

## การปรับระบบประสาทอัตโนมัติที่ควบคุมการทำงานของหัวใจในเด็กและวัยรุ่นที่เป็นโรคอ้วน

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### Modulation of Cardiac Autonomic Control in Children and Adolescents with Obesity

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เป็นที่ยอมรับกันดีว่าโรคอ้วนเป็นหนึ่งในปัจจัยที่สำคัญที่สุดในการทำให้เกิดการเปลี่ยนแปลงการทำงานของหัวใจและหลอดเลือด ผู้ที่เป็นโรคอ้วนมีความทุกข์ทรมานจากความเสี่ยงต่อการเสียชีวิตจากโรคดังกล่าว ซึ่งคาดว่าจะเกี่ยวข้องเนื่องกับการทำงานลดลงของระบบประสาทพาราซิมพาเทติก และ/หรือการกระตุ้นการทำงานของระบบประสาทซิมพาเทติก ในปัจจุบันมีวิธีการประเมินการทำงานของระบบประสาทอัตโนมัติที่ควบคุมการทำงานของหัวใจด้วยการวัดค่าความแปรปรวนของการเต้นของหัวใจ (heart rate variability, HRV) ซึ่งเป็นวิธีการที่ง่าย ไม่เป็นอันตราย และมีประสิทธิภาพในการประเมินปัจจัยทางสรีรวิทยาที่มีอิทธิพลต่อจังหวะการเต้นของหัวใจ HRV ที่สูงขึ้นจะเป็นสัญญาณที่ดีของการปรับตัวและเป็นเครื่องหมายของผู้ที่มีสุขภาพดีซึ่งหมายถึงมีการทำงานของระบบประสาทอัตโนมัติที่ดีและมีประสิทธิภาพ ในขณะที่การมี HRV ต่ำลงมักจะแสดงถึงการทำงานของระบบดังกล่าวที่ผิดปกติและการปรับตัวที่ไม่มีประสิทธิภาพ ส่งผลทำให้การทำงานของทางสรีรวิทยาของผู้ป่วยลดลง บทความนี้กล่าวถึงกลไกของ HRV การกระตุ้นระบบประสาทซิมพาเทติก และปัจจัยต่างๆ ที่มีผลต่อความดันเลือดในเด็กและวัยรุ่นที่เป็นโรคอ้วน

It is established that one of the most important characteristics of obesity is cardiovascular alterations. Obese individual suffers from an increased mortality risk supposedly due to cardiovascular disorders related to either continuously lowered parasympathetic and/or sympathetic activation. Presently, heart rate variability (HRV) is one of the ways to assess cardiac autonomic function. It is recognized as non-invasive and powerful means for evaluating physiological factors influencing the normal rhythm of the heart. Higher HRV is a signal of good adaptation and characterizes a healthy person with efficient autonomic mechanisms, while lower HRV is frequently an indicator of abnormal and insufficient adaptation of the autonomic nervous system (ANS), provoking poor patient's physiological function. In this paper, we have discussed mechanisms of HRV, the sympathetic nervous system activation in human obesity and various factors modulating blood pressure in obese children and adolescents.

**Keywords:** heart rate variability, obesity, children, adolescents

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## Introduction

Obesity is considered a serious health crisis.<sup>1</sup> The consequences of this condition include arterial hypertension, atherosclerosis, dyslipidemia, diabetes, obstructive sleep apnea, musculoskeletal abnormalities, depression and a poorer quality of life.<sup>2, 3</sup> Numerous studies have also demonstrated that obesity produces abnormalities in the function of the autonomic nervous system (ANS) in children and adolescents.<sup>4, 5</sup> Heart rate variability (HRV) is one of the ways to assess autonomic behaviour. It is a simple and non-invasive tool for detecting and studying autonomic heart dysfunction in various conditions, including obesity.<sup>6</sup> Analyses of HRV indices in the frequency domain suggest that obese children exhibit higher sympathetic activity and lower parasympathetic activity in comparison to children within the normal weight range.<sup>4, 7-10</sup> On the other hand, reductions in both sympathetic and parasympathetic activities are also reported in obese children.<sup>11, 12</sup> Besides, using functional autonomic tests, normal sympathetic activity and parasympathetic hypoactivity are demonstrated.<sup>13</sup> An increase in ratio between the sympathetic and parasympathetic elements of the ANS (low frequency power/high frequency power, LF/HF ratio) and a reduction in the parasympathetic activity on the heart (HF index) in obese children when compared to children within the normal weight range have also been shown.<sup>4</sup> Recently, we found that children and adolescents with overweight or obesity demonstrated comparable HRV parameters in either supine or upright positions compared to healthy normal weight peers indicating no modulation in the ANS function by obesity.<sup>14</sup> Nonetheless, investigating the sino-aortic baroreceptor heart rate reflex upon a postural change, a lying position (supine) to standing (upright) position, has shown a lower heart rate increase in obese adolescents compared to normal counterparts although there were no changes in HRV parameters (unpublished data). We suggest that obesity may induce impairment of baroreflex sensitivity.

## Definition and mechanisms of HRV

HRV is a non-invasive electrocardiographic marker indicating the activity of the sympathetic and vagal components of the ANS on the sinus node of the heart. It expresses the total amount of variations of both instantaneous HR and RR (or NN) intervals (intervals between QRS complexes of normal sinus depolarisations)<sup>15</sup> so that the tonic baseline autonomic function is analysed. In a normal heart with an integer ANS, there are continuous physiological variations of the sinus cycles reflecting a balanced sympathovagal state and normal HRV.<sup>16</sup> In a damaged heart suffered from myocardial necrosis, the changes in activity in the afferent and efferent fibers of the ANS and in the local neural regulation contribute to the resulting sympathovagal imbalance reflected by a diminished HRV.

## Measurements of HRV

HRV can be assessed in two ways: by calculation of indices<sup>17</sup> based on statistical operations on NN intervals (time domain analysis) or by spectral (frequency domain analysis) of an array of NN intervals.<sup>18</sup> Both methods involve accurate timing of R waves. The analysis can be performed on short electrocardiogram (ECG) segments (lasting from 0.5 to 5 minutes) or on 24-hour ECG recordings.

## Time domain analysis

The HRV time domain analysis expressed in unit time (milliseconds), every normal NN intervals (sinus beats) is quantified during a determined time interval and, it is calculated the translator indices of fluctuations during the cardiac cycles.<sup>19</sup> Indices in the time domain, corresponding to any point in time (Table 1), are<sup>20-22</sup>

- a) SDNN - Standard deviation of all normal NN intervals recorded in a time interval;
- b) SDANN - Represents the standard deviation of the normal NN intervals means, every 5 minutes in a time interval;
- c) SDNNi - It is the mean of the standard deviation of normal NN intervals every 5 minutes;

d) RMSSD - is the root-mean square of differences between adjacent normal NN intervals in a time interval;

e) pNN50 - Represents the percentage of adjacent NN intervals with a difference of duration greater than 50 ms.

The SDNN, SDANN and SDNNi obtained from long term records represent the sum of sympathetic and parasympathetic activities. They are not useful for distinguishing when changes in HRV are due to increased sympathetic tone or the withdrawal of vagal tone.<sup>23</sup> The RMSSD and pNN50 indices represent the parasympathetic activity<sup>20,21</sup> as they are found from the analysis of adjacent NN intervals.<sup>24</sup>

### Frequency domain analysis

This analysis decomposes the HRV in fundamental oscillatory components (Table 2), whereas the main ones are<sup>19</sup>:

a) High frequency component (High Frequency - HF), ranging from 0.15 to 0.4 Hz, which corresponds to the respiratory modulation and is an indicator of the vagal activity on the heart;

b) Low frequency component (Low Frequency - LF), ranging between 0.04 and 0.15 Hz, which is due to both the vagal and sympathetic activity on the heart, with a majority of the sympathetic ones;

c) Components of very low frequency (Very Low Frequency - VLF) and ultra-low frequency (Ultra Low Frequency - ULF) - Indices less used whose physiological explanation is not well established and seems to be related to the renin-angiotensin-aldosterone system, thermoregulation and the peripheral vasomotor tone.

The LF/HF ratio reflects the absolute and relative changes between the sympathetic and parasympathetic components of the ANS, by characterizing the sympathetic vagal balance on the heart.

**Table 1** Time domain parameters<sup>22</sup>

Variable	Units	Description
SDNN	ms	standard deviation of all NN intervals
SDANN	ms	standard deviation of averages of NN intervals in all 5-minute segments of the entire recording
SD (or SDDSD)	ms	standard deviation of differences between adjacent NN interval
RMSSD	ms	square root of the mean of the sum of the squares of differences between adjacent NN interval
pNN50	%	percent of difference between adjacent NN intervals that are greater than 50 ms

**Table 2** Frequency domain parameters<sup>22</sup>

Variable	Units	Description	Frequency range
Total power	ms <sup>2</sup>	variance of all NN intervals	<0.4 Hz
ULF	ms <sup>2</sup>	ultra low frequency	<0.003 Hz
VLF	ms <sup>2</sup>	very low frequency	<0.003-0.04 Hz
LF	ms <sup>2</sup>	low frequency power	0.04-0.15 Hz
HF	ms <sup>2</sup>	high frequency power	0.15-0.4 Hz
LF/HF ratio		ratio of low-high frequency power	

### The sympathetic nervous system activation in human obesity

In obese people with normal blood pressure, the sympathetic outflows to the kidneys and skeletal muscle vasculature are augmented, often 2- to 3-folds, and the sympathetic outflow to skin and the hepato-mesenteric circulation and the adrenal medullary secretion of epinephrine are normal, whereas the sympathetic outflow to the heart is reduced, with cardiac norepinephrine spillover being only 40% to 50% of that found in healthy, lean people.<sup>25, 26</sup> The sympathetic nervous system is activated in human obesity and in the analogous experimental obesity produced by overfeeding leading to hypertension. The causes remain doubtful and may be multiple (Figure 1).<sup>27</sup>

In obesity, adipocytes and other cells of adipose tissue synthesize and release a number of bioactive signaling molecules, namely adipokines. These comprise adiponectin and leptin, resistin and other inflammatory cytokines (secreted predominantly by stromal macrophages in adipose tissue), including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6).<sup>28, 29</sup> The production of several adipokines appears to be dysregulated in individuals with obesity; such anomalies potentially provide a direct link between obesity, inflammation and an insulin-resistant state (Figure 1).<sup>29-31</sup> Plasma levels of leptin are elevated in individuals with raised blood pressure.<sup>32</sup> We found similar findings in overweight and obese children and adolescents (unpublished data). Moreover, studies in rats demonstrate that the infusion of leptin induces an increase in arterial blood pressure (potentially mediated through the sympathetic nervous system)<sup>33, 34</sup>, impaired endothelial function<sup>35</sup> and an increase in oxidative stress.<sup>36</sup> By contrast, others have found that leptin exerts a vasodilatory effect, which appears to be mediated through an increase in the production of NO.<sup>37, 38</sup> The discrepancy in rats studies could be due to chronic infusion performed in conscious rats<sup>33, 34</sup> and bolus infusion in anesthetized rats.<sup>37, 38</sup> The expression of these cytokines in adipose tissue may act to exacerbate the inflammatory responses associated with atherosclerosis<sup>28, 30</sup>, and may equally contribute to

the development of insulin resistance.<sup>39</sup> Recently, we demonstrated increases in C-reactive protein (CRP), leptin, insulin and oxidative stress levels but decreases in nitrate/nitrite, redox ratio (GSH/GSSG ratio) in obese adolescents compared to normal weight ones (unpublished data).<sup>40</sup>

The increased activity of the renin-angiotensin system in obese patients may enhance vasoconstriction, as a result, leading to an increase in blood pressure (Figure 1).<sup>41-43</sup> Enhanced signalling through the vasoconstrictor angiotensin (Ang) II<sup>44</sup> and a direct stimulation due to expansion of fat mass<sup>42</sup> subsequently increased insulin resistance. Furthermore, Ang II may suppress adiponectin protein expression leading to development of insulin resistance and type 2 diabetes.<sup>44</sup> Chronic activation of the sympathetic nervous system in obese individuals may contribute to hypertension through sympathetic modulation of cardiac output, fluid retention and vascular resistance.<sup>43, 45</sup> Such a potentially harmful response may be mediated through leptin signalling<sup>33</sup>, or through increased levels of free fatty acids<sup>46</sup>, modifications in insulin sensitivity or a combination of these factors. Finally, obesity-related structural and functional changes in the kidney may further magnify the hypertensive effects of obesity through increased sodium and fluid retention, and these changes have also been linked to activation of the sympathetic nervous system and to enhanced renin-angiotensin signaling.<sup>47</sup>

Visceral obesity promotes an increase in the availability of free fatty acids, potentially mediated through the hydrolysis of stored adipocyte triglyceride by a range of lipases, including triglyceride lipase, lipoprotein lipase, hormone-sensitive lipase and endothelial lipase in adipose tissue.<sup>48-50</sup> Such increases in circulating free fatty acids lead to triglyceride accumulation in muscle and liver (in the form of hepatic steatosis), and to hypertriglyceridaemia subsequent to enhanced hepatic production of VLDL.<sup>51-53</sup> As free fatty acids may also compete with glucose for cellular uptake and metabolism, their action can potentiate a reduction in insulin sensitivity.<sup>54</sup> Increments in blood pressure may also be due to enhanced release of free fatty acids from adipose tissue in obese patients through a variety of

mechanisms including activation of  $\alpha$ 1-adrenoceptor-mediated vasoconstriction, attenuation of endothelial production of NO with induction of oxidative stress and inhibition of insulin-mediated vasodilation.<sup>53, 55</sup> Abundance of evidence supporting a role of free fatty acids as a direct cause of elevated blood pressure in obesity has been reviewed by Sarafidis and Bakris.<sup>53</sup>

OSA is, in fact, one causal mechanism of sympathetic activation in obesity.<sup>56</sup> It should be added that there are, however, 2 points of disagreement. The first is that no mechanism has yet been proposed by which nocturnal sympathetic stimulation during apneic episodes can be generalized to round-the clock sympathetic activation. The second is that the reversal of OSA with continuous positive airway pressure therapy does not lower sympathetic nervous system activity.<sup>57</sup>

Additionally, the rate of NO production in the central nervous system plays an important role in modulating the sympathetic/parasympathetic regulation of blood pressure.<sup>58, 59</sup> Existing evidence suggests that the NO pathway is central to mediating the vasodilatory action of insulin, an important determinant of glucose uptake that has been shown to be blunted in insulin-

resistant patients.<sup>60</sup> Indeed, NO signalling may be dysfunctional in individuals with insulin resistance and hyperglycaemia.<sup>61-63</sup> Clearly, defective NO signalling may represent a key mechanism in promoting hypertension in insulin-resistant patients. Similarly, insulin resistance leads to activation of the renin-angiotensin system while, as discussed above, elevated levels of Ang II can further promote insulin resistance, perpetuating this response.<sup>44</sup> Thus, it appears that on balance, the vasodilatory actions of insulin are blunted in insulin-resistant states, while the activity of vasoconstrictor systems is enhanced.

Insulin resistance and hyperinsulinaemia are associated with over-activity of the sympathetic nervous system not only in animal models<sup>64, 65</sup>, but also in both normotensive and hypertensive individuals<sup>66, 67</sup>; such hyperactivity may be responsible in part for elevations in blood pressure. Although the precise mechanisms involved in this response remain to be elucidated, enhanced sympathetic activity and hypertension in response to hyperinsulinaemia may be mediated by changes in baroreflex activity<sup>68, 69</sup> and by the action of insulin on the central nervous system.<sup>64</sup>

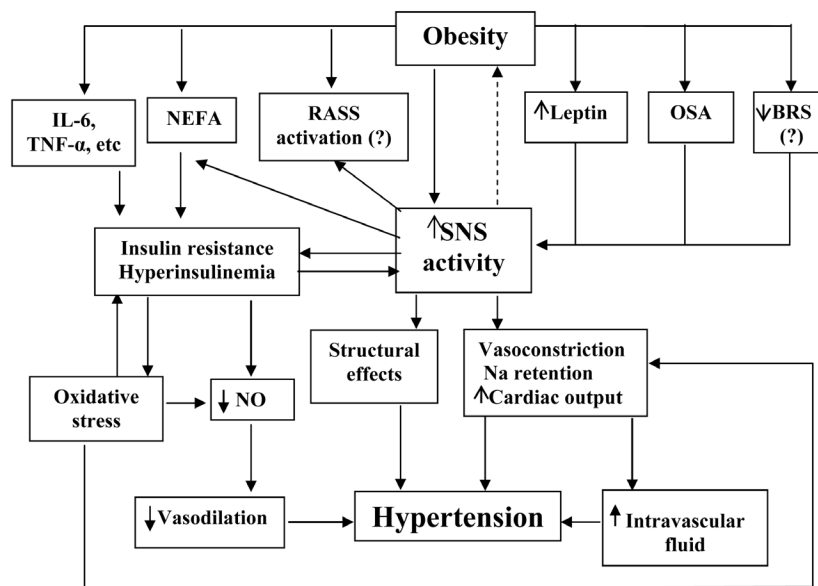


Figure 1 Possible pathophysiological mechanisms which may be responsible for obesity-induced hypertension. Mechanisms and interrelationships between the variables are discussed in the text. NEFA, nonesterified fatty acids; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; BRS, baroreflex sensitivity; NO, nitric oxide; OSA, obstructive sleep apnea (modified from Esler M, et al.).<sup>27</sup>

## Conclusions

HRV has gained importance today as a technique to explore the ANS, which has an important role in maintaining homeostasis. The widest possible use, the cost-effectiveness in the application of the technique and ease of data makes the HRV an interesting option for interpretation of the functioning of the ANS and a promising clinical tool to assess and identify impairments on health. Obesity in children and adolescents demonstrates decreased HRV which has been shown to be a strong predictor of increased cardiac and/or arrhythmic mortality. Several pathophysiological mechanisms may contribute to higher blood pressure in children and adolescents with obesity which may turn into hypertension in adulthood.

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