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Race/Ethnic Differences in Carotid Stiffness and Diameter Using PROC GLM

Matthew S. Markert, University of Miami – Miller School of Medicine

Dept. of Epidemiology and Public Health

Miami, Florida, USA

ABSTRACT

Race/ethnic differences in the dilatation and stiffening of the carotid artery are unknown. These differences might be modified by age, an important vascular risk factor. Carotid diameters were assessed by ultrasound in 1116 subjects from the Northern Manhattan Study (NOMAS). Multivariate linear regression models were performed using PROC GLM (SAS ® 9.2) to determine the relationship between race/ethnicity and carotid arterial stiffness (STIFF), and between race/ethnicity and carotid diastolic diameter (DDIAM). PROC UNIVARIATE was used to test for normality assumptions. Interactions between race/ethnicity and age for STIFF and for DDIAM were also assessed. After multivariate adjustment for age, gender, body-mass index, hypertension, diabetes, LDL, HDL, and presence of carotid plaque, Hispanics had a lower DDIAM ($p<0.05$) compared to whites. However, a significant interaction between age and race/ethnicity was observed for both outcomes. Age was associated with increased DDIAM in Hispanics only ($p<0.0001$). Stiffness increased with age in Hispanics ($p<0.0001$) and Blacks ($p<0.03$) but not among whites. This association was maintained in the fully adjusted model, which included pack/years smoking.

INTRODUCTION

Carotid arterial stiffness (STIFF) is a measurement of a vessel wall's tendency to resist deformation by systolic pressure during the cardiac cycle[1]. It is increased among individuals with atherosclerosis and is an early predictor of cardiovascular disease and stroke [2-4]. This process of arterial aging – arteriosclerosis – includes compensatory dilation of the larger vessels following separation of the elastic lamellae within the arterial media[5]. Intima-medial thickening and hyperplasia of the collagenous components[5] results in a less distensible vascular wall, and increased shear stress at location of stenosis that induces an expansion of luminal area. Increased stiffness has been associated with atherosclerosis[6], advanced age[7, 8] , type II diabetes[9-12], and the metabolic syndrome[13-15]

Although there are several studies that examine stiffness or luminal measures in populations [4, 13, 16-21] there is a paucity of stiffness data from longitudinal studies that include Hispanics, blacks and whites living in the same community. Further, variation of stiffness measures among race/ethnic groups across ages is not well understood or reported. Examination of race/ethnic differences in carotid artery stiffness and diastolic diameter may help in understanding race/ethnic differences in stroke incidence. Particularly, increased stroke incidence among blacks and Hispanics as compared to whites[22], and decreased mortality among Hispanics compared to blacks and whites[23].

We investigated race/ethnic differences in carotid stiffness in a multiethnic population-based cohort. We also examined whether these differences are due primarily to increased age, or to age-independent arterial lumen changes.

COLLECTING THE DATA

1. Subject Data

Standardized questions answered by 3298 study participants were adapted from the validated Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System [24]. The validity of these questions in the been described previously[25]. Carotid stiffness metrics were available for 1536 subjects following High-resolution carotid ultrasonography imaging as a part of an ancillary sub-study. Hypertension was defined as a current or previous diagnosis, or an in-clinic recorded diastolic pressure greater than 90mmHg or systolic pressure of greater than 140mmHg, or use of antihypertensive medication. Fasting blood samples were analyzed to determine glucose, cholesterol and triglycerides[25]. Fasting serum glucose was measured according to a standard glucose dehydrogenase method[26]. Participants were defined as diabetic if they had a previous diagnosis of diabetes, had a fasting blood sugar level greater than 126mg/dL, or were on medication for their blood sugar. Smoking status was self-reported, categorized as current, ever smoked, or never smoked, and calculated in pack-years.

2. Ultrasound Data

High resolution carotid ultrasonography was performed on study participants with a GE LOGIQ 700 system (GE Healthcare, Milwaukee, WI) equipped with a multifrequency 9/13-MHz linear array transducer. Both internal and common carotid arteries as well as bifurcations were imaged in transverse (short axis) and longitudinal planes (anterior, lateral, and posterior views) with standardized scanning and reading protocols that had a high degree of reproducibility and reliability[27]. Images were divided into three segments, defined as: segment 1 = from 10-20 mm

proximal to the tip of the flow divider into the common carotid artery (CCA); segment 2 = the near and far walls of the carotid bifurcation beginning at the tip of the flow divider and extending 10mm proximal to the flow divider tip; and segment 3 = the near and far walls of the proximal 10mm of the internal carotid artery (ICA). A real-time digital clip of the CCA was recorded for 10 seconds. Measurements of the CCA intraluminal systolic and diastolic diameters were performed off-line with IMAGE-Pro analysis software on a specialized work station. The best-visualized intima-media boundaries from up to 10 cardiac cycles on the M mode ultrasound were traced and the systolic (SDIAM) and diastolic (DDIAM) diameters were automatically computed, averaged and stored in a data file. Plaque presence was noted and number of plaques were characterized. The high reliability of the SDIAM and DDIAM measurements between the two readers in our laboratory was reported previously[27]. The inter-reader correlation coefficients were 0.96 for SDIAM and 0.95 for DDIAM.

The blood pressure (BP) in the right brachial artery was measured by a Dinamap Pro100 (Critikon Inc) after the participants had rested for 10 minutes in a supine position. Although BP is best measured in the arterial segment being studied for stiffness, brachial artery pressures have served as a suitable substitute[28].

Stiffness was calculated as: STIFF (β) = ln (SBP / DBP) / STRAIN, where SBP and DBP were mean brachial blood pressures in the systolic and diastolic cardiac cycle, respectively, and STRAIN = (SDIAM-DDIAM)/DDIAM; where SDIAM was systolic and DDIAM diastolic intraluminal CCA diameter. Strain therefore represents a ratio of the amount of stress deformation relative to the unstressed state, and stiffness is a dimensionless quantity that expresses the tendency of an individual's arteries to deform in the presence of a given blood pressure.

GENERATING THE DATASET

Since there were a variety of databases all referring the same patient, each from different interviews, visits, or test results, it was imperative to combine them according to the individual patient identifier (ID).

```
Library stiff 'c:\path\';
run;
proc sort data=stiff.vas; by id;     /*vascular data from ultrasound*/;
proc sort data=stiff.bds; by id;     /*birth and demographic data*/;
proc sort data=stiff.rfa; by id;     /*risk factor assessment*/;
proc sort data=stiff.lab; by id;     /*laboratory results*/;

data vas; set stiff.vas;
   if sdiam=. then delete;
   if first.id;
data mergedata;
merge vas stiff.bds stiff.rfa stiff.bds stiff.lab;
   by id;
   if first.id;
run;
/* eliminates duplicate entries, keeps only baseline data from first visit/
/=1598observations*/;
```

REPORTING THE DATASET

In order to understand what questions we might want to ask, and indeed in order to explain or limit our conclusions, it is important to describe the characteristics of the remaining subject set given that it is a subset of the larger cohort.

```
/*Table 1 Generation:*/
ods html;
proc freq data=mergedata;
      tables agegroup isex htn140 diabetes educ smoke;
proc means data=racethnicsummary;
      var age pckyr stiff ddiam sbpmn dbpmn bmi waisthiprat
      lchol lldl lhdl ltg _plaqnum;
proc sort data =mergedata; by group;
proc freq data=mergedata;
      tables agegroup isex htn140 diabetes educ smoke;by group;
```

```
proc means data=mergedata;
      var age pckyr stiff ddiam sbpmn dbpmn bmi waisthiprat
      lchol lldl lhdl ltg _plaqnum;
  by group;
run;
ods html close;
```

The ODS HTML code was used because HTML data retains spacial differences that are represented as cells in the output window. The result is data that is managed with spreadsheet softwares such as Excel allows simple copy/paste if you are working with prescribed templates for your table. Our results generated Table 1.

Table 1: Demographic Information for the Cohort

(ANOVA, *p< 0.05)	(Mean ± SD)			
Risk Factor	**(n) Total Cohort**	**(n) Hispanic**	**(n) Black**	**(n) White**
***Age**	(1536) 70.0 ± 9.2	(948) 68.1 ± 8.4	(317) 72.5 ± 9.2	(271) 74 ± 9.7
Age 50-64	(503) 60.1 ± 3.5	(377) 60.1 ± 3.5	(75) 60.3 ± 3.7	(51) 59.6 ± 3.9
*Age 65-74	(577) 69.9 ± 2.8	(379) 69.6 ± 2.8	(111) 70.5 ± 2.7	(87) 70.1 ± 2.7
Age ≥75	(456) 81.2 ± 4.9	(192) 80.7 ± 4.6	(131) 81.3 ± 4.9	(133) 82.0 ± 5.3
Female	(940) 61 %	(593) 62 %	(197) 62 %	(150) 55 %
***Hypertension**	(1073) 70 %	(667) 70 %	(241) 76 %	(165) 61 %
***Diabetes**	(294) 19 %	(204) 21 %	(65) 21 %	(25) 9 %
***Education**				
≤8th Grade	(602) 39 %	(556) 58 %	(27) 9 %	(19) 7 %
Some HS	(200) 13 %	(139) 15 %	(44) 14 %	(17) 6 %
Completed HS	(266) 17 %	(119) 13 %	(101) 32 %	(46) 17 %
Some College	(209) 14 %	(73) 8 %	(76) 24 %	(60) 22 %
≥ College Grad	(263) 17 %	(64) 7 %	(69) 22 %	(130) 48 %
***Ever Smoked**	(804) 52 %	(454) 48 %	(190) 60 %	(160) 59 %
Pack Years	12.1 ± 22.6	10.2 ± 22.8	13.9 ± 19.8	16.6 ± 24.2
***Stiffness**	8.6 ± 6.0	8.4 ± 5.7	9.2 ± 6.2	8.7 ± 6.9
***DDIAM (mm)**	6.2 ± 1.0	6.2 ± 0.9	6.3 ± 1.0	6.3 ± 1.0
***SBP mmHg**	140.5 ± 19.7	140.1 ± 19.6	144.1 ± 20.2	137.6 ± 19.1
***DBP mmHg**	83.1 ± 10.9	83.9 ± 10.6	83.9 ± 11.6	79.3 ± 10.5
BMI kg/m^2	28.2 ± 4.9	28.5 ± 4.7	28.6 ± 5.3	26.6 ± 5.2
Waist : Hip Ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
***Cholesterol mg/dL**	201.3 ± 38.7	201.8 ± 39.2	196.8 ± 39.9	204.9 ± 35.1
***LDL mg/dL**	127.6 ± 35.1	128.9 ± 35.0	122.6 ± 36.9	128.9 ± 32.9
***HDL mg/dL**	47.0 ± 14.8	44.4 ± 13.2	52.1 ± 16.0	50.3 ± 16.7
***Triglycerides mg/dL**	135.4 ± 80.9	144.6 ± 82.0	109.2 ± 61.6	132.7 ± 89.4
***Carotid Plaques (n)**	1.5 ± 1.7	1.2 ± 1.6	1.7 ± 1.7	1.9 ± 1.8

STATISTICAL ANALYSIS OF THE DATASET

Demographics and vascular risk factors were tested for differences across race/ethnic groups by Analysis of Variance (ANOVA). The differences in STIFF and DDIAM across race/ethnic groups (Hispanic, black, white) were analyzed with linear regression models controlling for age, sex, years of education, and vascular risk factors that were shown to be significantly ($p<0.05$) associated with STIFF or DDIAM in univariate analyses. Models were constructed as follows 1) univariate, 2) Model 1 + age, sex, years of education 3) Model 2 + BMI, hypertension, diabetes, LDL-cholesterol, HDL-cholesterol, presence/absence of carotid plaque, and pack-years history of smoking. Stiffness and diastolic diameter were each analyzed as dependent variables, and stiffness was log-transformed to satisfy normality assumptions. Tests for interactions between age and race/ethnicity in relation to STIFF or DDIAM were also performed. Following detection of a significant interaction between age and race/ethnic group ($p<0.05$), stratified analyses of the effect of age on STIFF and DDIAM performed using the fully-adjusted model 3.

DETERMINING NORMAL DISTRIBUTION AND ANOVA

Before we continue, it's important to understand the differences between our groups *de novo*. Given that we are attempting to draw conclusions that depend on linear models that make use of those differences in the form of covariates, we will need to know what covariates to choose, how powerfully they contribute to our model, and whether including them will help explain differences between the groups or would be an example of overcontrolling. A simple analysis of variance (ANOVA) will be used in the form of PROC ANOVA, but since an ANOVA relies on an assumption of normality, first we have to determine the distribution of our data, and transform it if necessary. Let's start with our outcomes of interest so we can make sure our subgroups are fair.

```
proc sort data=stiff;
   by group agegroup;
run;
PROC UNIVARIATE NORMAL PLOT DATA=agetest2;
      VAR DDIAM STIFF;
   by group usagegroup;
   HISTOGRAM DDIAM/NORMAL (COLOR=RED W=5);
   TITLE 'PROC UNIVARIATE EXAMPLE';
   FOOTNOTE 'Evaluate distribution of variable';RUN;
```

PROC UNIVARIATE EXAMPLE 662
15:32 Saturday, February 8, 2011

group=1 Age at Ultrasound Group, 1 is <60yoa, 2 is 60- <70yoa, 3 is >70yoa=2 ----------

The UNIVARIATE Procedure
Variable: ddiam

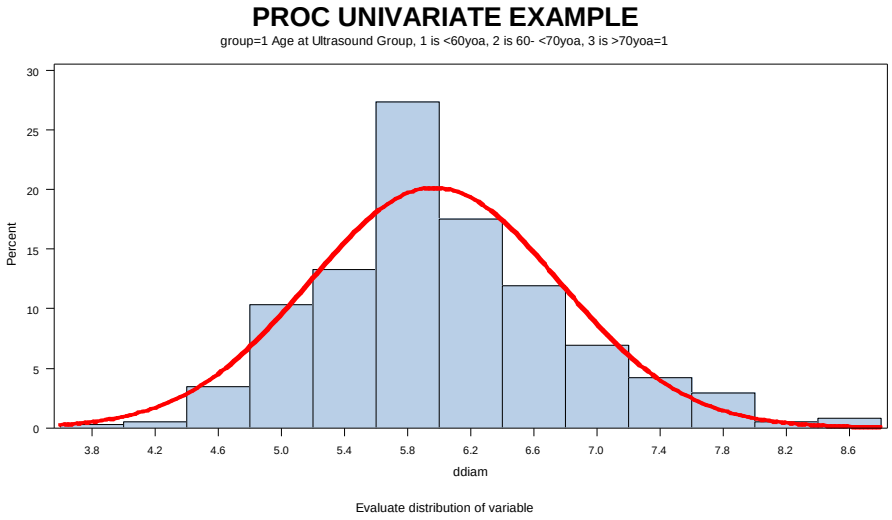
Moments

N	379	Sum Weights	379
Mean	6.28432454	Sum Observations	2381.759
Std Deviation	0.95723443	Variance	0.91629776
Skewness	0.54528458	**Kurtosis**	**0.22716168**
Uncorrected SS	15314.1071	Corrected SS	346.360553
Coeff Variation	15.2320974	Std Error Mean	0.0491698

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	**W**	**0.97801**	**Pr < W**	**<0.0001**
Kolmogorov-Smirnov	D	0.08869	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.463037	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	2.562853	Pr > A-Sq	<0.0050

Output 1. Summarized Output from PROC UNIVARIATE



Output 1b. Visual representation of the means from PROC UNIVARIATE

In cases where normality was not satisfied or was known to have a non-normal distribution, a natural-log transformation was applied, as in the case of stiffness:

```
data mergedata; set mergedata;
   logSTIFF = log(STIFF);
run;
```

Analysis of variance of the mean between the groups was accomplished using PROC ANOVA:

```
ods html;
proc anova data=mergedata;
      class group;
      model usage = group;
proc sort data=mergedata;
   by agegroup;
proc anova data=mergedata;
      class group;
      model usage = group;
   by agegroup;
run;
ods html close;
```

MULTIPLE REGRESSION MODELS

For the primary outcomes of interest, stiffness and diastolic diameter, we used a generalized linear model via PROC GLM to test the null hypothesis that there is no difference between the race/ethnic groups. We'll use white as a reference group, since the larger point of this study is to determine if there are race/ethnic differences that explain different manifestations of risk among minority populations.

```
ods html
proc glm data=mergedata;
class group;
      model ddiam logstiff = hispanic black age isex
      educ bmi htn140 diabetes lldl lhdl plaqyn pckyrs;
run;
ods html close;
```

It's important that we generate iterative models that build on each other. We see there is a disappearance and reappearance of significance between models 2 and 3. A test for interaction with age and with gender is performed as follows:

```
ods html;
proc glm data=mergedata;
class group;
      model ddiam logstiff = group age group*age isex isex*age;
run;
ods html close;
quit;
```

A summary of the results is contained below in Figure 2, showing that there is an effect due to age among our race/ethnic groups.

SUB-STRATIFICATION BY GROUP

NOTE: Since we're stratifying, it's important to determine if we could still detect an effect due to age if there happened to be one. There are a variety of ways to go about this, but since we don't have an a priori expectation of effect magnitude, you can use PROC POWER for given the standard deviation of our outcome variable (via PROC MEANS).

Since we detected a significant interaction between age and race-ethnicity for the dependent variables, it's important that we account for this in our model. Power calculations indicated there was enough of a sample size (or enough of an effect size) that stratification by group was acceptable, but not by age-group. While we could include an exponential term in our model (age*age), using age-group as our independent variable while controlling for the same covariates will allow us to determine among what group of people the effect of age is significant.

```
ods html;
proc sort data=mergedata;
   by group;
proc glm data=mergedata;
      model logstiff ddiam = age isex educ
      bmi htn140 diabetes lldl lhdl plaqyn pckyr;
   by group;
proc glm data=mergedata;
      model logstiff ddiam = agegroup2 agegroup3 isex educ
      bmi htn140 diabetes lldl lhdl plaqyn pckyr;
   by group
run;
ods html close;
quit;
```

Results from this test are included below in Figure 3.

RESULTS

Demographic characteristics for the study population (n=1536) stratified by race/ethnicity are shown in Table 1. The mean age was 70 +/-9 years, and 61% of subjects were women; 62% identified themselves as Hispanic, 20% as black and 18% as white. Significant ($p<0.05$) race/ethnic differences in risk factors were evaluated by an analysis of variance (PROC ANOVA) between groups for each covariate (Table 1) after first testing for normal distribution of the means (PROC UNIVARIATE).

The associations of race/ethnicity with STIFF and DDIAM in sequential multivariate models are shown in Figure 1. Hispanic ethnicity was significantly associated with increased DDIAM compared to whites in the fully adjusted model. An interaction was found between race/ethnicity and age for DDIAM ($p=0.0081$) and for STIFF ($p=0.013$), as shown in Figure 2. Stratified analyses were conducted with the fully adjusted model (Figure 3). Diastolic diameter increased with age among Hispanics ($\beta=0.02$, $p<0.0001$) but not among blacks or whites. Stiffness increased with age among Hispanics ($\beta=0.01$, $p<0.0001$) and blacks ($\beta=0.01$, $p=0.003$) but not among whites. These associations with age remained strongly significant for STIFF and DDIAM in models fully adjusted for demographic and vascular risk factors. Age-group subcategory (1 =age $\leq$64, 2= age 65-74, 3 =age $\geq$75) was also associated in Hispanics with STIFF ($\beta=0.12$, $p<0.0001$) and DDIAM ($\beta=0.27$, $p<0.0001$) but was not associated with either in whites. In Hispanics, when compared to the reference group of younger subjects (age$\leq$64) the group of older subjects were associated with STIFF ($\beta=0.12$, $p=0.004$) and DDIAM ($\beta=0.27$, $p<0.0001$).

Figure 1

Race : [ref]	Model 1				Model 2				Model 3			
	STIFF		DDIAM		STIFF		DDIAM		STIFF		DDIAM	
	β	p<t	β	p<t	β	p<t	β	p<t	β	p<t	β	p<t
Hispanic : [White]	-0.004	0.93	**-0.17**	**0.01**	0.04	0.42	-0.13	0.10	0.05	0.82	**0.08**	**0.04**
Black : [White]	**0.10**	**0.04**	-0.01	0.86	**0.11**	**0.02**	0.03	0.73	0.05	0.10	0.08	0.49
Hispanic : [Black]	**-0.10**	**0.01**	**-0.16**	**0.01**	-0.15	0.06	**-0.16**	**0.02**	-0.07	0.10	-0.11	0.13

Model 1) Univariate association of DDIAM or STIFF with race ethnic group
Model 2) Univariate model 1 + Demographic Factors
- Age, Gender, Years of Education

Model 3) Demographic Model 2 + Vascular Risk Factors
- Body/Mass Index, Hypertension, Diabetes, LDL-Cholesterol, HDL-Cholesterol

Figure 2

Test for Interaction	Stiff		DDIAM	
	β	p<t	β	p<t
Group*Age	**-0.005**	**0.0081**	**-0.008**	**0.013**
Gender*Age	-0.003	0.3144	-0.004	0.416

Figure 3

	Hispanic				Black				White			
	STIFF		DDIAM		STIFF		DDIAM		STIFF		DDIAM	
	β	p<t	β	p<t	β	p<t	β	p<t	β	p<t	β	p<t
Age	**0.01**	**<.0001**	**0.02**	**<.0001**	**0.01**	**0.003**	0.01	0.30	0.002	0.65	0.00	0.61
Agegroup	**0.13**	**<.0001**	**0.21**	**<.0001**	**0.09**	**0.02**	0.06	0.43	0.008	0.89	0.02	0.82
ref: Age (under 65)												
Age (65-74)	-0.06	0.11	-0.002	0.97	-0.02	0.75	**-0.31**	**0.01**	0.085	0.31	-0.10	0.48
Age (75-up)	**0.12**	**0.004**	**0.27**	**<.0001**	0.13	0.08	0.03	0.83	0.09	0.36	0.06	0.69

CONCLUSIONS

Carotid arterial stiffness has been associated with an increased risk for stroke, especially in the elderly population[4], [16, 29, 30]. We tested the hypothesis that race/ethnic differences exist in carotid arterial stiffness, which might in part explain observed differences in stroke risk among the different ethnic groups [19, 22, 23, 31]. We demonstrated increased carotid stiffness among blacks and Hispanics, which may suggest an increased risk for stroke among these race ethnic groups. Our finding is consistent with our previous report regarding an increased incidence of stroke among blacks and Hispanics in the NOMAS cohort[22]. We also demonstrated that age is independently associated with increased carotid diameter among Hispanics, but not among blacks or whites. The strongest association with diastolic diameter in Hispanics was found in the oldest group (≥75 years) even though the average age of those elder Hispanics (80.7 years) was lower than in blacks (81.3 years) or whites (82 years) in the same age-group. Likewise, the association between age and carotid stiffness was strongest among Hispanics, followed by blacks, and was not apparent among whites. Adjusting for subject height, pulse-pressure, mean-arterial pressure, or total average carotid intima-medial thickness (cIMT) did not affect these results.

Traditional vascular risk factors that are known to be associated with stiffness[32] including age[13, 33], hypertension[34-36], obesity[37, 38], smoking[39], hypercholesterolemia[40], plasma lipoproteins[41], diabetes[9-12] or presence[42] or number[43] of plaque did not explain the race/ethnic disparities in carotid stiffness associated with age observed in our study. Although stiffness is associated with increased stroke risk[2-4], wider diameters may mediate that observed association pathway by less compromised blood-flow to prevent brain ischemia in the presence of arterial stiffness. Our results are consistent with results from The National Longitudinal Mortality Study, which found that Hispanics have a similar risk assessment compared to Whites at younger ages, but that the risk for Hispanics is marginally lower at older ages [44]. Another review of all age-specific strokes and deaths from stroke in the United States from 1995-1998 (n=507,256)[45] showed that Hispanics have a significantly reduced rate of mortality from ischemic stroke compared to whites (RR 0.51, 95%CI 0.50-0.52). Our findings, that Hispanics have a relative widening with older age, may in part explain these results.

The primary limitation to this study was the cross-sectional design. We have inferred effects of aging on DDIAM and STIFF using individuals of different ages at the time of carotid ultrasound, but it would be better if we could do a repeated measures longitudinal analysis. Future studies are therefore needed to calculate DDIAM and STIFF within individuals over multiple time points to better elucidate changes in vasculature that occur with aging within individuals across different race-ethnic groups. There is no consensus on the best method for measuring arterial stiffness [30, 46], and comparison with a 'gold' standard (such as pathology) is yet to be performed. A final limitation is that unknown confounders are always a possible explanation for the observed association between Hispanic ethnicity and increased carotid diameter that was not found for blacks or whites. Genetic factors affecting carotid vasculature that are expressed differently in some population groups or are affected differently over time by similar exposures (epigenetic differences) might suggest that analyses should be adjusted genomically in addition to race/ethnically. Developments in these fields continue to add to our understanding of disease.

It is important to maintain a vigorous attitude with respect to identifying the assumptions in your model, and to the appropriate use of covariates while building it. *Independent testing of covariates must include assessment of normality assumptions*. Be sure to test for interactions terms, and check that your conclusions have a plausible scientific explanation. Our results suggest that Hispanics and blacks have increased stiffness with age in comparison to whites. In addition, aging is associated with increased carotid intraluminal diameter among Hispanics but not among blacks or whites. These findings may offer a possible explanation for reported disparities in stroke morbidity and mortality among Hispanics compared to blacks and whites.

CONTACT INFORMATION

Hope to hear from you – it's not too late for me to screw this up. I'm working on my dissertation and I promise that *every suggestion helps*.

Name: Matthew Markert
Enterprise: NCC-1701D
Address: 947 Lenox Avenue, #304
City, State ZIP: Miami Beach, FL 33139
Work Phone: (215) 803-1891
E-mail: matthew.markert@gmail.com
Web: www.PhotographyOnTheRoad.com

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