Anesthesiology 2006; 104:1124–30

Fructose Administration Increases Intraoperative Core Temperature by Augmenting Both Metabolic Rate and the Vasoconstriction Threshold

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Background: **The authors tested the hypothesis that intravenous fructose ameliorates intraoperative hypothermia both by increasing metabolic rate and the vasoconstriction threshold (triggering core temperature).**

Methods: **Forty patients scheduled to undergo open abdominal surgery were divided into two equal groups and randomly assigned to intravenous fructose infusion (0.5 $g \cdot kg^{-1} \cdot h^{-1}$ for 4 h, starting 3 h before induction of anesthesia and continuing for 4 h) or an equal volume of saline. Each treatment group was subdivided: Esophageal core temperature, thermoregulatory vasoconstriction, and plasma concentrations were determined in half, and oxygen consumption was determined in the remainder. Patients were monitored for 3 h after induction of anesthesia.**

Results: **Patient characteristics, anesthetic management, and circulatory data were similar in the four groups. Mean final core temperature (3 h after induction of anesthesia) was 35.7° ± 0.4°C (mean ± SD) in the fructose group and 35.1° ± 0.4°C in the saline group ($P = 0.001$). The vasoconstriction threshold was greater in the fructose group (36.2° ± 0.3°C) than in the saline group (35.6° ± 0.3°C; $P < 0.001$). Oxygen consumption immediately before anesthesia induction in the fructose group (214 ± 18 ml/min) was significantly greater than in the saline group (181 ± 8 ml/min; $P < 0.001$). Oxygen consumption was 4.0 l greater in the fructose patients during 3 h of anesthesia; the predicted difference in mean body temperature based only on the difference in metabolic rates was thus only 0.4°C. Epinephrine, norepinephrine, and angiotensin II concentrations and plasma renin activity were similar in each treatment group.**

Conclusions: **Preoperative fructose infusion helped to maintain normothermia by augmenting both metabolic heat production and increasing the vasoconstriction threshold.**

INTRAOPERATIVE hypothermia results initially from an internal redistribution of body heat, which causes the largest part of the reduction in body temperature during the first hour of anesthesia[1]; subsequently, hypothermia results largely from heat loss exceeding metabolic heat production.[2] In patients who become sufficiently hypothermic, further reduction in core temperature is limited by reactivation of thermoregulatory vasoconstriction.[3]

Perioperative hypothermia is associated with numerous adverse outcomes, including morbid myocardial outcomes,[4] coagulopathy,[5] surgical wound infections,[6] prolonged recovery,[7] and prolonged hospitalization.[6] It is therefore routine for anesthesiologists to prevent perioperative hypothermia unless hypothermia is specifically indicated.

Intraoperative forced-air heating is by far the most common warming strategy.[8,9] However, other strategies can be adopted to help maintain normothermia. This includes pharmacologic methods of reducing the magnitude of redistribution hypothermia,[10] along with prewarming[11,12] and other nonpharmacologic methods.[13]

An alternative approach is to pharmacologically increase metabolic heat production, thus reducing the disparity between heat production and loss. The primary basis for this approach is the increase in energy expenditure that follows ingestion or infusion of certain nutrients, a response known as diet-induced thermogenesis.[14,15] It is well established, for example, that amino acid infusions induce perioperative thermogenesis and help to prevent hypothermia.[16,17] But interestingly, amino acid infusions also slightly increase all major autonomic thermoregulatory defense thresholds and resting core temperature.[18] Amino acids thus have both metabolic and thermoregulatory properties that help to maintain intraoperative normothermia.

Fructose is known to provoke the greatest thermogenesis among various carbohydrates.[19,20] Fructose also provokes dietary-induced thermogenesis in awake healthy volunteers and does so far better than glucose.[15] Therefore, we tested the hypothesis that intravenous fructose increases metabolic heat production in anesthetized humans. We also tested the hypothesis that fructose, like amino acids, increases the vasoconstriction threshold and thus has a thermoregulatory as well as metabolic contribution to maintaining perioperative normothermia.

This article is accompanied by an Editorial View. Please see: Lindahl S: Setting the "furnace" during anesthesia. ANESTHESIOLOGY 2006; 104:1119–20.

Materials and Methods

With approval by the Review Board on Human Experiments of Kyoto Prefectural University of Medicine, Kyoto, Japan, and written informed consent, 40 patients were enrolled in this prospective, randomized, double-

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Received from the Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan; and Department of Outcomes Research, Cleveland Clinic Foundation, Cleveland, Ohio; and the Outcomes Research Institute and Department of Anesthesiology, University of Louisville, Louisville, Kentucky. Submitted for publication October 27, 2005. Accepted for publication January 12, 2006. Supported by grant No. GM 061655 from the National Institutes of Health, Bethesda, Maryland; the Gheens Foundation, Louisville, Kentucky; the Joseph Drown Foundation, Los Angeles, California; and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, Kentucky. Mallinckrodt Anesthesiology Products, Inc., St. Louis, Missouri, donated the thermocouples used in this study. None of the authors has a financial relationship with any company related to this research.

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blinded study. All had an American Society of Anesthesiologists physical status of I or II, were aged 29–61 yr, and were scheduled to undergo open lower abdominal surgery. None was obese, febrile, or receiving vasodilators or medications likely to alter thermoregulation; none had a history of thyroid disease or dysautonomia.

Randomization

Patients were randomly allocated to two treatment groups: fructose infusion (n = 20) and saline infusion (n = 20). In the fructose infusion group (Fructon; Otsuka Pharmaceutical Factory Inc., Tokushima, Japan), infusions were given according to the manufacturer's instructions at a rate of $0.5\ g \cdot kg^{-1} \cdot h^{-1}$, for 4 h (starting 3 h before the induction of anesthesia) by using an electric infusion pump (TE-172; Terumo Corp., Tokyo, Japan). In the control group, the same amount of saline solution was administered. The infusion was started in all patients at 6:00 AM.

Each group was divided into two subgroups (n = 10): one for the measurement of esophageal core temperature and thermoregulatory vasoconstriction threshold (thermoregulatory outcomes) and the other for the measurement of oxygen consumption (metabolic outcome). Patients were allocated to treatment based on a four-way randomization based on computer-generated codes that were maintained in sequentially numbered envelopes; the envelopes were opened 3 h before surgery.

Anesthetic Protocol

This study was generally performed as previously described.[7,9,10] Briefly, all operations were performed between 9:00 AM and 1:00 PM. Patients fasted for more than 8 h before surgery. Anesthesiologists and investigators were blinded to treatment.

Ambient temperature was maintained at 24°C, and relative humidity was maintained at 40%. We allowed 30 min for the patients to become acclimated to the operating room environment; during this time, an 18-gauge catheter was inserted into a left antecubital vein for administration of ambient-temperature acetated Ringer's solution at a rate of $10\ ml \cdot kg^{-1} \cdot h^{-1}$. A 22-gauge catheter was inserted into the left radial artery for blood pressure monitoring and blood sampling. In addition, an epidural catheter was inserted *via* the L1–L2 or the L2–L3 vertebral interspace with the patient in lateral position.

Anesthesia was induced by intravenous administration of 2 mg/kg propofol and 0.15 mg/kg vecuronium bromide and was maintained with 0.4% isoflurane and 66% nitrous oxide in oxygen. An intravenous infusion of vecuronium, initially set to $0.025\ mg \cdot kg^{-1} \cdot h^{-1}$, was adjusted to maintain one or two twitches in response to supramaximal stimulation of the ulnar nerve at the wrist. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide pressure between 35 and 40 mmHg. After an initial dose of 7 ml lidocaine, 1%, without epinephrine into the epidural catheter, 0.25% bupivacaine at a rate of 5 ml/h was infused for the reminder of surgery. Patients were covered with a cotton sheet preoperatively and by drapes during surgery but were allowed to cool passively.

Measurements

Blood pressure, heart rate, oxygen saturation, end-tidal partial pressure of carbon dioxide, and end-tidal isoflurane concentrations were recorded at 5-min intervals. Upper- and lower-body sensory block levels were evaluated after emergence from anesthesia by response to cold sensation.

In the 20 patients assigned to thermoregulatory measurements (10 with fructose infusion and 10 with saline), distal esophageal temperature (core) was measured for 3 h after induction of anesthesia with a thermistor (Mon-a-therm; Mallinckrodt, St. Louis, MO). The tip of the probe was inserted one fourth the distance of the subjects' standing height from the external nares. The thermistor probes were calibrated in the same environment as that of experiments by using distilled water. The resolution of the temperature measurement system was approximately 0.024°C.

We also recorded forearm-minus-fingertip, skin-temperature gradients.[21] Briefly, thermistor probes for skin-temperature measurement were attached to the right forearm halfway between the elbow and the wrist and to the right index finger (opposite the nail bed). To quantify thermoregulatory peripheral vasoconstriction, we calculated the forearm-minus-fingertip temperature gradient because a positive temperature gradient is closely correlated with reduction in blood flow in acral regions and less affected by ambient temperature than fingertip temperature alone. Temperatures were recorded at 5-min intervals. In the thermoregulatory measurement, anesthesia was performed by using an anesthetic machine (Aestiva 5; Datex-Ohmeda, Madison, WI) with 6 l/min fresh gas flow.

In the 20 patients assigned to oxygen consumption measurement (10 with fructose infusion and 10 with saline), oxygen consumption as well as carbon dioxide production and respiratory quotient were measured before fructose infusion and during surgery using a Deltatrac (Datex Instrumentarium, Helsinki, Finland). The Deltatrac Metabolic Monitor is an open-system, indirect calorimetry device equipped with a fast differential paramagnetic oxygen sensor to measure a differential signal between inspired and expired gases, an accurate carbon dioxide sensor with a resolution of 0.01%, and a gas dilution system to measure flow. Canopy mode and respiratory mode were used for awake and anesthetized patients, respectively. Anesthesia was performed by using a Servo Ventilator 900C equipped with isoflurane vaporizer 952 (Maquet Critical Care, Solna, Sweden),

Table 1. Patient Demographics and Preoperative Values

	Thermoregulation Measurement Groups		Oxygen Consumption Groups	
	Saline (n = 10)	Fructose (n = 10)	Saline (n = 10)	Fructose (n = 10)
Age, yr	52 ± 6.4	45 ± 7.5	47 ± 9.4	47 ± 4.8
Weight, kg	58 ± 12	52 ± 11	56 ± 4	54 ± 8
Height, cm	162 ± 14	156 ± 6	159 ± 6	162 ± 8
Mean arterial pressure, mmHg	85 ± 6	87 ± 18	90 ± 13	92 ± 16
Heart rate, beats/min	84 ± 6	84 ± 10	82 ± 8	80 ± 15
Core temperature, °C	36.7 ± 0.3	36.8 ± 0.2	36.7 ± 0.2	36.7 ± 0.3

There were no statistically significant differences between saline and fructose infusion groups. Data are presented as mean ± SD for 10 subjects.

whose expiratory outlet was connected to a Deltatrac. Each measurement was performed over a period of 5 min, obtaining one measurement every minute. All sets of five single measurements showed an SD of less than 10%, so effects of a fluctuating fraction of inspired oxygen on metabolic measurements could be excluded. The mean of these single measurements was used as the data at 15-min interval. All calibrations (gas calibration, pressure calibration, and flow calibration) were performed just before every patient measurement by using the calibration kit supplied by the manufacturer according to the manufacturer's manual. During measurement of oxygen consumption, anesthesia was maintained with 1% isoflurane in 33% oxygen without nitrous oxide. Measurements were averaged over 1-min intervals.

Among patients assigned to the thermoregulatory measurements, blood was sampled from the radial artery 20, 90, and 180 min after induction of anesthesia. Samples were immediately centrifuged at 4°C, and aliquots of the plasma were stored at −80°C until assayed. Plasma epinephrine and norepinephrine were measured by high-performance liquid chromatography with an electrochemical detector after alumina extraction. Radioimmunoassay kits were used to evaluate plasma renin activity (Renin RIABEAD; Dainabot, Tokyo, Japan) and plasma angiotensin II concentrations (Angiotensin II, Nichols Institute, CA). Also, the samples were used for the measurements for blood gas data and blood glucose level by using ABL 725 (Radiometer, Copenhagen, Denmark).

Data Analysis

As in previous studies, we defined the vasoconstriction threshold as the core temperature that triggered a rapid increase in the skin-temperature gradient. The threshold was determined *post hoc* for each patient by an investigator blinded to treatment. When the threshold was reached, thermal responsiveness (gain) was defined by the slope of a regression between the skin-temperature gradient and core temperature in each individual.

Baseline values were averaged over the 30 min immediately preceding induction of general anesthesia. Intraoperative values were presented over time or first averaged within each patient, and then averaged among the patients in each group.

The difference in oxygen consumption was converted to equivalent metabolic heat production, assuming the caloric value of oxygen to be 4.82 kcal/l (respiratory quotient = 0.82). We chose a standard value for the respiratory quotient because the caloric value of oxygen varies only slightly over the full range of respiratory quotients; use of a standard value thus introduces minimal error in the calculation of metabolic heat production.[22] The expected difference in mean body temperature between the two treatment groups was calculated by dividing the difference in metabolic heat production by body weight and the specific heat of humans (0.83 $kcal \cdot kg^{-1} \cdot °C^{-1}$).[23]

Thermal responsiveness (gain) and vasoconstriction thresholds were analyzed with general linear regression models for one-way analysis of variance (with one between factor), followed by Scheffé multiple comparison tests. The effects of fructose infusion and time on the cardiovascular, thermoregulatory, and hormonal responses were analyzed by general linear regression model procedures for two-way analysis of variance with repeated measures (one between and one within factor) and subsequently Scheffé multiple comparison tests. Results are presented as mean ± SD; $P < 0.05$ was considered statistically significant.

Results

Patients in the treatment groups had comparable morphometric and demographic characteristics (table 1). Because nitrous oxide was not used in the patients in whom oxygen consumption was measured, these patients required more isoflurane. However, anesthetic management was otherwise similar in the patients given fructose or saline (table 2). Upper and lower body sensory block levels (median, range) were also comparable between the fructose group (T10, T7–T12) and the saline group (T10, T8–T12).

Table 2. Intraoperative Data

	Thermoregulation Measurement Groups		Oxygen Consumption Groups	
	Saline	Fructose	Saline	Fructose
Final mean arterial pressure, mmHg	84 ± 6	78 ± 18	75 ± 15	90 ± 6
Final heart rate, beats/min,	70 ± 8	67 ± 12	67 ± 8	78 ± 5
End-tidal isoflurane, %	0.4 ± 0.3	0.4 ± 0.3	1.1 ± 0.2	1.1 ± 0.2
Final core temperature, °C	35.1 ± 0.4	35.7 ± 0.4*	NA	NA
Vasoconstriction threshold, °C	35.6 ± 0.3	36.2 ± 0.3†	NA	NA
Vasoconstriction gain	9.0 ± 4.1	10.8 ± 3.4	NA	NA
Fluid replacement at 180 min, ml	2,133 ± 516	2,075 ± 350	1,825 ± 200	1,950 ± 265
Blood loss at 180 min, g	238 ± 79	275 ± 93	162 ± 93	138 ± 125
Urine output at 180 min, ml	326 ± 113	382 ± 183	227 ± 124	294 ± 82

Isoflurane concentrations were greater in the oxygen consumption groups because nitrous oxide was not used in these patients. Data are presented as mean ± SD for 10 subjects.

* $P = 0.001$ for saline *vs.* fructose infusion group. † $P < 0.001$ for saline *vs.* fructose infusion group.

NA = not applicable.

Thermoregulatory Outcomes

Patients assigned to fructose infusion had significantly greater core temperatures than those given saline starting at 20 min after induction of anesthesia and persisting throughout the measurement period (fig. 1) Mean core temperature 180 min after induction of anesthesia was 35.7° ± 0.4°C in the fructose group and 35.1° ± 0.4°C in the saline group ($P = 0.001$).

The forearm-minus-fingertip temperature gradient immediately before induction of anesthesia was 3.5° ± 1.3°C in the saline group and 3.3° ± 1.4°C in the fructose group. Patients assigned to the fructose infusion group experienced vasoconstriction at a significantly higher esophageal core temperature (36.2° ± 0.3°C) than those in the saline infusion group (35.6° ± 0.3°C; $P < 0.001$; fig. 2). The gain of vasoconstriction (slope of the forearm-minus-fingertip temperature gradient/core temperature relation below the threshold) was not significantly altered by the fructose infusion: 10.8 ± 3.4 in the fructose group and 9.0 ± 4.1 in the saline group (table 2).

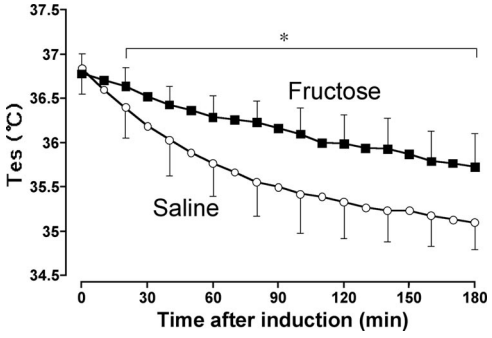

Fig. 1. Core temperature measured at the distal esophagus (Tes) during surgery. Patients receiving the fructose infusion had significantly greater core temperatures than those receiving saline (* $P = 0.001$) starting 20 min after induction of anesthesia until the end of the monitoring period (180 min after induction). Data are presented as mean ± SD for 10 patients in each group.

Metabolic Outcomes

Oxygen consumption before fructose administration was similar in the fructose (179 ± 13 ml/min) and saline (183 ± 17 ml/min) patients. Oxygen consumption just before induction of anesthesia in the fructose group (214 ± 18 ml/min) was significantly greater than in the saline group (181 ± 18 ml/min; $P < 0.001$). In addition, patients given fructose had significantly greater oxygen consumption for 135 min after induction of anesthesia (fig. 3). Oxygen consumption was 4.0 l greater in the fructose than saline patients over 3 h of anesthesia, which corresponded to an expected difference in mean body temperature of only 0.4°C.

Carbon dioxide production before infusion showed no significant difference between the saline group (147 ± 19 ml/min) and the fructose group (142 ± 16 ml/min) but increased significantly in the fructose group (201 ± 26 ml/min) just before induction of

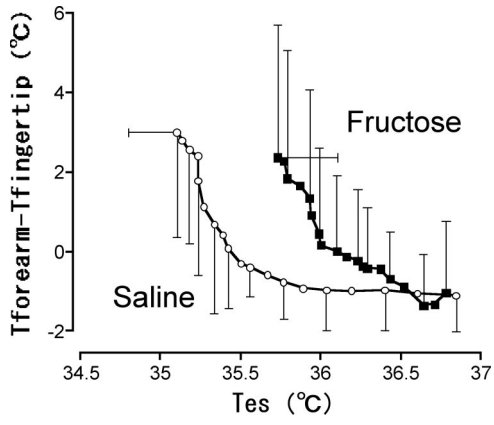

Fig. 2. Relationship between the forearm-minus-fingertip temperature gradient ($T_{forearm} - T_{fingertip}$) and distal esophageal (core) temperature (Tes). Patients assigned to fructose infusion vasoconstricted (increase in the gradient) at a significantly higher core temperature than did those receiving saline infusion ($P < 0.001$). Once started, though, the gain of vasoconstriction (incremental increase in the gradient) was similar in the two groups. Data are presented as mean ± SD for 10 patients.

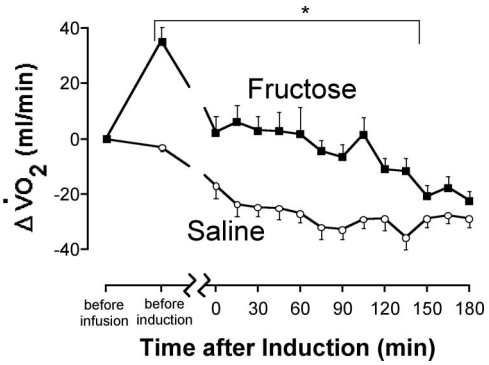

Fig. 3. Change in oxygen consumption ($\dot{V}o_2$) during the study. Oxygen consumption increased by 33 ± 16 ml/min in the fructose infusion group immediately before induction. It remained greater than the $\dot{V}o_2$ of the saline infusion group for 135 min after induction of anesthesia (*$P < 0.001$). Data are presented as mean ± SD for 10 patients.

anesthesia, compared with the saline group (146 ± 19 ml/min; $P < 0.001$). This increased level was maintained for 135 min after induction of anesthesia. Respiratory quotients before infusion were similar between the saline group (0.80 ± 0.04) and the fructose group (0.79 ± 0.03). Also, the respiratory quotient was significantly larger in the fructose group (0.93 ± 0.05) than that in the saline group (0.81 ± 0.03) before induction of anesthesia ($P < 0.001$). The significant increased level was maintained for 180 min after induction of anesthesia.

Arterial blood gas measurements, including pH and base excess, and blood glucose level were similar between the groups receiving fructose and those receiving saline during the study (data not shown). In addition, there were no significant differences in plasma epinephrine, norepinephrine, or angiotensin II concentrations or plasma renin activity (fig. 4).

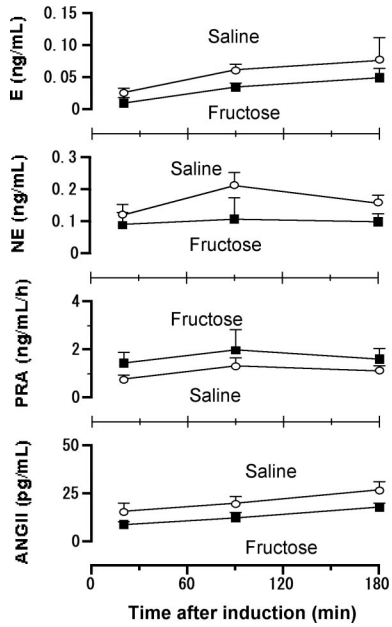

Fig. 4. Plasma epinephrine (E), norepinephrine (NE), plasma renin activity (PRA), and angiotension II (ANGII) serum concentrations during the study. The values did not differ between the infusion groups at any time. Data are presented as mean ± SD for the 10 patients in whom oxygen consumption was measured.

Discussion

The thermic effect of nutrition is divided into an obligatory component representing the theoretical metabolic costs for processing and storing ingested nutrients and a facultative component representing increased systemic energy expenditure.[24] Facultative thermogenesis is best characterized for amino acids which increase metabolic rate, thereby augmenting perioperative core temperature.[16,25,26] Typically, amino acids increase metabolic rate by approximately 50% during anesthesia,[26] which is greater than the increase observed in unanesthetized humans.[14] In this study, we showed approximately 20% increase in metabolic rate by fructose during anesthesia.

Amino acids, however, are hardly the only nutrient that can induce thermogenesis. Fructose, a natural carbohydrate found in fruit and honey, also induces facultative thermogenesis. Although fructose and glucose are both hexose monosaccharides, their metabolism differs considerably.[27] Much glucose is metabolized by peripheral muscle tissue whereas fructose is metabolized entirely in the liver.[28] Fructokinase, which is an enzyme responsible for the phosphorylation of fructose, is 10 times more active than the analogous enzymes glucokinase and hexokinase, which phosphorylate glucose.[29] Fructose is thus metabolized more rapidly than glucose because it bypasses phosphofructokinase, which is normally the rate-limiting enzyme for glycolysis.[30] Fructose induces a small increase in insulin concentration, which permits hepatic glucose production to continue at lower concentrations than it does with glucose alone. Fructose is therefore a better substrate for hepatic gluconeogenesis than glucose.

Among the common carbohydrates, fructose produces the most diet-induced thermogenesis.[19,20] For example, Tappy *et al.*[15] observed that the increment in energy expenditure after oral fructose ingestion was 62% greater than that observed with a comparable dose of glucose in awake healthy volunteers. They also reported that oral fructose increased oxygen consumption by 11% compared with the basal level in the awake state. Similarly, infusion of fructose at a rate of 50 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ increased thermogenesis by 7.5%.[31] A consequence is that fructose administration increases core temperature in unanesthetized volunteers, although glucose administration does not.[14] Overall, fructose administration is reported to be associated with an approximately 10% increase in metabolic rate in unanesthetized humans. It is advantageous for fructose administration to show a large thermic effect with little change in blood

glucose and insulin concentrations. The increases in glucose and insulin were reported to be significantly smaller with the fructose meal when compared with the glucose meal.[15,27] This study did not show any significant difference of blood glucose between the groups, although insulin concentration was not measured.

In our patients, fructose increased intraoperative oxygen consumption by approximately 20%. This enhanced metabolic response to fructose administration may simply result from the fact that we used intravenous rather than oral administration. However, it is also possible that, as with amino acids, general anesthesia *per se* enhances the metabolic response to fructose administration. The mechanism by which either type of nutrition might enhance diet-induced thermogenesis remains speculative but may involve central thermoregulation system, because these nutrients alter the thermoregulatory vasoconstriction threshold.

Over the 3-h anesthetic period, the metabolic rate was 19 kcal greater in the patients given fructose; this corresponds to a predicted increase in mean body temperature of 0.4°C, which is less than the actual difference of 0.6°C in core temperature after 3 h of anesthesia. Assuming accurate metabolic rate and core temperature measurements, the disproportionate increase in core temperature must have resulted from an alteration in the internal distribution of body heat. Specifically, the increase core temperature that was not explained by hypermetabolism in the fructose group must have resulted from an increase in the core-to-peripheral tissue temperature gradient.

Body heat is not normally evenly distributed: Instead, the core thermal compartment is usually 2°–4°C warmer than peripheral tissues[1]—a gradient that is required by the second law of thermodynamics if metabolic heat is to be dissipated to the environment. The temperature gradient between the core and peripheral thermal compartments at steady state is determined by environmental conditions, metabolic rate, and the vasomotor tone. In our patients, environmental conditions were similar in each group, and the effects of metabolism *per se* on heat production were accounted for above. That leaves vasomotor tone as the remaining major influence.

The vascular response to cold exposure is dominated by arteriovenous shunts in fingers and toes.[32] Although the shunts themselves are distal, constriction is effective in constraining metabolic heat to the core thermal compartment, thus increasing the core-to-peripheral tissue temperature gradient.[3] In fact, the threshold for vasoconstriction was 0.6°C greater in the patients given fructose (although gain was well preserved, when vasoconstriction was activated). Our results thus suggest that patients given fructose remained warmer both because fructose increased metabolic heat production and because arteriovenous shunt vasoconstriction constrained some metabolic heat to the core thermal compartment. Why fructose should increase the vasoconstriction threshold remains unknown but is analogous to the increase we observed previously with amino acid infusion during spinal anesthesia[17] and in unanesthetized volunteers,[18] suggesting that the increase may be a function of intraoperative nutrition rather than fructose *per se*.

The facultative component of diet-induced thermogenesis reportedly results from augmented central activation of the sympathoadrenal system.[14,24] We were unable to identify significant differences in plasma epinephrine, norepinephrine, or angiotensin II concentrations or in plasma renin activity after fructose infusion. Although these data might be taken to suggest that activation of the sympathoadrenal system was not the cause of fructose-induced thermogenesis, it is at least equally likely that plasma catecholamine concentrations poorly reflect turnover in the liver. Consistent with this theory, high-carbohydrate diets are known to increase norepinephrine turnover in rat liver.[33]

In summary, these findings suggest that preoperative fructose infusion helps to maintain intraoperative normothermia by maintaining a higher metabolic rate and increasing the threshold triggering thermoregulatory vasoconstriction. The protection offered by fructose infusion was similar to that observed previously with amino acids, suggesting that fructose is a reasonable alternative.

Nancy Alsip, Ph.D. (University of Louisville, Louisville, Kentucky), provided editorial assistance.

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