Biomechanical stress: Its Association with Atherosclerosis and Cardiovascular/Cerebrovascular Disease

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A chronic, inflammatory, fibroproliferative disease found in the intima of arterial vessels.

Although the entire vasculature is exposed to the atherogenic effects of risk factors (cholesterol, hypertension, diabetes,…) lesions generally occur in specific arteries (carotids, coronaries, infrarenal-abdominal and iliofemoral).
The resistance to flow in the circulation is determined by vessel geometry and hemorheology/viscosity ($\eta$).

\[ R = \left[ \frac{(8 \cdot l)}{(\pi \cdot r^4)} \right] \times \eta \]
Hemorheology is the science of blood flow in relation to pressure, flow, volumes, and resistances in blood vessels.

\[ \eta = \frac{R}{(8 \cdot l) / (\pi \cdot r^4)} \]

Shear stress
Shear rate
Hemorheological Principles

**Shear Stress:** the force per unit area applied to a fluid layer producing its movement relative to the adjacent layers or the force parallel to the vessel wall.

**Shear Rate:** the velocity gradient between two adjacent fluid layers.
Model of shear stress/rate

Wall shear rate = difference in velocity (ms\(^{-1}\)) \approx \frac{V_d}{d}

Wall shear stress = wall shear rate \times viscosity

Endothelial Mechanosensors of Shear Stress

Endothelial cell (EC) response to shear stress includes the synthesis of vasoactive mediators to control vascular tone, that is, nitric oxide causing an immediate reduction in shear stress, extracellular matrix proteins and matrix metalloproteinases to promote remodeling and repair, and growth factors expression such as TGF-β to control cell survival and proliferation.

Integrin-linked kinase (ILK) in the cardiovascular system. Overexpression leads to cardiac hypertrophy, whereas ILK suppression leads to dilated cardiomyopathy. ILK also plays a critical role in the recovery after myocardial infarction and atherosclerotic plaque development.

Viscosity of Newtonian (plasma/water) and Non-Newtonian (blood) Fluids

- Blood
- Plasma
- Water
Model of Atherogenesis and Shear Stress

Physiologic Arterial Shear Stress ($\tau_s > 15$ dyne/cm$^2$)
- Anticoagulant Antithrombotic State
- EC Quiescence
  - Proliferation
  - Apoptosis
- Paracrine Quiescent State
  - TGF-$\beta$
  - NO/eNOS
  - Prostaglandin Synthase
  - adrenomedullin
  - ED
- High EC Antioxidant Activity
  - COX-1, 2
  - Mn SOD
  - Cu/Zn SOD

Low Arterial Shear Stress ($\tau_s \approx 0-4$ dyne/cm$^2$)
- Oscillatory Slow Flow
- Procoagulant Prothrombotic State
- Monocyte Activation
  - $\tau_s$
  - NO
  - tPA

Hemodynamic Shear Stress in The Vasculature

**A**

- Radius ($R$)
- Blood Flow ($Q$)
- Blood Viscosity ($\mu$)
- Shear Stress ($\tau_s$)

**B**

- Normal Vein
- Normal Artery
- Atherosclerosis-Prone Arterial Regions
- High-Shear Thrombosis (Complex Plaque, Cardiac Valves, Stents)

Poiseuille's Law: $\tau_s = \frac{4\mu Q}{\pi R^3}$

Range of Wall Shear Stress Magnitude

- Normal Vein
- Normal Artery
- Atherosclerosis-Prone Arterial Regions
- High-Shear Thrombosis (Complex Plaque, Cardiac Valves, Stents)

Shear Stress, dyne/cm²

Effect of Flow Disturbances on Progression of Atherosclerosis (Carotid Artery)

Infrarenal-Abdominal Aorta
IMT* and Shear Stress

* Intima Media Thickness
Coronary Blood Flow During the cardiac Cycle

Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).
Different Heart Rates and Total Cardiac Beats Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Rates 60 Beats/min</th>
<th>Rates 80 Beats/min</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td>3,600</td>
<td>4,800</td>
<td>1,200</td>
</tr>
<tr>
<td>24 hours</td>
<td>86,400</td>
<td>115,200</td>
<td>28,800</td>
</tr>
<tr>
<td>1 Year</td>
<td>31,360,00</td>
<td>42,048,000</td>
<td>10,688,000</td>
</tr>
<tr>
<td>10 Years</td>
<td>315,360,000</td>
<td>420,480,000</td>
<td>106,880,000</td>
</tr>
</tbody>
</table>
Elevated HR (≥70 bpm) as a predictor of CV Death in a population with stable CAD and LV dysfunction.

$P = 0.0041$

Cardiovascular death

Event rate (%)

0 5 10 15

0 0.5 1 1.5 2

Years

Heart rate ≥70 bpm

Heart rate <70 bpm

Tardif J Br Med Bull 2009;90:71-84
Proposed Natural History of Atherosclerosis

## Blood Vessel Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean diameter</th>
<th>Mean wall thickness</th>
<th>Endothelium</th>
<th>Elastic tissue</th>
<th>Smooth muscle</th>
<th>Fibrous tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>4.0 mm</td>
<td>1.0 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriole</td>
<td>30.0 μm</td>
<td>6.0 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary</td>
<td>8.0 μm</td>
<td>0.5 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venule</td>
<td>20.0 μm</td>
<td>1.0 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein</td>
<td>5.0 mm</td>
<td>0.5 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Circulatory System

The Circulatory System

The Coronary Capillary Circulation

1) 8 million capillaries in the heart.
2) 90% of myocardial blood volume.
3) 1 ml of blood ≈ 1 year to travel through a single capillary.

Vascular Resistance in the Coronary Vessels

\[ R = \left[ \frac{8 \times l}{\pi \times r^4} \right] \times \eta \]

Vascular Resistance in the Coronary Vessels

\[ R = \left[ \frac{8 \times l}{\pi \times r^4} \right] \times \eta \]

Mediators of Blood Viscosity

- Hematocrit
- Shear Forces
- RBC Deformability
- Blood Viscosity
- RBC Aggregation
- Plasma Viscosity
- Plasma Proteins
- Lipoproteins

Red Blood Cell Deformability

RBC Life Cycle

water balloon → RBC Life Cycle → raisin

0 → Day 120
Effects of RLP* (0.5 mg of triglyceride/mL) on the shape of human RBCs

*RLP = Remnant lipoproteins

Erythrocytes and Capillary Flow

Healthy RBCs deform, passing through a capillary vessel.

Capillary plugging as RBCs lose deformability.
The Fahraeus-Lindqvist Phenomenon and the Dintenfass Inversion Phenomenon

Dintenfass L. Angiology. 1985;315-26
The Aggregation of RBC’s* is Influenced by:

- Mechanical shearing force
- Macromolecular bridging force among RBC’s
- Electrostatic repulsive force among RBC’s
- Bending force of the RBC membrane
- Shape of RBC’s
- Concentration of RBC’s

* RBC’s = red blood cells

Maeda N, shiga T. Biochimica et biophysica. (1986); 855:127-35
Plasma Proteins and RBC Aggregation

RBC electrostatic repulsion at a maximum of 25 nm. LDL (30 nm), IGM (100 nm) and Fibrinogen (47 nm) form RBC bridges. HDL (10 nm) occupy RBC binding sites and prevent bridge formation.

Moriarty PM, Gibson CA. Cur Opin Cardiol. 20:318-23. 2005
Fibrinogen and Plasma Viscosity

Fibrinogen is only 4% of plasma protein content but due to its size (341,000 MW) and shape it accounts for 20% of plasma viscosity

HDL Lowers Blood Viscosity

Blood Viscosity (100s⁻¹, mPa⋅s)

HDL (mmol/L)

R = -0.46, p = 0.0003

Corrected Blood Viscosity (100s⁻¹, mPa⋅s)

HDL (mmol/L)

R = -0.49, p < 0.0001

**Association between CV Risk factors and Hemorheological Variables**

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen</th>
<th>Plasma Viscosity</th>
<th>RBC deformability</th>
<th>RBC Aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Htn</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lipids</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tob</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DM</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stress</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Ernst E, Koenig W. Thrombosis and Hemostasis. Vol 19, No.2, 1993
Hematocrit differences from Cord and Maternal Blood
(patients n=23)

<table>
<thead>
<tr>
<th>Blood Vessel</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical Vein</td>
<td>48</td>
</tr>
<tr>
<td>Umbilical Artery</td>
<td>48</td>
</tr>
<tr>
<td>Placental Vein</td>
<td>49</td>
</tr>
<tr>
<td>Maternal Vein</td>
<td>38</td>
</tr>
</tbody>
</table>

## Viscosity differences between Cord and Maternal Blood

<table>
<thead>
<tr>
<th>Viscosity (cp)</th>
<th>Maternal</th>
<th>Cord</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>19.44</td>
<td>19.96</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma</td>
<td>1.86</td>
<td>1.12</td>
<td>P &lt; .0005</td>
</tr>
<tr>
<td>Serum</td>
<td>1.22</td>
<td>0.92</td>
<td>P &lt; .0005</td>
</tr>
</tbody>
</table>

### Plasma Proteins differences between Cord and Maternal Blood

<table>
<thead>
<tr>
<th>Proteins (g/L)</th>
<th>Maternal</th>
<th>Cord</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>65.37</td>
<td>59.35</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin</td>
<td>35.9</td>
<td>37.2</td>
<td>NS</td>
</tr>
<tr>
<td>IgM</td>
<td>2.38</td>
<td>0.48</td>
<td>P &lt; 0.0005</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>4.25</td>
<td>1.81</td>
<td>P &lt; 0.0005</td>
</tr>
</tbody>
</table>

Lipid-apheresis

• Lowers LDL-C by 70% in patients with Familial Hypercholesterolemia
• Improves hemodynamics
  – immediate increase in microvascular perfusion and myocardial blood flow.
  – Lowers vascular resistance.
• Thought to be a result of improved endothelial function and hemorheology.
Mean Percentage Reduction of Plasma Proteins with Different Methods of Lipid-apheresis

<table>
<thead>
<tr>
<th>Protein</th>
<th>MDF</th>
<th>Lipid Filtration</th>
<th>HELP</th>
<th>DALI</th>
<th>DSA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>56-62%</td>
<td>61%</td>
<td>55-61%</td>
<td>53-76%</td>
<td>49-75%</td>
<td>62-69%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>25-42%</td>
<td>6%</td>
<td>5-17%</td>
<td>5-29%</td>
<td>4-17%</td>
<td>9-27%</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>53-59%</td>
<td>61%</td>
<td>55-68%</td>
<td>28-74%</td>
<td>19-70%</td>
<td>51-71%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>37-49%</td>
<td>56%</td>
<td>20-53%</td>
<td>29-40%</td>
<td>26-60%</td>
<td>34-49%</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>52-59%</td>
<td>42%</td>
<td>51-58%</td>
<td>13-16%</td>
<td>17-40%</td>
<td>15-21%</td>
</tr>
</tbody>
</table>

*High variation of values are partially due to differences in treated plasma and blood volumes.  
*MDF, membrane differential filtration; HELP, heparin-induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; DSA, dextrum sulfate adsorption; IA, immunoadsorption.

Moriarty PM. Clinical Lipidology, Ballantyne: A Companion to Braunwald’s Heart Disease; 363-74. 2009
Improvement of RBC Deformability with Lipid-Apheresis


(r = -0.563)  
P<0.001
## Plasma Viscosity (PV) and RBC Aggregation (RBCA) after Lipid-Apheresis

<table>
<thead>
<tr>
<th></th>
<th>PV (mPa s)</th>
<th>RBCA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>1.30</td>
<td>7.9</td>
</tr>
<tr>
<td>After</td>
<td>1.1 (16%)</td>
<td>3.7 (53%)</td>
</tr>
</tbody>
</table>

**Acute Blood Viscosity reduction following Lipid-apheresis**

<table>
<thead>
<tr>
<th>Shear Rate (sec-1)</th>
<th>Pre-Apheresis (cP)</th>
<th>Post-Apheresis (cP)</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>3.72</td>
<td>3.08</td>
<td>-21*</td>
</tr>
<tr>
<td>90</td>
<td>4.54</td>
<td>3.82</td>
<td>-19*</td>
</tr>
<tr>
<td>45</td>
<td>5.21</td>
<td>4.43</td>
<td>-18*</td>
</tr>
<tr>
<td>11.2</td>
<td>7.94</td>
<td>6.92</td>
<td>-15*</td>
</tr>
</tbody>
</table>

*cP = centipoise  
*p <0.01

Moriarty PM; Gibson C. AJC 2004;1044-46
Endothelial Function Improvement Following Lipid-apheresis

FBF (forearm blood flow) | Ach (acetylcholine) | SNP (sodium nitroprusside)

Osamu T. Circulation vol 95, No1. 1/7/97
### Vasodilatation Capacity after Single Lipid-apheresis
(18 hours post therapy)

<table>
<thead>
<tr>
<th>Flow Dynamics</th>
<th>Pre-Apheresis</th>
<th>Post- Apheresis</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MBF</strong> (ml/min100g)</td>
<td>173</td>
<td>226</td>
<td>23%*</td>
</tr>
<tr>
<td><strong>CFR</strong></td>
<td>1.91</td>
<td>2.48</td>
<td>23%**</td>
</tr>
<tr>
<td><strong>MCR</strong> (mmHg per 100g/ml)</td>
<td>0.61</td>
<td>0.43</td>
<td>29%**</td>
</tr>
</tbody>
</table>

MBF = Myocardial Blood Flow
CFR = Coronary Flow reserve
MCR = Minimal Coronary resistance

*Mellwig KP. Atherosclerosis 1998; 139:173-178*

*p<0.01; **p<0.02
Hemodynamic Changes 3 weeks post Lipid-apheresis

<table>
<thead>
<tr>
<th></th>
<th>Before apheresis</th>
<th>After apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>143 ± 3</td>
<td>136 ± 3*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73 ± 3</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>85 ± 5</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>Mean pressure (mm Hg)</td>
<td>97 ± 3</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>24 ± 3</td>
<td>17 ± 4* (29%)</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; n = 10 patients.
PRU, peripheral resistance unit
*p<0.05 before vs. after apheresis.

Conclusion:

- Hemorheology plays an essential localizing role in microvascular disease and atherosclerosis plaque formation.

- Although hemodynamic forces are not by themselves responsible for the pathogenesis of atherosclerosis, they prime the local vascular wall in which the lesion develops.

- Lipid-apheresis acutely lowers blood viscosity. Its use may be considered for vascular diseases involving abnormal hemorheology.