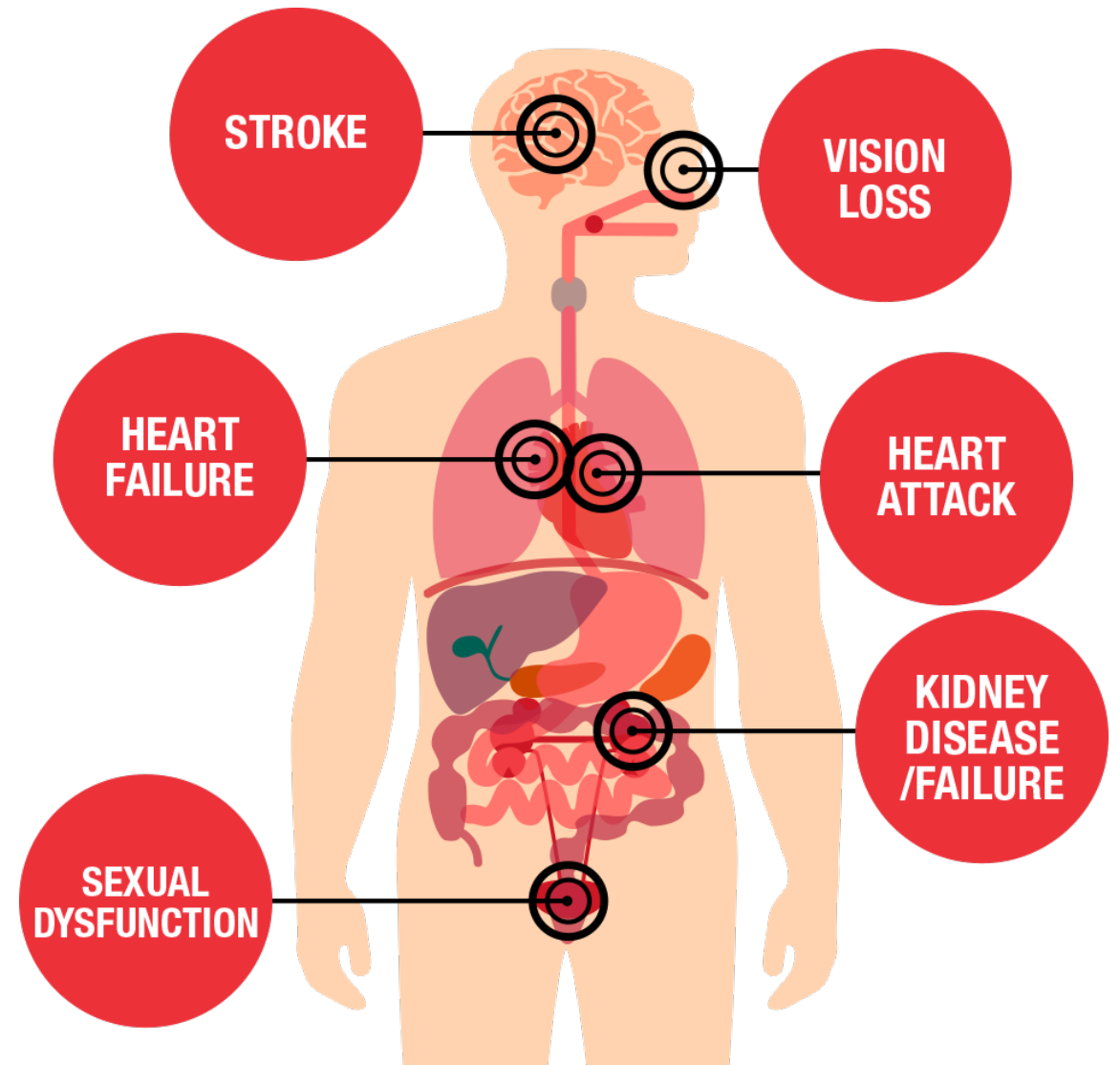


Influences of Diet and
Exercise on Racial
Differences in Nitric
Oxide Bioavailability for
Hypertensive Patients

Bryan Ko

Why is this important?

- Cardiovascular disease (CVD) is the #1 leading causes of death in the US and worldwide
- Hypertension (HTN) is a clinical sign of CVD and can lead to heart attack, heart failure or stroke
- ~45% Black adults have diagnosed HTN, twice as many as White adults
- HTN incidence from pre-hypertension in Black adults is ~76%, in White adults incidence is 40-55%



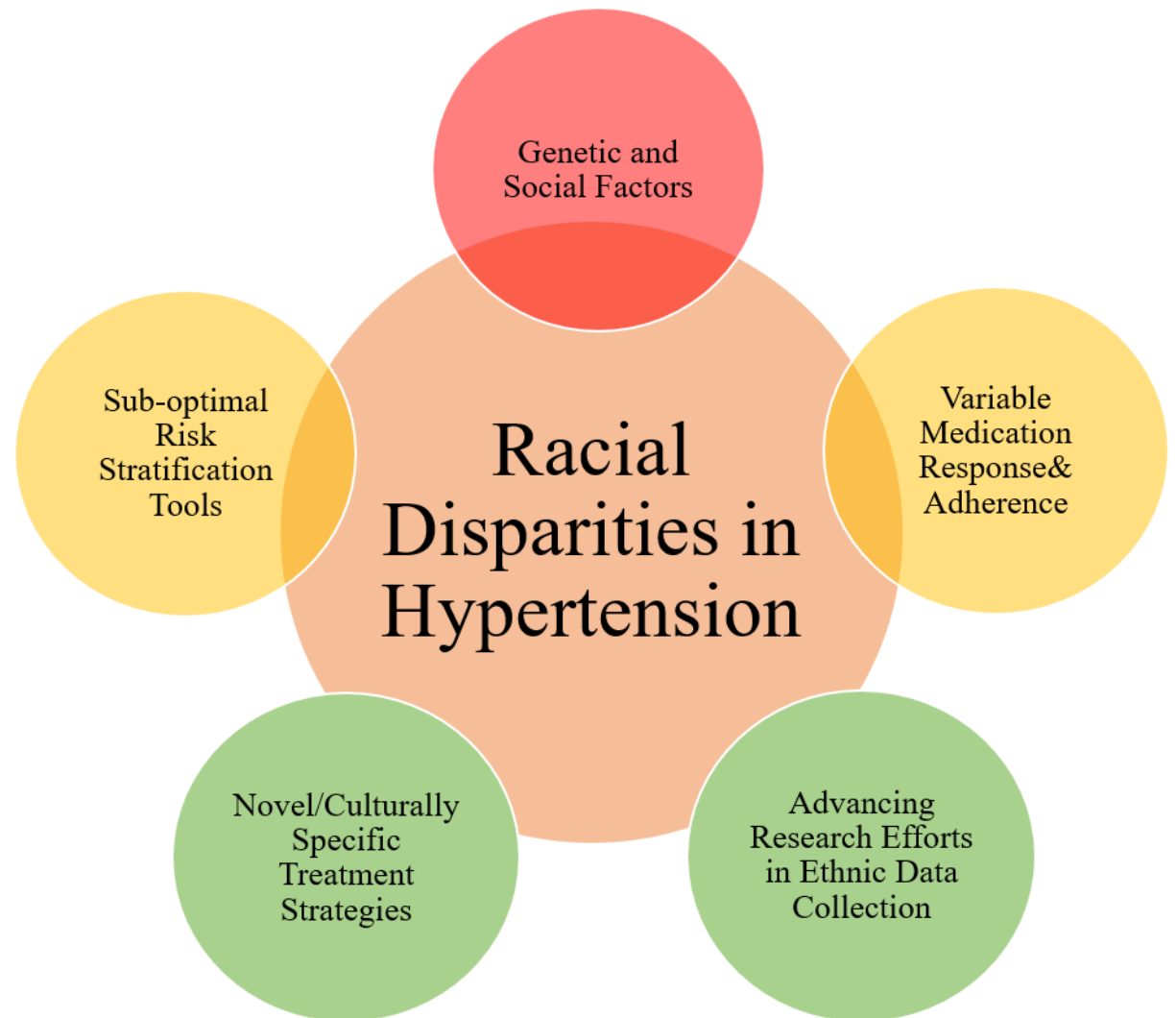
Racial differences in HTN treatment algorithms

| | All other racial identities | Black Identifying |
|---|--|---|
| First line HTN monotherapy | ACE-inhibitor and B-blockers | Ca-channel blockers and thiazides |
| Heart failure goal-directed medical therapy | ACE-i/ARB, B-blockers, mineralocorticoid receptor antagonist | Add hydralazine and isosorbide dinitrate (H-ISDN) * |
| Treatment aggression | | Most likely to receive combination therapy early in disease progression |

*H-ISDN is only used in ~11% of Black HF patients despite GDMT recommendations. Attributed to lack of PCP education

What is the evidence?

- Multiple physiologic differences unique to Black individuals have been proposed
 - Decrease bioavailability of and responsiveness to Nitric Oxide – a vasodilator
 - Genetically lower threshold to cardiac remodeling
 - Deficiency of natriuretic peptide
- Several genetic variations highly prevalent in, but not unique to, Black individuals have been studied to explain these proposed physiologic differences

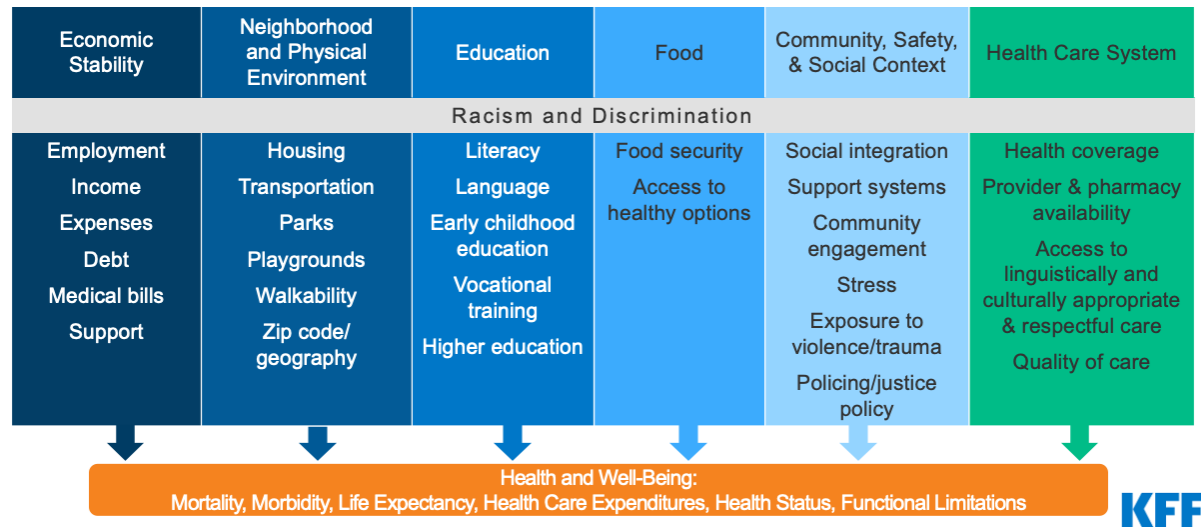


Promoting Race Conscious Medicine

- Race is a cultural identity
 - Based on phenotype not genotype
 - Includes other cultural identities including language, religion, and behavior
 - Not a good proxy for genetic ancestry
- Acknowledge other factors in HTN pathophysiology that are also correlated with Black patients
- Decrease racial bias that permeates into clinical practice

Figure 1

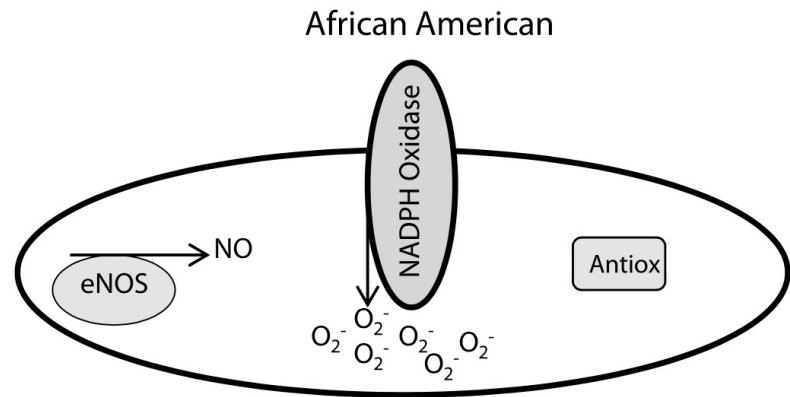
Health Disparities are Driven by Social and Economic Inequities



Design Limitations of Current Literature

- Studies for current race-based HTN treatment guidelines use race as differentiating variable between study populations
- Studies that we are evaluating also use race to divide their study groups
 - Some studies also use race and ethnicity interchangeably
- We acknowledge are conducting a study using the exact racial generalizations we hope to eliminate
 - This is a result of the current state of available literature, and we hope future studies will have enough resources to present a more nuanced view of HTN related variables

Why is NO important?



- Current evidence on Black patients relative to White patients:
 - Decreased serum NO levels
 - Increased endothelial oxidative stress leading to NO inactivation
 - Decreased endothelial response to endogenous and exogenous NO
- Used as the basis to justify different HTN treatment algorithms for Black patients
- Ignores other components of race that could be contributing to a difference on NO physiology

Questions to Address

- Does supplementation of nitrates, flavonoids, or aerobic exercise effect NO bioavailability or BP?
- Could we propose dietary deficiency or lack of exercise as a potential cause for altered NO physiology and HTN prevalence in Black patients?

Flavonoid consumption on NO bioavailability

- 14 young adults (7 African American and 7 Caucasian) with no health issues
- Measured cutaneous vascular conductance (CVC) as a measure of NO induced vasodilation
- CVC measured w/ and w/o flavonoid consumption
- Results: Flavonoid consumption equalized pre-existing racial differences in serum NO levels. No change in BP

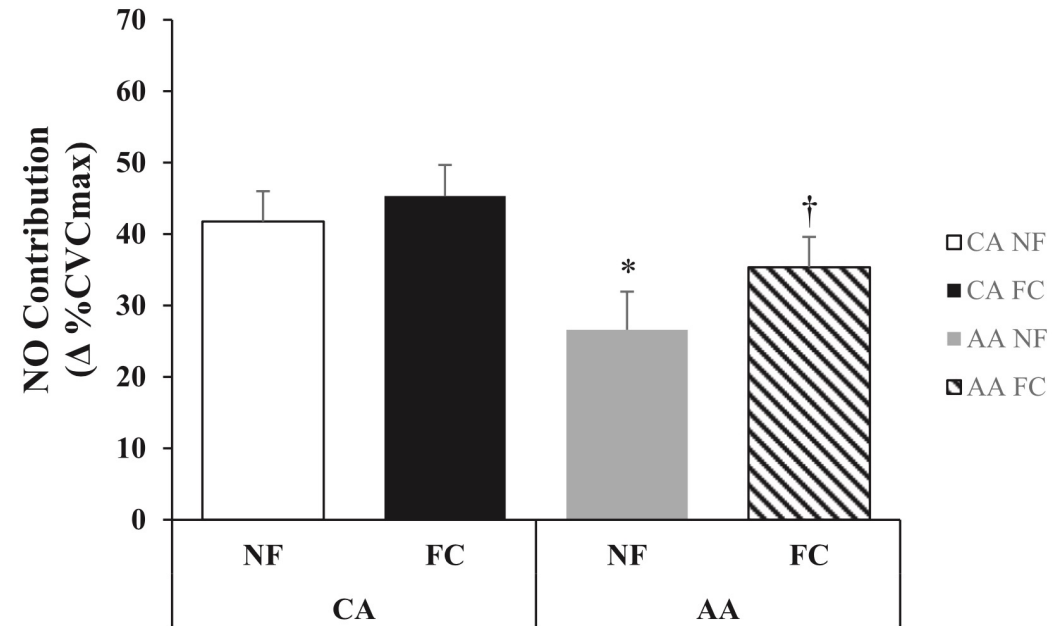


Fig. 2. NO contribution in response to local heating of skin. Open bar, Caucasian American (CA) group with NF; black-colored bar, CA group with FC; grey-colored bar, African American (AA) group with NF, pattern-filled bar, AA group with FC. The difference in cutaneous vascular conductance as a percentage of maximal vasodilation at 39 °C between the control site and NOS-inhibited site (Δ %CVCmax) was calculated to assess NO contribution as an index of NO bioavailability. * $P < .01$, significant difference vs. CA group on the same beverage condition; † $P < .05$, significant difference vs. NF within the group. Values are means \pm SEM.

Nitrate consumption on NO bioavailability

- 12 healthy young African American women
- Ingested either beetroot juice (high in nitrates) or orange juice (control)
- Directly measured serum NO and BP
- Results: Nitrate supplementation increases serum NO and decreases BP. NO levels and BP were not correlated

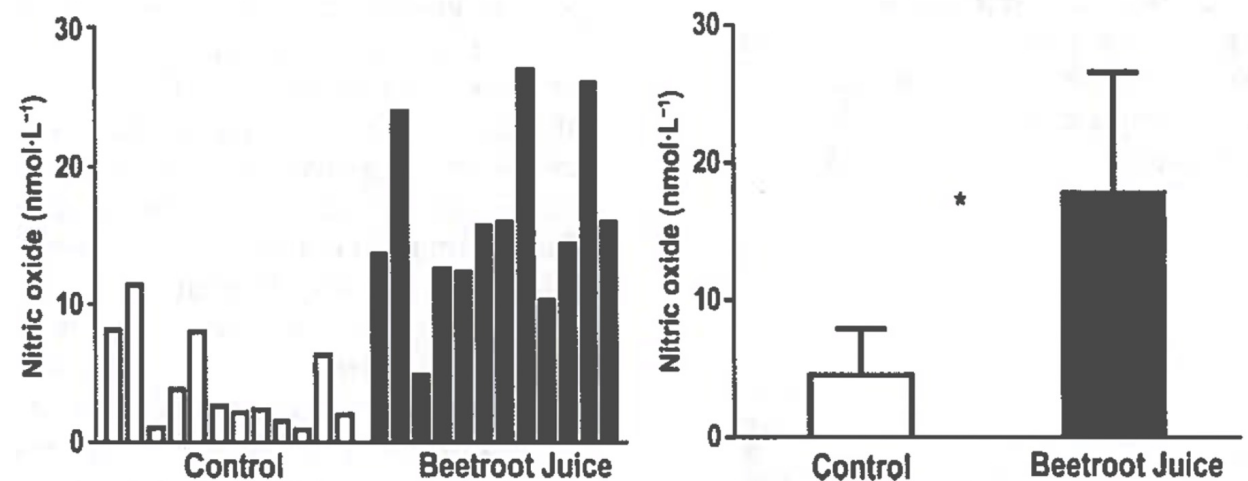


Fig. 1.

Effects of beetroot juice treatment on plasma nitric oxide. Left panel: Bars represent individual subject values of plasma nitric oxide concentrations, expressed in $\text{nmol}\cdot\text{L}^{-1}$, for a placebo control orange juice treatment and an isocaloric, isovolumetric beetroot juice treatment on separate days in 12 healthy, normotensive, young adult, African-American, female university students. The individual values for the 12 subjects are depicted as sequential bars for each treatment. *, Difference between the mean \pm SD placebo control orange juice treatment ($4.5 \pm 3.4 \text{ nmol}\cdot\text{L}^{-1}$) and the beetroot juice treatment ($17.8 \pm 8.8 \text{ nmol}\cdot\text{L}^{-1}$) was statistically significant at $p < 0.001$.

Exercise on NO bioavailability

- 26 middle aged African American sedentary individuals
- 16 had prehypertension/HTN
- Measured serum NO end products, brachial vasodilation, and BP before and after 6 months of aerobic exercise (20-40 min 3x/wk)
- Results: Exercise increases NO end product levels and vasodilatory capacity. No change in BP

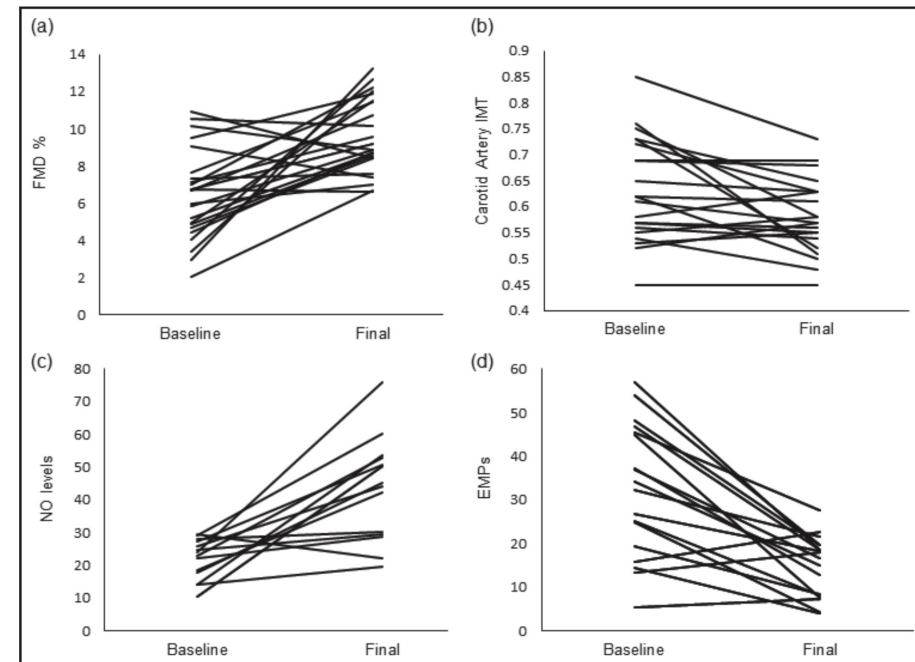


FIGURE. Individual exercise training responses in vascular health measures: (a) flow-mediated dilation (FMD), (b) carotid artery intima-media thickness (IMT), (c) nitric oxide end products (NO), and (d) endothelial microparticles (EMPs)

Simulated Exercise on NO bioavailability in vitro

- Exposed human umbilical vein endothelial cells (HUVECs) from African American and Caucasian individuals to laminar shear stress (LSS) to simulate increased cardiac output during exercise
- Measured culture NO levels, and endothelial NO synthase (eNOS) expression
- Results: African American HUVEC's had higher eNOS expression in static conditions. No differences in NO levels

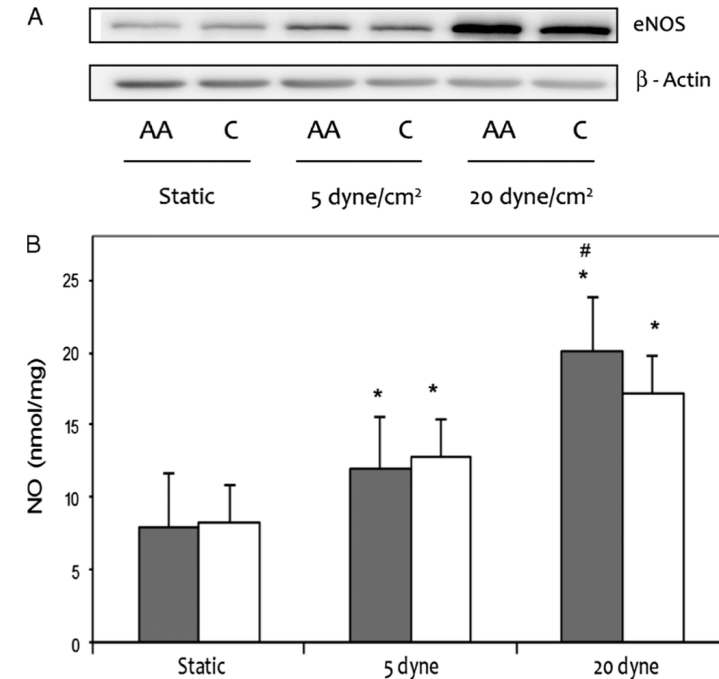
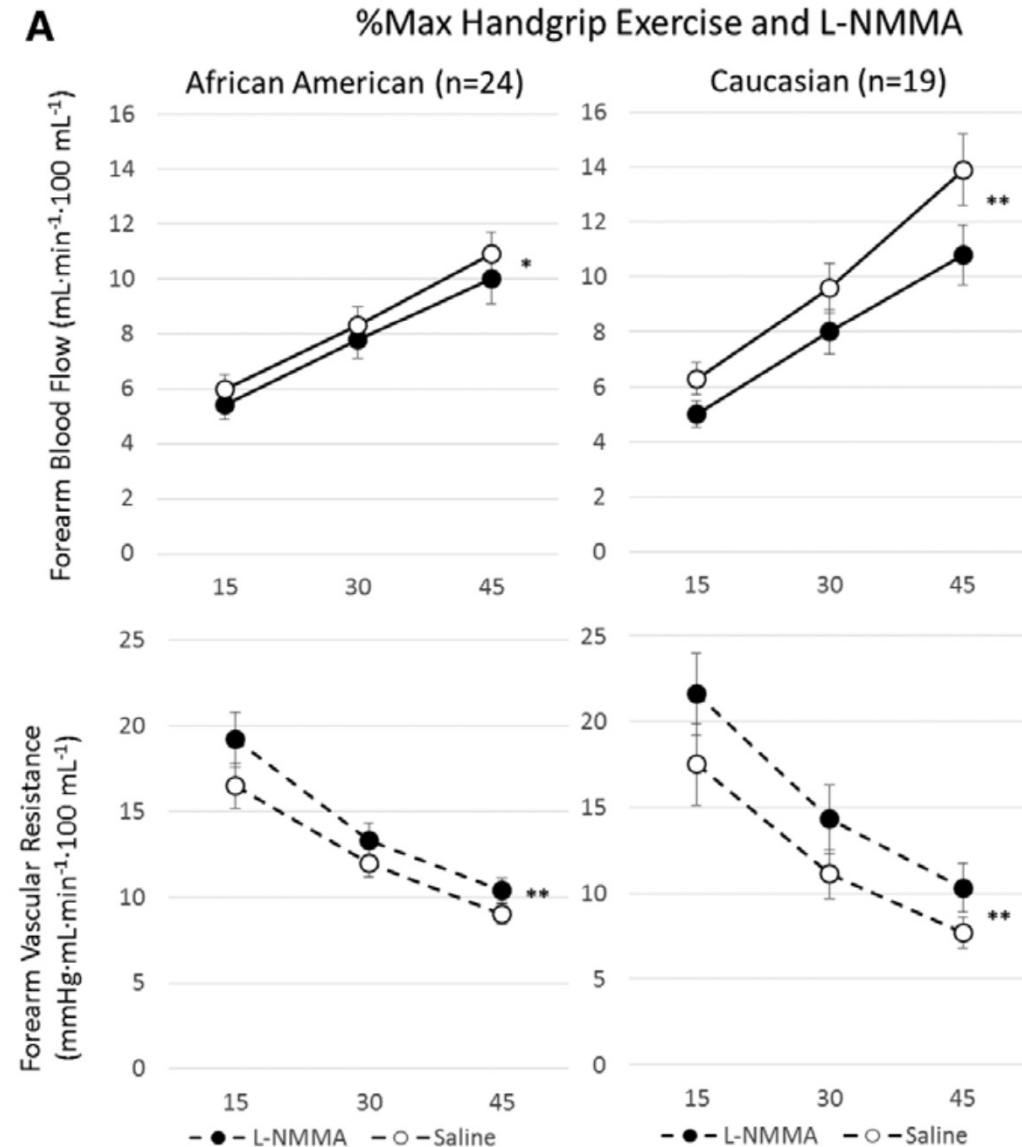


Figure 2. A. endothelial nitric oxide synthase (eNOS) protein expression under static and 5- and 20-dynes·cm⁻² conditions in African American (AA) and Caucasian (C) human umbilical vein endothelial cells (HUVEC). B. Nitric oxide (NO) concentrations in cell culture media under static and 5- and 20-dynes·cm⁻² conditions in AA and C HUVEC. Bars are mean \pm SE. * $P < 0.05$ from static; # $P < 0.05$ from 5 dynes·cm⁻². [Reprinted from (9). Copyright © 2011 Dove Medical Press Ltd. Used with permission.]

NO contribution to vasodilation during exercise

- 74 White and 86 Black healthy participants
- Measured vasodilation w/ and w/o a NO inhibitor (L-NMMA)
- Difference is NO contribution to vasodilation and HTN pathophysiology
- Results: NO influenced vasodilation more in White participants. NO is not primary mediator of vasodilation in Black individuals




Study Comparison


| Study author and Experimental Condition | Compare Black and White populations | NO in Black individuals w/ exp. condition | BP in Black individuals | Suggest NO deficiency as mechanism to HTN in Black individuals | Suggests experimental condition as contributory variable to HTN in Black individuals |
|--|-------------------------------------|---|-------------------------|--|--|
| Kim et al. (flavonoid supp) | ✓ | ↑ | -- | ✓ | ✓ |
| Bond et al. (nitrate supp) | X | ↑ | ↓* | ✓ | ✓ |
| Feairheller et al. (exercise) | X | ↑ | -- | ✓ | ✓ |
| Brown et al. (in vitro simulated exercise) | ✓ | ↑ | N/A | X | X |
| Ozkor et al. (NO response to exercise) | ✓ | N/A | Not measured | X | N/A |

* No correlation to NO increase

Conclusions from current literature

- NO bioavailability is decreased in Black individuals compared to White
 - This deficiency is likely not purely genetic
 - Variables such as flavonoid and nitrate consumption affect racial differences in NO, and potentially HTN
 - NO levels may not even be correlated with BP
 - Much of current race-based HTN guidelines assume racial differences in NO bioavailability
 - Current studies argue that these differences are more nuanced beyond racial identities
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Future questions to address

- Is race an effective way to gauge HTN risk compared to other components associated with race (eg genetics, diet and lifestyle)
 - Is assessment of these other components clinically feasible with regards to the time and money required to take a more complete history or run genetic testing in a primary care setting?
 - How can we structure future studies to avoid using the racial generalizations we hope to eliminate?
 - What is the best way to educate physicians and students on individualizing patient care based on HTN risk factors unassociated with minority bias?
 - Can such care be standardized?
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- A yellow triangular graphic is located in the bottom right corner of the slide, pointing towards the top right.