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The Road Connecting Obesity and Coronary Vasomotor Function: Straight Line or U-turn?

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Obesity as reached epidemic proportions globally with approximately half a billion people (12% of the world's population) considered obese (1). In the United States alone, the prevalence of obesity has increased by ~50% in the past 30 years to where now ~70% of all adults are classified as either overweight or obese.(2) More sobering is that > 30% of all children between 2–19 years of age fall into these 2 categories. (3). Obesity is typically defined as a body mass index (BMI) of ≥ 30 kg/m^2. The presence of obesity has a significant unfavorable impact on cardiovascular (CV) health through the complex interplay of systemic and direct cardiac effects (Table). For example, synergistic effects of an increase in total blood volume and the presence of hypertension and increased insulin resistance (e.g., diabetes mellitus) stimulate left ventricular remodeling resulting in significant left ventricular systolic and diastolic dysfunction with heart failure (with either reduced or preserved ejection) being the outcome. Similarly, the confluence of key risk factors for coronary heart disease (e.g., dyslipidemia, hypertension and insulin resistant states) with an inflammatory and pro-thrombotic environment appears to increase the prevalence of this disease in obese individuals. Finally, the amalgamation of these adverse cardiac effects results in an increase prevalence of atrial and ventricular arrhythmias. Consequently, obesity has been implicated as one of the major risk factors for heart failure, coronary heart disease, and sudden cardiac death. However, unlike other conventional risk factors such as hypertension and dyslipidemia where the relationship with CV events is continuous or linear, evidence from clinical cohorts of patients with established CV diseases indicates a more complex and even paradoxical relationship between obesity and CV disease. For example, the presence of obesity has been associated with a more favorable short- and long-term prognosis in patients with coronary heart disease and various forms of heart failure (4). Furthermore, post-mortem studies suggest a reduced atherosclerotic burden in individuals with obesity as well as morbid obesity (BMI > 40 kg/m^2 (5). This complex relationship has been termed the "obesity paradox". The reasons responsible for the dichotomous effects of obesity on CV health are poorly understood. Clearly, the difficulty in separating out the adverse CV effects from obesity alone, from the contributions of its other systemic abnormalities is one potential explanation. Moreover, the presence of obesity may mitigate the cachexia associated with advanced heart failure. That being said, other mechanisms are likely to be operational, particularly those contribute to the beneficial CV effects of obesity.

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Conflicts of Interest: None

In this issue of the Journal, Quercioli and colleagues attempt to provide further insight into the potential mechanisms responsible for the complex relationship between obesity and CV health (6). They focused their efforts on answering the question of whether abnormalities in coronary vasomotor function were more pronounced in morbidly obese individuals compared with obese individuals and if so, could differences in the systemic levels of leptin, adiponectin, endocannabinoids and C-reactive protein be contributory. Leptin and adiponectin are adipocyte-derived cytokines with divergent effects on vascular morphology and function. Leptin possesses pro-coagulant and anti-fibrinolytic properties, and it promotes thrombus and atheroma formation, probably through the leptin receptors by promoting vascular inflammation, proliferation, and calcification, and by increasing oxidative stress. Thus it appears to impair vascular morphology and function. In contrast, adiponectin inhibits the expression of key adhesion molecules (e.g., ICAM-1 and VCAM-1), interferes with monocyte adherence to endothelial cells and their subsequent migration to the subendothelial space, and exhibits potent anti-inflammatory effects by inhibiting the transformation of macrophages to foam cells and decreases their phagocytic activity. Thus it appears to enhance vascular morphology and function. Consequently, the increases in systemic leptin levels and decline in adiponectin levels in obesity are likely contributory the observed perturbations in vascular function. The endocannabinoids, such as anandamide and 2-arachidonoylglycerol, are endogenous bioactive lipid mediators derived from arachidonic acid. They are physiologically synthesized and released upon demand from a variety of tissues such as brain, peripheral organs, and adipose tissue. The endocannabinoids exert their biological effects via interaction with specific G-protein-coupled cannabinoid receptors type 1 and type 2 which appear to activate divergent functions. (7) For example increases in adipocyte-derived endocannabinoids have been suggested to exert proatherosclerotic effects by signaling via cannabinoid receptor type 1 and/or non- cannabinoid receptors in the vascular wall with resultant increases in oxidative stress, vascular smooth muscle cell proliferation, and recruitment of monocytes and neutrophils into the arterial wall. Conversely, stimulation of the cannabinoid receptor type 2 appears to mediate anti-inflammatory and antiatherosclerotic effects. Thus, systemic endocannabinoids levels may well contribute to obesity related abnormalities in vascular function.

The investigators studied 4 groups of subjects stratified by BMI; a control group (BMI 20–24.9), overweight group (BMI 25–29.9), an obese group (BMI 30–39.9) and a morbidly obese group (BMI ≥40). Coronary vasomotor function was determined by measuring myocardial blood flow with ^{13}N-ammonia PET/CT at rest in response to cold-pressor test to measure endothelium-dependent vasodilation and to pharmacologically-induced hyperemia. Results were compared with various anthropomorphic measurements and plasma adipokine, endocannabinoid and C-reactive protein levels.

Several interesting observations arose from this study. First, there was a progressive decline in endothelium-dependent vasodilation across the continuum of individuals who were normal weight, overweight and obese that did ***not*** continue in the presence of morbid obesity. Second, hyperemic blood flow was reduced to a comparable level among all groups with increases in body weight, suggesting a threshold effect for the impairment. Third, increases in plasma levels of anandamide and 2-arachidonoylglycerol were inversely associated with an impairment of the myocardial blood flow response to cold-pressor testing in obese individuals, suggestive of adverse effects of endocannabinoids on the coronary endothelium, but this association was ***not*** observed in individuals with morbid obesity. Finally, elevations in leptin and hs-CRP plasma levels were ***positively*** correlated with endothelium-related vasodilation.

The results of this study provide further credence that BMI alone is an inadequate marker of obesity-related CV risk and to the existence of a paradoxical relationship between obesity

and CV health and in particular sheds light on the impact of severity of obesity on coronary vasomotor function. It also raised several intriguing questions. The findings of relatively preserved vasomotor function and a positive association with leptin and hs-CRP levels in individuals with more severe obesity are consistent with prior reports.(8) It is well known that adipocytes are source of not only inflammatory mediators such as adipokines, but also endothelial progenitor cells. Although controversial, these cells may provide a protective and reparative function on the endothelium. Thus, is it possible that at a critical fat mass enough progenitor cells are produced and mobilized, perhaps via stimulation by the inflammatory microenvironment, to have a beneficial effect on endothelial function? Are the results of the study applicable to men and women and if so, what is the effect of menopausal status? The results of the current study would suggest that men might be more susceptible than women to obesity related abnormalities in coronary vasomotor function; but larger studies are needed to confirm this observation. Finally, what are the implications of the study on the use of weight loss in obese cardiac patients? Weight loss is routinely prescribed for obese cardiac patients with the intent of improving quality of life and decreasing CV risk. Indeed, recent data suggests that bariatric surgery in morbidly obese patients can greatly reduce various obesity-related CV risk factors with subsequent salutary effects on long-term CV outcome. (9) However, based on the results of the current study is there an early time window during weight loss when CV risk may actually increase and if so, is more intensive monitoring needed during this time? Moreover, given different metabolic, pro-inflammatory and potentially progenitor cell profiles of different types of adipose tissue (e.g., subcutaneous versus visceral fat), should weight reduction should be targeted to specific fat depots?

The performance of more high quality studies such as the one performed by Quercioli and colleagues should help further unravel the complex relationship between obesity and CV disease.

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Table

Effects of Obesity on the CV System

Systemic	**Cardiac**
Insulin resistance • Glucose intolerance • Metabolic syndrome • Diabetes mellitus	Altered Cardiac Geometry • LA enlargement • LV Concentric and eccentric hypertrophy • LV remodeling
Dyslipidemia • Elevations in total and LDL cholesterol and triglycerides • Decline in HDL cholesterol	LV dysfunction • Diastolic • Systolic
Hypertension	Endothelial dysfunction
Increased inflammation	Coronary artery disease
Pro-thrombotic state	Heart Failure
	Arrhythmias • Atrial fibrillation • Ventricular tachycardia and fibrillation

LDL- Low density lipoprotein; HDL – High density lipoprotein; LV – Left ventricle