Vascular Effects of Caffeine

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About Myself

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Current: Memorial Hermann Healthcare System, Hams Health System, The University of Texas Health Science Center at Houston, Harvard Medical School
Education: The George Washington University - School of Business

Houston Early Age Risk Testing & Screening Study (HEARTS™)

Photos from a high school event: Dr. John Higgins & Houston Fire/EMS center, Clive Mutumba team up to help save young athletes from sudden death.

What is HEARTS™?
HEARTS™ is a study to detect any abnormal heart conditions that can cause the heart to arrest suddenly and unexpectedly stop beating.

HEARTS™ study aims:
1. To develop an efficient & economical process whereby 6th grade students receive a 15-minute cardiovascular screen.

CLINICAL QUESTIONS

ON-THE-SPOT ANSWERS TO YOUR COMMON CLINICAL QUESTIONS

JOHN HIGGINS
ASIF ALI • DAVID FILSOOF

FOX 26
9-13 78°
VIRAL CARDIOMYOPATHY

THE SAN FRAN
MEMORIAL
Aramco Houston Marathon
Chevron Houston Marathon
3:11:49
Outline

• Endothelial Cell Function (ECF)
• Caffeine at rest improves ECF
• Caffeine blocks Adenosine Receptors
• Caffeine + exercise decreases ECF
• Energy Drink at rest decreases ECF
• Research at UTHealth
• Conclusions
Endothelial Cell Function (ECF)
Endothelial Cell (EC)

ECs:
- Form the inner lining of blood vessels
- Have basal & inducible metabolic/synthetic functions
- Carry out multiple important tasks

Normal ECF

Normal ECF is important to regulate vascular resistance (vessel tone & variation).

Dynamic continuum:
• Vascular tone
• Thrombosis
• Barrier

Normal ECF
- Vasodilating
- Thromboresistant
- Anti-adhesive
(NO, PG12, Endothelium-derived hyperpolarizing factor, Bradykinin)

Abnormal ECF
- Vasoconstricting
- Procoagulant
- Pro-adhesive
(Renin, Angiotensin, ET-1)
Abnormal ECF

- **Short Term**: During stress and with certain exposures, the impaired ability to dilate the coronary arteries could
  - Result in supply-demand imbalance/coronary spasm
  - Potentially leading to myocardial ischemia or cardiac arrhythmia.

- **Long Term**: Atherosclerosis
  - CVD, PAD, CAD
ECF

Improvement in ECF is a desirable goal:

• Exercise
• Smoking cessation
• Antioxidants (vit C, flavonoids-dark chocolate)
• Cholesterol lowering (Statins)
• Omega-3 fatty acids
• Glycemic control in DM
• L-arginine (\(\rightarrow\)NO)
• ACEI/ARB

Caffeine at Rest Improves ECF
Caffeine & ECF

Caffeine increases intracellular calcium

Expression of the endothelial nitric oxide synthase (eNOS) enzyme

Stimulates EC production of nitric oxide (NO)

NO diffuses to the vascular smooth muscle

VSMC vasodilation

Artery Relaxation

Figure 1: Relaxation of human arteries in the presence of increasing doses of caffeine. End (+): normal endothelial function; End (−): endothelial dysfunction. The data are presented as average ± standard error of the media, which is presented in only one direction to facilitate the reading of the figure. It is reproduced with the authorization of Biomédica.
## Caffeine at Rest

<table>
<thead>
<tr>
<th>n (male)</th>
<th>Mean Age (ys)</th>
<th>Caffeine (mg)</th>
<th>Test &amp; Measuring Tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 (33)</td>
<td>53 +/- 6</td>
<td>200 mg</td>
<td>Flow-mediated dilatation of the brachial artery. % flow-mediated dilation = (maximum diameter - baseline diameter)/baseline diameter x 100.</td>
<td>Resting flow-mediated dilation increased 10% after caffeine ingestion (P &lt; .001).</td>
</tr>
<tr>
<td>10 (10)</td>
<td>27 +/- 5</td>
<td>300 mg</td>
<td>Forearm blood flow responses to acetylcholine (an endothelium dependent vasodilator) and sodium nitroprusside (endothelium-independent vasodilator). Forearm blood flow was measured by using a strain-gauge plethysmograph.</td>
<td>Resting forearm blood flow was not affected by caffeine. Resting forearm blood flow response to acetylcholine was increased 25% (P &lt; .05).</td>
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Caffeine Blocks Adenosine Receptors
Adenosine

Caffeine competitively blocks all adenosine receptors.

<table>
<thead>
<tr>
<th>Vasculature</th>
<th>Effect</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>Vasodilation</td>
<td>A2a</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pulmonary artery</td>
<td>Vasoconstriction</td>
<td>A1</td>
</tr>
<tr>
<td>1. Pulmonary artery</td>
<td>Vasodilation</td>
<td>A2a</td>
</tr>
<tr>
<td>2. Microcirculation</td>
<td>Vasodilation</td>
<td>A2b</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>Vasodilation</td>
<td>Unknown</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. General circulation</td>
<td>Vasodilation</td>
<td>A2a</td>
</tr>
<tr>
<td>2. Afferent arteriole</td>
<td>Vasoconstriction</td>
<td>A1</td>
</tr>
<tr>
<td>Aorta</td>
<td>Vasodilation</td>
<td>A2b</td>
</tr>
</tbody>
</table>

Adenosine

Caffeine blocks adenosine receptors

 Increases plasma adenosine levels

 Stimulates circulation chemoreceptors

 Increases sympathetic tone, catecholamines, PVR, & renin secretion

 Results e.g. increased SBP 7mm, DBP 3mm noted 60 mins after 300 mg caffeine.

Caffeine + Exercise Decreases ECF
Regarding ECF, especially interested in myocardial blood flow, so measure:

- PET (myocardial perfusion)
- Flow Mediated Dilation (FMD)
  - Accurate method for measuring brachial artery ECF
  - Accepted surrogate for coronary artery ECF

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<td>Myocardial perfusion reserve using PET. Ratio of myocardial blood flow during bicycle stress divided by myocardial blood flow at rest.</td>
<td>Exercise-induced myocardial blood flow response decreased 14% after caffeine ingestion (P &lt; .05).</td>
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<tr>
<td>15 (5)</td>
<td>58+/−13</td>
<td>200 mg (tested 50 min later)</td>
<td>Exercise-induced myocardial blood flow response decreased 14% after caffeine ingestion (P &lt; .05).</td>
</tr>
<tr>
<td>18 (11)</td>
<td>27+/−6</td>
<td>200 mg (tested 50 min later)</td>
<td>Exercise-induced myocardial blood flow response decreased 22% after caffeine ingestion (P &lt; .01).</td>
</tr>
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Caffeine + Exercise

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<td>10 (3)</td>
<td>30 +/- 3</td>
<td>360 mg (6 mg/kg)</td>
<td>Forearm blood flow was made at baseline; performed 55 minutes bicycle ergometer and at 20-min intervals during dynamic leg exercise. Forearm blood flow was measured by using the indirect plethysmographic venous occlusion technique.</td>
<td>At rest, caffeine had no effect on forearm blood flow. During dynamic exercise, caffeine attenuated the increase in forearm blood flow by 53%, P &lt; .05.</td>
</tr>
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Energy Drinks at Rest Decreases ECF
Energy Drinks + ECF at Rest

- 50 healthy volunteers
- 34 male, 22+/-2 years
- ECF:
  - Adenosine diphosphate-induced platelet aggregation
  - Reactive Hyperemia Index (RHI) on peripheral arterial tonometry
- Tested before & 1 hour after 250 mL (1 can) of a sugar-free Energy Drinks.

ECF : Platelet Function

- Increase in platelet aggregation following EB:
  -0.3% [control] vs. 13.7% [EB]

* P<0.007

• RHI decreased following EB:
  0.07 RHI [control] vs. -0.33 [EB]

* P<0.05

Mean arterial pressure increased following Energy Beverage consumption.

* P<0.05

Research at UTHealth
Study of Heart effects from Adults Drinking Energy beverages: ON Endothelial function

Pilot Study: Me!
Energy Drink at Rest: ECF

90 min after drinking 24 oz Monster Energy Drink

Energy Drink at Rest: ECF

Flow Mediated Dilation after Energy Drink

- Percent Flow Mediated Dilation (%FMD)
  - 107.0
  - 106.0
  - 105.0
  - 104.0
  - 103.0
  - 102.0
  - 101.0
  - 100.0

Time after Energy Drink (minutes)

0 50 90

Conclusions
Conclusions

- Healthy individuals
- Aged 22-59 years
- Consume ~ 200-300 mgs caffeine

- Improved ECF
- Vasodilation at rest
Conclusions (cont.)

- Caffeine blocks adenosine receptors
- Reduces ability of adenosine to vasodilate
- Coronary and other blood vessels
- Reduced supply when demand increased
- Ischemia?
Conclusions (cont.)

- Healthy individuals
- Aged 21-71 years
- Consume ~ 200-300 mgs caffeine
- Perform aerobic exercise 1 hr later

- Reduction in ECF
- Reduction in myocardial blood flow
Conclusions (cont.)

- Healthy individuals
- Aged 20-47 years
- Consumed Energy Drinks

➢ Reduced ECF at rest
Conclusions (cont.)

Additional research needed:

- Effects/mechanisms of Caffeine & Energy Drinks on ECF
- Assess the safety of high-dose caffeine & Energy Drinks in
  - Younger
  - Caffeine naïve
  - Exercise 1-2 hours later
Q & A