Increasing adiposity is a disturbing experience for many people in middle age, determined by genetic factors, as well as environmental influences, including the mismatch between too high calorie intake and insufficient physical daily activity. Normally this leads to an annual increase of body weight amounting to 0.5 to 1.0 kg in many middle aged people. There is no doubt that this increasing body weight is associated with adverse health effects in numerous subjects, including the increased risk of type 2 diabetes mellitus and cardiovascular disease, and often accompanied by less variation of gut microbiota bacterial strains. As adiposity also shows a high degree of heritability, there is reason to think that the genetic influence on these changes could be of considerable importance. Several genetic markers of obesity have been determined, most importantly the FTO gene. The link between obesity and hypertension is well documented and this could be one of the mediating risk factors for increased risk of cardiovascular disease in obesity itself besides other obesity-related risk factors, such as hyperglycemia, dyslipidemia, and insulin resistance, factors that may cluster in what has been named the Metabolic syndrome, based on its most recent harmonized definition from 2009. A new genetic study based on Mendelian randomization analyses has documented that genes regulating either insulin resistance or insulin secretion are causally associated with increased cardiovascular disease risk, as seen in subjects with increasing hyperglycemia and overt type 2 diabetes mellitus.2

Arterial stiffness is the hallmark of what is now discussed as early vascular aging (EVA), and measured as pulse wave velocity (PWV), ideally between the carotid and femoral arteries.3 EVA involves all layers of the arterial wall but predominantly the media with less elastin and relatively more collagen content with increasing age. However, changes in the intima (endothelial dysfunction) and adventitia (impaired function by vasa vasorum and innervation) as well as the proinflammatory action of the perivascular adipose tissue surrounding the arteries could contribute to EVA. Epidemiological associations exist between arterial stiffness and various aspects of the metabolic syndrome across several populations, as documented within the Metabolic Syndrome and Arteries Research (MARE) consortium of mostly European studies.4 In fact, target organ damage including arterial stiffness could represent the core risk features of the cardiovascular risk factor cluster that is named metabolic syndrome. As the concept of the metabolic syndrome has been increasingly criticized ever since 2005, one could speculate whether arterial stiffness linked to the EVA concept could open up new ways to understand the development of cardiovascular risk, as arterial stiffness (atherosclerosis) is supposed to precede atherosclerosis, a condition starting in the arterial intima layer and more proximal to the future cardiovascular event.

In this issue of Hypertension, epidemiological data from the well-known Whitehall II study in the United Kingdom shows that different measures of adiposity in midlife before baseline are predictive of changes in arterial stiffness from baseline and after 4 years of follow-up in a cohort of 5172 civil servants of both sex.5 In fact, both body mass index and different measures of abdominal adiposity (waist circumference) as well as fat mass were predictive of increased PWV over four years, independent of other background factors. This was calculated, on theoretical grounds, to explain 12% of the increased cardiovascular risk associated with obesity (body mass index). One advantage of the study was the careful assessment of risk factors and measures of obesity, as well as of PWV and path length between the carotid and femoral arteries. In fact, this was 1 of the few studies to show data on repeated measures of PWV over time and therefore of a high value when compared with cross-sectional studies. Mean intraindividual difference in repeated PWV was 0.83 m/s at baseline and 0.89 m/s at follow-up, based on data from subgroups. This is a marker of high reproducibility, it itself a marker of high quality of the examination procedures. It should however be kept in mind that the mean age at baseline, when arterial stiffness was first measured, was 65.5 years for men and 66.4 years for women, a decade earlier than the age range that normally associates with biological involution when elderly people tend to lose both height and weight because of the aging process itself, not caused by disease. The finding of a positive association between increasing adiposity in midlife and increasing PWV around the age of retirement is therefore representative of the age-range studied and could be different in more elderly subjects. In fact, the predictive power of PWV for cardiovascular events is normally less strong or even absent in elderly or old subjects.

Interestingly enough the statistical adjustments for various confactors in the Whitehall II study could not fully explain the influence of obesity (body mass index, waist) or fat mass on the
increase of arterial stiffness during the follow-up. The adjustment included confounding factors, such as age, sex, ethnicity, mean arterial pressure, heart rate, dyslipidemia (triglycerides, high-density lipoprotein cholesterol), fasting glucose, hemoglobin A1c, inflammation (C-reactive peptide, interleukin-6), and chronic disease, as well as antihypertensive medication, but still could not fully explain the prediction of obesity on PWV changes. The authors mention that several unmeasured pathways could contribute to the explanation, such as endothelial dysregulation, secretion of proinflammatory adipokines, but also inadequate measurement of the biological pathways adjusted for. It should however be noted that neither smoking habits nor lipid-lowering drug treatment were adjusted for, even if this should normally be the case when external effects on arterial stiffness are analyzed.

Other studies have shown the importance of a correct estimation of the distance between the carotid and femoral arteries in subjects with pronounced abdominal obesity and increased waist line causing artefacts. For this reason, sometimes special devices have to be used to avoid bias when estimating the carotid–femoral distance in subjects with severe abdominal obesity and increased waist line. The authors of the Whitehall II study calculated path length at follow-up adjusted for the association between change in waist circumference and change in measured aortic path length. This is a way to take into account the changes in abdominal obesity for effects on pulse wave velocity.

The Importance of an Increase in Arterial Stiffness for Risk

Meta-analyses have shown that increased PWV is an independent predictor of cardiovascular morbidity and mortality, as well as of total mortality, more pronounced in the middle-aged population than in elderly subjects, probably because of differential aging being more visible in the former, according to a meta-analysis by Ben Shlomo et al. Even if a close association exists between increased blood pressure and arterial stiffness, there is also a blood pressure–independent component of arterial stiffness, as documented in a Swedish study on the nonhemodynamic components of vascular aging when mean arterial pressure and heart rate were adjusted for. The Whitehall II study findings highlight the importance of changes in adiposity as explaining some of this increased risk.

Interventions on Obesity to Improve Arterial Stiffness

What can be done about this increased arterial stiffness in relation to obesity in middle-aged subjects? A recent meta-analysis has shown that induced weight loss is associated with a small but significant lowering of PWV during a follow-up of 2 to 12 months based on 20 studies (3 randomized controlled trials), involving 1259 participants. These findings point at the potential for improving lifestyle, diet, and physical exercise in achieving weight control and the reduction of risk factors, including PWV. However, it has been more difficult to prove the clinical benefits of intentional weight loss on morbidity and mortality outcomes in randomized, controlled studies. Several antiobesity drug intervention trials have failed to show benefits, and even the costly Look-Action for Health in Diabetes (AHEAD) trial in obese patients with type 2 diabetes mellitus, randomized to intensive lifestyle and weight loss or control, was unable to show a reversal of risk associated with intensive lifestyle intervention. To date, only weight loss secondary to surgical interventions for obesity, that is, bariatric surgery or related procedures, has documented such clinical benefits and is therefore becoming more widely used for severe obesity.

A more realistic attitude to overweight and obesity could therefore be to aim for weight stabilization in middle for subjects without comorbidities, and a balanced weight loss for selected patients with comorbidities, keeping in mind that observational studies have documented a worse prognosis associated with weight loss in postmyocardial infarction patients or in those with congestive heart failure, the so-called obesity paradox.

In summary, the Whitehall II study has shown that different measures of obesity in middle life predict the changes of increased arterial stiffness over a few years in subjects around retirement age. This is important to recognize both for analyzing potential nonhemodynamic mechanisms of arterial stiffness and for possible interventions based on lifestyle. Normally such lifestyle interventions need to be combined with an active drug treatment of known cardiovascular risk factors to counteract the increased risk associated with arterial stiffness, as still no targeted therapy exists for reduction of end points related to arterial stiffness itself. In France, such study is ongoing named Cardiovasculaire Basée sur la Rigidité Arterielle Study (SPARTE), directed by S. Laurent with results to come.

More studies should aim for repeated measurements of arterial stiffness, just like the methods applied in the Whitehall II study.

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Adiposity and Vascular Aging: Indication for Weight Loss?
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