Effects of Fluid Shear on Endothelial Cell Response to Inflammation

by

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# Table of Contents

Acknowledgements ii  
List of Figures v  
List of Abbreviations vi  
Abstract vii  

## Chapter

1.0 Endothelium and Inflammation Response 1  
1.1 Increasing Prevalence of Cardiovascular Diseases 4  
1.2 Treating Chronically Inflamed Endothelium 7  
1.3 Literature Review of *In Vitro* Inflammation Models 9  
1.4 Thesis Aims 18  

2.0 Materials and Methods 21  
2.1 Endothelial Cell Source and Cell Culture Methods 22  
2.2 Parallel Plate Flow Chamber 24  
2.3 IL-1β Concentration 28  
2.4 Calculating Shape Factor 30  
2.5 Activation of Endothelial Cells 31  
2.6 E-selectin Site Density Quantification 32  
2.7 Neutrophil Binding Assays 36  
2.8 Treating Neutrophils with Synthetic Cannabinoid CP55,940 37  
2.9 Statistical Methods 40  

3.0 *In Vitro* Model of IL-1β Shear-Cytokine Activation of Naïve Endothelial Cells 41  
3.1 IL-1β Static Activation or Shear-Only Stimulation of Naive Endothelial Cell 43  
3.2 IL-1β Shear-Cytokine Activation of Naïve Endothelial Cells 48  
3.3 Mechanism of Shear-Influenced E-selectin Synthesis 53  
3.4 Endothelial Morphology 55  
3.5 Endothelial Functionality 58  
3.6 Discussion 60  
3.7 Conclusion 64  

4.0 Increasing Physiological Relevance of the *In Vitro* Model 65  
4.1 IL-1β Activation of Preconditioned Endothelial Cells 67  
4.2 Fluid Shear Effects on Redosed Endothelial Cells 71  
4.3 Discussion 76  
4.4 Conclusion 82
### List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Schematic of leukocyte recruitment</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Time frame of shear-cytokine based experimental protocols</td>
<td>14</td>
</tr>
<tr>
<td>2.1</td>
<td>Parallel plate flow chamber (PPFC)</td>
<td>26</td>
</tr>
<tr>
<td>2.2</td>
<td>Schematic of in vitro setup</td>
<td>27</td>
</tr>
<tr>
<td>2.3</td>
<td>IL-1β saturating concentration</td>
<td>29</td>
</tr>
<tr>
<td>2.4</td>
<td>Immunofluorescence microscopy of HUVEC monolayers</td>
<td>34</td>
</tr>
<tr>
<td>2.5</td>
<td>RFI calibration</td>
<td>35</td>
</tr>
<tr>
<td>2.6</td>
<td>Neutrophil interaction with endothelial monolayer</td>
<td>39</td>
</tr>
<tr>
<td>3.1</td>
<td>E-selectin expression density of static or shear-only activated endothelial cells</td>
<td>45</td>
</tr>
<tr>
<td>3.2</td>
<td>E-selectin and PECAM-1 site densities</td>
<td>46</td>
</tr>
<tr>
<td>3.3</td>
<td>Cell morphology under shear flow</td>
<td>47</td>
</tr>
<tr>
<td>3.4</td>
<td>E-selectin expression on 10 dyn/cm² shear-cytokine activated ECs</td>
<td>50</td>
</tr>
<tr>
<td>3.5</td>
<td>E-selectin expression on 0-20 dyn/cm² shear-cytokine activated monolayers</td>
<td>51</td>
</tr>
<tr>
<td>3.6</td>
<td>24 hrs comparison for shear-cytokine activated monolayers</td>
<td>52</td>
</tr>
<tr>
<td>3.7</td>
<td>E-selectin expression on CHX-treated monolayers</td>
<td>54</td>
</tr>
<tr>
<td>3.8</td>
<td>Endothelial cell shape factors</td>
<td>57</td>
</tr>
<tr>
<td>3.9</td>
<td>Neutrophil binding assay for activated monolayers</td>
<td>59</td>
</tr>
<tr>
<td>4.1</td>
<td>E-selectin expression on preconditioned monolayers</td>
<td>69</td>
</tr>
<tr>
<td>4.2</td>
<td>Timeline of exposure to fluid shear</td>
<td>70</td>
</tr>
<tr>
<td>4.3</td>
<td>E-selectin expression on redosed monolayers</td>
<td>74</td>
</tr>
<tr>
<td>4.4</td>
<td>Comparing redosing methods</td>
<td>75</td>
</tr>
<tr>
<td>4.5</td>
<td>Shear-cytokine experimental protocols</td>
<td>77</td>
</tr>
<tr>
<td>5.1</td>
<td>E-selectin site density of TNFα or IL-1β activation</td>
<td>88</td>
</tr>
<tr>
<td>5.2</td>
<td>E-selectin site density of TNFα or IL-1β activation of preconditioned cells</td>
<td>91</td>
</tr>
<tr>
<td>5.3</td>
<td>E-selectin site density of combined and individual TNFα or IL-1β activation</td>
<td>95</td>
</tr>
<tr>
<td>5.4</td>
<td>Additive E-selectin site density of combined TNFα or IL-1β activation</td>
<td>102</td>
</tr>
<tr>
<td>6.1</td>
<td>Distribution of THC in the body</td>
<td>111</td>
</tr>
<tr>
<td>6.2</td>
<td>CP55,940-treated neutrophil interaction in buffer perfusion</td>
<td>115</td>
</tr>
<tr>
<td>6.3</td>
<td>Varying shear rates in buffer perfusion</td>
<td>116</td>
</tr>
<tr>
<td>6.4</td>
<td>CP55,940-treated neutrophil interaction in whole blood perfusion</td>
<td>117</td>
</tr>
</tbody>
</table>
List of Abbreviations

ACD  Acetate-citrate-dextrose
BAECs  Bovine aortic endothelial cells
CAM  Cell adhesion molecule
CB1R, CB2R  Cannabinoid Receptor 1 and Cannabinoid Receptor 2
CVD  Cardiovascular Disease
CHX  Cycloheximide
DPBS  Dulbecco’s phosphate buffered saline
EC  Endothelial cells
FITC  Fluorescein isothiocyanate
HAECs  Human aortic endothelial cells
HSA  Human serum albumin
HUVECs  Human umbilical vein endothelial cells
I/R  Ischemia/reperfusion
ICAM-1  Intercellular cell adhesion molecule-1
IL-1R  Interleukin-1 receptor
IL-1β  Interleukin-1beta
LPS  Lipopolysaccharide
MMP  Matrix metalloproteinase
NF-κB  Nuclear factor kappa B
NK  Natural killer
PECAM-1  Platelet-endothelium cell adhesion molecule-1
PPFC  Parallel plate flow chamber
PS  Preshear, or precondition
RBCs  Red blood cells
RFI  Relative fluorescent intensities
SF  Shape factor
TNFR  Tumor necrosis factor receptor
TNFα  Tumor necrosis factor alpha
VCAM-1  Vascular cell adhesion molecule-1
Δ⁹-THC  Delta-9-tetrahydrocannabinol
ABSTRACT

Effects of Fluid Shear on Endothelial Cell Response to Inflammation

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Chair: Omolola E. Adefeso

The endothelium is a thin monolayer of cells (e.g. endothelial cells, ECs) that regulates several important processes including maintaining blood pressure, clotting, angiogenesis, barrier function, and inflammation. Inflammation, a natural process by which foreign particles are eliminated from vascular tissue, is of considerable importance due its prevalent role in a number of disease pathologies. Endothelial response to inflammation results in the differential expression of cell adhesion molecules, such as E-selectin, on the apical surface facing the bloodstream. Patterns and duration of adhesion molecule expression is critical to the balance between healthy and pathogenic inflammatory response. Chronic inflammation, due to endothelial dysfunction leads to a number of diseases, which include neurological disorders, cancers and metastatic tumor growths, and cardiovascular diseases. Despite its prominent roles in the disease pathogenesis, endothelial response has yet to be fully understood due to current in vitro
models failing to fully replicate relevant endothelial inflammatory response under human physiological conditions.

The influence of fluid shear stress on E-selectin expression due to inflammatory activation is investigated through simultaneous co-stimulation with fluid shear and cytokine interleukin-1β of naïve and preconditioned ECs using a novel laminar flow apparatus designed to study the broader time frame over which chronic inflammation is relevant. Naïve cells exposed to shear-cytokine activation display high E-selectin expression for up to 24 hr with peak expression occurring after 8-12 hr of activation contrary to the commonly observed 4-6 hr peak in statically activated cells. High shear preconditioned cells exhibited either elevated or muted E-selectin expression during acute and chronic time frames, respectively, depending on the preconditioning and subsequent shear-cytokine activation durations. The 8-12 hr peak E-selectin expression time in shear-cytokine activated cells coincides with the time frame observed for shear-exposed ECs to shift from a cobblestone to elongated morphology, highlighting a role for cell morphology determining EC response. Overall, the presented data suggest that a high laminar shear enhances acute EC response to interleukin-1β in naïve ECs as may be found in the pathological setting of ischemia/reperfusion injury while in preconditioned ECs, high laminar shear confers rapid E-selectin downregulation to protect against chronic inflammation. However, high laminar shear is protective against TNFα-induced acute and chronic inflammatory response.