Elevated plasma fatty acid concentrations stimulate the cardiac autonomic nervous system in healthy subjects

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ABSTRACT

Background: Fatty acids have been shown to stimulate the sympathetic nervous system in rats. Power spectral analysis of heart rate variability (HRV) is a safe and useful tool with which to evaluate cardiac autonomic nervous system (ANS) activity. Whether changes in plasma fatty acid concentrations affect the sympathetic nervous system or HRV in humans is unknown.

Objective: We investigated the possible changes in HRV after a significant increase in plasma fatty acid concentration.

Design: Subjects were randomly assigned to receive an infusion of lipid emulsion (10% triacylglycerol emulsion for 180 min) + heparin (a bolus of 200 U followed by 0.2 U · min⁻¹ · kg body wt⁻¹; n = 20) or 0.9% NaCl (for 180 min; n = 10).

Results: Lipid emulsion + heparin infusion was associated with a rise in plasma epinephrine and norepinephrine concentrations. The rise in plasma fatty acid concentration was associated with a significant decline in the RR interval (P < 0.03) and in total power (P < 0.03). Analysis of the different components of HRV showed that lipid emulsion + heparin infusion stimulated low-frequency (LF) components (P < 0.03 at the second hour and P < 0.01 at the third hour) and inhibited high-frequency (HF) components (P < 0.03 at the second and third hours). Consequently, the LF-HF ratio was significantly stimulated (P < 0.03 at the second hour and P < 0.01 at the third hour). Such results persisted, although attenuated, when the study was repeated in association with a propranolol infusion (n = 8).

Conclusion: Elevated plasma fatty acid concentrations may stimulate cardiac autonomic nervous system activity.


KEY WORDS Catecholamine, fatty acids, heart rate variability, Intralipid, propranolol, power spectral analysis, humans, lipid emulsion

INTRODUCTION

Despite a growing body of research, the effects of fatty acids on the cardiovascular system are not fully defined. In vitro, elevated fatty acid concentrations have been shown to have a proarrhythmic role through a detergent effect on plasma membrane composition (1) and a worsening of the activity of the plasma membrane Na⁺-K⁺-ATPase pump (2). In vivo, elevated plasma fatty acid concentrations have been associated with a greater number of ventricular premature complexes in both nondiabetic (3) and nons ischemic diabetic (4) patients. Additionally, an increase in plasma fatty acid concentrations was shown to stimulate sympathetic nervous system (SNS) activity in rats (5). Whether such an effect is reproducible in humans needs to be investigated, particularly because such a fatty acid–related increase in SNS activity might help to explain the occurrence of sudden death in obese patients (6).

Despite some criticism (7, 8), power spectral analysis of heart rate variability (HRV) is a safe and useful tool with which to evaluate cardiac autonomic nervous system (ANS) activity (9, 10) at the cardiac level. Among HRV parameters, the ratio of low-frequency (LF) to high-frequency (HF) components is considered an index of cardiac sympathetic and vagal activity (9–12). In fact, specific interventions increasing or lowering the LF-HF ratio may indicate a shift of the cardiac ANS balance toward a sympathetic or parasympathetic predominance (9). Whether changes in plasma fatty acid concentrations affect HRV in humans is still unknown.

In light of such experimental evidence, we investigated the possible changes in SNS activity after a significant increase in plasma fatty acid concentration. In particular, we tried to answer the following questions: Does an elevated plasma fatty acid concentration affect the ANS? If so, does such an effect involve cardiac and hemodynamic variables? To these ends, we investigated, using power spectral analysis, changes in HRV as well as leg blood flow and vascular resistance during infusions of a triacylglycerol emulsion + heparin and of saline solution.

SUBJECTS AND METHODS

Experimental subjects

Twenty healthy subjects volunteered for our study. Clinical characteristics of the study groups are shown in Table 1. All subjects were studied after a 14-h overnight fast and were required...
to refrain from drinking alcohol during the preceding 15 d. No smokers were recruited. Each subject was admitted to our department the day before each study and was fed an isocaloric diet containing 50% of energy as carbohydrate, 30% as fat, and 20% as protein. Sodium intake ranged from 4.5 to 6 g/d, depending on the weight-maintenance energy requirement. All women were studied in the follicular phase of their menstrual cycle. All subjects had been weight stable for ≥3 mo before the study and none were participating in any regular exercise program. All volunteers had normal glucose tolerance after a 75-g oral glucose load (13). All subjects gave informed consent to participate in the study, which was approved by the Ethical Committee of our Institution.

**Anthropometric determinations**

Weight and height were measured by using a standard technique. Body mass index (BMI) was calculated as body weight (kg)/height² (m). Body fat and fat-free mass (FFM) were measured by using a 4-terminal bioimpedance analyzer (BIA; RJL Spectrum Bioelectrical Impedance–IA 101/SC Akern; RJL System, Florence, Italy). Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest (normally umbilical level) and hip circumference at the level of the trochanter. Both circumferences were measured to the nearest 0.5 cm with a plastic tape and the waist-to-hip ratio (WHR) was calculated.

**Table 1**

Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th>Lipid emulsion + heparin</th>
<th>Saline solution</th>
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<tr>
<td>(n = 11 M, 9 W)</td>
<td>(n = 6 M, 4 W)</td>
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| Age (y)                  | 35.3 ± 5.1 | 35.1 ± 4.5 |
| BMI (kg/m²)              | 23.1 ± 1.8 | 23.5 ± 1.6 |
| Body fat (%)             | 22 ± 2     | 21 ± 3     |
| Waist-to-hip ratio       | 0.81 ± 0.04| 0.83 ± 0.03|
| Fasting plasma fatty acids (mol/L) | 441 ± 65 | 439 ± 70 |
| Fasting plasma glucose (mol/L)     | 5.1 ± 0.2 | 5.0 ± 0.1  |
| 2-h Plasma glucose (mol/L)         | 6.2 ± 0.2 | 6.1 ± 0.4  |
| Fasting plasma insulin (pmol/L)     | 61.5 ± 3.4| 62.1 ± 2.1 |
| Fasting plasma LDL cholesterol (mol/L) | 3.7 ± 0.8 | 3.9 ± 0.3 |
| Fasting plasma HDL cholesterol (mol/L) | 1.3 ± 0.7 | 1.4 ± 0.4 |
| Fasting plasma triacylglycerols (mol/L) | 1.6 ± 0.3 | 1.5 ± 0.5 |
| Fasting plasma norepinephrine (pmol/L) | 1.99 ± 0.1 | 2.01 ± 0.1 |
| Fasting plasma epinephrine (pmol/L)  | 228 ± 20.1 | 225 ± 21.5 |
| Fasting plasma cortisol (pmol/L)     | 218 ± 0.60 | 216 ± 0.72 |
| Fasting plasma renin (ng·L⁻¹·s⁻¹)   | 0.82 ± 0.01 | 0.79 ± 0.03 |
| Fasting plasma adrenocorticotropic (U/L) | 11.30 ± 0.45 | 12.1 ± 0.21 |
| Aspartate aminotransferase (U/L)     | 13 ± 3     | 14 ± 5     |
| Alanine aminotransferase (U/L)       | 14 ± 2     | 12 ± 3     |
| Mean arterial blood pressure (mm Hg)  | 85 ± 1.25  | 84 ± 2.01  |
| Leg blood flow (L/min)               | 0.231 ± 0.002 | 0.253 ± 0.001 |
| Leg vascular resistance             | 368 ± 7    | 371 ± 4    |
| (mm Hg·L⁻¹·s⁻¹)                    | Heart rate (beats/min) | 76.2 ± 9.2 | 75.8 ± 9.4 |
| Total power (m²·s⁻¹)                | 3975 ± 250  | 3964 ± 261 |
| RR interval (ms)                    | 795 ± 98   | 786 ± 89   |
| LF component (m²)                   | 832 ± 457  | 835 ± 463  |
| LF component (normalized units)     | 65.1 ± 5.1 | 64.7 ± 4.9 |
| HF component (m²)                   | 397 ± 192  | 391 ± 186  |
| HF component (normalized units)     | 31.1 ± 2.2 | 33.2 ± 1.9 |
| LF:HF                                | 2.08 ± 0.03 | 2.05 ± 0.04 |
| CFHF (Hz)                            | 0.26 ± 0.04 | 0.28 ± 0.02 |

*SD, LF, low frequency; HF, high frequency; CFHF, central frequency of the HF component. There were no significant differences between the 2 groups.*

**Experimental design**

The study protocol was designed to assess changes in HRV and hemodynamic variables that accompanied an infusion of 10% lipid emulsion + heparin. At 0700, a catheter was inserted into the right brachial vein of each subject for infusions. After 30 min, baseline 60-min HRV recording was started. At 0830, 20 subjects assigned to the intervention group received an infusion of lipid emulsion (10% Intralipid; Pharmacia, Upplands, Sweden) at an infusion rate of 0.4 mL/min + heparin (a bolus of 200 U followed by 0.2 U·min⁻¹·kg body wt⁻¹). On another day, a subset of 8 subjects also underwent a simultaneous infusion of propranolol (100 μg/kg over 10 min followed by 1 mg·kg⁻¹·min⁻¹, Inderal; Zeneca, Milan, Italy) and the same lipid emulsion + heparin.

Patients assigned to the control group received an infusion of 0.9% NaCl (n = 10). In the control study, the saline load was matched to the overall volume and duration of the infusions of lipid emulsion + heparin and lipid emulsion + heparin + propranolol. Because infusion of lipid emulsion is also associated with a rise in plasma glucose concentration, we made preliminary tests of the effect of glycerol (10% glycerol, 24.5 mmol/h for 180 min; Galenica Senese, Siena, Italy) on cardiac ANS activity (n = 5). Each study had 3 phases: 1) a baseline HRV recording period (0–60 min), 2) an infusion period (61–240 min), and 3) a recovery period (241–300 min). During this latter period, all subjects received 0.9% NaCl. Each volunteer was studied on separate occasions 3 d apart to ensure that values returned to baseline. The order of the studies was randomly assigned.

Measurements of mean arterial blood pressure (MABP), leg (muscle) blood flow (LBF), leg vascular resistance (LVR), and plasma metabolite and hormone concentrations were obtained at baseline and then every 60 min throughout the study. For all of these measures, each value represents the mean of ≥4 determinations.

**Cardiovascular determinations**

All cardiovascular measurements were carried out under quiet conditions in a room maintained at 21°C. Patients rested comfortably in a supine position for ≥30 min before measurements were taken. An effort was made to keep patients unaware of the sampling timing to avoid affecting heart rate; furthermore, subjects were advised to breathe at a constant rate and to avoid talking during the 5-h study.

Blood pressure and heart rate at baseline and during the infusion and recovery periods were monitored in real time by using a Finapres blood pressure monitor (Ohmeda, Englewood, CO). Respiratory frequency was also calculated over a period of 2 min before the test. Subjects with a respiratory rate ×10 breaths/min (ie, <0.15 Hz) were excluded from the study. Ambulatory electrocardiograph monitoring was performed with 2-channel frequency modulating tape recorders (Cardioline AD 35, recorder model LP103; Remco Italy, Milan, Italy). To ensure that variations did not introduce frequency components into the data, an expert technician checked the speed of the tape recorder. After depilation of skin, the electrodes were placed on the subject’s chest so that the bipolar chest leads at position CM1 (modified V1) were on the first channel and those at position CM4 (modified V4) were on the second channel. Holter monitoring started 30 min after the superficial veins were cannulated.
Two independent blinded, experienced investigators analyzed the ambulatory electrocardiograph recording tapes. Ectopic beats were corrected for linear interpolation with the adjacent complexes. Electrocardiograph tracings with > 1% premature beats were eliminated from the analysis. Power spectral analysis was performed on a consecutive series of 512 intervals. An autoregressive algorithm computed the power spectral densities. Autoregressive spectral analysis was undertaken after estimation of model coefficients by the Levinson-Durbin algorithm. The model order selection was performed according to the Akaike (14) information criterion. Spectral components were identified and estimated by using the spectral decomposition algorithm proposed by Johnsen and Andersen (15) and were then assigned, on the basis of their central frequency, to 1 of the 3 bands: very-low-frequency (VLF) (0–0.03 Hz), LF (0.04–0.15 Hz), and HF (0.16–0.45 Hz). Because the physiologic explanation of the VLF component is not as well defined as is that of the LF and HF bands and because the existence of a specific physiologic process attributable to these heart period changes has been strongly questioned (9), only the LF and HF components are normally considered. LF and HF components are always reported in normalized units, which represent the relative value of the power of each component in proportion to the total power minus the VLF component (9). Normalized units tend to minimize the effect of the changes in total power on the values of LF and HF components (9). Among the HRV parameters, we also calculated the RR interval, which is the interval between ≥2 beats, and total power, which is the variance of all RR intervals. The respiratory rate data for analysis was obtained from the central frequency of the HF component (CFHF; 16).

Blood flow in the calf was measured by venous occlusion plethysmography (model EC 5R; Hokanson, Milan, Italy) with mercury-in-silastic strain gauges. The calf was elevated 10–15 cm above the level of the atrium to collapse the veins. Circulation to the foot was arrested by inflating a cuff around the ankles during blood flow determinations, which were performed at 15-s intervals for 5 min at baseline and at the end of each 60 min of tests. LVR was calculated by dividing the MABP by the LBF and expressed in arbitrary units.

Analytic techniques

Plasma glucose was determined by the glucose oxidase method with an autoanalyzer (Beckman, Fullerton, CA) immediately after blood collection. Plasma fatty acids were determined according to the method of Dole and Meinertz (17). To avoid in vitro lipolysis, plasma fatty acids were determined in chilled plasma containing EDTA and 0.275 g Paraoxon/L (diethyl-p-nitrophenyl) phosphate; Sigma Chemical Co, St Louis), a lipoprotein lipase inhibitor. Plasma aspartate aminotransferase and alanine aminotransferase activities were determined by routine assay. Blood samples for plasma hormone measurements were collected in tubes with heparin. After centrifugation, plasma insulin (CV: 3.8 ± 0.4%), cortisol (CV: 3.8 ± 0.2%), adrenocorticotropic (CV: 3.5 ± 0.9%), and renin (CV: 4.2 ± 0.6%) concentrations were determined by radioimmunoassay (Sorin Biomedical, Milan, Italy). Blood samples for catecholamine determination were drawn from patients who had been at rest for ≥30 min and the samples were immediately placed on ice. Plasma epinephrine and norepinephrine concentrations were determined by HPLC. Samples were applied to a column (SP Sepharose Fast Flow; Pharmacia) with a mobile phase consisting of 70 mmol monobasic sodium phosphate/L, 2.75 mmol octane sulfonic acid/L, 0.25 mL EDTA, and 7% acetonitrile. The pH was adjusted to 4.3 with 85% phosphoric acid. All chemicals were reagent grade or better.

Statistical analyses

MABP was calculated as diastolic blood pressure plus one-third of pulse pressure. Changes in plasma insulin concentrations were calculated as if the basal value were equal to 100%. Because the distribution of the frequency domain measures of HRV and plasma insulin concentrations were extremely skewed, each value was log-transformed to improve normality for statistical testing and back-transformed for presentation in the figures. Individual changes in plasma hormone concentrations, LF-HF ratio, and LVR were calculated as the difference between the values found at the third hour of the infusion minus the baseline values. Analysis of variance (ANOVA) allowed calculation of the differences among the different experimental conditions. Analysis of covariance (ANCOVA) was also used to adjust each HRV variable for change in plasma insulin concentration. Two-way ANOVA was used for comparisons between groups and for evaluating time-dependent changes. When a P value < 0.05 was found, Scheffe’s test was also performed to determine which intervention most influenced the overall difference between groups. Pearson’s product-moment correlation coefficients were determined. Partial correlation allowed us to test the relation between 2 variables independent of a covariate. A P value of 0.05 was chosen as the level of significance. All calculations were made by using the SOLO software package (BMDP, Cork, Ireland).

RESULTS

Anthropometric, metabolic, and hormonal measures

All subjects were young, were nonobese, and had normal glucose tolerance. Infusion of lipid emulsion + heparin was associated with a significant rise in plasma fatty acid and insulin concentrations, whereas no significant changes occurred in plasma glucose concentrations (Figure 1). Thereafter, the above plasma measures declined and returned to basal values at the end of the recovery period.

Changes in plasma hormone concentrations are reported in Figure 2. Baseline plasma hormone concentrations were similar in both experimental conditions. Infusion of lipid emulsion + heparin significantly raised plasma norepinephrine and epinephrine concentrations at the second and third hours but infusion of saline solution did not; nevertheless, both plasma hormone concentrations returned to baseline values at the end of the recovery period. The plasma renin concentration rose during both the infusions of lipid emulsion + heparin and saline solution; notwithstanding, no significant differences between the 2 experimental conditions were found. Plasma cortisol and adrenocorticotropic concentrations were unaffected by infusion of lipid emulsion + heparin or saline solution. Aspartate aminotransferase and alanine aminotransferase activities were unchanged during the study (data not shown).

Cardiac measures

Glycerol and saline solution had similar effects on HRV measures. Thus, we used saline solution as the control. Before evaluating the influence of elevated plasma fatty acid concentrations on HRV, a preliminary analysis was carried out to assess the potential
role of respiration. The CFHF (reflecting the respiratory rate) was stable both before and during infusion of lipid emulsion + heparin and saline solution without differences between the different experimental conditions. The rise in plasma fatty acid concentration was associated with a significant decline in the RR interval and in total power. Analysis of the different components of HRV showed that infusion of lipid emulsion + heparin stimulated LF components and inhibited HF components at the second and third hours of the infusion. In contrast, total power, RR interval, LF components, HF components, and the LF-HF ratio returned to baseline values at the end of the recovery period. Changes in HRV parameters during infusion of lipid emulsion + heparin were still significant after adjustment for the changes in plasma insulin concentration ($P < 0.03$ for all HRV measures) (Figure 3).

Hemodynamic measures

Infusion of lipid emulsion + heparin was associated with a significant increase in MABP that peaked at the third hour of the infusion, whereas LBF showed a similar trend for both experimental conditions (Figure 4). Thus, LVR rose significantly with the infusion of lipid emulsion + heparin, whereas it declined during infusion of saline solution. MABP, LBF, and LVR returned to baseline values during the recovery period.

Effect of propranolol infusion

Similar values for plasma glucose, insulin, fatty acid, epinephrine, norepinephrine, and renin were found at baseline for
the groups infused with lipid emulsion + heparin and lipid emulsion + heparin + propranolol without differences between the different experimental conditions (data not shown). Addition of propranolol to the infusion of lipid emulsion + heparin did not affect the trend but it smoothed the changes in HRV measures (Figure 5). Thus, infusion of lipid emulsion + heparin showed a stronger stimulating role on HRV measures than did lipid emulsion + heparin + propranolol.

Baseline values of MABP, LBF, and LVR were not significantly different between the entire group of subjects submitted to lipid emulsion + heparin (n = 120) and the subgroup submitted to lipid emulsion + heparin + propranolol (n = 8). Lipid emulsion + heparin and lipid emulsion + heparin + propranolol had similar effects on MABP, LBF, and LVR, although there were no significant differences between the 2 experimental conditions (data not shown). At the end of the recovery period, both HRV and hemodynamic measures returned to baseline.

**Correlation analysis**

Individual changes in plasma epinephrine concentration correlated with changes in the LF-HF ratio ($r = 0.61$, $P < 0.005$) and LVR ($r = 0.54$, $P < 0.02$). Such changes were independent
DISCUSSION

The results of our study showed that elevated plasma fatty acid concentrations produce SNS activation that affects both cardiac ANS activity and hemodynamic measures. Elevated plasma fatty acid concentrations are a common finding in obese subjects and seem to be a consequence of increased visceral fat accumulation with a secondary exaggeration in lipolytic activity (18). Because elevated plasma fatty acid concentrations have been implicated as a causal factor in the derangement of endothelial function (19) and associated with a greater number of premature ventricular beats (3, 4), a possible negative effect of fatty acids on the cardiovascular system cannot be ruled out. Our study showed that elevated plasma fatty acid concentrations might affect the cardiovascular system through activation of the SNS.

The relation between plasma fatty acid concentration and the ANS was suggested by Bulow et al (20, 21), who used a lipid emulsion with heparin to raise blood pressure and total peripheral resistance in pigs. Although the mechanism of this effect was not elucidated, the authors showed previously that local perfusion of adipose tissue with fatty acids causes vasoconstriction (21). Later, Stepniakowski et al (22) reported that infusion of a lipid emulsion with heparin reduced vein distensibility in healthy volunteers and increased responsiveness to phenylephrine. The latter observation suggested a direct pressor effect of fatty acids on vascular beds. Grekin et al (5) reported that portal fatty acid infusion also has significant pressor effects, which may be mediated by increased sympathetic tone.

However, several other mechanisms of action may underlie the interaction between plasma fatty acid concentration and the cardiovascular system. First, fatty acids may act as an Na⁺-K⁺-ATPase inhibitor (23), a factor that does not seem to be operating in our study. Inhibitors of Na⁺-K⁺-ATPase may increase blood pressure under some circumstances, but the response to systemic delivery is slow, requiring several hours or days (23–25). Second, humoral response to infusion of a lipid emulsion may also mediate the sympathetic response. Indeed, in this study we observed a significant increase in plasma renin concentration, although the groups receiving lipid emulsion + heparin and saline solution had similar trends in renin concentrations without differences between the 2 experimental conditions. Thus, it is likely that the increase in plasma renin concentration was not a specific effect of elevated plasma fatty acid concentration but the result of volume depletion associated with blood sampling. On the other hand, increased sympathetic discharge could also cause an increase in renin secretion. Third, it is possible that the pressor response observed in our study was a manifestation of a toxic rather than a physiologic effect. Fatty acids have detergent properties, and infusion of high doses has been used to induce experimental lung (25) and pancreatic (26) damage. The increase in catecholamines would be consistent with a stress response. However, hepatic enzyme concentrations did not change, which suggests that major hepatic damage did not occur. Fourth, hepatic neural reflex in response to alterations in delivered metabolites should also be taken into account. Glucose infusion into the portal vein alters vagal nerve traffic and activity in the hypothalamus and nucleus tractus solitarius (27). Hepatic glucose delivery increases insulin secretion mediated by the neural reflex loop. Orbach and Andrews (28) reported that infusion of long-chain fatty acids into the hepatic arteries of rabbits increased vagal afferent nerve activity. Thus, there is precedent to proposing neural reflex discharge in response to alteration in hepatic fatty acid delivery. If such a pathway was operating in humans, however, the result would likely be overactivity of the parasympa-

![FIGURE 5. Mean (±SD) cardiac measures: RR intervals, total power (TP), low-frequency (LF) components, and high-frequency (HF) components after infusion of lipid emulsion + heparin (●) and lipid emulsion + heparin + propranolol (▲). *Significantly different from lipid emulsion + heparin: *P < 0.05.](image-url)

of age, sex, and BMI. After further adjustment for the changes in plasma fatty acid concentration, the correlations were no longer significant.
The most likely mechanism to explain the fatty acid–mediated cardiac sympathetic activation found in our study. The marked rise in plasma norepinephrine and epinephrine concentrations during the infusion of lipid emulsion + heparin indicates increased SNS activity. This latter mechanism seems the most likely explication for the effect of fatty acids on the cardiac ANS. Increased sympathetic discharge in response to increased plasma fatty acid concentrations is consistent with the report that obesity is associated with an increase in SNS activity. Morgan et al. (29) reported increased renal SNS activity in obese Zucker rats and Scherrer et al. (30) found that body fat is the major determinant of muscle SNS discharge in humans. More recently, our group showed that glucose-mediated stimulation of cardiac ANS is also dependent on the amount of body fat (31). The increased heart rate during infusion of lipid emulsion + heparin also suggests a general increase in sympathetic tone. In our study, activation of the neural response was further shown by the rise in plasma epinephrine and norepinephrine found with lipid emulsion delivery, a phenomenon that is fully reversible, as shown by its disappearance 60 min after cessation of the lipid infusion. The link between plasma fatty acid concentrations and cardiac ANS activity is also strengthened by our data showing a correlation between individual changes in plasma epinephrine concentrations and the LF-HF ratio, a relation that is dependent on changes in plasma fatty acid concentration. To assess whether the effect of fatty acids on cardiac ANS activity was due to a rise in plasma catecholamine concentrations or to some other effects either at the cardiac level or at the level of the central nervous system, we compared the changes induced by the lipid emulsion on cardiac ANS activity with and without propranolol infusion. Our study showed that adding propranolol to a lipid emulsion produces a smoothed stimulatory effect on cardiac ANS activity. Thus, we conclude that the effect of plasma fatty acids on the cardiac ANS is not only direct but is mediated, at least in part, through an increase in plasma catecholamine concentrations, and in turn, a stimulation of the myocardial β1-receptors. Note that the infusion of lipid emulsion + heparin was associated with a significant increase in plasma insulin concentration, which in turn might be responsible for a stimulation of cardiac SNS activity (32). However, such a hypothesis seems unlikely because a previous study already showed that fatty acids and not insulin are responsible for adrenergic overactivity in the dorsal hand vein (33). Furthermore, in our study, all the changes in HRV measures were independent of the changes in plasma insulin concentrations. Our study also showed that infusion of lipid emulsion + heparin enhances LVR with or without the addition of propranolol. Such data agree with previous studies showing fatty acids to enhance α1-adrenergic receptor mediated pressor sensitivity (33, 34). On the other hand, our hemodynamic data allowed us to rule out the idea that the stimulator effect of lipid emulsion on HRV measures was due to an increase in LBF. In conclusion, the results of our study show that elevated plasma fatty acid concentrations may stimulate cardiac ANS activity through an increase in plasma catecholamine concentrations because simultaneous infusion of propranolol made the rise in plasma fatty acid concentrations less effective. Our results seem especially interesting in light of data showing that overweight subjects are at high risk of sudden death (6, 35). One might hypothesize that weight loss could lower cardiovascular risk through a decline in plasma fatty acid concentrations.

REFERENCES