Medical Bio Trial Use Proposal: Medical Bio EX Proposal Report

Proposal Number: 2008A1756

Title: Phase-contrast imaging of blood shear past stenosis and occlusion

Project Leader Name: Dr Andreas Fouras
Project Leader Affiliation: Div. Biological Engineering, Monash University, AUSTRALIA

Beamline Used: BL20XU

Research Purpose and Background:

Aims: This study aims to develop a new quantitative measure of in-vivo blood flow using the penetrating and high intrinsic contrast afforded by Phase Contrast X-ray Imaging coupled with the accurate and quantitative fluid dynamics information provided by Particle Image Veclocimetry (PIV). The ability to image flow using such a technique would find widespread application in the study of vascular disease. This study has two desired outcomes:

1. Development of the experimental methodology towards physiologically meaningful flow rates;
2. Application of the method to achieve significant measurements of both morphology and function of stenosed and occluded ex-vivo vasculatures.

Atherosclerosis is the leading cause of death in the developed world and nearly the leading cause in the developing world. It is associated with systemic risk factors including hypertension, smoking, hyperlipidemia, and diabetes mellitus. Nonetheless, atherosclerosis remains a geometrically focal disease, preferentially affecting the outer edges of vessel bifurcations. In these predisposed areas, hemodynamic shear stress, the frictional force acting on endothelial cell surface as a result of blood flow, is weaker than in protected regions.

In-vitro and low-resolution ultrasound imaging studies have identified hemodynamic shear stress as an important determinant of endothelial function and phenotype. The functional regulation of the endothelium by local hemodynamic shear stress provides a model for understanding the focal propensity of atherosclerosis in the setting of systemic factors and may help guide future therapeutic strategies.

The relation between shear stress and atherosclerosis is based almost exclusively on low-resolution observational studies in humans and large animals. In-vitro data have shown that subtle shear stress changes can modulate the response of cultured endothelial cells, leukocyte adhesion and thrombus formation, which has been shown to mediate atherogenesis and the final stages atherosclerotic plaque rupture (stroke, myocardial infarction etc), respectively.

To date the in-vivo data on flow velocimetry is limited to thin walled vasculature. More specifically high-resolution near-wall fluorescent micro particle image velocimetry has been used in mouse cremaster muscle venules. Whilst these studies provide information on flow velocities associated with cell adhesion in the microvasculature, they do not provide insight into the role of shear stress and atherosclerosis in resistant vessels. To provide such evidence, an appropriate in-vivo model that can generate complex shear stress fields is required. To calculate shear stress accurately very high-resolution measurements of velocity are required (Fouras and Soria 1998). Other measurement modalities such as MRI and ultrasonography are incapable of the required resolution.

Recent studies (Fouras et al., 2007, Lee and Kim 2006,) have demonstrated the remarkable potential of X-ray phase contrast imaging to provide high resolution in-vitro blood flow field measurements by use Particle Image Velocimetry (PIV), an optical technique routinely used by engineers, for example in aerodynamics. Explained in it most simple form, PIV is an image processing technique which uses statistical (by use of correlation functions) inter-frame comparisons of sub-regions of images to determine motion between those frames in all of those sub-regions. Figure 1 shows a 3D velocity vector field of the flow within a tube measured by use of the single projection PIV algorithm described in Fouras et al., 2007.

Using the penetrating ability of X-rays, we can measure flows inside blood vessels but our pilot studies have revealed that there is a need for very high flux (and low exposure times) to accurately characterize physiological

flows. Using X-ray phase contrast, the blood cells themselves provide the seed particles for tracking flow, eliminating the need for tracking particles or other contrast agents. The very high speed, time resolved, phase contrast images that are uniquely available on BL20XU will allow in-vivo PIV flow measurements of the vascular flow.

Aims:

This study aimed to develop a new quantitative measure of in-vivo blood flow using the penetrating and high intrinsic contrast afforded by Phase Contrast X-ray Imaging coupled with the accurate and quantitative fluid dynamics information provided by Particle Image Veclocimetry (PIV). The ability to image flow using such a technique would find widespread application in the study of vascular disease. This study has two desired outcomes:

1. Development of the experimental methodology towards physiologically meaningful flow rates;
2. Application of the method to achieve significant measurements of both morphology and function of stenosed and occluded ex-vivo vasculatures.

Method and Results:

Initial experiments were conducted to gain necessary statistical information on the phase contrast speckle patterns caused by tissue, blood and contrast agent. This experiment used whole blood and blood+contrast agent pumped through custom-built in-vitro models. Dynamic sequences of phase contrast images were acquired. Due to unexpected differences in power (60Hz -vs- 50Hz) the contrast agent activation machine failed to operate properly and could not be used for flow measurements. We have now found a way to provide 50Hz, 240V power in the experimental hutch and this problem should not be repeated.

The methodology was advance significantly over this time. Improvements to experimental configuration allowing exposure times to be decreased by a factor of 300 were achieved. PIV flow data from these in-vitro models is of excellent quality and could lead to up to 3 publications.

Arteries were excised from mice and rats and placed in a custom design tissue chamber. Blood was perfused through the vessels at highest possible flow rates. Due to the success of experiments conducted as part of aim1, complete analysis of this data is yet to be completed and understanding of the success or lack of success of this aim is till limited. Despite problems with activation equipment for the contrast agent used, success with the contrast agent for use of visualisation has been achieved (see figure). At this time contrast agent was not able to be used for flow measurement.

Status of Publication and Patent:

1. Irvine, S.C., Paganin, D.M., **Jamison, R.A.**, **Dubsky, S.** & **Fouras, A.** (2009) Vector tomographic X-ray phase contrast velocimetry utilizing dynamic blood speckle. Submitted to Optics Express.
2. **Dubsky, S.**, **Jamison, R.A.**, Irvine, S.C., Siu, K.K.W., **Hourigan, K.** & **Fouras, A.** (2009) Computed tomographic X-ray velocimetry. Submitted to Applied Physics Letters.