

Effects of Fluid Shear on Endothelial Cell Response to Inflammation

by

Ryan B. Huang

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Doctoral Committee:

Assistant Professor Omolola E. Adefeso, Chair
Professor Jennifer J. Linderman
Professor Shuichi Takayama
Assistant Professor Peter J. Woolf

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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 <i>In Vitro</i> 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-1 β 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 <i>In Vitro</i> Model of IL-1 β Shear-Cytokine Activation of Naïve Endothelial Cells	41
3.1 IL-1 β Static Activation or Shear-Only Stimulation of Naive Endothelial Cell	43
3.2 IL-1 β 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 <i>In Vitro</i> Model	65
4.1 IL-1 β Activation of Preconditioned Endothelial Cells	67
4.2 Fluid Shear Effects on Redosed Endothelial Cells	71
4.3 Discussion	76
4.4 Conclusion	82

5.0	Comparing TNF α and IL-1 β Activation	84
5.1	TNF α Activation of Naïve Endothelial Cells	86
5.2	TNF α Activation of Preconditioned Endothelial Cells	89
5.3	TNF α and IL-1 β Co-Stimulation	92
5.4	Discussion	96
5.5	Conclusion	103
6.0	Potential Applications in Therapeutic Treatment	104
6.1	Anti-Inflammatory Effects of Cannabinoids	106
6.2	CP55,940 Concentration	109
6.3	CP55,940 Effect on Neutrophils in Buffer and Whole Blood	112
6.4	Discussion	118
6.5	Conclusion	121
7.0	Conclusion	123
7.1	Future Direction	127
	References	132

List of Figures

Figure		
1.1	Schematic of leukocyte recruitment	3
1.2	Time frame of shear-cytokine based experimental protocols	14
2.1	Parallel plate flow chamber (PPFC)	26
2.2	Schematic of in vitro setup	27
2.3	IL-1 β saturating concentration	29
2.4	Immunofluorescence microscopy of HUVEC monolayers	34
2.5	RFI calibration	35
2.6	Neutrophil interaction with endothelial monolayer	39
3.1	E-selectin expression density of static or shear-only activated endothelial cells	45
3.2	E-selectin and PECAM-1 site densities	46
3.3	Cell morphology under shear flow	47
3.4	E-selectin expression on 10 dyn/cm ² shear-cytokine activated ECs	50
3.5	E-selectin expression on 0-20 dyn/cm ² shear-cytokine activated monolayers	51
3.6	24 hrs comparison for shear-cytokine activated monolayers	52
3.7	E-selectin expression on CHX-treated monolayers	54
3.8	Endothelial cell shape factors	57
3.9	Neutrophil binding assay for activated monolayers	59
4.1	E-selectin expression on preconditioned monolayers	69
4.2	Timeline of exposure to fluid shear	70
4.3	E-selectin expression on redosed monolayers	74
4.4	Comparing redosing methods	75
4.5	Shear-cytokine experimental protocols	77
5.1	E-selectin site density of TNF α or IL-1 β activation	88
5.2	E-selectin site density of TNF α or IL-1 β activation of preconditioned cells	91
5.3	E-selectin site density of combined and individual TNF α or IL-1 β activation	95
5.4	Additive E-selectin site density of combined TNF α or IL-1 β activation	102
6.1	Distribution of THC in the body	111
6.2	CP55,940-treated neutrophil interaction in buffer perfusion	115
6.3	Varying shear rates in buffer perfusion	116
6.4	CP55,940-treated neutrophil interaction in whole blood perfusion	117

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-1 β	Interleukin-1 beta
LPS	Lipopolysaccharide
MMP	Matrix metalloproteinase
NF- κ B	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
TNF α	Tumor necrosis factor alpha
VCAM-1	Vascular cell adhesion molecule-1
Δ^9 -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-1 β 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-1 β 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 TNF α -induced acute and chronic inflammatory response.