Arterial Stiffening Precedes Systolic Hypertension in Diet-Induced Obesity

Robert M. Weisbrod, Tina Shiang, Leona Al Sayah, Jessica L. Fry, Saumendra Bajpai, Cynthia A. Reinhart-King, Heinrich E. Lob, Lakshmi Santhanam, Gary Mitchell, Richard A. Cohen, Francesca Seta

See Editorial Commentary, pp 1003–1004

Abstract—Stiffening of conduit arteries is a risk factor for cardiovascular morbidity. Aortic wall stiffening increases pulsatile hemodynamic forces that are detrimental to the microcirculation in highly perfused organs, such as the heart, brain, and kidney. Arterial stiffness is associated with hypertension but presumed to be due to an adaptive response to increased hemodynamic load. In contrast, a recent clinical study found that stiffness precedes and may contribute to the development of hypertension although the mechanisms underlying hypertension are unknown. Here, we report that in a diet-induced model of obesity, arterial stiffness, measured in vivo, develops within 1 month of the initiation of the diet and precedes the development of hypertension by 5 months. Diet-induced obese mice recapitulate the metabolic syndrome and are characterized by inflammation in visceral fat and aorta. Normalization of the metabolic state by weight loss resulted in return of arterial stiffness and blood pressure to normal. Our findings support the hypothesis that arterial stiffness is a cause rather than a consequence of hypertension. **(*Hypertension*. 2013;62:1105-1110.)** ● **Online Data Supplement**

Key Words: hypertension ■ inflammation ■ obesity ■ pulse wave velocity ■ vascular stiffness

The aorta and its major branches stiffen with age[1] and obesity,[2] independently of atherosclerosis.[3] In recent epidemiological and clinical studies, arterial stiffness emerged as an independent predictor of cardiovascular events, even after adjusting for risk factors such as age, sex, body mass index, and blood pressure.[4]

Hypertension is associated with arterial stiffness,[5,6] and conventional thinking suggests that hypertension stimulates aortic remodeling and stiffening, in addition to vascular smooth muscle cell hypertrophy,[7] as an adaptive process to increase wall-to-lumen width ratio in response to long-term changes in hemodynamic forces.[8–10] However, a large longitudinal study of the general population recently established that arterial stiffness precedes an increase in systolic blood pressure and newly diagnosed hypertension.[11] In contrast, initial blood pressure was not independently predictive of subsequent aortic stiffening measured in the same individuals 4 to 10 years later. Although stiffness-induced hemodynamic changes have been implicated in the development of hypertension,[12,13] lack of animal models for studying the relationship between arterial stiffness and hypertension has hampered the discovery of mechanisms and has led to a recent effort by the National Heart, Lung, and Blood Institute of the National Institutes of Health to establish such models.[14]

Because of the rising prevalence of obesity-associated type 2 diabetes mellitus and the cardiovascular complications thereof,[15–17] we sought to determine whether arterial stiffness occurs in a mouse model of diet-induced obesity. Arterial stiffness is increased in obese and diabetic individuals, even at a young age (10–24 years),[18] and in a genetic model of obesity (*ob/ob* mice).[19] Conversely, weight loss in overweight and obese individuals is associated with a reduction in arterial stiffness.[20] Understanding the mechanisms underlying the development and regression of arterial stiffness might lead to additional options for prevention and treatment of hypertension and associated complications.

The goals of this study were to determine the temporal relationship between the development of arterial stiffness and hypertension and the potential reversal of stiffness and hypertension by return to normal diet (ND), as well as the mechanisms thereof.

Received May 20, 2013; first decision June 6, 2013; revision accepted August 22, 2013.

From the Vascular Biology Section, Boston University School of Medicine, Boston, MA (R.M.W., T.S., L.A.S., J.L.F., R.A.C., F.S.); Biomedical Engineering (S.B., C.A.R.-K.) and Department of Biomedical Sciences, College of Veterinary Medicine (H.E.L.), Cornell University, Ithaca, NY; Department of Anesthesiology and Critical Care Medicine, John Hopkins University, Baltimore, MD (L.S.); and Cardiovascular Engineering, Inc, Norwood, MA (G.M.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.01744/-/DC1.

Correspondence to Francesca Seta, Vascular Biology Section, Boston University School of Medicine, 650 Albany St, Boston, MA 02118. E-mail setaf@bu.edu

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.113.01744**

Methods

A detailed description of Methods can be found in online-only Data Supplements.

Results

High-Fat/High-Sucrose Diet Recapitulates Human Metabolic Syndrome in Mice

High-fat/high-sucrose (HFHS) feeding significantly increased body weight (Figure S1A in the online-only Data Supplement) and fat mass compared with ND by 2 months, whereas lean mass remained unchanged over time (Figure S1B). Also within 2 months, mice became glucose intolerant (Figure S1C) and insulin resistant (Figure S1D). In addition to obesity and glucose intolerance, HFHS-fed mice developed chronic inflammation, as evidenced by substantial infiltration of activated macrophages in the visceral fat surrounding the kidneys (Figure S2A). Microalbuminuria, an indicator of kidney damage, was significantly increased after 4 months of HFHS diet (Figure S2B).

Arterial Stiffness Is Increased by HFHS Diet and Precedes Systolic Hypertension

Pulse wave velocity (PWV), an index of arterial stiffness measured by ultrasonography, was significantly increased by 2.4-fold after 1 month of HFHS compared with ND, and it remained elevated ≤8 months (Figure 1A). PWV was similarly elevated when assessed from the aortic arch to abdominal aorta as it was in the abdominal aortic segment (6.3±1.3 versus 3.4±0.6 mm/ms in ND and 5.7±0.9 versus 2.8±1.0 mm/ms in ND, respectively; $P<0.05$). The increase in PWV was confirmed by invasive hemodynamic measurements both at baseline and after phenylephrine (Figure 1B and Table S1).

To address the temporal relationship between arterial stiffness and hypertension, young mice (8 weeks old) were implanted with radiotelemetry pressure transducers and followed after starting HFHS for ≤1 year. The first statistically significant increase in systolic blood pressure (Figure1C) and mean arterial pressure (Figure S3A) was observed after 6 months, whereas diastolic blood pressure was not significantly different (Figure S3B). Pulse pressure, an indirect index of arterial stiffness, gradually increased and reached statistical significance at 6 months (from baseline 26.4±2.0 to 37.8±2.2 mm Hg, n=4–6; Figure S3C). Systolic blood pressure (Figure 1D), mean arterial pressure (Figure S3D), and pulse pressure (Figure S3F) were also significantly and consistently elevated in HFHS-fed mice (n=11) compared with ND-fed mice (n=9) when blood pressure transducers were implanted between 5 and 6 months of diet and values were recorded for 1 month thereafter.

Spectral analysis of high-frequency telemetry recordings, performed to assess whether obesity-associated activation of the sympathetic nervous system[21] could contribute to the hypertension observed after 6 months of HFHS diet, showed increased sympathetic modulation of blood pressure and heart rate in mice fed HFHS diet for 8 months compared with ND (Table S2). This was accompanied by significantly increased plasma norepinephrine in mice fed HFHS for 8 months compared with ND but not for 2 months (Table S3). Consistent with HFHS-associated sympathetic activation, heart rate was slightly but significantly elevated in HFHS-fed mice (Figure S3G) compared with ND-fed mice (Figure S3H), and this was reduced to normal values when obese mice were reversed to ND (Figure S3I).

Early Vascular Changes in HFHS-Fed Mice

Within 2 months of diet when the increase in PWV because of HFHS diet was fully developed, the aortas from HFHS mice had impaired relaxation to acetylcholine (Figure 2A), indicating reduced endothelial nitric oxide (NO) function. In addition, the activity of tissue transglutaminase-2 (TG-2), an NO-sensitive enzyme that contributes to arterial stiffening in aged mice and rats by increasing extracellular matrix cross-linking,[22] was significantly increased in aortic lysates from HFHS-fed mice, consistent with reduced NO bioavailability

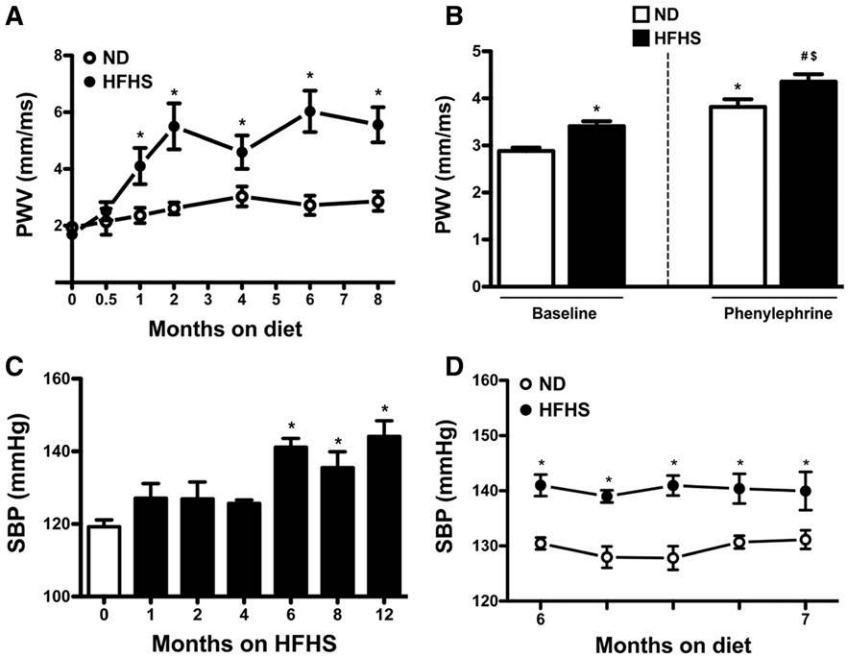

Figure 1. Arterial stiffness precedes hypertension in diet-induced obese mice. Pulse wave velocity (PWV, mm/ms), an index of arterial stiffness, measured by Doppler echocardiography, mean±SD, n=4 to 10 each group (**A**) and invasively with high-fidelity pressure catheters, mean±SEM, n=8 each group (**B**) is increased in high-fat/high-sucrose (HFHS)–fed mice within 2 months. Mean arterial pressure was modulated by intravenous infusion of phenylephrine (0.1 μg/g body weight). **P*<0.05 vs normal diet (ND) or ND baseline; #*P*<0.05 vs HFHS baseline; $*P*<0.05 vs ND-phenylephrine. Mice develop systolic hypertension after 6 months of HFHS (**C**) compared with ND (**D**). **P*<0.05 vs baseline (time 0) or ND. SBP indicates systolic blood pressure.

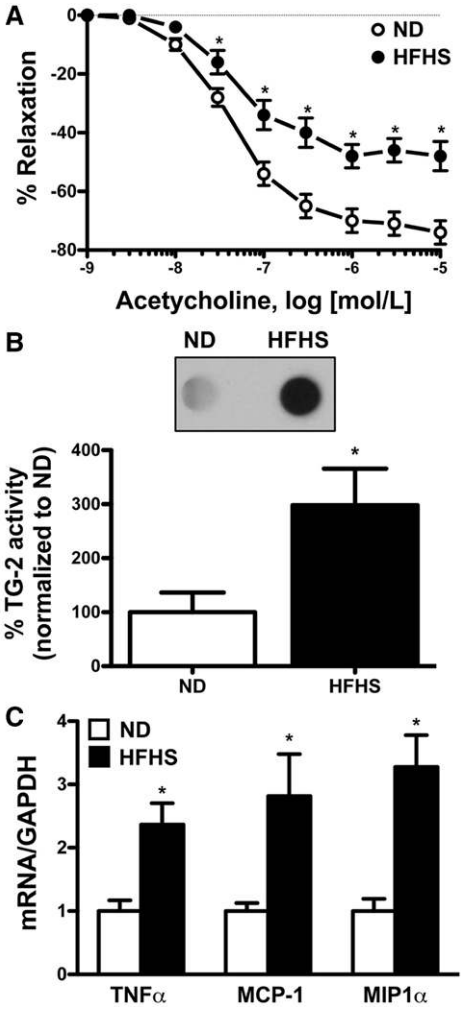

Figure 2. Impaired nitric oxide (NO) bioavailability and aortic inflammation in diet-induced obese mice. **A**, Vasorelaxation to acetylcholine (1×10^{-9} to 1×10^{-5} mol/L) in aortas from mice fed normal diet (ND) or high-fat/high-sucrose (HFHS) diet (n=5 each group; *P<0.05). **B**, Transglutaminase-2 (TG-2) activity, an index of NO bioavailability, measured on aortic lysates from ND- and HFHS-fed mice. Dot blot intensity quantification expressed graphically as % ND (n=4 each group. *P<0.05). **C**, Inflammatory cytokines tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-1α mRNA were significantly upregulated in aortic extracts from HFHS-fed mice (n=8) compared with ND-fed mice (n=8). Data are expressed as fold change over ND (*P<0.05).

(Figure 2B). Inflammation associated with obesity was evidenced at 2 months by ≈3-fold increases in aortic mRNA expression of tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP1α) (Figure 2C). There was no significant increase in collagen content in aortas from obese mice compared with ND-fed mice (Figure S4).

Arterial Stiffness and Hypertension Are Reversed by Return to ND

To determine whether arterial stiffness in obese mice is reversible, mice fed HFHS diet for 5 months were reverted to ND (henceforth referred to as HFHS/ND versus ND/ND control mice that were on ND for the entire duration). In just 2 weeks, obese mice lost 12.5% of body weight and returned to the body weight of ND-fed mice within 2 months of diet reversal (Figure 3A, left). A 50% loss in fat mass occurred with no significant change in lean mass and was accompanied by normalization of hyperinsulinemia (Figure 3B), indicating amelioration of metabolic state.

Similarly, PWV was reduced to control values within 2 months of diet reversal (Figure 3A, right). At this time point, systolic blood pressure and mean arterial pressure were significantly reduced to values not significantly different from those in control mice (Figure 3C).

In Vitro Aortic Stiffness, Aortic Inflammation, and Oxidant Stress Are Reduced After Return to ND

The force required for a fixed indentation of the basement membrane of endothelium-denuded aorta showed that HFHS significantly increased stiffness by 2-fold (52±4.8 kPa, n=7 versus 24±2.8 kPa in ND, n=10). This returned to normal levels after diet reversal in HFHS/ND (30.5±3.7 kPa, n=8; Figure 4A).

HFHS diet stimulated aortic hypertrophy compared with ND (medial area: 0.135±0.014 in HFHS versus 0.100±0.005 mm^2 in ND; P<0.05). Although this might have contributed to aortic stiffness, medial area remained unchanged after reversal to ND (0.14±0.02 mm^2, n=8; Figure 4B).

HFHS-induced upregulation of inflammatory genes in aortas was normalized after reversal to ND (Figure 4C). In addition, immunostaining of aortic sections with a specific anti–N-ε-(γ-glutamyl)-lysine antibody, indicative of TG-2 activity, revealed reduced extracellular matrix cross-links after diet reversal (Figure 5A) despite no change in TG-2 expression between different diet groups (Figure S5). Aortic immunostaining with a specific antisulfonylated sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) showed that HFHS increased SERCA oxidation, used as an index of oxidant stress,[23–25] compared with ND, and this was decreased by reversal to ND (Figure 5B).

Discussion

Here, we report for the first time that in an animal model of diet-induced obesity arterial stiffness develops rapidly and precedes the onset of hypertension. In mice fed a diet rich in fat and sucrose, PWV, measured both by Doppler ultrasonography and invasively, was elevated coincident with increased fat mass, glucose intolerance, and hyperinsulinemia but preceded the gradual onset of kidney damage, manifested by albuminuria, cardiac diastolic dysfunction,[26] and hypertension. In accordance with increased PWV, we found evidence of increased material stiffness of the aortic intimal extracellular matrix, measured in vitro by atomic force microscopy, in response to HFHS feeding that was normalized by reversal to ND. Extracellular membrane stiffening of the intima can increase endothelial permeability, potentially contributing to the development of atherosclerosis.[27] Material stiffness of the aortic extracellular matrix[28] or vascular cells[29] have recently emerged as novel biomechanical paradigms of aging-associated arterial stiffness.

Tachycardia-associated sympathetic hyperactivity is found in obese hypertensive individuals and is explained, in part,

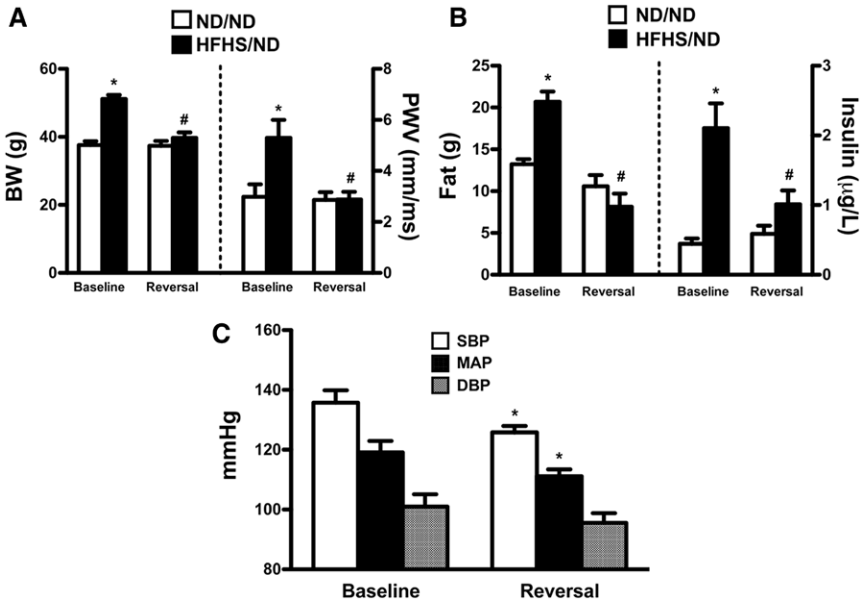

Figure 3. Reversal to normal diet (ND) reduces arterial stiffness and hypertension in high-fat/high-sucrose (HFHS)–fed mice. **A**, Body weights (BW, g) and pulse wave velocity (PWV, mm/ms) in HFHS-fed mice decreased to control values after reversal to ND. n=8 each group; **P*<0.05 vs ND baseline; #*P*<0.05 versus HFHS baseline. **B**, Reversal to ND rapidly reduced fat mass (g, left *y* axis) and plasma insulin levels (μg/L, right *y* axis) in obese mice (n=4–14 in each group). **C**, Systolic blood pressure (SBP) and mean arterial pressure (MAP) of obese mice were significantly decreased after reversal to ND, whereas diastolic blood pressure (DBP) did not change (n=6). **P*<0.05 vs baseline. Baseline indicates 5 months on diet (ND or HFHS), and reversal indicates 4 months of ND after 5 months of HFHS or ND.

by impaired baroreflex.[21] Similar to obese individuals, we found sympathetic activation and tachycardia in HFHS-fed mice that could, in part, contribute to hypertension in these mice. Notably, aortic stiffening could impair the activation of carotid and aortic baroreceptors because artery distensibility is the main stimulus for a baroreflex. Although the causal link between arterial stiffness and the development of hypertension is lacking partially because of the inherent functional relationship between arterial wall stiffness and distending pressure,[30] our findings support the hypothesis that arterial stiffness contributes to later hypertension in our model of diet-induced obesity. Interestingly, normalization of metabolic state achieved by weight loss after reversing obese mice to ND was associated with a rapid reduction in HFHS-induced arterial stiffness and systolic hypertension, suggesting that normalization of metabolic state may contribute to amelioration of abnormal vascular function.

HFHS-fed mice recapitulate many aspects of the metabolic syndrome, including insulin resistance, increased plasma triglycerides, and hypertension,[31,32] making them an excellent model to study obesity-linked cardiovascular complications. Proinflammatory cytokines TNF-α, MCP-1, and MIP1α were upregulated by ≈3-fold in aortas from HFHS-fed mice and returned to control levels after reversing obese mice to ND. Inflammation and reduced vascular NO bioavailability are known important determinants of cardiovascular diseases, including arterial stiffness, particularly in settings of aging and diabetes mellitus.[33,34] In patients with rheumatoid arthritis, TNF-α is associated with an increase in carotid–femoral PWV and L-arginine/asymmetric dimethylarginine ratio, indicative of reduced cellular NO-producing capacity. Thus, TNF-α may contribute to aortic stiffness, at least in part, by regulating NO bioavailability in settings of chronic inflammation.[35] Aortas of HFHS-fed mice had both increased expression of TNF-α and impaired aortic relaxation to acetylcholine, indicative of reduced endothelial NO production, as early as 2 months on HFHS diet. The reduced NO bioavailability was also evident by an increase in tissue TG-2 activity in aortic lysates from HFHS-fed mice (Figure 2B),

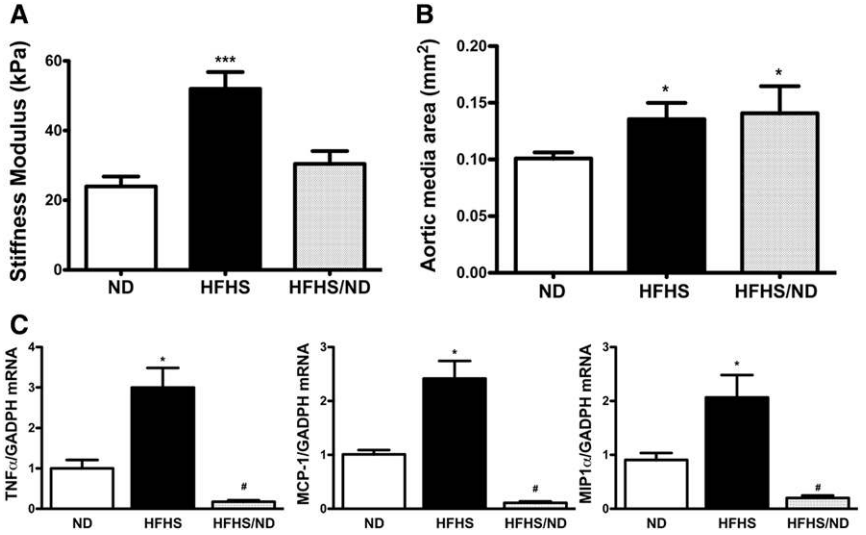

Figure 4. In vitro aortic stiffness and medial area are increased in diet-induced obesity. **A**, Stiffness modulus (kPa) on aortic rings subjected to 0.1 μm indentation was increased in high-fat/high-sucrose (HFHS)–fed mice and reduced to normal values after reversal to normal diet (ND; HFHS/ND; n=7–10 each group; ****P*<0.0005 vs ND). **B**, Medial area of thoracic aortas from HFHS-fed mice was significantly increased compared with ND-fed mice and was not affected by reversal to ND (n=4–8; **P*<0.05 vs ND). **C**, HFHS-induced inflammatory cytokines tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-1α mRNA in aortic extracts were reduced to normal levels after reversal to ND (n=8 each group). Data are expressed as fold change over ND. **P*<0.05 vs ND; #*P*<0.05 versus HFHS.

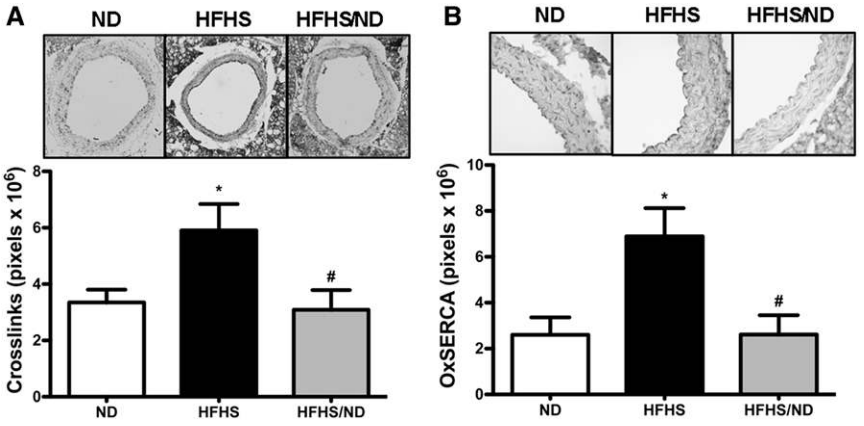

Figure 5. Aortic extracellular matrix cross-links and oxidant stress are induced by high-fat/high-sucrose (HFHS) diet and reduced after diet reversal. Representative pictures of (**A**) extracellular matrix N-ε-(γ-glutamyl)-lysine cross-links (×10 magnification), indicative of transglutaminase-2 activity, and (**B**) sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) sulfonylated at cysteine 674 (OxSERCA; ×40 magnification), used as index of oxidants, in aortas from normal diet (ND)-fed mice and HFHS-fed mice and after reversal to ND (HFHS/ND). n=8–16; **P*<0.05 vs ND; #*P*<0.05 vs HFHS. Graphs indicate immunostaining intensities (expressed in millions of pixels). For a color version, see Figure S6.

which was decreased after reversal to ND (Figure 5A). TG-2 is ubiquitously expressed in vascular cells and catalyzes a transamidation reaction to form strong N-ε-(γ-glutamyl)-lysine bonds between extracellular matrix proteins. TG-2 activity is inhibited by S-nitrosylation such that in settings of low NO bioavailability, it translocates to the extracellular space and becomes more active in forming matrix cross-links associated with arterial stiffness.[22] Furthermore, vascular extracellular matrix cross-links known as advanced glycosylation end products could form nonenzymatically in settings of chronic hyperglycemia,[36] possibly contributing to arterial stiffness in HFHS-fed mice.

In addition to decreased NO bioavailability, we found increased sulfonylated SERCA, a marker of oxidant stress,[24,25,37] in aortas from obese mice compared with ND-fed mice or mice reversed to ND. Oxidative post-translational modifications, such as sulfonylation of SERCA at cysteine 674, prevent NO-mediated SERCA-dependent Ca^{2+} uptake into the sarco/endoplasmic reticulum and, therefore, impair vascular smooth muscle cell relaxation.[38] Decreased SERCA activity and endothelial NO in settings of HFHS-induced oxidant stress could therefore contribute to HFHS-induced arterial stiffness, at least in part, by increasing vascular smooth muscle tone. Taken together, our findings indicate that inflammation and decreased NO function could play a causative role in aortic and extracellular matrix remodeling and tone in obesity-induced arterial stiffness.

In conclusion, we showed for the first time in an animal model of diet-induced obesity that arterial stiffness precedes hypertension. Multiple mechanisms involving inflammatory mediators, matrix cross-linking, and decreased NO bioactivity may contribute to vascular remodeling and stiffness in advance of hypertension that may be, at least in part, a result of arterial stiffness causing undue stress on resistance vessels. The finding that reversal to ND improves vascular function in addition to the metabolic state indicates that arterial stiffness can be a novel target for early pharmacological or lifestyle interventions to prevent hypertension and associated complications in settings of obesity.

Perspectives

Arterial stiffness is an independent risk factor for cardiovascular events. Hypertension is associated with arterial stiffness although their temporal relations remain controversial. Here, we report that in diet-induced obesity, arterial stiffness precedes the onset of hypertension. Weight loss improves not only the diet-induced metabolic impairment in obese mice but also arterial stiffness and hypertension. When considering the epidemic incidence of obesity in the United States, mainly because of excessive consumption of fat- and sucrose-rich diets, arterial stiffness could represent a novel therapeutic target to prevent obesity-associated cardiovascular complications including hypertension.

Acknowledgments

We thank Pratibha Chauhan and Xiuyun Hou for their technical assistance.

Sources of Funding

This work was supported by National Heart, Lung, and Blood Institute (NHLBI) R01 grants HL105287 to R.A. Cohen and HL097296 to C.A. Reinhart-King and was partially supported by the Evans Center for Interdisciplinary Biomedical Research ARC (Affinity Research Collaborative) on Molecular, Biomechanical and Genetic mechanisms of Arterial Stiffness at Boston University (http://www.bumc.bu.edu/evanscenteribr/), as well as NHLBI Contract Number HHSN268201000031C to R.A. Cohen.

Disclosures

G. Mitchell is the owner of Cardiovascular Engineering, Inc, a biomedical device manufacturer from which some instrumentation, used to conduct this study, was purchased. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- Arterial stiffness is increased in a diet-induced model of obesity and precedes hypertension.
- Arterial stiffness and high blood pressure are reversed to normal when the metabolic state of obese mice is normalized by weight loss.

What Is Relevant?

- Arterial stiffness could represent a novel therapeutic target to prevent obesity-associated cardiovascular complications including hypertension.

Summary

Whether arterial stiffness could develop in advance of hypertension is unknown. Here, we report that in a model of diet-induced obesity, arterial stiffness precedes the onset of hypertension. Normalization of metabolic state by weight loss in obese mice returned arterial stiffness and high blood pressure to normal. Arterial stiffness could be a novel therapeutic target to prevent cardiovascular complications, including hypertension, in settings of obesity.