# The need for a marker predicting benefit following cardiovascular disease risk reduction treatment

Carola S Koenig[1,2] Mark Atherton[2] Nick Rogers[2] Corinna Gomm[3] Cliff Bailey[4] Richard C Strange[5] Kate Shipman[3] Ian Haliday[6] Francisco Leyva[4] Sudarshan Ramachandran [3,7]

Brunel Institute for Bioengineering, Brunel University London, England[1], College of Engineering, Design and Physical Sciences, Brunel University London, England[2], Heart of England Foundation Trust, West Midlands, England[3]
School of Life & Health Sciences, Aston University, Birmingham, England[4], Institute of Science and Technology in Medicine, Keele University, Staffordshire, England[5], Materials and Engineering Research Institute, Sheffield Hallam University, England[6]
University Hospitals of North Midlands, Staffordshire, England[7]

## Introduction

Cardiovascular Disease (CVD) risk reduction is based on treating modifiable risk factors such as dyslipidaemia, hypertension, diabetes and smoking. Clustering of risk factors in individuals is often evident.

Evidence suggests this approach will lead to risk reduction though the reduction seen in RCTs may not be obtained in routine care.
Currently there is no non-invasive method to study cumulative risk reduction when multifaceted risk reduction interventions are applied.

Vascular wall properties such as endothelial function, inflammation and smooth muscle proliferation are important in the pathogenesis of atherosclerosis (Fig 1).

Both CVD risk and protective factors influence endothelial integrity . Endothelial dysfunction is considered to be reversible by risk factor modification.

Vascular flow patterns can be affected by characteristics of the arterial wall and endothelial dysfunction and vice versa (Fig 1).

## Aim of the Study

To develop a robust method to study characteristics of vascular flow using ultrasound to assess endothelial function and vasodilatation.
There are four stages:

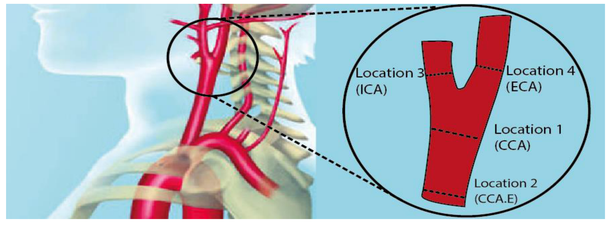
1. To standardise and validate the methodology to enable computational risk flow data and other flow characteristics to be used clinically. (Current Study). Further development of fluid modelling methods will enable investigation of particulate haemodynamics (Fig 2).
2. To study different patient groups to investigate associations between the derived vascular flow measurents and estimated risk .
3. Use prospective studies to establish if computational flow dynamic data can predict outcome following treatment in patient groups.
4. Our recent presentation at the ADA shows significant reduction in mortality in type 2 diabetics treated with PDE5 inhibitors (Fig 3). Mechanism is unknown. PDE5Is are potent vasodilators with beneficial effects on endothelial function and putative cardio-protective properties. Endothelial benefits from PDE5Is may occur at lower doses than required to improve sexual health.

Vascular flow studies may be useful in gaining an understanding of these findings

## Method

The common carotid artery is of significant pathological importance with respect to stenosis and flow prior to the bifurcation.
The lack of a coherent methodology protocol for ultrasound (to standardise the measurement of plaque) was addressed in 2009 with the publication of 'Joint recommendations for Reporting Carotid Ultrasound Investigations in the United Kingdom'.
The following characteristics of vascular flow will be assessed by ultrasound measurements of velocities at peak systole and at end diastole at different locations in the carotid artery (52 individuals; 26 with IHD and 26 healthy volunteers).

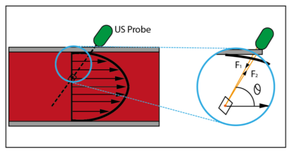
1. Velocity & Velocity Gradient
2. Dynamic Velocity Profiles
3. Wall Shear Stress
4. Dilation & Artery Stiffness

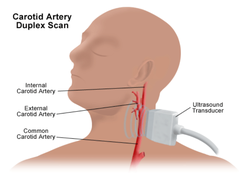



Funding: Astra Zeneca
Conflict of Interest: None

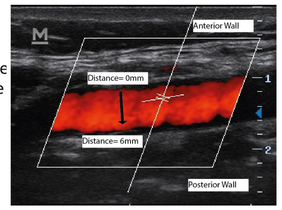
We would like to acknowledge the contribution of Professor Michael Collins who sadly passed away in August 2014.

## Velocity & Velocity Gradient Evaluation



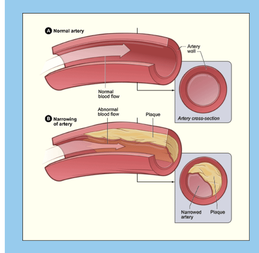

Velocity will be measured at equidistant intervals across the vessel diameter. The flow will be measured in a line across the lumen in the direction of flow. This will be at 90 degrees to the wall when no plaque is present.




Current limitations & difficulties:

» Minimum distance between measurement point ~ 0.5mm.
» Consistency of intervals operator dependent.
» Measurement line may not be perpendicular to vessel wall if plaque is present,

**Figure 1. A diagrammatic representation of atherosclerosis and risk factors, both local and systemic, with resulting disrupted vascular flow**




A → B

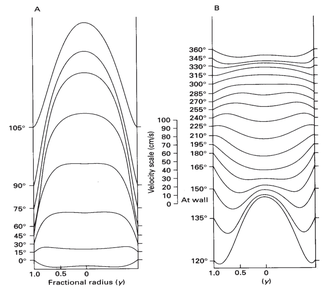
Disrupted blood flow leading to decreased shear stress around curvature of vessel

**Modifiable Risk Factors**
Diabetes
Hypertension
Dyslipidaemia
Smoking

**Factors affecting the Endothelium**
↓ eNOS
⇓ Endothelial repair
↑ ROS
Inflammation
⇑ Lipoprotein permeability
⇑ Leukocyte adhesion

## Dynamic Velocity Profiles

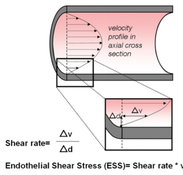
The velocity profile in straight pipes at steady state is parabolic.
Due to the pulsatile nature of blood flow velocity profiles are very different and indeed vary significantly over the cardiac cycle .

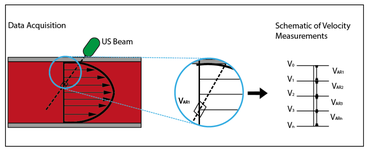



Calculated velocity profiles from measured pressure gradients in the femoral artery in the dog (Blood Flow in Arteries, D.A. McDonald, 2nd Ed., 1974)

## Wall Shear Stress Evaluation

Changes to the endothelial surface layer, the glycocalyx, are the precursor to vascular injury and atherosclerosis. Both typically develop at branches and bends in the arterial tree that are exposed to disturbed patterns of blood flow.
The glycocalyx provides a barrier against leakage of fluid, proteins and lipids across the vascular wall. In addition it modulates the adhesion process of inflammatory cells and platelets to the endothelial surface, and it functions as a sensor and mechanotransducer of the fluid shear forces to which the endothelium is exposed and which is the trigger for the release of nitric oxide (NO).
There is experimental evidence that hyperglycaemia causes damage to the vascular glycocalyx .
Vink et al have shown that glucose itself alters the structure of the glycocalyx .

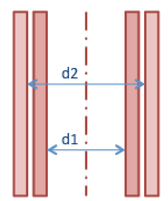


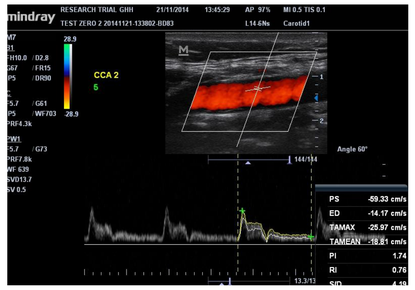




Adapted from Wentzel JJ, Chatzizisis YS, Gijsen FHJ, Giannoglou GD, Feldman CL, Stone PH. Cardiovascular Research 2012; 96: 234–243.

## Distensibility/Stiffness of Arteries

Arteries are known to become stiffer and less flexible as we age. This manifests itself in higher blood pressure values and higher pulse wave velocities (PWV) due to the pulse wave being less well absorbed.
Artery stiffness to be determined noninvasively by measuring change in diameter by US and blood pressure measurement.
Studies using aortic PWV measurements found PWV to be significantly higher in hypertensive-diabetics compared to patients with diabetes or high blood pressure alone, and in turn, PWV in these patients were found to be higher than in healthy controls. Thus, the additive nature of hypertension and diabetes to cardiovascular risk is reflected by abnormalities in PWV measurements.

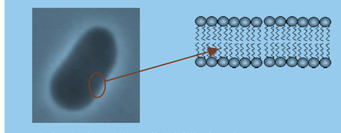


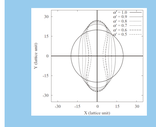

## Bibliography


- Chiu JJ, Chien S. Physiol Rev 2011; 91: 327-87.
- Chhabra N. Internet Journal of Medical Update 2009; 4(1): 33-41.
- Cunningham KS, Gotlieb AI. Lab Invest 2005; 85: 9-23.
- Oates CP, Naylor AR, Harthorne T et al Eur J Vasc Endovasc Surg 2009; 37: 251-61.
- Blood Flow in Arteries. D.A. McDonald, 2nd Ed., Edward Arnold, London, 1974.
- Nieuwdorp M, van Haeften TW, Gouverneur MC et al. Diabetes 2006 55: 480-486.
- Zuurbier C, Demicri C, Koeman A et al. J Appl Physiol 2005, 99:1471-6.
- Gamble G, Zorn J, Sanders G, MacMahon S, Sharpe N. Stroke 1994; 25(1); 11-6.
- Lim HS, Lip GYH. Journal of Human Hypertension 2004; 18, 467–468.
- Wentzel JJ, Chatzizisis YS, Gijsen FHJ, et al. Cardiovascular Research 2012; 96: 234–243

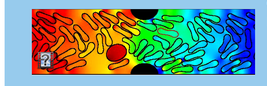

**Figure 2. Particulate haemodynamics affecting flow dynamics**



Biological vesicles - fluid filled sacks separated by a bilayer = 2D incompressible fluid.



The boundary conditions between the fluids are now different.
surface tension
conservation of volume
conservation of area
bending rigidity



Colour indicates relative pressure

Parallel LB simulation on 100
node Beowulf Cluster

A basic science approach to blood flow simulation using explicitly resolved cellular component avoids use of empirical models: is the only way correctly to account for interaction with vessel boundary- as cells pass endothelial location, WSS fluctuates. There is no such thing as steady haemodynamic flow.

The membrane makes RBC behaviour more complicated than e.g. a drop of oil in water, because its membrane imparts a preferred curvature, a bending rigidity and conserved area leading to the bicuspid shape seen evolving to the left. To obtain correct fluid dynamics all these properties must be considered.

These constraints gives rise to different phenomena ...

- tumbling
- tank treading
- deformation
- lift

Problem of blood flow is mathematically intensive: need to account for flow of internal and external fluids and the constraining effect of membrane (method must have physical accuracy) AND need to be able to simulate many cells without loss of efficiency and accuracy. Necessitates use of niche CFD methods. We will use lattice Boltzmann equation simulation

**Figure 3. Data presented at the American Diabetes Association Boston, June 5th-9th 2015.**

Testosterone Replacement Therapy and Phosphodiesterase 5 Inhibitor use are independently associated with a reduction in All-Cause Mortality in men with Type 2 Diabetes
Geoff Hackett Adrian H Heald Alan Sinclair Peter W Jones Richard C Strange Sudarshan Ramachandran