

Autonomic cardiovascular regulation in obesity

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Abstract

Obese persons suffer from an increased mortality risk supposedly due to cardiovascular disorders related to either continuously lowered parasympathetic or altered sympathetic activation. Our cross-sectional correlation study establishes the relationship between obesity and autonomic regulation as well as salivary cortisol levels. Three patient cohorts were sampled, covering ranges of body mass index (BMI) of 27–32 ($n=17$), 33–39 ($n=13$) and above 40 kg/m² ($n=12$), and stratified for age, sex and menopausal status. Autonomic cardiovascular regulation was assessed by use of heart rate variability and continuous blood pressure recordings. Spectral analytical calculation (discrete Fourier transformation) yields indices of sympathetic and parasympathetic activation and baroreflex sensitivity. Morning salivary cortisol was concurrently

collected. Contrary to expectation, BMI and waist/hip ratio (WHR) were inversely correlated with sympathetic activity. This was true for resting conditions ($r=-0.48$, $P<0.001$; $r=-0.33$, $P<0.05$ for BMI and WHR respectively) and for mental challenge ($r=-0.42$, $P<0.01$ for BMI). Resting baroreflex sensitivity was strongly related to the degree of obesity at rest (BMI: $r=-0.35$, $P<0.05$) and for mental challenge ($r=-0.53$, $P<0.001$). Salivary cortisol correlated significantly with waist circumference ($r=-0.34$, $P=0.05$). With increasing weight, no overstimulation was found but a depression in sympathetic and parasympathetic activity together with a significant reduction in baroreflex functioning and in salivary cortisol levels.

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Introduction

Obesity causes a whole spectrum of subsequent health problems. The major ones are cardiovascular, metabolic, orthopedic, gastroenterological, pulmonary and psychosocial disorders. It is thus evident that obese persons suffer from an increased mortality risk due to cardiovascular complications (Drenick *et al.* 1980, Garrison *et al.* 1983, Kannel *et al.* 1984, Gordon & Kannel 1986, Hubert *et al.* 1993). Chronic sympathetic overstimulation and increased catecholamine levels have been incriminated in obesity (Peterson *et al.* 1988, Rossi *et al.* 1989, Petretta *et al.* 1995, Piccirillo *et al.* 1996). However, the contribution of sympatho-adrenal activity to obesity is still an unresolved issue (Landsberg & Young 1984, Dulloo & Miller 1987, Bray 1991, Tuck 1992, Young & Macdonald 1992). Some of the authors have suggested that the obese display altered reactions to stressors (Piccirillo *et al.* 1996). Equally unresolved is the question whether aberrations of the sympathetic system contribute to obesity, or are rather a consequence of it (Macdonald 1995).

Having used spectral analysis, Piccirillo *et al.* (1996) reported that obesity was associated with decreased sympathetic responsiveness. Obese subjects showed a higher

presynaptic activation level as indices by plasma norepinephrine levels. At the same time postsynaptic sympathetic responsiveness was diminished. The decreased sympathetic stress reactivity was thought to play a role as a factor for higher mortality. A lower sympathetic activity was also found by Peterson *et al.* (1988), who reported an inverse correlation of sympathetic and parasympathetic activity with increasing body fat. Rossi *et al.* (1989) could also find a lower parasympathetic function but reported no differences in sympathetic functions in obese subjects. The former finding was again suggestive of a causal role of parasympathetic tone in sudden death. A decreased parasympathetic activity has equally been reported by Aronne *et al.* (1995). However, in contrast to other studies these authors reported an increase in sympathetic control. Zahorska-Markiewicz *et al.* (1993) observed an overreactivity of the sympathetic nervous system, but a depression in parasympathetic activity analogous to that of Piccirillo *et al.* (1996). A study by Aronne *et al.* (1997) assessed moderately overweight subjects with increasing or decreasing weight. They reported an increase in parasympathetic activity with weight loss and an inverse behavior of sympathetic drive. However, these results only included short-term differences in a population of rather fast weight

changes. In a study on weight gain, Hirsch *et al.* (1991) described an inverse relationship of the amount of weight gain with lower parasympathetic drive. In obese women higher sympathetic and parasympathetic activity have been found by Gao *et al.* (1996), especially when there is a combination of upper body obesity and visceral obesity.

Objectives

Spectral analysis of heart rate and blood pressure variability has proven to be a useful means to gain insight into sympathetic and parasympathetic control of heart activity (Various 1996, Berntson *et al.* 1997). Several studies found a different behavior of the sympathetic and parasympathetic activity in obese patients. A decrease in parasympathetic activity has consistently been reported. However, findings of alteration in sympathetic drive are inconsistent. These differences might be interpreted as a consequence of the disparate use of spectral analysis techniques or conflicting interpretation of the various frequency spectra. Typically the design of those studies essentially relied on group comparisons between obese and non-obese subjects without taking relative weight differences into account. Beyond the well-known effects of obesity on well-being (Laederach-Hofmann *et al.* 1999a) a dysfunctional autonomic nervous system (ANS) may also give rise to various symptoms in obesity as has been shown in patients with diabetes mellitus (Laederach-Hofmann *et al.* 1999b).

Our study therefore investigates the aberrations in cardiovascular regulation in relation to the degree of obesity. We hypothesize that with increasing body mass in healthy obese subjects dysfunctions in autonomic cardiovascular regulation become more pronounced. This should be true for sympathetic and parasympathetic function, and for reduced heart rate variability.

Patients and Methods

Three patient cohorts, covering body mass indices (BMI) in the ranges 27–32 kg/m² ($n=17$, ten female, seven male (including five postmenopausal women)), 33–39 kg/m² ($n=13$, seven female, six male (including three postmenopausal women)) and above 40 kg/m² ($n=12$, seven females, five males (including four postmenopausal women)) were sampled. In each group, the mean age of females and males was identical. Additionally, estrogen is known to influence heart rate variability (Sato *et al.* 1995) and so all premenstrual women were investigated only in the first half of their cycle. The status in the menstrual cycle was evaluated by a thorough interview. Pre- and postmenopausal women were then included in the three weight cohorts in equal numbers. This was done to parallel the effects of age, gender and estrogen status in the weight

cohorts and to allow the detection of even minimal influences of weight on spectral data (Ramaekers *et al.* 1998). In addition we included morning salivary cortisol determination. This was done because of the well-known effects of cortisol on insulin sensitivity and thereby on blood glucose and catecholamine levels (Peeke & Chrousos 1995, Bjorntorp 1997). Spectral activity might eventually be related to changes in cortisol excretion over the measuring period (Miki *et al.* 1998, Rosmond *et al.* (1998).

All obese subjects were inpatients of the Psychosomatic Hospital St-Franziska-Stift (Bad Kreuznach, Germany) taking part in a 4–8 week inpatient rehabilitation program. One of the aims of such an inpatient rehabilitation program is to initiate treatment in obese patients in order to produce weight reduction. Additionally, subsequent psychological conditions can be treated under hospital conditions in order to ensure compliance of patients and offer various opportunities for the treating team to influence the patients' course of disease (medical, psychological and social).

In our patients, obesity was typically accompanied by various other psychological and medical conditions, such as backache, knee pain or depressed mood (without fulfilling criteria of minor or major depression). Secondary diagnoses were randomly spread across the psychosomatic spectrum of disorders and concern mainly depressive and neurotic reactions as well as functional disorders. All medication which could presumably influence autonomic functions (especially antihypertensives, antidepressants, tranquilizers) was ruled out by the inclusion criteria. Equally, no hypertensive subjects (systolic BP >160 mmHg, and diastolic BP >95 mmHg) were included in the study. The diagnosis of arterial hypertension was performed using WHO criteria (Vallée 1999).

All patients participated in the study during the first week of hospitalization. Testing took place in the psychophysiological laboratory of the St-Franziska-Stift from 0800 to 1000 h. Subjects were informed about the nature of the recording, their tasks and the different test phases. Throughout the whole session subjects remained comfortably seated in a reclining chair. After application and adjustment of measuring devices an equilibration period of 20 min was applied (Sato *et al.* 1995) and thereafter baseline values were recorded for a 5-min period. As a mental stress test the Bonn-Det reaction-time device (Langewitz *et al.* 1987) was used. Against a white background brief flashes of five differently colored lights (white, red, blue, green, orange) had to be continuously monitored and immediately responded to by pressing the corresponding response key. Stimulus frequency was adjusted automatically by a computer program referencing to the actual speed and correctness of performance. This procedure ensured inter-individually comparable and intra-individually constant levels of mental challenge throughout the whole recording period.

Measuring devices

An electrocardiogram was recorded using a standard three-point electrode array and amplified by a device (Fa. ZAK). Self-adhesive electrodes were attached to the right and left side of the chest just below the collar bones and below the rib cage on the left side of the body. For determination of R-peak-time (1 ms accuracy) the Einthoven lead II was used. Finger blood pressure was assessed continuously by a FINAPRES device (OHMED A, Becton Dickinson Med. Tech., GmbH, Erlangen, Germany) with pressure cuffs being attached to the left middle finger and held in proper height by an adjustable arm-rest. To measure breathing activity a strain gauge (Fa. ZAK GmbH Med. Tech., Kirchdorf, Austria) was positioned around the chest at the level of the xyphoid process. Depth of breathing was estimated by taking the s.d. of the respective breathing signals into account. For all subjects, breathing signals were recorded at the same amplifier settings, and at comparable positions. However, strain signals are not, *per se*, comparable between subjects. Therefore, the ratio of the s.d. of the breathing recordings between mental challenge and resting phase was calculated for each subject to describe the relative change in breathing depth between the two experimental phases.

Spectral analysis of heart rate variability was performed with the CARSPAN program (Mulder 1988). Data acquisition was performed with a sampling frequency of 512 Hz. The program uses a discrete Fourier transformation of the succession of cardiac events. To account for the inter-dependency of power values with the respective heart rate, raw values of power spectral density were divided by the mean heart rate of the respective experimental phase. In addition, this procedure helps to minimize age and sex effects of heart rate interference on power spectra (Mulder 1988). The remainder was squared to yield a so-called squared modulation index. Frequency bands were defined as follows. A low-frequency component encompassed the range 0.02–0.06 Hz. The mid-frequency ranged from 0.07 to 0.14 Hz. In other studies this frequency band is often defined as a low-frequency band (Sato *et al.* 1995, Berntson *et al.* 1997, Ramaekers *et al.* 1998). The high-frequency band covered fast fluctuations in the range 0.15–0.40 Hz. The respiration frequency band covered the area ± 0.03 Hz around the median respiratory frequency. Total power represents fluctuations of the whole spectrum from 0.02 to 0.40 Hz. For later analysis mid- and high-frequency bands were considered relevant. The mid-frequency band reflects a mix of sympathetic and parasympathetic tone, whereas the high-frequency band is mainly influenced by parasympathetic activity (Various 1996, Berntson *et al.* 1997). Correspondingly, continuous blood pressure was subjected to spectral analysis. For the respective frequency ranges the modulus was determined on the basis of coherence values between systolic finger blood pressure amplitude and heart

rate variation above 0.50. Mulder (1988) was able to show that the modulus within the mid-frequency band expresses the momentary gain of baroreflex sensitivity (Robbe *et al.* 1987, Honzikova *et al.* 1992). Several groups have confirmed the validity of non-invasively assessed baroreflex sensitivity compared with the more traditional tests (Ewing 1978, Various 1996) such as the phenylephrine method (Robbe *et al.* 1987).

A salivary cortisol profile was established on the day following testing. Subjects were asked to gather a saliva sample immediately after waking up (usually 0645 h), 20 min later, and then again at 0730 and 0930 h. All samples were stored in a refrigerator and were analyzed after termination of the study. The measurements were performed by HPLC using internationally standardized procedures (Miki *et al.* 1998). To represent the individually secreted amount of cortisol (Peeke & Chrousos 1995, Rosmond *et al.* 1998), the resulting area under the curve (AUC) of the morning values ($n=4$, from waking to 0930 h) was taken and expressed as a concentration. This procedure is valid for both sexes (Pasquali *et al.* 1998).

Data transformation and statistical analysis

Values were calculated for resting and mental stress phase respectively. Statistical analyses were performed with a PC-based SAS package. As a consequence of our research design, correlative statistics are considered to fulfill the optimal use of variance in the data sets. In order to account for possible skewness of data, Spearman rank-order coefficients were calculated.

Results

Descriptive statistics

Basic values and patient characteristics are presented in Table 1.

Beside the expected group differences, the only significant difference concerns the age of male and female subjects ($t=2.03$; $P=0.05$). Using the same descriptive approach, Table 2 presents blood pressure data, spectral power values and moduli for both experimental phases.

It must be noted that no significant differences in mean values of spectra between women and men were discernible. Equally, no differences were noted in spectral values of pre- and postmenopausal women. The respective values for pre- and postmenopausal women (all with age partialled out) were for systolic blood pressure 120.1 ± 13.4 and 129.7 ± 18.7 mmHg ($P=NS$), for diastolic pressure 79.8 ± 7.9 and 86.0 ± 7.4 mmHg ($P=NS$), for resting heart rate mid-frequency band 1372 ± 1994 and 337 ± 196 ($P=NS$), for resting heart rate high-frequency band 2162 ± 2341 and 396 ± 245 ($P<0.05$), and for the modulus 9.6 ± 6.4 and 5.1 ± 4.8 ($P<0.05$). For the mental stress testing the values were for the mid-frequency band

Table 1 Mean values of age, size and parameters reflecting obesity for the whole group, separated for males and females, and for the three weight cohorts (mean \pm S.D.)

	Whole sample (n=42)	Sex		Weight cohort (kg/m ²)		
		Female (n=24)	Male (n=18)	27–33 (n=17)	33–40 (n=13)	>40 (n=12)
Age (years)	42.7 \pm 9.3	44.2 \pm 8.2	40.7 \pm 10.6	45.3 \pm 9.1	42.6 \pm 9.2	39.3 \pm 9.8
Weight (kg)	112.9 \pm 37.3	102.6 \pm 29.3	126.6 \pm 42.8	85.3 \pm 11.1	110.1 \pm 9.3	155.0 \pm 42.5
Height (cm)	171.6 \pm 9.3	165.5 \pm 6.7	179.6 \pm 5.5	168.3 \pm 9.8	174.2 \pm 10.3	172.5 \pm 7.0
BMI (kg/m ²)	38.0 \pm 11.2	37.1 \pm 8.8	39.3 \pm 14.0	29.9 \pm 1.6	36.3 \pm 2.3	51.6 \pm 12.3
Waist circumference (cm)	113.8 \pm 21.2	106.4 \pm 15.6	123.3 \pm 23.9	97.1 \pm 8.6	114.6 \pm 5.8	130.0 \pm 21.7
Hip circumference (cm)	123.9 \pm 20.7	124.3 \pm 17.4	123.3 \pm 24.9	109.8 \pm 8.4	119.1 \pm 6.2	149.8 \pm 19.2
WHR	0.92 \pm 0.09	0.86 \pm 0.05	1.0 \pm 0.06	0.88 \pm 0.09	0.96 \pm 0.07	0.92 \pm 0.09
Salivary cortisol AUC (μ g/dl/3 h)	24.2 \pm 10.9	25.3 \pm 11.5	22.3 \pm 10.3	26.5 \pm 13.5	25.1 \pm 9.0	19.1 \pm 7.7

514 \pm 816 and 235 \pm 220 (P =NS), for the high-frequency band 362 \pm 408 and 121 \pm 111 (P =NS), and for the modulus 4.8 \pm 2.5 and 5.1 \pm 4.8 (P =NS).

Correlative statistics

For the whole group of patients Spearman rank-order correlations were calculated between parameters reflecting obesity and indices of autonomic cardiovascular regulation and cortisol secretion. Table 3 presents the resulting coefficients for the whole sample.

Since age has known effects on autonomic cardiovascular regulation and was found to differ between male and female subjects, the influence of age was partialled out. Thereby, however, no significant changes to the former results were discernible. In order to highlight

aberrations in reactivity, difference measures of autonomic regulation indices between test phases were included as well.

Mid-frequency values were negatively correlated with BMI and waist/hip ratio (WHR) and reached significance at rest and in response to mental challenge for BMI and for WHR at rest. The high-frequency band, which represents autonomic parasympathetic tone, was negatively correlated with various indices of obesity. This effect was most pronounced when subjects were mentally challenged. This picture is completed by the finding of lower baroreflex sensitivity values concurrent with increasing body mass in resting conditions and mental challenge. Aspects of reactivity to stress were covered by difference values. Here the mid-bands came up with significant negative correlations with increasing body mass (see Fig. 1).

Table 2 Mean values of blood pressure, spectral power values (squared modulation indices) for mid- and high-frequency bands, and estimates of baroreflex sensitivity at rest and when mentally challenged (Bonn-Det), as well as difference values between experimental phases separated for males and females, and for the three weight cohorts (mean \pm S.D.)

	Whole sample (n=42)	Sex		Weight cohort (kg/m ²)		
		Female (n=24)	Male (n=18)	27–33 (n=17)	33–40 (n=13)	>40 (n=12)
Blood pressure, systolic (mmHg)	124.6 \pm 14.4	123.7 \pm 15.9	126.1 \pm 12.2	121.6 \pm 10.0	122.9 \pm 12.6	130.8 \pm 21.2
Blood pressure, diastolic (mmHg)	81.5 \pm 9.8	82.1 \pm 8.2	80.7 \pm 12.0	80.4 \pm 9.1	80.4 \pm 9.1	84.0 \pm 12.0
Rest						
Mid-band	948 \pm 1578	978 \pm 1678	911 \pm 1487	957 \pm 1398	1431 \pm 2268	413 \pm 439
High-band	1634 \pm 3009	1489 \pm 2075	1819 \pm 3958	2164 \pm 4169	1685 \pm 2541	873 \pm 1062
Modulus	7.1 \pm 5.8	7.6 \pm 6.0	6.4 \pm 5.7	6.9 \pm 5.3	8.9 \pm 7.2	5.2 \pm 4.4
Mental challenge						
Mid-band	417 \pm 621	405 \pm 656	433 \pm 592	346 \pm 328	696 \pm 980	210 \pm 252
High-band	254 \pm 351	268 \pm 342	237 \pm 371	198 \pm 176	438 \pm 553	129 \pm 100
Modulus	4.3 \pm 2.7	4.4 \pm 2.6	4.3 \pm 3.0	4.6 \pm 2.1	5.5 \pm 2.8	2.7 \pm 2.9
Difference (rest – mental challenge)						
Mid-band	531 \pm 1218	572 \pm 1077	477 \pm 1409	611 \pm 1128	735 \pm 1769	203 \pm 268
High-band	1379 \pm 2906	1221 \pm 1789	1582 \pm 3956	1965 \pm 4129	1246 \pm 2231	743 \pm 1031
Modulus	2.7 \pm 4.7	3.1 \pm 4.9	2.0 \pm 4.5	2.3 \pm 4.1	3.3 \pm 6.1	2.4 \pm 3.9

Table 3 Spearman rank-order correlation coefficients between parameters of obesity and indices of autonomic cardiovascular regulation and of cortisol secretion in the two experimental phases as well as for difference measures for the whole sample of patients ($n=42$) with age partialled out

	BMI	WHR	Waist (cm)
Rest			
Mid-band	-0.48***	-0.33*	-0.44**
High-band	-0.21	-0.34*	-0.14
Modulus	-0.35*	-0.28	-0.43**
Mental challenge			
Mid-band	-0.42**	-0.15	-0.29
High-band	-0.30*	-0.18	-0.24
Modulus	-0.53***	-0.08	-0.47**
Difference (rest - mental challenge)			
Mid-band	-0.33*	-0.34*	-0.23
High-band	-0.12	-0.27	-0.10
Modulus	-0.11	-0.34*	-0.00
Cortisol secretion	-0.24	-0.25	-0.34*

* $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Parasympathetic withdrawal in this instance was apparent, albeit not to a significant degree, and only WHR was correlated with diminished baroreflex functioning.

The amount of cortisol secretion in the morning hours was inversely correlated with increasing waist circumference ($r = -0.34$, $P = <0.05$).

Discussion

The main goal of the study was to detect changes of autonomic cardiovascular regulation in obesity. An increase in body weight was expected to accompany higher sympathetic activation. However, on the basis of 42

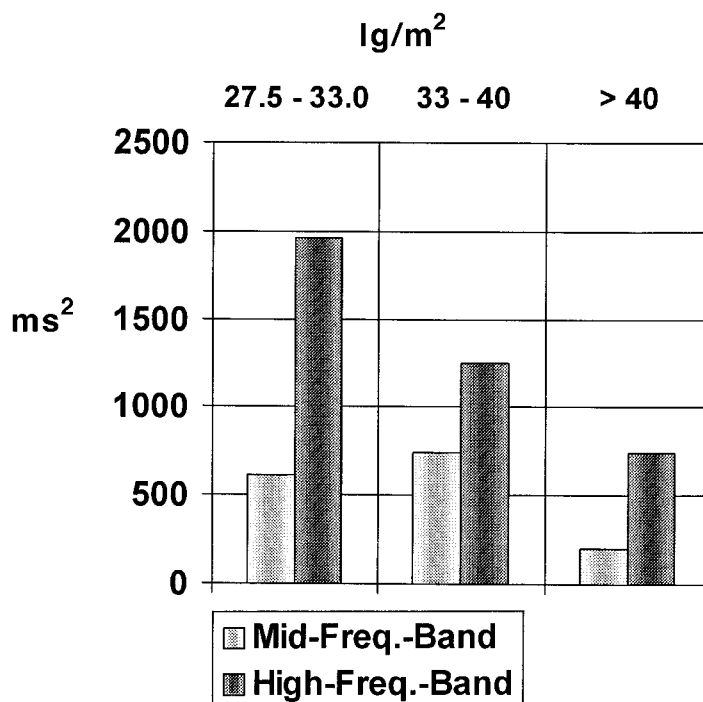


Figure 1 Difference values of mid- and high-frequency bands in obese patients of different weight classes.

patients who have an excess BMI of 28–83 kg/m² the hypothesis of heightened sympathetic activity could not be substantiated. Nevertheless, several aspects within the emerging pattern of correlations seem worthy of note. The correlation coefficients of the mid-frequency band – reflecting a mixture of sympathetic and parasympathetic tone – are negatively correlated with BMI and WHR reaching significance at rest for WHR and additionally during mental stress for BMI. The high-frequency band, which represents autonomic parasympathetic tone, is again negatively correlated with BMI for resting conditions and with WHR for mental stress. Obviously, an increase in body weight decreases both sympathetic and parasympathetic activity. This effect is most pronounced when mentally stressed, pointing to an aggravation of parasympathetic withdrawal under stress conditions. Higher sympathetic drive, on the basis of these data, does not accompany an increase in body mass. This finding is clearly against the expectation evolving from animal studies (Scheurink *et al.* 1996). Whereas it might be difficult to define the different parts in mid-frequency which are associated with either sympathetic or parasympathetic activity, a lower or possibly higher sympathetic tone that is exerted might not have a detrimental effect, but might cause a deficit in parasympathetic counter-regulation which is obviously particularly pronounced under stressful circumstances. This picture is completed by the finding of lower values of baroreflex sensitivity which appear with increasing body mass. Here again mental stressing seems to affect baroreflex functioning in a more pronounced fashion. Aspects of the reactivity to stress are covered by difference values. There is a significantly negative relationship between the mid-bands and an increasing BMI. Due to the way differences were calculated (resting values minus mental stress values, with resting values being higher than stress values), the resulting correlation coefficients express diminished autonomic tone to mental stress testing. The extent of the parasympathetic withdrawal is statistically not significant in this instance, and only WHR is correlated significantly with diminished baroreflex functioning. There was a negative correlation between cortisol values and waist circumference, indicating a decrease with growing abdominal obesity. Again sympathetic reactivity was found to diminish with growing body mass (see Fig. 1).

Some of the researchers who used the same methodology found similar results. Piccirillo *et al.* (1996), for instance, reported findings equivalent to ours. In their study obesity was found to be associated with decreased sympathetic responsiveness. Similarly, Peterson *et al.* (1988) reported an inverse correlation of sympathetic and parasympathetic activity with increasing percentages of body fat whereas Rossi *et al.* (1989) could not find any differences in sympathetic functions. Also, Zahorska-Markiewicz *et al.* (1993) noted an overreactivity of the sympathetic nervous system, but depression in para-

sympathetic activity – the latter in accord to our study and reported by others as well.

Another interesting finding was the decrease in parasympathetic power with growing body weight, BMI and WHR. Decreased parasympathetic activity has also been reported by Aronne *et al.* (1995) and Rossi *et al.* (1989). In a study on weight gain Hirsch *et al.* (1991) described an inverse relationship with the amount of weight gain which leads to lower parasympathetic power.

The novel finding of diminished baroreceptor function (i.e. resistance of the baroreceptor) with increasing weight may lead to intriguing speculations about similarities of the ANS to other organ systems that are involved in obesity. Arterial hypertension (Egan 1991) contributing to insulin resistance and the links between insulin sensitivity and fat metabolism (Dowling *et al.* 1995, Macor *et al.* 1997) closely relate to central obesity, known to be an additional risk factor in cardiovascular death (Gao *et al.* 1996, Scheurink *et al.* 1996). Gaining weight combines regularly with metabolic changes revealing adaptation processes towards ‘resistance’ of feedback loops involved especially in organ systems ensuring supply and utilization of energy. In addition, it has been argued that the hyperactivation of the stress axis involved in obesity is associated with a lower survival in obese patients (Peeke & Chrousos 1995) but may over time lead to lower salivary cortisol levels (i.e. ‘resistance’) (Rosmond & Bjorntorp 1998), as was found in this study. Our findings and similar results from other studies point out the importance of lowered parasympathetic activity known to exert deleterious effects on metabolism, psychosocial functioning, and survival in obese patients (Bjorntorp 1997). This applies also for normo-weight patients, especially when they suffer from diabetes mellitus (Claus *et al.* 1994, Laederach-Hofmann *et al.* 1999b).

Limitations

The different findings of activities of sympathetic or parasympathetic influences might question the reliability of the mid-frequency band as a sympathetic indicator. We agree with the Task Force report (Various 1996) and with Berntson *et al.* (1997), both of which showed that sympathetic contribution is mixed with mainly parasympathetic and other influences. Nevertheless it seems important to note decreased sympathetic and parasympathetic activity with growing body weight as we have reported in this study. We postulate that the results of this study are reliable due to an absence of secondary diagnoses that might have had a confounding influence. Equally, the possible influences of breathing depth have to be kept in mind. From the mathematical point of view it is obvious that depth of breathing (which was not different in our groups) can not have any influence on the spectral values (Lane *et al.* 1992). The breathing cycles have not been traced by a breathing volume tracer (e.g. Resptrace).

Therefore an approximation was calculated including the s.d. of breathing frequency. The respective values in s.d. were +21.3 for resting and +22.4 for mental stress phases. The ratio between resting and mental stress testing phases in s.d. can be taken as a representation of alterations in the breathing depth within each subject as well as between subjects. The calculated Spearman correlations showed no significance even when the breathing frequency changed (26.2 ± 6.7 in resting and 34.7 ± 7.9 in mental stress testing). However, in several disease states, especially when the breathing pattern is clearly abnormal (e.g. as in sleep apnea syndrome) an influence of depth of breathing on spectral values (mainly on mid-band frequency) has been reported by Khoo *et al.* (1999). In our patients, there has not been traced any abnormal breathing pattern in this respect to breathing depth or frequency. Therefore we assume that our differences found between the three weight cohorts must be a specific finding related to obesity and its physiological alterations.

In conclusion the important alterations of ANS function depending on weight are a promising avenue to conduct long-term studies on weight loss and weight gain.

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