The danger of sedentism: endothelium at risk

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HABITUAL PHYSICAL inactivity, otherwise known as sedentism, is a leading cause of excessive and preventable cardiovascular risk (4). Less than half of U.S. adults met recommended physical activity standards in 2007, and nearly one-quarter of the U.S. population reported no leisure time physical activity in 2008 with rates of sedentism above 30% for those over the age of 65 (3). While the exact magnitude of the societal cost of sedentism is difficult to quantify, estimates suggest that the direct medical costs of sedentary individuals complicates attempts to determine the contribution of physical inactivity alone to both enterism and obesity significantly complicates attempts to measure in at-risk populations, the strong colinearity of sedentism and physical activity has been shown to improve both

Sedentarism’s deleterious mechanisms of action remain unclear. Much of the risk of physical inactivity has been attributed to the onset of obesity secondary to excessive caloric intake relative to energy requirements. Obesity is a well-recognized risk factor for the development of dyslipidemia, systemic inflammation, hypertension, and insulin resistance. In this setting, the vascular endothelium becomes dysfunctional. Endothelial dysfunction is characterized by a proinflammatory, prothrombotic, and vasoconstrictive phenotype and is a known harbinger of adverse cardiovascular events (13). While obesity has been linked to endothelial dysfunction and insulin resistance and physical activity has been shown to improve both measures in at-risk populations, the strong colinearity of sedentism and obesity significantly complicates attempts to determine the contribution of physical inactivity alone to both endothelial dysfunction and insulin resistance.

Table 1. Strict physical inactivity studies measuring endothelial function

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of Bed Rest, days</th>
<th>Basal Conduit Vessel</th>
<th>Conduit Vessel Function</th>
<th>Microvascular Function</th>
<th>Blood Pressure</th>
<th>Lipid Profile</th>
<th>Insulin Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoemaker et al., 1998 (11)</td>
<td>20</td>
<td>14</td>
<td>N/A</td>
<td>Impaired postischemic hyperemia (10-min occlusion period, arm)</td>
<td>No change in MAP</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bleecker et al., 2005 (1)</td>
<td>16</td>
<td>25 and 52</td>
<td>Reduced femoral artery diameter N/A</td>
<td>Increased FMD</td>
<td>N/A</td>
<td>No changes</td>
<td>N/A</td>
</tr>
<tr>
<td>Hesse et al., 2005 (8)</td>
<td>10</td>
<td>13</td>
<td>Reduced brachial luminal diameter</td>
<td>N/A</td>
<td>Impaired (forearm)</td>
<td>No change in MAP</td>
<td>N/A</td>
</tr>
<tr>
<td>Hamburg et al., 2007 (7)</td>
<td>20</td>
<td>5</td>
<td>Reduced brachial luminal diameter</td>
<td>N/A</td>
<td>Impaired by day 3 and on day 5 in both forearm and calf</td>
<td>↑ SBP</td>
<td>↑ Triglycerides and total cholesterol</td>
</tr>
<tr>
<td>Demiot et al., 2007 (5)</td>
<td>16</td>
<td>56</td>
<td>N/A</td>
<td>Impaired post-bed rest in calf</td>
<td>No change in MAP</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Navasiolava et al., 2010 (9)</td>
<td>8</td>
<td>7</td>
<td>N/A</td>
<td>Impaired by day 7</td>
<td>No change in MAP</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N, number of subjects; FMD, flow-mediated dilation; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; N/A, not applicable (data not reported).

To isolate the potential adverse effects of sedentism alone, multiple research groups have employed model protocols that enforce strict, acute bed rest on otherwise healthy persons to determine the vascular, hemodynamic, and metabolic consequences of sedentism (1, 5, 7, 8, 11). The results of these studies are delineated in Table 1. While the conclusions resulting from the comparisons of these studies need to be tempered by their heterogeneity of methods and outcome measurements, these data suggest that strict bed rest as a model of acute physical inactivity results in significant alterations to vascular homeostasis. These alterations appear to be most prominent in vessels feeding the most affected muscle beds and include rapid impairment of microvascular endothelial function, reduction of resting blood flow, and reduced conduit vessel luminal diameter suggesting an increase in resting arterial tone. Furthermore, studies with comparison groups that performed recumbent exercise during the bed rest period consistently report a blunting of adverse effects of strict bed rest on microvascular function and conduit vessel homeostasis (1, 5, 8). Only one of these studies concomitantly evaluated the inflammatory and metabolic impact of severely restricted physical activity (7). In that study, an acute insulin-resistant state developed in parallel with endothelial dysfunction in these otherwise healthy subjects. These data are in agreement with prior work demonstrating insulin resistance due to short-term physical inactivity (12). When examined together, these data also suggest that physical inactivity can acutely impart a metabolic syndrome-like state, even in the absence of obesity.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Navasiolava and colleagues (9) employed a novel, “dry immersion” protocol to simulate weightlessness for 7 days in a group of eight healthy volunteers.
to investigate the effects of extreme physical inactivity on endothelial homeostasis. This protocol involves suspending volunteers in an elastic waterproof film that suspends them in a pool of water, more completely reducing muscle tonic activity relative to bed rest protocols by eliminating support stimuli. Using laser Doppler and iontophoresis, the authors found that basal skin blood flow and microvascular function began to be impaired within 3 days of dry immersion. These data largely confirm prior data from bed rest studies, consistently showing an impairment of microvascular function with strict physical inactivity.

The experimental results involving the measurement of circulating microparticles and soluble biomarkers are novel and provide interesting insight into potential mechanisms behind physical inactivity-induced endothelial dysfunction. While the mechanisms of microparticle formation remain incompletely understood, they appear to originate from blebs in the plasma membrane of endothelial cells, platelets, and leukocytes. Elevations in circulating levels of microparticles represent increased cellular inflammatory activation and/or apoptotic signaling and are associated with increased cardiovascular risk (6). In the case of endothelial cells, both apoptosis and factors also associated with the activation of endothelial cell proinflammatory and prothrombotic phenotypes, including low shear stress, inflammatory cytokines exposure, and excessive oxidative stress, have been shown to lead to an increased endothelial microparticle production (2). Endothelial microparticles also appear to be functional and can reduce local endothelial nitric oxide bioavailability, thus impairing endothelial function both locally and systemically.

Interestingly, Navasiolava and colleagues (9) showed that circulating endothelial cell microparticles increased within 3 days of dry immersion, concomitant with the development of microvascular dysfunction and impaired basal blood flow. Furthermore, the adverse changes in endothelial cell homeostasis occurred in the absence of evidence of endothelial inflammation as measured by circulating E-selectin and leukocyte and platelet activation as measured by microparticle levels. While more definitive measurements of microparticle content, mononuclear cell activation, and direct measurements of endothelial cell inflammatory markers would have more clearly defined the overall vascular homeostasis and inflammatory state in the study participants before and during dry immersion, their findings do suggest that physical inactivity-induced endothelial dysfunction may at least in part originate from an apoptotic-centered process rather than an inflammatory one. Unfortunately, measurements of insulin sensitivity in this study were not robust. The authors did measure fasting glucose levels (which were unchanged throughout the study) and did note a trend toward an increase in circulating triglyceride levels during dry immersion. However, the study lacked a direct assessment of insulin sensitivity. Simple measurements of insulin sensitivity such as the insulin sensitivity index or homeostatic model assessment tracked throughout the study would have given a stronger sense of the timing of the onset of insulin resistance relative to the endothelial dysfunction. The lack of evidence of inflammatory activation suggests that the onset of insulin resistance either occurs in parallel or following the development of endothelial dysfunction, but further evidence is needed to corroborate this hypothesis.

The investigative groups that have gone through the effort and expense to perform physical inactivity study protocols should be commended for their efforts. This investigative model has the potential to reveal the origins of vascular and metabolic dysregulation in inactive humans given its ability to rapidly induce both endothelial dysfunction and insulin resistance in previously healthy individuals. Future work in this area should concentrate on a broad measurement approach that includes measurements of vascular function, insulin sensitivity, and local and systemic inflammation to better elucidate the origins of and relationships between these physical inactivity-induced derangements.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

REFERENCES


