Strategic Promotion of Ageing Research Capacity

Cardiovascular Ageing

Blood vessels Heart failure Free radicals Hypertension

Blood Vessel and Cardiac Function in Ageing

Andrew Trafford, Katy Garner, Katharine Dibb & Helen Graham

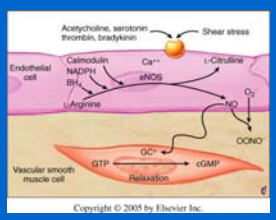
Unit of Cardiac Physiology, University of Manchester

The Investigation

Background

- Ageing is the major risk factor for the development of heart failure and related morbidity/mortality and is also strongly linked to the development of certain types of cardiac arrhythmias.
- Many of the deleterious cardiac events in later life may be related to blood vessel dysfunction.
- Restoring blood vessel and cardiac function in ageing, or preventing deterioration of function during ageing, will increase life expectancy and the quality of life.

Normal Blood Vessel Function



Agonists lead to an increase in $NO^{\bullet}$ production in endothelial cells and activation of guanylate cyclase in underlying smooth muscle cells producing hyperpolarisation and relaxation

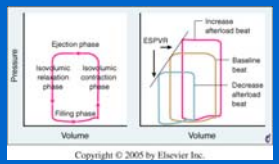
From Braunwald's Heart Disease 7th Edition.

Objectives

1) to determine the changes in the mechanical and functional properties of the heart and blood vessels in ageing
2) to identify the role of nitric oxide in alterations in blood vessel and cardiac function in ageing
3) to determine if altering nitric oxide availability can restore normal blood vessel function in ageing.

Experimental Approach

- Sheep model of ageing (♀, 18months & > 10years).
- *in vivo* assessment of blood pressure, pulse wave velocity, left ventricular function and cardiac electrophysiology in anaesthetised animals.
- Investigate haemodynamic and cardiac responses to manoeuvres that modulate endothelial function either acutely e.g. $NO^{\bullet}$ donors or NOS inhibitors or chronically e.g. following dietary supplementation to modulate $NO^{\bullet}$ bioavailability.

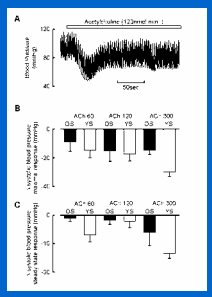


The Conductance-Catheter Technique. Left ventricular pressure and volume are simultaneously measured. Shifts in slope = altered mechanics/function.

From Braunwald's Heart Disease 7th Edition.

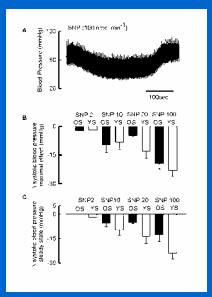
Experimental Data

Impaired endothelial function in the aorta of aged sheep



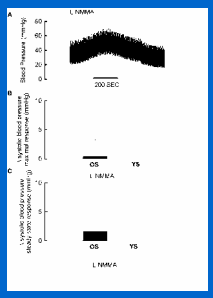
A. Ascending aortic blood pressure in response to acetylcholine administration. **B.** Mean peak blood pressure response. **C.** Mean steady state blood pressure response. OS – old sheep, YS – young sheep. *N* = 3-4 per group. *P* <0.05

$NO^{\bullet}$ donors mediate identical blood pressure responses independently of age.



A. Ascending aortic blood pressure in response to the $NO^{\bullet}$ donor sodium nitroprusside. **B and C.** Mean peak and steady state blood pressure responses. OS – old sheep, YS – young sheep. *N* = 3 per group. *P* = n.s.

Does inhibiting $NO^{\bullet}$ production affect aortic function more in the young?



A. Ascending aortic blood pressure in response to L-NMMA. **B and C.** Mean peak and steady state blood pressure responses. *N* = 3 per group. *P* = n.s. although trend indicates greater hypertensive response in the young.

Summary

Targeting therapies at restoration of blood vessel function in older people may help restore normal blood pressure and prevent adverse cardiac remodelling in ageing.

Contact Details

Principal Investigator

Dr. Andrew Trafford

Andrew.W.Trafford@manchester. ac.uk

Unit of Cardiac Physiology

3.08 Core Technology Facility

University of Manchester

46 Grafton

Manchester, M13 9NT

☏ +44 (0) 161 275 7969

Researcher

Katy Garner