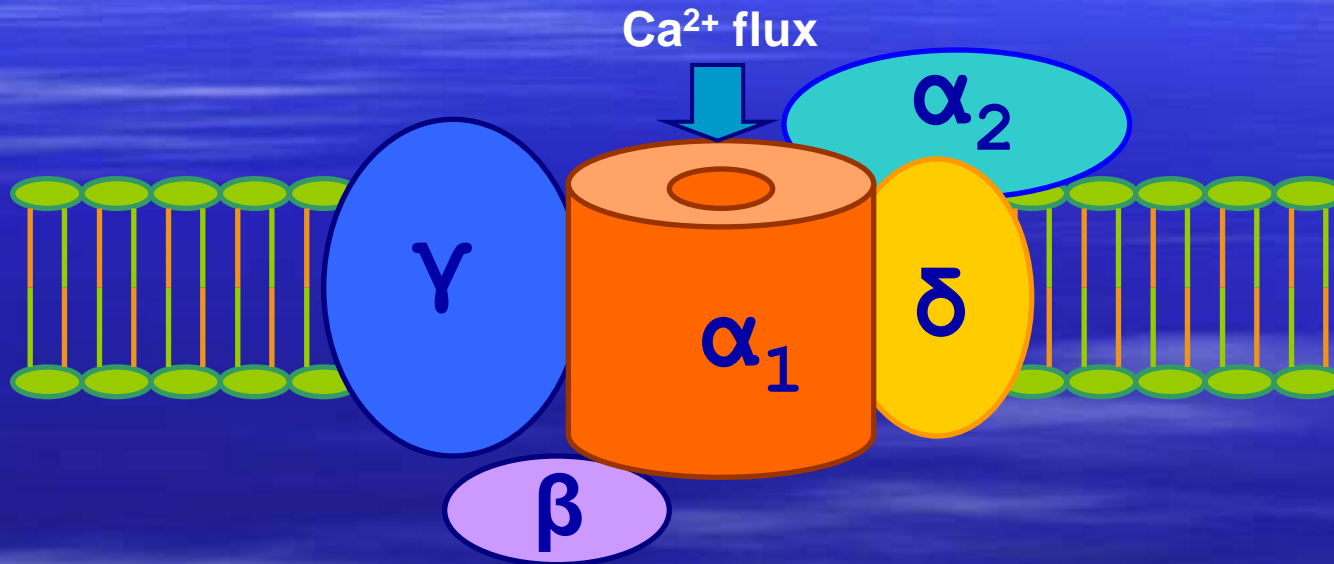


# Ion channel electrophysiology



Joseph Yanni

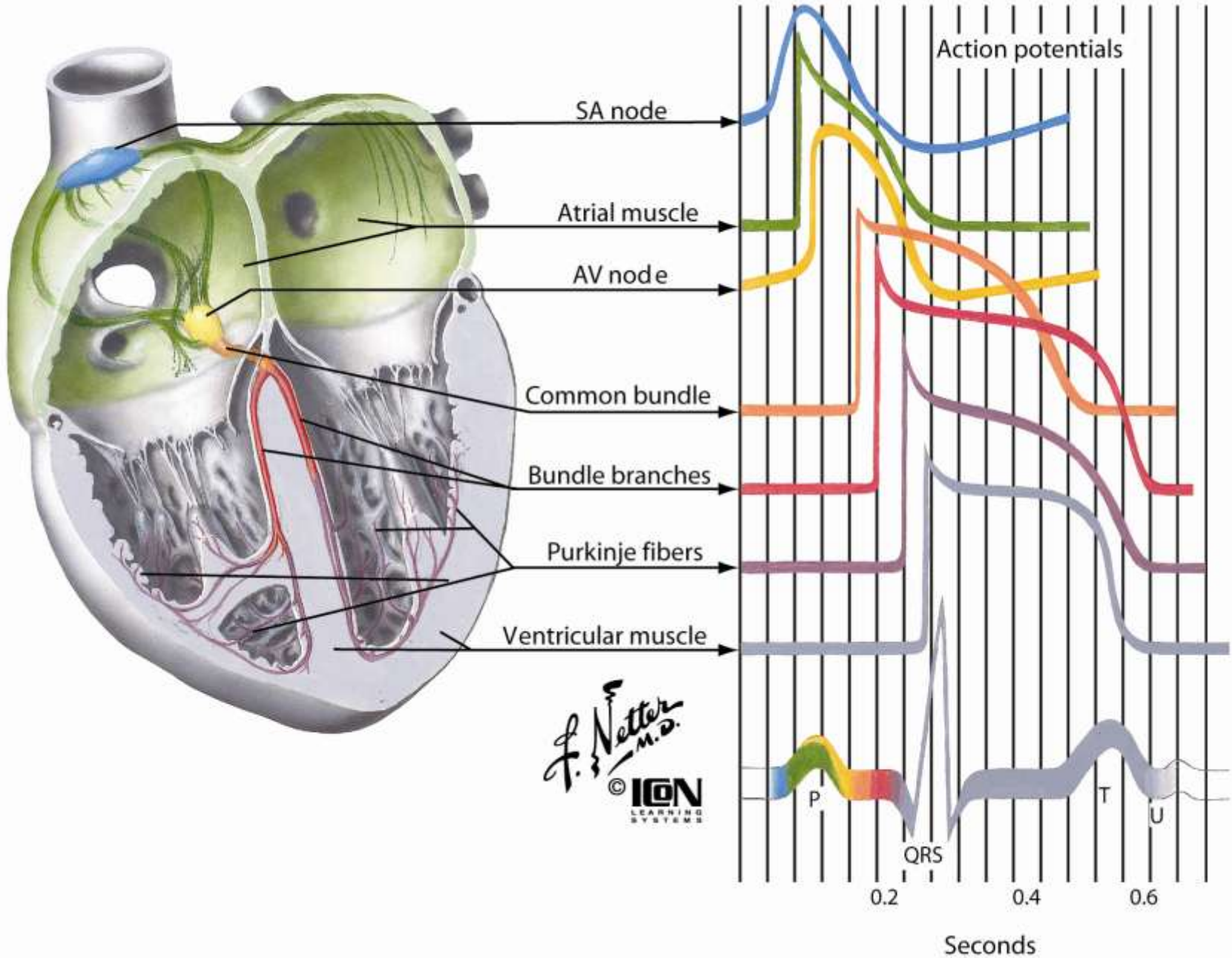
Cardiovascular Medicine  
University of Manchester

# Outline

♥ Ion channels in the heart

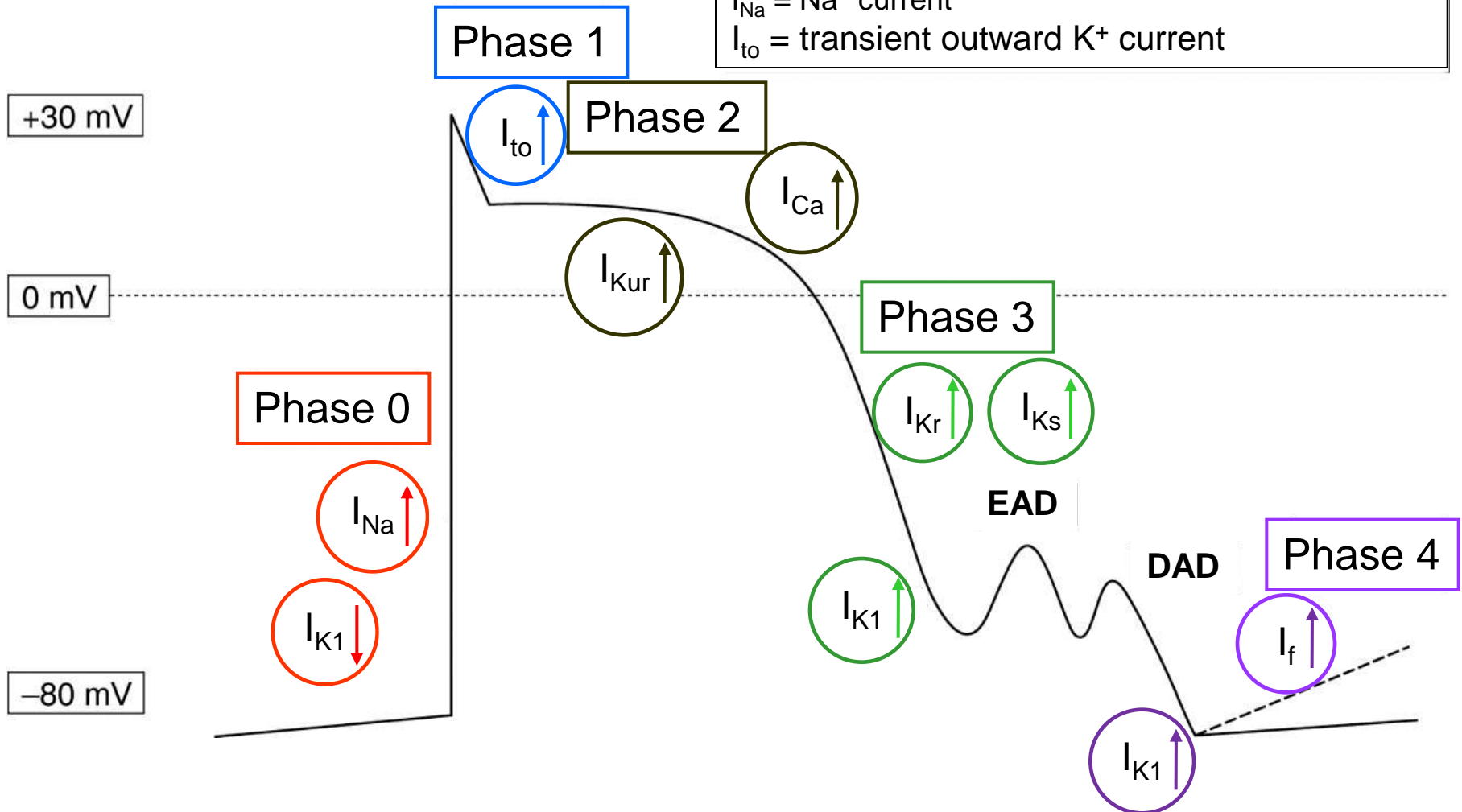
♥ Remodelling of ion channels in heart failure

# Heart and Cardiac Conduction System



# Ionic contributions to cardiac action potential

$I_{Ca}$  =  $Ca^{2+}$  current  
 $I_f$  = hyperpolarisation activated current  
 $I_{K1}$  = inward rectifier  $K^+$  current  
 $I_{Kr}$  = rapid component of delayed rectifier current  
 $I_{Kur}$  = ultrarapid  $K^+$  current  
 $I_{Ks}$  = slow component of  $I_K$   
 $I_{Na}$  =  $Na^+$  current  
 $I_{to}$  = transient outward  $K^+$  current



# Ion channels underlying ionic currents

**$K_v1.4, K_v4.2,$   
 $K_v4.3, KCHIP2$**

$I_{to}$

$I_{Ca}$

**$Ca_v1.2, Ca_v1.3, Ca_v3.1$**

$I_{Kur}$

**$K_v1.5$**

**ERG**

$I_{Kr}$

$I_{Ks}$

**$K_vLQT1, minK$**

**$Na_v1.1, Na_v1.5$**

$I_{Na}$

**$HCN1,$   
 $HCN2, HCN4$**

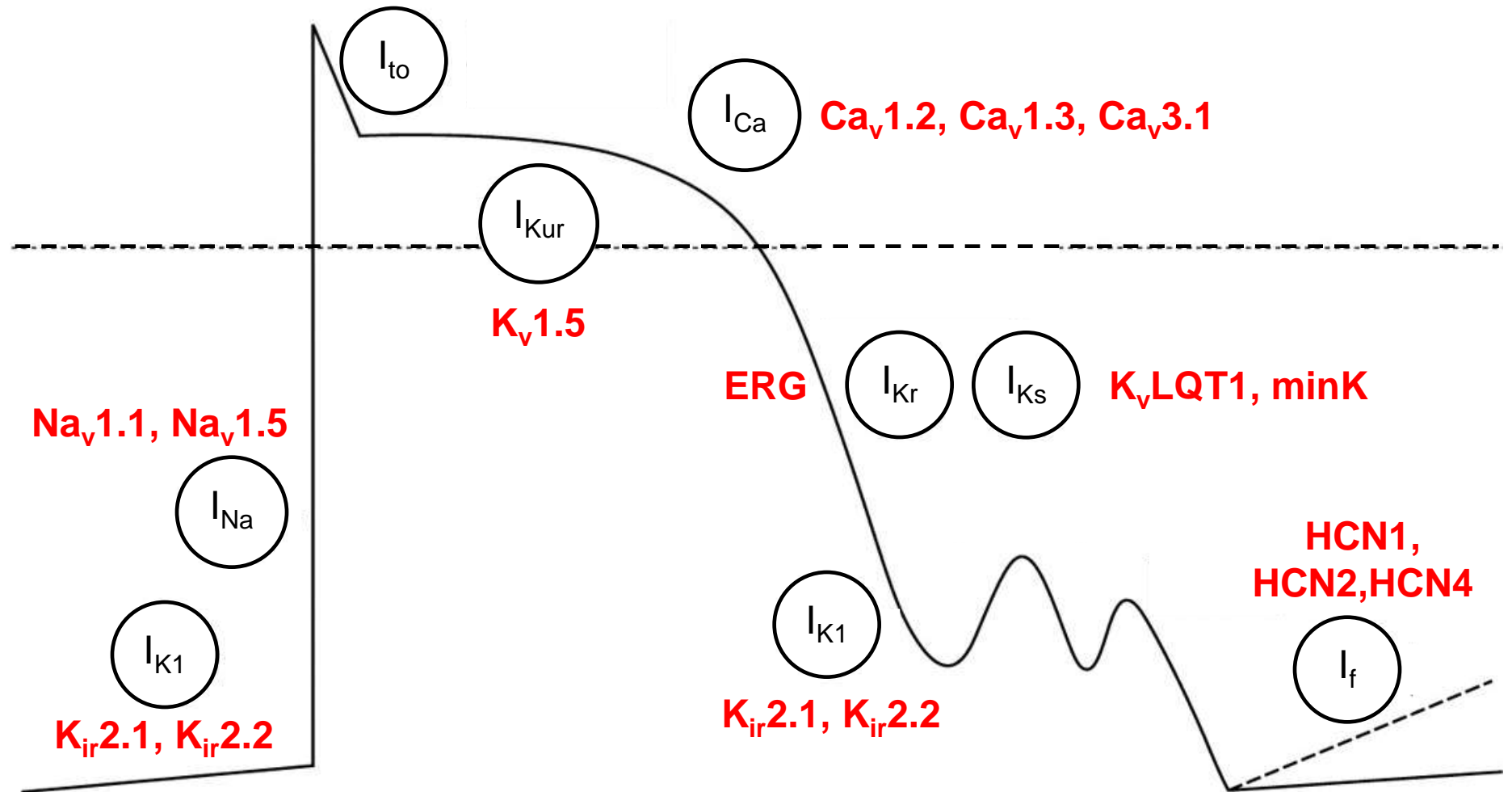
$I_{K1}$

**$K_{ir}2.1, K_{ir}2.2$**

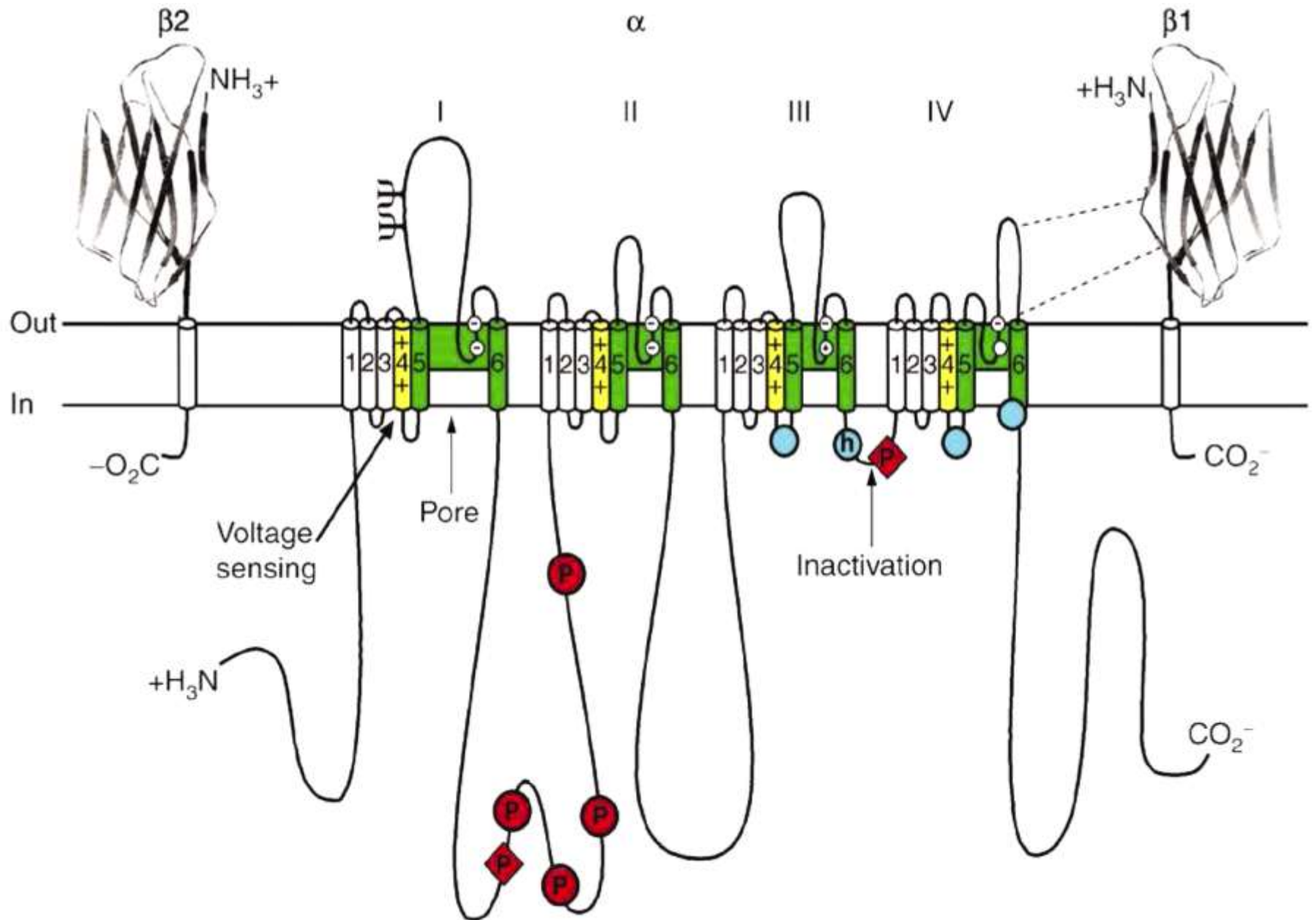
$I_{K1}$

**$K_{ir}2.1, K_{ir}2.2$**

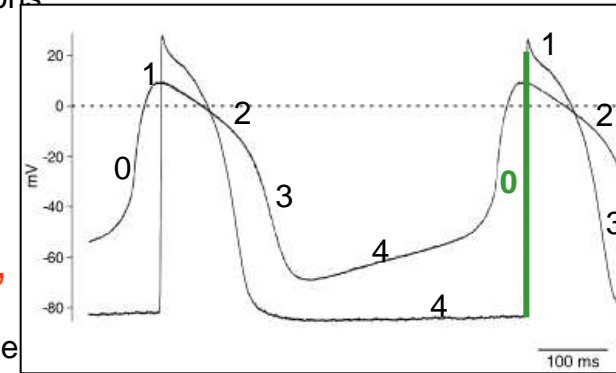
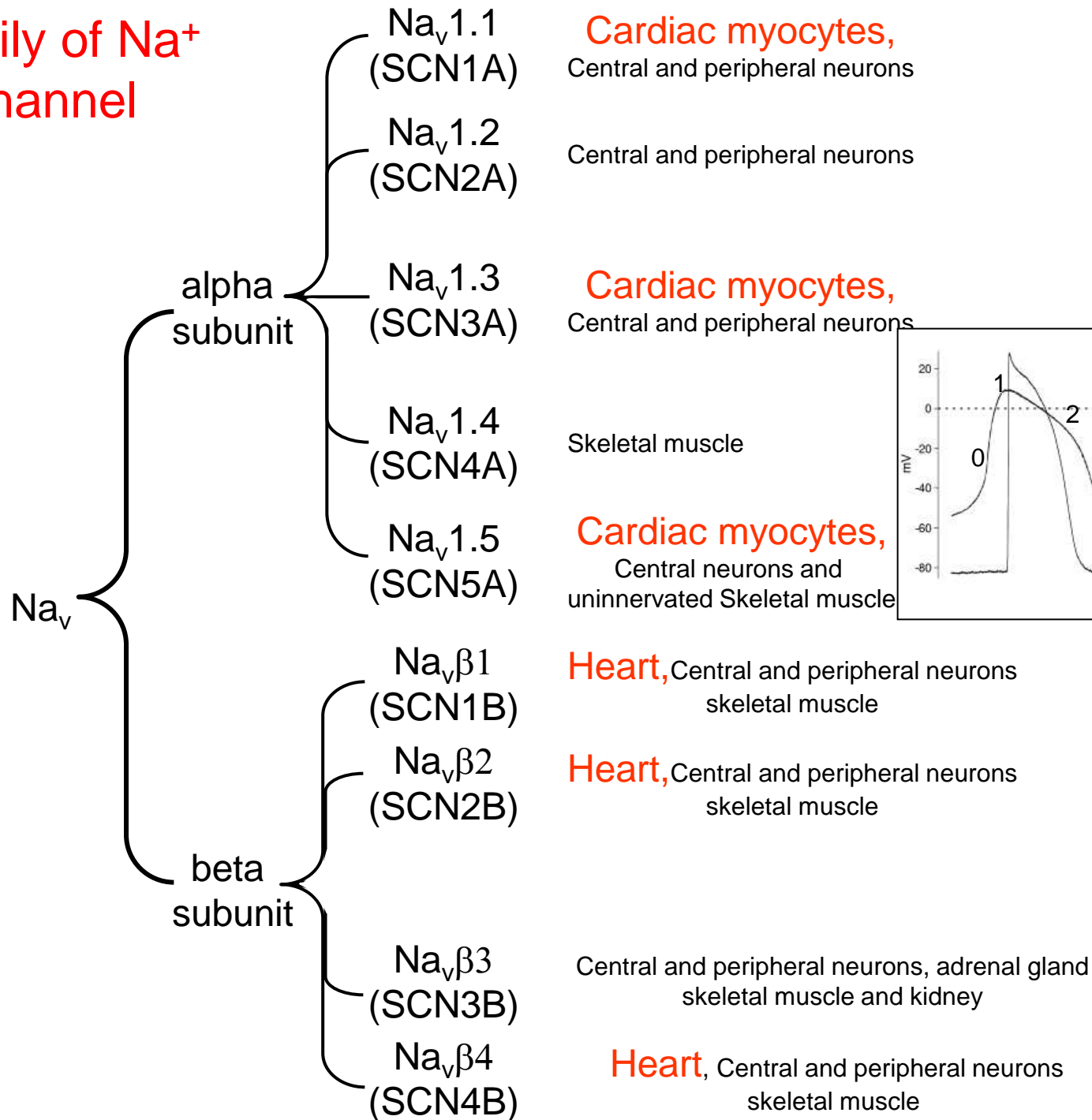
$I_f$



# Structure of Na<sup>+</sup> channel



# Family of Na<sup>+</sup> channel



# Immunohistochemistry of Na<sub>v</sub>1.5

Interatrial  
septum

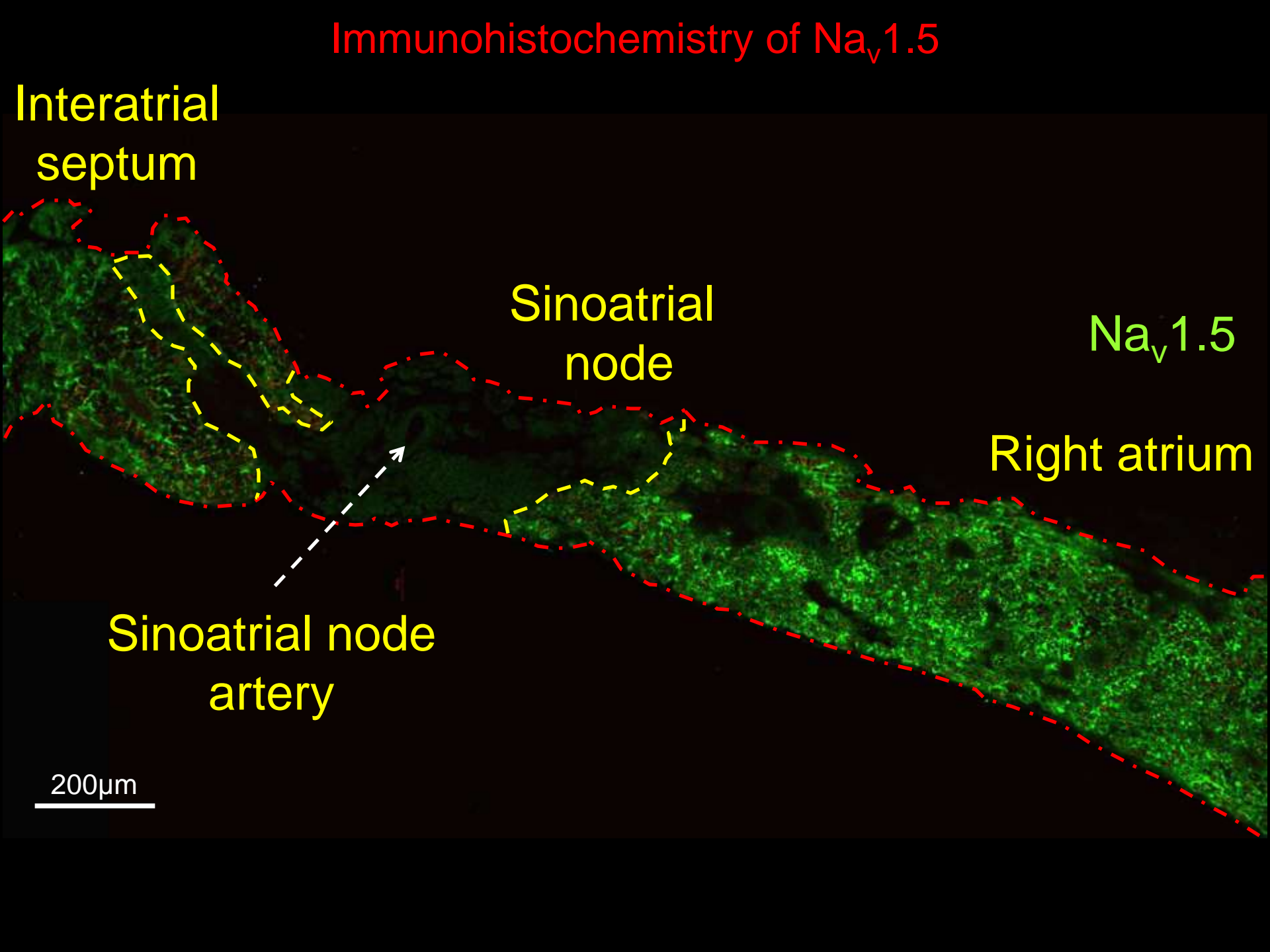
Sinoatrial  
node

Na<sub>v</sub>1.5

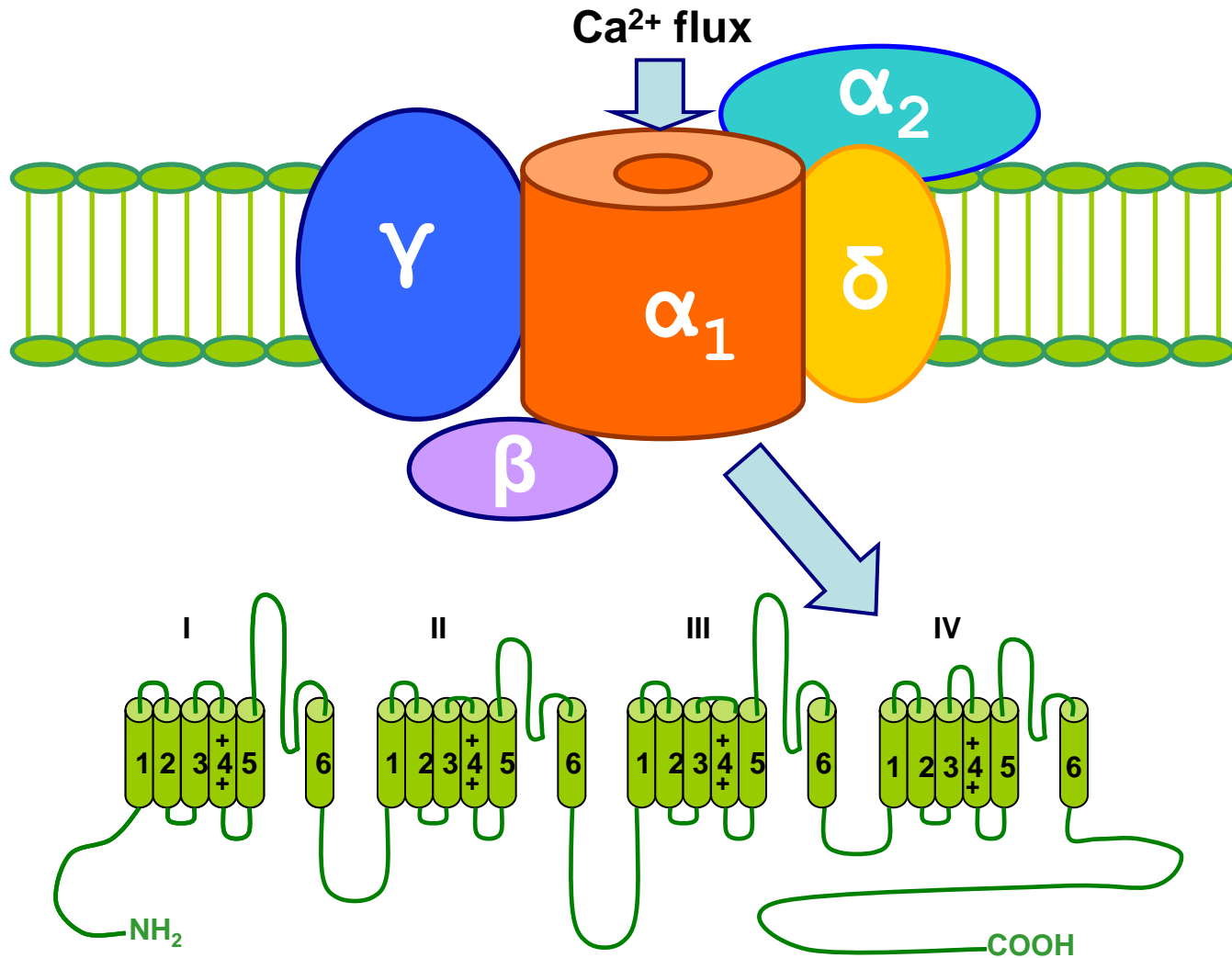
Right atrium

Sinoatrial node  
artery

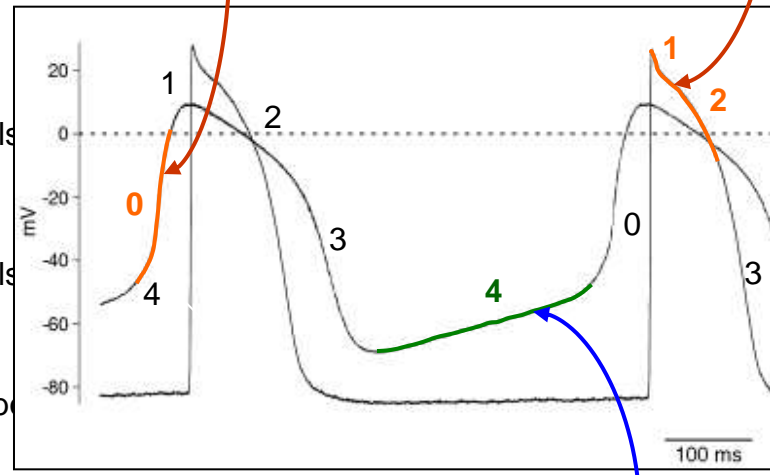
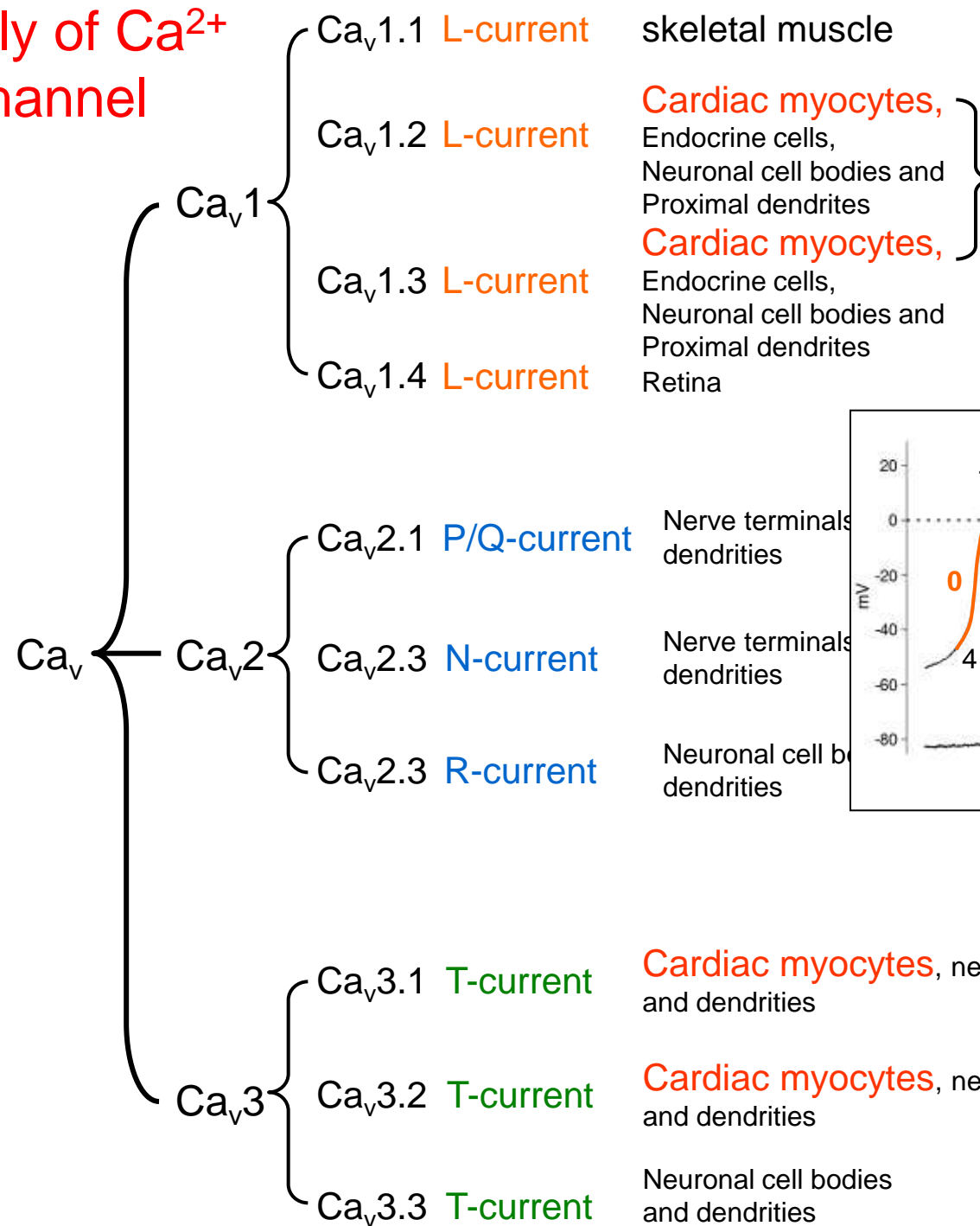
200μm



# Structure of voltage-gated $\text{Ca}^{2+}$ channels ( $\text{Ca}_v$ 's)



# Family of Ca<sup>2+</sup> channel



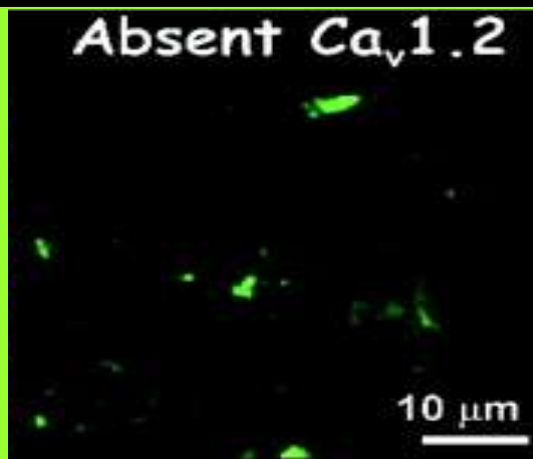
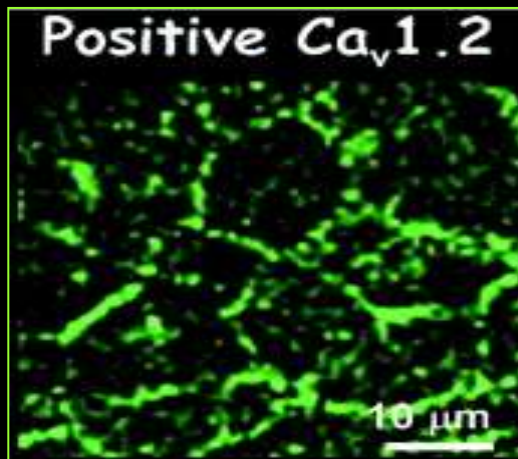
Cardiac myocytes, neuronal cell bodies and dendrites

Cardiac myocytes, neuronal cell bodies and dendrites

Neuronal cell bodies and dendrites

Right atrium

Sinoatrial node



Right atrium

Sinoatrial node

Confocal

Interatrial septum

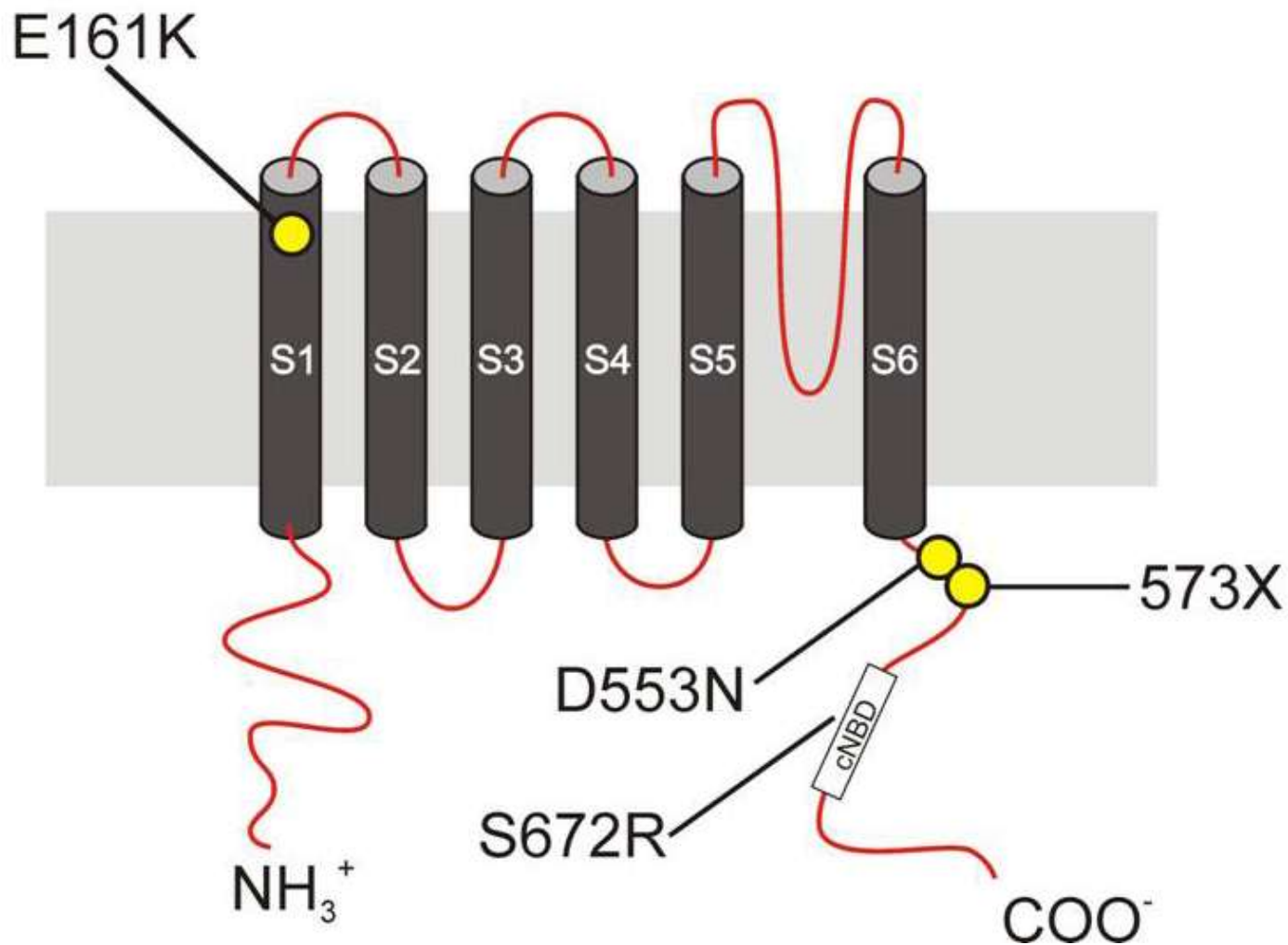
Schematic



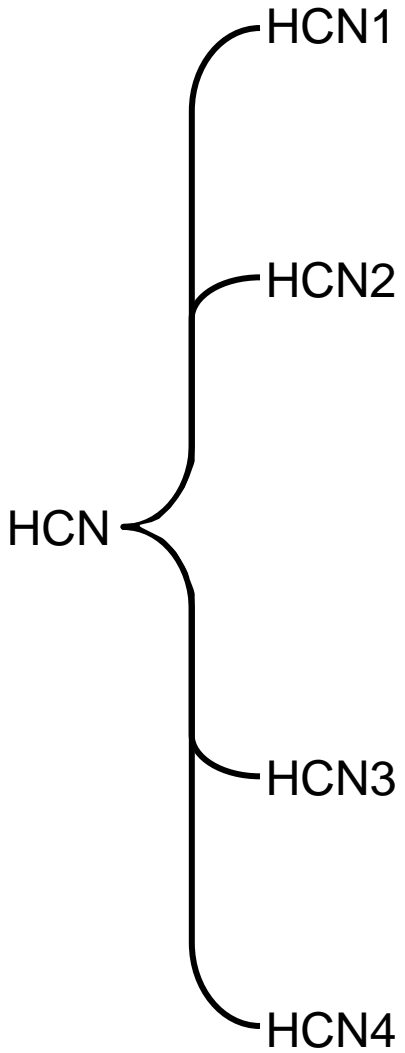
■  $Ca_v1.2$  absent  
■  $Ca_v1.2$  positive

I<sub>f</sub>

# Structure of hyperpolarisation-activated cyclic nucleotide-gated channels (HCN's)



# Family of HCN channels



**Heart (sinoatrial node & Purkinje fibres)**  
 Brain (neocortex, hippocampus, superior colliculus and cerebellum)

Pacemaking

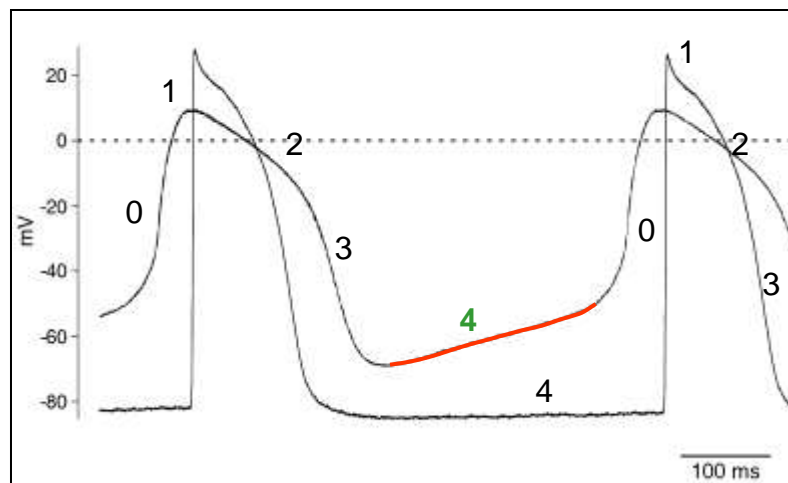
**Heart (ventricle, atrium and sinoatrial node)**  
 Brain (olfactory bulb, cerebral cortex, hippocampus, thalamus, cerebellum and brainstem)

Pacemaking

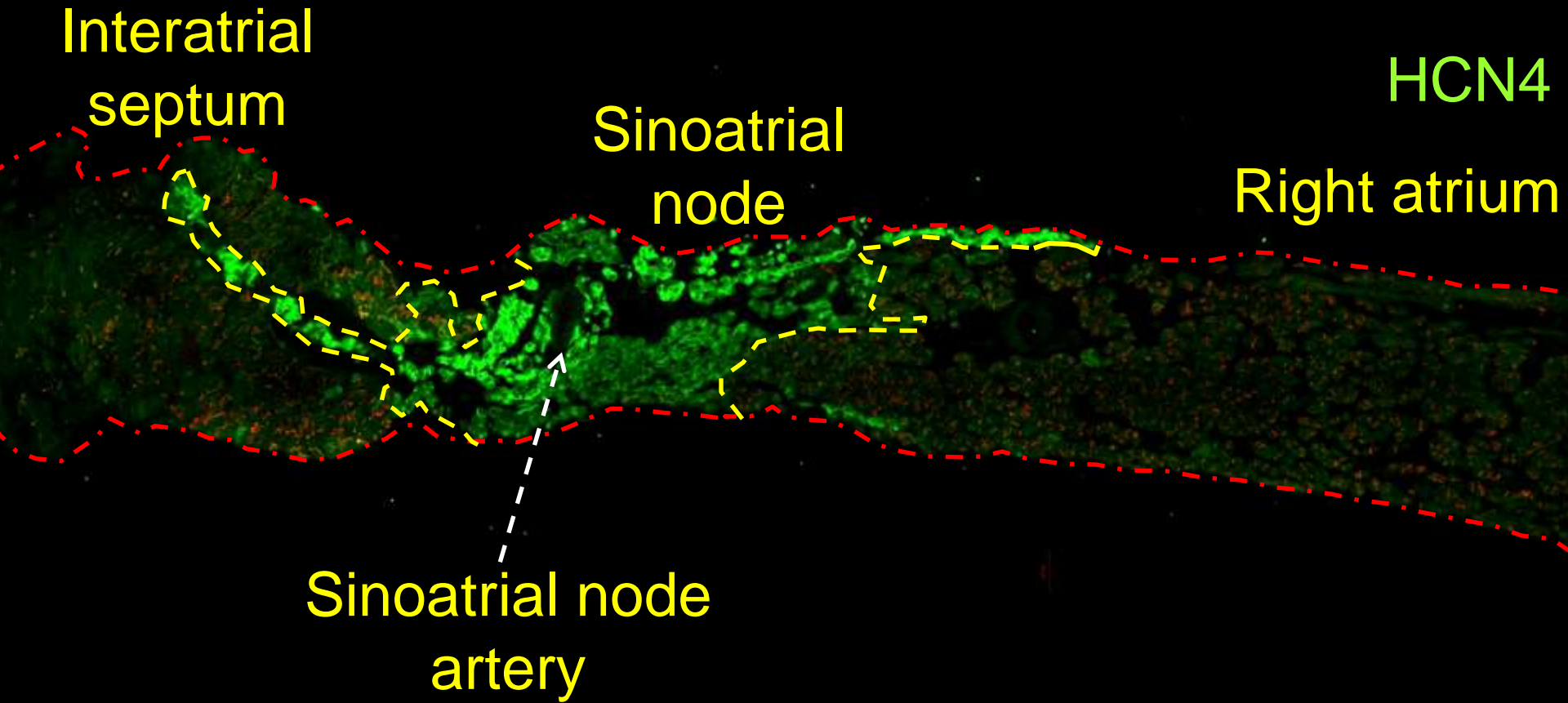
Brain (olfactory bulb), liver, lung and kidney

**Heart (sinoatrial node, atrioventricular node & Purkinje fibres)**  
 Brain (olfactory bulb, thalamus and substantia nigra)

Pacemaking



# Immunohistochemistry of HCN4



200µm

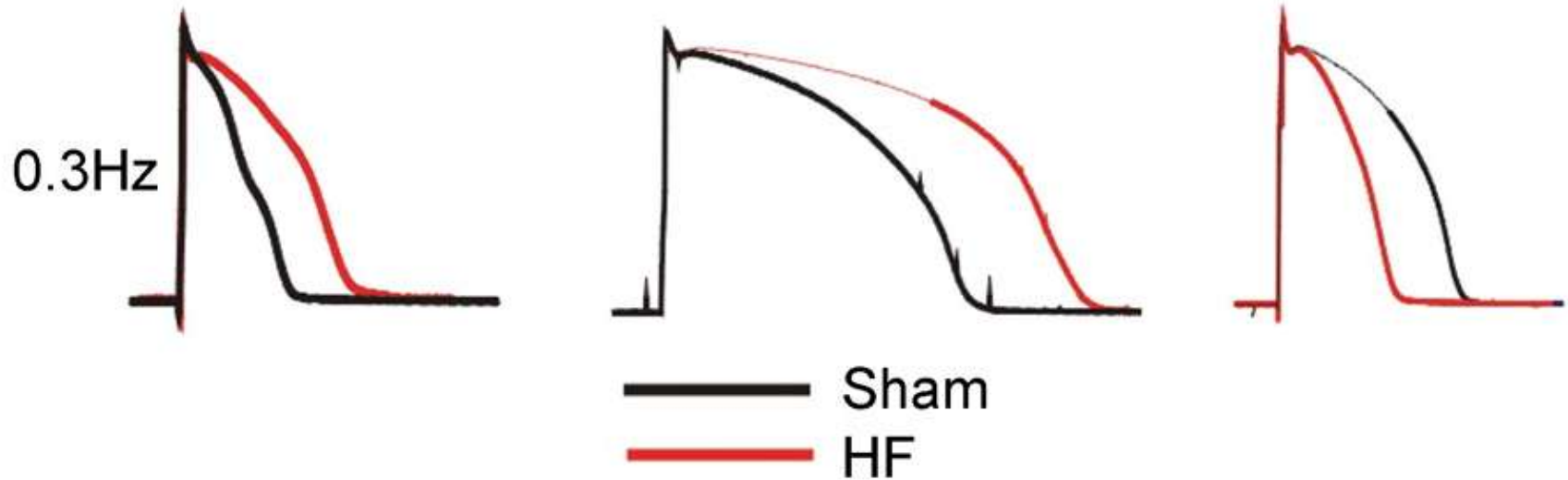
♥ Remodelling of ion channels  
in heart failure

# HF causes ion channel remodelling in ventricle

Subepicardial cells

M-cells

Subendocardial cells

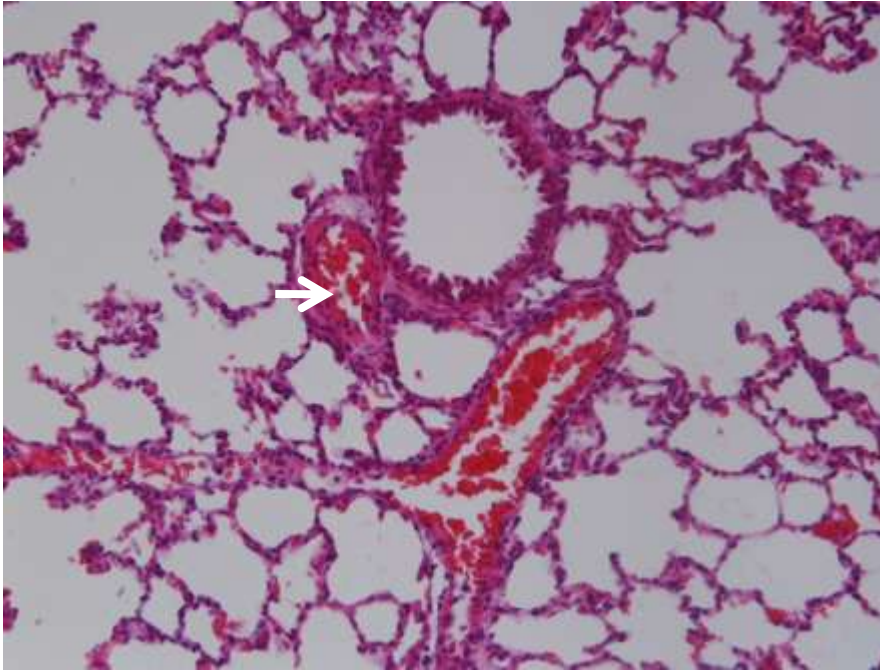


| Changes in LV end-stage heart failure | Subepicardial cells                          |  | M-cells  |  | Subendocardial cells             |                                  |
|---------------------------------------|--|--|--|--|----------------------------------|----------------------------------|
|                                       | increase                                     | Na Nav1.5                                    | Ca(L) Cav1.2   | K1 Kir2.1  | K1 Kir2.1                        | K1 Kir2.1                        |
| no change                             | Ca(L) Cav1.2                                 | Kr Kv11.1                                    | Kr Kv11.1  | Kr Kv11.1  | K-Ach Kir3.1                     | K-Ach Kir3.1                     |
| decrease                              | Ca(T) Cav3.2                                 | Ks Kv7.1                                     | Ks Kv7.1   | Ks Kv7.1   | K-Ach Kir3.4                     | K-Ach Kir3.4                     |
|                                       | to Kv4.3                                     | Kur Kv1.5                                    | Kur Kv1.5  | Kur Kv1.5  | K-ATP Kir6.2                     | K-ATP Kir6.2                     |
|                                       |  | Kp K2p1.1                                    |  |  |                                  |                                  |
|                                       | <i>inward and transient outward currents</i> | <i>inward and delayed rectifier currents</i> | <i>delayed rectifier and inward rectifier currents</i> | <i>delayed rectifier and inward rectifier currents</i> | <i>inward rectifier currents</i> | <i>inward rectifier currents</i> |

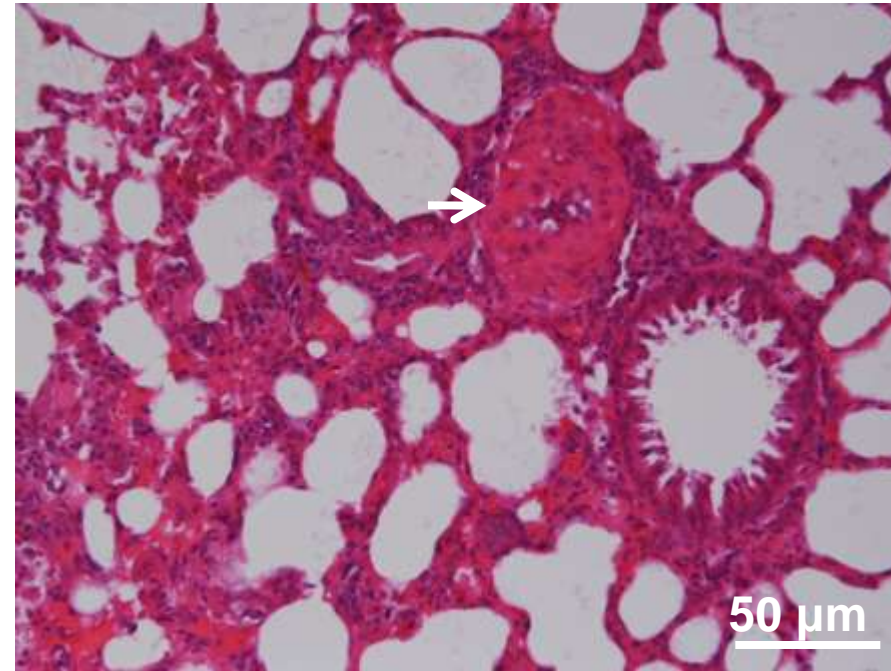
# Monocrotaline causes pulmonary hypertension

## Lung

Control



Congestive heart failure

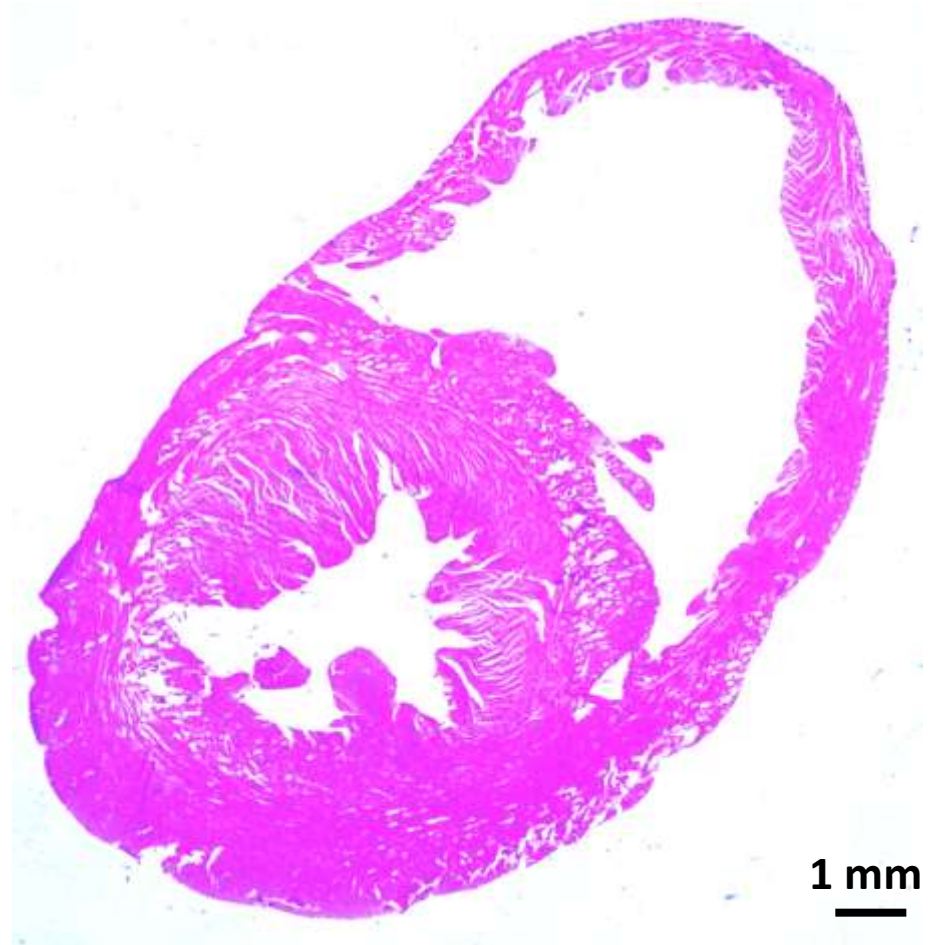


# Pulmonary hypertension causes cardiac hypertrophy

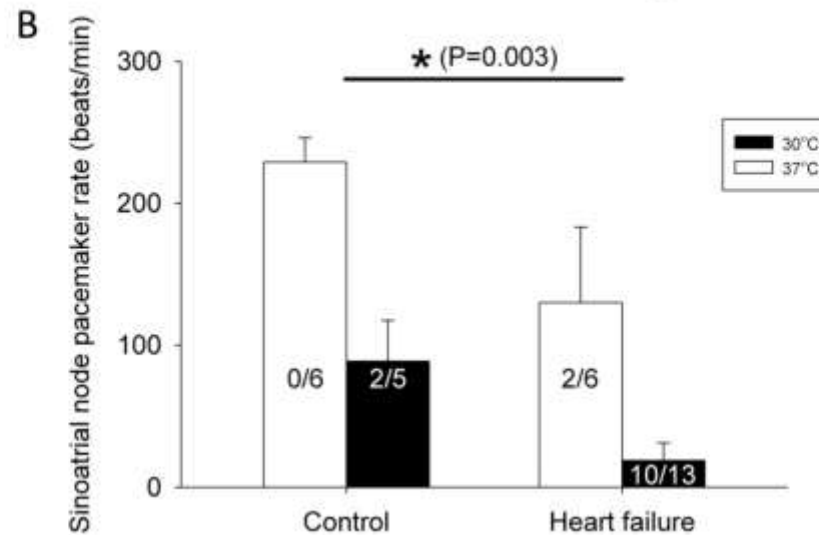
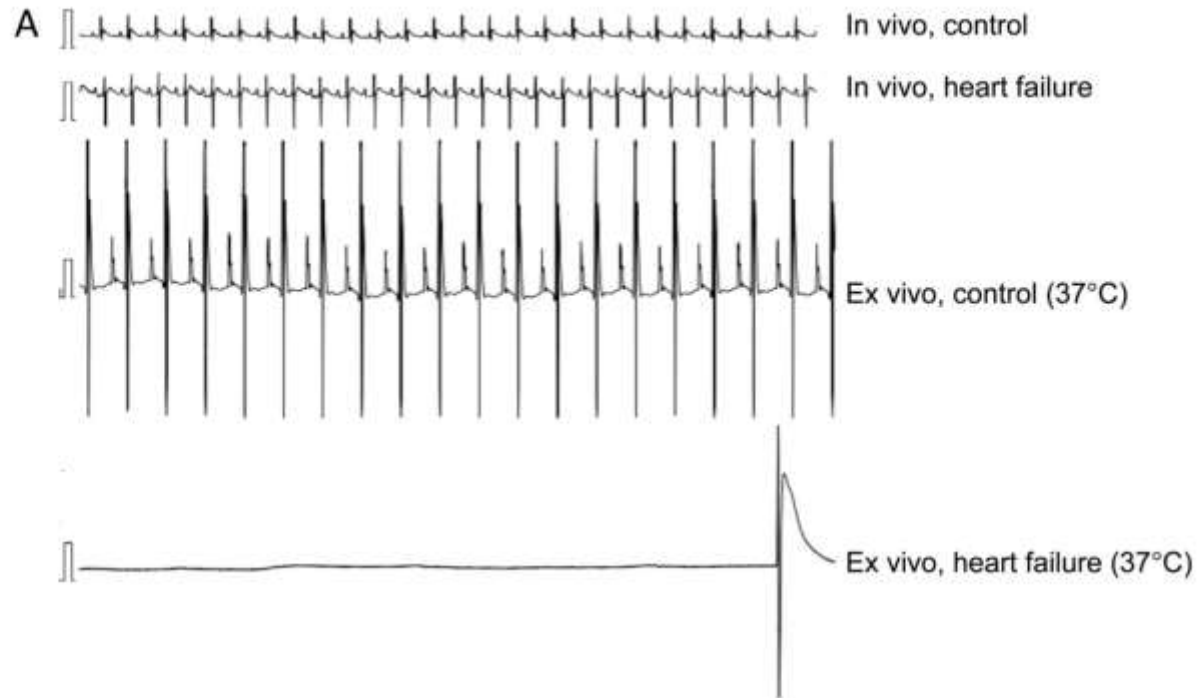
Control



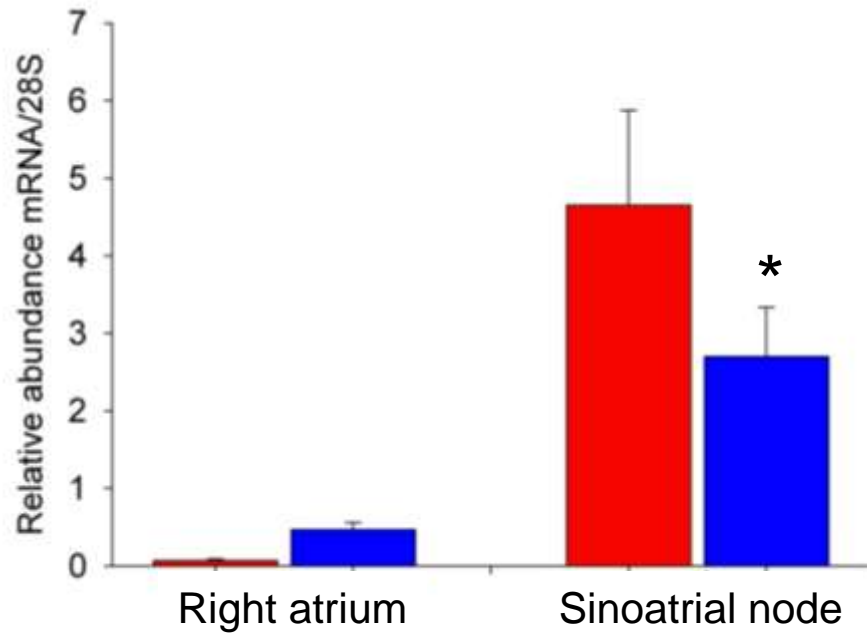
Congestive heart failure



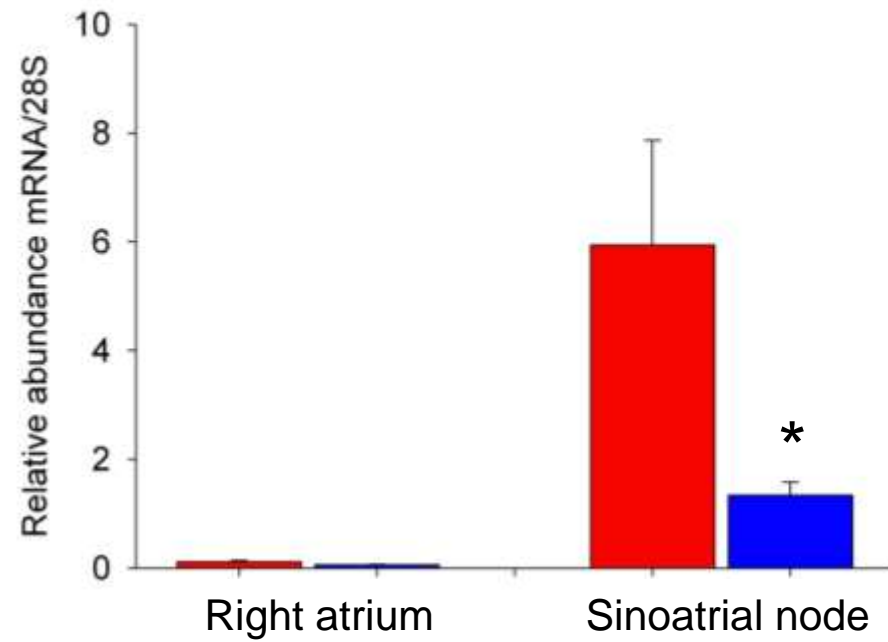
# Pulmonary hypertension causes bradycardia



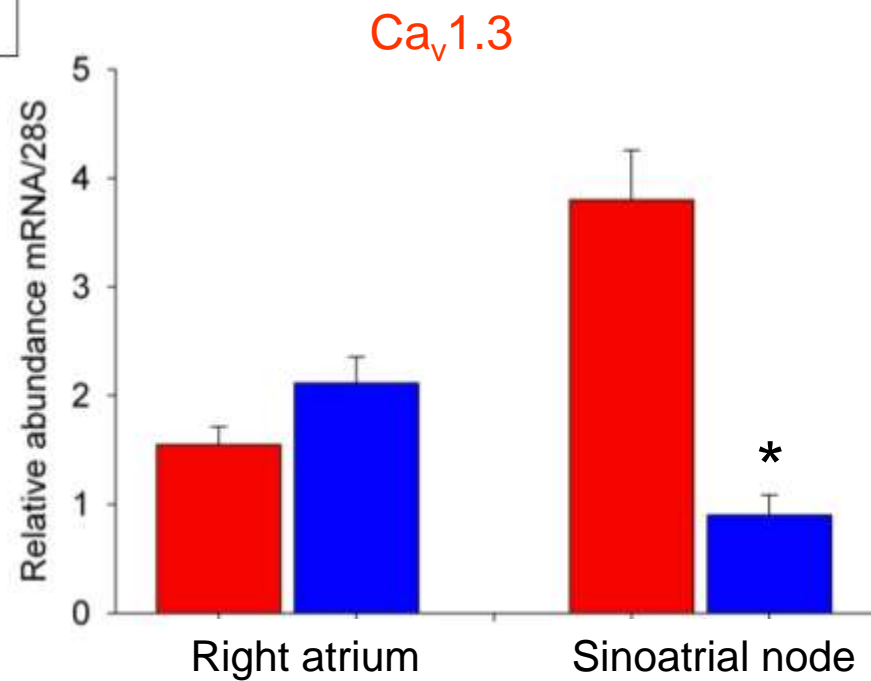
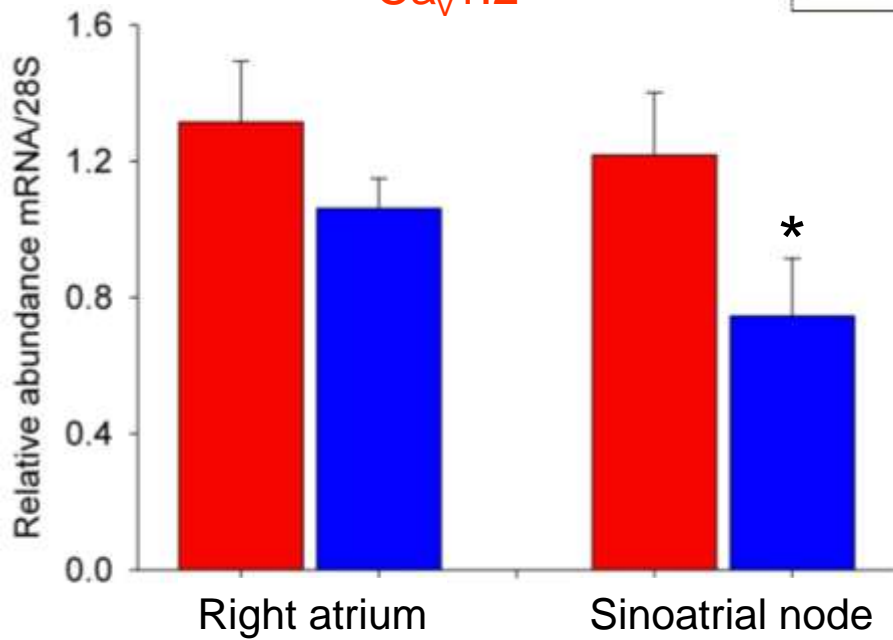
## HCN1



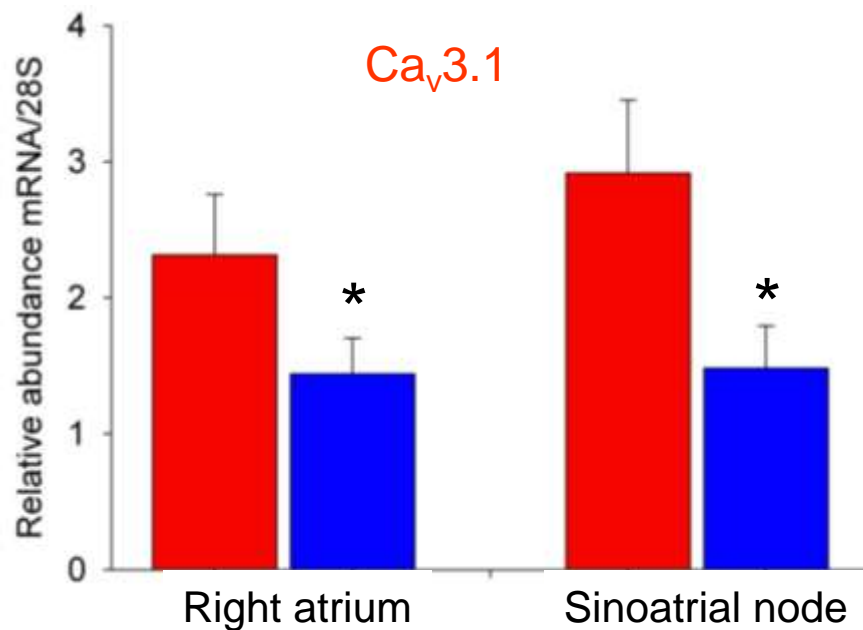
## HCN4



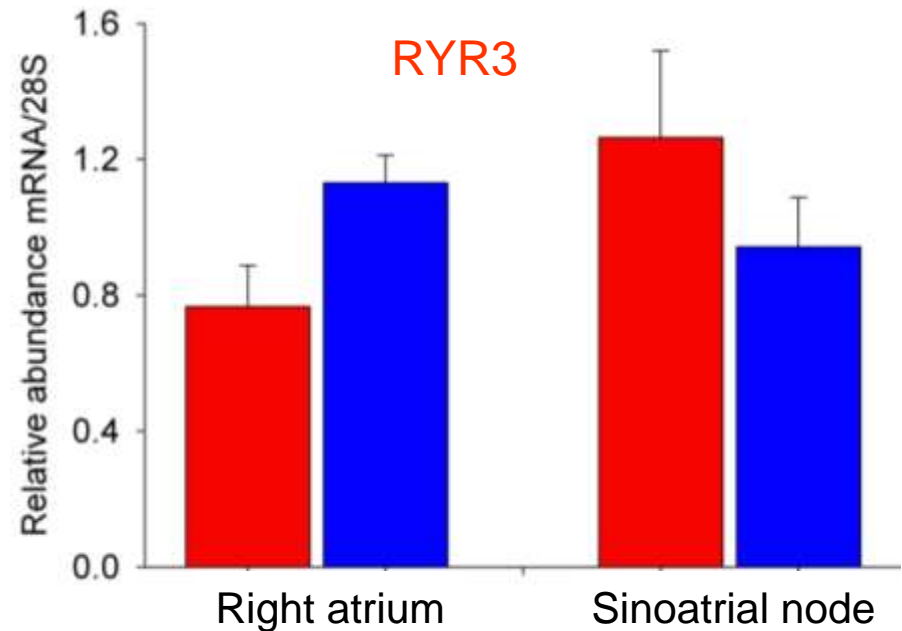
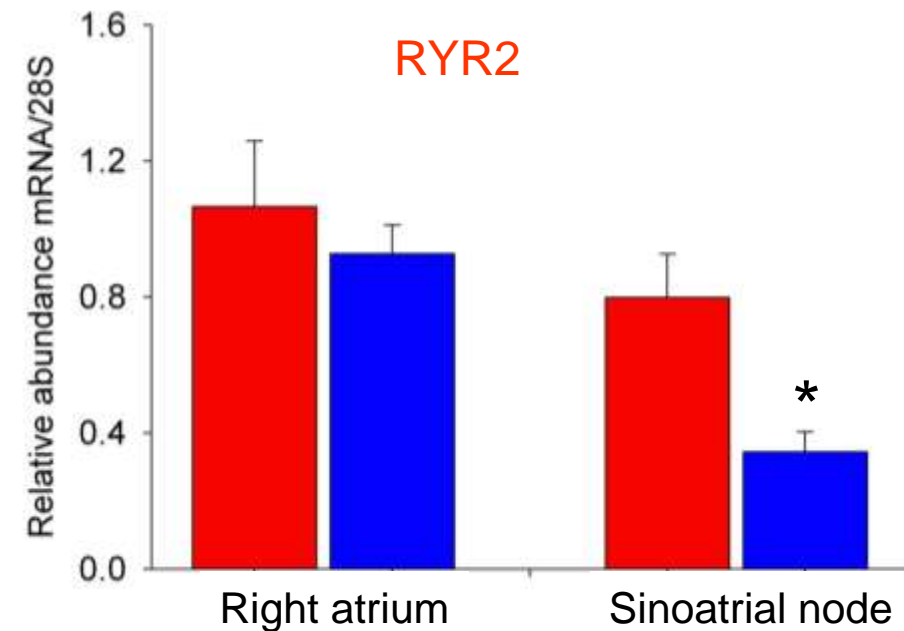
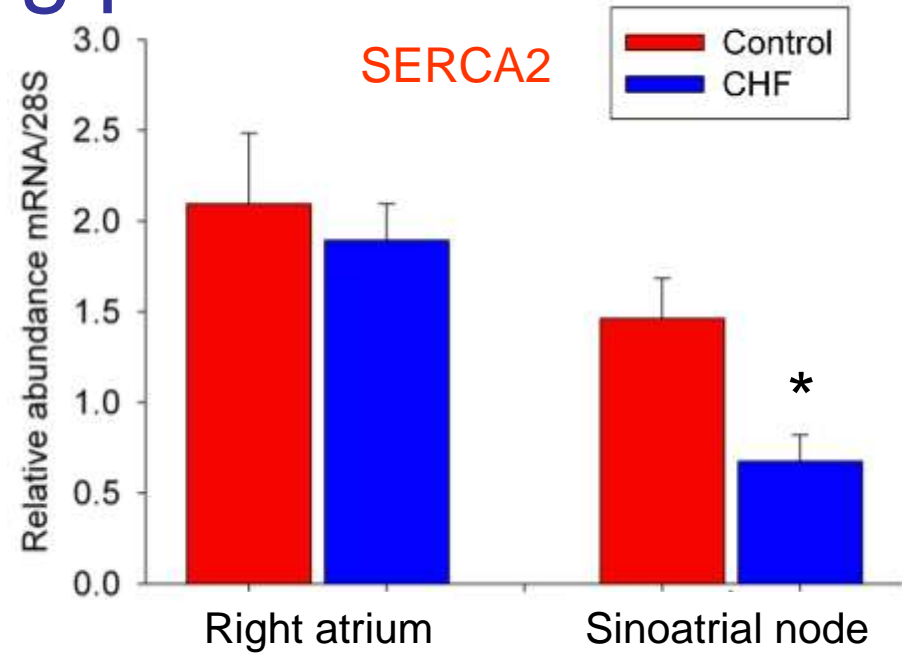
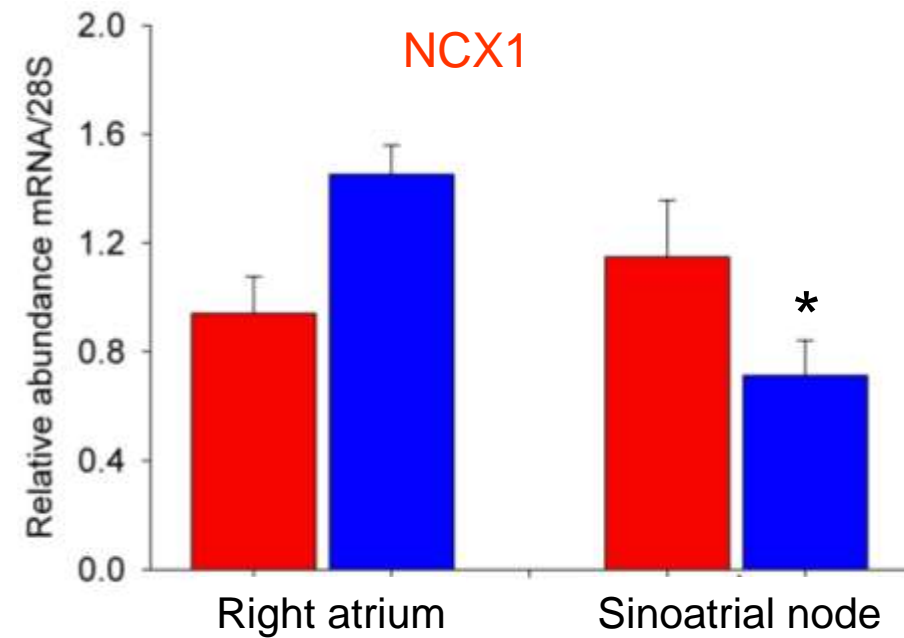
**Ca<sub>v</sub>L**



**Ca<sub>v</sub>T**

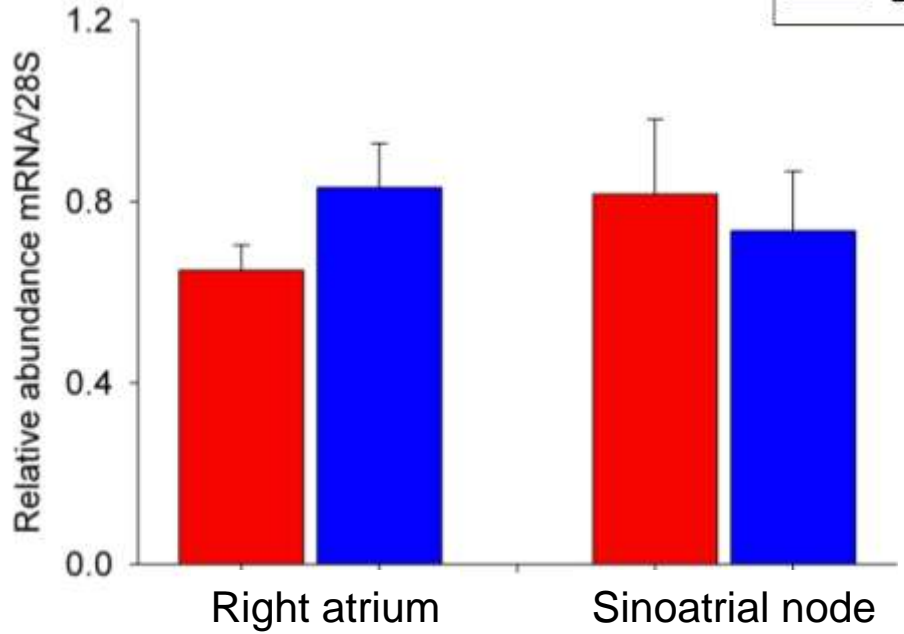
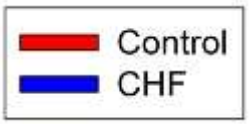


# Ca<sup>2+</sup>- handling proteins

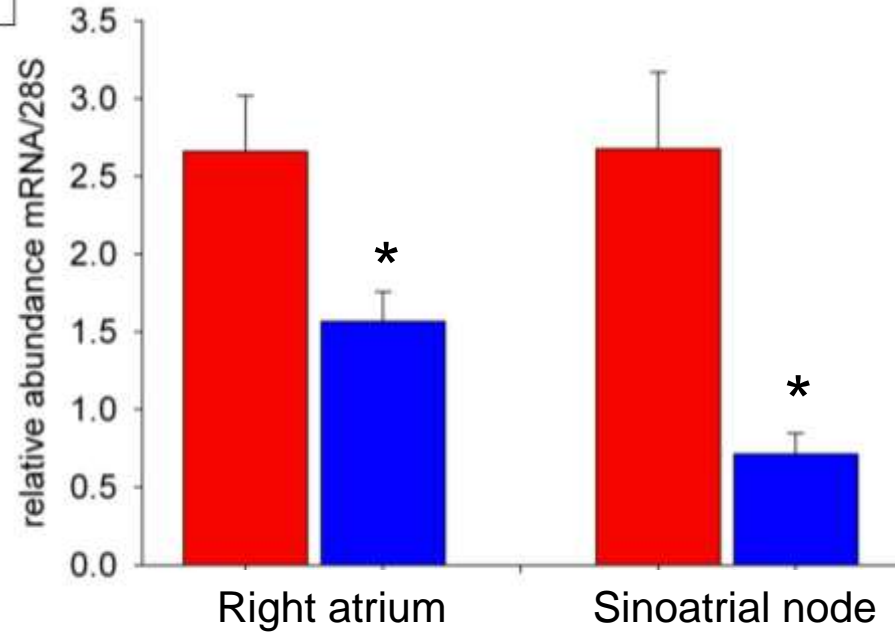


**K<sub>ATP</sub>**

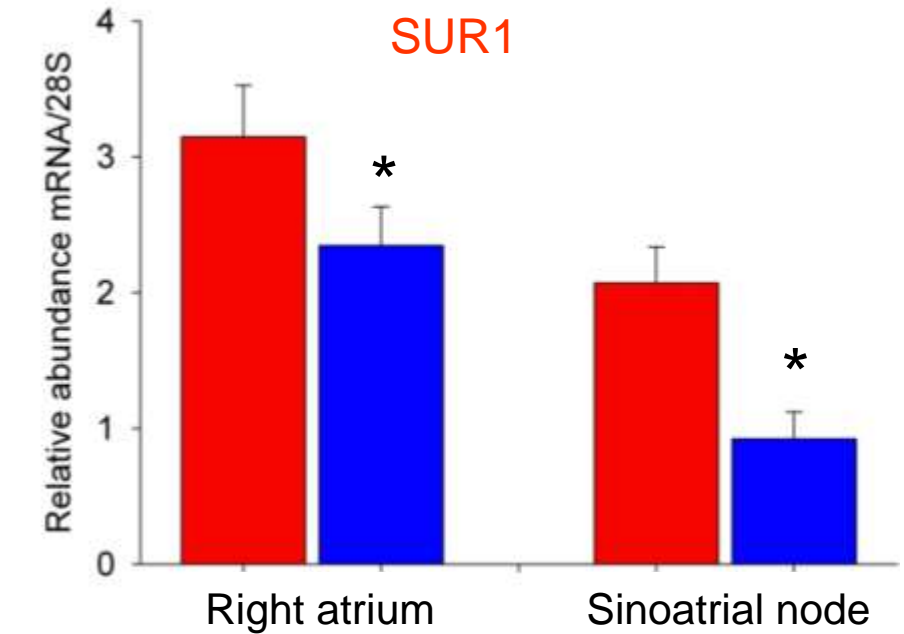
**K<sub>ir</sub>6.1**



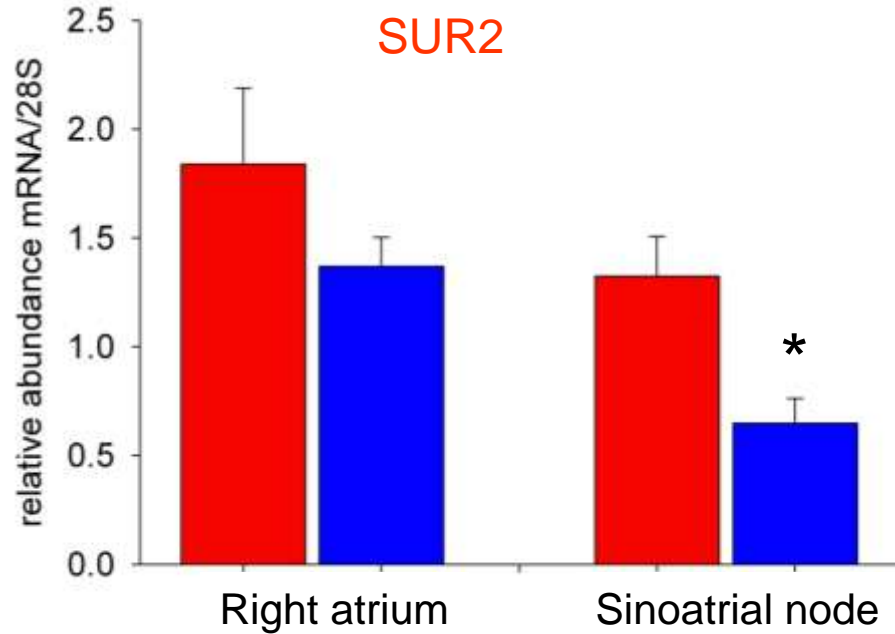
**K<sub>ir</sub>6.2**



**SUR1**



**SUR2**



| Ion channel         | Right ventricle | Right atrium | Sinoatrial node |
|---------------------|-----------------|--------------|-----------------|
| Tbx3                | -               | -            | ↓               |
| HCN1                | -               | -            | ↓               |
| HCN4                | -               | -            | ↓               |
| Ca <sub>v</sub> 1.2 | ↓               | -            | ↓               |
| Ca <sub>v</sub> 1.3 | -               | -            | ↓               |
| Ca <sub>v</sub> 3.1 | -               | -            | ↓               |
| NCX1                | ↑               | -            | ↓               |
| SERCA2a             | ↓               | -            | ↓               |
| RYR2                | -               | -            | ↓               |
| RYR3                | ↑               | -            | -               |
| Cx40                | -               | -            | ↑               |
| Cx43                | -               | ↑            | -               |
| Cx45                | -               | ↑            | -               |
| K <sub>v</sub> 1.4  | ↓               | -            | ↓               |
| K <sub>v</sub> 1.5  | ↓               | -            | ↓               |
| K <sub>ir</sub> 2.1 | -               | -            | -               |
| K <sub>ir</sub> 2.2 | -               | -            | ↓               |
| K <sub>ir</sub> 3.4 | -               | -            | -               |
| K <sub>ir</sub> 6.1 | ↑               | -            | -               |
| K <sub>ir</sub> 6.2 | ↓               | ↓            | ↓               |
| SUR1                | ↓               | ↓            | ↓               |
| SUR2                | -               | -            | ↓               |

| Ion channel         | Rat myocardial infarction | Rat pulmonary hypertension |
|---------------------|---------------------------|----------------------------|
| HCN1                | ↔                         | ↓                          |
| HCN4                | ↑                         | ↓                          |
| Ca <sub>v</sub> 1.2 | ↑                         | ↓                          |
| Ca <sub>v</sub> 1.3 | ↔                         | ↓                          |
| Ca <sub>v</sub> 3.1 | ↑                         | ↓                          |
| NCX1                | ↔                         | ↓                          |
| SERCA2a             | ↔                         | ↓                          |
| RYR2                | ↔                         | ↓                          |
| RYR3                | ↑                         | ↔                          |
| K <sub>v</sub> 1.2  | ↑                         | ↔                          |
| K <sub>v</sub> 1.4  | ↑                         | ↓                          |
| K <sub>v</sub> 1.5  | ↔                         | ↓                          |
| ERG                 | ↑                         | ↓                          |
| KvLQT1              | ↑                         | ↓                          |
| Kir2.4              | ↑                         | ↔                          |
| TWIK2               | ↑                         | ↔                          |
| Cx30.2              | ↑                         | ↓                          |

# Summary

- ♥ Approximately 100 ion channels are expressed in the heart. Regional differences in the expression of ion channels are responsible for regional differences of the action potentials in different parts of the heart
- ♥ Ion channels are dynamically expressed in the heart
- ♥ There are two pathways to SAN dysfunction in HF, one involving a downregulation of inward current-carrying channels and one involving an upregulation of outward current-carrying channels.



MANCHESTER  
1824



British Heart  
Foundation