

## Obesity-Induced Hypertension: Heavy on the Accelerator

George C. Roush, MD

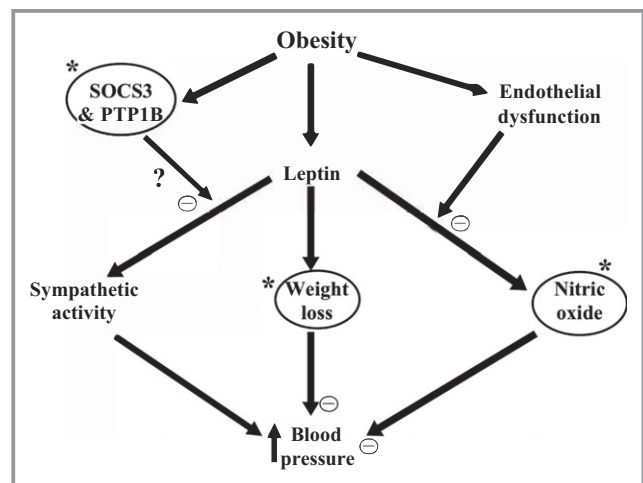
**H**ypertension is the most important cause of morbidity and mortality worldwide, with 182 million disability-adjusted life years and 10.4 million deaths annually.<sup>1</sup> In the Framingham population, the fraction of hypertension attributable to excess fat was 56% in women and 73% in men.<sup>2</sup> Approximately two thirds of US adults have become overweight and more than one third are obese.<sup>3</sup> This epidemic increasingly affects developing societies (including China). The body mass index (BMI) has increased globally by 20% in just 10 years, and elevated BMI is now the fourth leading cause of morbidity and mortality.<sup>1</sup>

In this issue of the *Journal of the American Heart Association (JAHA)*, Zhang et al examine both the level of BMI and the change in BMI in young Chinese adults who underwent repeated measurements of BMI and blood pressure and who were followed an average of 5.5 years.<sup>4</sup> (Measures of central adiposity were not obtained, but BMI is similar to those measures in predicting hypertension.<sup>5</sup>) As expected, the level of BMI was an important risk factor for incident hypertension. However, individuals with a sharp increase in BMI had a relative risk for new-onset hypertension that was many times the risk in those with a low-stable trajectory. The crucial period for incident hypertension associated with the sharply increasing trajectory was in those 20 to 30 years of age, a relationship that was independent of achieved BMI level. Before 30 years of age, the rate of increase in BMI was found to be a better predictor of hypertension than BMI level.

The relationship between the sharply increasing trajectory in BMI and new-onset hypertension persisted after adjustment for baseline BMI, baseline systolic blood pressure, and other risk factors: hazard ratio 12.3 (95% CIs 8.1 and 18.9). However, salt

consumption was not measured and is correlated with both obesity and hypertension.<sup>6</sup> Exercise reduces blood pressure independently of reductions in body weight and is also a potential confounder.<sup>7</sup> Because of increased upper arm circumference and a conical shape, accurate measurement of blood pressure in obese individuals may be challenging.<sup>8</sup> However, the high upper and lower 95% confidence limits make it virtually impossible to explain the results on the basis of unmeasured parameters. Nonetheless, it would be valuable to repeat such a study with measurements of salt consumption and exercise and to examine these relationships in other populations.

Endothelial dysfunction and arterial stiffness precede hypertension in animals and humans.<sup>9,10</sup> However, arterial stiffness has been shown to be reversible.<sup>11–13</sup> This suggests that there are mechanisms for adapting to stressors such as obesity (Figure). Obesity promotes the activity of factors (SOCS3 and PTP1B) that appear to counter the obesity-induced increase in sympathetic tone. The obesity-induced increase in leptin suppresses appetite through the arcuate nucleus in the hypothalamus and may lead to weight loss.<sup>14</sup>



**Figure.** Counterbalancing effects\* on blood pressure from SOCS3, PTP1B, weight loss, and nitric oxide, adapted from Hall et al<sup>14</sup> with permission. Copyright ©2015, Wolters Kluwer Health, Inc. Obesity and increased sympathetic activity both activate the RAAS, which fosters hypertension. Nitric oxide mitigates the pro-hypertensive effects of RAAS by reducing RAAS activation and by buffering the angiotensin II-induced peripheral vasoconstriction. PTP1B indicates protein tyrosine phosphatase 1B; RAAS, renin–angiotensin–aldosterone system; SOCS3, suppressor of cytokine signaling 3.<sup>16</sup>

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the NYU School of Medicine, New York, NY.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

**Correspondence to:** George C. Roush, MD, NYU School of Medicine, 217 East 70th St, #708, New York, NY 10021. E-mail: groush@gcr0.com  
*J Am Heart Assoc.* 2019;8:e012334. DOI: 10.1161/JAHA.119.012334.

© 2019 The Author. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Another counterbalancing mechanism involves the renin–angiotensin–aldosterone system, which is known to be activated in obesity.<sup>14–16</sup> How the renin–angiotensin–aldosterone system relates to endothelial dysfunction and hypertension has been clarified.<sup>16</sup> Renin–angiotensin–aldosterone system inhibition can reverse arterial stiffness, and this takes place in a manner that is partly independent of reductions in blood pressure.<sup>11,12</sup> A key regulator is nitric oxide (NO), which modulates endothelial function.<sup>17</sup> The bioavailability of NO depends on (1) the CAT1 transporter (responsible for moving extracellular L-arginine into the cell), (2) the intracellular concentration of unsequestered L-arginine, and (3) the enzyme endothelial NO synthase. The obesity-induced increase in leptin fosters the bioavailability of NO,<sup>14</sup> and there is evidence that NO can reverse arterial stiffness and can enhance arterial elasticity.<sup>13,18</sup> Thus, one speculation in response to the observations of Zhang et al is that accelerated obesity overwhelms 1 or more of these 4 counterbalancing mechanisms, which would more effectively oppose new-onset hypertension when obesity increases more gradually. It would be interesting to test this hypothesis in studies of animals.

If verified, the findings of Zhang et al would have important implications for prevention of hypertension. Lifestyle practices tend to be self-reinforcing, and intervention at younger ages may minimize obesity later in life. In the best of circumstances, reductions in body weight are 3 to 8 kg from lifestyle interventions,<sup>19</sup> 3 to 7 kg from medications,<sup>20</sup> and 20 to 45 kg from bariatric surgery<sup>19</sup> with remission of hypertension in 75% of individuals.<sup>21</sup> These reductions in body weight are of course desirable, but less ambitious goals may be worthwhile. For example, while the constituents of the Dietary Approach to Stop Hypertension (DASH) diet may reduce blood pressure, it has also been shown in adolescents that the DASH diet retards the rate of increase in BMI over the long term.<sup>22</sup> Clinicians may sink into despair over attempts to reduce body weight in their patients. However, favorable effects on blood pressure may occur, even if the only impact from interventions is to reduce the BMI's rate of increase.

## Disclosures

None.

## References

- GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioral, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1923–1994.
- Garrison RJ, Kannel WB, Stokes J III, Castelli WP. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med*. 1987;16:235–251.
- Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315:2284–2291.
- Fan B, Yang Y, Dayimu A, Zhou G, Liu Y, Li S, Chen W, Zhang T, Xue F. Body mass index trajectories during young adulthood and incident hypertension: a longitudinal cohort in Chinese population. *J Am Heart Assoc*. 2019;8:e011937. DOI: 10.1161/JAHA.118.011937.
- Jayedi A, Rashidy-Pour A, Khorshidi M, Shab-Bidar S. Body mass index, abdominal adiposity, weight gain and risk of developing hypertension: a systematic review and dose-response meta-analysis of more than 2.3 million participants. *Obes Rev*. 2018;19:654–667.
- Ma Y, He FJ, MacGregor GA. High salt intake: independent risk factor for obesity? *Hypertension*. 2015;66:843–849.
- Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, Miller EPR III, Polonsky T, Thompson-Paul AM, Vupputuri S. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e116–e135.
- Irving G, Holden J, Stevens R, McManus RJ. Which cuff should I use? Indirect blood pressure measurement for the diagnosis of hypertension in patients with obesity: a diagnostic accuracy review. *BMJ Open*. 2016;6:e012429.
- Weisbrod RM, Shiang T, Al Sayah L, Fry JL, Bajpai S, Reinhart-King CA, Lob HE, Santhanam L, Mitchell G, Cohen RA, Seta F. Arterial stiffening precedes systolic hypertension in diet-induced obesity. *Hypertension*. 2013;62:1105–1110.
- Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012;308:875–881.
- Safar ME, van Bortel LM, Struijker-Boudier HA. Resistance and conduit arteries following converting enzyme inhibition in hypertension. *J Vasc Res*. 1997;34:67–81.
- Uchida H, Nakamura Y, Kaihara M, Sugimoto T, Norii H, Sasaki M, Sato H, Makino H. Practical efficacy of telmisartan for decreasing morning home blood pressure and pulse wave velocity in patients with mild-to-moderate hypertension. *Hypertens Res*. 2004;27:545–550.
- Fujie S, Hasegawa N, Sato K, Fujita S, Sanada K, Hamaoka T, Iemitsu M. Aerobic exercise training-induced changes in serum adropin level are associated with reduced arterial stiffness in middle-aged and older adults. *Am J Physiol Heart Circ Physiol*. 2015;309:H1642–H1647.
- Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res*. 2015;116:991–1006.
- Susic D, Varagic J. Obesity: a perspective from hypertension. *Med Clin North Am*. 2017;101:139–157.
- Rajapakse NW, Head GA, Kaye DM. Say NO to obesity-related hypertension: role of the L-arginine–nitric oxide pathway. *Hypertension*. 2016;67:813–819.
- Chin-Dusting JP, Willems L, Kaye DM. L-arginine transporters in cardiovascular disease: a novel therapeutic target. *Pharmacol Ther*. 2007;116:428–436.
- Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, Ganz P. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. *Hypertension*. 2001;38:1049–1053.
- Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934.
- Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, Suttrop M, Solomon V, Shekelle PG, Morton SC. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142:532–546.
- Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg*. 2014;149:275–287.
- Bricarello L, Poltronieri F, Fernandes R, Retondario A, de Moraes Trindade EBS, de Vasconcelos FAG. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on blood pressure, overweight and obesity in adolescents: a systematic review. *Clin Nutr ESPEN*. 2018;28:1–11.

**Key Words:** Editorials • hypertension • leptin • obesity • renin angiotensin system