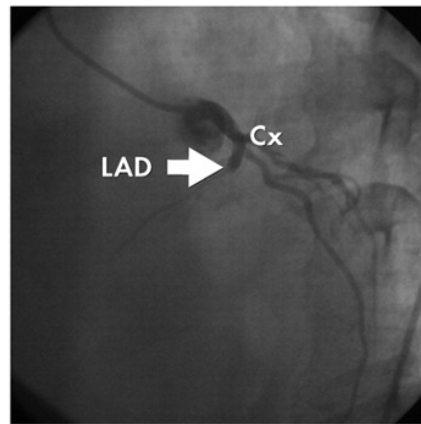


**Modulation of Gap Junctional Coupling as an
Anti-Arrhythmic Strategy to
Prevent Reperfusion Arrhythmias**

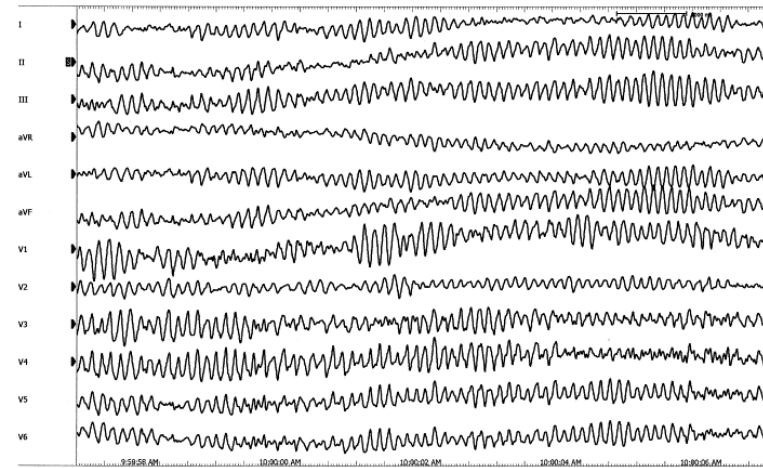
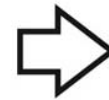
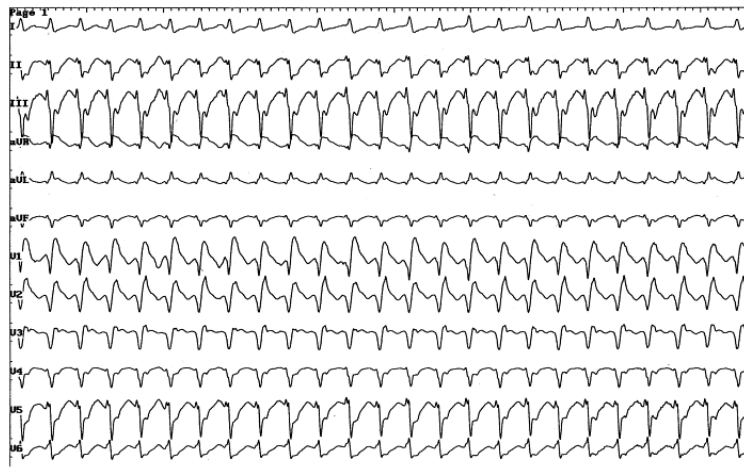
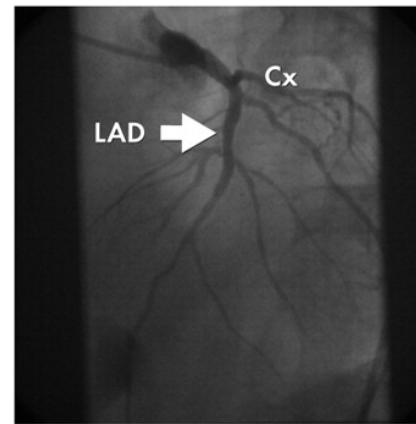
Fu Siong Ng, AR Lyon, RA Chowdhury, E Dupont, NS Peters

Reperfusion Ventricular Arrhythmias

Pre-PCI (TIMI 0 Flow)



Post-PCI (TIMI 3 Flow)



Reperfusion VT/VF: 133/3,065 (4.3%) Primary PCI cases (Mehta *et al*, JACC 2004)

Reperfusion Ventricular Fibrillation

THE EFFECT OF CORONARY OCCLUSION ON MYOCARDIAL CONTRACTION¹

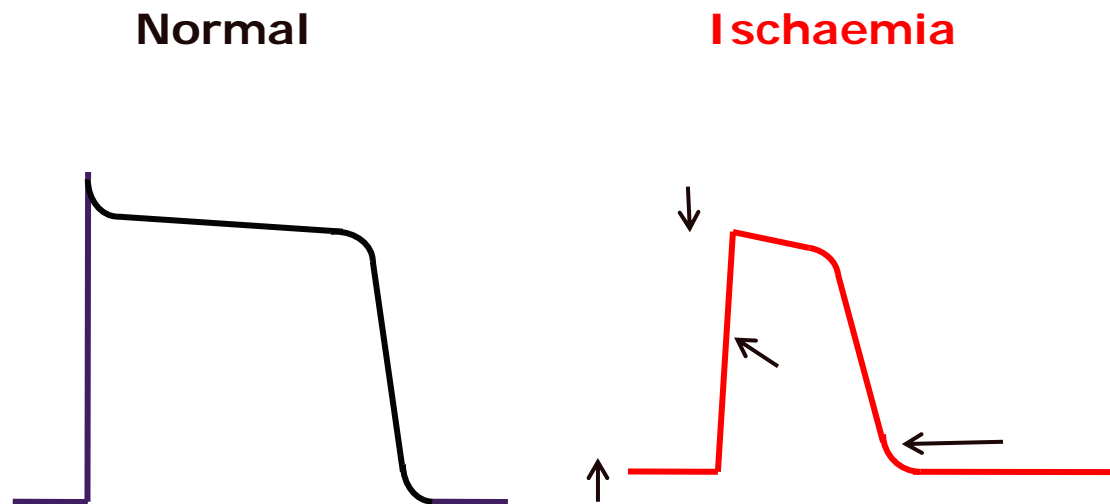
ROBERT TENNANT² AND CARL J. WIGGERS

From the Department of Physiology, Western Reserve University Medical School, Cleveland, O.

Received for publication March 22, 1935

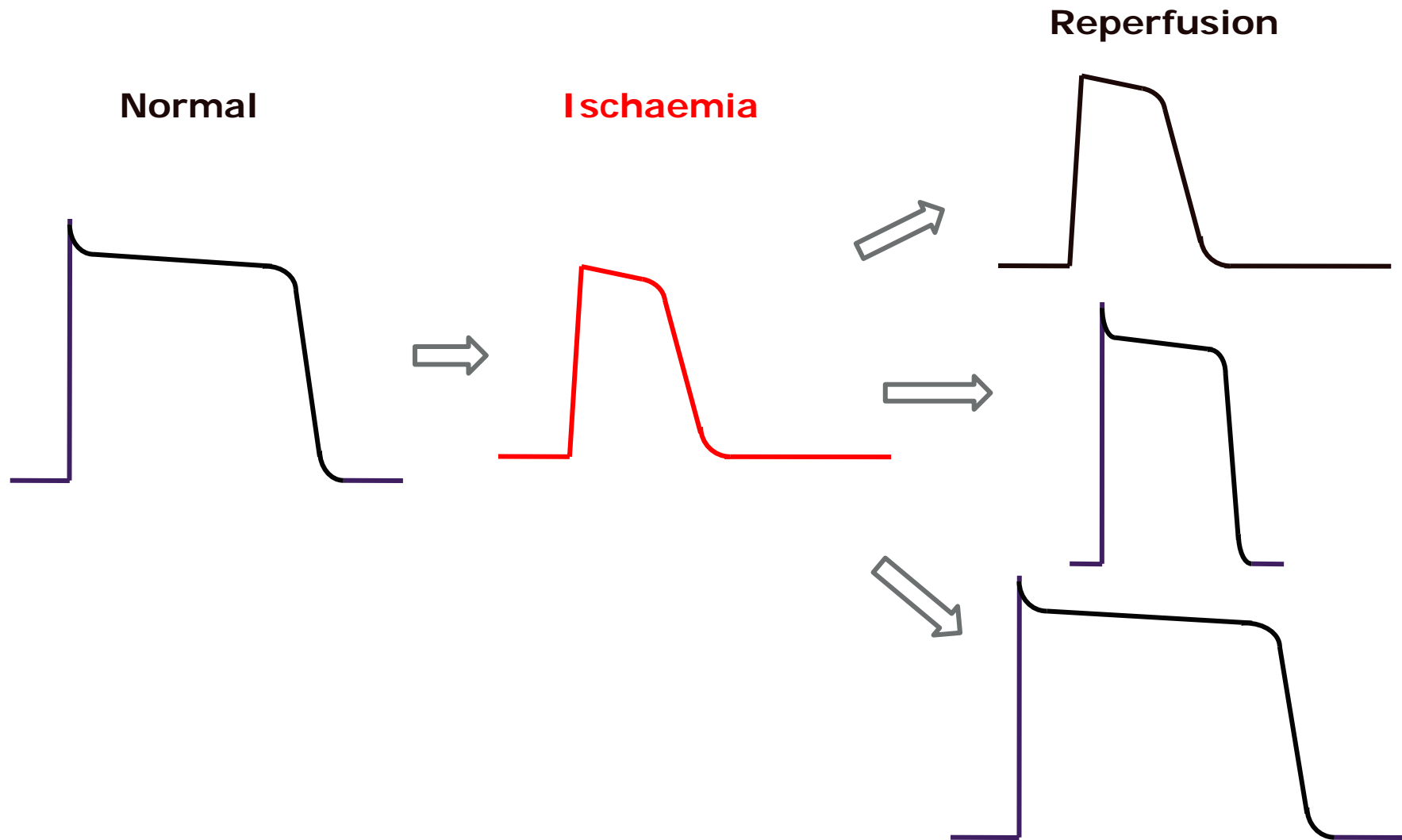
EXP. NO.	DURATION OF LIGATION	TIME INTERVAL BETWEEN LIGATION AND FAILURE	RECOVERY	TIME INTERVAL BETWEEN RELEASE AND RECOVERY	REMARKS
1	1 min. 40 sec.	50 sec.	Yes	45 sec.	Without fibrillation
2	2 min. 20 sec.	50 sec.	Yes	30 sec.	Without fibrillation
3	2 min. 30 sec.	35 sec.	No		<u>Fibrillation</u> without revival
4	2 min. 30 sec.	20 sec.	No		<u>Fibrillation</u> without revival
5	3 min.	75 sec.	No		<u>Fibrillation</u> without revival
6	3 min.	150 sec.	No		<u>Fibrillation</u> without revival
7	4 min.	55 sec.	Yes	11 min.	<u>Fibrillation</u> revived
8	4 min. 44 sec.	90 sec.	Yes	1 min. 40 sec.	Without fibrillation
9	4 min. 45 sec.	70 sec.	Yes	14 min.	<u>Fibrillation</u> revived
10	10 min. 30 sec.	40 sec.	Yes	5 min. 30 sec.	<u>Fibrillation</u> revived
11	23 min.	65 sec.	Partial	8 min.	<u>Fibrillation</u> revived
12	45 min.	150 sec.	No		Heart beat for 2 hours after release
13	46 min.	80 sec.	No		<u>Fibrillation</u> without revival
14	1 hr. 50 min.	31 sec.	No		<u>Fibrillation</u> 14 minutes after release and revived for 8 minutes

Heterogeneous Restoration Of Action Potentials in Reperfused Myocardium

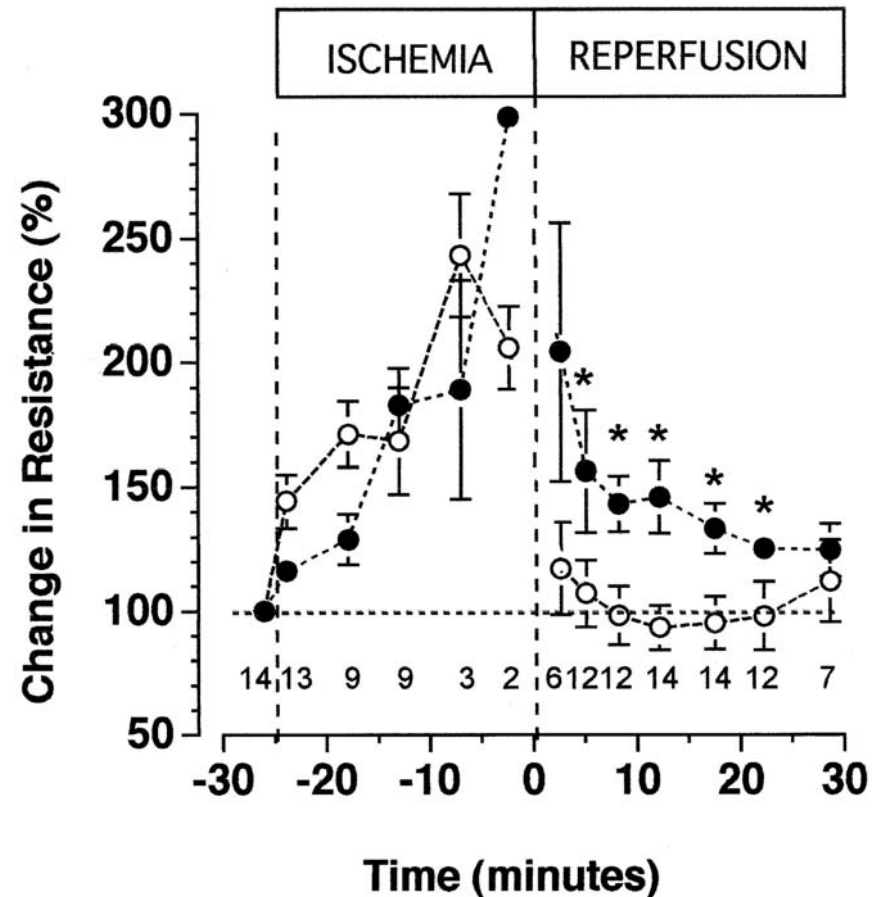
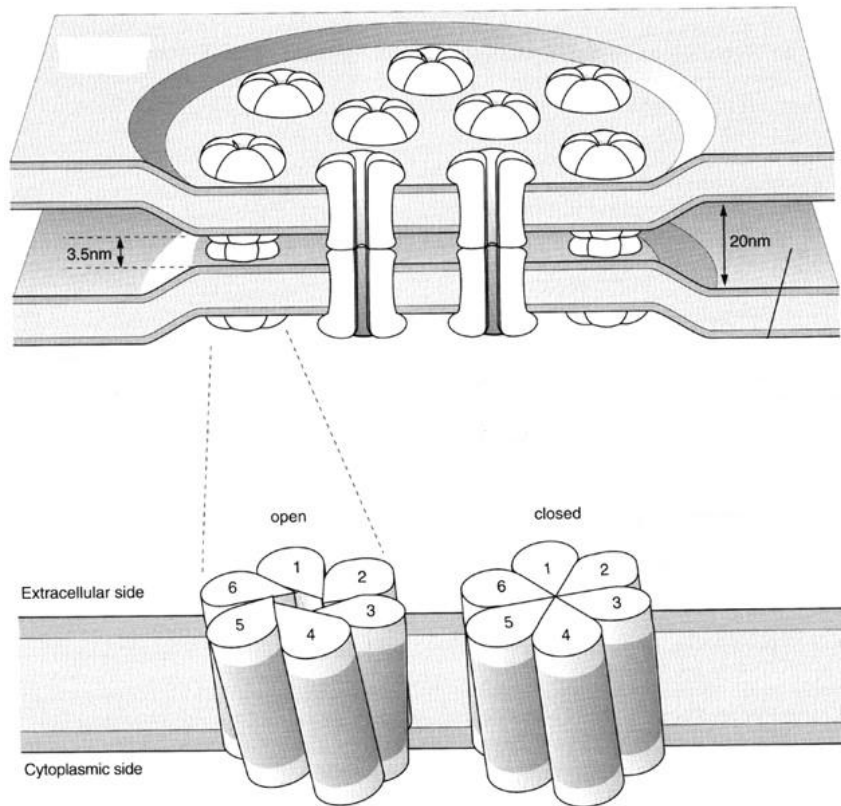


- (1) Relative depolarization of resting potential
- (2) Slowing of AP upstroke
- (3) Shortening of AP duration
- (4) Reduction of AP amplitude

Heterogeneous Restoration Of Action Potentials in Reperfused Myocardium



Delayed recovery of gap junctional coupling after reperfusion



Gap junctional function → Cellular coupling → Conductance → Conduction velocity

● Intracellular resistance
○ Extracellular resistance

(Casco et al, Circ Res 2001)

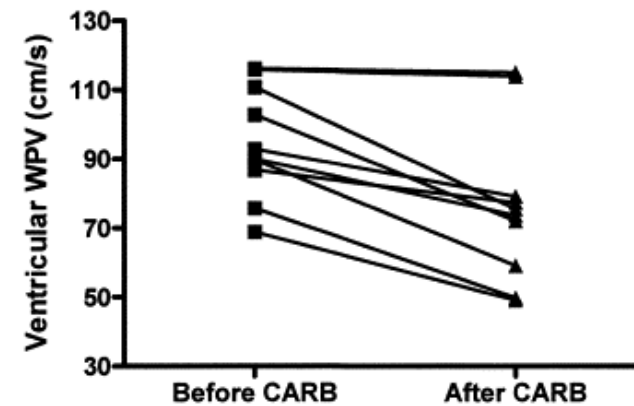
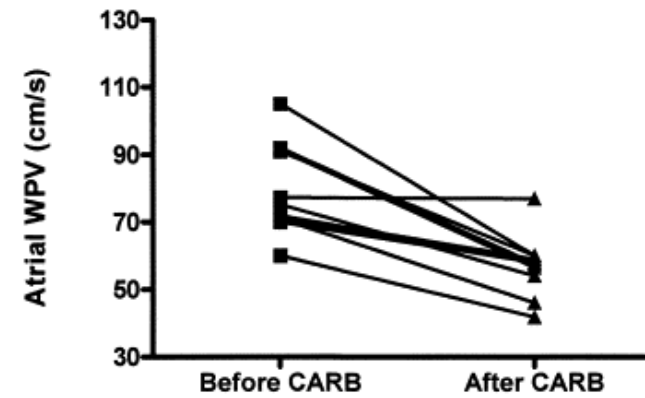
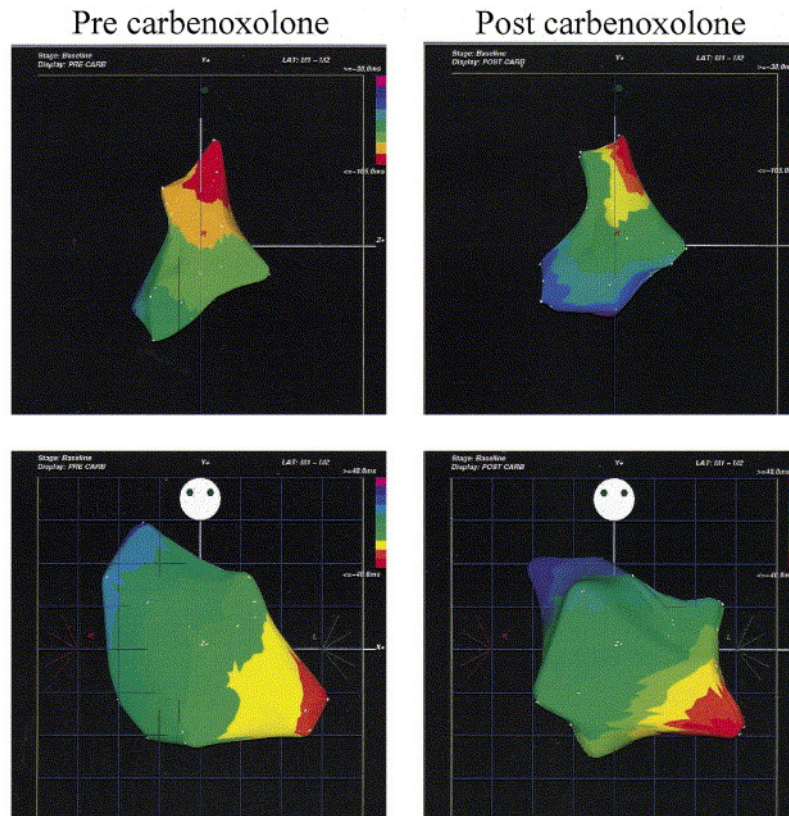
Anti-Arrhythmic Potential of Gap Junction Modulation

Opening Gap Junctions → Normalization of action potential heterogeneity

Closing Gap Junctions → Electrical isolation of ischaemic myocardium/border zone

Gap junction modulators – “Closers”

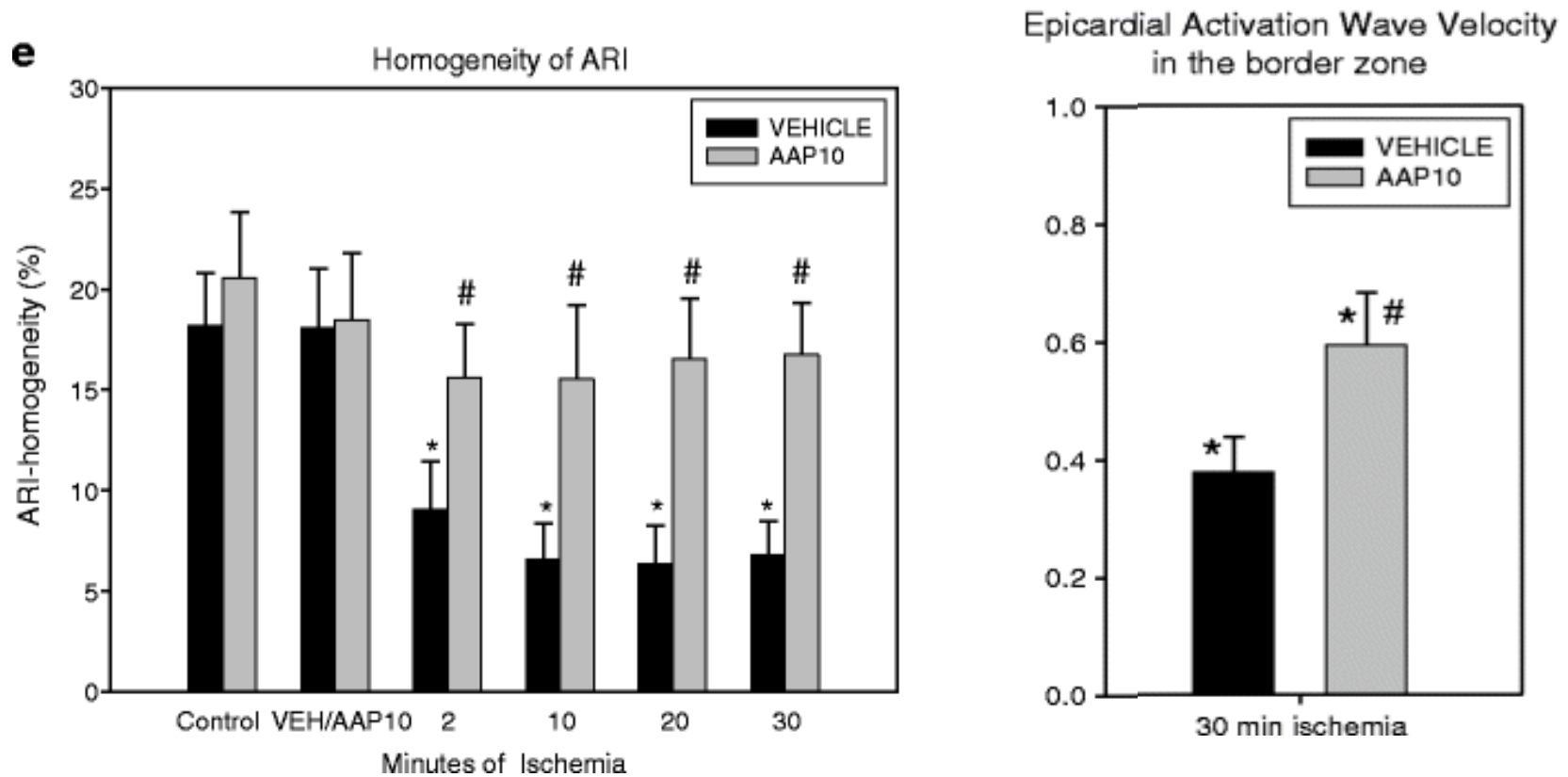
Gap junction closer - Carbenoxolone



(Kojodjojo et al, JACC 2006)

Gap junction modulators – “Openers”

Gap junction opener - AAP10



(Jozwiak et al, Naunyn Schmiedebergs Arch Pharmacol 2008)

Hypothesis

Hypothesis:

Pharmacological modulation of gap junctional coupling modifies the incidence of reperfusion VT and VF

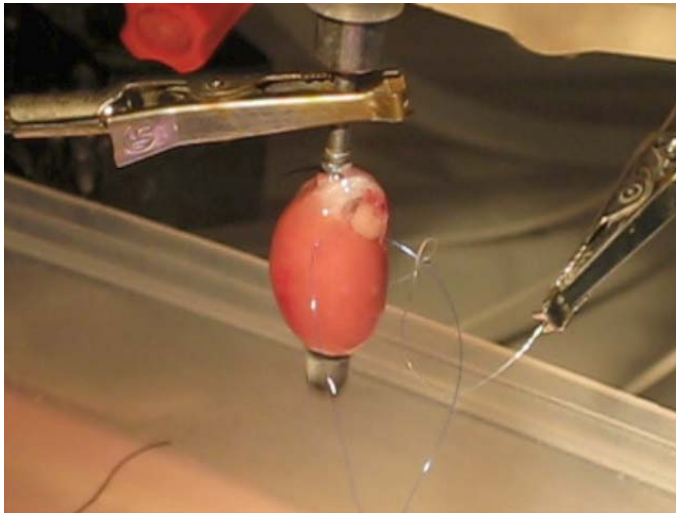
- Opening gap junctions – anti-arrhythmic
- Closing gap junctions – pro-arrhythmic

Methods

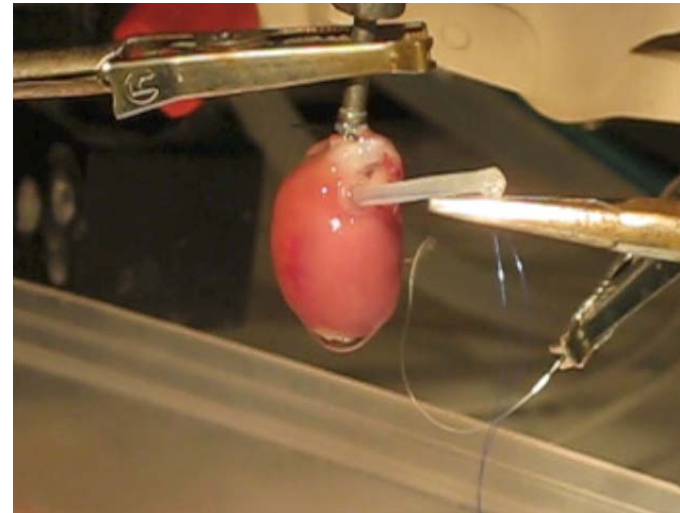
- *Ex vivo* model of ischaemia-reperfusion
- Male Sprague-Dawley rats (250g – 300g)
- Hearts rapidly explanted, attached to Langendorff cannula
- Perfused with oxygenated Krebs-Henseleit solution
- Unipolar silver electrode to record epicardial electrograms
- LAD artery ligated with 6-0 Prolene suture

Methods – Ischaemia & Reperfusion

Pre-
Ligation



LAD
Occluded



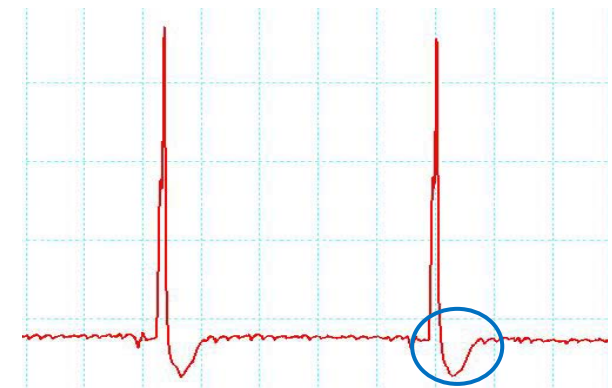
Pre-Ischaemia



2 mins after
onset of ischaemia

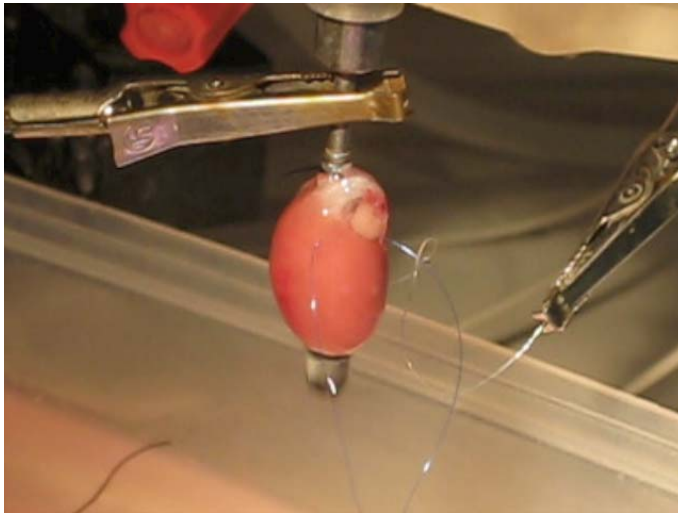


4 mins after
onset of ischaemia

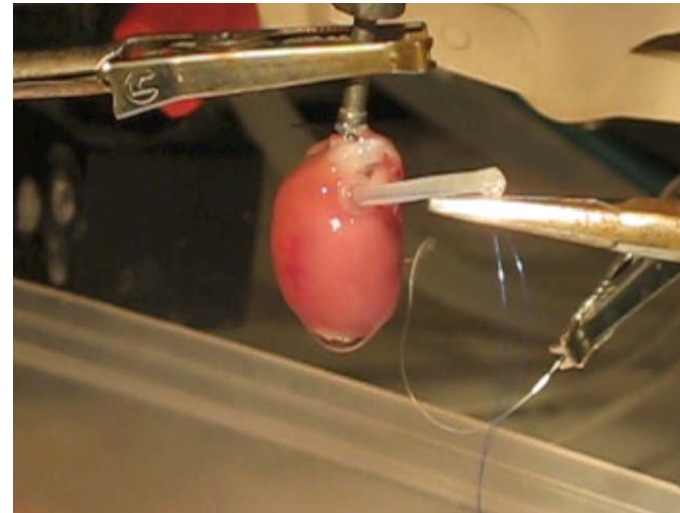


Methods – Ischaemia & Reperfusion

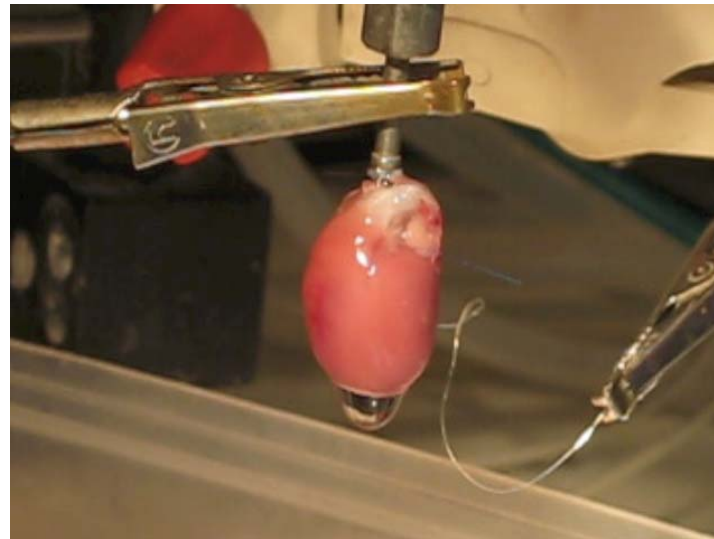
Pre-
Ligation



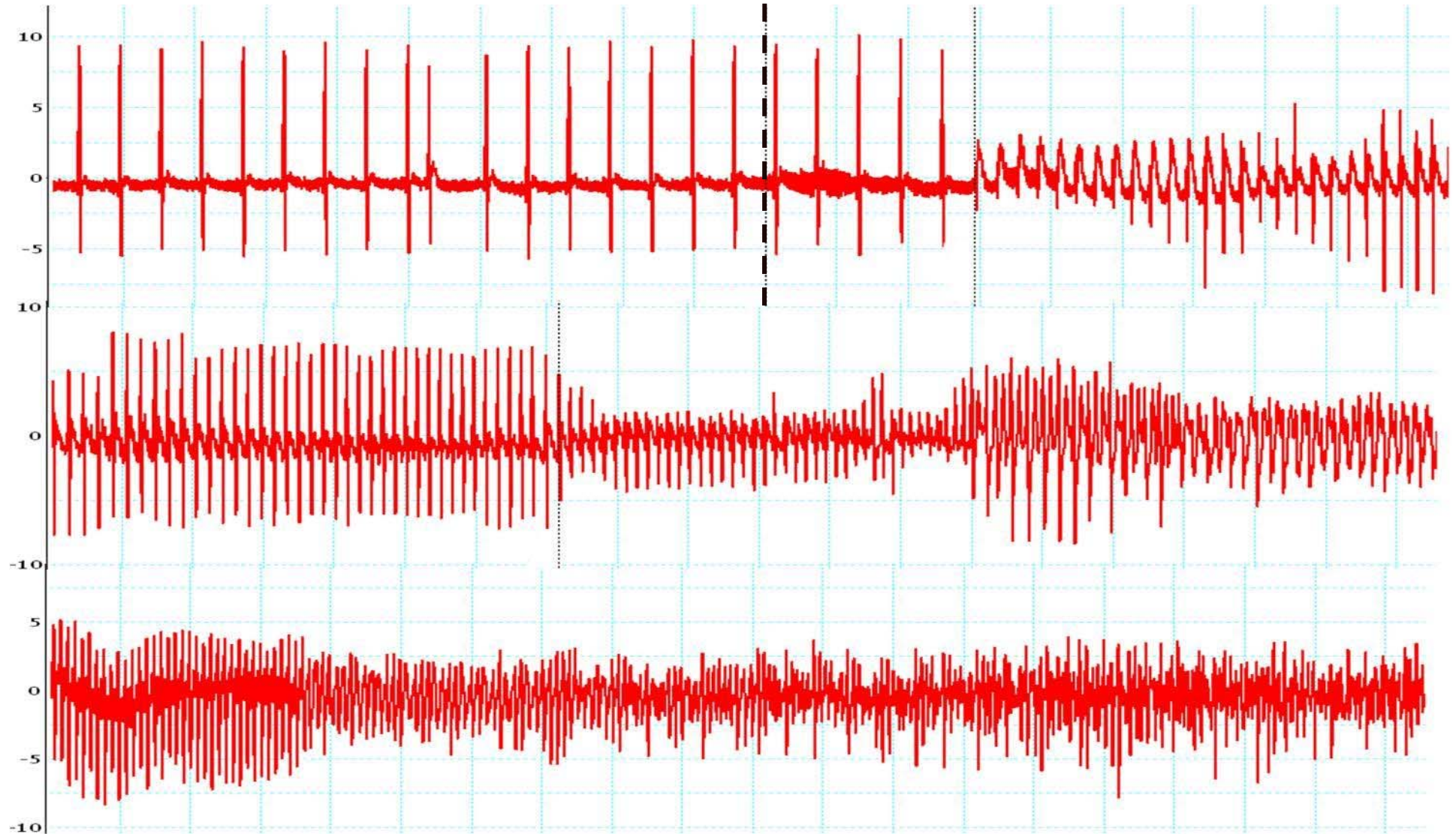
LAD
Occluded



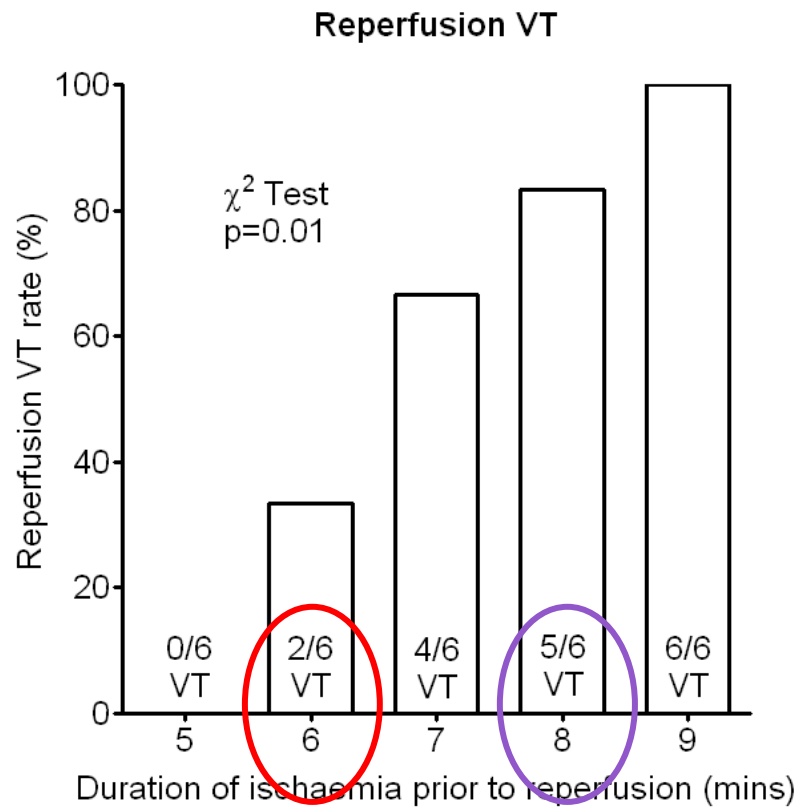
Reperfusion –
VT/VF



Reperfusion VT & VF



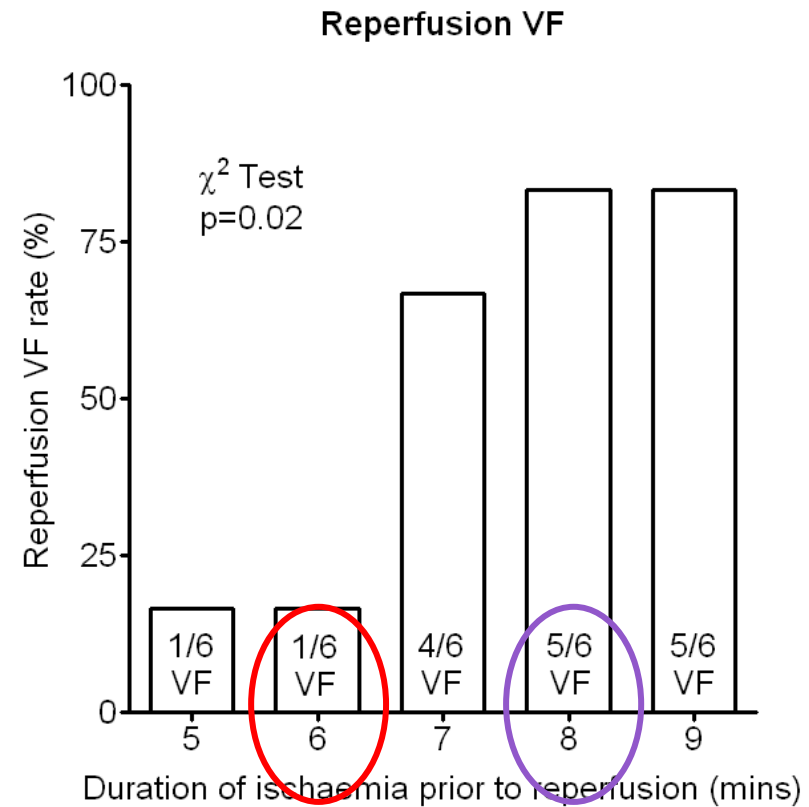
Methods – Ischaemia-Reperfusion Controls



**VT/VF
Incidence**

Low

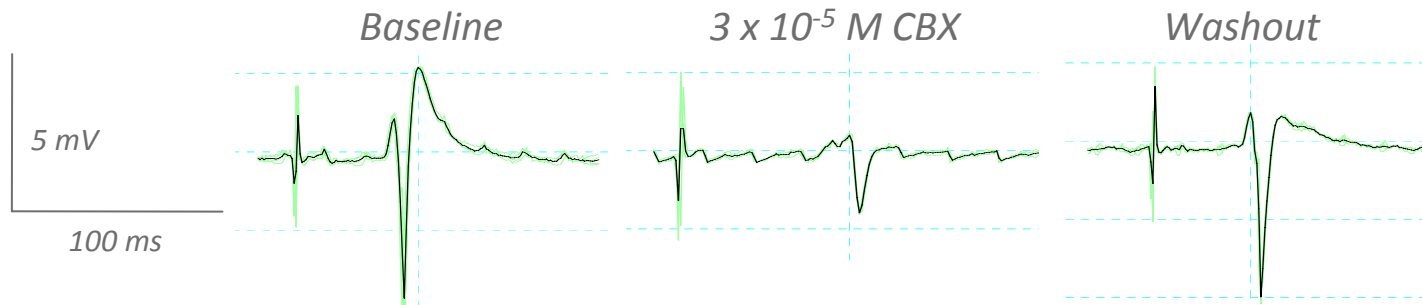
High



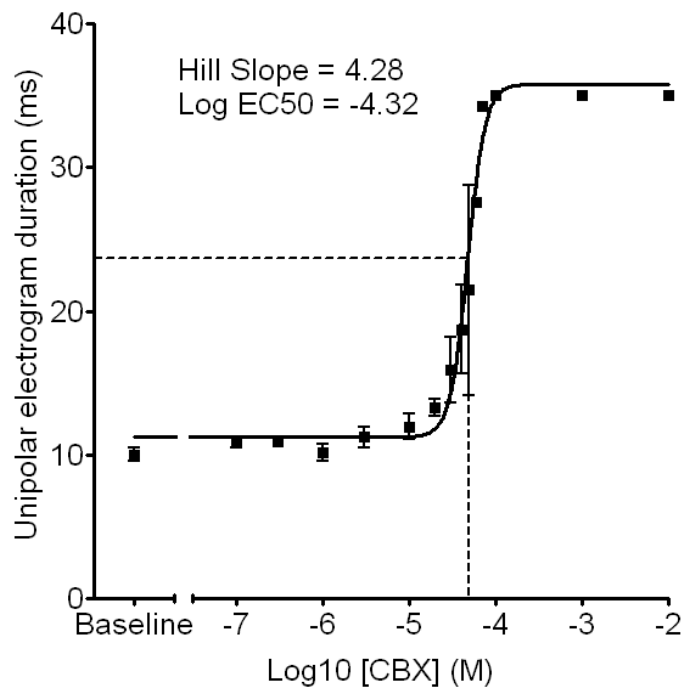
Low

High

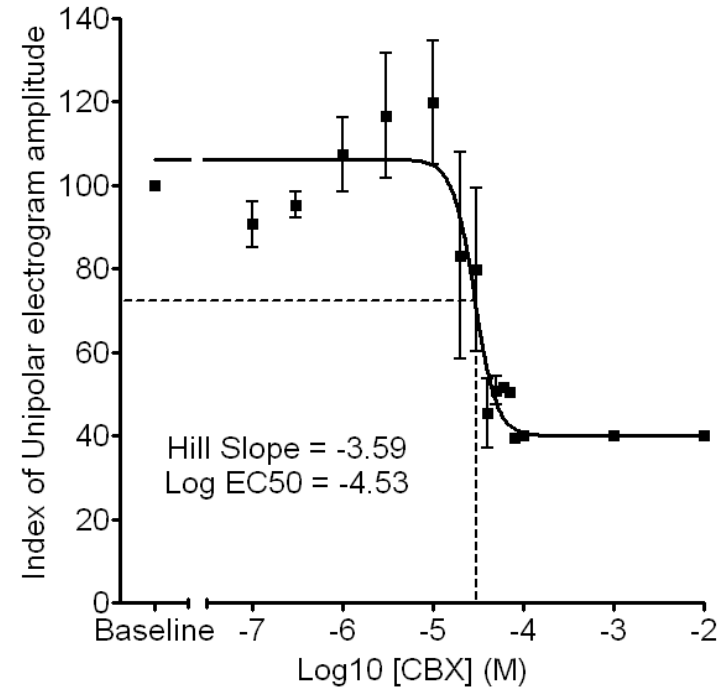
Dose Finding Experiments - Carbenoxolone



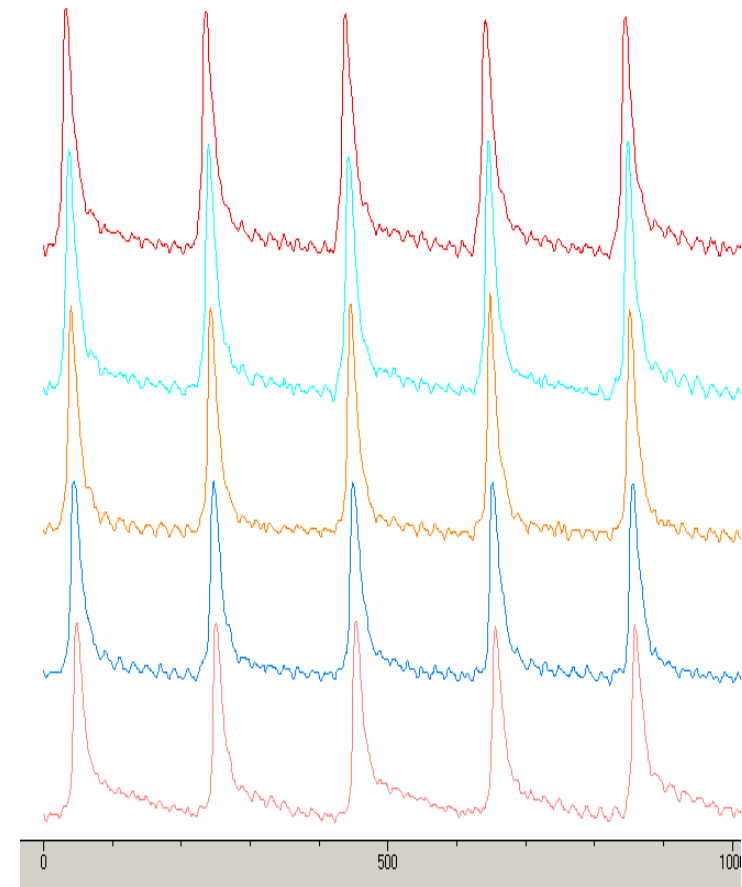
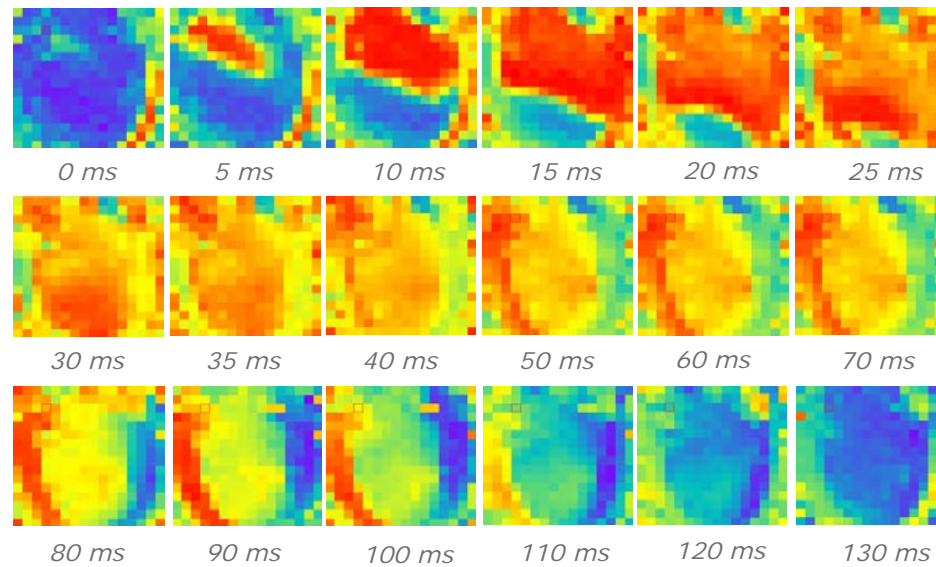
Carbenoxolone Dose-Response Curve



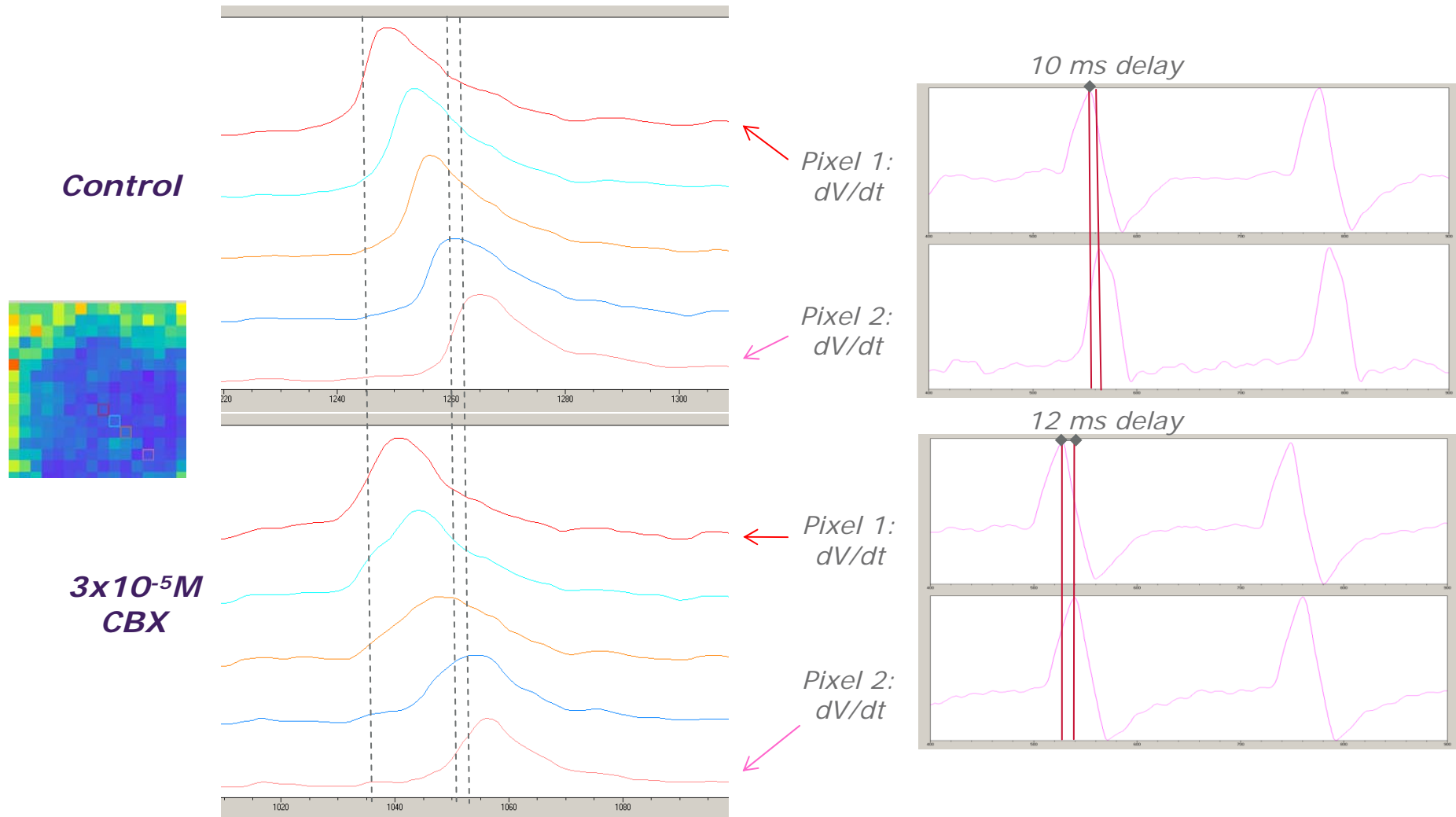
Carbenoxolone Dose-Response Curve



Dose Finding Experiments - Carbenoxolone



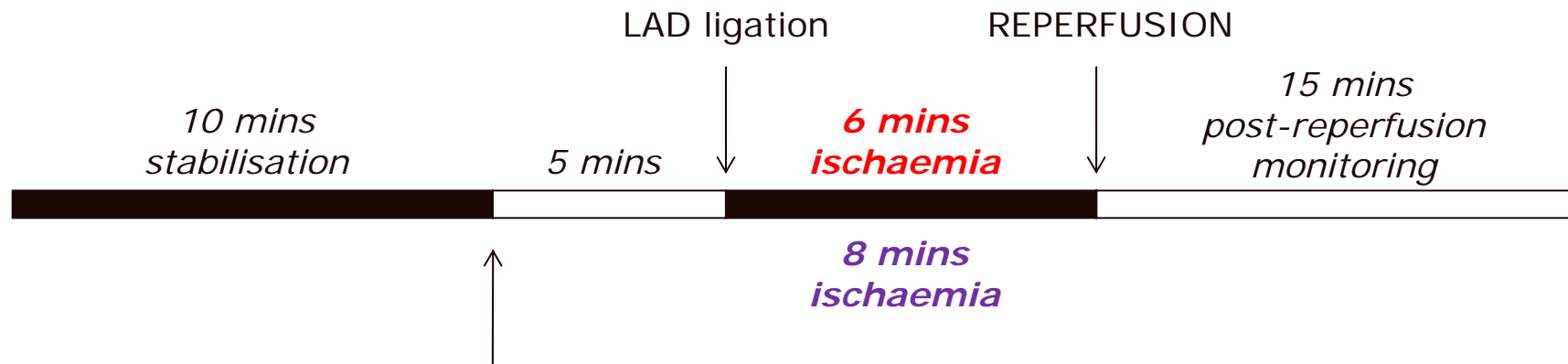
Dose Finding Experiments - Carbenoxolone



Study Protocols

(1) 6 minute ischaemia-reperfusion protocol

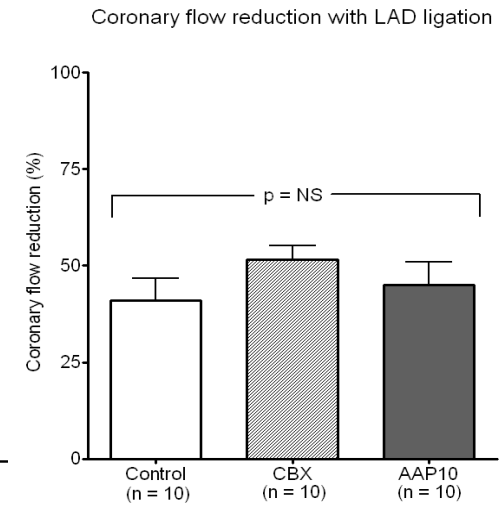
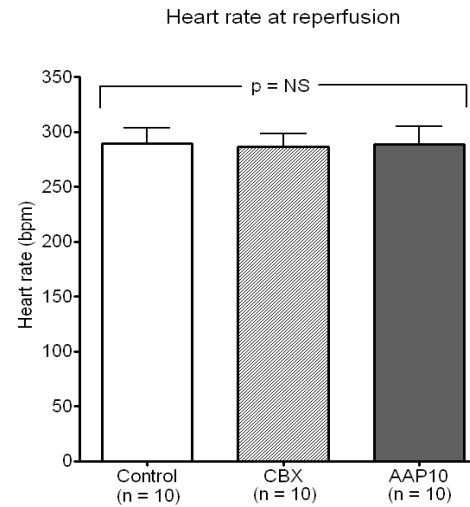
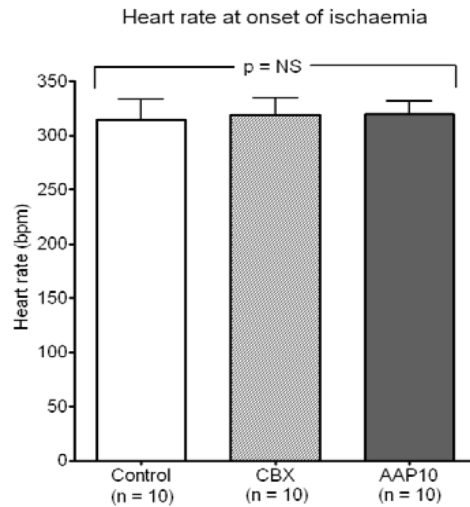
(2) 8 minute ischaemia-reperfusion protocol



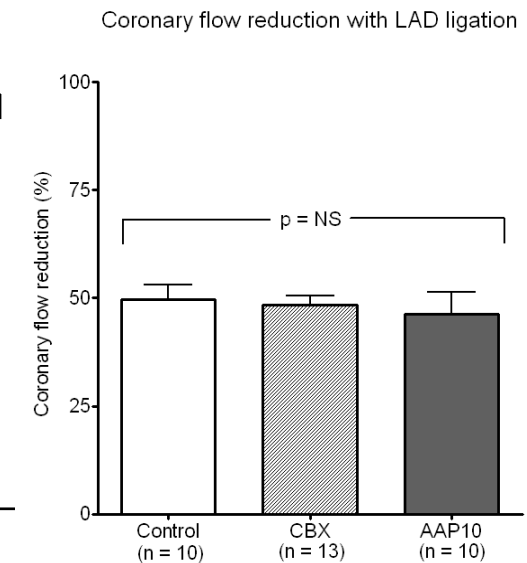
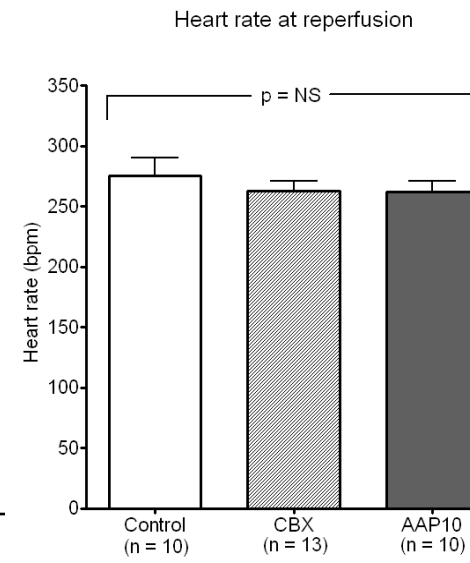
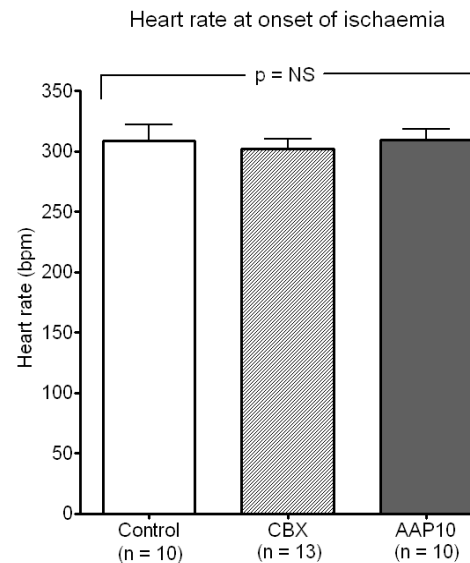
Start treatment:
(1) 50nM AAP10 (n=10)
(2) 30 μ M CBX (n=10)
(3) Control Krebs (n=10)

Baseline parameters/Potential Confounders

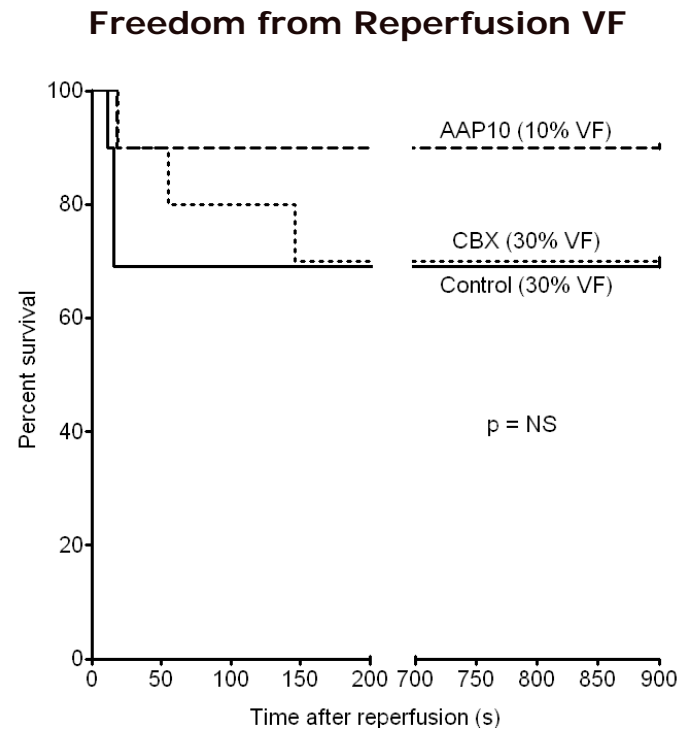
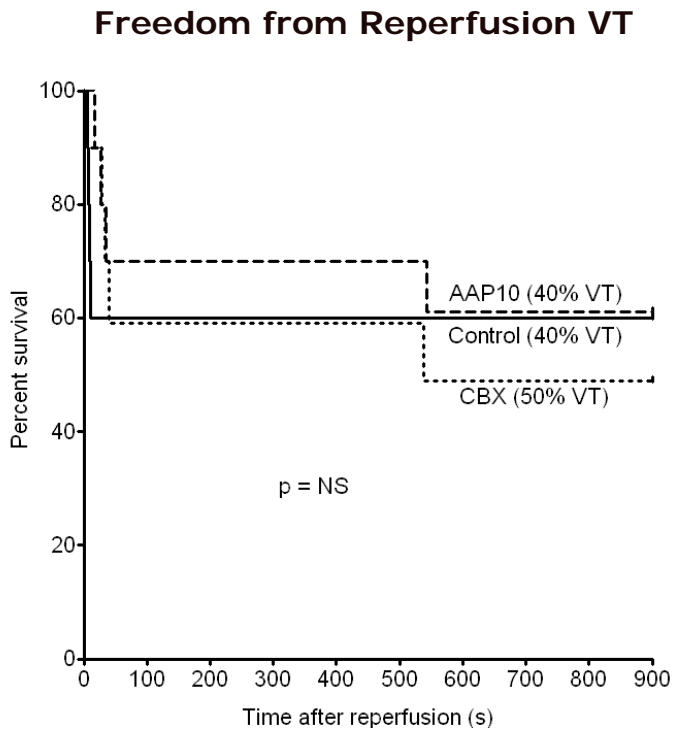
**6 minute
ischaemia-
reperfusion
protocol**



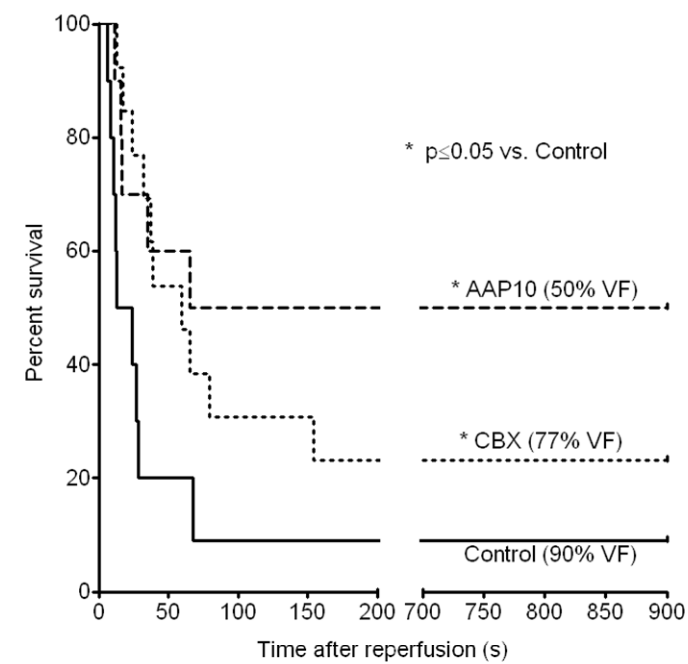
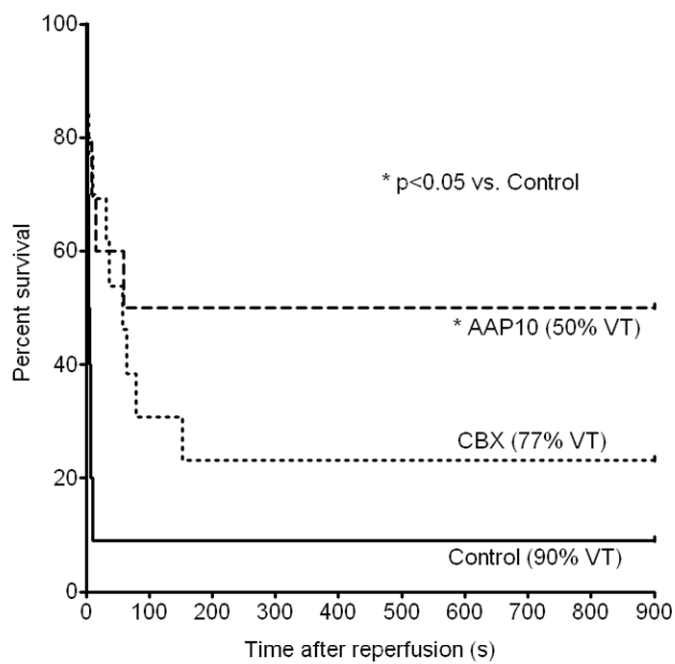
**8 minute
ischaemia-
reperfusion
protocol**



6 minute ischaemia-reperfusion protocol

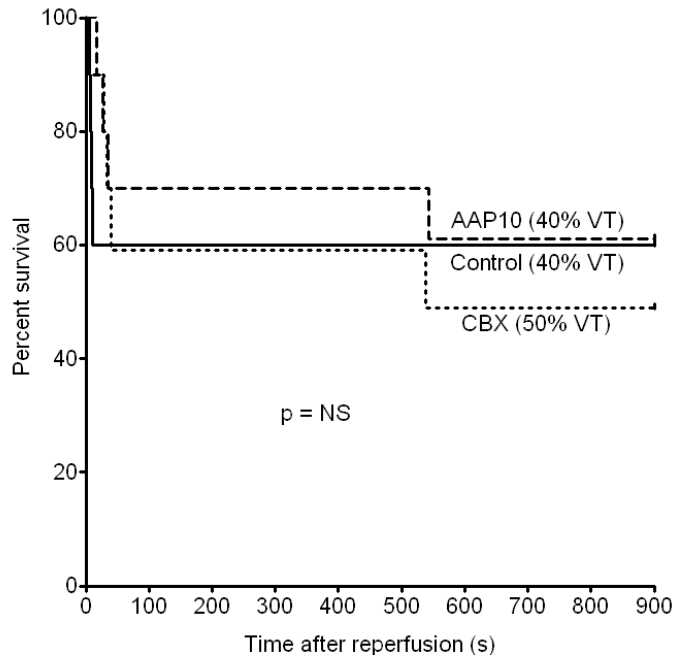


8 minute ischaemia-reperfusion protocol

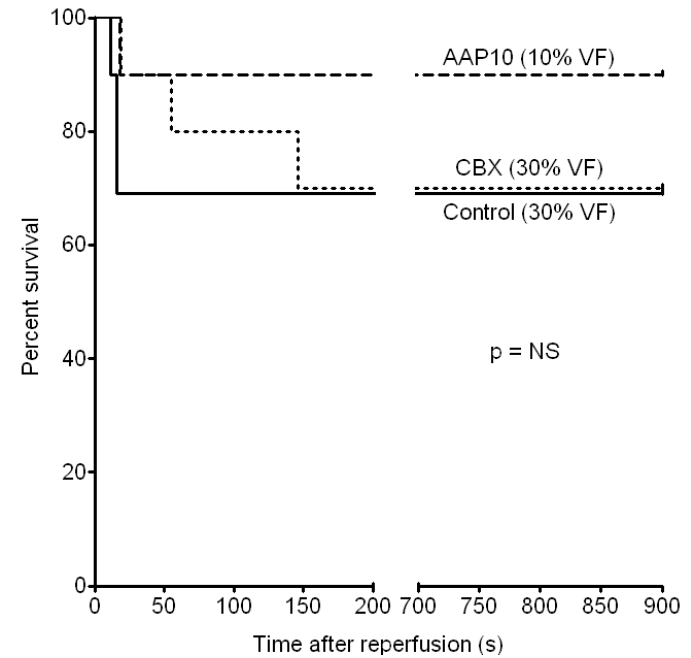


6 minute ischaemia-reperfusion protocol

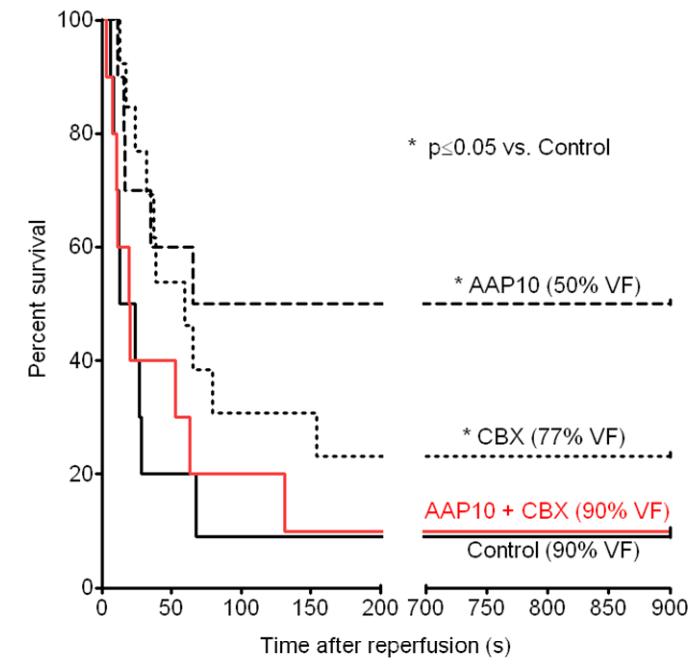
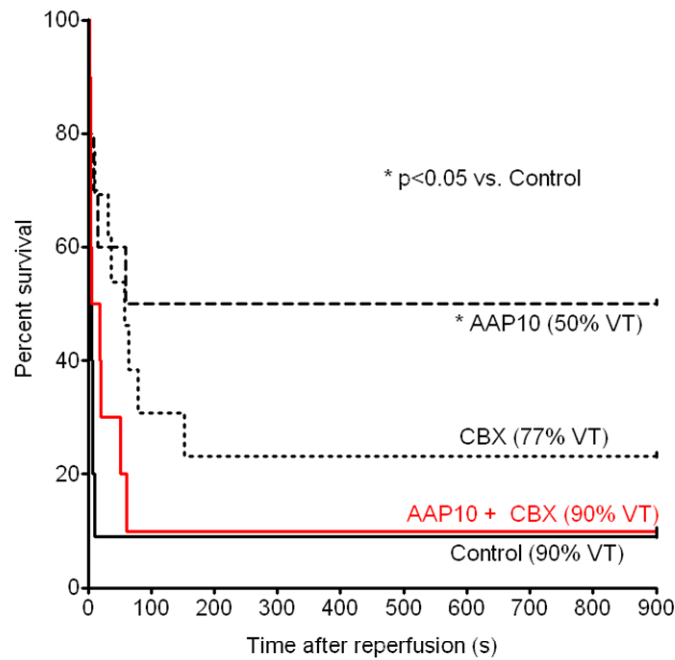
Freedom from Reperfusion VT



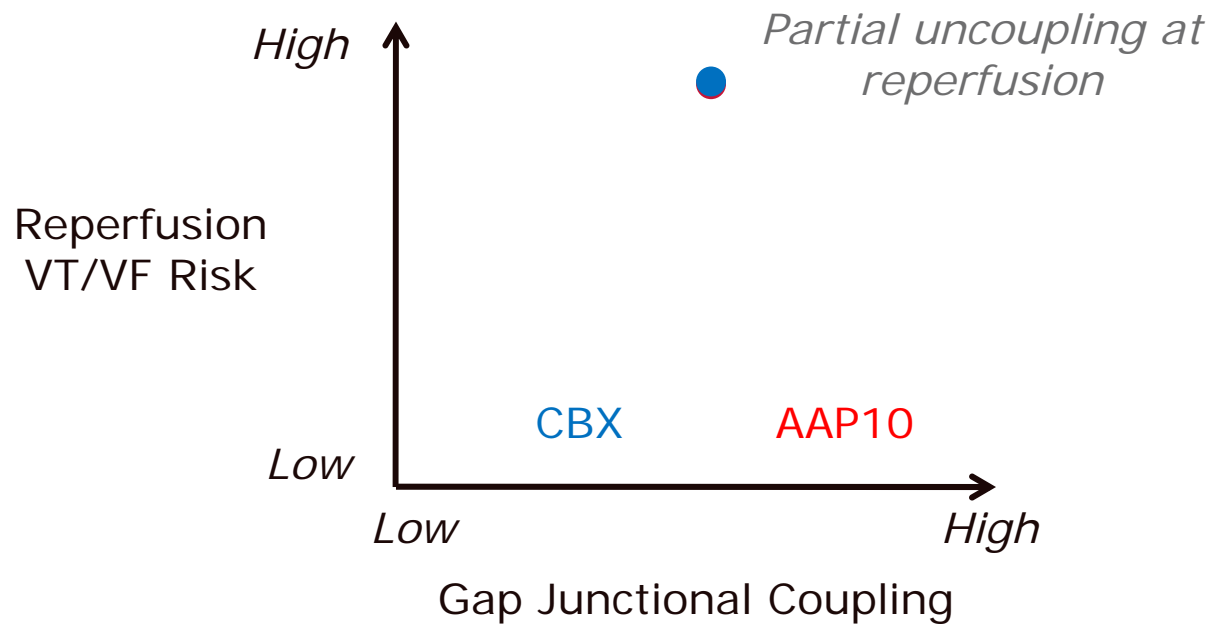
Freedom from Reperfusion VF



8 minute ischaemia-reperfusion protocol



Conclusions

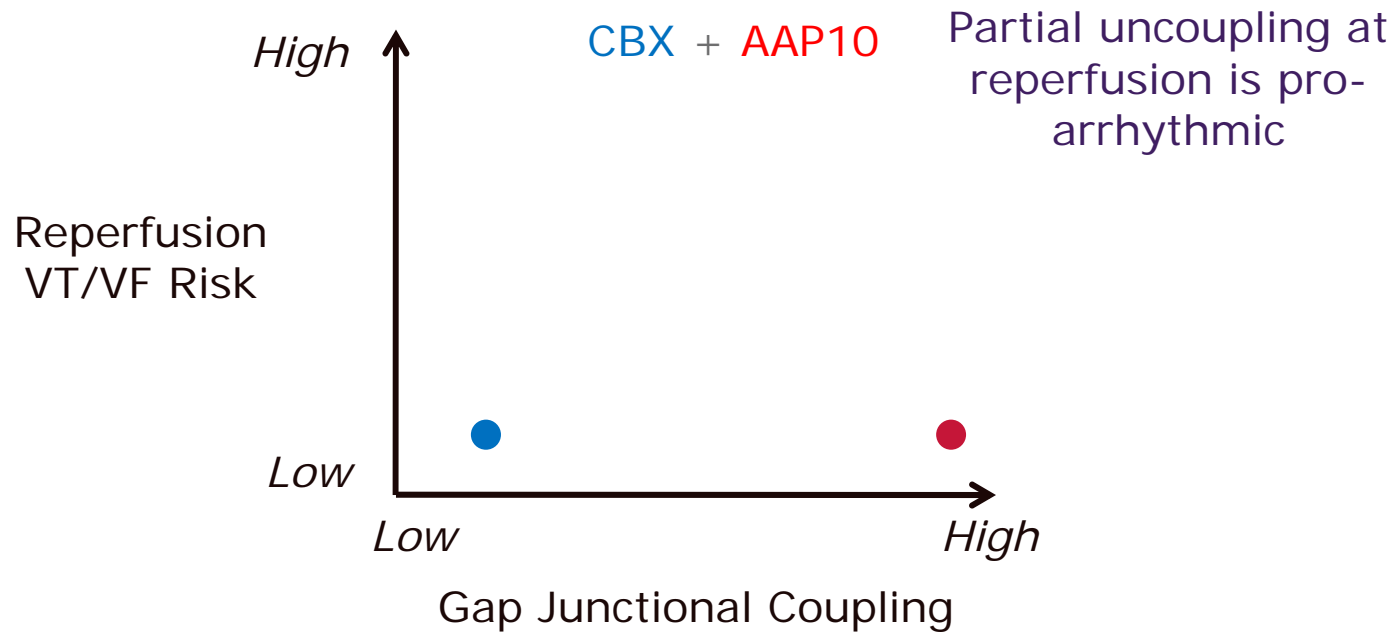


Gap junctional coupling plays a role in reperfusion arrhythmias

Increasing gap junctional coupling is anti-arrhythmic

Reducing gap junctional coupling is anti-arrhythmic

Conclusions



Gap junctional coupling plays a role in reperfusion arrhythmias

Increasing gap junctional coupling is anti-arrhythmic

Reducing gap junctional coupling is anti-arrhythmic

Protective effects of CBX & AAP10 abolished when co-administered

Acknowledgements

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Alexander Lyon

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Iqbal Shadi
Eugene Chang
Linda Inuabasi
Pravina Patel
Vanaja Kakarla
Mark Turner

**Modulation of Gap Junctional Coupling as an
Anti-Arrhythmic Strategy to
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