Aortic Stiffness, Impaired Fasting Glucose, and Aging

Thore Dietrich, Ute Schaefer-Graf, Eckart Fleck, Kristof Graf

The arterial wall is subject to a continuous process of structural, cellular, and molecular modifications that involve cellular growth processes, apoptosis, cell migration, inflammation, and fibrosis, resulting in changes of wall structure and dimension, as well as contractile and elastic properties. Physiological remodeling is an adaptive response to hemodynamic changes in the sense of repair or adjustment. Cardiovascular (CV) diseases, such as diabetes mellitus (DM) and hypertension, as well as aging, lead to enhancement of vascular maladaptive processes and the formation of atherosclerotic lesions and calcifications. One essential consequence of these maladaptive processes is the change of the arterial wall structure and dimension, as well as contractile and elastic properties. Impaired Fasting Glucose, DM, and Arterial Stiffening

DM is associated with a high risk for CV morbidity and mortality, including myocardial infarction, left ventricular (LV) hypertrophy, heart failure (HF), and stroke. DM leads to abnormal stiffening of the aorta and the large arteries, abnormal ventricular vascular coupling, elevated cardiac filling pressures, LV hypertrophy, and HF with systolic and diastolic dysfunction. In the smaller arteries, DM causes endothelial dysfunction, vascular inflammation, and atherosclerosis.

The Hoorn Study investigated the occurrence of arterial stiffness in patients with DM and individuals with impaired fasting glucose (IFG). Arterial stiffness was ultrasonically estimated by distensibility and compliance of the carotid, femoral, and brachial arteries and by the carotid elastic module. DM was associated with increased arterial stiffness in the muscular brachial and femoral arteries, and as well in the more elastic carotid artery, where, as in IFG, only brachial and femoral indices were increased. The effect of glycemic status on central aortic stiffness was assessed using total systemic arterial compliance, aortic pressure augmentation index, and carotid-femoral transit time in the same cohort. IFG and DM were associated with increased central artery stiffness, which was more pronounced in DM.

The Rotterdam Study, a Dutch population-based cohort study with 2987 subjects aged ≥60 years, showed that aortic PWV is a strong predictor of coronary heart disease and stroke. Aortic PWV improved the prediction of CV disease when added to known risk factors, measures of atherosclerosis, and pulse pressure. In this cohort, arterial stiffness was assessed by measuring common carotid arterial distensibility and glucose status classified into 3 categories, individuals with normal fasting glucose (NFG), those with IFG, and those with DM. Increasing impairment of glucose metabolism was strongly associated with a decrease in carotid distensibility. Below 75 years of age there was no difference between IFG and NFG in this cohort. Only individuals aged ≥75 years with IFG had stiffer arteries than subjects with NFG.

Two studies coming from the Multi-Ethnic Study of Atherosclerosis (MESA) Trial used aortic MRI for the first time to analyze aortic distensibility (stiffness) in a large-scale, population-based study. The high spatial resolution of the MRI provides exceptional image quality to assess minimal and maximal cross-sectional areas of the ascending aorta and its wall to calculate aortic distensibility. Using the main pulmonary artery as an anatomic landmark, the method provides high accuracy and reproducibility. Furthermore, the MESA Trial enabled the investigators to analyze ∼3500 MRI data sets obtained by a standardized protocol in 6 study imaging centers from a multiethnic cohort of men and women in the age range of 45 to 84 years, who did not present clinical signs of CV disease at the time of recruitment.

Using aortic and cardiac MRI data from this cohort, Rerkpattanapipat et al demonstrated that middle-aged and older individuals with IFG did not exhibit abnormal aortic distensibility or LV hypertrophy compared with individuals with NFG. Total vascular stiffness, however, which was assessed by the division of MRI-measured stroke volume with pulse pressure, demonstrated increased stiffness also in the IFG group compared with persons with NFG. The authors
Aortic stiffness and distensibility measurements by MRI are obtained by measurements of velocity-encoded flow imaging on 2 levels (orange lines), pulmonary artery level and 10 cm below the diaphragm, as shown on the proton density-weighted black-blood anatomic image of the aortic “candy cane.” The PWV (meters per second) was calculated by dividing the distance between measurement levels by the time difference between the arrival of the pulse wave at these levels. Arrival time of the pulse wave at each level was defined as the time point when the mean velocity reached half of its maximum value. Courtesy of Valentina Puntmann, Imperial College London, Hammersmith Campus.

A further data analysis from the same cohort, which is presented in this issue of Hypertension, provides additional evidence about the relationship between the glycemic status and age on aortic distensibility. Stacey et al12 analyzed the MRI-derived measurements in the same MESA participants for age-related effects and glycemic status. The authors observed a strong relationship between aging and aortic stiffness in the whole cohort. There was also a significant difference of aortic stiffening among the 3 groups <65 years of age, whereas IGF behaved as an intermediate between diabetes mellitus and individuals with NFG. Over the age of 65 years, the effect of the glycemic status on aortic distensibility decreased continuously and was no longer different between IGF and NFG individuals. However, it was still preserved in diabetic patients. In contrast to the data published from the same cohort by Rerkpattanapipat et al,11 who could not find a significant difference of central aortic stiffness between individuals with IFG and NFG, the present analysis of the same cohort revealed age as an important discriminator for decreased aortic distensibility in individuals below the age of 65 years. The significant relationship between IFG and aortic stiffness disappeared with increasing age. The apparent differences to the results from the Rotterdam Study are not surprising; they can probably be best explained by differences in the higher sensitivity of the MRI and type of artery, as well as by different population characteristics.

**Why Is Aortic Stiffening So Relevant?**

Arterial stiffening occurs as a consequence of aging and is increased by CV risk factors, such as hypertension and diabetes mellitus. It predicts CV events independent of the traditional risk factors.5 Recent studies demonstrate that there is a close relationship between aortic and ventricular stiffening that is increased in older individuals and women.1,13 The present cardiac and vascular MRI studies obtained in participants of the MESA Trial demonstrated that arterial stiffness is associated with early and asymptomatic systolic and diastolic cardiac dysfunction.14

HF is the major cause of CV morbidity and mortality. HF is predominantly a disease of the elderly. The mean age of HF patients is >70 years in most developed countries, and the prevalence of HF rises dramatically with age, from 1% to 2% among individuals aged 45 to 54 years to >10% among those aged >75 years.15 Aging predisposes to HF through multiple mechanisms. Especially in elderly patients, HF with preserved ejection fraction is the prominent finding. Aging is associated with reduced aortic and LV compliance, increased aortic stiffness, and abnormal LV diastolic function. These conditions lower the threshold for the development of HF when the heart is exposed to precipitating factors, such as hypertension and/or tachyarrhythmias (especially atrial fibrillation). The coupling of ventricular and vascular stiffening processes lead to load-dependent impairment of systolic ventricular function without primarily affecting the systolic function. Using MRI as it was used in the MESA Trial, Fernandes et al14 reported that patients with isolated diastolic HF had reduced aortic distensibility, which was beyond that which occurs with normal aging. Redfield et al13 speculated that the combined ventricular-vascular stiffening might contribute to the increased prevalence of HF with preserved ejection fraction in elderly and especially in elderly women.

There is substantial evidence that alteration of the elastic and contractile properties of the large arteries is closely related to CV morbidity and mortality. The data from the MESA Trial underline how early these pathological changes occur in individuals with intermediate risk (IFG). There is not yet sufficient evidence that a reversibility of aortic stiffness modifies outcome, except in 1 study in patients with end-stage renal failure.16 The recent findings from the MESA urge for an assessment of interventional strategies in individuals with intermediate risk and parameters of increased aortic stiffness or distensibility.

**Sources of Funding**

None.

**Disclosures**

None.

**References**


Aortic Stiffness, Impaired Fasting Glucose, and Aging
Thore Dietrich, Ute Schaefer-Graf, Eckart Fleck and Kristof Graf

Hypertension. 2010;55:18-20; originally published online November 23, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.135897

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/55/1/18

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/