

Abstract 185 Figure 1

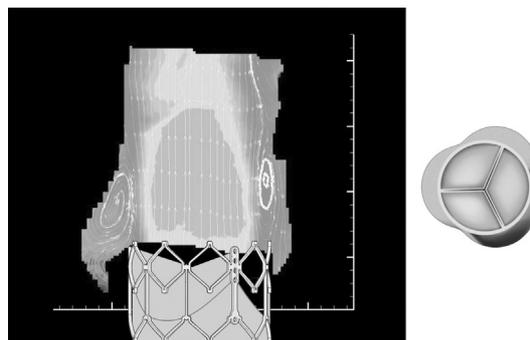
Purpose Many Transcatheter Aortic Valve Implant (TAVI) devices currently on the market offer little control over the rotational alignment of the bioprosthesis with the aortic root they are being inserted into, and the resultant flow dynamics are not fully understood. This study aims to identify how the valve orientation affects haemodynamics, both neglecting and including the presence of the native leaflets.

Methods Using an *in vitro* approach, commercially available TAVI devices were implanted into a mock silicone aortic root in four configurations encompassing the variations of aligned/non-aligned and without/with native leaflets present (Figure 1). Global flow information was obtained using pressure and flow transducers, and 2D Particle Image Velocimetry (PIV) was used to provide local and instantaneous flow data across the various configurations.

Results Analysis of the PIV images shows that a vortex is generated above each opening leaflet of the TAVI device, and another above or within the sinus of the root. If the commissures of the root and prosthetic valve are aligned, this results in these vortices merging to form only one major vortex. On the contrary, if the valve and root are misaligned, the two vortices remain separate, each impinging the central jet of fluid flow (Figure 2). This raises pressure losses, decreasing valve performance, and increasing turbulence and Reynolds shear stresses. This effect occurs both with and without the native leaflets, whose presence results in a significant reduction in the flow velocity observed in the sinuses.

Conclusion These results show that misalignment of a TAVI device with its destination root can lead to an alteration in vortical behaviour, leading to diminished valve performance. There is also increased occurrence of conditions which are conducive to the generation of thrombosis. The presence of native leaflets does not mitigate this vortical behaviour, and also reduces the systolic flow in the sinuses, possibly leading to increased stagnation. This fluid behaviour should be taken

into account when considering design and insertion of TAVI devices.



Abstract 185 Figure 2

186 REDUCED PERICYTE INSULIN SIGNALLING CAUSES ABNORMAL DEVELOPMENTAL ANGIOGENESIS

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Introduction Microvascular endothelial cells (ECs) are surrounded and supported by mural cells called pericytes. Via paracrine signalling and gap junctions, pericytes interact with ECs, modulating angiogenesis and vessel homeostasis. Diabetes-associated vascular complications are characterised by vascular leakage and dysfunctional neovascularization, both associated with pericyte loss in various vascular beds, including the retina. Pericytes are particularly sensitive to a hyperglycaemic environment, which results in their apoptosis and subsequent changes in vascular health. Insulin also has important

effects on pericyte biology *in vitro*, yet the significance of this *in vivo* and in regard to diabetes remains unexplored.

Methods Using a mouse model with a pericyte specific knock-out of the insulin receptor (PIR^{-/-}), created by crossing PDGFR β -Cre mice with insulin receptor – floxed – mice, we investigated the role of pericyte insulin signalling in developmental retinal angiogenesis *in vivo* and on pericyte function *in vitro*.

Results At postnatal day 5, PIR^{-/-} retinas show hyper-vascularized venous regions with an increase in venous vascular density (57.6 \pm 1.0% compared to 52.1 \pm 0.6% in littermate controls, $p=0.0003$) along with an increase in sprouting tip cell formation at the vascular front (1.7 \pm 0.05 versus 1.5 \pm 0.06 per 100 μ m in controls, $p=0.006$). Pericyte coverage at postnatal day 5 appears comparable in PIR^{-/-} and control, but pericyte abundance is strikingly reduced by 20% in the mature adult retinal vasculature (0.8 \pm 0.03 and 1.0 \pm 0.05 per 100 μ m in controls, $p=0.002$). However, the differential vascularity of neonatal retinas did not persist in adulthood (18.1 \pm 0.7 mm versus 18.3 \pm 0.5 mm per mm² region of interest in control). Basic metabolic phenotyping of adult mice shows no difference in body weight or fasting blood glucose levels (5.0 \pm 0.2 mmol/L and 4.7 \pm 0.2 mmol/L in PIR^{-/-} and control mice, respectively), but interestingly, preliminary assessment of pericyte function *in vitro* suggests enhanced proliferation of PIR^{-/-} pericytes.

Conclusions Pericyte-specific insulin receptor knockout affects developmental retinal angiogenesis *in vivo*. Sprouting and remodelling of the retinal vasculature are altered, associated with a reduction in pericyte coverage in adulthood, recapitulating some characteristics of proliferative diabetic retinopathy. The underlying molecular mechanism remains unclear, but these results indicate that adequate pericyte insulin signalling is important for pericyte function, and hence vascular stability.

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NOVEL THIENOPYRIDINES ARE POTENT ANTI-PLATELET DRUGS, INHIBITING PLATELET ACTIVATION, AGGREGATION AND SHOWING SYNERGY WITH ASPIRIN

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Background Management of Acute Coronary Syndromes (ACS) often involves the use of platelet inhibitors. The most commonly used drug, clopidogrel, belongs to a class of thienopyridine molecules which targets the P2Y₁₂ receptor on platelets and it is commonly used in combination with the COX-1 inhibitor acetylsalicylic acid (ASA). However, the effect of these treatments is variable amongst patients, highlighting a need for a refinement of this class of P2Y₁₂ inhibitor. The aim of this study was to assess the efficacy of six novel thienopyridine derivatives synthesised by our group by examining their potential as *in-vitro* inhibitors of platelet function.

Methods Healthy human platelets were isolated and incubated with novel thienopyridine compounds (DJ0081, DJ0199, DJ0021, DJ0206, DJ0171, DJ0097) (10 μ M, 30 min) prior to

stimulation with ADP (10 μ M) and analysis of alpha granule secretion (CD62P expression), GPIIb/IIIa activation (PAC1 expression) and platelet leukocyte aggregate (PLA) formation using flow cytometry. Furthermore, light transmission aggregometry (LTA) was used to assess ADP-stimulated aggregation after these treatments. Synergy with ASA (30 μ M) was also analysed by LTA following incubation with ASA and thienopyridine. All results were compared to ADP-stimulated samples and samples treated with clopidogrel (10 μ M, 30 min) prior to ADP stimulation.

Results All six novel compounds demonstrated a significant reduction in ADP-mediated platelet aggregation ($p<0.001$), CD62P expression ($p<0.001$), PAC1 expression ($p<0.01$) and PLA formation ($p<0.05$). These compounds were also shown to enhance the inhibitory effects of ASA. DJ0171 and DJ0199 were particularly potent, displaying greater inhibitory effect than clopidogrel.

Conclusion The study demonstrates the potential for new thienopyridine compounds as modulators of platelet function and points to the possibility of future use in patients at risk of platelet hyperactivity and thrombosis.

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DEVELOPMENT OF A NOVEL SOFTWARE PACKAGE FOR HIGH-THROUGHPUT PROCESSING AND ANALYSIS OF CARDIAC OPTICAL MAPPING DATA

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Background Optical mapping is a powerful research tool that is revolutionising study of cardiac electrophysiology. However, processing and analysis of optical mapping data is computationally challenging to design and implement, a difficulty further enhanced by novel camera technology providing higher temporal and spatial resolution. We have previously developed algorithms capable of objective processing and analysis of electrophysiological parameters acquired using a second-generation complementary metal-oxide semiconductor camera.¹ Here we report development of improved algorithms packaged in a user-friendly graphical interface, capable of high-throughput processing and analysis of voltage and calcium optical mapping data from a wide spectrum of cameras. Functionality and processing speed is further improved through automated recognition of pacing frequency and analysis of activation and repolarisation of electrophysiological parameters at high spatio-temporal resolution (200 \times 2400 pixels; sampling rate 1 kHz). Processing options allow averaging of multiple beats as well as individual beat segmentation within the whole experimental trace, thus allowing for study of dynamic changes in key parameters such as action potential duration (APD), activation times, conduction velocity (CV) and phase mapping.

Methods and results We have compared how our software performs in terms of analysis and processing time with our