Intralipid Infusion Combined With Propranolol Administration Has Favorable Metabolic Effects in Elderly Malnourished Cancer Patients

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Previous studies have shown that an elevated basal metabolic rate (BMR) is present in elderly malnourished cancer patients. A possible dysfunction of the autonomic nervous system needs to be demonstrated. In aged weight-losing cancer patients (n = 40), aged non–weight-losing cancer patients (n = 30), and aged weight-losing noncancer patients (n = 18), the baseline BMR and heart rate variability were studied. Aged weight-losing cancer patients (n = 40) underwent bioimpedance analysis, ambulatory electrocardiographic monitoring with analysis of heart rate variability, and determination of the BMR. Then, the patients received infusion of Intralipid (Pharmacia, Uppsala, Sweden) without and with propranolol (6 days of 40 mg twice daily) administration. At baseline, a simple correlation between the BMR and the low-frequency component (LF) ($r = .42$, $P < .006$) and LF to high-frequency (HF) ratio ($r = .51$, $P < .001$) was found. After propranolol administration, the percent decline in the BMR was significantly correlated with the percent decline in the LF ($r = .39$, $P < .01$) and LF/HF ratio ($r = .53$, $P < .001$). The percent decline in the BMR was not correlated with the HF ($r = .13$, $P < .34$) or the plasma noradrenaline concentration ($r = .21$, $P < .20$) at any time. With regard to the BMR and substrate oxidation, 6-day propranolol administration plus Intralipid infusion produced the strongest decline in the BMR. This study demonstrates that autonomic nervous system dysfunction occurs and is responsible for the elevated BMR in elderly cancer patients, propranolol administration rectifies the autonomic dysfunction, and Intralipid infusion combined with propranolol administration is useful for enhancing the daily caloric intake without a strong increase in energy expenditure.

WEIGHT LOSS FREQUENTLY OCCURS in late-stage cancer patients as a consequence of elevated energy expenditure associated with poor energy intake. The reason that cancer patients have cachexia is still debated. An elevated basal metabolic rate (BMR) most likely due to overactivity of the sympathetic nervous system (SNS) has been suggested to play a role.[1-2] Nevertheless, to the best of our knowledge, no study has investigated the activity of the autonomic nervous system in cancer patients. Heart rate spectral (HRS) analysis is a useful and safe tool to evaluate SNS and parasympathetic nervous system (PNS) activity.[3] With this technique, vagal activity is the major contributor to the high-frequency (HF) component,[3] while the low-frequency (LF) component is a quantitative marker of sympathetic activity. Thus, the LF/HF ratio is an index of cardiac sympatho-vagal balance reflecting autonomic input to the heart.[3] If SNS overactivity is a determinant of the elevated BMR in cancer patients, β-blocker administration should provide metabolic benefits. Indeed, it has been shown that propranolol administration decreases the BMR in cancer patients.[2] Nevertheless, whether this effect is due to a more balanced effect between the SNS and PNS activity ratio or to a change in plasma catecholamine concentrations has not been investigated.

To prevent and counteract weight loss, a high-carbohydrate diet or daily glucose infusion are used frequently. Nevertheless, glucose administration is associated with an increase in energy expenditure[4]; thus, the amount of calories gained by glucose administration will be wasted by the effect of glucose on energy expenditure.[4] Ideally, weight loss may be prevented by a diet in which caloric intake parallels the decline in energy expenditure. A fat-rich diet, such as a diet producing obesity, may increase the caloric intake and reduce the energy expenditure to a greater extent versus a glucose-rich diet.[4] Therefore, in weight-losing cancer patients, a fat-rich diet or Intralipid infusion, as compared with glucose, may enhance daily energy intake with a restrained stimulatory effect on energy expenditure. Nevertheless, whether the combined effect of Intralipid infusion plus β-blocker administration has a more favorable metabolic effect than Intralipid or β-blocker alone remains to be demonstrated.

Our study aims to investigate (1) the potential pathophysiological link between autonomic nervous system overactivity and an elevated BMR in elderly cancer patients and (2) the metabolic benefits deriving from combined Intralipid and β-blocker administration in elderly cancer patients. For these reasons, 40 elderly patients with a solid cancer underwent bioimpedance analysis, HRS, determination of the plasma catecholamine concentration, and indirect calorimetry to assess body composition, autonomic nervous system activity, and changes in substrate oxidation throughout the different experimental conditions.

SUBJECTS AND METHODS

Subjects

Forty elderly patients with a solid cancer were studied (Table 1). All patients were malnourished, with a weight loss of about 7 kg in the prior 3 months, normotensive and euglycemic, and hospitalized at the time of study, and ate a balanced hospital diet before the study for at least 4 days. None were bedridden or received chemotherapy or radiation therapy for at least 30 days before the study. Liver function tests were within the normal range. Tumor type was assessed by histologic examination. Thirty non–weight-losing cancer patients and 18 malnourished cachectic patients were also studied. In this last group, weight loss was due to psychogenic anorexia. All patients provided informed consent to participate in the study, which was approved by the Ethics Committee of our institution.

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Table 1. Clinical Characteristics of the Study Groups

Characteristic	Weight-Losing Cancer Patients (n = 40)	Non–Weight-Losing Cancer Patients (n = 30)	Weight-Losing Noncancer Patients (n = 18)
Age (yr)	70 ± 2.6	69 ± 2.3	74 ± 3.5
BMI (kg/m²)	17.9 ± 1	21.2 ± 1.2*	18.3 ± 0.2
FFM (kg)	41.9 ± 3.5	54.3 ± 1.1*	42.4 ± 2.2
BF (%)	15 ± 1	20.1 ± 2.1*	18.4 ± 0.5*
WL (kg)	7.4 ± 1.3	1.5 ± 1.1†	5.4 ± 1.6
FFA (mmol/L)	401 ± 68	197 ± 3.3*	250 ± 48*

NOTE. Results are the mean ± SD.
Abbreviations: BF, body fat; WI, weight loss in the prior 3 months.
*$P < .03$, †$P < .005$, *v* weight-losing cancer patients.

Experimental Design

All groups of patients were studied in the morning starting at 7 AM after a 12 to 14-hour overnight fast. Patients underwent indirect calorimetry and Holter monitoring to study basal metabolic rate and baseline heart rate variability, respectively. Weight-losing cancer patients were also submitted to a further test to investigate the metabolic effect of Intralipid infusion and propranolol administration. This latter experimental design is summarized in Fig 1. Weight-losing cancer patients were placed on bed rest and kept supine throughout the whole experiment. Fat-free mass (FFM) and percent body fat were assessed by bioimpedance analysis (BIA 101; Akern, Florence, Italy) with the patients having an empty bladder. In each patient, a venous catheter was inserted into an antecubital vein for blood sampling. On day 1, indirect calorimetry measurements were started 60 minutes before Intralipid infusion (to measure the preload BMR and respiratory quotient [Rq]). Then, patients were in a fasting state until 8 PM, when 20% Intralipid infusion (Pharmacia, Uppsala, Sweden) was started, continuing until the next morning. At 8 AM, with Intralipid infusion stopped, a new indirect calorimetry test was performed and continued for 240 minutes. The same experimental protocol was repeated on day 7 with the patients submitted to 6-day propranolol (40 mg twice daily Inderal; Zeneca, Milan, Italy) administration (Fig 1). During this period, patients were hospitalized and all had the same diet. All determinations (BMR and heart rate variability) were made on the same day of Intralipid infusion and propranolol administration. Blood samples were drawn before (−30 and 0 minutes) and at the end of each Intralipid infusion to determine plasma metabolites at baseline and at the end of Intralipid infusion. Urine was collected at the end of the experiment for estimation of urinary flow and urinary nitrogen loss.

Cardiovascular Determinations

Blood pressure was determined in real time by a Finapres (Omheda, Englewood, CO). All determinations were made with the subject at rest after 15 minutes in the supine position on three occasions separated by an interval of 5 minutes; the average of the mean value of three measurements for each day was then calculated. Ambulatory electrocardiographic monitoring was performed with a three-channel frequency-modulated tape recorder (Spacelabs 90208; Spacelabs, Redmond, WA) with a frequency range of 0.05 to 100 Hz and a calibration of 100 mm/mV. To ensure that variations did not introduce frequency components in the data, after each experiment an expert technician checked the speed of the tape recorder. After accurate skin preparation, electrodes were placed on the chest to obtain the tripolar chest leads CM1 (modified V1) on the first channel, CM2 (modified V2) on the second channel, and CM5 (modified V5) on the third channel. Holter monitoring started 30 minutes after the superficial vein was cannulated. The electrocardiogram was recorded for a 240-minute period. Two experienced investigators analyzed the ambulatory electrocardiographic recording tapes at 1/60 real speed with a Marquette 8500 device (Marquette Electronics, Milwaukee, WI). To prevent the processing of artifacts, the quality of the signal was checked by visual inspection on the computer while sampling the RR intervals. Besides the heart rate, the heart rate standard deviation and heart rate variability histogram were analyzed by a computer program that allowed spectral analysis of the heart rate using a fast Fourier transform method based on a windowed periodgram technique.[5] Spectral plots for each phase of the protocol were derived from the average of three 2-minute segments of data. The reproducibility of RR intervals at each phase of the study was evaluated by calculating interclass correlation coefficients using a one-way random-effects ANOVA model. The interclass correlation coefficient is an assessment of the intrasubject variability of a measure and reflects its reproducibility. A coefficient greater than .8 indicates excellent reproducibility. The coefficient at phase 0 was .91, at phase 60 .83, at phase 120 .89, and at phase 180 .90. The data were stored on a computer disc. Rhythm disturbances and other noise artifacts, when present, were automatically removed by linear interpolation between the two preceding and two succeeding normal RR intervals. The power spectra were computed using Bartleet's procedure in which sequential windowed segments of the RR interval are transformed into the frequency domain and averaged.[6]

Power spectra were quantified by measuring the area in three frequency bands: (1) less than 0.04 Hz (very–low-frequency [VLF]), (2) 0.04 to 0.15 Hz (LF), and (3) 0.15 to 0.40 Hz (HF). Since the physiological explanation for the VLF component is much less defined and the existence of a specific physiologic process attributable to the heart period change has been strongly questioned,[3] only LF and HF periods are normally considered. LF and HF are reported in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component.[3] Normalized units tend to minimize the effect on the values for LF and HF components of the changes in total power.[3] Since LF is mainly the result of SNS and PNS activity and HF is mainly the result of PNS activity, the LF/HF ratio (as normalized units) rather than LF as a normalized unit per se[3] was used for calculating and reporting the data.

Before recording in our laboratory, all patients were asked to rest comfortably in the supine position for at least 30 minutes. An effort was made to keep patients unaware of the sampling time to avoid affecting

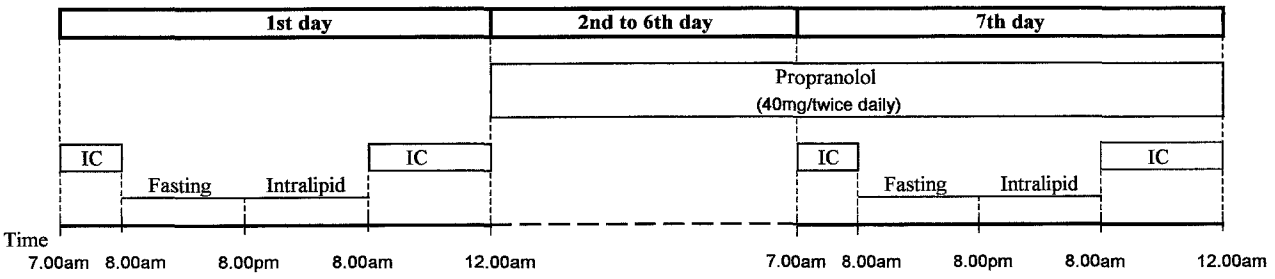

Fig 1. Study design. IC, indirect calorimetry.

the heart rate; furthermore, all subjects were accustomed to breathing at a constant rate and advised to avoid talking during the study.

Indirect Calorimetry Measurements

Respiratory gas-exchange measurements were performed by an open-circuit ventilated-hood system (Deltatrac monitor; Datex, Helsinki, Finland). The energy expenditure and Rq were calculated from oxygen consumption, carbon dioxide production, and the urinary nitrogen excretion rate according to the method of Ferrannini.[7] These formulas remain valid even during periods when lipogenesis exceeds lipid oxidation. However, in this situation, the total glucose oxidation value indicates the amount of glucose oxidized in addition to that converted into lipid. The value for fat oxidation became negative, but is numerically equal to the amount of fat synthesized.[7]

Analytical Methods

Blood samples for hormone and metabolite determinations were centrifuged immediately after each experiment and the plasma was stored at −20°C until assay, except for plasma glucose, which was determined immediately after the experiment. Blood samples for insulin were collected in 5-mL heparinized tubes containing 0.5 mL EDTA-Kyr solution (Kyr; Lepetit, Milan, Italy; 5,000 U/mL and disodium-EDTA; 1.2 mg/mL). Samples for plasma glucose were collected in tubes containing a trace of sodium fluoride. The plasma insulin concentration was determined by radioimmunoassay (Sorin Biomedica, Milan, Italy; coefficient of variation, 4.1%), and plasma glucose was quantified by an enzymatic method (Beckman, Fullerton, CA). Plasma free fatty acids (FFAs) were determined according to the method of Dole et al,[8] and plasma triglyceride and cholesterol concentrations were measured spectrophotometrically (Boehringer Mannheim, Milan, Italy). The plasma catecholamine concentration was determined by high-performance liquid chromatography.

Nonprotein urinary nitrogen was determined as reported elsewhere[7] and reported as the renal flow rate.

Liver function tests (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and prothrombin time) and the plasma fibrinogen concentration were assessed by routine spectrophotometric methods.

To calculate the urinary flow rate, we collected the urine from the Foley catheter and then divided the volume by the time (in minutes) elapsed from the last urination.

Statistical Analyses

Results are presented as the mean ± SD. Percent changes were calculated relative to the baseline values equal to 100%. All comparisons among different groups and/or experimental conditions were made by ANOVA. When a P level less than .05 was found, Scheffe's test was also applied. Simple linear regression analysis was performed by a standard technique. Analysis of covariance allowed adjustment of the Rq and BMR for age, fat mass, FFM, and protein oxidation. For each subject, only adjusted values for the Rq and BMR are reported, calculated as the mean value for the group plus the difference between the measured and predicted value for the subject. Multivariate analysis allowed study of the determinants of the BMR. All statistical calculations were made on a IBM computer (IBM, Portsmouth, England) using a SOLO software package (BMDP, Cork, Ireland).

RESULTS

Metabolic and Cardiovascular Differences Among the Study Groups

Differences in anthropometric parameters and biochemical indices among all groups are reported in Table 1. Briefly, weight-losing cancer patients had a BMI and FFM that were significantly lower versus the other groups, while fasting plasma triglyceride and FFA were more elevated in weight-losing cancer patients. Cardiovascular parameters and the BMR in the three study groups are reported in Table 2. Weight-losing cancer patients had the highest heart rate and LF/HF ratio, with the latter due to the highest LF and the lowest HF. Finally, weight-losing cancer patients also had a BMR that was more elevated than in the other study groups.

Effect of Intralipid Infusion and Propranolol Administration in Weight-Losing Cancer Patients

All patients were malnourished (Table 1). Baseline anthropometric and oncologic characteristics of the weight-losing cancer patients are reported in Table 3. Fasting plasma glucose, FFA, and triglyceride concentrations showed the strongest increase after Intralipid and Intralipid plus propranolol administration (Table 4). Nevertheless, no significant differences were found between these two metabolic conditions. Fasting plasma adrenaline and noradrenaline concentrations were unaffected by the different experimental conditions investigated.

Cardiovascular paramenters throughout the different experimental conditions are reported in Table 5. The heart rate, systolic and diastolic arterial blood pressure, LF, and LF/HF ratio were significantly decreased by propranolol administration, but there was no difference between propranolol administration and Intralipid infusion plus β-blocker administration. In contrast, HF was not significantly affected by propranolol administration. At baseline, plasma noradrenaline was significantly correlated with LF ($r = .43$, $P < .007$) and the LF/HF ratio ($r = .45$, $P < .005$), while no correlation with HF ($r = .21$, $P < .22$) was found. In contrast, plasma adrenaline was not correlated with any of the spectral analysis parameters. At baseline, the fasting plasma FFA concentration was also correlated with LF ($r = .48$, $P < .001$) and the LF/HF ratio ($r = .46$, $P < .005$).

The change in energy expenditure is reported in Fig 2. Compared with baseline values, all of the experimental procedures significantly decreased energy expenditure. Notwithstanding this, 6 days of propranolol administration associated with Intralipid infusion produced the strongest decline in energy

Table 2. Difference in Cardiovascular Parameters and BMR Among the Study Groups

Parameter	Weight-Losing Cancer Patients (n = 40)	Non–Weight-Losing Cancer Patients (n = 30)	Weight-Losing Noncancer Patients (n = 18)
HR (bpm)	100 ± 5.5*	81 ± 3.3	79 ± 4.1
SBP (mm Hg)	125 ± 4.5	130 ± 3.8	110 ± 3.3
DBP (mm Hg)	85 ± 2.1	80 ± 2.3	75 ± 2.4
LF (NU)	71 ± 4.3†	41 ± 3.8	46 ± 5.1
HF (NU)	24 ± 1.2*	37 ± 2.5	40 ± 3.8
LF/HF ratio	2.96 ± 0.14†	1.11 ± 0.33	1.15 ± 0.47
BMR (kJ/24 h)	10,459 ± 3,416*	6,757 ± 1,688	7,118 ± 1,193

NOTE. Data are the mean ± SD. No differences between non–weight-losing cancer patients and weight-losing noncancer patients were found. BMR was adjusted for age and fat mass.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DPB, diastolic blood pressure; NU, normalized units.

*$P < .005$; **$P < .001$, v other groups.

Table 3. Oncologic Characteristics of the Study Group Submitted to Intralipid and Intralipid Plus Propranolol Administration

Patient No.	Gender	Age (yr)	Tumor Diagnosis	BMI (kg/m²)	FFM (kg)	BF (%)	WL (kg)	CHO (mmol/L)	TG (mmol/L)	FFA (mmol/L)	Heart Rate (bpm)	Tumor Stage
1	M	72	Lung	17	43	18	8.0	3.02	0.81	285	100	T3N2M1
2	M	71	Prostate	18	45	19	7.5	3.23	0.94	330	98	T3N2M1
3	M	69	Colon	17	38	14	5.5	3.44	1.68	449	96	T3N2M1
4	F	65	Breast	19	41	18	7.0	2.98	0.56	245	95	T2N1M1
5	M	67	Gastric	18	46	17	8.0	2.79	0.92	423	95	T4N2M1
6	M	74	Prostate	18	44	16	7.0	3.61	1.21	386	100	T4N2M1
7	F	67	Colon	17	38	16	9.0	3.02	1.58	438	95	T3N1M1
8	F	70	Ovary	18	40	17	6.0	3.85	1.43	410	105	T2N1M1
9	M	67	Soft tissue	19	47	16	7.0	2.75	0.86	490	94	T2N2M1
10	F	71	Gastric	17	38	17	9.0	3.48	0.78	410	100	T3N2M1
11	M	72	Lung	19	49	17	8.0	3.69	1.35	403	95	T2N1M1
12	F	68	Melanoma	16	39	15	7.0	3.22	1.05	402	98	T3N2M1
13	F	69	Colon	18	40	15	6.8	3.69	1.24	387	110	T3N2M1
14	F	68	Breast	17	37	16	6.5	3.03	1.12	370	97	T3N2M1
15	F	68	Pleura	19	39	17	7.5	3.62	1.35	400	98	T3N1M0
16	M	65	Colon	17	38	16	8.5	3.07	1.79	429	100	T3N2M1
17	M	70	Lung	18	46	15	8.5	2.98	1.24	369	98	T4N1M1
18	F	68	Bladder	19	45	17	6.5	3.69	1.52	420	100	T3N2M1
19	F	71	Breast	20	46	18	8.0	2.87	0.74	462	102	T2N1M1
20	M	65	Pleura	17	41	16	6.5	3.67	1.61	430	95	T3N2M0
21	M	72	Lung	19	46	18	7.5	2.99	0.98	496	100	T4N2M1
22	M	70	Colon	17	40	17	8.0	3.03	0.93	443	95	T3N1M1
23	F	68	Breast	19	43	16	7.8	3.67	1.39	401	90	T2N1M1
24	M	69	Bladder	18	44	15	9.5	3.49	1.33	397	96	T3N2M1
25	M	67	Prostate	18	39	17	6.0	3.31	1.25	348	101	T3N2M1
26	F	69	Rectum	16	38	15	7.5	3.02	1.27	428	100	T4N2M1
27	F	70	Pleura	19	41	18	8.5	3.56	0.95	433	95	T3N2M0
28	F	69	Colon	18	37	17	6.5	2.97	0.94	498	100	T3N2M1
29	M	68	Esophagus	18	47	16	8.0	3.12	1.15	310	110	T3N2M1
30	M	65	Esophagus	19	46	17	9.0	3.10	1.26	389	106	T3N1M1
31	M	72	Prostate	17	39	16	8.5	3.62	1.29	343	98	T3N2M1
32	F	67	Colon	18	41	17	7.0	3.23	0.73	480	105	T2N1M1
33	F	68	Breast	17	40	16	6.5	3.62	1.32	380	98	T2N1M1
34	M	66	Lung	20	51	16	7.0	3.02	0.95	478	95	T3N1M1
35	M	71	Bladder	19	43	18	6.5	3.11	1.01	356	101	T3N1M1
36	F	68	Ovary	18	38	17	8.0	3.41	1.33	354	115	T2N2M2
37	F	78	Lung	17	40	16	7.0	2.88	0.75	475	102	T3N2M1
38	M	70	Colon	17	42	15	6.5	3.35	1.43	396	108	T2N1M1
39	M	69	Rectum	18	44	16	8.6	3.78	1.22	387	97	T3N1M1
40	F	66	Breast	19	40	18	6.0	3.45	0.82	487	99	T2N2M1
Mean ± SD		70 ± 2.6		17.9 ± 1	41.9 ± 3.5	1.5 ± 1.1	7.4 ± 1	3.32 ± 0.3	1.1 ± 0.3	401 ± 68	100 ± 5.5	

Abbreviations: BF, body fat; WL, weight loss in the prior 3 months; CHO, cholesterol; TG, triglyceride.

expenditure compared either with the baseline study or the other experimental conditions. Interestingly, the percentage decline in energy expenditure found after propranolol administration plus Intralipid infusion was even stronger than the effects of Intralipid infusion and β-blocker administration considered separately (Fig 2). At baseline, a simple correlation between the BMR and LF ($r = .42$, $P < .006$) and LF/HF ratio ($r = .51$, $P < .001$) was found. After propranolol administration, the percent decline in the BMR was significantly correlated with the percent decline in LF ($r = .39$, $P < .01$) and the LF/HF ratio ($r = .53$, $P < .001$). The percent decline in the BMR was not correlated with HF ($r = .13$, $P < .34$) or the plasma noradrenaline concentration ($r = .21$, $P < .20$) at any study time. With regard to substrate oxidation compared with baseline, Intralipid infusion and propranolol administration produced a significant decline in the Rq; notwithstanding this, such effects were of similar extent (Fig 2). In contrast, 6-day propranolol administration combined with Intralipid infusion produced the strongest decline in the Rq compared with either Intralipid or propranolol administration separately (Fig 2). The Rq was significantly correlated with fasting plasma FFA at baseline ($r = .46$, $P < .003$); similarly, the percent decline in the Rq was correlated with the percent increase in fasting plasma FFA after Intralipid infusion ($r = .49$, $P < .001$), propranolol administration ($r = .48$, $P < .002$), and Intralipid plus propranolol administration ($r = .51$, $P < .001$).

Multivariate analysis allowed study of the significant determinants of the BMR. A model containing the age, gender, FFM, plasma noradrenaline concentration, and LF/HF ratio explained 76% of the baseline BMR variability. In this model, the FFM ($P < .005$), gender ($P < .01$), and LF/HF ratio ($P < .001$) showed the strongest association with the BMR.

Table 4. Changes in Plasma Metabolic Parameters in the Different Experimental Conditions (N = 40)

Parameter	Baseline	Intralipid	Propranolol	Intralipid + Propranolol
Fasting glucose (mmol/L)	5.0 ± 0.4	5.5 ± 0.3*	5.1 ± 0.2	5.7 ± 0.3*
Fasting FFA (mmol/L)	401 ± 68	887 ± 177*	301 ± 102	918 ± 211*
Fasting triglycerides (mmol/L)	1.55 ± 0.45	3.77 ± 0.65*	1.61 ± 0.47	3.89 ± 0.61*
Fasting insulin (pmol/L)	78 ± 3.4	91 ± 4.5*	81 ± 6.1	97 ± 5.8*
Fasting adrenaline (nmol/L)	0.23 ± 0.05	0.26 ± 0.04	0.24 ± 0.06	0.23 ± 0.04
Fasting noradrenaline (nmol/L)	3.21 ± 0.41	3.51 ± 0.44	3.37 ± 0.48	3.34 ± 0.48

NOTE. Results are the mean ± SD.
*$P < .001$ *v* baseline.

DISCUSSION

This study demonstrates that (1) weight-losing cancer patients had a BMR and LF/HF ratio that were more elevated than in non–weight-losing cancer patients and weight-losing noncancer patients; (2) an elevated BMR in weight-losing cancer patients seems to be associated with autonomic nervous system dysfunction; (3) Intralipid infusion associated with propranolol administration is useful for decreasing the BMR and/or energy expenditure despite the increase in caloric intake in weight-losing cancer patients; and (4) the metabolic effects of Intralipid infusion combined with propranolol administration in weight-losing cancer patients were even stronger than with the two treatments separately.

The relation between an elevated BMR or energy expenditure and weight loss is widely known in cancer patients. Luketic et al[9] demonstrated that abnormal energy expenditure in cancer patients was ablated by curative tumor resection. Hyltander et al[1] showed that elevated energy expenditure preceded weight loss in unselected patients with solid tumors, suggesting that an elevation in metabolism may be a cause of cachexia rather than a consequence. The reason that cancer patients have an elevated BMR or energy expenditure is still debated. An overdrive of the SNS might play a role. Hytlander et al[2] suggested β-blockers as useful for treating cancer patients, since propranolol administration was associated with a significant reduction in the BMR. It was also suggested that the heart may be an organ compartment where energy is expended at an increased rate during cancer progression. Such indirect data were also supported by experimental results showing that hearts from tumor-bearing rats consumed oxygen at an increased rate during various experimental conditions.[10] This elevated oxygen consumption was also associated with increased sensitivity and reactivity to β-agonists in perfused hearts from tumor-bearing rats, in part explained by the appearance of altered adrenergic receptors in the myocardium from tumor-bearing hosts.[11] A previous study comparing control subjects and cancer patients showed cancer patients to have a higher basal heart rate than controls; nevertheless, the plasma catecholamine concentration was not assessed. Since an elevated basal heart rate is indirect evidence of SNS overdrive in cancer patients,[2] it was speculated that an elevated plasma catecholamine concentration contributed to an enhanced availability of substrate as an energy source. It has also been hypothesized that SNS overactivity in cancer patients might only be due to impaired PNS activity rather than an increase in plasma catecholamines.[12-13] In other words, an unbalanced SNS/PNS ratio may exist.[12-13]

In the present study, the activity of the autonomic nervous system was studied by spectral analysis at the cardiac level.[3,5,6]

Table 5. Changes in Cardiovascular and Spectral Analysis Parameters in Different Experimental Conditions (N = 40)

	Baseline	Intralipid	Propranolol
HR (beats/min)	100 ± 5.5	91 ± 3.3	64 ± 3.1*
SBP (mm Hg)	125 ± 4.3	125 ± 3.8	115 ± 2.1*
DBP (mm Hg)	85 ± 2.1	85 ± 2.0	80 ± 1.8*
LF (NU)	71 ± 4.3	70 ± 5.1	40 ± 4.8*
HF (NU)	24 ± 1.2	25 ± 1.8	20 ± 1.7
LF/HF ratio	2.96 ± 0.14	2.81 ± 0.21	1.82 ± 0.15*

NOTE. Data are the mean ± SD.
*$P < .001$ *v* baseline.

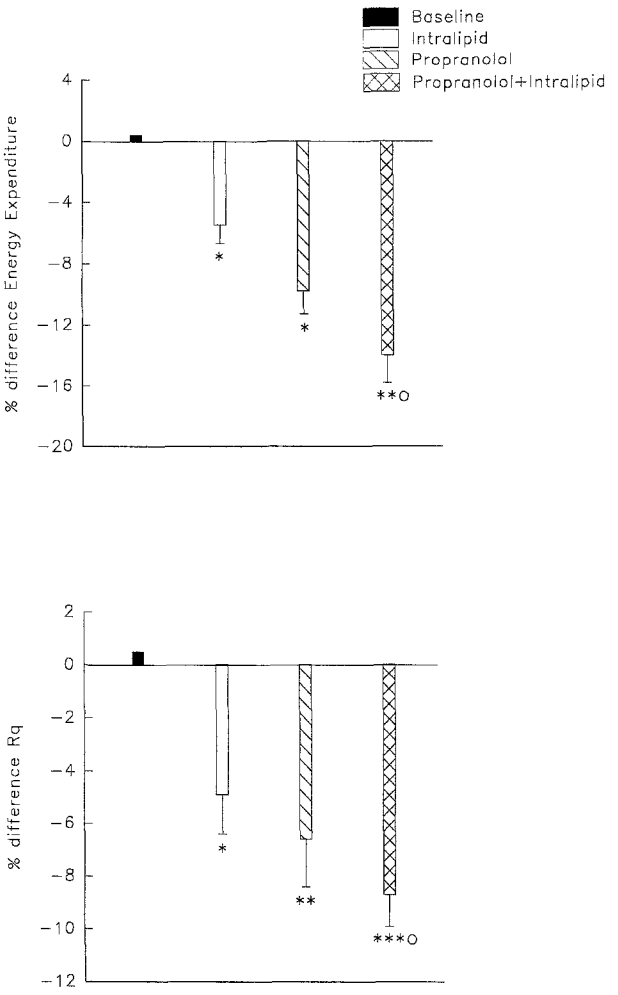

Fig 2. Changes in the percent energy expenditure and Rq throughout the different experimental conditions. Statistically significant differences *v* baseline, *$P < .01$, **$P < .007$, ***$P < .005$; statistically significant differences *v* Intralipid and propranolol administration separately, °$P < .03$.

In the spectral analysis, we mainly recognize two peaks: HF and LF. Efferent vagal activity is a major contributor to the HF component, as observed in clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy.[3] More debated is the interpretation of the LF component, which is considered a marker of sympathetic modulation (especially when expressed in normalized units). Consequently, the LF/HF ratio is considered an indirect index of sympatho-vagal balance.[3] By this technique, unbalanced SNS activity in weight-losing cancer patients seems to occur. Such unbalanced autonomic nervous system activity might be responsible for an elevated BMR and energy expenditure. Such a hypothesis is supported, albeit not demonstrated, by the following observations: (1) β-blocker administration affects the LF and LF/HF ratio without changing the plasma catecholamine concentration, (2) HF was unusually low compared with data reported by other groups[3] and our group,[14] and (3) the LF/HF ratio was particularly high, most likely due to the fact that impaired PNS activity occurs. Furthermore, the main impact of SNS activity in the upregulation of the BMR and energy expenditure was demonstrated by (1) a baseline LF and LF/HF ratio more correlated with the BMR, (2) the LF/HF ratio as a significant determinant of the BMR in multivariate analysis, and (3) β-blocker administration (alone or combined with Intralipid infusion) that caused a significant decline in both the LF/HF ratio and BMR, a phenomenon also significantly correlated between them. Thus, one can suggest that β-blocker administration may be useful to counteract the negative impact of the SNS on metabolic pathways.

In terms of nutritional support, despite the occurrence of insulin resistance,[15] a carbohydrate-rich diet or glucose infusion is frequently administered to cancer patients. Unfortunately, glucose stimulates the BMR[4]; thus, the additional daily energy intake as glucose intravenously is wasted through the increase in the BMR and energy expenditure. In other words, the glucose is not stored but instead overutilized to produce energy.[16] In contrast, long-chain polyunsaturated fatty acid administration as Intralipid has been demonstrated to increase daily energy intake without a strong stimulation of the BMR.[4] This metabolic mechanism has been described already in obese subjects and highlighted as the main metabolic cause of fatness.[17-20] In addition, several metabolic studies showed that Intralipid infusion stimulates the BMR to a lesser extent than glucose infusion.[17-20] In fact, an exaggerated plasma FFA concentration is associated with overactivity of the Randle cycle.[21] As consequence of a prevailing lipid oxidation, glucose oxidation will be inhibited with a secondary impairment of glycogen synthesis; the final metabolic effect will be a secondary shift of the glucose itself and the amount of lipid, not used for producing energy, to storage fuel. The evidence that such metabolic processes were operating in our study is represented by the fact that compared with baseline, Intralipid infusion decreased the BMR with simultaneous stimulation of lipid oxidation as shown by the decline in the Rq. When propranolol is combined with Intralipid infusion, the negative effect of catecholamine on energy expenditure can be prevented or reduced. In fact, in our study, Intralipid infusion and β-blocker administration determined the strongest decline in the BMR and Rq when administered in a combined manner. The potentiating effect of β-blocker on the metabolic processes started by Intralipid infusion is also demonstrated by the evidence that propranolol administration associated with Intralipid infusion had a net final effect stronger than the two metabolic effects found in the two experimental conditions considered separately.

In whole, our data support the hypothesis that metabolic abnormalities due to cancer itself can greatly contribute to the genesis and development of cachexia, which in turn is also responsible for worsening the metabolic derangement of cancer patients. Thus, a vicious cycle could be operating, producing and sustaining the weight loss. In light of this hypothesis, our study seems particularly interesting, since it provides a new perspective in the nutritional support therapy of cancer patients. The latter point is particularly important in elderly patients, in whom malnutrition might worsen more rapidly than in adult patients.

In conclusion, our study demonstrates that autonomic nervous system dysfunction, mainly due to deficient PNS activity, is associated with the elevated BMR in cancer patients; further, propranolol administration seems useful to rectify such autonomic dysfunction. Finally, propranolol administration combined with a lipid-rich diet or Intralipid infusion seems the most useful tool for enhancing daily caloric intake without a strong increase in the BMR and energy expenditure.

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