Changes in Sympathetic Nervous System Activity in Male Smokers After Moderate-Intensity Exercise

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OBJECTIVE: To investigate the effects of moderate-intensity exercise on the sympathetic nervous system in male smokers. METHODS: Twenty-eight men (14 smokers and 14 non-smokers, ages 21–46 y) were recruited. The activity of the autonomic nervous system was measured by power spectral analysis of heart rate variability. Spectral power in the frequency domain was quantified by integrating the area under the curve of the very-low-frequency power (0.007–0.035 Hz), low-frequency power (0.035–0.15 Hz), high-frequency power (0.15–0.5 Hz), and total power (0.007–0.5 Hz) bandwidths. We assessed heart rate, thermoregulatory sympathetic nervous system activity (very-low-frequency power/total power), sympathetic nervous system activity (low-frequency-power/high-frequency power or [very-low-frequency power + low-frequency power]/high-frequency power), and parasympathetic nervous system activity (high-frequency power/total power) of the smokers before and after moderate-intensity exercise. RESULTS: The smokers exhibited a greater degree of sympathetic nervous system activity (as quantified by very-low-frequency power/total power). The sympathetic nervous system activity of smokers (as indicated by [very-low-frequency power + low-frequency power]/high-frequency power) also showed a tendency to increase after exercise. Parasympathetic activity, as indicated by high-frequency power/total power, reduced after exercise in the smokers. These findings are contrary to findings previously reported in obese subjects. CONCLUSIONS: Increased sympathetic nervous system activity, including thermoregulatory activity, might contribute to cachexia in smokers. *Key words: smoker; exercise; heart rate variability; autonomic responsiveness; power spectral analysis; very-low-frequency power; sympathetic nervous system activity; cachexia.* [Respir Care 2013;58(11):1892–1898. © 2013 Daedalus Enterprises]

Introduction

Cachexia is a complex metabolic syndrome characterized by loss of muscle, with or without loss of fat mass, and is most often associated with underlying illness.[1] Many patients with chronic and end-stage diseases, including infection, cancer, and congestive heart failure, demonstrate nutritional changes characteristic of cachexia.[1,2] Patients in the early stages of COPD also display systemic features such as reduced fat mass,[3] muscle loss, and skeletal muscle wasting.[4,5] The pathogenesis of these features is complex and may result from multiple factors, including energy imbalance, disuse atrophy, and systemic inflammation.[6] Furthermore, cigarette smoking, which is a major risk factor for COPD, cancer, and congestive heart failure,[7] has been linked to reductions in body weight and body mass index.[8] These effects are thought to be due to increased energy expenditure and a reduction in appetite.[8] Thus, cigarette smoking may be associated with weight loss even before the development for COPD or other pathologies.

Energy expenditure antagonizes the activity of the autonomic nervous system, which controls the heart rate and rhythm. The R-R interval, also known as the inter-beat interval, is determined by the net effect of sympathetic and

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parasympathetic inputs, and can be measured via electrocardiogram. Spectral analysis of heart-rate variability has gained general acceptance as an indicator of autonomic nervous system function.[9] Power spectral analysis of heart-rate variability has demonstrated at least 2 distinct regions of periodicity within the electrocardiogram R-R interval: high-frequency power (> 0.15 Hz), which solely reflects parasympathetic nervous system activity, and low-frequency power (< 0.15 Hz), which is dually mediated by sympathetic nervous system and parasympathetic nervous system activity.[9]

Previous studies using power spectral analysis have demonstrated that inactivity of the autonomic nervous system, particularly the sympathetic nervous system, may indicate a risk of future weight gain and development of obesity.[10] Furthermore, recent obesity studies have suggested that very-low-frequency power (0.007–0.035 Hz) of heart-rate variability is selectively lowered in obese individuals, in response to several thermogenic perturbations such as acute cold exposure and food intake.[11,12] That research demonstrated that spectral analysis of very-low-frequency power of heart-rate variability is a means of evaluating energy metabolism and thermoregulatory sympathetic nervous system function in humans.

To our knowledge, the effect of moderate-intensity exercise on the very-low-frequency power of heart-rate variability has not previously been investigated in smokers. The primary objective of this study was to evaluate, via power spectral analysis of heart-rate variability, the very-low-frequency activity of heart-rate variability in smokers and non-smokers after moderate-intensity exercise. We hypothesized that smokers would display continual hyperactive very-low-frequency power of heart-rate variability.

QUICK LOOK

Current knowledge

Cachexia is a complex metabolic syndrome characterized by muscle loss, with or without loss of fat mass, and is associated with underlying illnesses such as COPD.

What this paper contributes to our knowledge

Smokers had a greater degree of sympathetic nervous system activity than non-smokers. Increased sympathetic nervous system activity, including thermoregulatory activity, may contribute to cachexia in smokers.

Methods

The ethics board of Kio University and the hospital ethics committee of Tsu Seikyou Hospital approved the study protocol. Written informed consent was obtained from all subjects.

Subjects

Height- and weight-matched male non-smokers ($n = 14$) and smokers ($n = 14$) between the ages of 21 and 46 years were recruited for the study. In previous studies, autonomic nervous system activity was found to vary with body type.[10-12] Therefore, we matched body types among the subjects to isolate the effects of cigarette smoking. The smokers were asked about the duration and frequency of their smoking. The weight and fat-free mass of each subject were measured with a bioelectrical impedance analyzer (InnerScan 50V, Tanita, Tokyo, Japan). Body mass index and fat-free mass index were calculated as body weight/height^2 and fat-free mass/height^2, respectively. Subject demographics are presented in Table 1. Members of both the smoking and non-smoking groups were in good health and had no evidence of hypertension, cardiovascular disease, diabetes mellitus, or other disease. Every subject kept regular hours at the university and/or at jobs. None of the subjects reported engaging in regular exercise. Each subject was instructed to avoid alcohol, coffee, and tea, and to fast for 8 hours preceding the study, to reduce the effects of alcohol, caffeine, and food on the autonomic nervous system. None of the subjects reported a history of heavy drinking, a habit of staying up late, or engaging in extreme exercise the day before the study. Subjects who smoked were asked to abstain from smoking for 8 hours before the study, to limit the acute effects of smoking, such as increased heart rate, on the measurements.[13,14] The continuous exercise load used in this study was determined using the Karvonen formula, so that the increased heart rate would place the same load on the bodies of smokers and non-smokers. On the day of the study the subjects stayed in a quiet, comfortable room with minimal stimuli from 2:00 PM to 6:00 PM. This period of the day was chosen to reduce the effects of the circadian rhythm on autonomic nervous system activity. In accordance with previous studies,[11,12] the temperature and humidity of the room were strictly regulated (see Table 1), and all subjects were dressed uniformly in T-shirts and shorts, made of the same material.

Experimental Procedures

Subjects were seated in comfortable chairs and allowed to rest for at least 20 min before the start of the experiment. Each subject breathed in time with a metronome set at 15 beats/min, to ensure that respiratory-linked variations in heart rate did not interfere with low-frequency (< 0.15 Hz) heart rate fluctuations from other sources.

Table 1. Subject Demographics

	Non-Smokers $n = 14$	Smokers $n = 14$
Age, y	28.3 ± 7.2	27.6 ± 6.8
Height, cm	168.3 ± 6.9	170.9 ± 6.4
Weight, kg	65.43 ± 9.98	63.65 ± 8.95
Body mass index, kg/m^2	23.0 ± 2.5	21.7 ± 2.8
Fat-free mass, kg	50.51 ± 6.37	49.26 ± 5.09
Fat-free mass index, kg/m^2	17.8 ± 1.4	16.8 ± 1.3
Room temperature, °C	24.4 ± 1.5	24.0 ± 0.7
Humidity, %	45.6 ± 4.3	44.3 ± 1.6
Smoking history		
Duration, y		8.8 ± 6.5
Cigarettes per day		10.8 ± 7.5
Pack-years		6.3 ± 9.9
Blood pressure, mm Hg		
Systolic	121.3 ± 7.1	116.9 ± 8.7
Diastolic	75.9 ± 8.0	69.7 ± 6.7

Values are mean ± SD.
Blood pressure was measured before exercise.
The only significant differences between the groups were in duration of cigarette smoking, cigarettes per day, and pack-years.

The breathing frequency was regulated for 10 min before the exercise commenced, and during the recovery period. The regulation of respiration prevented placing a substantial load on the subject during the exercise period. The recovery period lasted for 30 min after exercise. The target heart rate for the continuous exercise load was set using the Karvonen formula:

$$(\text{Maximum heart rate} - \text{at-rest heart rate}) \times 60\% \text{ intensity} + \text{at-rest heart rate}$$

The intensity level was set at 60% of the estimated maximal heart rate, which was calculated as (220 – age). Moderate-intensity exercise was performed on a bicycle ergometer (Combi, Tokyo, Japan), and consisted of pedaling at 60 revolutions/min. The initial power output was 25 W. The subjects achieved 60% intensity within 5 min, and the exercise was continued at this intensity for another 15 min. Heart rate was continuously measured using a sports heart rate meter (S801i, Polar Electro, Kempele, Finland).

R-R Interval Power Spectral Analysis

Periodic components of heart-rate variability tend to aggregate within several frequency bands.[9] Autonomic nervous system activity can therefore be measured noninvasively by heart-rate variability power spectral analysis, which deconstructs a series of sequential R-R intervals into a sum of sinusoidal functions of different amplitudes and frequencies, via the Fourier transform algorithm. In the present investigation, 3 frequency components of heart-rate variability were detected and analyzed. This approach has been used in basic medical science to assess a diverse range of conditions, and its validity and reliability have been confirmed in the literature.[11,12] The spectral powers in frequency domains were quantified by integrating the area under the curve for the following bandwidths: very-low-frequency power (0.007–0.035 Hz), reflecting energy metabolic and thermoregulatory sympathetic function; low-frequency power (0.035–0.15 Hz), reflecting both sympathetic nervous system and parasympathetic nervous system activity; high-frequency power (0.15–0.5 Hz), which solely reflects parasympathetic nervous system activity; and total power (0.007–0.5 Hz), which represents overall autonomic nervous system activity.[11,12] Thermoregulatory sympathetic nervous system activity was calculated as very-low-frequency/total. Sympathetic nervous system activities was calculated as low-frequency/high-frequency and (very-low-frequency + low-frequency)/high-frequency ratio. Parasympathetic nervous system activity was calculated as high-frequency/total.

The pre-exercise rest period was 5 min, and the post-exercise recovery period was 30 min, which we analyzed in 5-min stages: 5–10 min post-exercise, 10–15 min post-exercise, 15–20 min post-exercise, 20–25 min post-exercise, and 25–30 min post-exercise. The segments provide a direct view of time-series changes in autonomic nervous system activity. We did not analyze data from the 5-min period immediately following exercise.

Statistical Analysis

Data analysis was performed using statistics software (SPSS 19.0, SPSS Chicago, Illinois). Differences between groups were analyzed by comparing the heart rate, very-low-frequency/total, low-frequency/high-frequency, (very-low-frequency + low-frequency)/high-frequency, and high-frequency/total for the 6 time periods. The data distribution was analyzed with the Kolmogorov-Smirnov test. The heart rate, very-low-frequency/total, low-frequency/high-frequency, (very-low-frequency + low-frequency)/high-frequency, and high-frequency/total values were compared with the Mann-Whitney U test, because these data were not normally distribution. The results of these analyses were consistent in all cases. Data are expressed as median (minimum–maximum). Statistical significance was defined as $P < .05$.

Results

Figure 1 and Table 2 show the heart rate and power values. The very-low-frequency/total values were signifi-

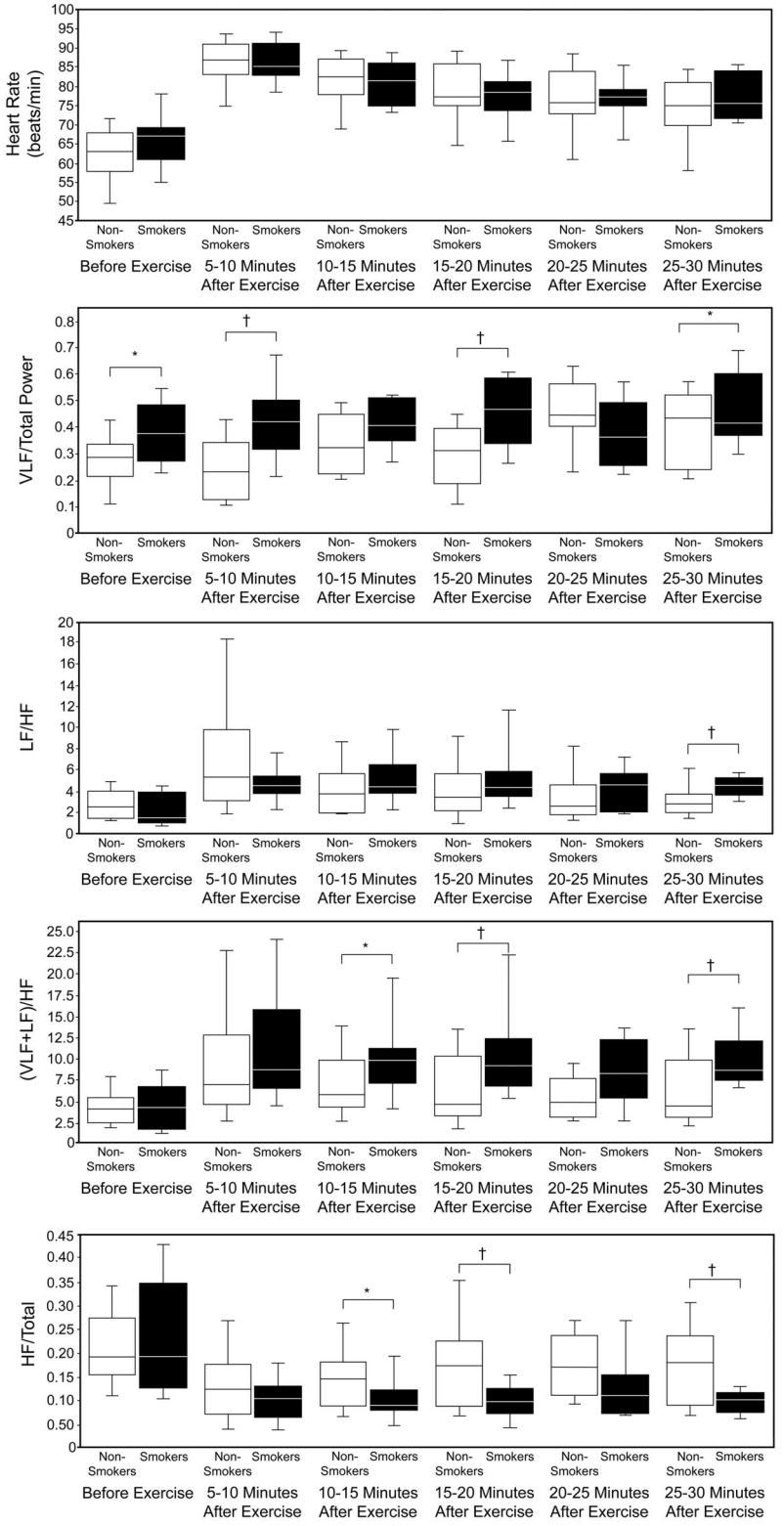

Fig. 1. Heart rate, ratio of the very-low-frequency (VLF) power component to the total power, ratio of the low-frequency (LF) power component to the high-frequency (HF) power component, ratio of (VLF + LF) to the HF power component, and ratio of the HF power component to total power. In the data bars the horizontal line represents the median, the tops and bottoms of the bars represent the first and third quartiles, and the whisker bars represent the 10th and 90th percentiles. The test periods were analyzed with the Mann-Whitney U test: * $P < .10$, † $P < .05$.

Table 2. Comparison of Combined Heart Rate Variability in Non-Smokers and Smokers Over the Course of 6 Time-Periods

	Non-Smokers Median (min–max)	Smokers Median (min–max)	P*
Heart rate, beats/min			
Before exercise	63.0 (47–76)	66.5 (50–79)	.32
5–10 min after exercise	87.0 (66–110)	85.0 (75–98)	.96
10–15 min after exercise	85.5 (60–103)	81.5 (68–96)	.78
15–20 min after exercise	77.5 (53–101)	78.5 (66–93)	.98
20–25 min after exercise	76.0 (53–94)	77.0 (58–91)	.73
25–30 min after exercise	75.0 (50–99)	75.5 (70–92)	.55
Low-frequency/high-frequency			
Before exercise	2.55 (0.87–6.71)	1.57 (0.60–6.47)	.36
5–10 min after exercise	5.28 (1.73–18.58)	4.62 (1.87–17.10)	.61
10–15 min after exercise	3.78 (1.65–10.50)	5.22 (2.25–12.38)	.12
15–20 min after exercise	3.44 (0.88–11.10)	4.37 (2.35–12.42)	.18
20–25 min after exercise	2.64 (1.21–8.62)	4.67 (1.72–10.92)	.15
25–30 min after exercise	2.80 (1.46–10.76)	4.70 (2.77–9.26)	.01
High-frequency/total			
Before exercise	0.19 (0.09–0.36)	0.20 (0.06–0.43)	.78
5–10 min after exercise	0.12 (0.03–0.30)	0.10 (0.03–0.18)	.25
10–15 min after exercise	0.15 (0.07–0.32)	0.09 (0.05–0.22)	.09
15–20 min after exercise	0.18 (0.05–0.39)	0.10 (0.31–0.18)	.02
20–25 min after exercise	0.17 (0.08–0.28)	0.11 (0.04–0.29)	.12
25–30 min after exercise	0.18 (0.05–0.31)	0.10 (0.03–0.13)	.048
Very-low-frequency/total			
Before exercise	0.29 (0.09–0.62)	0.38 (0.22–0.56)	.09
5–10 min after exercise	0.24 (0.05–0.50)	0.43 (0.18–0.86)	.005
10–15 min after exercise	0.33 (0.16–0.58)	0.41 (0.10–0.55)	.13
15–20 min after exercise	0.31 (0.10–0.48)	0.47 (0.18–0.63)	.005
20–25 min after exercise	0.36 (0.12–0.56)	0.37 (0.21–0.64)	.46
25–30 min after exercise	0.28 (0.07–0.68)	0.42 (0.29–0.70)	.054
(Very-low-frequency + low-frequency)/high-frequency			
Before exercise	4.23 (1.82–9.72)	4.14 (1.30–15.47)	.78
5–10 min after exercise	7.10 (2.31–37.18)	8.72 (4.45–35.07)	.25
10–15 min after exercise	5.89 (2.18–14.03)	9.82 (3.58–19.54)	.09
15–20 min after exercise	4.66 (1.55–17.90)	9.10 (4.65–31.30)	.02
20–25 min after exercise	4.90 (2.54–11.00)	8.19 (2.45–22.50)	.12
25–30 min after exercise	4.55 (2.26–19.73)	8.64 (6.61–33.22)	.048

* *P* values via Mann-Whitney U test.

cantly higher in the smokers during the 5–10-min post-exercise period ($P = .005$) and the 15–20-min post-exercise period ($P = .005$). The low-frequency/high-frequency value was significantly higher in the smokers during the 25–30-min post-exercise period ($P = .01$). The (very-low-frequency + low-frequency)/high-frequency values were significantly higher in the smokers during the 15–20-min post-exercise period ($P = .02$) and the 25–30-min post-exercise period ($P = .048$). The high-frequency/total value was significantly lower in the smokers in the 15–20-min post-exercise period ($P = .02$) and the 25–30-min post-exercise period ($P = .048$). The very-low-frequency/total value in the pre-exercise period and the 25–30-min post-exercise period, and the (very-low-frequency + low-frequency)/high-frequency value in the 10–15-min post-exercise period were higher in the smokers. And the high-frequency/total value in the 10–15-min post-exercise period was lower in the smokers. None of the other measured parameters differed significantly.

Discussion

After moderate-intensity exercise, the very-low-frequency/total and (very-low-frequency + low-frequency)/high-frequency values were higher, and the high-frequency/total value was lower in the smokers than in non-smokers with identical exercise loads. In addition, the very-low-frequency/total value before exercise and the low-frequen-

cy/high-frequency value were higher in the smokers. These findings are contrary to those previously reported for obese subjects.[11,12] Exercise in smokers may thus induce excessive increases in sympathetic nervous system activity, including thermoregulatory sympathetic nervous system activity.

The very-low-frequency activity of thermoregulatory sympathetic function reflects lipid metabolism. In obese individuals, very-low-frequency activity does not increase after thermogenic perturbations,[11,12] and can be altered through dietary modification and exercise training.[15,16] Very-low-frequency activity is associated with mutations in uncoupling proteins and β_3-adrenergic receptors within adipose tissue.[17,18] The activation of uncoupling proteins 1, 2, and 3, which are located in white adipose tissue, brown adipose tissue, and skeletal muscle, respectively, converts energy from the substrate into heat without using adenosine triphosphate.[19] Thermoregulatory sympathetic nervous system activity significantly correlates with plasma leptin concentration.[20] Thus, our results suggest that the elevated very-low-frequency/total in smokers reflects increased thermoregulatory sympathetic nervous system activity, both before and after exercise, which may over-stimulate the catabolism of fat in adipose tissue.

The changes we observed in very-low-frequency/total, low-frequency/high-frequency, (very-low-frequency + low-frequency)/high-frequency, and high-frequency/total in smokers persisted for 30 min after exercise. These changes affect the sympathetic nervous system via metaboreflex, baroreflex, and central command.[21] In a previous study, smokers had higher resting energy expenditure, mediated by caffeine as a thermogenic perturbation.[22] Caffeine and nicotine during casual physical activity increase energy expenditure in smokers.[23] Analysis of expired gas has revealed that the total thermic response of smokers is significantly greater than that of non-smokers over a period of 4–24 hours.[24,25] Normal-weight smokers have a higher energy expenditure at rest for 30 min after smoking than do obese smokers.[26] Therefore, the already over-activated sympathetic nervous system in normal-weight smokers may be further activated in very-low-frequency/total, low-frequency/high-frequency, and (very-low-frequency + low-frequency)/high-frequency by exercise.

These findings are clinically important. We deduce that the sympathetic nervous system of smokers may mobilize against adipose tissue, triggering cachexia when calorie intake is deficient. Elevation of the hypothalamic-sympathetic nervous system by leptin occurs indirectly, through oxidation of fatty acids in muscle.[27] Smokers also experience muscle wasting[28] and loss of type-1 muscle fibers.[29] Furthermore, weight loss, including cachexia, is associated with increased morbidity and mortality.[5,30,31] Thus, normal-weight smokers may benefit from anti-smoking measures to prevent weight loss.

These changes in autonomic nervous system activity are presumably due to the action of nicotine. Subjects in this study abstained from cigarette smoking for 8 hours to limit the acute effects of cigarette smoking. No significant differences were observed in the heart rate or low-frequency/high-frequency values between smokers and nonsmokers during any of the 6 time periods. This observation demonstrates that the acute effects of cigarette smoking were absent in these subjects. However, the effects of nicotine persist for at least 6 hours after cessation of smoking.[14] Nicotine activates sympathetic neurotransmission by inducing the release of ganglion catecholamine from postganglionic nerve endings.[32] In the present study, the low-frequency/high-frequency value in the 5–10-min post-exercise period was lower in the smokers, with an increase in the very-low-frequency/total value. The sympathetic nervous system activity (very-low-frequency/total and [very-low-frequency + low-frequency]/high-frequency) of smokers remained elevated throughout the post-exercise period. Thus, the thermoregulatory sympathetic nervous system value in smokers may be more sensitive to nicotine than the low-frequency/high-frequency value.

Limitations

First, we did not conduct all the tests at the same room temperature and humidity. Temperature and humidity do play a role in autonomic nervous system activity, so inconsistencies may be present in the results. Second, we did not directly measure lipid metabolism and cannot conclusively say that thermoregulatory sympathetic nervous system activity corresponds to lipid metabolism. To compensate, we used only healthy subjects with normal weight. Future studies should include subjects with cachexia, semi-starvation condition, or muscle atrophy. Additionally, metabolic and nutritional studies are required to confirm the relationship between sympathetic nervous system activity, body weight, and metabolic profiles.

Conclusions

Exercise induced hyperactivity of the sympathetic nervous system (thermoregulatory sympathetic nervous system and [very-low-frequency + low-frequency]/high-frequency) in smokers. Furthermore, the high-frequency/total value did not return to the pre-exercise level after exercise in smokers. This sympathetic nervous system hyperactivity in smokers may over-stimulate fat catabolism in adipose tissue over an extended period and trigger cachexia.

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