The Location of Arterial Stiffening Differs in those with Impaired Fasting Glucose versus Diabetes: Implications for Left Ventricular Hypertrophy from the Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Objective: To determine if middle aged and older individuals with impaired fasting glucose (IFG), but no clinical evidence of cardiovascular disease, exhibit abnormal changes in proximal thoracic aortic stiffness or left ventricular mass when compared to healthy counterparts.

Research Design and Methods: From the Multi-Ethnic Study of Atherosclerosis, 2240 subjects with normal fasting glucose (NFG), 845 with IFG, and 414 with diabetes mellitus (DM), all aged 45 to 85 years without pre-existing coronary artery disease, underwent magnetic resonance imaging (MRI) determinations of total arterial and proximal thoracic aortic stiffness, and left ventricular mass. The presence or absence of other factors known to influence arterial stiffness were assessed.

Results: After adjustment for clinical factors known to modify arterial stiffness, proximal thoracic aortic stiffness was not increased in those with IFG compared to those with NFG (1.90±0.05 vs 1.91±0.04 10^{-3} \text{mmHg}^{-1}, \text{respectively}, p=0.83). After accounting for clinical factors known to influence LV mass, LV mass was increased in those with DM relative to those with NFG (150.6±1.4 vs 145.8±0.81 gms \textit{[p<0.0009]}), but not in those with IFG in comparison with NFG (145.2±1.03 vs 145.8±0.81 gms \textit{[p=0.56]}).

Conclusions: Middle aged and older individuals with the pre-diabetes state of impaired fasting glucose do not exhibit abnormal proximal thoracic distensibility nor left ventricular hypertrophy relative to individuals with normal fasting glucose. For this reason, an opportunity may exist in those with IFG to prevent LV hypertrophy and abnormal aortic stiffness that is observed in middle and older age individuals with diabetes.
Abnormal Arterial Stiffness in IFG

Individuals with diabetes mellitus (DM) exhibit increased arterial stiffness that is associated with future cardiovascular morbidity and mortality, peripheral arterial disease, impaired myocardial function, left ventricular hypertrophy, and congestive heart failure (1-6). For those with DM, different clinical sequelae occur depending on the location of abnormal stiffening within the arterial system (7-9). For example, abnormal proximal thoracic aortic stiffness contributes to abnormal ventricular vascular coupling, left ventricular (LV) hypertrophy and dysfunction, and exercise intolerance (10). In peripheral arteries, abnormal arterial stiffness is associated with endothelial dysfunction, and arteriosclerosis (11,12).

Individuals with impaired fasting glucose (IFG) exhibit a higher rate of cardiovascular events compared to those with normal fasting glucose (NFG) (9,13-15). Importantly however (7,8), studies to date have not clarified whether subjects with IFG exhibit abnormal arterial stiffness, especially within the proximal thoracic aorta, that in other populations is associated with cardiac dysfunction and exercise intolerance (10).

To determine if middle aged and older individuals with IFG, but no clinical cardiovascular disease, exhibit abnormal changes in arterial stiffness, including the proximal thoracic aorta compared to healthy counterparts, we analyzed magnetic resonance imaging (MRI) measures of arterial stiffness in participants from the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that total arterial and proximal thoracic aortic stiffness would be altered in participants with impaired fasting glucose as well as diabetes when compared to individuals with NFG. We also sought to determine if LV mass, which is directly influenced by proximal thoracic aortic stiffness, was abnormal in individuals with IFG and DM.

RESEARCH DESIGN & METHODS

Study Subjects. The recruitment criteria of those individuals in MESA have been previously described (16). MESA is a large population based sample of men and women from four ethnic groups (Caucasian, African-American, Hispanic, and Chinese) aged 45-84 years without clinical cardiovascular disease. Five thousand and four MESA participants received cardiovascular MRI studies of which 3499 participants had examinations of proximal thoracic aortic stiffness. Institutional review committees in each participating site approved the study, and all participants provided written informed consent.

Participants in this study were characterized using criteria established by the American Diabetes Association into 1 of 3 groups using their fasting plasma glucose level (17). This included those with NFG (fasting glucose level of <100 mg/dl), IFG (fasting glucose level of 100-125 mg/dl), and DM (fasting glucose level of ≥126 mg/dl). Participants with history of diabetes (with or without treatment) were classified into the DM group regardless of their fasting glucose level. Blood pressure was measured after 5 minutes of rest with sequential Dinamap measures after a five-minute rest period between each sampling. Hypertension was defined by a systolic blood pressure (SBP) of ≥ 140 mmHg or a diastolic blood pressure (DBP) of ≥ 90 mmHg that occurred as the average of the second and third Dinamap measures on the initial clinic visit. Participants were also identified as hypertensive if they self-reported the presence of hypertension, and they used any antihypertensive medication. Cigarette smoking was defined as ever smoked (>100 cigarettes in one’s lifetime).

Magnetic Resonance Imaging Technique.

Using MRI, two previously described noninvasive measures of cardiovascular stiffness were obtained and used as the
primary stiffness outcomes for the study. The first was assessment of proximal thoracic aortic distensibility: a measure of cardiac cycle dependent changes in aortic area after accounting for brachial pulse pressure and resting vessel area (10). The second was an assessment of total cardiovascular stiffness that involved determination of change in LV stroke volume after accounting for brachial pulse pressure. In addition to these measures, LV mass was measured (3).

MRI studies were performed at 6 participating sites using 1.5 Tesla magnets (3 were General Electric Medical Systems [Waukesha, WI] CV/i or LX platforms, and 3 were Siemens Medical Solutions [Erlangen, Germany] Symphony or Sonata platforms). Participants were scanned in a supine position using a torso phased array coil placed anteriorly and posteriorly, and equipment approved for the MRI environment.

**Left ventricular parameters.** The left ventricle was imaged according to previously published techniques in short axis slices starting from the base at the mitral valve plane to the apex (18). According to previously published methods (18), LV stroke volume was determined in each individual for use in the calculation of total vascular stiffness (19-21). For left ventricular volume and mass determinations, the epi and endocardial border of each slice was planimetered manually at end diastole and end systole, and volumes were calculated by summation (Simpson's rule) as previously described. The LV ejection fraction was calculated from the ratio of the difference between LV end-diastolic and end-systolic volumes relative to end-diastolic volumes. The LV mass was calculated from summation of the LV myocardial volumes during end-diastole in each short axis slice at end-diastole, and multiplied by 1.05. The variability of the MRI readings was determined from a set of 155 duplicate readings to be 4.77% (CI 3.63, 6.02) for end-diastolic volume, and 11.61% (CI 9.55, 13.71) for end-systolic volume (18).

**Total and proximal thoracic aortic stiffness.** Images of the proximal thoracic aorta were obtained axially at the level of the main pulmonary artery identified on a sagittal scout image. Imaging parameters included a phase-contrast gradient-echo sequence with a 34 cm field of view, a 10 msec TR, a minimal full TE, a 20º flip angle, an 8 mm thick slice, a 256x224 matrix, 20 phases per cardiac cycle, 2 excitations (NEX), a 32 kHz bandwidth, and a velocity encoding of 150 cm/sec. Brachial arterial pressure was measured noninvasively with a nonferromagnetic arm blood pressure cuff and recorded before and after at the time of the phase-contrast acquisition and then averaged to derive mean values. The pulse pressure was calculated from the difference between systolic and diastolic blood pressure.

Determination of stiffness in the ascending thoracic aorta was accomplished by measuring aortic distensibility according to previously published methods using the following formula whereby the area of the ascending aorta was identified from the phase-contrast, gradient echo images throughout all phases of the cardiac cycle (10,22):

\[
Aortic\ distensibility\ (10^3\ mmHg^{-1}) = \frac{\text{maximal aortic area} - \text{minimal aortic area}}{\text{brachial pulse pressure} \times \text{minimal aortic area}}
\]

To examine total vascular stiffness, the total arterial compliance was calculated according to the following previously published formula (Figure 1) (19-21):

\[
Total\ arterial\ compliance\ (mL\times mmHg^{-1}) = \frac{LV\ stroke\ volume}{\text{pulse\ pressure}}
\]

Also, the inverse of total arterial compliance pulse pressure (PP) / stroke...
Abnormal Arterial Stiffness in IFG

Volume (SV) ratio was indexed for body surface area (PP/SVi) to account for potential differences in body size that may influence arterial stiffness. Total arterial elastance was determined using the change in LV stroke volume/mean arterial pressure.

Statistical analyses. Results were expressed as mean ± the standard error of the estimate, unless stated otherwise. Descriptive statistics were first examined stratified by fasting glucose status (NFG, IFG, and DM). Next, comparisons across the three levels of fasting blood glucose were made using an analysis of covariance approach (ANCOVA) using PROC GLM in SAS 9.1 (Copyright 2002-2003 by SAS Institute, Inc., Cary, NC, USA). We fit a series of progressively more complex models to examine the relationship of glucose tolerance status (coded as a 3-level class variable: NFG, IFG, and DM) and two outcomes of interest (total arterial and proximal thoracic aortic stiffness). There were a total of three models fit.

These included:

Model 1, adjusted for age (continuous variable), race/ethnicity, gender, and participating site;

Model 2, adjusted for variables from Model 1 along with gender, race/ethnicity, age, site, weight, total cholesterol, high-density lipoproteins (HDL), triglycerides, mean arterial pressure (MAP), waist-hip ratio, statin therapy, smoking and estimated glomerular filtration rate (GFR);

Model 3, adjusted for variables from Model 2 and hypertension (defined as the use of blood pressure medicine or a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on the first clinic exam);

For each of these models, we first examined the overall main effect for glucose tolerance status. When this was significant, two specific pairwise comparisons among the three groups (NFG vs IFG and NFG vs DM) were examined using 2-sample t-tests based on the adjusted mean values from the model (using the LSMEANS option in PROC GLM).

RESULTS

Of the 3499 subjects (mean age:61±10 years), 1596 (46%) were men, 1468 (42%) were Caucasian, 1049 (30%) were African-American, 385 (11%) were Hispanic, and 597 (17%) were Chinese. As shown in Table 1, compared to those with NFG, those in the IFG group exhibited a higher body mass index, waist-to-hip ratio, systolic blood pressure, and triglyceride level, as well as a lower HDL cholesterol level. As shown in Table 1, similar differences were also present in those with DM. When compared, those subjects with NFG were younger and more frequently women and/or Caucasian.

Across the study population, total and proximal thoracic aortic stiffness were not increased in those with NFG compared to those with IFG or DM (unadjusted data, Table 2). Also, arterial elastance (“defined from the mean arterial pressure rather than pulse pressure/the LV stroke volume”) was different in NFG (1.06±0.01) relative to IFG (1.12±0.01: p=0.0005) or DM (1.14±0.02: p=.007) participants. The differences in total vascular stiffness between subjects with NFG and IFG or DM persisted after adjustment for age, race/ethnicity, gender, and study site (Model 1, Table 2). We examined gender by glucose status (NFG, IFG, DM) interactions for all stiffness measures and found none to be significant (all with p≥ 0.15).

After adjusting for the variables included in Model 1 of Table 2, the difference in
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proximal thoracic aortic stiffness remained present between those with NFG and DM, but not between those with NFG and IFG (Model 2, Table 2 and Figures 2 and 3). Age was the variable most associated with the difference in proximal thoracic aortic stiffness observed between subjects with NFG and IFG.

After the adjustments in Model 3, total vascular stiffness remained increased in those with IFG compared to those with NFG (Figure 2). However, the proximal thoracic aortic stiffness in those with IFG remained similar to that of those with NFG (Figure 3). Across the study, the LV unadjusted mass in those with IFG and DM was increased when compared to those with NFG (150.8±1.3 vs 140.4±0.8 gms, p<0.0001 and 158.7±1.9 vs 140.4±0.8 gms, p<0.0001, respectively). When compared to individuals with NFG, and after accounting for the same covariates in Figures 2 and 3, LV mass was increased in those with IFG (145.2±0.9 vs 144.9±1.0 gms, p=NS) (Figure 4).

To determine if the variables in the numerators (LVSV for total, and aortic area for proximal thoracic aorta) or denominators (pulse pressure for both) of our measures of stiffness were more influential in accounting for our results, we performed additional analyses adjusting Model 3 (results graphed in Figures 2-4) stiffness measure for the variables in the numerator and denominator. After adjusting for LVSV, the total stiffness was 1.82±0.01 $\text{ml*mmHg}^{-1}$ for NFG, 1.79±0.02 $\text{ml*mmHg}^{-1}$ for IFG (p=0.004 from NFG), and 1.74±0.02 $\text{ml*mmHg}^{-1}$ for DM (p=0.0005 from NFG); and after adjusting for pulse pressure, the total stiffness was 1.85±0.01 $\text{ml*mmHg}^{-1}$ for NFG, 1.78±0.01 $\text{ml*mmHg}^{-1}$ for IFG (p<0.0001 from NFG) and 1.77±0.02 $\text{ml*mmHg}^{-1}$ for DM (p<0.0007 from NFG). After adjusting for the cardiac cycle dependent change in aortic area, proximal thoracic aortic stiffness was 1.89±0.03 $10^3 \text{mmHg}^{-1}$ for NFG, 1.90±0.04 $10^3 \text{mmHg}^{-1}$ for IFG (p=0.74 from NFG), and 1.81±0.05 $10^3 \text{mmHg}^{-1}$ for DM (p=0.14 from NFG); and after adjusting for pulse pressure, proximal thoracic aortic stiffness was 1.91±0.04 $10^3 \text{mmHg}^{-1}$ for NFG, 1.90±0.05 $10^3 \text{mmHg}^{-1}$ for IFG, and 1.68±0.06 $10^3 \text{mmHg}^{-1}$ for DM (p=0.0007 from NFG). Since many of the differences noted between the groups in Model 3 remain (Figures 2, 3, 4), the results of these adjustments suggest that both values in the numerators and denominators were important for influencing the differences or similarities in vascular stiffness noted between the groups assessed in this study.

We tested for interactions between gender and measures of vascular stiffness by glucose group (NFG, IFG, DM) and found them all to be non-significant. For vascular stiffness the p-value was 0.58, for LV end-diastolic mass it was 0.17 and for aortic distensibility (stiffness) it was 0.95. These non-significant interactions suggest that there were no gender differences in the relationship between glucose group and outcomes.

To determine if the findings relating to proximal aortic distensibility were influenced by the resting arterial diameter or geometry of the aorta, we measured aortic compliance in our 3 patient groups. After adjusting for variables in Model 3 (Figures 2, 3, and 4), aortic compliance was 1.48±0.02, 1.44±0.03, and 1.32±0.04 in those with NFG, IFG, and DM, respectively. As with aortic distensibility, compliance in participants with DM was reduced compared to that found in those with NFG (p=0.0001), but not in those with IFG relative to those with NFG (p=0.22).

Of the 414 subjects with DM, 256 provided data on the duration of receipt of oral or insulin therapy. The duration of treatment ranged from 0 (current year) to 41 years, with a median of 6 years. As shown in Figure 5, total and proximal thoracic aortic stiffness were worse for those treated ≥ as
opposed to the median of 6 years. Also, LV mass trended higher in those treated >6 years for diabetes.

In addition to measuring total arterial elastance, a stiffness measure dependent on mean arterial pressure, rather than pulse pressure, we also performed analysis adjusting our models for measures of mean arterial pressure rather than the prespecified diagnosis of hypertension. The differences and similarities between our participant groups persisted using mean arterial pressure as a co-variate.

The use of statin therapy was 14.2% across the study population (11% of NFG, 16% of the IFG, and 26% of the DM participants). This may have influenced the lower LDL level observed in our study population. After adjusting the total and proximal aortic stiffness for statin use (Model 2, Table 2) differences between groups persisted.

Often, patients with DM or IFG exhibit features of the metabolic syndrome. We performed analyses to determine if the pressure of the metabolic syndrome would change the relationships we observed in total arterial stiffness and proximal thoracic stiffness between our 3 groups. After accounting for the metabolic syndrome, all pairwise comparisons between NFG and PM or IFG remained unchanged.

DISCUSSION
Abnormally stiffened arteries are present in individuals with DM and are associated with an increase in cardiovascular events, LV afterload, and exercise intolerance (1,4,9). In this study, we sought to determine if individuals with IFG exhibited abnormal stiffening of the arterial tree (including the proximal thoracic aorta), that in studies of individuals with DM, is associated independently with adverse cardiovascular events. There are 2 important findings in this study. First, total vascular stiffness is worse in subjects with IFG compared to those with NFG. This finding is true regardless of age, gender, ethnicity, or other factors associated with abnormal vascular stiffening (Table 2 and Figure 2). Second, after adjustment for factors known to influence vascular stiffness, proximal thoracic aortic stiffness and LV mass are similar in individuals with IFG and NFG (Figures 3 and 4). In diabetics, however, both proximal thoracic aortic stiffness and LV mass are elevated (Figures 3 and 4).

In this cross-sectional analysis of the data from the MESA cohort study, subjects with IFG demonstrated a higher body mass index, blood pressure, total cholesterol, and serum triglyceride compared to those with NFG. These are all clinical features of the metabolic syndrome which affects 47 million Americans, and is associated with hyperinsulinemia and insulin resistance (23). After adjusting for these variables, the subjects with IFG demonstrated greater total arterial stiffness than those with NFG. The data in this study indicate that mild elevations of blood sugar adversely affect cardiovascular stiffening independent of other common cardiovascular risk factors associated with the metabolic syndrome.

There are several mechanisms by which total arterial stiffness becomes elevated in individuals with IFG or DM. Elevations in blood sugar lead to the formation and deposition of advanced glycation end products (24,25). These products promote the cross-linking of collagen that stiffens the structural components of the arterial wall (24,25). Diabetes also promotes increased lipid oxidation, vasoconstriction, tissue remodeling, low-grade inflammation, atherosclerosis, and sympathetic nervous system activation (26,27). Many of these processes inhibit endothelial nitric oxide synthase, which consequently impairs peripheral endothelial function, and adversely effects vascular stiffness (24,25,28-30).
It is important to note that some of the mechanisms by which arteries stiffen after exposure to elevations in blood sugar occur rapidly, whereas others require more time to develop. For example, peripheral arterial endothelial function is known to deteriorate an hour after a high glucose oral intake (31). Also, there is emerging evidence that postprandial hyperglycemia is associated with the development of atherosclerosis, which in turn heightens peripheral arterial stiffness (32). It is not surprising that those with IFG or DM exhibit abnormal total vascular stiffness of the entire vascular tree since both IFG and DM adversely impact endothelial function, atherosclerosis, and vasomotor tone, each of which influences peripheral artery stiffness after a short duration of exposure.

The use of MRI in this study provided the opportunity to assess proximal thoracic aorta stiffness. The proximal thoracic aorta stiffens abnormally in those with DM (27), and several studies have identified the adverse impact of proximal thoracic aortic stiffness on LV performance and exercise capacity in those with diabetes and those with heart failure (10,22).

As an example, our group and others have demonstrated an independent relationship between proximal thoracic aortic stiffness and increased LV mass and exercise intolerance in individuals with heart failure (10,22).

The results of this study indicate that the stiffening of the ascending aorta may not be increased in those with IFG relates to the effects of atherosclerotic plaque burden. Diabetes is one of the most important risk factors for the presence of aortic atherosclerotic plaque and a positive association has been shown between the presence of atherosclerotic plaque and arterial stiffness (34). Underlying inflammation may be less operative in patients with IFG. Scuteri et al., reported that increased large arterial stiffness and impaired endothelial function was found in the normotensive normoglycemic first-degree relatives of diabetic patients independent of the presence of the metabolic syndrome (35). These data suggest that mechanisms other than the level of serum glucose, such as endothelial dysfunction or low-grade inflammation, may affect the stiffness of proximal thoracic aorta (36,37). Sengstock et al. (38), also demonstrated that insulin resistance was an important factor in the stiffening of arteries. Potential mechanisms mediating this factor include endothelial dysfunction and/or vascular smooth muscle proliferation.

To address the relationship between prolonged exposure to high serum levels of glucose and arterial (both total and proximal thoracic aortic) stiffness, we reviewed the results of MESA participants that responded to the question of duration of diabetes treatment. We were able to assess the relationship between the duration treatment, central aortic stiffness, and LV mass. As
shown in Figure 5, after accounting for variables known to influence proximal thoracic aortic stiffness, total and aortic stiffness was worse for individuals treated for diabetes >6 years. Also, there was a strong trend toward an increase in LV mass for those treated for diabetes > a median of 6 years.

What are some of the clinical applications of our study results? First, those with IFG do not exhibit abnormalities of proximal thoracic aortic stiffness to the magnitude observed by those with DM. Data to date indicate that stiffening in the central aorta has hemodynamically detrimental effects on the cardiovascular system and a strong association with increased cardiovascular mortality. Therefore, this may be one of the possible explanations why those with IFG have no increase in LV mass and perhaps lower rates of cardiovascular events compared to those with DM. Theoretically, preventing pre-diabetes states from developing into DM could prevent stiffening of central aorta and associated adverse clinical sequela.

Second, therapies designed to reduce stiffness in the proximal thoracic aorta may differ for middle aged and older individuals with IFG versus DM. Studies involving the collagen cross-link breaker thiazolidinedione for the purpose of attenuating aortic stiffness and regressing LV hypertrophy are underway in patients with heart failure (39,40). In the absence of other clinical conditions known to stiffen the aorta, those older individuals with IFG do not exhibit stiff aortas, so suitability for participation in these studies may differ.

Previously, in primary prevention strategies, statin therapy has been shown to reduce cardiovascular events(41), improve endothelial function, and regress atherosclerotic plaques in the aorta (42,43) in diabetic patients. In patients with diabetes or IFG and concomitant hypercholesterolemia, guidelines exist for prescribing statin therapy to reduce LDL levels (44). At present however, guidelines do not exist for using vascular stiffness measures as surrogate endpoints for treatment in primary or secondary prevention strategies that involve patients with IFG or DM. Further study is needed to explore in this issue.

Third, since individuals with IFG and DM often exhibit reduced exercise capacity (45,46), our results indicate that mechanisms other than abnormalities of aortic stiffness, such as higher myocardial oxygen consumption at rest, an inability to adapt coronary flow adequately to higher metabolic demands during peak exercise, or abnormal peripheral arterial endothelial function may be more likely responsible for exercise intolerance in middle aged and older individuals with IFG (45,46).

Fourth, the investigators from The Hoorn Study (8) have reported that subjects with impaired glucose tolerance and diabetes had arterial stiffening in both central and peripheral arterial system and that central arterial stiffness of those with impaired glucose tolerance was intermediate in severity between the group with normal glucose tolerance and diabetes. Our study had a similar finding on peripheral arterial stiffening, but our measure of aortic distensibility arterial stiffness was not increased in those with IFG. There are possible explanations on the difference of this finding. First, the criteria for classification of subjects with impaired glucose metabolism was different in our study and the Hoorn Study. Our study used fasting glucose from the American Diabetes Association (ADA) criteria, but the Hoorn Study defined glucose tolerance according to the World Health Organization (WHO) criteria. Subjects with IFG (ADA criteria) and impaired glucose tolerance (WHO criteria) are not identical and the pathophysiology of the disorders are different. When comparing subjects with IFG to those with impaired glucose tolerance, those with IFG are more strongly correlated with insulin resistance, whereas impaired
glucose tolerance is more strongly correlated to impaired insulin secretion (47,48).

Second, aortic stiffness was measured differently in the 2 studies. Our study used aortic distensibility, whereas the Hoorn Study used aortic augmentation index. Aortic distensibility measures stiffness in the proximal ascending thoracic aorta which has direct implications for stimulating LV hypertrophy; aortic augmentation index measures stiffness within the entire aorta. This latter value seems more similar to the assessment of total vascular stiffness that we report currently. As shown, we noted differences in total arterial stiffness between NFG, IFG, and DM (similar to the Hoorn results). Third, participants in the Hoorn Study were on average older than ours. Age is an important influence on aortic stiffening: stiffening within the cardiovascular system increases with age.

Our study has the following limitations. First, up to 5% of subjects with IFG exhibit diabetes if they undergo 2-hour glucose tolerance testing. Since those with DM exhibit stiffer arteries than those with IFG, it stands to reason that moving 5% of the IFG participants that are truly diabetic into the DM group would further reduce differences between our NFG and IFG groups. Second, brachial cuff pressure, rather than an invasive measure of central aortic pressure was used in our calculations of total and proximal thoracic aortic stiffness. Our noninvasive determinations of arterial stiffness (ratios involving pulse pressure) are based on the principle that in a steady-state condition, the arterial tree can be modeled as an elastic chamber with a constant compliance (49). Although these measures have been validated with standard invasive assessment of arterial compliance in animals (50) and humans (21), and have been shown to be an independent predictor for cardiovascular death (21), younger, healthier individuals may have more amplification of PP than older individuals. To provide for this possibility we accounted for age in our statistical models. Of note, the difference we observe between our IFG and NFG groups is present in our total arterial stiffness measure, but not in our aortic distensibility measure. This observation suggests that the lack of difference between NFG and IFG in aortic distensibility is in fact true. Also, LV mass which parallels proximal thoracic stiffness is not different in the NFG and IFG groups. Our LV mass determination does not involve pulse pressure.

Third, it is important to recognize that our results reflect those generated from participants aged 45 to 85 years of age. We are uncertain of the effects of IFG and DM on stiffness parameters in individuals including children, teenagers, and younger adults.

**CONCLUSION**

In middle aged and older adults, the prediabetes state of impaired fasting glucose is associated with an increase in arterial stiffening that primarily impacts regions exclusive of the ascending thoracic aorta. Perhaps prevention of DM in those with IFG would be associated with preservation of more favorable heart weight and proximal thoracic aortic distensibility, known risk factors for adverse cardiac events.
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structure and function following statin initiation: Quantification by magnetic resonance imaging. Atherosclerosis 2008 April;197(2):951-58.


### Table 1. Baseline Characteristics (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>NFG (2240)</th>
<th>IFG (845)</th>
<th>DM (414)</th>
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<td>62.2 ± 9.9*</td>
<td>63.5 ± 9.4*</td>
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<td>Male (%) †</td>
<td>926 (41)</td>
<td>459 (54)</td>
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<td>Races/ethnicity (%)</td>
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<td>101 (24)</td>
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<td>African-American</td>
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<td>368 (16)</td>
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<tr>
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</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.94 ± 0.20</td>
<td>0.97 ± 0.22</td>
<td>0.97 ± 0.57</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>197 (10)</td>
<td>139 (16)</td>
<td>80 (19)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>4 (002)</td>
<td>1 (001)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, HDL = high density lipoprotein, IFG = impaired fasting glucose, LDL = low density lipoprotein, NFG = normal fasting glucose, *p<0.05 compared to NFG, †p<0.05 among groups.
Table 2. Multivariate analysis of total arterial stiffness and proximal thoracic aortic stiffness among those with normal fasting glucose, impaired fasting glucose, and diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Total Vascular Stiffness (ml/mmHg⁻¹)</th>
<th>Proximal Thoracic Aortic Stiffness (10⁻¹⁰mmHg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFG</td>
<td>IFG</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.87±0.01</td>
<td>1.73±0.02*</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.84±0.01</td>
<td>1.74±0.02*</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.86±0.01</td>
<td>1.78±0.02*</td>
</tr>
</tbody>
</table>

0.05 compared to NFG

†p<0.001 compared to NFG

**t** = hypertension is defined by a systolic blood pressure or SBP ≥ 140mmHg or DBP ≥ 90mmHg that occurred as the average of the second and third Dinamap measures on the initial clinic visit.

NFG = normal fasting glucose; IFG = impaired fasting glucose; DM = diabetes mellitus

**Model 1.** Adjusted for age, race/ethnicity, gender, and participating site

**Model 2.** Adjusted for variables from Model 1 and gender, race/ethnicity, age, site, weight, total cholesterol, high-density lipoproteins, triglycerides, mean arterial pressure, waist-hip ratio, statin therapy, smoking and estimated glomerular filtration rate
Figure 1. Formula for determining magnetic resonance imaging measures of total vascular stiffness (left panel) and proximal thoracic aortic stiffness (right panel). In the left panel, color within the vessels demarcate portions of the vascular system encompassed by the stiffness measure. In the right panel coronal and transaxial views of the left ventricle (LV) ascending thoracic aorta are provided. The red circle demarcates the boundary of the ascending aorta (Ao) from which dimensions are determined by the calculation of proximal thoracic aortic stiffness.

**Figure 1. Total and proximal thoracic aortic stiffness measurements**

<table>
<thead>
<tr>
<th>Total Arterial Stiffness</th>
<th>Proximal Thoracic Aortic Stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular stroke volume</td>
<td>Area aorta end-systole – Area aorta end-diastole</td>
</tr>
<tr>
<td>Brachial artery pulse pressure</td>
<td>Brachial artery pulse pressure x Area aorta end diastole</td>
</tr>
</tbody>
</table>
Figure 2. Comparison of adjusted total arterial stiffness of those with IFG or DM, and those exhibiting NFG (DM=diabetes mellitus, IFG=impaired fasting glucose, and NFG=normal fasting glucose).

Figure 2. Total arterial stiffness and fasting glucose status
(mean ± standard error of the estimate)

*Adjusted for recruited age, race/ethnicity, gender, site, weight, total cholesterol, HDL triglycerides, mean arterial pressure, waist-hip ratio, statin therapy, smoking, estimated glomerular filtration rate and hypertension
Figure 3. Comparisons of adjusted proximal aortic stiffness of those with IFG or DM, and those exhibiting NFG (DM=diabetes mellitus, IFG=impaired fasting glucose, and NFG=normal fasting glucose).

Figure 3. Proximal thoracic aortic stiffness and fasting glucose status (mean ± standard error of the estimate)

*Adjusted for recruited age, race/ethnicity, gender, site, weight, total cholesterol, HDL, triglycerides, mean arterial pressure, waist-hip ratio, statin therapy, smoking, estimated glomerular filtration rate and hypertension
Figure 4. Comparison of adjusted left ventricular mass of those with IFG or DM, and those exhibiting NFG (DM=diabetes mellitus, IFG=impaired fasting glucose, and NFG=normal fasting glucose).

Figure 4. LV mass and fasting glucose status
(mean ± standard error of the estimate)

*Adjusted for recruited age, race/ethnicity, gender, site, weight, total cholesterol, HDL triglycerides, mean arterial pressure, waist-hip ratio, statin therapy, smoking, estimated glomerular filtration rate and hypertension
**Figure 5.** Mean ± standard error of the estimates of total and proximal thoracic aortic stiffness, and left ventricular mass for participants with diabetes treated > 6 years (gray bars) and ≤ 6 years (white bars).

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*Adjusted for recruited age, race/ethnicity, gender, site, weight, total cholesterol, HDL, triglycerides, mean arterial pressure, waist-hip ratio, statin therapy, smoking, estimated glomerular filtration rate and hypertension*