

**Lower Ankle-Brachial Index within the Normal Range is Associated with Reduced Mitochondrial Energy Production, Explaining the accompanying Poor Walking Endurance**

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Objective:

Reduced walking endurance in peripheral arterial disease, defined as ABI <0.9, has been attributed to impaired muscle mitochondrial energetics. Individuals with borderline ABI between 0.9 and 1.0, or low normal ABI between 1.0 and 1.1 have been also found more likely to develop reduced walking endurance than those with higher ABI. Therefore, we hypothesized that poor walking endurance in individuals with lower ABI in borderline and normal ranges is mediated by impaired mitochondrial energy production.

Methods:

We examined data of 382 men and women participating in the Baltimore Longitudinal Study of Aging, who were free of PAD. Walking endurance was assessed by 400 meter rapid gate speed (RGS-400). Muscle mitochondrial energy production was assessed by post-exercise phosphocreatine recovery rate constant (KPCr) measured by phosphorus magnetic resonance spectroscopy (31P-MRS) of the left thigh; reduced KPCr reflects decreased mitochondria energy production. Ipsilateral ABI was measured by the Colin system. Multivariate models were adjusted for age, gender, glucose, and smoking status.

Results:

The sample mean age was 71 ± 12 years; about 18% of the participants had diabetes; 4% were current and 40% were former smokers. There were significant associations between KPCr and each of ABI and RGS-400 (Figure 1); these remained significant after adjustment. Lower ABI was independently associated with slower RGS-400 ( $\beta=-0.60$ ,  $P=0.0339$ ). Adding KPCr to the model weekend the association between RGS-400 and ABI by 15%, rendering it statistically insignificant ( $\beta=-0.51$ ,  $P=0.09$ .)

Conclusion:

The association between lower ABI in the normal range and slower walking speed is mediated by decreased mitochondrial energy production. Hence, even within the normal range, lower ABI could represent a preclinical reduction in lower extremity perfusion negatively affecting energy production. Prospective studies are needed to confirm these association and their long terms effects.

