Increasing adiposity with a clinical endpoint of obesity is associated with a progressive increase in risk of cardiovascular diseases (CVD). However, we are only beginning to understand the physiological and pathophysiological mechanisms by which excessive body fat storage causes CVD.

In this issue of Hypertension, the findings of Wildman et al1 extend and strengthen previous observations2–5 by showing that changes in arterial stiffness, as measured by aortic pulse-wave velocity (PWV), are related to changes in body weight over a 2-year follow-up period in healthy men and women aged 20 to 40 years. Weight gain was associated with an increase, whereas weight loss was associated with a decrease in aortic PWV, independent of changes in blood pressure. The greatest increases in aortic PWV were observed in those subjects who gained the most weight (≥4.5 kg). Importantly, the changes in aortic PWV were related to changes in body mass index (BMI), indicating that the associations with body weight were mediated by changes in adiposity (rather than fat-free mass). Changes in aortic PWV over time also were related to baseline body weight, BMI, and waist circumference (an indirect measure of abdominal adiposity), providing evidence that higher initial levels of total and abdominal body fatness are associated with greater future increases in arterial stiffness. The study included subjects with a broad range of BMI, suggesting that the findings are applicable to both nonobese and obese adults in the general population. An important finding was that black adults demonstrated greater increases in weight gain-adjusted and blood pressure-adjusted aortic PWV over time, suggesting that they undergo greater increases in arterial stiffness in response to the same age-associated weight gain compared with whites.

These observations provide further support for the emerging concept that adiposity-driven weight gain during adulthood contributes significantly to the adverse changes in cardiovascular function and structure that provide the essential substrate for age-associated CVD. That is, advancing age and increasing adiposity, likely amplified by worsening of other risk factors, form a dangerous partnership that accelerates the development and clinical expression of a variety of cardiovascular disorders. The effect of adiposity on arterial stiffness may begin during childhood,6 thereby increasing the duration of exposure to this stimulus and causing greater CVD risk at an earlier age in adulthood. Certain high-risk groups including individuals with a family history of CVD, pre-existing risk factors (diabetes, hypertension, dyslipidemia), and older adults may turn out to be particularly vulnerable to the negative cardiovascular effects of elevated adiposity.

Increased arterial stiffness, particularly stiffening of the large elastic arteries in the cardio-thoracic circulation, is a key and, potentially, lethal trigger in the etiology of age-associated CVD.7 Arterial stiffening initiates a series of adverse cardiovascular events that include increases in central and peripheral arterial systolic blood pressure and pulse pressure, as well as increases in aortic input impedance, ie, the resistance imposed on left ventricular ejection by the systemic arterial vasculature. These changes cause or contribute to vascular endothelial injury, aneurysms, left ventricular hypertrophy, altered diastolic filling, decreased left ventricular systolic reserve, and reduced baroreflex sensitivity, resulting in increased risk of vascular occlusive diseases, hemorrhagic stroke, exercise intolerance, heart failure, and cardiac arrhythmias.

The mechanisms by which increasing adiposity and obesity cause arterial stiffening are not well understood. Currently, we have only fragments of insight, discrete physiological links among a likely myriad of players involved, but no integrated picture. Arterial stiffness is determined by a number of factors that influence vascular structure and function. Among the primary factors influencing arterial structure are the key extracellular matrix proteins, elastin and collagen. Increased fragmentation/reduced density of elastin, along with an increased concentration and cross-linking of collagen molecules, leads to increased arterial stiffness, and vice versa. The production of advanced glycation end-products (which act to increase collagen cross-linking), the bioactivity of matrix metalloproteinases (important effectors of vascular remodeling), vascular smooth muscle cell (VSMC) hypertrophy, and a variety of growth factors also modulate the structural and functional properties of the arterial wall. In addition, several factors influence arterial stiffness by changing VSMC tone, including sympathetic nerve activity and norepinephrine release, circulating vasomotor hormones, local (endothelium-derived) vasodilators (nitric oxide, prostacyclins) and vasoconstrictors (endothelin-1, angiotensin II), pro-/anti-inflammatory molecules, and reactive oxygen species, as well as myogenic tone. Body fatness likely modulates arterial stiffness by affecting several of these intermediary influences.

The physiological/pathophysiological coupling between body fat and arterial stiffness may be mediated in part via stimulation of a pro-inflammatory state, resulting in activation of oxidant enzyme systems, increased production of reactive oxygen species such as superoxide anions, and the development of oxidative stress (Figure 1). Both pro-inflammatory molecules and increased superoxide activity can alter expression of extracellular matrix proteins by
influencing matrix metalloproteinase activity or through other mechanisms. This pro-inflammatory/high-oxidant state also produces a vascular endothelial phenotype characterized by reduced nitric oxide bioavailability and VSMC relaxation and augmented production of endothelin-1 and angiotensin II-associated VSMC contraction, with resulting arterial stiffening. Elevated adiposity also is associated with elevated sympathetic nerve activity and norepinephrine-evoked VSMC contraction, which also likely contributes to obesity-related arterial stiffness. Moreover, increased body fatness results in elevated circulating leptin concentrations, which are linked to increased arterial stiffness by as yet unknown mechanisms. It remains to be determined if the modulation of arterial stiffness by these mechanisms is more tightly linked to changes in abdominal visceral or subcutaneous fat, or to total adiposity.

Although changes in aortic PWV were not significantly related to changes in arterial blood pressure in the study of Wildman et al, we should not overlook the normally close association between the 2 events. Whereas arterial stiffening will increase arterial blood pressure, an intervention that increases or decreases arterial blood pressure will result in a corresponding increase or decrease in arterial stiffness. It is often difficult to tease out whether the change in arterial stiffness leads to the change in arterial blood pressure or vice versa (or if both occur). Moreover, subtle interactions between arterial stiffness and blood pressure, eg, expressed as blood pressure variability or nighttime dipping of blood pressure, could have been missed in the absence of 24-hour blood pressure recordings.

Regardless of the mechanisms involved, the implications of body fatness-related arterial stiffening for maintaining physiological function and health during adult aging are clear. Total body and abdominal fat are strong independent correlates of 24-hour systolic blood pressure and pulse pressure, both of which are determined primarily by the stiffness of the large elastic arteries and represent a major CVD risk factor for adults 50 years of age and older. Age-associated increases in 24-hour systolic blood pressure and pulse pressure do not occur in the absence of increases in total and abdominal adiposity and arterial stiffness, and correcting for abdominal fat and arterial stiffness abolishes the significance of age-related elevations in 24-hour systolic blood pressure and

Hypothetical model of the integrative pathophysiological mechanisms by which increased adiposity may combine with advancing age and other risk factors to increase arterial stiffness and its cardiovascular sequelae. MMPs indicates matrix metalloproteinases; TIMPs, tissue inhibitor of metalloproteinases; NO, nitric oxide; PGI2, prostacyclin; ET-1, endothelin 1; Ang II, angiotensin II; SNA, sympathetic nervous activity; NE, norepinephrine; AGES, advanced glycation end products; VSMC, vascular smooth muscle cell; BP, blood pressure; LV, left ventricle.
pulse pressure. Increasing total and abdominal fat also contributes to left ventricular remodeling and reduced diastolic function with adult aging, driven in part by arterial stiffness-mediated increases in aortic input impedance.

Wildman et al emphasize the importance of their findings in supporting the need for weight-loss interventions, especially in blacks. The fact that weight reductions were associated with decreases in aortic PWV in their study certainly is consistent with this idea, at least in young to early middle-aged men and women. However, sustained weight-loss without regain, particularly in obese adults, is difficult and currently has a very poor long-term success rate. Moreover, some individuals or groups (eg, patients with long-standing obesity–hypertension) may with time develop an arterial stiffness phenotype that is resistant to weight loss. As such, a key focus of our future efforts in this area must be directed toward the primary prevention of adult weight gain. Because the association between weight gain and arterial stiffness was observed even in nonobese adults in this study, one aim of the overall strategy should be to prevent the development of overweight and obesity in presently lean individuals. However, increases in arterial stiffness over the follow-up period were greater in those subjects with higher initial BMI and waist girth. Thus, preventing additional abdominal and total fat storage appears to be important for minimizing future increases in arterial stiffness in both nonobese and obese adults. Given new evidence that childhood obesity predicts arterial stiffness during adulthood, this strategy likely needs to be extended to adolescence.

Recently it was emphasized that for 20- to 40-year-old adults, the average weight gain is only ~2 pounds/year, and that reducing energy accumulation by 50 to 100 kcal/d would offset this weight gain in 90% of the population. It also was emphasized that only small behavioral changes involving some combination of increased physical activity-related energy expenditure and reduced energy intake would be required to maintain energy balance. Habitual aerobic exercise may be a particularly effective element of body weight management in this context given its favorable independent modulatory influence on age-associated arterial stiffening. Thus, maintaining healthy arterial compliance and the associated reduced risk of CVD by limiting adult weight gain appear to be attainable goals with relatively modest and palatable adjustments to our modern lifestyle. The importance of making these adjustments is becoming increasingly apparent as we recognize that uncoupling the deadly combination of aging and obesity is a critical battleground in the fight against CVD.

References