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Physical Activity, Inactivity and Sedentary Behavior: Mediators of Vascular Health

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Physical activity, inactivity and sedentary behavior: mediators of vascular health

Molecular and Cardiovascular Physiology Laboratory
Sarah Witkowski, Ph.D.
Vascular-related complications in diabetes

- 28.5% have retinopathy
- 2-4 times greater rates of CHD & Stroke
- 60-70% have neuropathy
- 44% of new cases of kidney failure
- 67% have high BP
- 30% have PVD
- 60% of nontraumatic amputations

2-4 times greater rates of CVD
Kvan et al 2007, Norhammar et al 2004

Adapted from Bernardi, et al. 2012
Vascular endothelium

Sena, et al. 2012
Vascular endothelium

Nitric Oxide

↑ vasodilation
↓ endothelin
↓ platelet aggregation
↓ monocyte, platelet adhesion
↓ SM contraction, proliferation
↓ Oxidation of LDL
Vascular dysfunction in cardiometabolic disease

- Insulin Resistance
- Hyperglycemia
- Dyslipidemia
- Pro-thrombotic state
- Inflammation
- Oxidative stress

Endothelial dysfunction precedes
- atherosclerosis
- metabolic syndrome
- insulin resistance
- Type 2 DM

McVeigh and Cohn 2003

Ihlemann, et al Diabetic Medicine 2002

*P = 0.02
Physical activity and pre-diabetes

n=20/group
BMI=25-34.9
6 weeks of exercise
150min/wk (unsupervised)

Sen, Lagoy, Islam, and Witkowski, AHA Scientific Sessions 2011
Physical activity and sedentary behavior

- Known benefits of physical activity
- Known harms of inactivity
  - “avoid inactivity”, “something is better than nothing”

**Novel Questions**

Is there a unique physiology of sedentary behavior?
Can bouts of exercise or breaks from sitting completely reverse the detrimental effects of sitting?
Physical activity and CVD risk

Highest levels of PA were related to a **50% reduction** in incidence of CHD (Powell, et al. 1987)

Most active subjects had a **30-35% reduction** of risk in developing CVD or CHD (Shiroma and Lee. Circulation. 2010)

- 20 prospective cohort studies (1995-2007)

  The **SAME reduction** in CVD risk is found in older individuals! (60-80-year olds)

  Similar reduction in women as in men!
Perfect storm for disease?

- Adherence to 30’/day ~ 5% (NHANES, Troiano, et al 2008)
- Occupational physical activity decreased by 142Kcal/day between 1960-2006
- Sedentary jobs increased 83% since 1950
- Physically active jobs make up ~25% of our workforce
- Workweek is longer: 47hr/wk
Sedentary behavior

- Sedentary = 1.0 - 1.5 METS, non-upright (Ainsworth, et al. MSSE 2000)

- Sedentary behaviors
  - Workplace sitting, computer use, TV, car commuting

- Sedentary time
  - ~1/3 of waking time
  - 7.7hr/13.9hr wear time

Canada fitness survey: CVD mortality

<table>
<thead>
<tr>
<th></th>
<th>Almost none of the time</th>
<th>One fourth of the time</th>
<th>Half of the time</th>
<th>Three fourths of the time</th>
<th>Almost all of the time</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men &amp; Women</strong></td>
<td>1.0</td>
<td>1.01 (0.77-1.31)</td>
<td>1.22 (0.94-1.6)</td>
<td>1.47 (1.09-1.96)</td>
<td>1.54 (1.09-2.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>1.0</td>
<td>0.91 (0.65-1.29)</td>
<td>1.08 (0.76-1.52)</td>
<td>1.25 (0.86-1.83)</td>
<td>1.35 (0.85-2.13)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>1.0</td>
<td>1.23 (0.80-1.90)</td>
<td>1.50 (0.98-2.31)</td>
<td>1.77 (1.11-2.82)</td>
<td>1.81 (1.07-3.07)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Multivariate model is adjusted for age, smoking, alcohol consumption, and leisure time PA

Katzmarzyk, et al 2009
Sedentary time and CVD: NIH AARP Study

Matthews, et al 2012
Sedentary time and CVD: WHI

Chomistek, et al 2013
Models to study inactivity and vascular function

- Bed rest
- Spinal cord injury
- Dry water immersion
- Unilateral Limb immobilization/casting
- Withdrawal of structured exercise
- Reduced step count
- Sitting

Methods
- venous occlusion plethysmography
- brachial flow mediated dilation (FMD)
- circulating factors
Bed rest and vascular function


Flow-mediated vasodilation with reactive hyperemia

Athletes
Sedentary

Flow-mediated vasodilation with reactive hyperemia

Witkowski S, et al 2010
Individual differences to reduced physical activity

Witkowski S, et al 2010

Responders

Non-responders

Witkowski S, et al 2010
Reduced physical activity

- <5000 steps/day, no structured exercise

Boyle L, et al 2013
Circulating markers of endothelial health

- CAC (i.e. CD34+) contribute to vessel repair
- CD31-/CD42b- released from apoptotic endothelial cells
- CD62E+ shed from activated endothelium
Circulating Angiogenic Cells

A

CFU CAC number

baseline  rPA

B

CD34+ cell number (x10^6)

baseline  rPA

*
CAC intracellular nitric oxide

**A**

<table>
<thead>
<tr>
<th>CFU CAC NOi (RFUs/1.5x10^5 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
</tr>
<tr>
<td>14000</td>
</tr>
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</table>

**B**

<table>
<thead>
<tr>
<th>CD34^+ NOi (RFUs/1.5x10^5 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
</tr>
<tr>
<td>20000</td>
</tr>
</tbody>
</table>
CAC and inactivity in older men

Participants were 63 years old, groups were BMI matched

Witkowski S, et al 2010
Endothelial microparticles

Boyle L, et al 2013
Potential Mechanisms

- Shear stress
- Vasodilator/Vasoconstrictor changes
- Insulin resistance
- Circulating glucose
Conclusion

- Vascular endothelial dysfunction is an early hallmark of CVD
- Vascular function changes in response to alterations in physical activity
  - Response is rapid
  - Response occurs with relatively mild changes in activity
  - Functional measures/cellular measures
- Unknown whether bouts of exercise or activity ameliorate the detrimental effects
- Unknown whether these changes are due to increased sedentary time
Physical activity monitoring
Future directions

- influence of diet
  - poor diet/snacking habits associated with sedentary behavior
- sex differences
- age and inactivity
- inactivity and vasodilator vs. vasoconstrictor pathways
- improvements in measurement
Potential Impact and Perspectives

- Workplace policy
- Population recommendations
- Exercise prescription
- Clinical risk assessment
- Interventions for risk reduction in diseased populations
Acknowledgements

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Stephanie Simoes
Angel Baez
Cory Serviente
Thank you
Potential Mechanisms

A) 

![Bar chart A)](image)

- Steps/Day
- Week 1 vs Week 12
- Comparison between < 20 Minutes/Day in Bouts and > 20 Minutes/Day in Bouts

B) 

![Bar chart B)](image)

- FMD%
- Week 1 vs Week 12
- Comparison between < 20 Minutes/Day in Bouts and > 20 Minutes/Day in Bouts

Suboc T, et al 2014
Vascular dysfunction in diabetes

Endothelial dysfunction has been shown in non-insulin dependent and insulin dependent diabetes

Ihlemann, et al Diabetic Medicine 2002
7D aerobic exercise and NIDDM

Longer time spent sitting was associated with increased risk of all 3 causes of death.
Longer time spent sitting was associated with increased risk of CVD and all-cause mortality.
warren (blair) 2010, MSSE TV viewing and car riding ACLS 21 year follow up
Physical activity and CVD risk

Figure 3. Median relative risks of CHD/CVD by dose of physical activity.
Sedentary behavior and CVD

- Ford and Caspersen 2012
- HR per 2hr increase for CVD
  - Screen time $= 1.17$ (95% CI: 1.13-1.20), 6 studies
  - Sitting time $= 1.05$ (95% CI:1.01-1.09), 2 studies
Vascular health in cardiometabolic disease

- Microcirculation
- Resistance vessels
- Conduit arteries
- Macrovascular

Endothelium
- vasodilation/constriction
- procoagulant/fibrinolytic
- permeability/adhesion
- growth/differentiation
Canada Fitness Survey: All-cause mortality

Katzmarzyk, et al 2009