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Biomechanics Models Predict Increasing Smooth Muscle Tone as a Novel Therapeutic Target for Central Arterial Dysfunction in Hypertension

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Abstract

Introduction: Vasodilation can paradoxically increase arterial stiffness in older, hypertensive adults. This study modeled increasing smooth muscle tone as a therapeutic strategy to improve central arterial dysfunction in hypertension using participant specific simulations.

Methods: Participant-specific models of the carotid artery were parameterized from vascular ultrasound measures of nitroglycerin induced vasodilation in 18 hypertensive Veterans. The acute changes in carotid artery mechanics were simulated for changes of ±2%, ±4%, and ±6% in smooth muscle tone and ±5, ±10, and ±15 mmHg in mean arterial pressure (MAP). The chronic carotid artery adaptations were simulated based on the hypothesis that the carotid artery will remodel wall-cross sectional area to maintain mechanical homeostasis.

Results: A 6% increase in smooth muscle tone acutely decreased cPWV from 6.89±1.24 m/s to 5.83±1.73 m/s and a 15mmHg decrease in MAP decreased cPWV to 6.17±1.23 m/s. A 6% increase in smooth muscle tone acutely decreased wall stress from 76.2±12.3 kPa to 64.2±10.4 kPa and a 15 mmHg decrease in MAP decreased wall stress to 60.6±10.7 kPa. A 6% increase in smooth muscle tone chronically decreased wall cross-sectional area (WCSA) from 18.3±5.4 mm^2 to 15.2±4.9 mm^2 and a 15mmHg decrease in MAP decreased WCSA to 14.3±4.6 mm^2.

Conclusion: In participant specific simulation, increasing smooth muscle tone can have a stronger or equivalent effect on carotid artery mechanics compared to decreasing blood pressure. Increasing central arterial smooth muscle tone may be a novel therapeutic target to improve central arterial dysfunction in older, hypertensive adults and should be a focus of future research.

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Keywords

Vascular stiffness; hypertension; vasodilation; smooth muscle; extracellular matrix

Introduction

Hypertension and poor blood pressure control affects the majority of adults worldwide[1,2] and is particularly challenging to manage in older adults. Central arterial dysfunction and stiffening occur with both aging and hypertension[3]. Elevated arterial stiffness is associated with increased rates of cardiovascular disease events, end organ damage, and all-cause mortality[4–7]. However, the ability to incorporate arterial stiffness measurements into clinical decision making and treatment planning is limited because there are no therapies proven to decrease arterial stiffness independent of lowering blood pressure (BP).

Several small clinical studies have shown that arterial stiffness can be acutely altered independently of the effect of BP[8–10]. The mechanisms underlying these acute changes are not definitively understood, but may be due to changes in vascular smooth muscle tone or sympathetic nervous system activity. Pharmacologically induced vasodilation can acutely increase arterial stiffness in older adults in addition to increasing arterial diameter[8,11]. The similarity of acute vasodilation to the arterial effects of aging[12,13] and hypertension[14,15] indicates that decreased smooth muscle tone may be a component of central arterial dysfunction. The aim of the present study was to identify if increasing central arterial smooth muscle tone is a potential therapeutic target for improving arterial function in hypertension. This was accomplished using participant specific simulations of arterial mechanics based on our previously published study[8].

Methods and Materials

This study was reviewed and approved by the University of Wisconsin and Madison Veterans Hospital Institutional Review Board. All participants gave written, informed consent to participate in this study

Study Participants

This analysis included 40 Veteran participants (20 normotensive controls and 20 with a diagnosis of hypertension) from the ongoing Functional Arterial STiffness in Veterans (FAST-Vets) study at the Madison Veterans Affairs Hospital (MVAH). Ambulatory, community-dwelling, hypertensive, older Veterans (>60 years old) were recruited from the MVAH and surrounding clinics. Inclusion criteria were: male and female participants over the age 60 years. Exclusion criteria were: known cardiovascular disease, secondary hypertension, chronic kidney disease, changing antihypertensive medication in the last month, active cancer (other than untreated, non-metastatic prostate cancer and non-melanoma skin cancer), hypoxemic pulmonary disease, active rheumatologic diseases (i.e., systemic lupus erythematosus, rheumatoid arthritis, etc.), human immunodeficiency virus, or illness with any infectious etiology or fever >38°C or hospitalization for any reason within the prior 4 weeks. Participants who were unable to walk on a treadmill were also excluded.

A diagnosis of hypertension was assessed based on medical record review as two or more office systolic BP measurements >140 mmHg, a mean home systolic BP reading of >135 mmHg for over 7 days, or active use of antihypertensive medications.

Experimental Study Protocol

This analysis uses previously published experimental data on the effects of nitroglycerin (NTG) induced vasodilation on carotid artery stiffness[8]. Briefly, participants rested in a supine position in a temperature-controlled room for 10 minutes and serial baseline oscillometric brachial blood pressure (Cheetah Starling Fluid Management System, Baxter Healthcare, Deerfield, IL, USA) and radial artery tonometry (Atcor Sphygmacor, Atcor Medical, Sydney, Australia) were performed. Brachial artery ultrasound flow mediated dilation (FMD) was performed. After a 20-minute washout period following FMD, right common carotid artery stiffness was measured with vascular ultrasound. Baseline arterial stiffness measurements were performed in duplicate and averaged. Participants were then administered 400 micrograms sublingual NTG and right common carotid artery stiffness was measured every 1-minute following NTG administration for at least 10 minutes or until the participant's heart rate and blood pressure had returned to baseline.. The post NTG carotid artery stiffness measures were calculated from the two time points with the largest end-diastolic diameters, which represent the time point with the maximal vasodilatory effect on the carotid artery.

Arterial Mechanics Modeling

We used a recently developed arterial mechanics model based on pressure-diameter relationships that incorporates the contributions to arterial stiffness from both the passive extracellular matrix (ECM) and active Vascular Smooth Muscle (VSM) components of the arterial wall[11]. The combined passive and active contributions to mechanics are modeled as

$$P = P_{ref}\left[e^{\beta 0,\,Pas}\left(\frac{D}{D_{ref}}-1\right)+\frac{k}{k_{ref}}e^{\beta 0,\,Act}\left(\frac{D}{(1-k)D_{ref}}-1\right)\right]. \quad \#(1)$$

Here, P_{ref} is a reference pressure (mmHg), D_{ref} is a reference diameter (mm), $\beta_{0,Pas}$ is the passive arterial stiffness (dimensionless), k is the smooth muscle tone (dimensionless), k_{ref} is a reference smooth muscle state (dimensionless), and $\beta_{0,Act}$ is the active arterial stiffness (dimensionless). When k=0% the smooth muscle is completely relaxed and there is no active contribution to arterial stiffness. The reference pressure was chosen to be 80 mmHg and k_{ref} was chosen to be 10%. These values are both physiologically relevant. This model is advantageous because it's simple enough to use with limited data available in clinical studies but has physiologically relevant parameters which include passive stiffness, active stiffness and active smooth muscle tone. The model was used to analyze the effects of smooth muscle tone and BP on arterial stiffness. Details of the model fitting to participant specific experimental data have previously been published[8]. Model parameters are listed in supplemental Table S1.

The effects of smooth muscle tone in hypertensive participants were simulated by changing the smooth muscle tone parameter by 0%, ±2%, ±4%, and ±6% to represent small, medium,

and large changes in smooth muscle tone. 6% was chosen as a large change in smooth muscle tone because this is the approximate amount by which nitroglycerin decreases carotid artery smooth muscle tone[8,11]. The effects of BP in hypertensive participants were simulated by changing MAP by 0, ±5, ±10, and ±15 mmHg to similarly represent small, medium, and large changes. The variations in MAP were achieved by changing SBP by 0, ±7.5, ±15, and ±22.5 mmHg and DBP by half of the SBP changes (equivalent to assuming MAP= [SBP+2*DBP]/3). All combinations of smooth muscle tone and MAP were simulated resulting in up to 49 model predictions per participant. Participants with a baseline smooth muscle tone less than 6% had fewer predictions because smooth muscle tone cannot be negative.

The acute changes in diastolic and systolic diameter were calculated from Equation 1. The acute change in intima-media thickness was calculated assuming constant wall-cross sectional area (WCSA). The acute changes in carotid pulse wave velocity (cPWV) were calculated from the Bramwell-Hill equation

$$cPWV = \sqrt{\frac{1}{\rho}\frac{D_d^2(SBP - DBP)}{D_s^2 - D_d^2}}, \quad \#(2)$$

where D_s represents the internal arterial diameter at peak systole, D_d represents the internal diameter at end-diastole, and ρ is the mass density of blood (1050 kg/m^3). Acute changes in Young's elastic modulus (YEM) were calculated from the Moens-Korteweg equation

$$YEM = \rho\, cPWV^2 \frac{D_d}{IMT}. \quad \#(3)$$

The acute changes in circumferential wall stress (σ_θ) at peak systole were calculated from the Young-Laplace equation,

$$\sigma_\theta = \frac{1}{2}\frac{SBP * D_s}{IMT_s}. \quad \#(4)$$

The chronic changes in IMT and WCSA were calculated based on the hypothesis of mechanical homeostasis[16–18], where an artery will remodel its thickness to return to its homeostatic, or original, stress value. The chronic changes in systolic IMT were calculated

$$IMT_s^c = \frac{1}{2}\frac{SBP * D_s}{\sigma_\theta^H}, \quad \#(5)$$

where the superscript "c" refers to chronic and the superscript "H" refers to homeostatic. In this calculation we assumed that the chronic changes in SBP and systolic diameter were the same as the acute changes. The chronic changes in diastolic IMT and WCSA were then calculated from systolic IMT assuming a constant WCSA.

The local sensitivity of simulation predictions for each participant was calculated using centered finite differences for both first order (dk and $dMAP$) and second order derivatives

(*dk*dk*, *dMAP*dMAP*, and *dk*dMAP*). Sensitivities were calculated from ±2% changes in smooth muscle tone and ±5 mmHg changes in MAP. To present sensitivities on a physiologically meaningful scale, the results are presented as the percent change in outcome per 2% change in smooth muscle tone or 5 mmHg change in MAP.

Statistical Analysis

Continuous variables are presented as mean and standard deviation. Categorical variables are presented as number and percentage. Baseline characteristics for controls and hypertensive participants were compared using independent sample t-tests for continuous variables and χ^2 tests for categorical variables. The simulation predictions in hypertensive participants were analyzed with a repeated-measures mixed-effects linear model. The fixed effects were Δk, ΔMAP, Δk*Δk, ΔMAP*ΔMAP, and Δk*ΔMAP. The intercept was included as a random effect to account for different participants having different baseline values. To present results on a physiologically meaningful scale, regression coefficients are presented per 2% increment in smooth muscle tone (*k*) and per 5 mmHg increment in MAP.

Results

Participant Characteristics

Participant characteristics are shown in Table 1. Two hypertensive participants were excluded from the arterial mechanics modeling analysis due to error when fitting the model to their measured, experimental data.

Acute Carotid Artery Changes

Outcome variables for each participant are shown in Figure 1 for both control participants (measured) and hypertensive participants (baseline: measured; changes in smooth muscle tone and MAP: simulated). Heatmaps of the average response for all simulations are shown in the Supplemental Figure S1. A 6% increase in smooth muscle tone decreased carotid artery diameter from 6.58±0.66 mm to 5.99±0.65mm and a 15 mmHg decrease in MAP decreased carotid artery diameter to 6.44±0.66 mm. A 6% increase in smooth muscle tone increased carotid IMT from 0.83±0.16mm to 0.92±0.18 mm and a 15 mmHg decrease in MAP increased carotid IMT to 0.84±0.16 mm. A 6% increase in smooth muscle tone decreased cPWV from 6.89±1.24 m/s to 5.83±1.73 m/s and a 15 mmHg decrease in MAP decreased cPWV to 6.17±1.23 m/s. A 6% increase in smooth muscle tone decreased YEM from 380±124 kPa to 239±147 kPa and a 15 mmHg decrease in MAP decreased YEM to 295±111 kPa (Supplement). A 6% increase in smooth muscle tone decreased wall stress from 76.2±12.3 kPa to 64.2±10.4 kPa and a 15 mmHg decrease in MAP decreased wall stress to 60.6±10.7 kPa.

From the mixed-effects, repeated measures analysis (Table 2), both changes in smooth muscle tone and MAP had statistically significant associations ($p<0.001$) with the acute changes in carotid geometry and mechanics. A statistically significant interaction ($p<0.001$) of smooth muscle tone and MAP was found for the acute changes in diastolic diameter, IMT, and wall stress. There was not a significant interaction for cPWV ($p=0.46$).

Longitudinal Carotid Artery Changes

The chronic changes in IMT and WSCA for each participant are shown in the bottom panel of Figure 1. Heatmaps of the average response for all simulations are shown in the supplemental data. A 6% increase in smooth muscle tone decreased carotid IMT from 0.83±0.16 mm to 0.78±0.17 mm and a 15 mmHg decrease in MAP decreased carotid artery IMT to 0.67±0.14mm. A 6% increase in smooth muscle tone decreased WSCA from 18.3±5.4 mm^2 to 15.2±4.9 mm^2 and a 15mmHg decrease in MAP decreased WSCA to 14.3±4.6 mm^2.

From the mixed-effects, repeated measures analysis (Table 2), both changes in smooth muscle tone and MAP had statistically significant associations ($p<0.001$) with the chronic changes in carotid IMT and WSCA. A statistically significant interaction of smooth muscle tone and MAP was found for the chronic changes in IMT ($p=0.002$) and WSCA ($p=0.001$).

Local Sensitivity

Results from local sensitivity analysis are shown in Supplemental Figure S2. The three strongest effects of smooth muscle tone (per 2% increment) were to acutely decrease cPWV (−6.1±1.1%), chronically decrease WSCA (−5.2±1.2%), and acutely decrease wall stress (−4.7±1.1%). The three strongest effects of MAP (per 5 mmHg increment) were to chronically increase WSCA (7.8±1.3%), acutely increase wall stress (7.0±1.2%), and chronically increase IMT (6.4±1.0%). For every simulated outcome measure, the order (quadratic) effect of smooth muscle tone was greater than that of MAP and the smooth muscle tone-MAP interaction.

Discussion

This study demonstrated in a simulated model of arterial mechanics, that increasing central arterial smooth muscle tone is predicted to improve central arterial dysfunction in older, hypertensive adults. Increasing carotid artery smooth muscle tone was predicted to have the beneficial acute effects of decreasing stiffness and wall stress and the beneficial long-term effect of decreasing carotid artery wall cross-sectional area. For the outcomes of decreasing carotid artery stiffness, wall stress, and wall cross-sectional area the effect of increasing smooth muscle tone was predicted to be greater than or comparable to the effect of decreasing blood pressure.

Our computational findings, along with preclinical and clinical data, highlight that lowering blood pressure and increasing smooth muscle tone could have a congruent impact on arterial stiffness. Our results highlight that proximal VSMCs could be a potential novel target in treating hypertension. In current clinical practice this aspect of arterial hemodynamics is ignored. We propose that our findings could be utilized in two ways: First, the proximal VSMC could be a target for future central arterial vasoconstriction therapies in combination with previously established interventions that reduce systemic vascular resistance in the distal arteries. Second, our findings may be viewed in the light of existing antihypertensive treatments, which likely affect aortic VSMC tone in different ways and with varying intensities. For example, treatment with a diuretic has limited effects on the aorta, whereas

treatment with a direct vasodilator, which lowers blood pressure and increases the diameter of both elastic and muscular arteries, could lead to inadvertent and potentially adverse large artery stiffening.

Studies of hypertensive rodents have previously shown beneficial effects of increased central arterial smooth muscle tone. Fridez et al., found that increased carotid artery smooth muscle tone acutely decreases arterial stiffness in rats with hypertension induced by aortic ligation[19–21]. In this animal model, the increase in smooth muscle tone was an acute phenomenon, only lasting a few weeks. Studies of mice with angiotensin II induced hypertension have also found that a genetic background predisposed to increased aortic contractility is associated with adaptive remodeling such as reduced vessel wall thickening, stiffening, and inflammation[22]. Smooth muscle cell stiffness syndrome has been proposed as a mechanism for increased arterial stiffness in spontaneously hypertensive rats[23–25]. However, the smooth muscle cell stiffness syndrome hypothesis cannot account for findings that increasing smooth muscle tone can decrease arterial stiffness[11]. Our modeling predictions add to these previous preclinical studies in rodents by showing that increasing carotid artery smooth muscle tone could improve carotid artery mechanics and structure in older Veterans who have, on average, had hypertension for over a decade. Decreasing central arterial stiffness could have the further benefit of decreasing pulse pressure in older hypertensive adults. Elevated pulse pressure are associated with both all-cause and cardiovascular mortality in older adults[26] and reducing pulse pressure through decreasing arterial stiffness could be of great benefit.

Many antihypertensive medications are vasodilators which could decrease central arterial smooth muscle tone and increase stiffness in older adults. While it may seem paradoxical, the available preclinical and clinical data instead supports increasing central artery smooth muscle tone as a therapeutic strategy to improve vascular function in hypertension. The main concern with this treatment approach is that a medication to increase central arterial smooth muscle tone could also cause peripheral vasoconstriction and increase vascular resistance. There currently are no treatments known to increase central artery smooth muscle tone without causing vasoconstriction of the resistance vessels. It should be noted though that VSMC populations are highly heterogenous throughout the arterial tree[27] and vasoactive agents can have differential effects on the microvasculature, muscular conduit arteries, and the central elastic arteries[28]. Our simulated predictions of increasing carotid artery smooth muscle tone bear striking resemblance to the effects of an angiotensin receptor blocker (ARB) in middle aged hypertensive adults with metabolic syndrome[29]. In this patient population, ARBs had the dose-dependent effects of both decreasing carotid artery stiffness and diameter, which could be due to remodeling, a change in smooth muscle tone, or a combination of both. Increasing carotid artery smooth muscle tone was predicted to have very similar effects in our arterial mechanics simulations. Changes in carotid artery smooth muscle tone may be a mechanistic explanation for the beneficial effects of renin angiotensin aldosterone inhibitors on arterial stiffness compared to other classes of antihypertensive medications[30].

In any modeling study assumptions will need to be made and these assumptions deserve critical evaluation for their appropriateness. The major assumptions made in both our acute

and chronic arterial mechanics simulations are reasonable based on prior experimental and clinical data. The assumption that there is not an acute change in WSCA is in line with experimental observations that artery walls are nearly incompressible materials. The assumption that BP will acutely change and then remain constant for a chronic amount of time is reasonable at least for an average behavior. Data from the SPRINT trial shows that after starting an intervention the group average BP can quickly decrease over a 3-month period and then maintain at a roughly constant level for a long period of time[31]. The assumption that diastolic diameter will remain constant in chronic remodeling is in line with the hypothesis that an artery will remodel to maintain wall shear stress homeostasis[32]. If the flow rate through the artery is not changing, then the artery diameter also will not change[18]. The assumption that the vessel will remodel to achieve mechanical homeostasis has been observed in many experimental studies[18,33,34], although this only considers adaptive remodeling. Processes such as excessive inflammation can cause maladaptive remodeling and prevent an artery from achieving homeostasis[22]. That we did not consider such maladaptive processes, which are beyond the capability of our chosen modeling techniques, is a limitation.

Additional limitations of this study include the small number of participants and that the findings are limited to an older patient population. Our simulation predictions of changes in arterial mechanics were based on participant specific data, but require confirmation in future experimental studies. In addition to the chronic adaptations of wall-cross sectional area to maintain mechanical homeostasis, there will be other long-term adaptations in the mass-fractions of arterial wall constituents that we did not consider. We did not investigate these adaptations as they would have required more complicated growth and remodeling simulations and we did not have the requisite longitudinal and histologic data from our study to parameterize these models.

Conclusion

This study utilized participant-specific biomechanics simulations to predict that increasing central arterial smooth muscle tone may be a novel therapeutic target to improve central arterial dysfunction in older, hypertensive adults. Increasing carotid artery smooth muscle tone was predicted to have the beneficial acute effects of decreasing stiffness and wall stress and the beneficial long-term effect of decreasing carotid artery wall cross-sectional area. For the outcomes of decreasing carotid artery stiffness, wall stress, and wall cross-sectional area the effect of increasing smooth muscle tone was greater than or comparable to the effect of decreasing blood pressure. These simulation predictions require experimental validation in future long-term empirical studies. Future research should also be aimed at identifying if there are medications and therapeutic strategies to improve or limit central arterial dysfunction through eliciting increased central arterial smooth muscle tone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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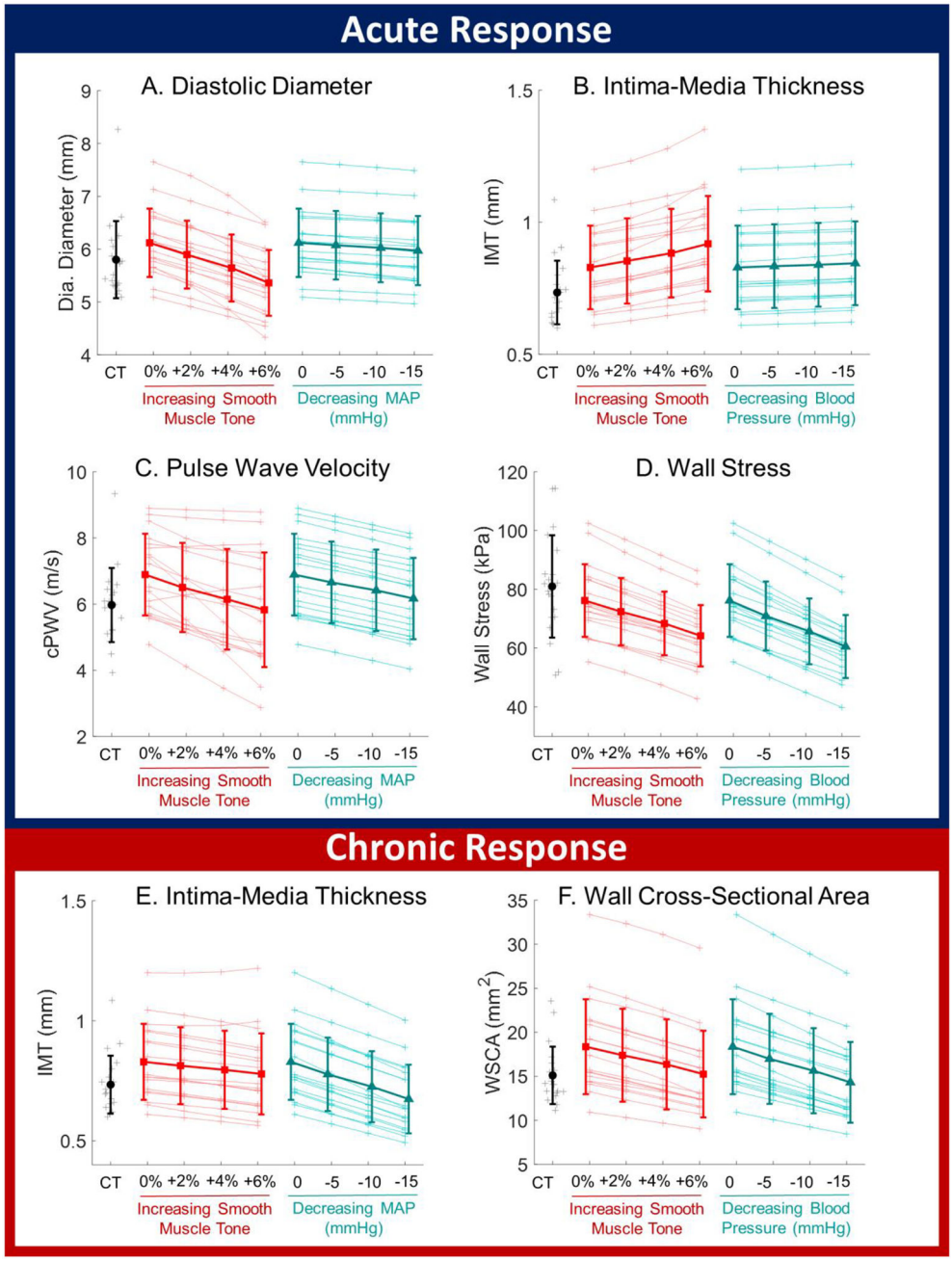

Figure 1:

Effects of smooth muscle tone and mean arterial pressure (MAP) on A. acute changes in diastolic diameter, B. acute changes in intima-media thickness (IMT), C. acute changes in carotid pulse wave velocity (cPWV), D. acute changes in wall stress, E. chronic changes in IMT, and F. chronic changes in wall cross-sectional area (WCSA). Measured values for control (CT) participants are shown in black. Simulations of changing smooth muscle tone in hypertensive participants are shown in red. Simulations of changing MAP in hypertensive

participants are shown in aqua. Note that the 0% and 0 mmHg points are the experimentally measured values for hypertensive participants.

Table 1:

Participant Characteristics

	Control (n=20)	Hypertensive (n=20)	p-value
Age (years)	72.0±9.3	70.8±6.6	0.64
BMI (kg/m^2)	27.6±4.5	27.0±6.5	0.72
Sex			0.53
Female (n, %)	8 (40%)	10 (50%)	
Race/Ethnicity			1.0
White (n, %)	19 (95%)	19 (95%)	
Black (n, %)	1 (5%)	1 (5%)	
Diabetes Mellitus (n, %)	2 (10%)	6 (30%)	0.11
Smoking Status			0.41
Current (n, %)	2 (10%)	3 (15%)	
Former (n, %)	9 (45%)	12 (60%)	
Never (n, %)	9 (45%)	5 (25%)	
Pack Years	14.7±19.2	16.7±18.7	0.74
Supine Blood Pressure			
SBP (mmHg)	127±13	134±13	0.095
DBP (mmHg)	76±8	80±7	0.084
MAP (mmHg)	93±8	98±8	0.054
cSBP (mmHg)	119±10 (n=19)	121±14	0.77
24hr ABPM	N=19	N=16	
24hr SBP (mmHg)	121±9	125±11	0.19
24hr DBP (mmHg)	69±6	73±7	0.09
24hr BP < 125/75 (n, %)	10 (53%)	8 (50%)	0.88
Antihypertensive Medications (n,%)			--
0		3 (15%)	
1	--	11 (55%)	
2	--	6 (30%)	
Antihypertensive Medication Classes (n,%)			--
ACE Inhibitor	--	2 (10%)	
Angiotensin II Receptor Blocker	--	8 (40%)	
Calcium Channel Blocker	--	5 (25%)	
Beta Blocker	--	3 (15%)	
Thiazide Diuretic	--	3 (15%)	
Unknown	--	2 (10%)	
Self-Reported Years Since HT Diagnosis	--	14.7±14.3	--

Abbreviations: BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, cSBP – central systolic blood pressure, ABPM – ambulatory blood pressure monitor, HT - Hypertension

Table 2:

Mixed-Effects Model Regression Coefficients

	Acute Response				Chronic Response	
	Diastolic Diameter (μm)	**IMT (μm)**	**cPWV (m/s)**	**Stress (kPa)**	**IMT (μm)**	**WSCA (mm^2)**
Δk	−209.7 ± 2.7 *	−23.3 ± 0.4 *	−0.39 ± 0.01 *	−3.53 ± 0.06 *	−15.8 ± 0.1 *	−0.93 ± 0.02 *
ΔMAP	46.7 ± 2.2 *	−5.2 ± 0.3 *	0.23 ± 0.01 *	5.23 ± 0.05 *	51.9 ± 0.4 *	1.39 ± 0.01 *
ΔMAP*Δk	6.3 ± 1.1 *	−1.1 ± 0.2 *	0.00 ± 0.01	−0.12 ± 0.03 *	0.7 ± 0.2 *	−0.04 ± 0.01 *
Δk*Δk	−15.4 ± 1.5 *	−2.3 ± 0.2	0.01± 0.01 *	−0.18 ± 0.04 *	−0.3 ± 0.3	−0.03 ± 0.01 *
ΔMAP*ΔMAP	−1.7 ± 1.2	−0.3 ± 0.2	0.00 ± 0.01	0.03 ± 0.03	0.1 ± 0.2	0.01 ± 0.01

* $p<0.05$. Regression coefficients with standard error of fixed effects calculated per 2% increment in smooth muscle tone (k) and 5 mmHg increment in MAP. Model intercept was a random effect. Abbreviations: IMT – Intima-media thickness, cPWV – carotid pulse wave velocity, WSCA – wall-cross sectional area, k – smooth muscle tone, MAP – mean arterial pressure