Physics of Carotid Artery Stenosis and Plaque Stability

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Burden of Carotid Artherosclerotic Disease

**Case:** 62 year old female, with 30 pack year h/o smoking, on simvastatin for hyperlipidemia and HCTZ for hypertension presents with a single episode of weakness and numbness in her right arm. The episode lasted 20 minutes and resolved completely within one hour. On exam, patient has an audible bruit over the left carotid artery. In the vascular lab, carotid duplex showed:

![Carotid Artery Image]

- PSV = 380 cm/sec
- EDV = 155 cm/sec
- ICA/CCA ratio = 7.5

Post-stenotic turbulence is noted, plaque is described as heterogeneous primarily echo-lucent with areas of echo-dense calcifications.

**Diagnosis:** transient ischemic attack (TIA) 2/2 left internal carotid disease
Burden of Carotid Artherosclerotic Disease

- carotid disease comprises up to 45% of all stroke (30% from ischemic damage as a stenotic internal carotid artery closes and 15% from embolic sources as carotid plaques rupture and embolise).

- stroke remains the 3rd leading cause of death in the United States - accounting for an average 500,000 yearly deaths.
Does Treating Carotid Disease Make a Difference?

• Symptomatic patients (h/o TIA or amaurosis fugax) with >70% stenosis

  *North American Symptomatic Carotid Endarterectomy Trial (NASCET)* and *European Carotid Surgery Trial (ECST)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2-year stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>~ 40%</td>
</tr>
<tr>
<td>medical (asprin)</td>
<td>~ 26%</td>
</tr>
<tr>
<td>surgical (CEA)</td>
<td>~ 9%</td>
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</tbody>
</table>

• Asymptomatic patients with >70% stenosis (incidental finding)

  *Asymptomatic Carotid Artery Stenosis Study (ACAS)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2-year stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>medical (asprin)</td>
<td>~ 10%</td>
</tr>
<tr>
<td>surgical (CEA)</td>
<td>~ 5%</td>
</tr>
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</table>
Determining the threshold for symptoms

- in asymptomatic carotid disease necessary to characterize the **stability** of carotid athroslerotic plaque - three major parameters:

1. **Degree of artery narrowing**
   - arterial angiography gold standard but largely replaced with duplex doppler ultrasound method - direct measurement vs. velocity correlation

2. **Mechanical stability of athrosclerotic plaque**
   - calcified vs. non-calcified, homogeneous vs. heterogeneous, irregular vs. regular endoluminal geometry

3. **Thrombogenicity of luminal (plaque) surface**
   - proximity of necrotic core to lumen, lumen irregularities and eccentricity, complex fluid dynamics within narrowing producing strong regions of stagnant pro-thrombotic flow
Degree of Artery Narrowing using Duplex US

Principles of Doppler US \((r = \text{receiver}, s = \text{source})\)

\[
f = \left(\frac{v + v_r}{v + v_s}\right) f_o \quad \Rightarrow \quad f = \left(\frac{v}{v + v_s} + \frac{v_r}{v + v_s}\right) f_o \approx \left(1 + \frac{v_r}{v}\right) f_o \quad \text{for } v >> v_{s,r}
\]

\[
f - f_o = \frac{v_r}{v} f_o \quad (\text{Doppler Shift Frequency})
\]

\[
v_r (\text{velocity of blood cells}) = \frac{f - f_o}{f} v
\]

\(f_o = \text{US probe frequency}\)

\(f = \text{measured reflected frequency}\)

\(v = \text{velocity of US waves in tissue - constant}\)

Sweep through frequency range of 2=10 MHz, FFT reflected frequency, convert to blood velocity
Important considerations in Doppler

\[ f = \left( \frac{v + v_r}{v + v_s} \right) f_o \quad \Rightarrow \quad v_r(\text{velocity of blood cells}) = \frac{f - f_o}{f} \]

• reflected signal sensitive to angle between probe and flowing cells (typical angle used ~ 60 degrees)

• to average out noise frequency sweep must be extensive so that Fourier transform is well powered

• blood velocity measurements using Doppler US are accurate but very sensitive to operator parameters necessitating a good well validated vascular lab.

• most Doppler derived velocities in trials are for 2D measurements that provide velocity data for a given axial cut of the artery only - 3D integrated velocities would be more representative of the actual flow fields.
Correlating Blood Velocity to Artery Geometry

- comparison studies of Doppler US velocities in patients having simultaneous angiography - 2003 Consensus Panel thresholds:

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>PSV (cm/sec)</th>
<th>EDV (cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>125</td>
<td>40</td>
</tr>
<tr>
<td>60%</td>
<td>170</td>
<td>n/a</td>
</tr>
<tr>
<td>70%</td>
<td>230</td>
<td>100</td>
</tr>
</tbody>
</table>

- physical basis of increasing velocity with increasing stenosis

*Bernouilli’s principle*: in non-dissipating liquid (inviscid flow) the energy within each pocket of fluid must be conserved; meaning the fluids kinetic energy (velocity) and potential energy (pressure) add up to a constant value.

*Conceptual Bernouilli*: if the length of $\chi\alpha = \alpha\beta$, the fluid density can *NOT* change, then the volume of fluid passing across $\chi\alpha$ must equal that across $\alpha\beta$ in any given time interval.
Bernouilli and why velocity increases in a narrower pipe

\[ I_{\chi \alpha} = \frac{dV_{\chi \alpha}}{dt_{\chi \alpha}} = \frac{dV_{\alpha \beta}}{dt_{\alpha \beta}} = I_{\alpha \beta} \]

\[ V_{\chi \alpha} = A_{\chi \alpha} h > A_{\alpha \beta} h = V_{\alpha \beta} \]

\[ \frac{d(A_{\chi \alpha} h)}{dt_{\chi \alpha}} = A_{\chi \alpha} \frac{dh}{dt_{\chi \alpha}} + h \frac{dA_{\chi \alpha}}{dt_{\chi \alpha}} \quad \frac{d(A_{\alpha \beta} h)}{dt_{\alpha \beta}} = A_{\alpha \beta} \frac{dh}{dt_{\alpha \beta}} + h \frac{dA_{\alpha \beta}}{dt_{\alpha \beta}} \]

\[ \frac{d(A_{\chi \alpha} h)}{dt_{\chi \alpha}} = A_{\chi \alpha} \frac{dh}{dt_{\chi \alpha}} = A_{\alpha \beta} \frac{dh}{dt_{\alpha \beta}} = \frac{d(A_{\alpha \beta} h)}{dt_{\alpha \beta}} \]

given that \( A_{\chi \alpha} > A_{\alpha \beta} \) the equality holds provided \( \frac{dh}{dt_{\chi \alpha}} < \frac{dh}{dt_{\alpha \beta}} \)
Poiseuille and viscous flow

- Bernouilli’s principle tells us that velocity in a narrow carotid artery should increase simply because of the geometry and conservation of volume. Blood however is a viscid fluid thus a narrower vessel should have higher flows also due to Poiseuille’s principle for viscous flows:

By Bernouilli’s principle we know there is a pressure drop across the stenosis

$$\Delta P = \left( \frac{8\mu LI}{\pi r^4} \right)$$

Using Poiseuille’s law, the pressure drop coupled with the degree of narrowing can be related to an increase in blood velocity across the stenosis.

$$I = \left( \frac{\pi \Delta Pr^4}{8\mu L} \right)$$

*Both viscous and inviscid effects couple to produce the velocity increase in stenotic arteries - providing a conceptual physical picture as to why velocities should increase as a non-linear function of increasing stenosis.*
Further complexity to the real artery problem

• pipe flow equations are derived with the assumption of rigid walls while arteries and plaques are soft and flexible.

\[
\frac{d(A_{\alpha\beta} h)}{dt_{\alpha\beta}} = A_{\alpha\beta} \frac{dh}{dt_{\alpha\beta}} + h \frac{dA_{\alpha\beta}}{dt_{\alpha\beta}} \quad \text{where} \quad \frac{dA_{\alpha\beta}}{dt_{\alpha\beta}} \neq 0
\]

\[
\frac{dA_{\alpha\beta}}{dt_{\alpha\beta}}
\]
represents the dynamic elastic strains that a stretchable and bendable artery can experience as a function of pressure waves during the cardiac cycle as well as fluid mechanical/elastic coupling.

• new area of richness in artery/plaque stability:

\[
\Rightarrow \quad \text{softer plaques will bend more easily and be more subject to pinch-off closure instabilities}
\]
* Marks area where stenotic artery is under high compressive stress and likely to buckle, possibly producing closure even in the absence of plaque rupture and thrombosis.
High flow rates equal high shear at artery wall

(a) Symmetric Stenosis. SO=70%, Ecc=0%

\[
\begin{align*}
&z=2.2\text{cm} \\
&V_{\text{max}} = 564.8\text{cm/s} \\
&V_{\text{max}} = 21.3\text{cm/s}
\end{align*}
\]

(b) Asymmetric Stenosis. SO=70%, Ecc=50%

\[
\begin{align*}
&z=2.2\text{cm} \\
&V_{\text{max}} = 529.8\text{cm/s} \\
&V_{\text{max}} = 22.4\text{cm/s}
\end{align*}
\]

\[
\begin{align*}
&z=9.2\text{cm} \\
&V_{\text{max}} = 60.2\text{cm/s} \\
&V_{\text{max}} = 65.0\text{cm/s}
\end{align*}
\]

FIGURE 6. Flow velocity plots showing that asymmetric stenosis leads to larger region of flow separation.

- as stenosis progresses, velocity and shear rate, the amount of fluid energy transferred from the blood to the arterial wall, increase:

\[
\frac{d\gamma}{dt} = \left( \frac{4I}{\pi r^3} \right)
\]

Velocity \((I)\) increasing and \(r\) decreasing both drive shear rate increase - making plaque very vulnerable to embolization!
Factors in plaque stability

Mechanical determinants of plaque modeling, remodeling and disruption

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Table 1
Morphological correlates of plaque instability

Factors associated with disruption
- Large plaque with marked stenosis
- Juxtaposed regions of contrasting composition (calcification, necrotic core, fibrosis, hematomas)
- Lumen irregularities and asymmetry (thromboses and cavitations)
- Focal thinning or defects of the fibrous cap (erosion, inflammation, neoformation of atherosclerosis)
- Proximity of the necrotic core to the fibrous cap or lumen surface

Features implying resistance to disruption
- Uniform plaque fibrosis on cross-section
- Circular, regular lumen contour
- Demarcated fibrous cap of uniform thickness (with absence of focal erosion, inflammation and proximity of necrotic core)

Table 2
Clinical evaluation of advanced plaques: problems arising in establishing reliable morphological criteria

Geometric factors
- Circumferential asymmetry of plaque localization
- Axial and circumferential variation in plaque size and composition

Plaque evolution
- Uncertainty of plaque evolution
- Occurrence of focal disruptions in apparently stable plaques
- Often small, inapparent nature of sites of actual or potential disruption
- Uncertain nature of lumen irregularities

Technological
- Current limits (in specificity and sensitivity) of imaging methods
Calcium and Plaque Stability

Calcium is well known to condense self-assembled lipid systems.

Addition of calcium for many lipids is equivalent to decreasing the temperature.

Possibly in lipid rich plaques the presence of high concentrations of calcium changes the phase behavior of the lipids making them more condensed thus mechanically stiffer and more resilient to the fluid mechanical and elastic stresses.