The Nitric Oxide System in Peripheral Artery Disease

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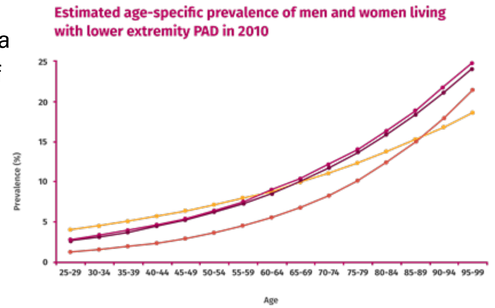
Introduction

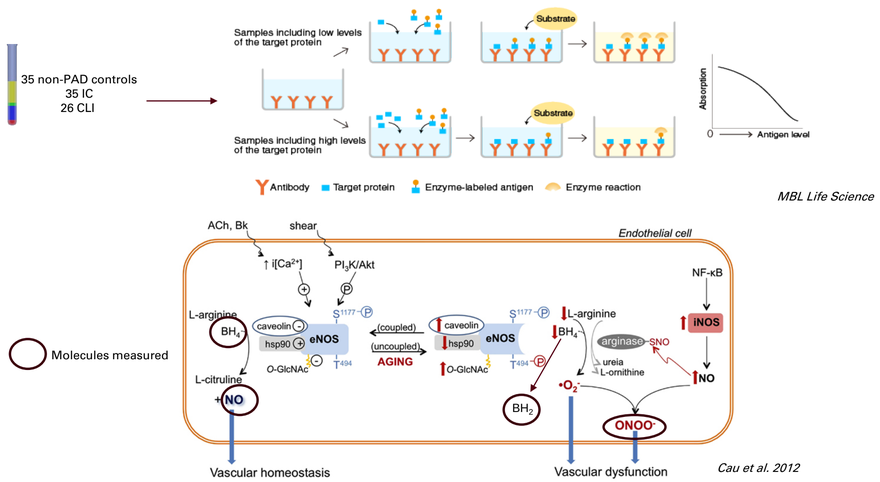
Peripheral artery disease (PAD) is an atherosclerotic condition characterized by a narrowing of the arteries supplying the lower extremities.[1] In the earlier stages of the disease, patients present with severe functional limitations and intermittent claudication (IC), or walking-induced leg pain, and in the end stages, PAD manifests as critical limb ischemia (CLI), which is defined by rest pain and tissue loss.[1]

PAD is common in older adults, with a prevalence that rises to nearly 25% of adults 80 years and older in the U.S.[2] The odds of PAD increase with every decade of life, and with the expected increases in the elderly population, PAD is quickly becoming a major cause of morbidity, mortality, and healthcare expenditure.[2]



While reduced blood flow is one mechanism operating in the pathophysiology of PAD, there is evidence that other factors also play a role. In this study, we aimed to assess whether the nitric oxide (NO) system and its regulators are altered in the setting of PAD.

Methods



Results

Table 1. Participant demographics at enrollment.

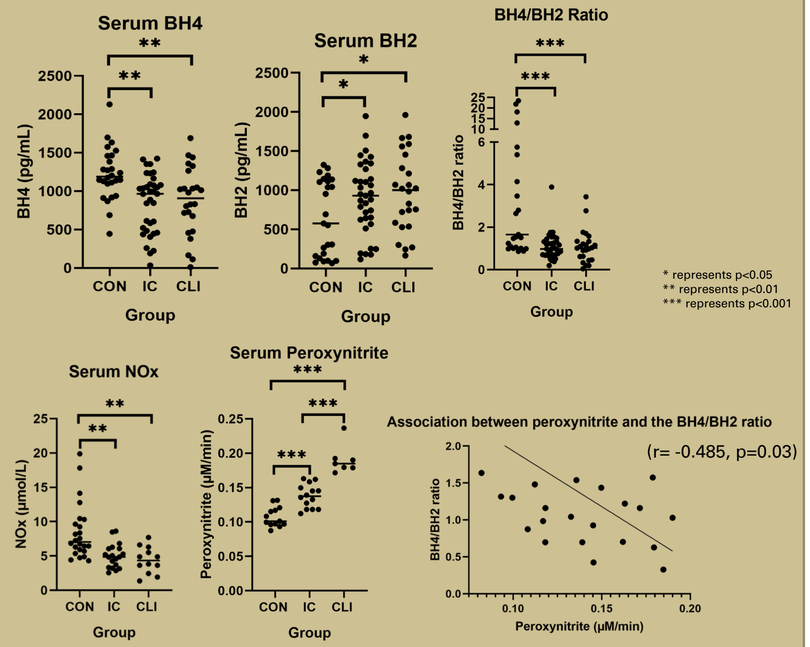
	Control (n=35)	IC (n=35)	CLI (n=26)	*P*
Age (years)	62.11 ± 7.83	62.71 ± 8.93	64.54 ± 9.35	0.544
Male sex (%)	72.2%	86.8%	84.6%	0.466
ABI	1.08 ± 0.05	0.55 ± 0.25*	0.27 ± 0.28*	**<0.001**

Table 2. Concentrations of NOx and NO synthesis regulators.

	Control (n=26)	IC (n=35)	CLI (n=24)	*P*
BH4 (pg/mL)	1,226.16 ± 342.39	846.01 ± 384.91*	870.04 ± 445.29*	**0.001**
BH2 (pg/mL)	646.87 ± 478.70	907.19 ± 459.56*	969.16 ± 508.59*	**0.045**
BH4/BH2	5.28 ± 6.71	1.08 ± 0.64*	1.09 ± 0.78*	**<0.001**
NOx (μmol/L)	8.49 ± 4.08	5.01 ± 1.75*	4.40 ± 1.95*	**<0.0001**
Peroxynitrite (μM/min)	0.107 ± 0.014	0.138 ± 0.017*	0.191 ± 0.022*,†	**<0.0001**

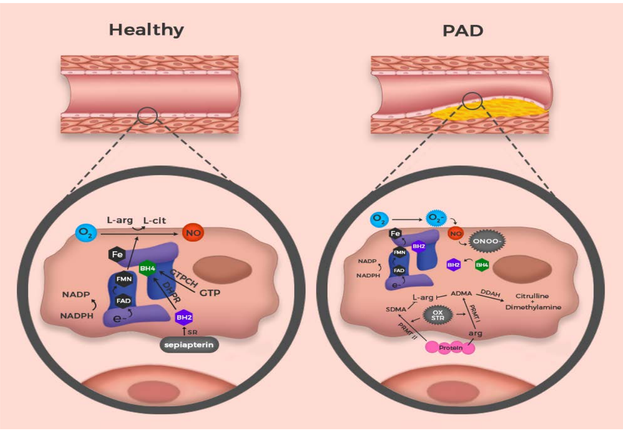
Note: The values presented in the column "*p*-value" represent the overall difference between three groups; bold font indicates a significant difference between groups ($p<0.05$); *post-hoc* differences in comparisons between individual groups are denoted as: * = significant difference from control, $p<0.05$, † = significant difference from IC, $p<0.05$.

Figure 1. Serum nitric oxides (NOx) and regulators in control (CON), IC, and CLI



Discussion

We provide evidence that NO bioavailability is reduced in PAD, which may be the result of enhanced oxidative stress and BH4 depletion. Recognition of the degree of NO dysfunction and its regulators in PAD may form the basis for better understanding PAD pathophysiology and for developing new therapeutic strategies in this disease. Our findings warrant further assessment of contributors such as NO, BH4, and ROS in a larger sample of PAD patients and in association with walking endurance, morbidity and mortality.



References

1. Kullo IJ, Rooke TW. CLINICAL PRACTICE. Peripheral Artery Disease. N Engl J Med. 2016;374(9):861-871.
2. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease. Circulation. 2017;135(12):e686-e725.