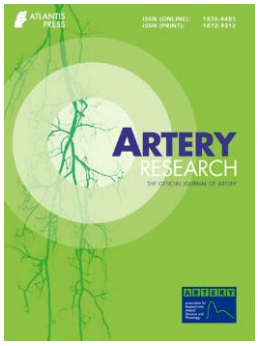

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# PO-07: RACIAL DIFFERENCES IN CIRCULATING csRAGE AND ALTERNATIVELY SPLICED esRAGE IN HEALTHY ADOLESCENTS: RELATION WITH AORTIC STIFFNESS

Ericka Tank, Lauren Wegman-Points, Mohana Pajaniappan, Katherine Darracott, Gary L. Pierce

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[a]*Department of Exercise Science, Syracuse University, Syracuse, NY, USA*
[b]*Department of Psychology, Syracuse University, Syracuse, NY, USA*
[c]*Department of Public Health, Syracuse University, Syracuse, NY, USA*
[d]*Cardiovascular Engineering, Inc., Norwood, MA, USA*

The matching of vascular supply to neuronal metabolic demand during cognitive engagement is known as neurovascular coupling (NVC). Excessive hemodynamic pulsatility may have a detrimental effect on neural function and affect NVC. Arterial stiffness is a prominent determinant of pulsatility in the brain.[1, 2]

**Objectives**: We explored changes in arterial stiffness and cerebrovascular hemodynamic pulsatility *during* cognitive engagement in healthy adults.

**Methods**: Twenty-seven adults (age 39 ± 3 yrs, BMI 24±1 kg/m$^2$) underwent Doppler ultrasonography and applanation tonometry of the common carotid artery (CCA) to derive 1) CCA elastic modulus (Ep) and β-stiffness index; 2) CCA flow pulsatility index (PI); 3) CCA pulse pressure (PP), and 4) CCA augmentation index (AIx). Transcranial Doppler was used to assess cerebral PI at the middle cerebral artery (MCA). All measures were made simultaneously at rest and during a 4-minute Stroop task.

**Results**: CCA PI was reduced ($p<0.05$) while MCA PI was unchanged ($p>0.05$) during Stroop. Brachial PP increased during Stroop ($p<0.05$) while CCA PP was unchanged ($p>0.05$). Similarly, CCA Ep ($p>0.05$) and β-stiffness ($p>0.05$) were unchanged. CCA AIx increased ($p<0.05$).

**Conclusion**: Carotid pressure pulsatility and cerebral flow pulsatility is unaltered while carotid flow pulsatility is reduced during cognitive engagement. Carotid stiffness does not change suggesting that factors other than the elastic properties of the vessel moderate cerebrovascular pulsatility during cognitive engagement.

**Table 1** Hemodynamic and vascular parameters at rest and during Stroop task.

| Variable | Baseline | Stroop | *P*—value |
|---|---|---|---|
| Brachial pulse pressure, mmHg | 43 ± 1 | 46 ± 1 | 0.002 |
| Carotid pulse pressure, mmHg | 36 ± 1 | 35 ± 1 | 0.324 |
| Carotid β-stiffness, aU | 4.4 ± 0.4 | 4.2 ± 0.3 | 0.224 |
| Carotid Ep, kPa | 54.5 ± 5.5 | 53.8 ± 4.9 | 0.670 |
| Carotid pressure AIx, % | 1 ± 4 | 13 ± 4 | 0.001 |
| Carotid distension AIx, % | 4 ± 2 | 8 ± 2 | 0.001 |
| Carotid mean diameter, mm | 5.62 ± 0.13 | 5.74 ± 0.13 | 0.010 |
| Carotid pulsatility index | 1.75 ± 0.06 | 1.57 ± 0.06 | 0.016 |
| Cerebral pulsatility index | 0.75 ± 0.02 | 0.75 ± 0.01 | 0.841 |

References
1. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The age, gene/environment susceptibility–reykjavik study. *Brain*. 2011;134:3398-3407
2. Tarumi T, Ayaz Khan M, Liu J, Tseng BM, Parker R, Riley J, Tinajero C, Zhang R. Cerebral hemodynamics in normal aging: Central artery stiffness, wave reflection, and pressure pulsatility. *Journal of cerebral blood flow and metabolism*. 2014

## PO-06
## EFFECTS OF SYSTEMIC NIACIN INFUSION ON SYMPATHETIC ACTIVITY, ARTERIAL STIFFNESS AND AORTIC WAVE REFLECTION: A PILOT STUDY

M. Mozer [a], J. L. Taylor [a], M. J. Joyner [a], T. B. Curry [a], D. P. Casey [b]
[a]*Mayo Clinic, Rochester, MN, USA*
[b]*University of Iowa, Iowa City, IA, USA*

**Objective**: Free fatty acids (FFA) may increase sympathetic activity and arterial stiffness. Niacin decreases FFA, however, little is known regarding the direct effects of niacin on sympathetic activity and arterial stiffness. We tested the hypothesis that niacin would decrease arterial stiffness, central aortic blood pressures, indices of aortic wave reflection, and muscle sympathetic nerve activity (MSNA).

**Methods**: High-fidelity radial arterial pressure waveforms and carotid-femoral pulse wave velocity (c-f PWV) were measured noninvasively by applanation tonometry before and during intravenous infusion of niacin (2.8 mg/min) at t=60, 90, 120 and 150 minutes in 5 healthy adults (2M/3F; aged 29±9 years). FFA (HPLC), MSNA (microneurography), arterial blood pressure (brachial arterial catheter) and heart rate (HR, ECG) were measured before and during niacin.

**Results**: While niacin produced a 75% reduction in FFA, contrary to our hypothesis, MSNA increased by 28-56% over all time points. After 60 minutes of niacin infusion, augmentation index (AIx) corrected for HR (AIx@75bpm) increased compared to baseline (Table 1; $P<0.05$). Repeated measures ANOVA also revealed trends for a main effect of niacin over time for AIx (P=0.12), augmented pressure (AP; P=0.18), and c-f PWV (P=0.13) (Table 1). When only comparing changes between baseline and t=60 (via paired t-test), both AIx and AP were both significantly increased ($P<0.05$).

**Conclusions**: Our preliminary results in a small group of subjects suggest that although IV niacin dramatically reduces FFA, it causes increases in MSNA and aortic wave reflection (AIx@75bpm). Inclusion of more subjects is needed to statistically confirm the strong trends for increased indices of wave reflection and arterial stiffness with niacin. Additionally, further studies are warranted to determine if chronic oral niacin therapy exerts similar effects.

**Table 1** Hemodynamic and vascular measurements before and during niacin.

| | | Baseline | 60 min | 90 min | 120 min | 150 min |
|---|---|---|---|---|---|---|
| HR (bpm) | | 73±6 | 71±5 | 69±7 | 71±8 | 76±9 |
| BSP (mmHg) | | 122±4 | 128±5 | 126±7 | 126±6 | 126±6 |
| BDP (mmHg) | 76±2 | 79±3 | 79±3 | 77±3 | | 78±3 |
| BPP (mmHg) | 47±2 | 49±3 | 48±4 | 48±4 | | 48±4 |
| ASP (mmHg) | 105±4 | 115±6 | 112±8 | 110±6 | | 110±6 |
| ADP (mmHg) | 77±3 | 80±4 | 80±3 | 79±3 | | 79±3 |
| APP (mmHg) | 28±1 | 34±3 | 32±5 | 31±4 | | 30±5 |
| PPA (%) | 165±6 | 146±8 | 154±10 | 159±9 | | 165±10 |
| AIx (%) | 6.9±2.1 | 18.6±4.7 | 14.5±5.2 | 12.3±4.4 | | 8.6±5.6 |
| AIx@75bpm (%) | 5.0±3.3 | 15.8±4.8* | 10.9±3.4 | 9.8±2.7 | | 8.6±2.5 |
| AP (mmHg) | 1.9±0.6 | 6.9±2.0 | 5.6±2.7 | 4.6±2.2 | | 3.7±2.6 |
| c-f PWV (cm/s) | 7.1±0.4 | 7.8±0.8 | 7.8±1.0 | 7.3±0.6 | | 7.2±0.5 |

Data are mean±SE; N=5;
*$P<0.05$; BSP, brachial systolic pressure; BDP, brachial diastolic pressure; BPP, brachial pulse pressure; ASP, aortic systolic pressure; ADP, aortic diastolic pressure; APP, aortic pulse pressure; PPA, pulse pressure amplification.

## PO-07
## RACIAL DIFFERENCES IN CIRCULATING csRAGE AND ALTERNATIVELY SPLICED esRAGE IN HEALTHY ADOLESCENTS: RELATION WITH AORTIC STIFFNESS

Ericka Tank [a], Lauren Wegman-Points [a], Mohana Pajaniappan [c], Katherine Darracott [c], Gary L. Pierce [a,b]
[a]*Department of Health and Human Physiology, University of Iowa, Iowa City, IA, USA*
[b]*Fraternal Order of Eagles Diabetes Research Center, University of Iowa, Iowa City, IA, USA*
[c]*Georgia Prevention Institute, Department of Pediatrics, Georgia Health Science University, Augusta, GA, USA*

**Background**: Binding of ligands to the receptor for advanced glycation end products (RAGE) triggers pro-inflammatory/oxidant signaling in the vascular wall. Increased circulating soluble forms of RAGE (sRAGE) are associated with decreased vascular risk and may be protective by acting as a decoy to prevent ligand binding to full-length RAGE. Sheddases, such as matrix metalloproteinase-9 (MMP 9) proteolytically cleave cell surface receptors including RAGE, forming cleaved soluble RAGE (csRAGE). However, sRAGE also includes endogenous secretory RAGE (esRAGE), an isoform of RAGE without receptor function derived from alternative splicing of RAGE pre-mRNA. sRAGE is lower in African-American (AA) compared with Caucasian adults and is hypothesized to contribute to elevated arterial stiffening and vascular risk in AAs. Indeed, we have previously demonstrated that sRAGE (1567±68.9 vs. 955±101.1 pg/mL, $p<0.001$) but not MMP9 is higher in Caucasian compared with AA adolescents and associated with lower carotid-femoral pulse wave velocity (CFPWV) (5.3±0.2 vs. 5.9±0.2 m/sec, $p<0.05$).

**Objectives**: We hypothesized that increased sRAGE in Caucasian versus AA adolescents is from increased circulating esRAGE through alternative splicing of RAGE pre-mRNA.

**Methods and results**: Circulating esRAGE (ELISA) was significantly higher (369±24.8 vs. 242±26.5 pg/mL, $P<0.01$) in Caucasian (n=24, age 16.5±0.3 yrs; BMI 22.9±0.8 kg/m$^2$) vs. AA (n=15, age 16.8±0.3 yrs; BMI 24.5±1.0 kg/m$^2$) adolescents ($P>0.05$). esRAGE was correlated with sRAGE (r=0.708, $P<0.001$), but esRAGE:sRAGE ratio did not differ between race (0.24±0.01

vs. 0.33±0.09, $p>0.05$). Preliminary data in pooled Caucasian (n=3) human umbilical vein endothelial cells (HUVECs) demonstrates greater esRAGE mRNA (qRT-PCR) than AA HUVECs, but similar full-length RAGE mRNA.
**Conclusion**: These preliminary data suggest that higher sRAGE in Caucasian compared with AA adolescents is likely not from higher esRAGE but a combination of cleavage from non-MMP9 sheddases and alternative splicing of RAGE.

## PO-08
## EFFECTS OF ACUTE DIETARY NITRATE SUPPLEMENTATION ON AORTIC WAVE REFLECTION IN YOUNG ADULTS

D. Treichler, K. Ueda, C. Ganger, A. Schneider, D. P. Casey
University of Iowa, Iowa City, IA, USA

**Objective**: Evidence suggests that dietary nitrate supplementation (i.e. beetroot juice) decreases measures of peripheral blood pressure. However, the effects of acute dietary nitrates on central aortic pressures are unclear. Thus, the objective of this study was to investigate the effects of beetroot juice consumption on central aortic pressures and indices of aortic wave reflection.
**Methods**: 13 healthy, normotensive, non-smoking, untrained young adults (25±1year) consumed 500ml of beetroot juice (BR). High-fidelity radial arterial pressure waveforms using applanation tonometry and venous blood samples were taken at baseline, 60, 90, 120, 150 and 180 minutes post BR consumption (Study 1). Indices of aortic wave reflection (Augmentation Index; AIx and AIx normalized for heart rate; AIx@75bpm) were analyzed using the generated central aortic blood pressure waveforms (SphygmoCor). To control for the potential confound of fluid ingestion on blood pressure, 7 of the subjects came back for an additional study visit which consisted of drinking 500ml of water (Study 2; control trial). Applanation tonometry measurements were performed at the same time points as Study 1.
**Results**: Study 1: Central systolic pressures were reduced after 90 min following BR (~3-4mmHg; $P<0.05$). Additionally, AIx and AIx@75bpm were reduced at all-time points following BR ($P< 0.05$; Figure 1). Study 2: Compared to the control trial, AIx was lower at all-time points following BR ($P<0.05$). However, AIx@75bpm was only reduced relative to the control condition at 150 and 180 min post consumption ($P<0.05$; Figure 2).
**Conclusion**: Our data provide evidence that in addition to the beneficial effects on peripheral blood pressures, acute dietary nitrate supplementation (via beetroot juice) also decreases central aortic pressures and wave reflection in young healthy adults. These effects on central aortic hemodynamics appear to be greatest 2.5-3 hours after BR consumption and are likely mediated by an increase in NO bioavailability via nitrate-nitrite-NO pathways.

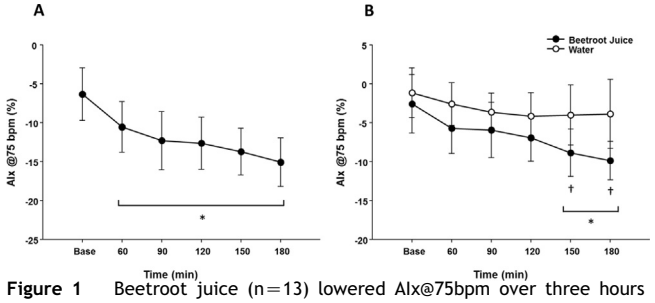


**Figure 1** Beetroot juice (n=13) lowered AIx@75bpm over three hours (A; Study 1). When compared to water (control trial; n=7), BR decreased AIx@75bpm at 150 and 180 minutes post consumption (B; Study 2). * $P<0.05$ vs Baseline. † $P<0.05$ vs control.

## PO-09
## SPIRONOLACTONE AS ADD-ON THERAPY TO CHLORTHALIDONE IMPROVES ENDOTHELIAL FUNCTION, ARTERIAL STIFFNESS AND INSULIN RESISTANCE IN EUROPEAN AND AFRICAN AMERICAN PATIENTS WITH ESSENTIAL HYPERTENSION — A DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED STUDY

T. Dudenbostel [a], T. Whigham, Jr. [a], R. Pisoni [b], M. C. Acelajado [c], D. A. Calhoun [a]
[a]*Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA*
[b]*Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA*
[c]*Department of Medicine, University of South Alabama, Mobile, AL, USA*

Diuretics have been shown to have a neutral effect on cardiovascular (CV) biomarkers like arterial stiffness and endothelial function despite their blood pressure (BP) lowering effect. Thiazide diuretics generally have harmful effects on glucose metabolism, however, the effect of mineralocorticoid receptor antagonists on insulin resistance in essential hypertension (eHTN) is only partially elucidated. We hypothesized that chlorthalidone (CHT) in combination with spironolactone (SPL) results in better arterial compliance then CHT therapy alone through additional improvement of glucose metabolism parameters.
**Methods**: This double-blind placebo-controlled randomized single center study aimed to identify SPL add-on therapy to CHT treatment alone on CV risk markers such as BP, 24-h ambulatory blood pressure monitoring (24-H ABPM), aortic BP (aBP), augmentation index (AIx), pulse wave velocity (cfPWV), flow-mediated dilation (FMD), fasting glucose, plasma insulin levels and insulin sensitivity (by homeostasis model assessment: HOMA-IR). A total of 34 patients (21.7% male, 40% white) were randomized to either CHT 25 mg + Placebo or CHT 25 mg + SPL 25 mg once daily. At baseline and after 3 months office BP, 24-H ABPM, markers of arterial stiffness, FMD, fasting glucose, plasma insulin levels and HOMA-IR.
**Results**: The study showed statistically significant improvements after three months in patients treated with CHT+ SPL in clinic BP, 24-hour ABPM, FMD, markers of arterial stiffness, and glucose metabolism. In detail, clinic SBP (131.5±14.6 to 119.1±14.3 mmHg ($P = 0.034$), aortic SBP (122±13 vs 113±13.7 mm Hg, $p = 0.048$), 24-H ABPM SBP (151.5±15.1 to 131.7 ±10.4 mm Hg, $p=0.0049$, 24-H ABPM DBP 83.2±6.1 to 74 ±9.3 mm Hg, $p=0.032$, 24-H ABPM. Fasting plasma glucose, plasma insulin levels decreased and insulin sensitivity (by homeostasis model assessment: HOMA-IR) improved with SPL as compared to CHT alone ($p<0.001$), AIx (28±9 versus 25.4±6.9 %) and cfPWV (9±2 vs 7.5±1.8 m/s) in the CHT+SPL group. Endothelial function improved significantly in the CHT+SPL group as compared to the control group (5.5 ± 1.7 to 8.8 ± 2.7 ($p = 0.004$)).
**Conclusion**: These results suggest that SPL as add-on therapy to CHT improves BP, markers of arterial compliance, and glucose metabolism in patients with eHTN, while CHT only therapy may have unfavorable effects. Treatment with SPL additional to CHT may represent a novel approach to improve unfavorable metabolic disturbances and CV risk markers.

## PO-10
## A MULTI-MODALITY 4D SYSTEM FOR ANALYSIS OF THE AORTIC MORPHOLOGY AND FUNCTION FROM MR OR CT

Honghai Zhang [a], Xiangmin Zhang [b], Thomas Scholz [a], Gardar Sigurdsson [a], Andreas Wahle [a]
[a]*University of Iowa, Iowa City, IA, USA*
[b]*Medical Imaging Applications, LLC, Coralville, IA, USA*

**Objective**: Develop an integrated system for multi-modality 4D (3D+time) aortic data analysis including data construction, interactive pre-segmentation, accurate multi-surface segmentation and refinement, and quantitative index measurement. Provide a graphical user interface (GUI) with intuitive data visualization and workflow control. Test the capabilities of the system on MR and CT data.
**Methods**: 4D image with isotropic 3D voxels is constructed from DICOM images of a study. Candy-cane and LVOT MR data are fused together to benefit from their combined information. Lumen pre-segmentation is achieved by a few mouse clicks with instant feedback. Lumen (and outer wall for CT) surfaces are segmented in 3D by optimal graph search with embedded geometric constraints that guarantees to be global optimum. The result is refined using approximate clues instead of tediously redrawing individual contours. Quantitative indices — cross-sectional area, eccentricity and distensibility, centerline curvature and motion, wall thickness and calcification volume — are computed from complete 4D aortic surfaces. Due to its modularized design, each component can be independently fine-tuned for performance or extended to handle new modality or imaging protocol. The developed system provides simultaneous visualization of image, volume and surface data. The segmentation and quantitative analysis are guided by GUI with clear instructions and examples.
**Results**: Preliminary evaluation of segmentation accuracy on 20 dataset (10 MR, 10 CT) showed good absolute surface positioning errors (MR: 1.5±1.4mm, CT: 0.4±0.6mm). The user only needs to specify two aortic end points and several points inside the lumen on one 3D image. The computational time is approximately 20 seconds for 2.5GB 10-phase CT data or 500MB 20-phase MR data.
**Conclusion**: We develop a multi-modality 4D aorta analysis system with user-friendly interface and powerful segmentation and refinement tools. Various novel quantitative indices are computed from the complete 4D aortic surfaces, thus enabling comprehensive analysis of aortic physiology and morphology.