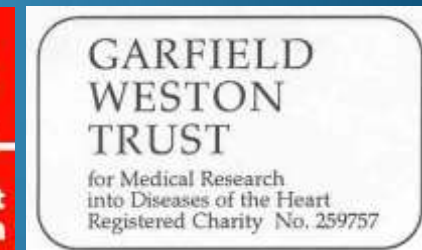


A non-cholinergic NO release and NO-dependent anti-fibrillatory effect of vagal efferent stimulation on the cardiac ventricle

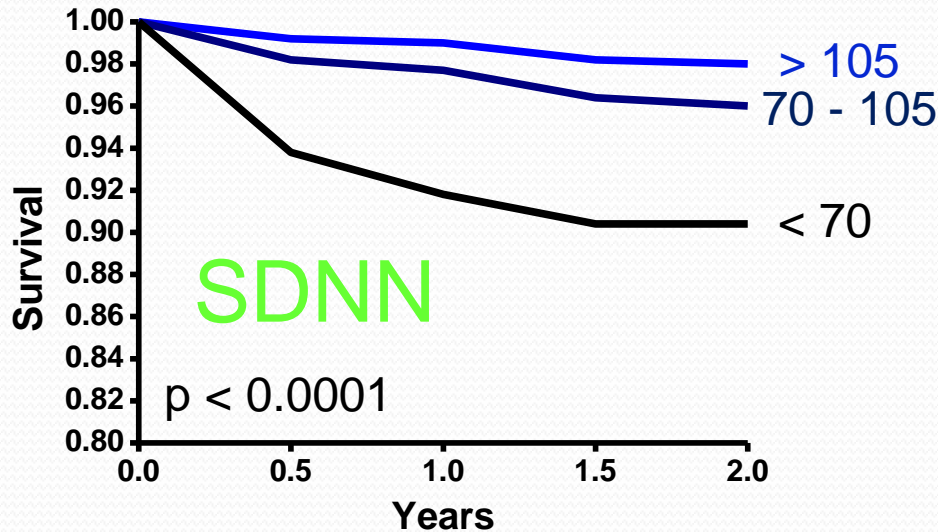
Kieran E Brack, Vanlata H Patel, John H Coote, G André Ng

University of Leicester, United Kingdom

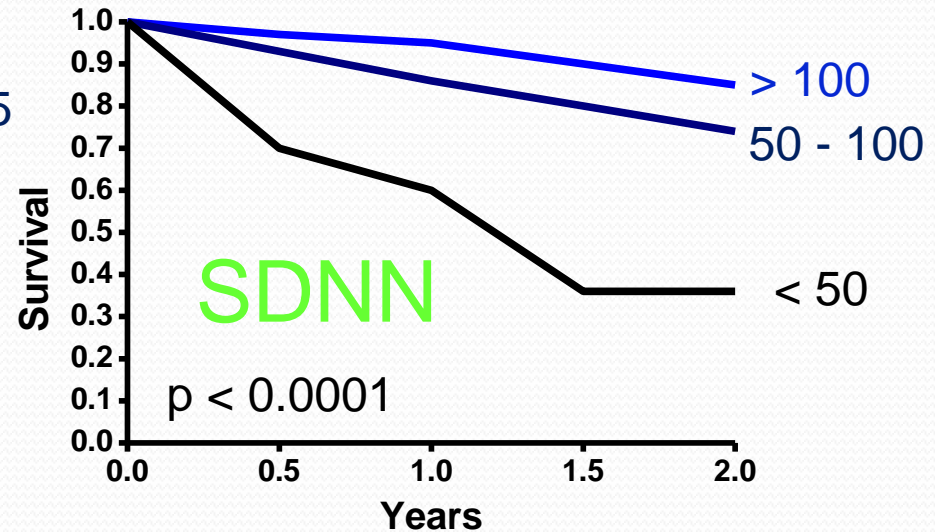
HRC, Monday October 4th 2010



Heart Rate Variability – strong prognostic marker



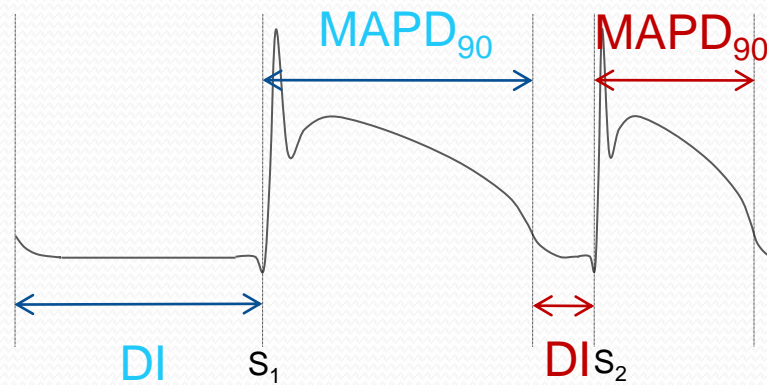
ATRAMI



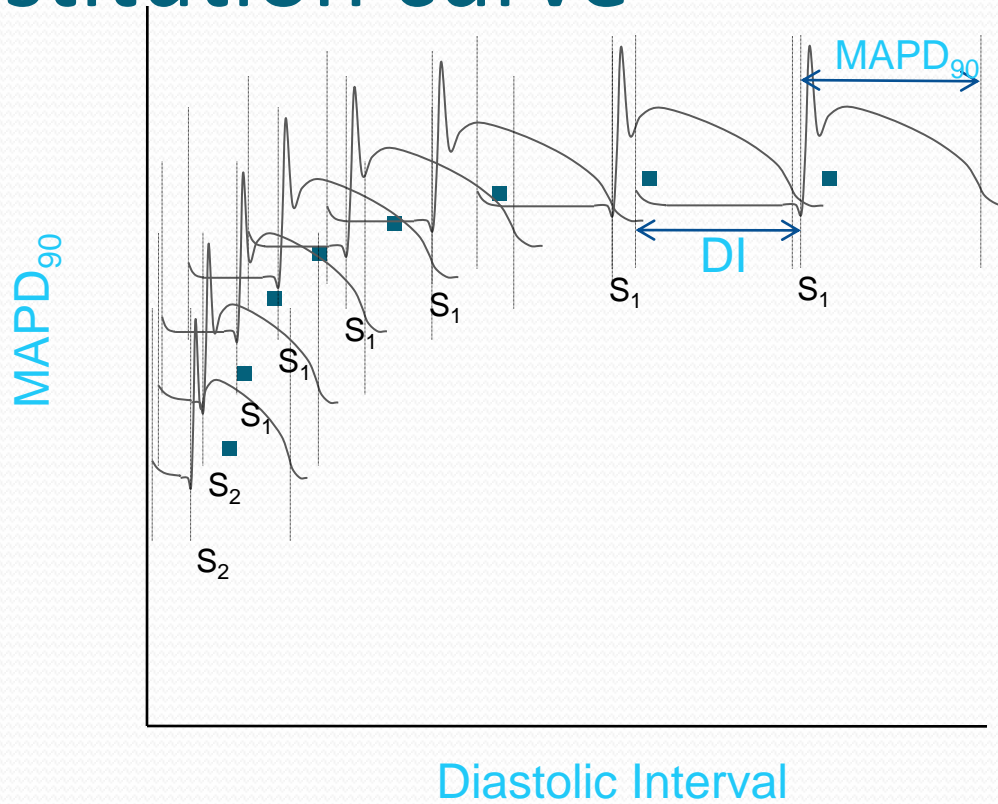
UK-HEART

Action Potential Duration Restitution

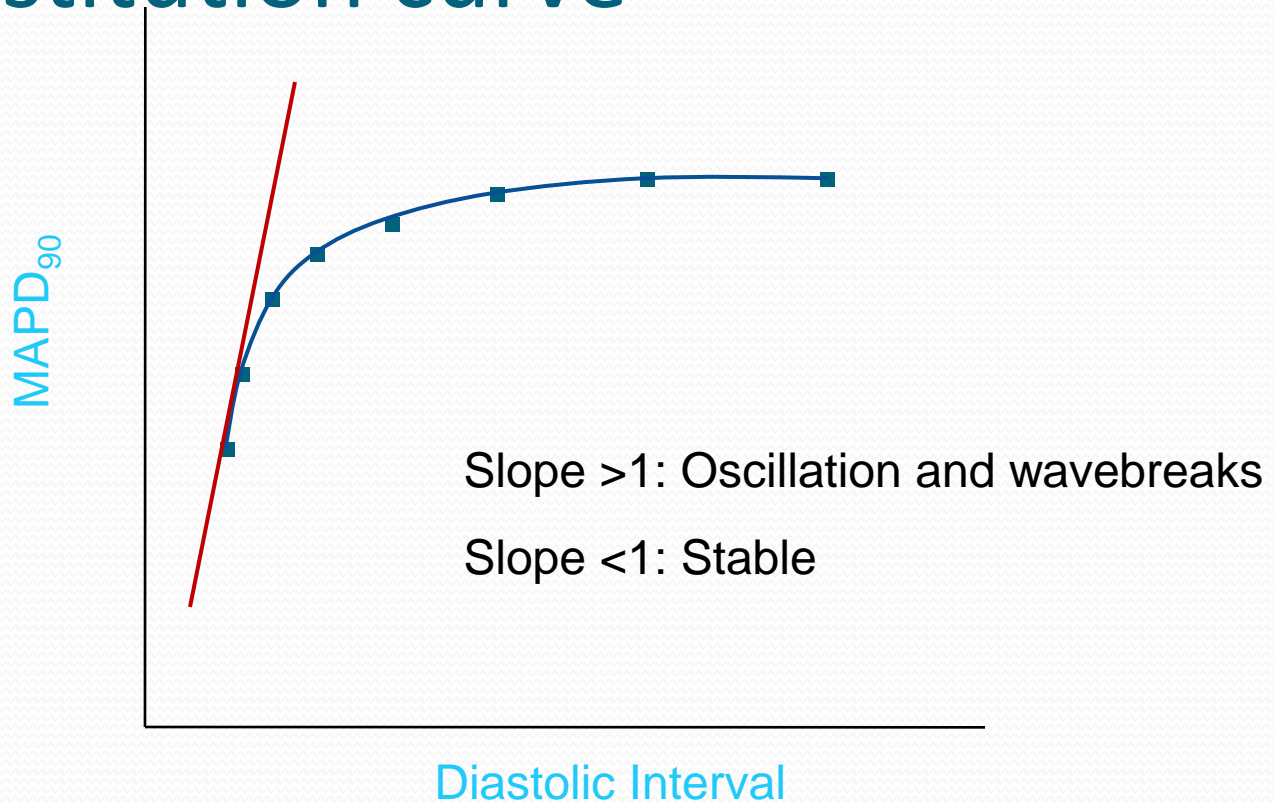
Myocyte action potential duration is determined by the preceding diastolic interval



APD Restitution curve



APD Restitution curve



Background and Aim of study

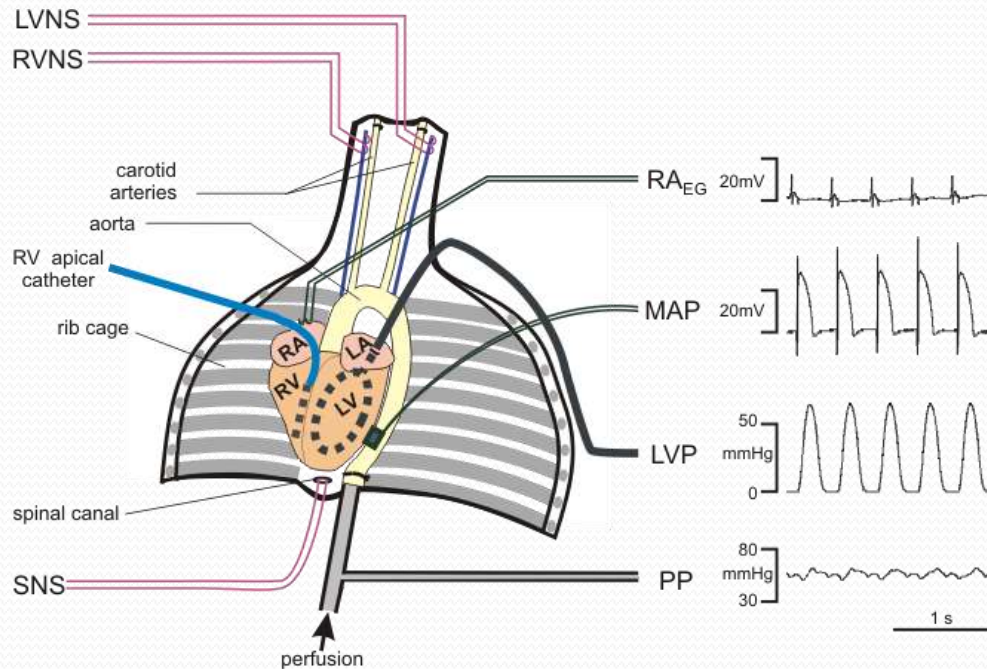
- VNS: ↓ action potential duration restitution slope whilst simultaneously protecting against ventricular fibrillation (VF)¹
- This effect is mediated via nitric oxide (NO)²
- Vagus nerve stimulation (VNS) is classically considered to be entirely mediated via muscarinic (M₂) receptor activation

Aim: to determine if the protective effects of VNS against VF and release of NO are dependent on muscarinic activation

1. Ng GA *et al*, 2007. *Card Res*;73:750-760.

2. Brack KE *et al*, 2007. *J Physiol*;583.2:695-704.

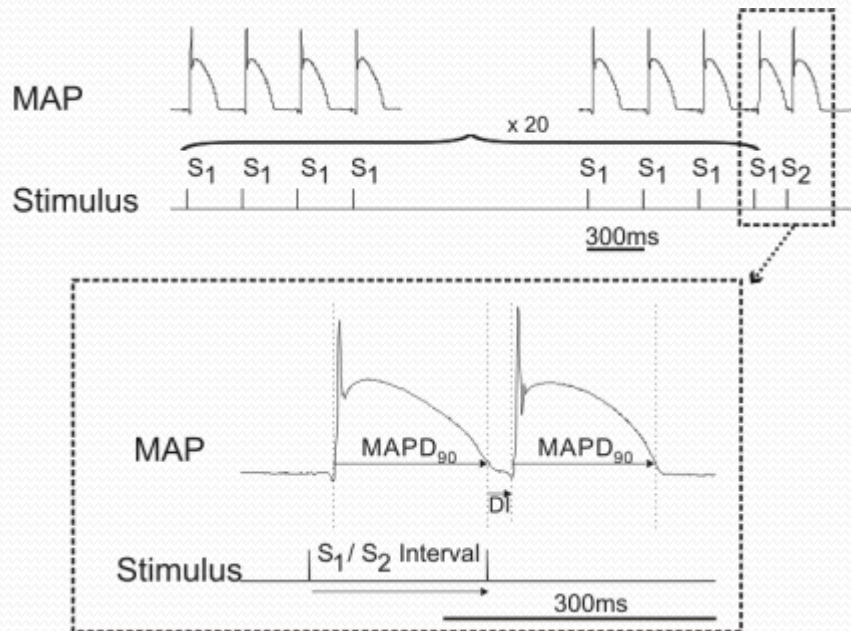
Methods 1: Innervated isolated heart preparation



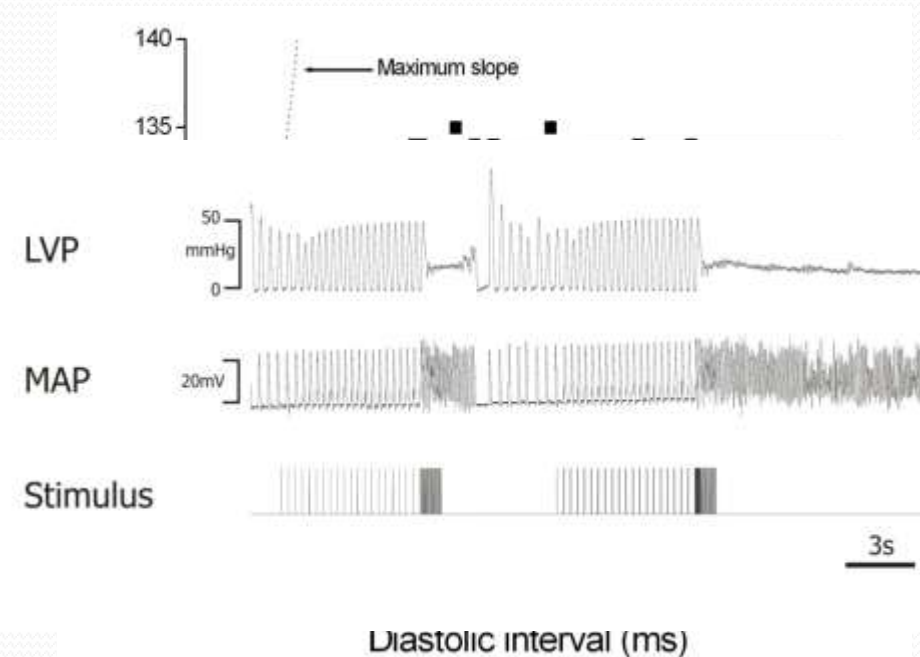
- NZW Rabbits (n=17)
- 2.9 ± 0.1 Kg
- Const. Flow 100ml/min
- Cervical VNS
 - 9.6 ± 1.0 Hz, 9.4 ± 1.0 V

Methods 2: Protocols

Effective refractory period (ERP) & APD Restitution

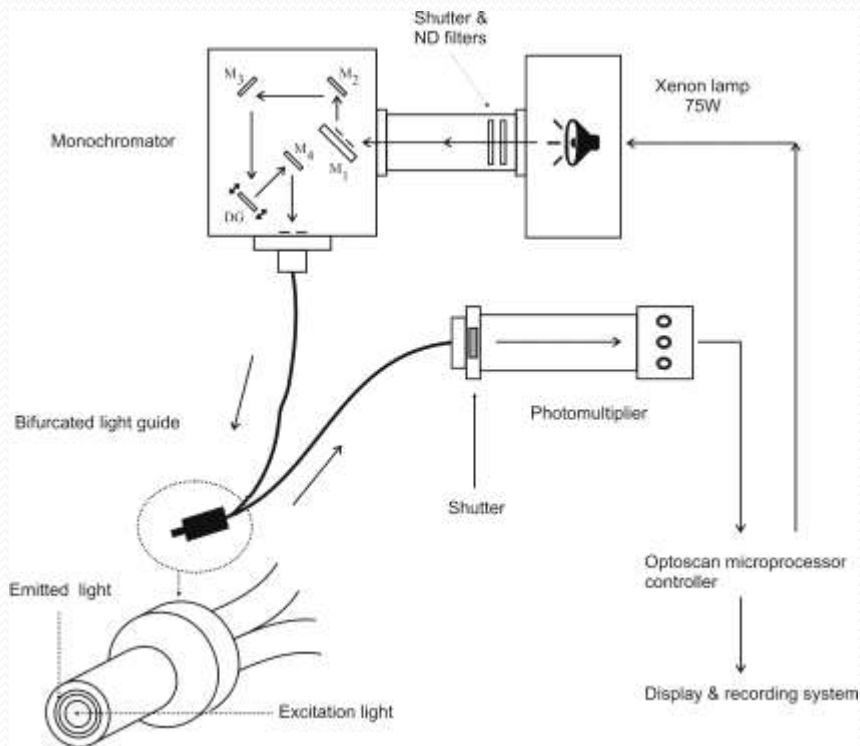


Ventricular fibrillation threshold (VFT)



Methods 3: Protocols

NO fluorescence



- DAF-2 DA
- 150-250 μ L
- Administered via right carotid artery
- Fluorescence at 490nm (F490)

Patel et al, 2008 Pflugers Arch 456;635-345

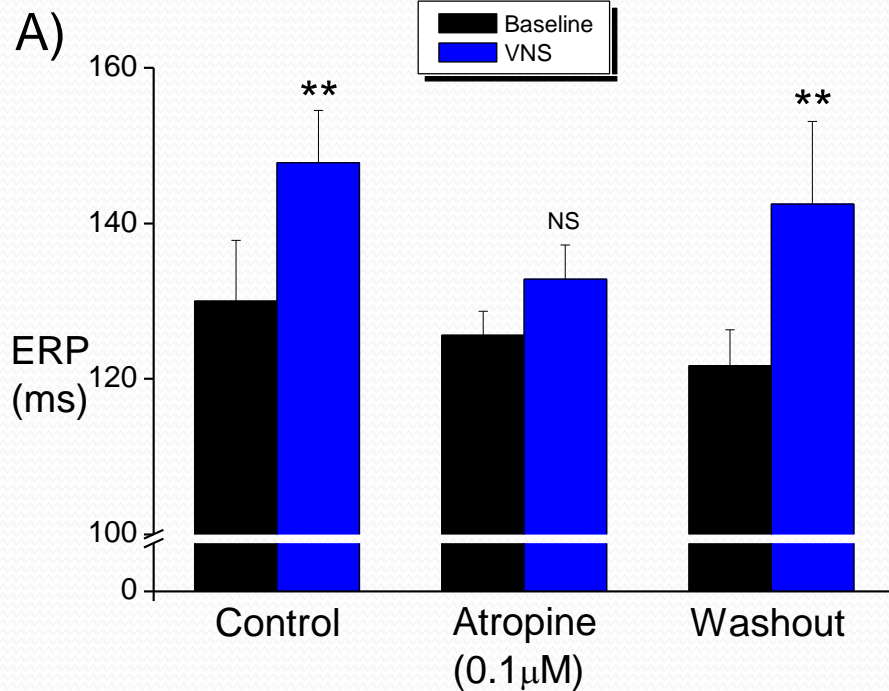
(A) Control, (B) 0.1 μ M Atropine, (C) Washout

Results 1: HR, ERP and VFT

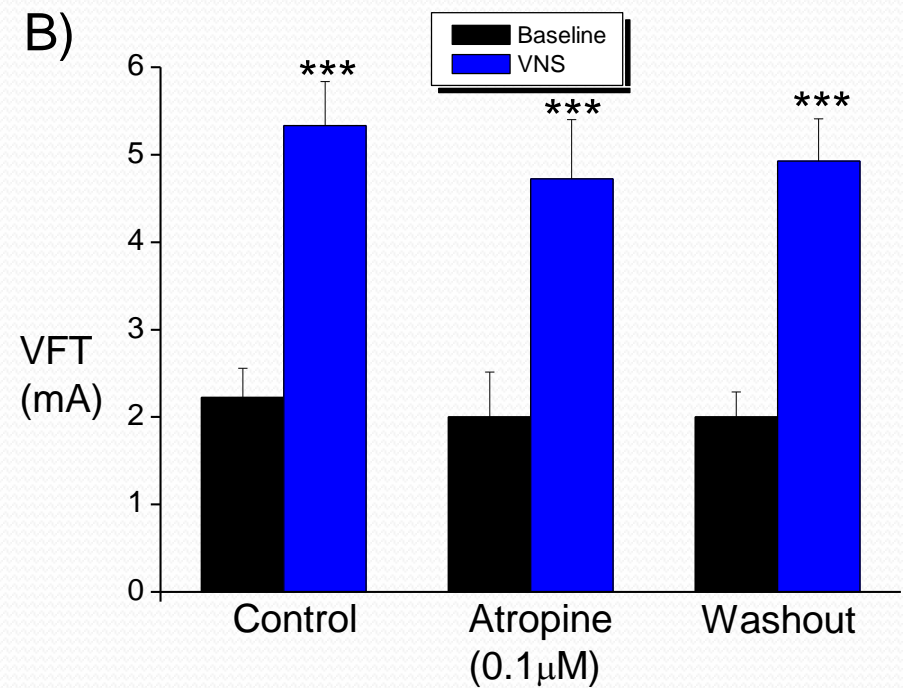
HR

	Baseline	VNS	
Control	147.8±6.5	88.9±6.4	***
Atropine	143.1±9.8	142.2±9.3	NS
Washout	141.9 ±7.1	88.8±15.2	***

ERP

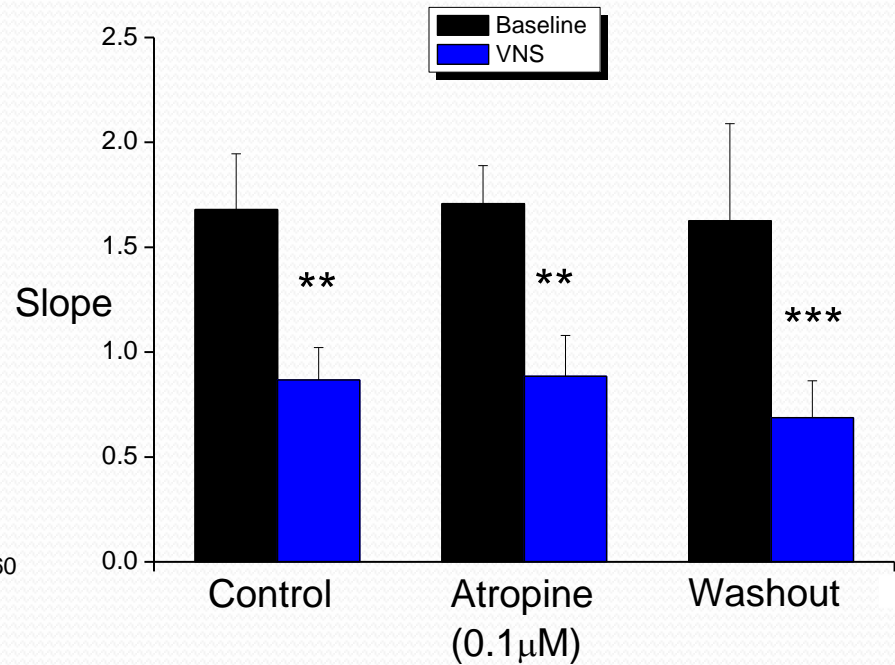
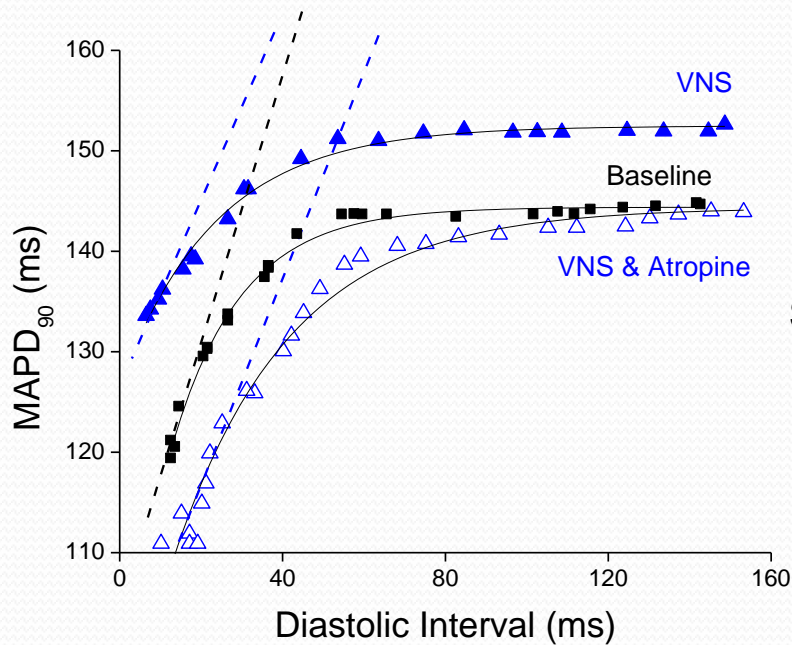


VFT

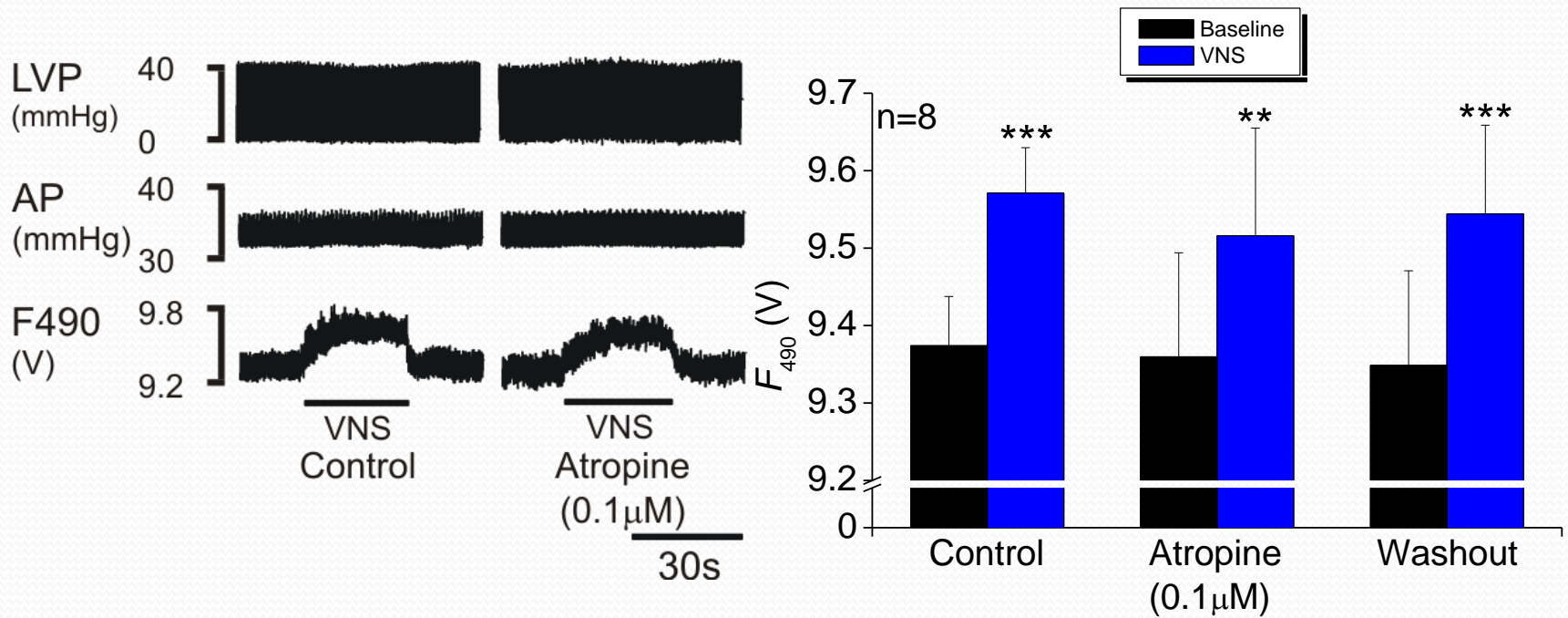


Results 2: APD Restitution

Restitution slope



Results 3: NO fluorescence



Summary

M2 dependent

	HR	ERP	RT slope	VFT
VNS	↓	↑	↓	↑
VNS & atropine	↔	↔	↓	↑

*Brack KE *et al*, 2007. *J Physiol*;583.2:695-704.

NO dependent

Conclusions

- Vagus nerve stimulation affords antiarrhythmic protection at the ventricular level against VF
- This effect appears to be mediated via APD restitution and is dependent on NO but not muscarinic activation
- A putative direct VNS-NO pathway may be responsible for this important mechanism underlying the autonomic modulation of ventricular electrophysiology