MANCHESTER 1824

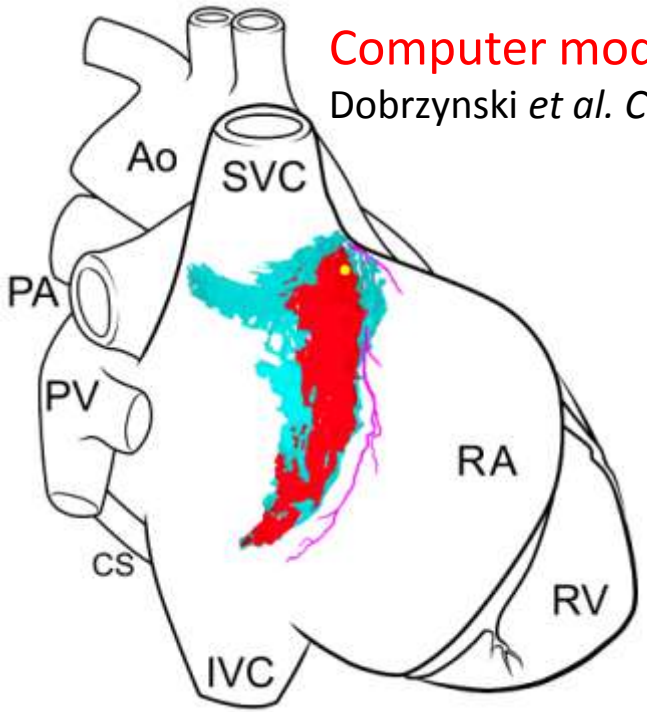
The University of Manchester

Arrhythmogenic molecular and structural remodelling

Professor Mark Boyett
Cardiovascular Medicine

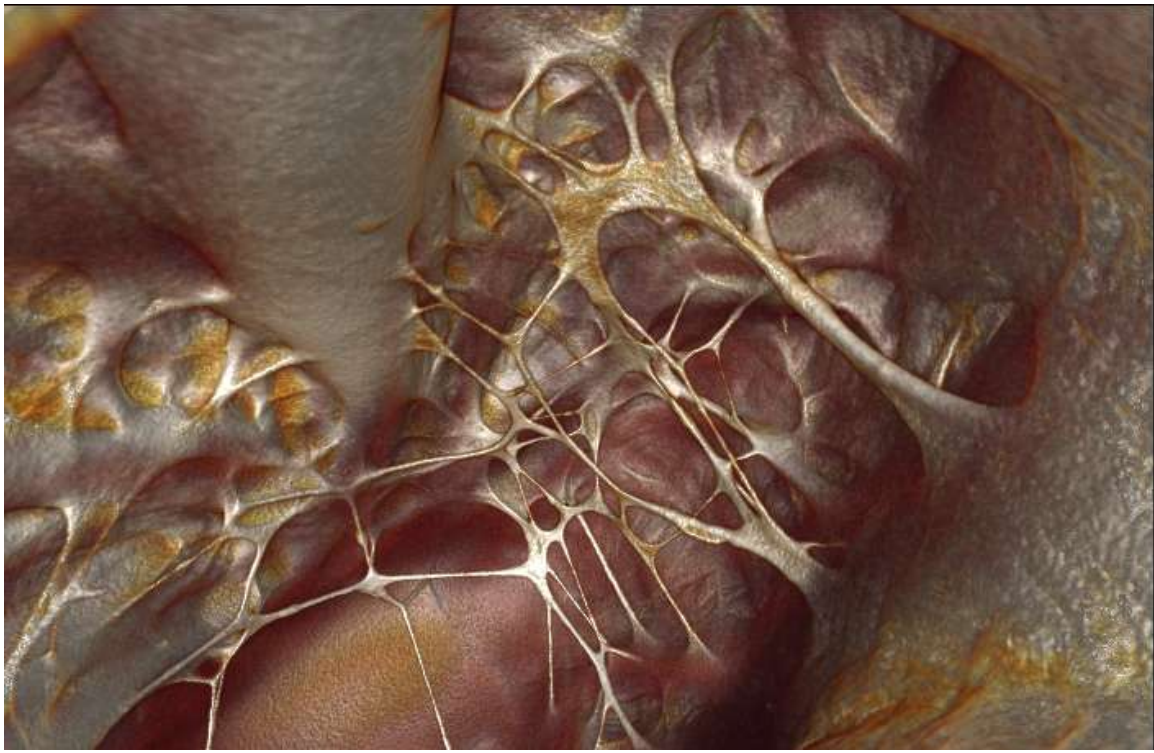
Computer model of rabbit SA node

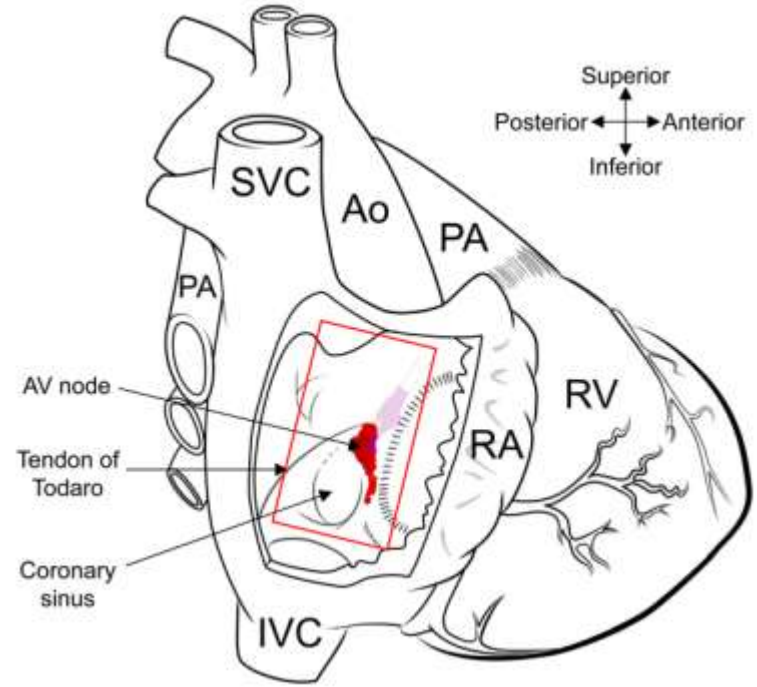
Dobrzynski *et al. Circulation Research* (2005)



CT image of rabbit Purkinje network

Stephenson and Jarvis (unpublished)





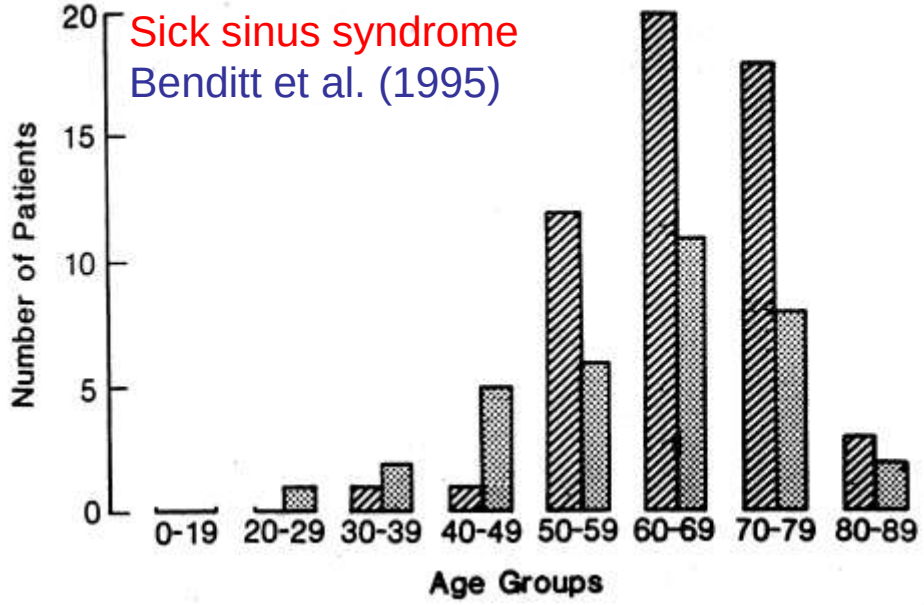
Computer model of rabbit AV node

Li *et al. Circulation Research* (2008)

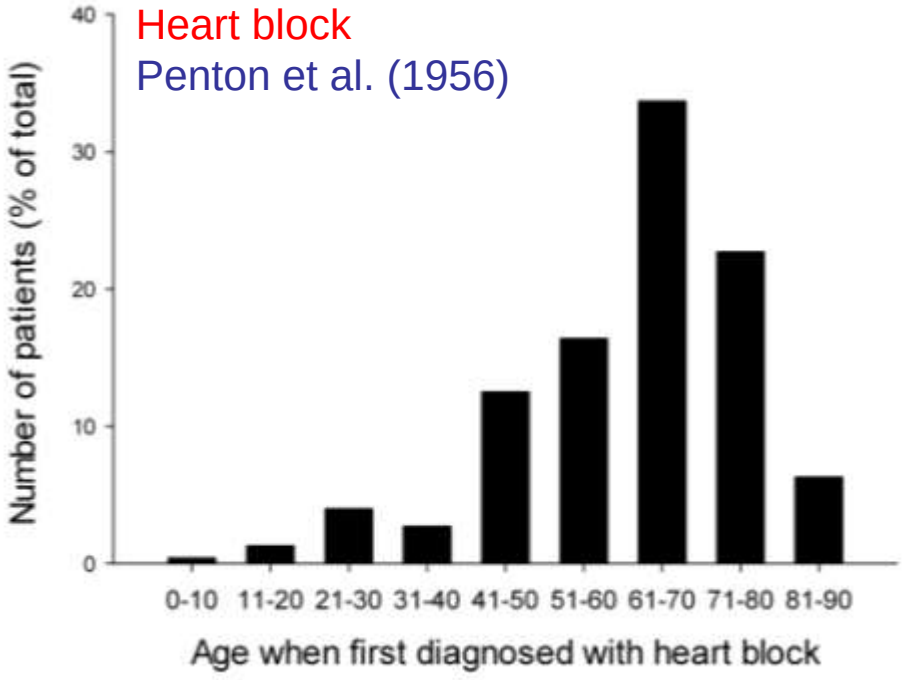
Ageing and heart failure and bradyarrhythmias

Cardiac conduction system disease is a disease of ageing

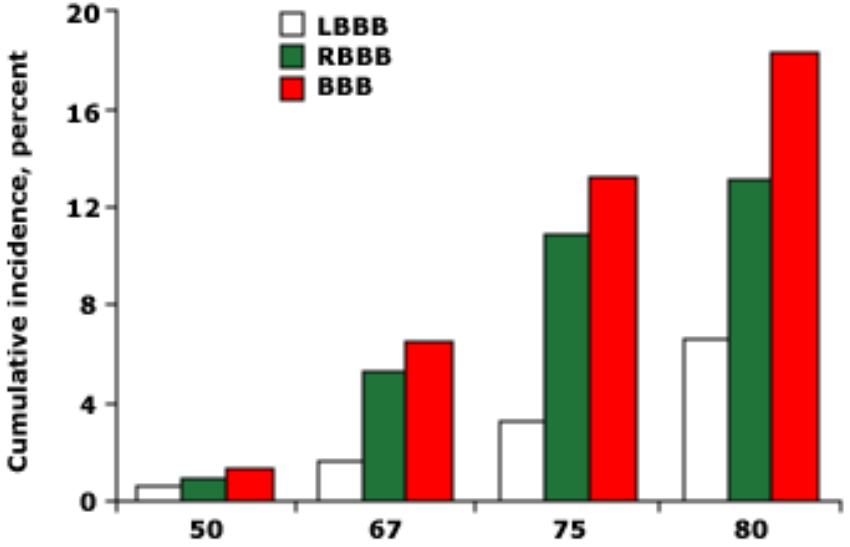
Sick sinus syndrome
Benditt et al. (1995)



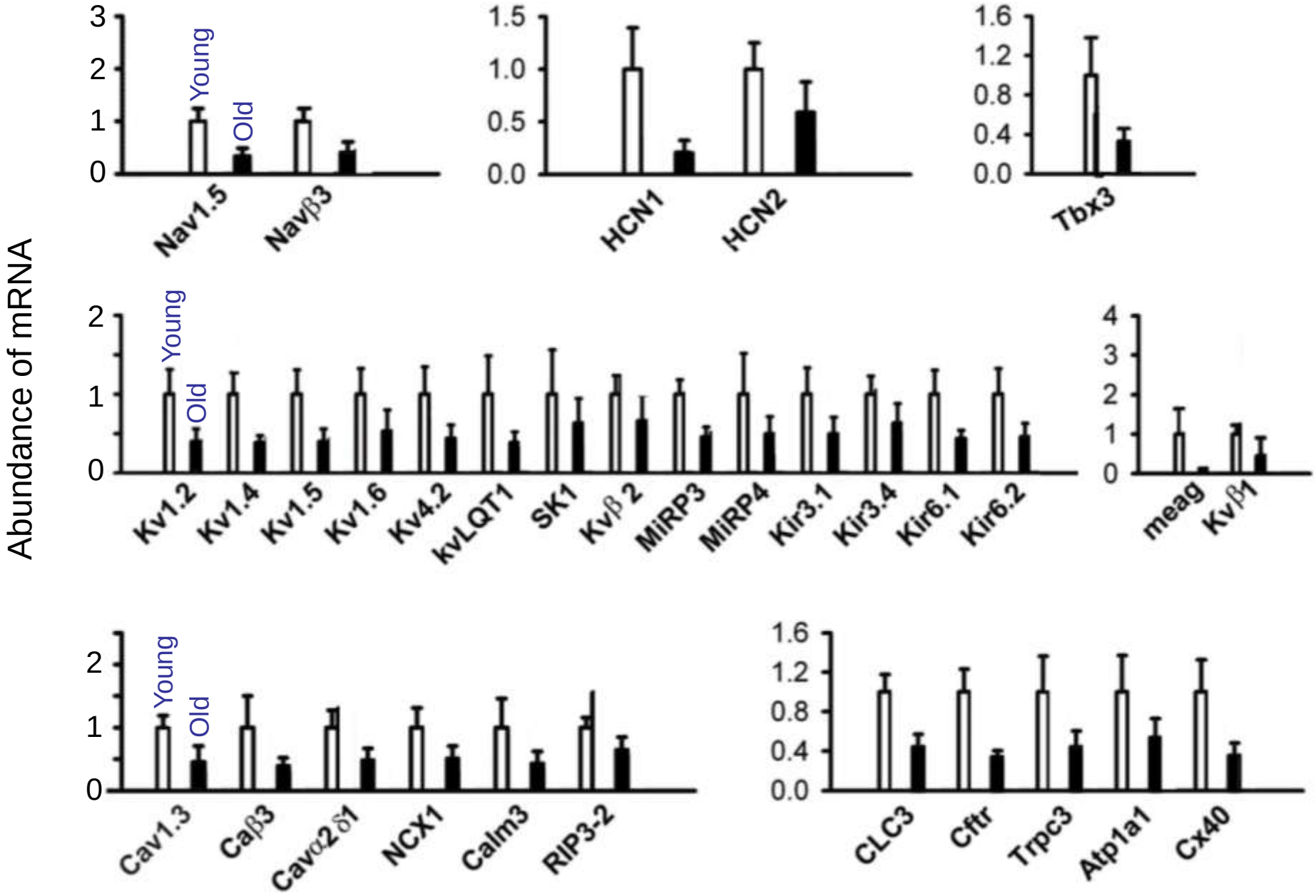
Heart block
Penton et al. (1956)



Bundle branch block
Eriksson et al. (1998)



Downregulation of many ion channels in sinoatrial node in ageing mouse



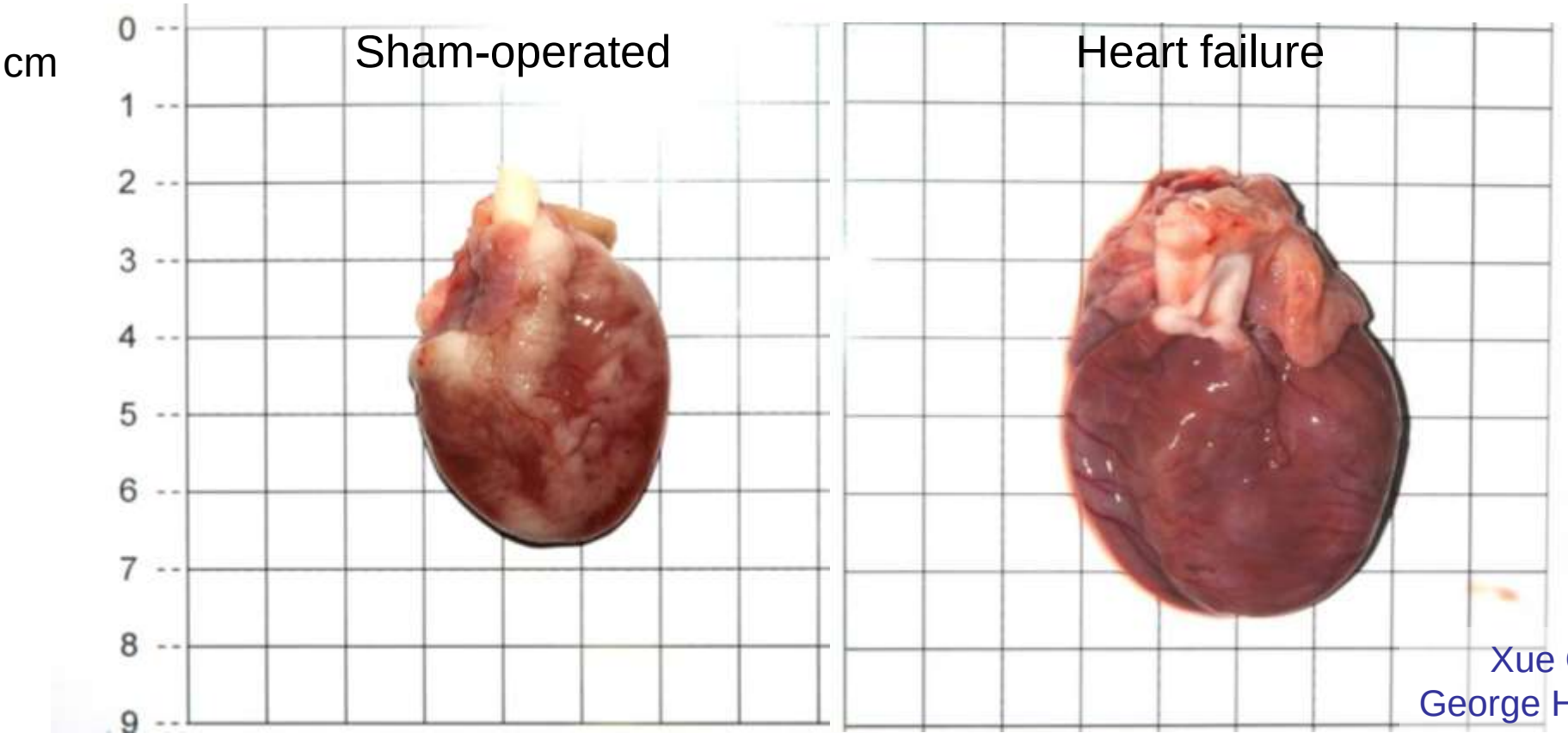
Xiao Hao, Ming Lei et al. *Circulation: Arrhythmia and Electrophysiology* (2011)

Heart Failure

- **Up to 80% of heart failure patients die of sudden cardiac death**
  (Uretsky and Sheahan. *J.Am.Coll.Cardiol.* 30:1589-1597, 1997)
- **A significant proportion of heart failure patients dying of sudden cardiac death die of bradyarrhythmias**
  (Stevenson et al. *Circulation* 88:2953-2961, 1993; Faggiano et al. *Am.J.Cardiol.* 87:655-1, 2001**)**
- **Heart failure causes dysfunction of the sinoatrial node**
  (Sanders et al. *Circulation* 110:897-903, 2004**)**
- **Heart failure may cause dysfunction of the atrioventricular node**
  (Gervais et al. *Eur.J.Heart Fail.* 11:699-705, 2009**)**
- **There is left bundle branch block in 26% of heart failure patients**
  (Padeletti *et al. J.Card.Fail.* 16:320-326, 2010**)**

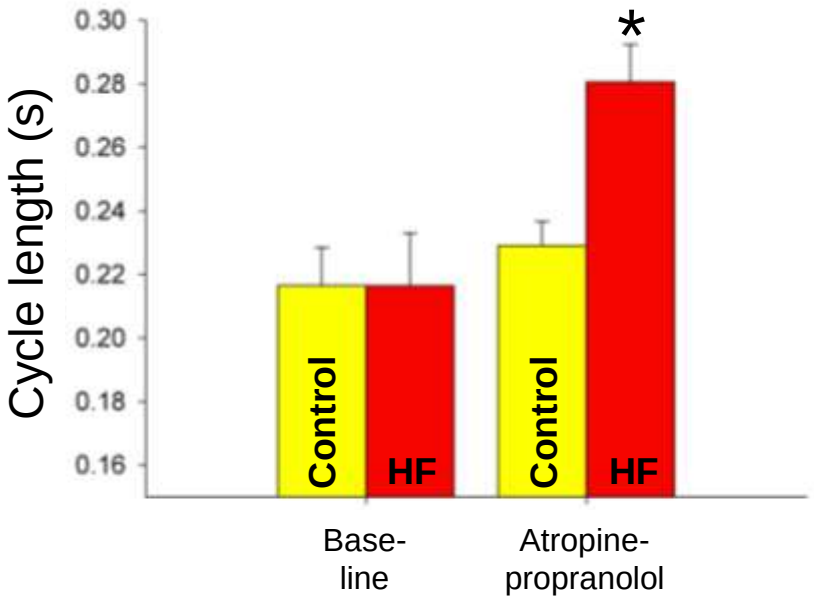
Rabbit model of volume and pressure overload

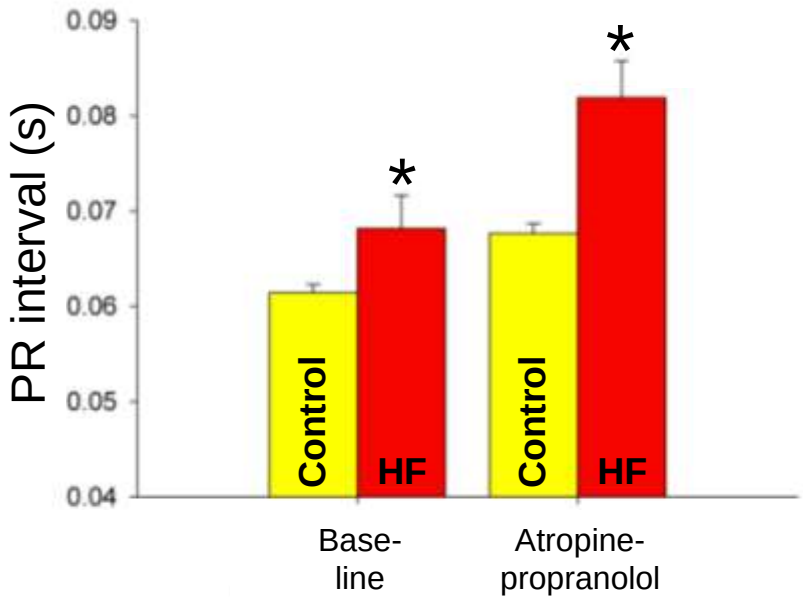
1) Destruction of aortic valve (week 0)
2) Banding of abdominal aorta (week 3)
3) Termination (week 8)

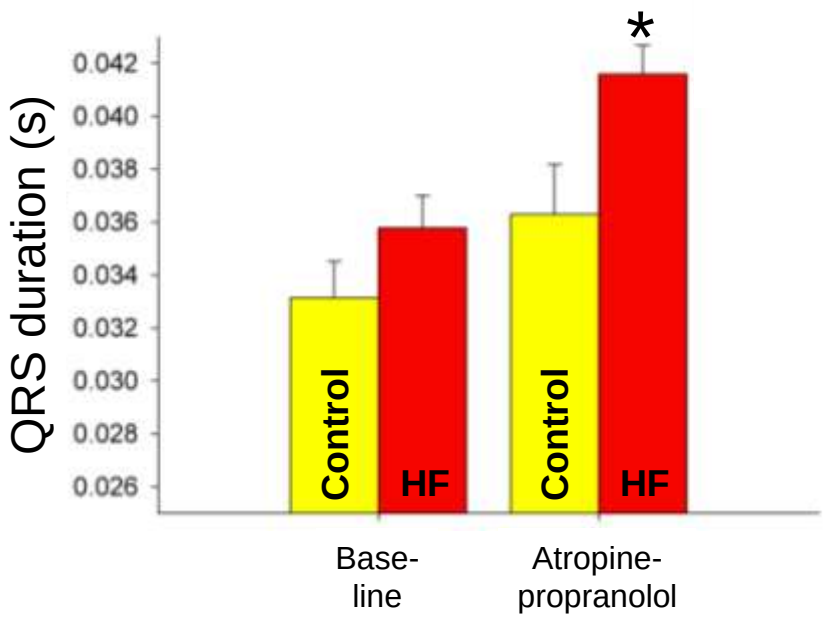


Xue Cai
George Hart

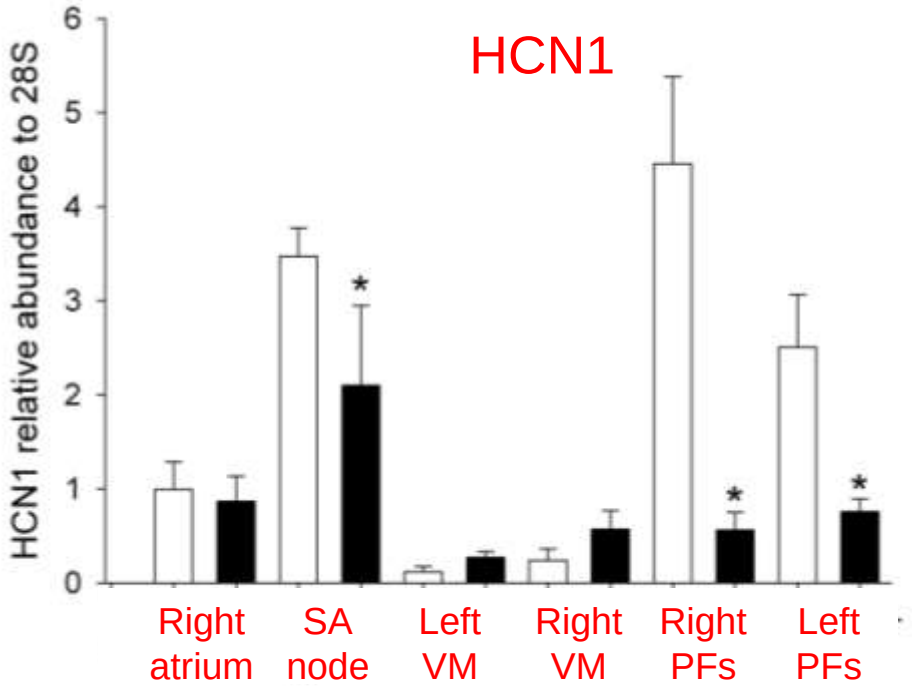
Dysfunction of CCS in rabbit model of volume and pressure overload

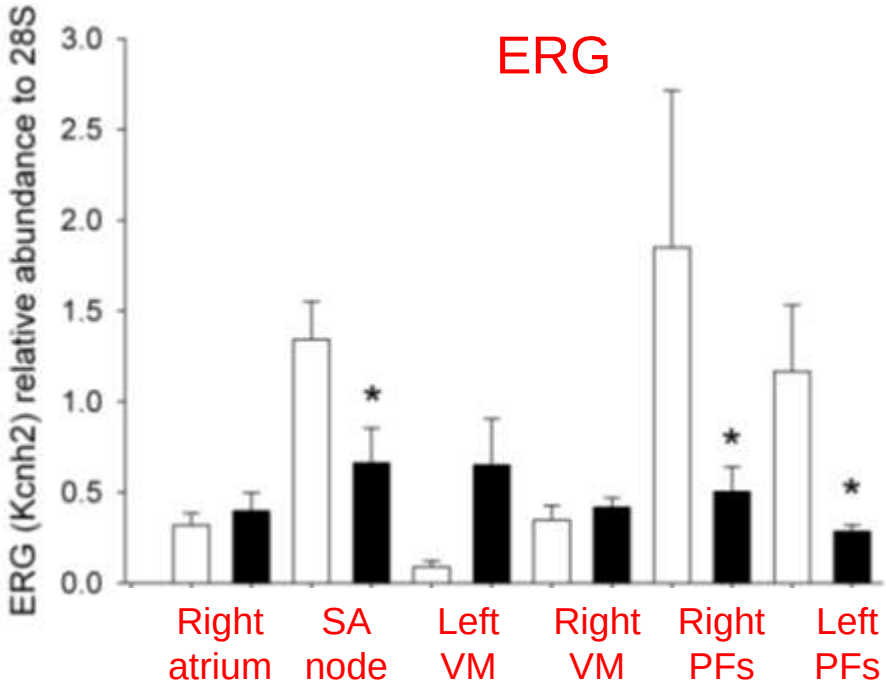


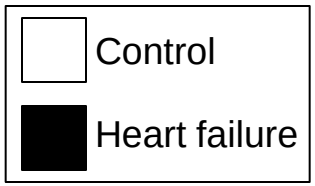


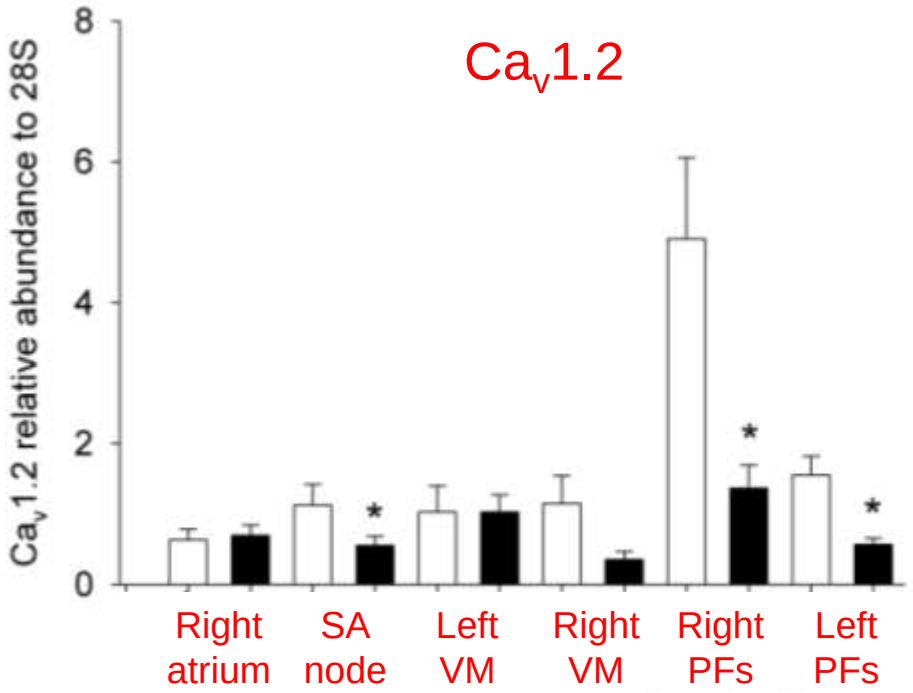


Oliver Monfredi
Xue Cai
George Hart









Joseph Yanni
Xue Cai
George Hart

CCS is peculiarly sensitive to heart failure

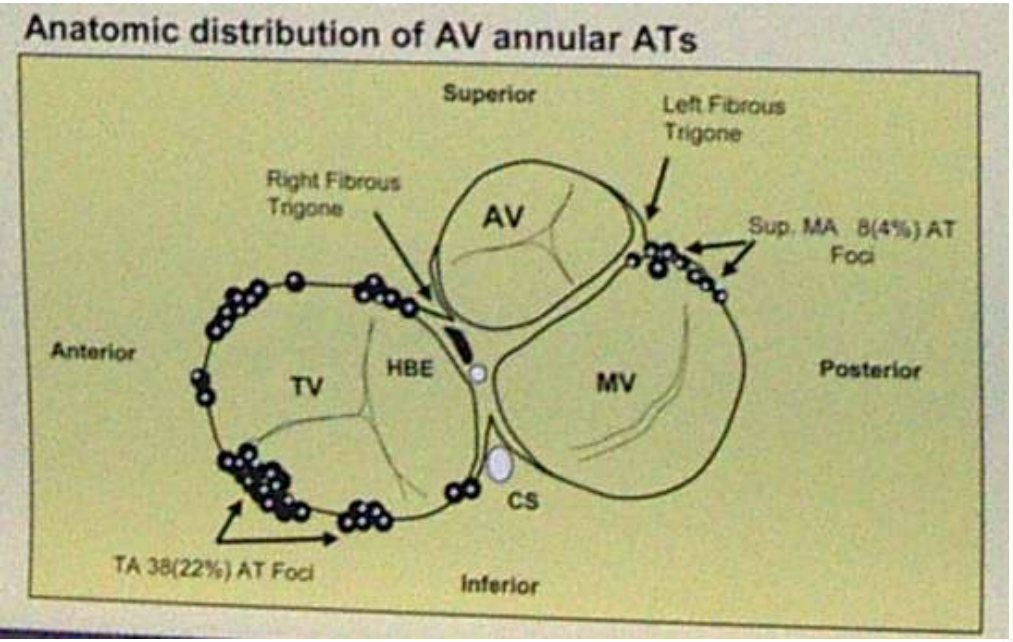
Sinoatrial node: 48%
Right atrium: 6%
Right ventricular Purkinje fibres: 33%
Left ventricular Purkinje fibres: 79%
Right ventricle: 3%
Left ventricle: 21%

	Sinoatrial node	Right atrium	Right ventricle	Left ventricle	Left Purkinje fibres	Right Purkinje fibres
HNC1	↓				↓	↓
HCN4	↓				↓	
$Na_v1.1$					↓	
$Na_v1.5$	↑			↑	↓	
$Ca_v1.2$	↓				↓	↓
$Ca_v1.3$	↓				↓	
$Ca_v3.1$		↑				
$K_v1.4$						
$K_v4.2$						
$K_v4.3$			↓			↓
KChIP2				↓		
$K_v1.5$	↓				↓	↓
ERG	↓				↓	↓
K_vLQT1	↓				↓	↓
minK						↓
$K_{ir}2.1$	↓			↑	↓	
$K_{ir}2.2$	↓				↓	
$K_{ir}3.1$					↓	
$K_{ir}6.2$					↓	↓
SUR2a		↑		↑	↓	
Na/K ATPase α1	↓					
Cx40					↓	
Cx43					↓	
NCX1	↓			↑	↓	
RYR2				↑	↓	
RYR3	↓				P↓	P↓
SERCA2	↓				↓	
Tbx3	↓				↓	↓
BNP					↓	↓
Col3					↑	
NFM	↓				↓	
β MCH				↑	↓	
NHE1					↓	
	16/33	2/33	1/33	7/33	26/33	11/33

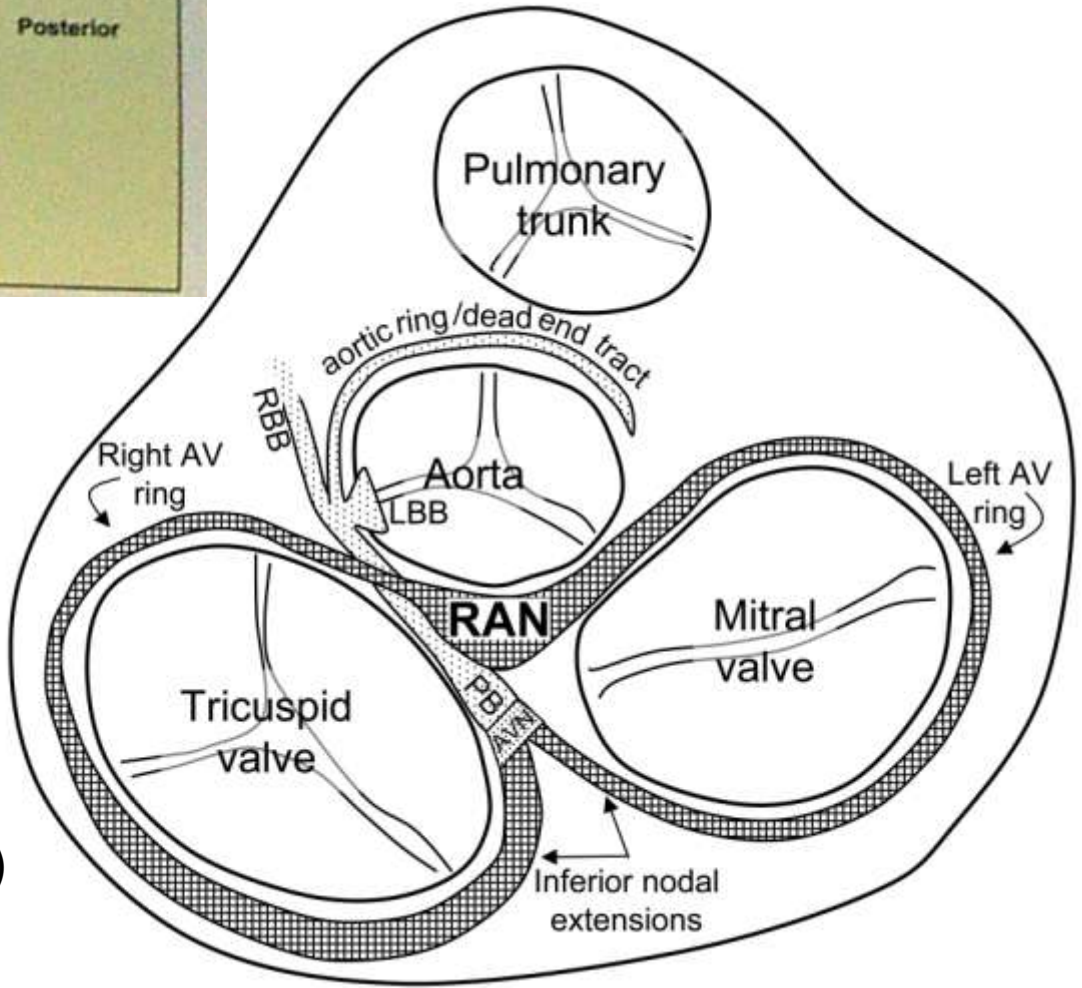
Joseph Yanni
Xue Cai
George Hart

Arrhythmias and vestiges of the cardiac conduction system

Atrioventricular ring tissue and focal atrial tachycardia



Kistler *et al.*



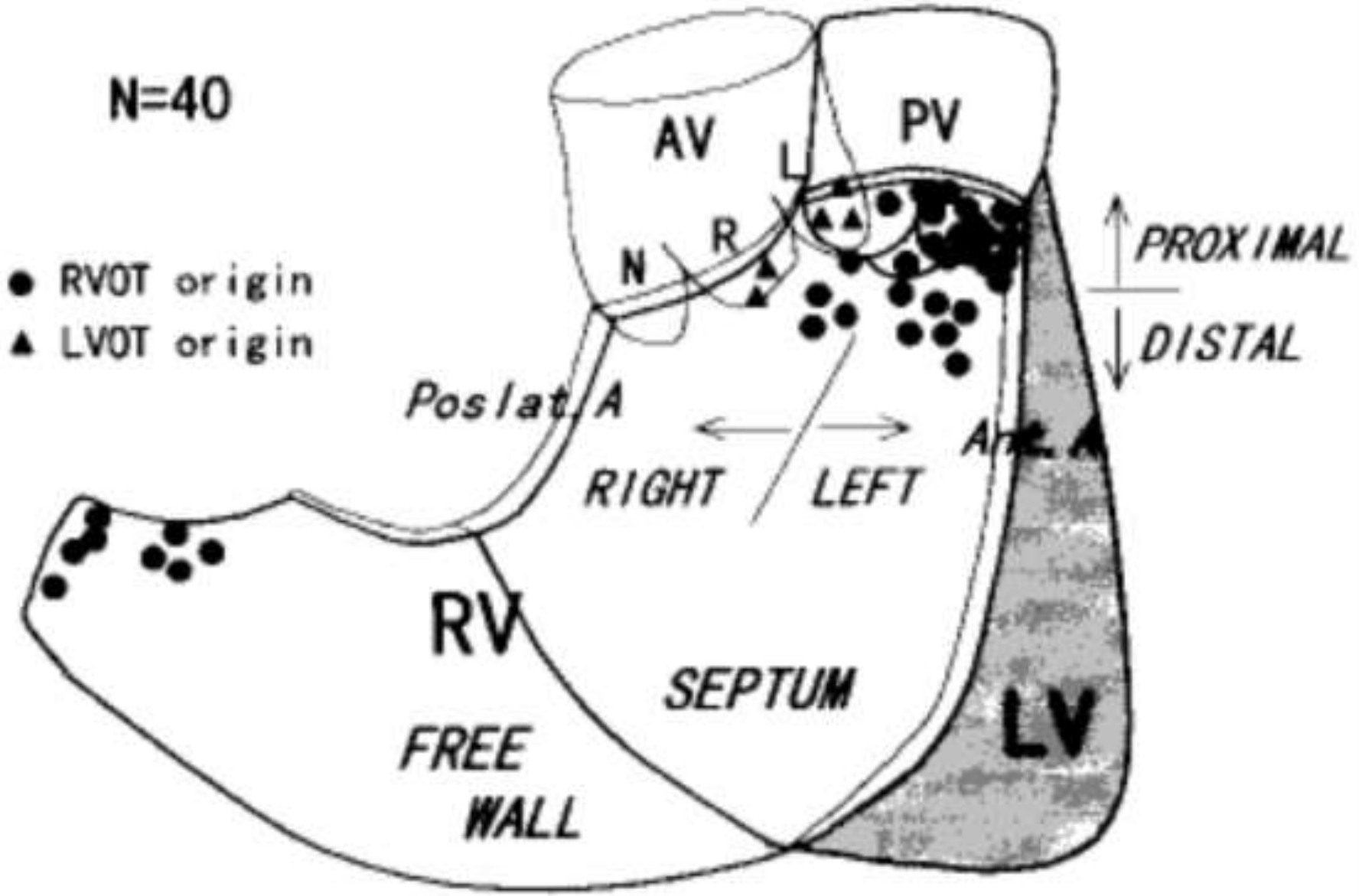
Yanni *et al. Heart Rhythm* (2009)
Atkinson *et al.* (unpublished)

Right ventricular outflow tract

High burden of arrhythmias:

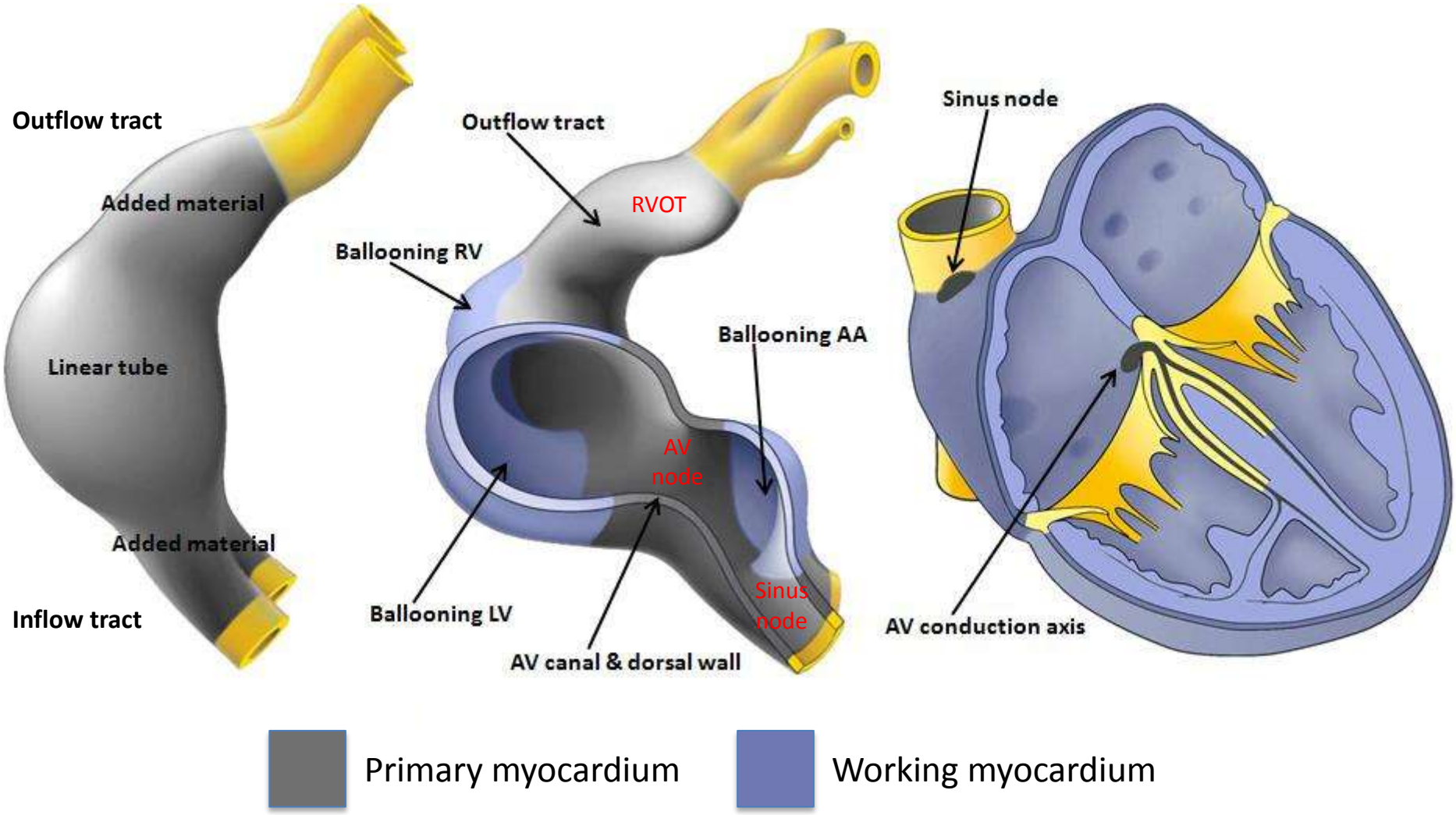
- Right ventricular outflow tract VT
- Brugada syndrome
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy
- Catecholaminergic polymorphic VT

Outflow tract tachycardias

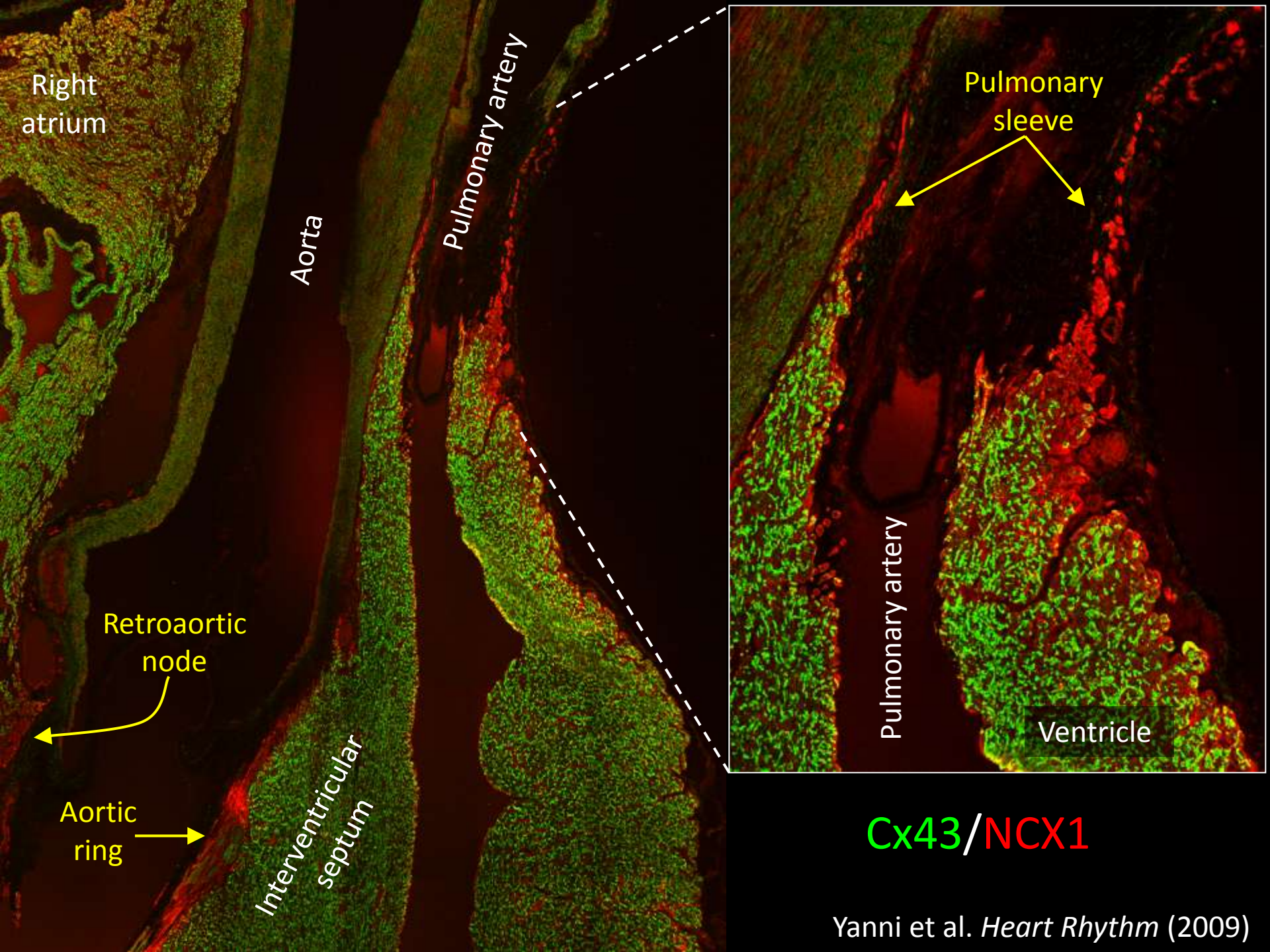


Kamakura *et al*. *Circulation* (1998)

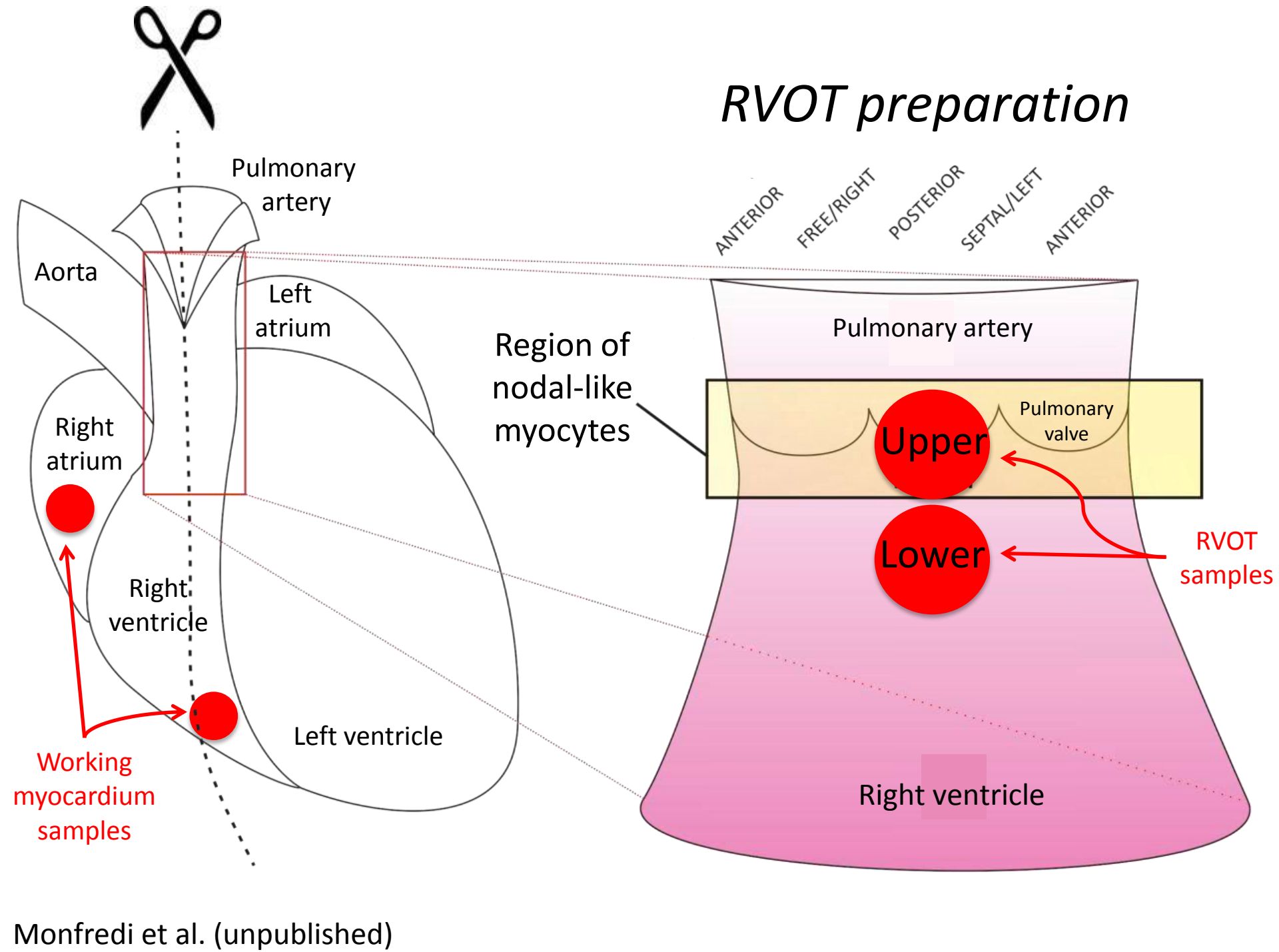
Outflow tract has same embryonic origin as the sinoatrial and atrioventricular nodes



From Moorman and Anderson

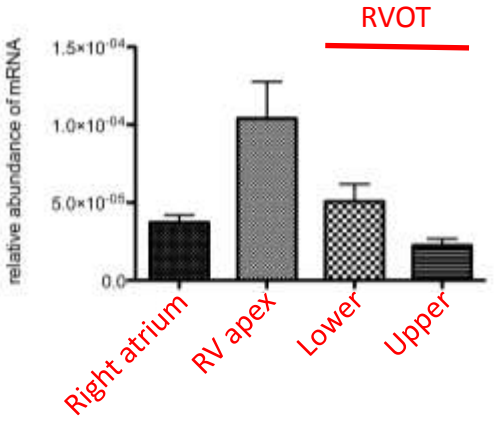


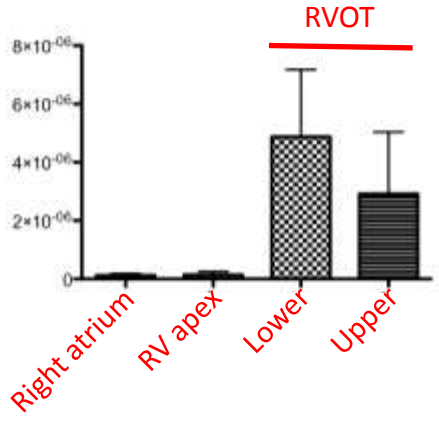
Yanni et al. *Heart Rhythm* (2009)



Monfredi et al. (unpublished)

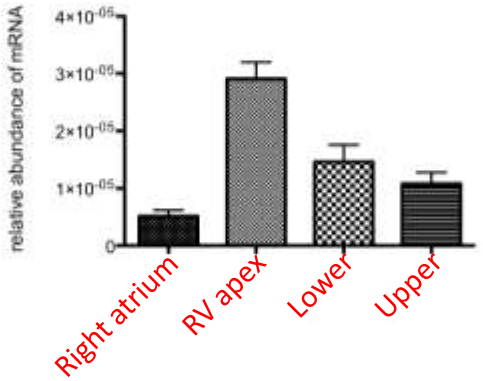
$Na_v1.5$

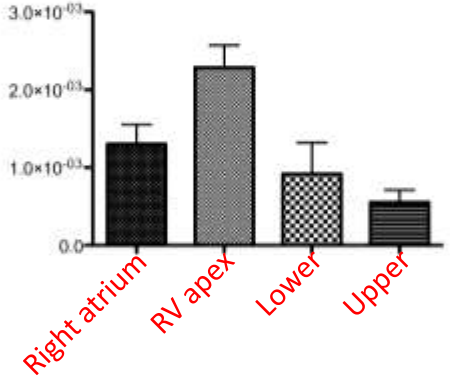




$Ca_v1.3$

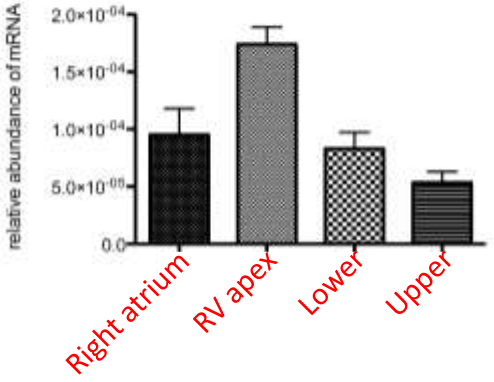
$K_{ir}2.1$

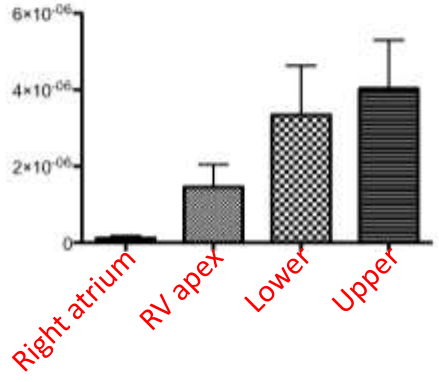




SERCA2

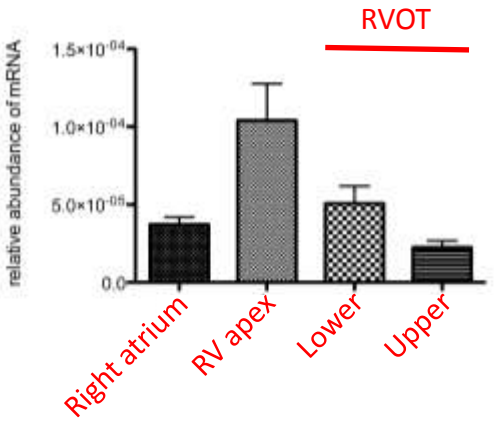
Cx43





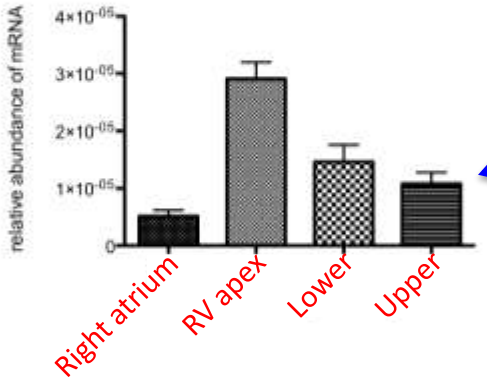
α3 Na^+-K^+ pump

$Na_v1.5$



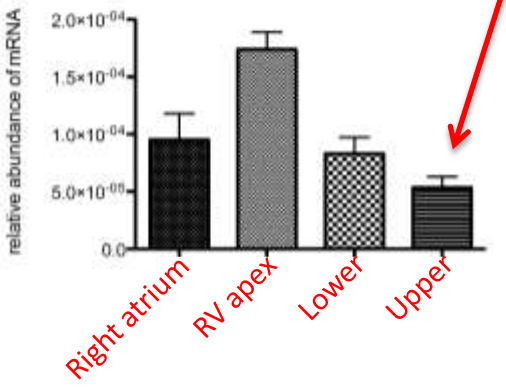
Slowly conducting action potential - will facilitate reentry

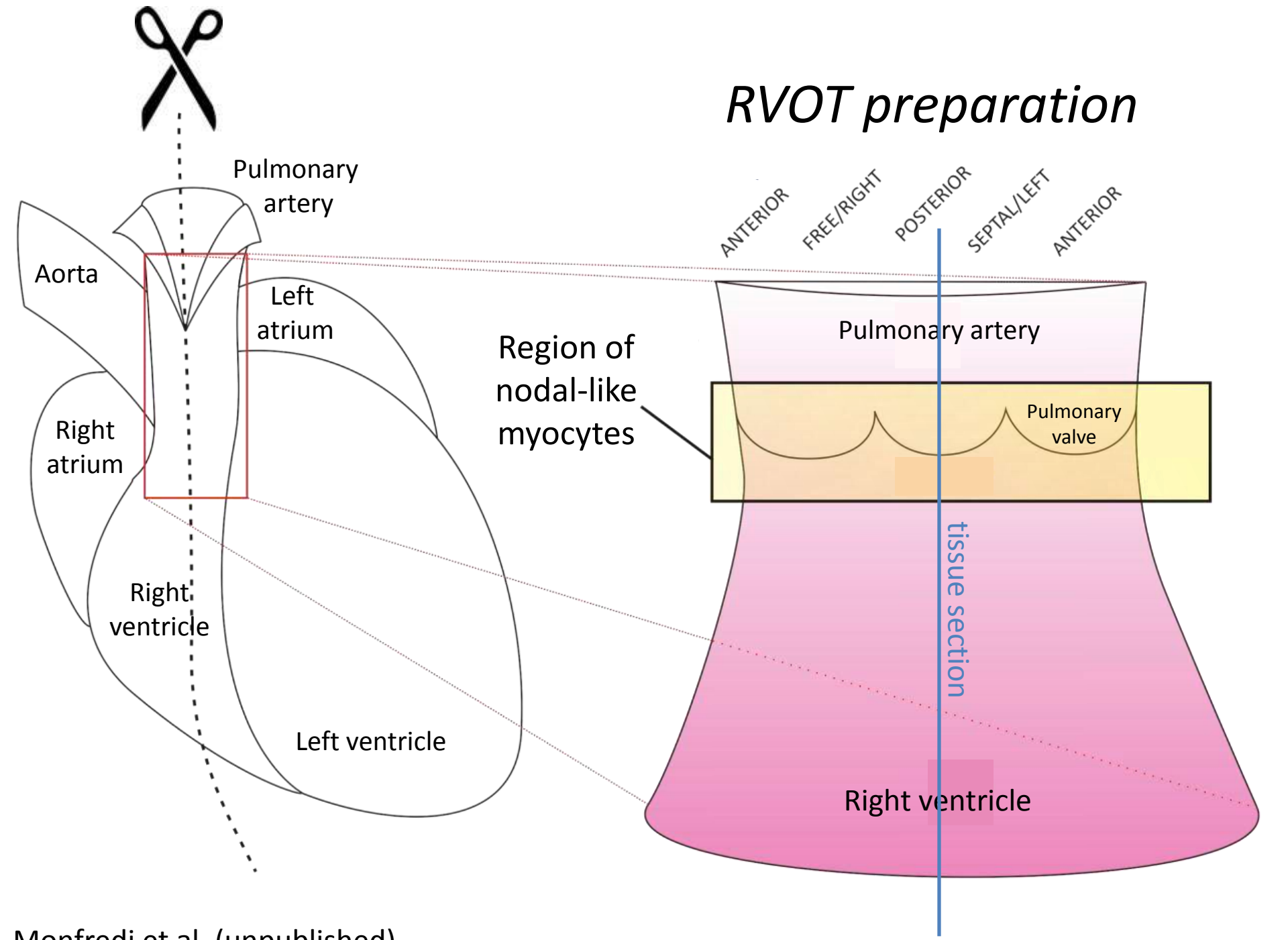
$K_{ir}2.1$



Unstable resting potential - will facilitate ectopic pacemaker activity

Cx43

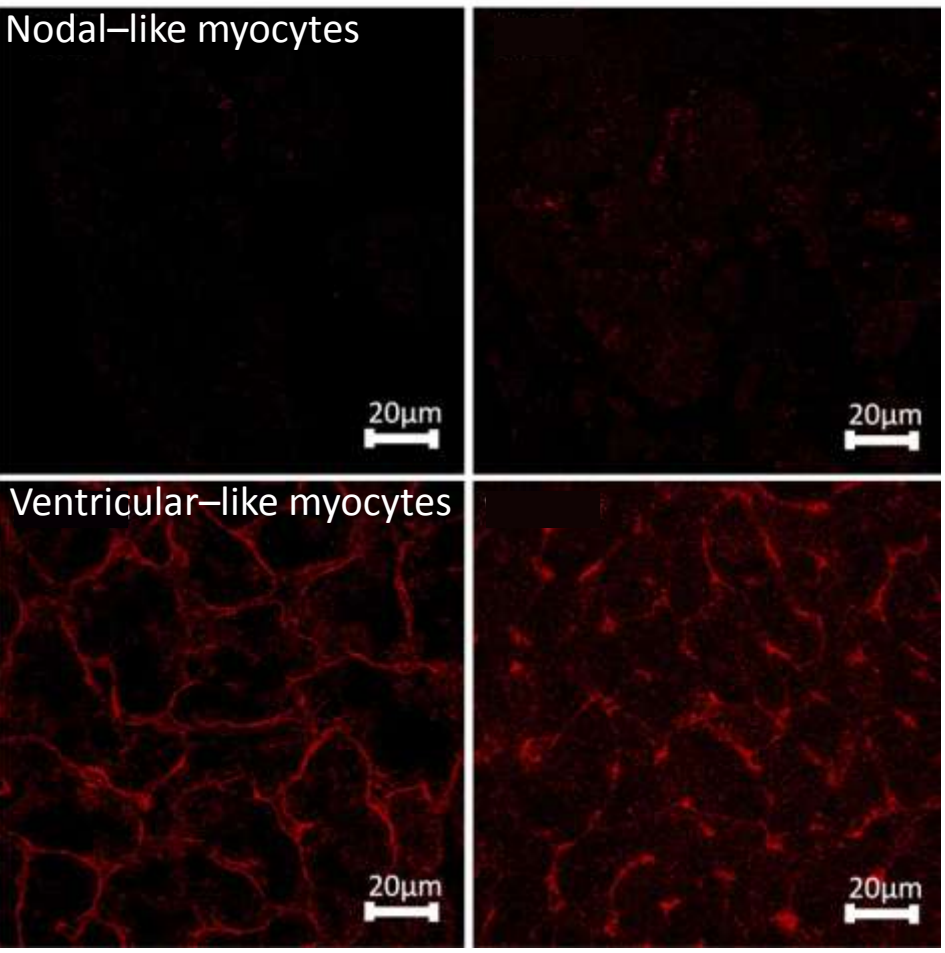


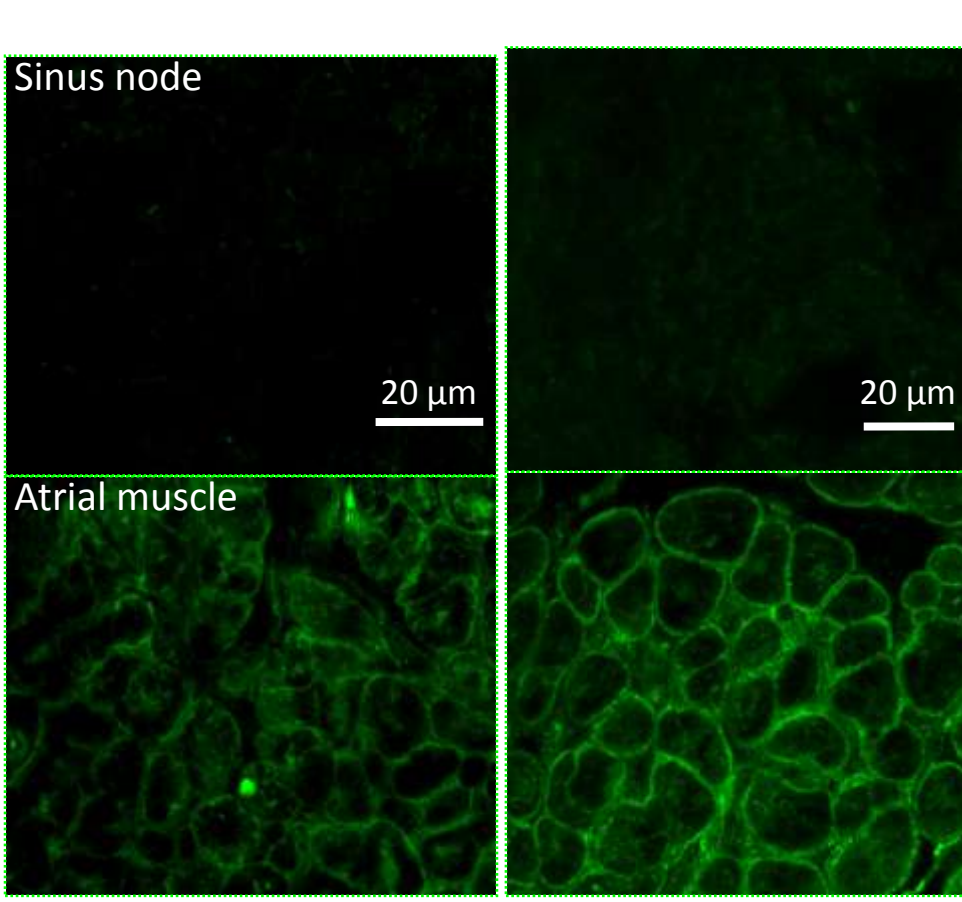


Monfredi et al. (unpublished)

Monfredi *et al.* (unpublished)
- Rat RVOT

Dobrzynski *et al. Circulation* (2007)
– Human sinus node





RVOT is different from the ordinary ventricular muscle

		Right ventricular apex (vs right atrium)	RVOT1 (vs right ventricular apex)	RVOT2 (vs right ventricular apex)
Na^+ channels	$Na_v1.1$	↑	↓	↓
	$Na_v1.5$	↑		↓
Ca^{2+} channels	$Ca_v1.2$	↑		
	$Ca_v3.1$	↓		
	$Ca_v\alpha2\delta1$	↑	↓	
	$Ca_v\beta2$	↑		↓
HCN channels	HCN2	↑		
	HCN4		↓	
Transient outward K^+ channels	$K_v1.4$			↓
	$K_v4.2$	↑		
	KChIP2	↑		
Outward rectifying K^+ channels	$K_v2.1$	↑		↓
	K_vLQT1	↑	↓	↓
Inward rectifying K^+ channels	$K_{ir}2.1$	↑	↓	↓
	$K_{ir}2.2$			↓
	$K_{ir}3.1$	↑		
	$K_{ir}3.4$	↓	↓	↓
	$K_{ir}6.2$	↑		↓
	SUR1			↓
Other K^+ channels	SK1	↑		
	SK2	↑		
	SK3	↑		
	TRPC	↑		
Cl^- channels	CFTR	↓		
	CLCN2	↑		
	CLCN3	↑		
Ca^{2+}-handling proteins	NCX1	↑		↓
	SERCA2	↑		↓
	PMCA1	↑		↓
	Phospholamban	↑	↓	↓
	RYR2			↓
	Type 2 IP_3 receptor	↑		
	Type 3 IP_3 receptor	↑		
	Calsequestrin 2			↓
	Ca^{2+}-calmodulin protein kinase II	↑		↓

		Right ventricular apex (vs right atrium)	RVOT1 (vs right ventricular apex)	RVOT2 (vs right ventricular apex)
Connexins	Cx43	↑	↓	↓
	Cx40	↑		
	Cx45	↑		
Na^+-K^+ pump	Na^+-K^+ pump α_1 subunit		↓	↓
	Na^+-K^+ pump α_2	↑		
	Na^+-K^+ pump α_3			↑
	Na^+-K^+ pump β_1 subunit	↑		↓
Receptors	M_2 muscarinic receptor		↓	↓
	Adenosine A_1 receptor	↑		
	α_{1A} adrenergic receptor	↑		↓
	α_{1B} adrenergic receptor	↑		
	α_{1D} adrenergic receptor	↑		
Intracellular signalling	Ca^{2+}-calmodulin phosphodiesterase 1B	↑		
	Phosphodiesterase 2A	↑		↓
	Phosphodiesterase 3B	↑		↑
	Adenylate cyclase 4	↑		
	Adenylate cyclase 5	↑		↓
	cAMP protein kinase α	↑		↓
	cAMP protein kinase β	↑		
	cAMP protein kinase Type Iα	↑		↓
	cAMP protein kinase Type IIα	↑		↓
	cAMP protein kinase Type IIβ			↓
Miscellaneous	Collagen 1	↑		↓
	Collagen 3	↑		
	Tbx3	↑		
	TGF beta	↑		
	ANP	↓		
	BNP	↓		

Summary

- In ageing and heart failure, there are bradyarrhythmias resulting from failure of the cardiac conduction system
- The bradyarrhythmias are likely caused by a widespread remodelling of ion channels etc.
- The atrioventricular ring tissues and outflow tract share a common embryological origin with nodal tissue
- In terms of ion channels, the atrioventricular ring tissues and outflow tract are nodal-like and this may explain their arrhythmogenic potential