Cardiometabolic Benefits of Low Intensity Physical Activity

Marc Hamilton, Ph.D.
Professor
Pennington Biomedical
Baton Rouge, Louisiana, USA
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My Goal For Inactivity Physiology

To discover a potent solution for millions of people who can’t (or won’t) exercise.

Well beyond expectations
How Can This Be Achieved?

That is the holy grail of healthy lifestyles!
Inactivity Physiology Explained Simply

Some of the most potent mechanisms at the root cause of chronic disease are caused by inactivity (generally sitting) because the body needs frequent muscular activity.

See - ESSR, 2004 & Diabetes, 2007
Simple But Profound Rationale-
Cells receive input from their environment every minute of every day.
An Increasingly Inactive World

- Inactive: muscular inactivity
- LIPA: Low Intensity
- MVPA: Moderate + vigorous

4%
Understanding Why LIPA is Non-Fatiguing & Abundant

Skeletal Muscle Fiber Type Recruitment

Flat-line signals alert to dysfunctional tissue
Inactivity Physiology focuses on the benefits of large durations of intermittent muscular contractile activity during Low-Intensity Physical Activity (LIPA) instead of sitting inactive.
Human physiology is naturally well geared for a large daily duration of muscular activity

Hamilton et al. Diabetes, 2007
Saying that *people* spend too many **hours each day being sedentary (mostly sitting)** is actually the same as saying *people* don’t spend enough **hours each day being active**.
30 min is $\frac{1}{48}$th of one day
Are you an “exercising couch potato”?

Hamilton et al. *Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior*  
*Current Cardiovascular Risk Reports, 2008*
Even in the minority of people who achieve the recommended 150 min/week of moderate activity…

…this still leaves ~16 hrs, ~1400 minutes of each waking day with physical inactivity!!!

Hamilton, Diabetes, 2007
INACTIVITY PHYSIOLOGY STUDIES

The Early Years 1998-2003
Exercise Physiology versus Inactivity Physiology: An Essential Concept for Understanding Lipoprotein Lipase Regulation

Marc T. Hamilton,¹,² Deborah G. Hamilton,¹ and Theodore W. Zderic¹

¹Department of Biomedical Sciences and ²Dalton Cardiovascular Research Center, University of Missouri-Columbia, Columbia, MO

HAMILTON, M.T., D.G. HAMILTON, and T.W. ZDERIC. Exercise physiology versus inactivity physiology: An essential concept for understanding lipoprotein lipase regulation. Exerc. Sport Sci. Rev., Vol. 32, No. 4, pp. 161–166, 2004. Some health-related proteins such as lipoprotein lipase may be regulated by qualitatively different processes over the physical activity continuum, sometimes with very high sensitivity to inactivity. The most powerful process known to regulate lipoprotein lipase protein and activity in muscle capillaries may be initiated by inhibitory signals during physical inactivity, independent of changes in lipoprotein lipase messenger RNA. Key Words: dose response, coronary heart disease (CHD), transcription, posttranslational, signaling, sedentary, aging
Why does sitting inactive have potent and hazardous effects on the body?

And are these processes independent of traditional exercise (“leisure time physical activity”), diet, and weight?
In 2004 and 2007, **We Reinterpreted** the Classical Vocational Studies by Morris (c 1953)

- Death From CHD middle age men

- Conductors

- Drivers (sitters)

Hamilton, Hamilton, Zderic ESSR, 2004
Hamilton, Hamilton, Zderic Diabetes, 2007
### Meta-analysis for Sedentary Time

<table>
<thead>
<tr>
<th>Type 2 Diabetes</th>
<th>Metabolic Syndrome</th>
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<tbody>
<tr>
<td><strong>Relative Risk (95% CI / CrI)</strong></td>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td>2.87 (1.46, 5.65)</td>
<td>Hu et al</td>
</tr>
<tr>
<td>1.70 (1.19, 2.42)</td>
<td>Hu et al</td>
</tr>
<tr>
<td>2.34 (1.41, 3.90)</td>
<td>Dunstan et al</td>
</tr>
<tr>
<td>1.86 (1.54, 2.24)</td>
<td>Krishnan et al</td>
</tr>
<tr>
<td>2.18 (1.95, 2.43)</td>
<td>Tonstad et al</td>
</tr>
<tr>
<td>1.63 (1.17, 2.27)</td>
<td>Ford et al</td>
</tr>
<tr>
<td>2.75 (1.83, 4.13)</td>
<td>Stamatakis et al</td>
</tr>
<tr>
<td>1.85 (1.41, 2.43)</td>
<td>Wijndaele et al</td>
</tr>
<tr>
<td>1.22 (0.87, 1.72)</td>
<td>Hawkes et al</td>
</tr>
<tr>
<td>4.00 (3.62, 4.42)</td>
<td>Matthews et al</td>
</tr>
<tr>
<td><strong>2.12 (1.61, 2.78)</strong></td>
<td><strong>Refs Pooled</strong></td>
</tr>
</tbody>
</table>

Wilmot et al 2012

Edwardson et al 2012
Mortality From Recent Studies

Mortality Hazard Ratio in 1,906 persons >50 yrs of age (averaging 63.8±10.5 yrs) from accelerometry (adjusted for age, gender, race/ethnicity, education)  
Distinct Effects of Inactivity Physiology Independent from Exercise

- A focus on the research discovery that is focused on the *root causes* to explain why a lifestyle of sitting all day is hazardous for cardiovascular disease, diabetes, metabolic syndrome, inflammation, and blood clotting.
Plasma Lipid Traffic
LPL enzyme is a key mediator

TG-rich lipoproteins

LPL

ADIPOSE

ACTIVE SKELETAL MUSCLE

HEART

INACTIVE SKELETAL MUSCLE

DIAPHRAGM

GUT

Food
Suppression of skeletal muscle lipoprotein lipase activity during physical inactivity: a molecular reason to maintain daily low-intensity activity

Lionel Bey and Marc T. Hamilton
Understanding Why LIPA is Non-Fatiguing & Abundant

Skeletal Muscle Fiber Type Differences

Number of Active Muscle Fibers

- slow oxidative muscle (fatigue resistant)
- fast glycolytic muscle (fatigue sensitive)

Inactivity  Low  Moderate  Vigorous

Relative Intensity of Physical Activity

Lipoprotein metabolism is stalled during inactivity

$^3$H -Triglyceride uptake in oxidative muscle

Bey & Hamilton. J.Physiol. 2003
One day of physical inactivity suppresses LPL activity in human skeletal muscle

HUMAN SKELETAL MUSCLE (N=10)

Zderic and Hamilton, unpublished observations
Inactivity Powerfully Shuts Off Lipoprotein Lipase

“The muscular vacuum for TG-rich lipoproteins becomes unplugged.”

Bey and Hamilton, *J Physiol (Lond)* 2003
Sitting Time Is Associated With Atherogenic Lipoproteins And Hyperinsulinemia Independent Of BMI, VO2max, And MVPA

Individuals in the top quartile of sitting (11 ± 1 h/day) compared to the lowest quartile (7 ± 1 h/day), had…

-106% greater mean insulin concentrations,
-48% more total VLDL particles,
-45% more small VLDL particles,
-0.3 nm smaller mean LDL diameter

In Review
Sex Specific Associations Between Screen Time and Lipoprotein Subfractions

Frazier-Wood et al 2013

Physical Activity versus Sedentary Behavior: Associations with Lipoprotein Particle Subclass Concentrations in Healthy Adults

Aadland et al 2013
What is underlying signal for decreased LPL activity during inactivity?
High dose niacin prevented fall in LPL activity caused by acute inactivity
Physical inactivity amplifies the sensitivity of skeletal muscle to the lipid-induced downregulation of lipoprotein lipase activity.
The Specificity Principle

The signals harming the body during physical inactivity are specific and distinct from exercise.

(one reason why “too much sitting is not the same as too little MVPA”)
A vigorous bout of exercise on skeletal muscle LPL activity in humans

Revised measures design (N=8 men)

High correlation between the 2 exercise trials, R=0.91

Harrison, Zderic et al. 2012
Run training does NOT have the same potency

Inactivity Physiology is opening doors for a novel solution to the elusive and dangerous condition of deep venous thrombosis (DVT).

Too much sitting can cause DVT – not too little exercise.
Inactivity-Responsive Genes

Perfect Match

Mismatch

~980,000 oligonucleotide probes for ~33,000 genes
The Homeostasis for Expression of Hundreds of Genes is Rapidly Disturbed By Contractile Inactivity

Physiological Genomics, 2003 Bey and Hamilton
Identification of hemostatic genes expressed in human and rat leg muscles and a novel gene (LPP1/PAP2A) suppressed during prolonged physical inactivity (sitting)

Theodore W Zderic* and Marc T Hamilton*
HEMOSTASIC GENE EXPRESSION IN SKELETAL MUSCLE

COAGULANT FUNCTIONS
Coagulation factor VIII
Coagulation factor VII
Vitamin K epoxide reductase complex
von Willebrand factor (vWF)
Tissue factor
Gamma-glutamyl carboxylase

ANTI-COAGULANT FUNCTIONS
LPP1
Platelet-activating factor acetylhydrolase
Annexin A5
Tissue factor pathway inhibitor
Protein C receptor

FIBRINOLYTIC FUNCTIONS
Annexin A2
Tetranectin
Tissue plasminogen activator
Urokinase plasminogen activator

LPP1 was robustly sensitive to contractile inactivity and LIPA in both rats and humans
LPP1 is Suppressed During Sitting & Resistant to Exercise
A Reminder of the Public Health Guidelines

Physical Activity Guidelines for Americans
http://www.health.gov/paguidelines

JAMA, 1995 – ACSM
Circulation and MSSE, 2007 - AHA/ACSM
How much time do people in modern societies sit, or alternatively do upright activities?
A sobering thought about the historical focus on *Moderate-Vigorous Physical Activity* in public health recommendations:

3.5-10% of the people do them!
Are exercisers less sedentary?
Total Weekly Exercise (minutes)

EXERCISE GROUPS

None/Low  Intermediate  Meeting/Exceeding Rec

*†

A POP QUIZ

Is it odd to you that this person is categorized by experts as “very physically active”?

Hamilton, Diabetes, 2007
Who ACTUALLY spends more time in physical activity?

Generally doing ~45 min/hr doing LIPA

Minutes per hour in each activity

Sitting

Generally doing <20 min/hr of any activity

Minutes per hour in each activity

Sitting

Hamilton et al. Diabetes, 2007
Exercisers are not less sedentary (sit less) than people who do not exercise
Exercisers sit just as much as people who don’t exercise

Exercisers are not less sedentary (sit less) even on the days they exercise.
Regardless how much time was spent doing moderate activity there was the same sedentary time and total physical activity.
Evidence that women meeting physical activity guidelines do not sit less: An observational inclinometry study.

Inactivity Physiology

To discover a potent solution for millions of people who can’t (or won’t) exercise.

Well beyond expectations
“The dire concern for the future may rest with growing numbers of people unaware of potentially insidious dangers of sitting too much.”

Hamilton Diabetes 2007
FIG. 1. A major question raised by the inactivity physiology paradigm is whether the typical person who already does not perform structured exercise regularly will have increased risks of metabolic diseases in the coming years as a result of too much sitting. The red circle shadows the median of 13,344 middle-aged men and women (adapted from ref. 86). As described in the text, the majority of people in the general population already do not follow the prescription for enough moderate-vigorous exercise. It logically follows that in people who already do not exercise, it is impossible for higher rates of age-adjusted metabolic syndrome, type 2 diabetes, obesity, and CVD over the coming years to be caused by further exercise deficiency. Inactivity physiology is a discipline concerned with the future of people who may be sitting too much. (Please see http://dx.doi.org/10.2337/db07-0882 for a high-qual-
Inactivity physiology is a new field seeking solutions in ways never studied before.

Total daily sedentary time (predominantly sitting) is abundant, and independent of how much time someone exercises.

There are some very potent metabolic mechanisms in skeletal muscle responding to low-intensity activity. These mechanisms are qualitatively distinct from exercise.