Sympathovagal imbalance in obesity: Cardiovascular perspectives

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Abstract

Obesity is an independent predictor of cardiovascular (CV) morbidity and mortality. Irrespective of the etiology, sympathovagal imbalance (SVI) in the form of sympathetic overactivity and vagal withdrawal has been recognized as the central pathophysiological mechanism involved in the genesis of obesity. Also, SVI has been reported to be the potential contributor to the obesity related co-morbidities such as diabetes, insulin resistance, hypertension, dyslipidemia and CV dysfunctions. In this review, we have analyzed the role of SVI in the development of obesity and its association with the genesis of CV dysfunctions. We have emphasized the role of lifestyle modification and pharmacological therapy in restoring the sympathovagal balance and its link to prevent the occurrence of CV diseases in overweight and obese individuals.

Key words: Antherogenic index, cardiovascular disease, obesity, sympathovagal imbalance

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INTRODUCTION

Obesity is a complex disorder of energy balance, which continues to be a growing global health challenge. Recently, more than 37% adults and 24% youth worldwide are reported to be either overweight or obese. The co-morbidities associated with obesity such as hypertension, pro-inflammatory state, dyslipidemia and type 2 diabetes mellitus, significantly increase the adverse CV outcomes. Especially in developing countries like India and other Asian countries, abrupt changes in the economic and social environments due to the increasing sedentary lifestyle and easy availability of fast food rich in fat have contributed to the rapid increase in the incidence of obesity and its co-morbid conditions. Irrespective of its genesis, obesity produces dysfunctions of the autonomic nervous system (ANS) either independently or in association with the other co-morbidities. Recently, sympathovagal imbalance (SVI) due to inequality between the sympathetic and parasympathetic activities has emerged as the key pathophysiological mechanism to explain the role of autonomic neuro-physiological mechanisms in various clinical disorders. In this article, we have reviewed the concept, cause, mechanism and effects of SVI in obesity and its possible link to CV disorders. Also, we have suggested the possible methods for preventing CV risks in overweight and obese subjects by restoring sympathovagal homeostasis.

SYMPATHOVAGAL IMBALANCE: CONCEPT AND IMPORTANCE

Autonomic responses are the emotional responses of the body to the environment that occurs without the conscious effort of an individual. These responses are executed through the autonomic part of the nervous system, known as ANS. ANS through its two major subdivisions: The sympathetic and the parasympathetic systems innervate all viscera organs to control the major functions of the body, such as circulation, respiration, digestion, excretion, reproduction, immunity, and metabolism. Broadly, the sympathetic system is involved in energy mobilization and utilization, and the parasympathetic system in energy restoration and storage. In a healthy person, the body tries to maintain a balance between the
sympathetic and parasympathetic (vagal) systems, known as sympathovagal balance, which contributes to effective internal homeostasis.[26]

SVI is a state of the functional disharmony in which sympathetic and vagal components of the ANS function either in excess or deficit. In SVI, usually the sympathetic system is hyperactive, and the parasympathetic system is hypoactive.[24] There is growing evidence that dysfunction of the ANS in the form of SVI is involved in the etiopathogenesis of a wide range of diseases and could be the final pathway of degeneration and death.[27] Spectral analysis of HRV is a non-invasive electrocardiographic method used for assessing sympathovagal balance or imbalance.[28‑30] HRV analysis is widely used to evaluate the nature and degree of autonomic imbalance in various clinical disorders including cardiovascular (CV) dysfunctions, and to assess morbidity and mortality.[30,31] The frequency domain indices of HRV such as total power (TP), high frequency power (HF) and normalized high frequency power (HFnu) are measures of parasympathetic activity or the vagal drive.[30,32] The low frequency power (LF) and normalized low frequency power (LFnu) are measures of sympathetic activity and the ratio of low frequency power to high frequency power (LF:HF ratio) is the measure of sympathovagal balance.[30,32] The magnitude of HRV, that is, the quantum of the TP of HRV, is an independent predictor of mortality.[33,34] Decreased HRV is a risk factor for CV disease morbidity and mortality.[35‑37] Recent studies have demonstrated that the autonomic imbalance in the form of increased sympathetic and decreased parasympathetic activity plays a vital role in the genesis and the clinical course of several disorders including cardiovascular, inflammatory, metabolic, and neurological diseases.[38]

ROLE OF SVI IN THE ETIOPATHOGENESIS OF OBESITY

ANS plays a crucial role in regulating the body weight and can be considered as a fundamental factor controlling food intake and energy expenditure.[39‑43] Studies have reported that the lesion of the lateral hypothalamus in rats have the tendency to lose weight faster than the sham lesioned rats subjected to the same level of food deprivation.[42,44,45] Monda et al. have reported reduced firing rate of the sympathetic nervous system following food intake in rats when the ventromedial hypothalamus was lesioned.[46] These studies demonstrated that the long-term decreased sympathetic activation after food intake could induce body weight gain in individuals by reducing the satiety signals to the hypothalamus and post-ingestional energy expenditure. According to the ‘Mona Lisa hypothesis’, alteration in the sympathetic activity could be the possible cause for the most categories of obesity.[47] On the other hand, Messina et al. have observed an increase in the resting energy expenditure (REE) in sportswomen inspite of increased parasympathetic activity which is usually related to lower REE.[48] Therefore, these studies suggest that not only the sympathetic activation but also the parasympathetic inhibition plays a vital role in the genesis and pathophysiology of obesity by regulating food intake and energy homeostasis.

Although SVI has been reported in obesity,[12,14,15] it has not been clearly defined whether SVI is the initiating mechanism for the causation of obesity or SVI is the outcome of obesity. It has been well established that in obesity, there is increased levels of adipokines such as leptin, adiponectin and so on. Leptin has been strongly implicated in the pathophysiology of obesity.[49] Hyperleptinemia activates sympathetic system in obese individual and the adrenergic blockade abolishes the effect of leptin which categorically indicates that leptin effects are mediated by sympathetic stimulation.[49] Adiponectin, the other adipocyte-derived hormone has also been implicated in the alteration of sympathetic activity in obesity,[50] though the exact influence has not yet been established. Nevertheless, autonomic imbalance has been reported in obesity which turn contributes to obesity-related metabolic problems. As adipose tissues are innervated by both sympathetic and parasympathetic system,[51,52] it was suggested that chronic SVI could lead to increased adipocyte mass causing obesity. However, the contribution of SVI in obesity is not very clear, it appears that a closed-loop system operates in which adipose tissue mass regulates hypothalamic control of autonomic functions, affecting both sympathetic and parasympathetic influences in the regulation of metabolic functions and dysfunctions in obesity. As CV functions are closely controlled by both sympathetic and parasympathetic systems, SVI is the key physiological link between adiposity and CV morbidity in obesity, which is discussed in the succeeding section.

ROLE OF SVI IN THE CAUSATION OF CV RISKS/DYSFUNCTION IN OBESITY

Obesity is as an independent risk factor for the CV morbidity and mortality.[4‑7] In obesity, there is altered sympathovagal balance in the form of increased sympathetic and decreased parasympathetic activity,[15,53‑57] which in combination with the other risk factors such as hypertension, dyslipidemia, pro-inflammatory state, diabetes, insulin resistance, and physical inactivity are known to significantly increase the probability of adverse CV outcomes.[15,23,27,58‑62] Adipocytokines secreted from the adipose tissue plays a central role in regulating the synthesis of
both the pro-inflammatory cytokines such as leptin, interleukin 6 and tumour necrosis factor alpha, and the anti-inflammatory cytokines such as adiponectin and resistin.\textsuperscript{[63,64]}

**SVI and inflammatory cytokines**

Interleukins are the multifunctional cytokines that play a central role in inflammatory responses, and the acute phase reactant C-reactive protein is reported to be produced in more quantity from the liver in response to interleukin 6.\textsuperscript{[63]}

Lampert et al. have reported that decreased HRV is associated with these inflammatory markers, suggesting that the autonomic dysfunction is associated with inflammation, which provides a link for the development of the CV disease.\textsuperscript{[63]} However, from this cross-sectional study, it was not clear whether the autonomic dysfunction mediates the inflammatory process or the mechanism is vice versa. Therefore, future prospective studies should be carried out to assess the cause-effect relationships between SVI and inflammation.

**SVI and adipocytokines**

Adipocyte hypertrophy associated with obesity, results in the imbalance between the between the pro-inflammatory and anti-inflammatory adipocytokines, which in turn aggravates the chronic low-grade inflammation and CV risks in obesity.\textsuperscript{[64,65]}

Hyperleptinemia could be a plausible contributor to the development of CV dysfunctions in obesity. Leptin is a peptide hormone secreted from adipocytes into circulation. It acts on hypothalamus to decrease food intake and increase thermogenesis and energy expenditure through stimulation of the ANS via secretion of α-melanocyte stimulating hormone and the decreased expression of agouti-related peptide and neuropeptide Y.\textsuperscript{[64,65]} But, there is selective resistance to the metabolic actions of leptin in obesity,\textsuperscript{[66-68]} and the sympathetic activation apparently remains unaltered. However, Paolisso et al. have reported increased leptin levels to be associated with an increase in LF: HF ratio (shift of sympatho-vagal balance towards sympathetic activation) in non-obese adults.\textsuperscript{[69]}

Adiponectin is a protective adipocytokine, regulated by the ANS. In vivo studies using a mouse model, have shown the role of sympathetic nervous system in regulating adiponectin synthesis from white adipose tissue.\textsuperscript{[90]} In humans, the LF: HF ratio of HRV and insulin resistance were reported to be negatively correlated with the adiponectin levels.\textsuperscript{[70,71]} Therefore, adipocytokines could be the major link for the risk factors contributing to the CV dysfunctions associated with obesity.

**SVI and Insulin resistance**

In obesity, there is increased circulating insulin and reduced sensitivity to metabolic actions defined as insulin resistance. Studies have reported administration of insulin causes increased muscle sympathetic activity and norepinephrine release in both normotensive and borderline hypertensive subjects.\textsuperscript{[72,73]} Another effect of insulin infusion is the tachycardia induced by the withdrawal of the parasympathetic tone mediated by β-adrenergic mechanism, which is believed to be the mechanism for causation of hypertension by the altered vascular functions.\textsuperscript{[74,75]} Thus, insulin resistance in obesity could be due to the effect of heightened sympathetic drive, mediated through β-adrenergic stimulation and vasoconstriction with the subsequent reduction in muscular blood flow.\textsuperscript{[76,77]}

**SVI and endothelial dysfunctions**

Obesity represents a state of both systemic and vascular inflammation, resulting in a pro-inflammatory and pro-thrombotic state that predisposes to the development of hypertension. Insulin resistance in obesity down regulates the synthesis of the potent vasodilator nitric oxide (NO), which is known to influence the CV functions by acting on both central and peripheral sites.\textsuperscript{[78,80]} In addition, hyperinsulinemia as occurs in obesity increases the vasoconstrictor endothelin-1.\textsuperscript{[81,82]} As a result, an imbalance between the levels of vasodilator and vasoconstrictor in the vascular endothelium, which is indirectly mediated by sympathetic overactivity, is the major contributor to the genesis of CV diseases in obesity.\textsuperscript{[83]} Hyperleptinemia in obesity is reported to promote endothelium toxicity by altering the expression of endothelial NO synthase.\textsuperscript{[84,85]} Also, the neuropeptide Y released from neural sites by sympathetic activation acts as a vasoconstrictor and are critically involved in the pathogenesis of obesity-related hypertension.\textsuperscript{[86]}

**SVI and hypertension**

As blood vessels of systemic circulation is primarily innervated by the sympathetic vasoconstrictor fibers, sympathetic overactivity is considered as the major pathophysiological mechanism for the development of hypertension.\textsuperscript{[87-91]} Chronically increased sympathetic activity causes thickening of the vessel wall (increase in the wall: lumen ratio),\textsuperscript{[92,93]} which in turn amplifies the vascular reactivity by increasing the blood vessel response to the circulating endogenous vasoconstrictors.\textsuperscript{[94,95]} Further, studies have also reported the decreased parasympathetic activity as a possible cause of hypertension in these subjects, even after adjustment for age, race, BMI, gender, smoking, and diabetes.\textsuperscript{[96,97]} There are reports of sympathetic overactivity and vagal inhibition in obesity.\textsuperscript{[12,14,15]} Thus, these reports suggest the crucial role of autonomic modulation in determining the vasomotor tone and as a potent risk factor in the pathogenesis of chronic CV diseases.\textsuperscript{[4,6,98-100]}
Therefore, CV dysfunctions could be directly linked to the degree and magnitude of SVI in obesity. Moreover, SVI and CV dysfunctions in obesity appear to be interdependent and reciprocal [Figure 1]. Gerritsen et al. reported the principal role of sympathetic overactivity in the genesis of CV dysfunctions in obesity using HRV.\(^{[34]}\) Pima Indians are reported to have the highest prevalence of obesity and hyper insulinaemia in the world.\(^{[101]}\) However, there is a relatively low incidence of hypertension and atherosclerotic disease in this ethnic group.\(^{[101]}\) Weyer et al. reported the low sympathetic activation observed in this ethnic group appears to influences the mechanism of obesity‑related hypertension.\(^{[101]}\)

Therefore, this review has discussed the impact of SVI in the form of increased sympathetic activity and vagal withdrawal in the genesis of obesity and its associated co-morbidities. Also, we have revealed the contribution of SVI and its link to the CV morbidity and mortality in overweight and obese subjects.\(^{[15,27,63-67]}\)

**PREVENTION OF CV RISKS IN OBESITY BY RESTORING SYMPATHOVAGAL BALANCE**

Lifestyle changes such as calorie restriction, body weight reduction and aerobic exercise reduces 25% of the risk for developing cardiac autonomic dysfunctions by increasing the vagal activity in obese subjects.\(^{[102]}\) As ANS plays a key role in regulating the activities of the CV system by maintaining heart rate and BP within

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**Figure 1:** Link of sympathovagal imbalance and altered biomarkers in the genesis of cardiovascular dysfunctions in obesity. hs-CRP: High specific-C-reactive protein, TNF-α: Tumor necrosis factor-alpha, FFA: Free fatty acids, NPY: Neuropeptide Y, AgRP: Agouti-related peptide, SNS: sympathetic nervous system, PNS: Parasympathetic nervous system, α-MSH: Alpha-melanocyte stimulating hormone, NO: Nitric oxide, ET-1: Endothelin-1
physiological limits, impaired ANS activity in the form of sympathetic overactivity and attenuated vagal tone delays heart rate recovery, which is associated with increased mortality.\textsuperscript{103,104} Endurance training with aerobic exercise increases HRV by improving the cardiovagal tone in subjects with minimal cardiac autonomic abnormalities but not in severe autonomic dysfunctions.\textsuperscript{106-109} Thus, these studies emphasize the need for early aggressive intervention and control of the altered sympathovagal balance in obese subjects to avoid future CV morbidities.

Moderate nutritional restriction of saturated fats and cholesterol with increased consumption of fruits, vegetables and whole grains are recommended, as these approaches have been proved to increase HRV and restore sympathovagal balance.\textsuperscript{[41,103-105,110,111]} There is evidence that practice of yoga such as asanas, meditation and pranayama attenuate weight gain and improve the CV health by achieving homeostasis of the ANS.\textsuperscript{[112-115]} Especially, practice of slow breathing pranayamic exercises has been reported to decrease sympathetic activity and promote vagal activity.\textsuperscript{[112]}

Studies have reported the beneficial effect of several pharmacological agents in restoring sympathovagal balance such as aldose reductase inhibitors, angiotensin converting enzyme inhibitors (quinapril, ramipril), angiotensin receptor blockers (losartan, telmisartan), C peptide and a potent antioxidant α-lipoic acid.\textsuperscript{[116,117]} Due to the complex nature of the pathogenesis involved in the genesis of obesity and its co-morbidities; long-term cohort and clinical trials are essential to understand the basis for the prevention and management of CV dysfunctions in overweight and obese subjects.

**CONCLUSION AND FUTURE PERSPECTIVE**

SVI in the form of sympathetic overactivity and decreased parasympathetic activity facilitates the development of obesity and its related co-morbidities. Sympathetic activation leads to chronic low-grade inflammation, insulin resistance, increased vasomotor tone, endothelial dysfunctions, type 2 diabetes and hypertension that could link and act as a key contributing factor to CV dysfunctions in obese subjects. Vagal withdrawal increases heart rate and decreases HRV. Decreased HRV is known to cause CV morbidity and mortality. All these factors mediated by SVI in overweight and obese subjects predispose them to adverse CV events. Hence, it is advised that the non-pharmacological and pharmacological therapies should be adopted by overweight and obese subjects for achieving effective sympathovagal homeostasis and to reduce the associated CV dysfunctions.

Future studies should address the scientific basis of lifestyle modifications and pharmacological therapies in the management of overweight and obesity and their associated CV morbidities.

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