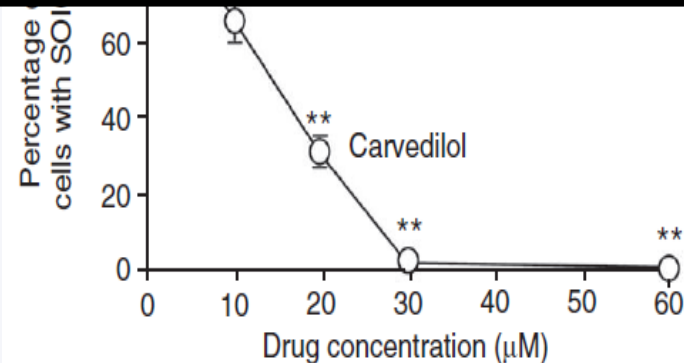
a
Inhibition (%)



Great!

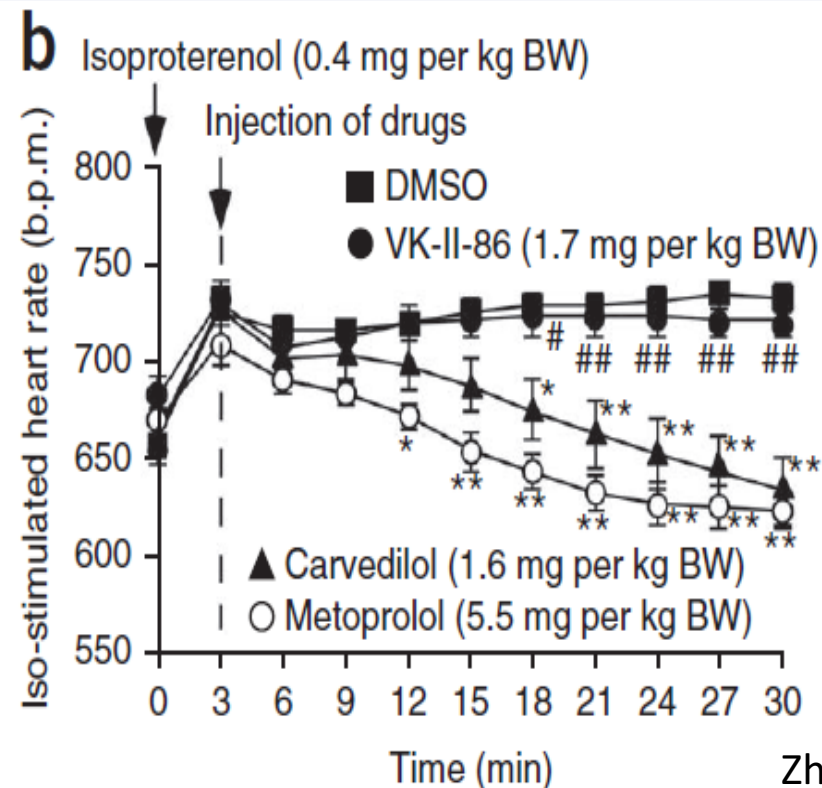
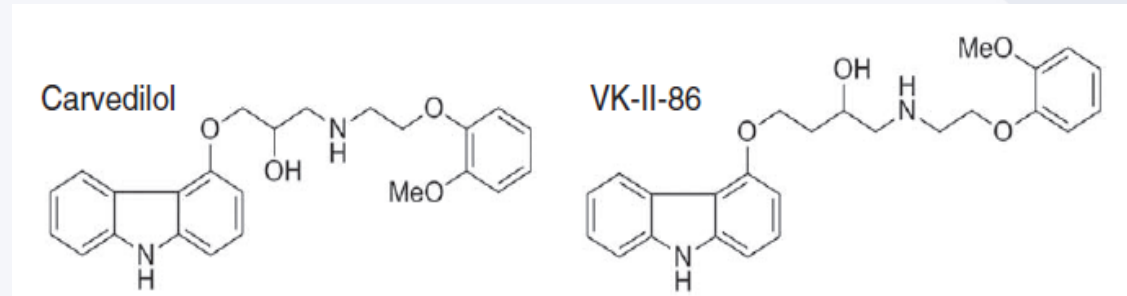
However:

- Problem with β -blockers is their compliance is low



Its Not All Bad News!

- Can we make an inhibitor of RyR2 that is not a β -blocker?

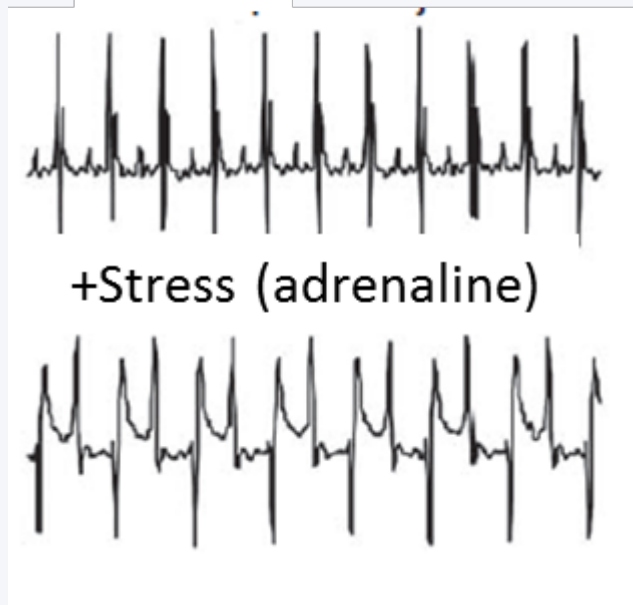


Its Not All Bad News!

- Does VK-II-86 prevent arrhythmias?

Untreated

At rest



Treated for 2 weeks

At rest

