Effects of Adipocyte Expansion on Cardiovascular System and Ongoing Debate over Obesity Paradox

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In the last few decades, the prevalence of obesity, traditionally defined as a body mass index (BMI) being equal to or greater than 30 kg/m², has risen dramatically in both industrialized and less industrialized countries across the world.¹⁾ Obesity increases the risk of developing cardiovascular diseases and has been strongly associated with increased mortality.^{2,3)} As such, the meta-analysis reported by H. Chen, *et al.* in this journal is feasible showing that excess weight is associated with an increased risk of sudden death due to cardiovascular diseases.⁴⁾ Here we outline the effects of adipose tissue expansion on the cardiovascular system.

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Adipocytes uptake lipids and store them in the form of triglycerides within lipid droplets to prevent ectopic lipid deposition and lipotoxicity in other cell types, while adipocytes release fatty acids and glycerol to target tissues in need of energy. When caloric excess continues to exceed energy expenditure, overnutrition yields adiposity. In adult visceral adipose tissue, the capacity of adipogenesis is impaired, and adipocyte hypertrophy is more likely induced instead of hyperplasia.^{5,6)} In the step of adipose expansion, extracellular matrix remodeling is required and leads to mechanical stress and hypoxia in this tissue.⁷⁾ It has become evident that white adipose tissues are not merely organs that passively store excess energy as a reservoir, but also secrete a variety of hormones and communicate with innate and adaptive immune systems in their interstitials for homeostasis.⁸⁻¹⁰⁾ Dysfunctional adipocytes with hypertrophy modulate the adipokine secretome and lead to inflammation.

Adiponectin, one of the representative adipokines, has pleiotropic properties favorable for the cardiovascular system, although its expression is reduced in hypertrophic adipocytes and plasma levels are decreased in obesity.¹¹⁾ Circulating adiponectin exerts vasodilating actions on systemic vascular walls through activation of 5'-AMP-activated protein kinase (AMPK) and restored endothelial nitric oxide synthase (eNOS) coupling, as well as adi-

ponectin derived from perivascular adipose tissue in a paracrine manner.^{12,13)} Anti-inflammatory effects of adiponectin to inhibit endothelial activation and monocyte attachment by inhibition of nuclear factor kappa-B (NF-κB) pathway contribute to protection from atherosclerotic injury.¹⁴⁾ Regarding cardiac functions, adiponectin secreted from adipose tissue and partly epicardial fat exerts antioxidant effects on cardiomyocytes,¹⁵⁾ which suppresses myocardial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity by preventing membrane translocation of Ras-related C3 botulinum toxin substrate 1 (RAC1) and p47phox via AMPK dependent and independent pathways, thus maintaining the myocardial redox state. Loss of these beneficial actions on the cardiovascular system in obese patients might render them susceptible to ischemic events and deleterious arrhythmogenesis.

Leptin secreted from white adipose tissue in response to lipid storage acts on the satiety centers in the brain to suppress food intake and promote energy expenditure.¹⁶⁾ It has been recently observed that leptin engages presynaptic potentiation of γ-aminobutyric acid (GABA) release to inhibit orexigenic agouti-related peptide (AgRP) neurons in the arcuate nucleus (ARC) of hypothalamus for the regulation of appetite,¹⁷⁾ and that leptin increases lipolysis via the activation of sympathetic neuronal projections onto adipocytes in adipose tissue.¹⁸⁾ However, the regulatory circuits in the central nervous system have an inherent complexity. AgRP neurons and proopiomelanocortin (POMC) neurons in the ARC modulate second-order neurons cooperatively, and the contribution of AgRP neurons and POMC neurons to sympathetic nerve activation differ in different sites of the body from the fat depot to the kidney, the adrenal gland, and other subserving organs.^{19,20)} In addition, the anorexic effects of leptin in obesity turn to be blunted, known as leptin resistance, whereby leptin's effects of increasing sympathetic nerve activity are preserved, although the underlying mechanism of selective leptin resistance remains elusive. Hyperleptinemia induced autonomic activation and endothelial dysfunction in obesity dismiss nitric oxide production as a beneficial effect of leptin and might be associated with adverse cardiovas-

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These promising findings might deepen future perception about the relationship between obesity and cardiovascular diseases.

Disclosures

Conflicts of interest: None.

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