Impaired glucose tolerance after brief heat exposure: a randomized crossover study in healthy young men

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A high demand on thermoregulatory processes may challenge homeostasis, particularly regarding glucose regulation. This has been understudied, although it might concern millions of humans. The objective of this project was to examine the isolated and combined effects of ion. Two experimental randomized crossover studies were conducted. Ten healthy young men participated in study A, which comprised four sessions in a fasting state at two metabolic levels (rest and exercise at 60% of maximal oxygen uptake for 40 minutes) in two environmental temperatures (warm: 31°C and control: 22°C). Each session ended with an ad e healthy young men underwent two 3-hr oral glucose tolerance tests (OGTT) in warm and control environmental temperatures. Venous blood was sampled at several time points. In study A, repeated measure ANOVAs revealed higher postprandial serum glucose and insulin levels with heat exposure. Glycemia following the OGTT was higher in the warm temperature load was also affected by the environmental temperature (temperature-by-time interaction, $P = 0.030$), with differences between the warm and control conditions evidenced up to 90 minutes after the glucose load (all $P < 0.033$). These studies provide evidence that heat exposure alters short-term glycoregulation. The implication of this environmental factor in the

SUMMARY STATEMENT

The aim of this project was to determine if environmental temperature alters glucose crease in blood glucose when the environmental temperature is warm.

Short title: Glycoregulation challenge in the heat

Keywords: metabolism; exercise; environment; oral glucose tolerance test; glucose; glucoregulation

INTRODUCTION

[illegible] glucose metabolism has potentially serious health consequences. The main factors that challenge glucose homeostasis include dietary carbohydrate restriction and ingestion and exercise. Exercise markedly increases glucose uptake, but this is usually compensated by hepatic and muscle glycogenolysis so that blood glucose remains stable or increases only slightly in most [illegible] seem to modulate glucose regulation (3–5).

Insulin is the primary mediator of carbohydrate fuel fluxes under most circumstances. Exercise causes the translocation of GLUT4 glucose transporters to the cell surface, which then increases insulin sensitivity. The combination of exercise and heat stress poses a [illegible] for blood glucose and its determinants during the recovery period have never been described.

Thus, our aim was to examine the isolated and combined effects of exercise and moderate heat stress on the subsequent recovery and postprandial glycemic response. The first study presented in this report (study A) investigated the effects of ambient temperature (warm vs. [illegible] lism. The second study (study B) investigated the effects of ambient temperature on glucose tolerance as assessed by a 3-hr oral glucose tolerance test (OGTT).

MATERIALS AND METHODS

Both studies were performed after an overnight fast, starting from 6:30 AM. The participants were instructed to abstain from high intensity exercise and alcohol intake the day before each session and to have sufficient carbohydrate intake the day before their first session and comparable food intake from one session to another.

The study consisted of an initial evaluation and familiarization session followed by four experimental sessions using a latin square-based randomized crossover design, with at least 4 days between sessions. The participants were tested in random order in each of the following conditions: rest in a control ambient temperature (rest-22°C), rest in a warm ambient [illegible] xercise in a warm ambient temperature (ex-31°C). The exercise and corresponding rest period lasted 40 minutes. They were followed by 35 minutes of recovery or additional rest and then an ad libitum meal that lasted 25 minutes. In each experimental session, six blood samples were drawn: 5 minutes before the exercise/rest period (T0), after 20 minutes of exercise/rest (T20), [illegible] (T55 and T70), and at the end of the meal (T100).

Study B - OGTT

The aim was to produce recent data on heat-acclimated subjects performing a standard glucose tolerance test, so as to potentially replicate data reported previously by others The

22°C) and warm (31°C), presented in a random order. They drank a solution containing 75 g glucose (Gluco75; ODILsas, Dijon, France) within 5 minutes. Blood samples were drawn at 0, 30, 60, 90, 120 and 180 min (T0, T30, T60, T90, T120, T180). The participants remained in a seated position throughout the entire OGTT and engaged in quiet activities.

Participants and ethics

Ten men with normal body mass index (21.3±1.7 kg/m^2) participated in study A, three of whom also participated in study B. Twelve men (23.2±2.4 kg/m^2) participated in study B (Table 1). Participants were recruited from October 2013 to November 2014. Advertisements urrounding sports centers were used. During the initial contact by phone or e-mail, the eligibility requirements were explained to the potential participants and some of them were immediately discarded (smokers, dieters, individuals with diseases or low or high weight at birth). The others were asked to come for a second screening, during which they completed invited to participate in the study and signed a written informed consent form before the first session. They were financially compensated for completing the study. All procedures used in this study were in accordance with institutional guidelines, and were in accordance with the Helsinki Declaration of 2013. The study procedures were approved by the Human Subject gistered in EudraCT (2013-003206-25) and ClinicalTrials (NCT02157233).

Cardiopulmonary exercise testing (study A)

An incremental exercise test to exhaustion was performed on a cycle ergometer. The ed using a breath-by-breath ergospirometry system (MetaLyzer 3B, Cortex, Leipzig, Germany).

Physical fitness was assessed by maximal or peak oxygen uptake ($\dot{V}O2$) and the ventilatory anaerobic threshold, determined as the point at which the ventilatory equivalent for oxygen starts to rise nonlinearly while the ventilatory equivalent for carbon dioxide remains minimum of 15 minutes of rest, the subjects were familiarized with the material and procedures used during the exercise sessions. The ergometer power target to reach 60-65% of maximal oxygen uptake was identified based on individual energetic cost and then adjusted according to the ventilatory anaerobic threshold and the metabolic parameters observed at quasi-stable state at

Exercise / Rest sessions (study A)

During the rest sessions, the participants rested by lying comfortably supine on a medical examining table in the laboratory for 40 minutes while breathing periodically (first 8 minutes, ed with a pneumotachograph, for the collection and analysis of their inspired and expired air with the

ergospirometry system (MetaLyzer 3B, Cortex, Leipzig, Germany). During the corresponding period of the exercise sessions, they cycled on the ergometer used in the initial session and the exercise intensity was set at the power identified during the familiarization rectangular

Ad libitum meal (study A)

Thirty-five minutes after each experimental session, the participants moved to an isolated part of the room. They were presented with a tray of 12 pieces of ham and cheese sandwiches of ition table (8)), along with a glass of water equal to 4mL/kg body weight. The meal lasted 25 minutes. They were instructed to eat until they were "comfortably full" and were given another fresh tray of sandwich portions 10-15 minutes after starting the meal. Total energy intake from the meal was calculated by weighing all products before and after the breakfast meal in a on s (1082 ± 267 kcal, mean ± standard deviation).

Blood sampling and analysis

In each session, an intravenous cannula was inserted into an antecubital vein after the n. Venous blood was collected into serum separator gel tubes at each sampling time. Blood samples were immediately placed in a refrigerator at 4°C.

At each sampling time, a subsample of blood was also collected for immediate blood lactate assay using the Lactate Pro IITM analyzer (KDK Corporation, Arkray, Kyoto, Japan) and in 2 hours on a Cobas 6000 automatic platform (Roche, Mannheim, Germany) (<c501> module for glucose and <e601> module for insulin and cortisol). The total area under the curve (AUC) for lactate, glucose, insulin and cortisol was calculated according to the trapezoidal rule. Insulin sensitivity was calculated using the Matsuda index and the HOMA insulin resistance

Clinical measurements

Before the incremental exercise test for study A, and during the session in control environmental temperature for study B, the participant's height and weight were measured an Inbody S10 body composition analyzer (Biospace, Seoul, South Korea).
During the familiarization period and all experimental sessions, aural canal temperature was measured with a tympanic thermocouple probe (Mon-atherm Tympanic; Mallinckrodt Medical) held in position and isolated from the external environment with cotton and surgical

Statistical analyses

The required number of participants was a priori calculated using G*power 3.1 for Mac.

Alpha error probability threshold and power were 0.05 and 0.90, respectively. The [illegible] d 0.85 for correspondence among repeated measures.

All results were analyzed with the SPSS v.20 software package (SPSS Inc, Chicago, IL, USA). Data are presented as mean [95% interval confidence] or median [lower-upper quartile] according to the distribution, except in figures where SEMs are used.

[illegible] VAs were performed to determine the effects of metabolic level (2 levels: rest and exercise, in study A only), environmental temperature (2 levels: control and warm), time (6 levels), and their interactions on the outcome variables measured over the study period. Data were tested for sphericity using Mauchly's test and if the assumption of sphericity was violated, the [illegible] m. As the single effect of time was significant for all the variables, one-factor ANOVA was performed at each time of measurement, followed by Tukey's post hoc tests to identify mean differences among conditions. The AUC were analyzed with two-factor (study A: 2 levels of metabolic activity and 2 levels of environmental temperature) and one-factor (in study B) ANOVAs [illegible] n-normally distributed, Wilcoxon's rank-sum tests were used to assess the effect of environmental temperatures on the Matsuda and HOMA indices.

Correlation analyses were performed using Spearman's nonparametric rank correlation coefficients to test associations between glucose values at different time points.

No significant variation in tympanic temperature was observed throughout the sessions, indicating that the thermoregulatory process were efficient and not seriously challenged by the environmental conditions.

Study A focused on the understanding of exercise performed in the heat on glucose [illegible] ercise. The warm environmental temperature resulted in a significantly increased heart rate at exercise (at T40, single effects of metabolic level and environmental temperature: P< 0.0001, interaction: P = 0.037, Table 2), with no significant difference with the control temperature on oxygen uptake (P = 0.720). The significant interaction (P = 0.021) of environmental temperature and [illegible] 31°C than at 22°C, as another marker of increased metabolic solicitation in the exercise in warm conditions. Lactatemia (Fig. 2A) was higher in the exercise sessions than the rest sessions (2.0 [1.7-2.4] mmol/l vs. 1.2 [1.1-1.4], P < 0.0001), and higher in the control (22°C) than at warm (31°C) temperature (1.7 [1.5-2.0] mmol/l vs. 1.5 [1.3-1.7], P = 0.006). The interactions of [illegible] 0.009 and P < 0.0001, respectively).

Glycemia and insulinemia (Figs. 2B and 2C) were affected by the environmental temperature (glycemia: 4.5 [4.4-4.7] mmol/l vs. 4.9 [4.7-5.1], P < 0.0001; insulinemia: 68.6 [50.0-87.2] pmol/l vs. 98.5 [68.6-128.4], P = 0.012, in control and warm environment, respectively), as [illegible] pectively).

Environmental temperature, and the temperature-by-metabolic level interaction also had significant effects on glucose AUC ($P < 0.0001$ and $P = 0.025$, respectively).

The single effect of metabolic level on glycemia and insulinemia was not significant, nor was their interaction with time (all $P > 0.208$). The temperature-by-metabolic level interaction
230 8). Insulin AUC was affected by the environmental temperature ($P = 0.022$). The metabolic level and the temperature-by-metabolic level interaction effects on insulin AUC were not significant (all $P > 0.482$).

Glucose values at T0 were significantly correlated with other glucose values. The strength of
235 ions (from rho = 0.718 at T20 to rho = 0.319 at T100, all $p<0.045$). On the other hand, post-prandial glucose values were not significantly associated with glucose measured from blood sampled immediately before the meal (rho = 0.299, $p=0.061$), and the strongest association was observed with T20 (rho = 0.425, $p=0.006$).

240 (499 [423-576] mmol/l vs. 384 [336-433], $P = 0.016$, Fig. 2D). The metabolic level-by-time interaction was significant ($P = 0.003$). No effect involving environmental temperature reached significance (single effect: $P = 0.686$, interactions with time, environmental temperature, or both, all $P > 0.095$).

245 the warm environmental temperature as compared with the control: 5.7 [5.4-5.9] mmol/l vs. 5.0 [4.5-5.6], $P = 0.026$). ANOVAs revealed that the kinetics of glucose response to the glucose load was also affected by the environmental temperature, with a significant temperature-by-time interaction ($P = 0.030$). Differences between the warm and control conditions were evidenced
250 before the glucose load, 120 or 180 minutes after glucose ingestion (all $P > 0.325$).

Insulinemia (Fig. 3B) was not affected by the environmental temperature (single effect: $P = 0.701$, environmental temperature-by-time interaction: $P = 0.388$). Insulin AUC did not differ with environmental temperature (single effect, $P = 0.652$).

255 d by the environmental temperature. The Matsuda index values were 7.5 [5.7-12.7] and 6.6 [5.9-7.5] ($P = 0.308$) at 22°C and 31°C, respectively. The HOMA insulin resistance index values were 1.4 [1.0-2.1] and 1.2 [1.1-1.7] ($P = 0.308$) at 22°C and 31°C, respectively.

There were single effects of environmental temperature ($P < 0.0001$) and time ($P < 0.0001$) on
260 46).

DISCUSSION

We hypothesized that metabolic level and environmental temperature would influence glucose regulation, separately or by interaction. Our main findings are that 1) a meal or a
265 ent, and 2) 40 minutes of preliminary exercise provides no significant short-term improvement in this temperature-related alteration in glucose metabolism.

Increased hepatic glucose production via augmented sympathetic stimulation is a first track for the interpretation of blunted glucose tolerance in the warmth. The liver is indeed critical to combined. Hargreaves et al. (12) demonstrated that hyperglycemia during exercise at 40°C is caused by an increase in liver glucose output. The association between glucose data observed at T100 and those observed earlier in the session suggests some early drive of the post-prandial glucose excursion, as if the meal would accentuate the preliminary glucose variation. It occur quite early. The kidneys also contribute to this regulation (13). It has been demonstrated in dogs that an infusion with cortisol, glucagon, and epinephrine increases renal glucose release (14). In our study, cortisol rose during the exercise in both environmental temperatures, and decreased during the corresponding period at rest. Thus, the high level of glucose during the sed hepatic and renal glycogenolysis and gluconeogenesis driven by sympathetic stimulation reinforced by epinephrine and cortisol. However, the discrepancies between the patterns of glucose and cortisol levels suggest that the increased glucose release from these organs did not make a major contribution to the relative hyperglycemia observed in the early postprandial state. g exercise, concomitantly with high quantities of the gluconeogenic precursors: glutamine, glycerol and lactate. Intestinal territories are another potential source of glucose output, since splanchnic glucose is increased in animal during exercise and heat stress (15). Because we observed large environmental temperature-related blood glucose differences in the postprandial state (study intestinal gluconeogenesis was the primary explanation for our results. Another possible gut phenomenon is the absorption rate. Because heat stress shifts blood volume from thoracic and splanchnic regions presumably to aid in heat dissipation (16), these adaptations seem likely to lead to underestimation of glucose tolerance limitation in a hot environment.

ose uptake by muscle or other tissues. It is widely acknowledged that the environmental temperature influences substrate use at rest and during exercise (17,18), with a shift toward increased carbohydrate metabolism during exercise and heat stress and a concomitant decrease in fat oxidation. Muscle glycogenolysis is increased in the heat through direct mechanisms (19), as evels have frequently been observed during exercise at intensities and environmental temperatures comparable to those of our study (21) and are known to activate glycogenolysis. Adrenalin and cortisol levels are generally analyzed together since cortisol has a permissive effect on adrenalin. Accordingly, the lactatemia and cortisolemia in study A were higher during and) and T40) performed in a warm environment than in control, although there was no significant temperature-related difference in cortisol. It can be interpreted as an evidence that the increased arterialization in the heat and at exercise does not bias these studies. This also suggests that glucose or glycogen utilization was increased during exercise, in particular when our studies were all acclimated and this probably reduced sympathetic stimulation and the adrenalin release in the warm condition, which would explain the absence of a temperature-related difference in the respiratory exchange ratio (as a reflection of substrate use) during exercise. Cortisol release appeared more related to the metabolic level, and either slightly or not rhythm of cortisol was normal, in both the warm and control sessions. A shift toward higher values at

22°C was observed, probably reflecting the relative stress of this environmental temperature for the heat-acclimated participants.

Muscle glucose utilization and adipose tissue glucose storage are also widely influenced by membrane. Decreased translocation inhibits glucose entry and subsequent utilization or storage. The effect of heat, combined with rest or exercise, on insulin-dependent and -independent GLUT4 translocation is not straightforward. In vivo and in vitro studies evidence that an elevated muscle temperature per se stimulates muscle glucose uptake through amplification of the enhanced glycogenesis when heat is locally applied (23). However, glycogen resynthesis after exercise is slowed down with whole-body heat exposure (24), the latter observation fitting very well with ours in the sense that it suggests some form of glucose intolerance, if not insulin resistance. The exact mechanisms involved cannot be specified from this project, but direct study B, in particular the absence of significant difference related to the environmental temperature on insulinemia. There are hypotheses to explain transiently blunted glucose tolerance in the heat. A systemic deleterious effect of heat on insulin signaling or GLUT4 translocation mechanisms is a candidate. A change in the sympathovagal balance might also occur in warm renal axis, which is known to influence glucose tolerance (25), could occur in the heat. If this is the case, an exacerbated response would occur at exercise, characterized by a greater decrease in parasympathetic activity and an increase in sympathetic activity. This would explain why the preliminary 40-minute-exercise did not lead to a short-term improvement in the altered).

The higher blood glucose values during the sessions in moderate heat could also be related to changes in the peripheral blood flow. The arteriovenous glucose difference is expected to be reduced in the territories of the blood sample in the sessions performed at 31°C due to increased arterialization of the antecubital blood in relation with the opening of the se vascular considerations have been highlighted in the very few studies on the question, so that authors consider as “apparent” the impairment of glucose tolerance at 30-35°C as compared with 20-25°C (4,5) on studies at rest. We observed (in study A) and others reported (3–5,11) an elevation of postprandial (or post glucose load) insulin concentration. This bears out that the nenon.

So, despite limitations in sample size and duration of the postprandial observation period, the study A results can be interpreted as demonstrating that environmental temperature has a stronger short-term effect on glucose regulation than metabolic level, although the latter is widely acknowledged as a strong determinant of metabolic health, including the prevention of

To the best of our knowledge, this is the first randomized crossover study including exercise and rest which is focused on the association between glucose tolerance and warm ambient temperature. In this way, our observations from study A and B are complementary to previous isolated studies reporting increased glycemia and/or insulinemia in a warm environment (3– ed by high environmental temperature in acclimated individuals and that preliminary exercise does not provide significant short-term improvement in this temperature-related alteration in glucose metabolism.

Whether to not this effect is time-limited and related to peripheral vascular adaptations, it is o a greater understanding of glucose tolerance and type 2 diabetes in populations living in tropical and equatorial regions or exposed to warm temperatures. If our observations are confirmed and identified as acute only, this would indicate the need for standardizing or correcting for the temperature during glucose tolerance testing. This point has been raised by others reporting gh not yet acted upon. Given that elevated blood glucose induces oxidative stress and inflammation and alters insulin sensitivity, postprandial glycemia may ultimately have a strong impact on the pathophysiology of metabolic and cardiovascular disease (28). Long-term consequences can theoretically be expected. In our studies on young healthy trained men acclimated to the heat in a warm environment, the effect was not present at all time points, and we did not observe significant difference in insulin values or insulin sensitivity during the OGTT. Collection of data on similar protocols with participants with less physical fitness and established metabolic impairments would be of interest.

ıs living in warm regions like India, the Caribbean, or the Middle East. If future studies demonstrate chronicity, this would suggest that the prevalence cannot be explained only by a given populations' genetic background or lifestyles, but that high mean temperature may be involved. This study clearly indicates the need for further investigation of the mechanistic

These studies provide evidence that heat exposure alters short-term glycoregulation. Whether environmental temperature has a chronic impact on the pathophysiology of type 2 diabetes has not been determined. We propose that it should be considered it as a potential contributor to the diabetes epidemic.

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CLINICAL PERSPECTIVES

- Millions of humans reside in regions chronically or temporarily exposed to heat, m regions (India, Caribbean, Middle-East).
- We report an exaggerated increase in blood glucose after a meal or a glucose load taken in a warm environmental temperature.
- Our results evidence the need for standardization or correction of the temperature s of type 2 diabetes in warm regions cannot be explained only by a given populations' genetic background or lifestyles, but that high environmental temperature may be involved.

REFERENCES

) Biochem Physiol B Biochem Mol Biol [Internet]. 1998 May [cited 2015 Jun 24];120(1):89–107. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9787780

2. Wahren J, Felig P, Ahlborg G, Jorfeldt L. Glucose metabolism during leg exercise in man. J Clin Invest [Internet]. 1971 Dec [cited 2015 Jun 24];50(12):2715–25. Available http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=292221&tool=pmcentrez&rendertype=abstract
3. Akanji AO, Bruce M, Frayn K, Hockaday TD, Kaddaha GM. Oral glucose tolerance and ambient temperature in non-diabetic subjects. Diabetologia [Internet]. 1987 Jun from: http://www.ncbi.nlm.nih.gov/pubmed/3678662

4. Frayn KN, Whyte PL, Benson HA, Earl DJ, Smith HA. Changes in forearm blood flow at elevated ambient temperature and their role in the apparent impairment of glucose tolerance. Clin Sci (Lond) [Internet]. 1989 Mar [cited 2015 Jun 24];76(3):323–8.

5. Moses RG, Patterson MJ, Regan JM, Chaunchaiyakul R, Taylor NA, Jenkins AB. A non-linear effect of ambient temperature on apparent glucose tolerance. Diabetes Res Clin Pract [Internet]. 1997 Apr [cited 2015 Jun 24];36(1):35–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9187413

ess. Sports Med [Internet]. 2001 Jan [cited 2015 Jun 11];31(1):47–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11219501

7. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol. 1973;35:236–43.

from: https://pro.anses.fr/TableCIQUAL/index.htm

9. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care [Internet]. 1999 Sep [cited 2015 Apr 15];22(9):1462–70. Available from:

10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia [Internet]. 1985 Jul [cited 2015 Jan 20];28(7):412–9. Available from:

11. Akanji AO, Oputa RN. The effect of ambient temperature on glucose tolerance. Diabet Med [Internet]. 1991 Dec [cited 2015 Jun 24];8(10):946–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1838046

12. Hargreaves M, Angus D, Howlett K, Conus NM, Febbraio M. Effect of heat stress on

l 2015 Jun 11];81(4):1594–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8904574

13. Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. Diabetes Care [Internet]. 2001 Feb [cited 2015 May 19];24(2):382–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11213896

al. Impact of chronic stress hormone infusion on hepatic carbohydrate metabolism in the conscious dog. Am J Physiol [Internet]. 1993 Aug [cited 2015 Jun 24];265(2 Pt 1):E314–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8368302

15. Rowell LB, Brengelmann GL, Blackmon JR, Twiss RD, Kusumi F. Splanchnic blood

Apr [cited 2015 May 3];24(4):475–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5643395

16. Crandall CG, Wilson TE, Marving J, Vogelsang TW, Kjaer A, Hesse B, et al. Effects of passive heating on central blood volume and ventricular dimensions in humans. J

able from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2375541&tool=pmcentrez&rendertype=abstract

17. Jensen TE, Richter EA. Regulation of glucose and glycogen metabolism during and after exercise. J Physiol [Internet]. 2012 Mar 1 [cited 2015 May 7];590(Pt 5):1069–76.

from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3381815&tool=pmcentrez&rendertype=abstract

18 Jeukendrup AE. Modulation of carbohydrate and fat utilization by diet, exercise and environment. Biochem Soc Trans. 2003;31:1270–3.

Effect of temperature on muscle metabolism during submaximal exercise in humans. Exp Physiol [Internet]. 1999 Jul [cited 2015 Jun 24];84(4):775–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10481233

20. Febbraio MA, Snow RJ, Hargreaves M, Stathis CG, Martin IK, Carey MF. Muscle ion. J Appl Physiol [Internet]. 1994 Feb [cited 2015 Jun 11];76(2):589–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8175568

21 Febbraio MA, Lambert DL, Starkie RL, Proietto J, Hargreaves M. Effect of epinephrine on muscle glycogenolysis during exercise in trained men. J Appl Physiol ole from: http://www.ncbi.nlm.nih.gov/pubmed/9475854

22. Koshinaka K, Kawamoto E, Abe N, Toshinai K, Nakazato M, Kawanaka K. Elevation of muscle temperature stimulates muscle glucose uptake in vivo and in vitro. J Physiol Sci [Internet]. 2013 Nov [cited 2015 Jun 24];63(6):409–18. Available from:

23. Slivka D, Tucker T, Cuddy J, Hailes W, Ruby B. Local heat application enhances glycogenesis. Appl Physiol Nutr Metab [Internet]. 2012 Apr [cited 2015 Jun 24];37(2):247–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22409451

24. Naperalsky M, Ruby B, Slivka D. Environmental temperature and glycogen (8):561–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20464645

25. Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obes Relat Metab Disord [Internet]. 2000 Jun [cited 2015 Jun 24];24 609

26. Lund S, Holman GD, Schmitz O, Pedersen O. Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin. Proc Natl Acad Sci U S A [Internet]. 1995 Jun 20 [cited 2015 Jun 24];92(13):5817–21. Available from: centrez&rendertype=abstract

27. Schmidt MI, Matos MC, Branchtein L, Reichelt AJ, Mengue SS, Iochida LC, et al. Variation in glucose tolerance with ambient temperature. Lancet (London, England) [Internet]. 1994 Oct 15 [cited 2015 Jun 24];344(8929):1054–5. Available from:

28 Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diabetes Care [Internet]. 2011 Oct [cited 2015 Jun 24];34(10):2237–43. from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3177732&tool=pmcentrez&rendertype=abstract

TABLE 1: Characteristics of the participants.

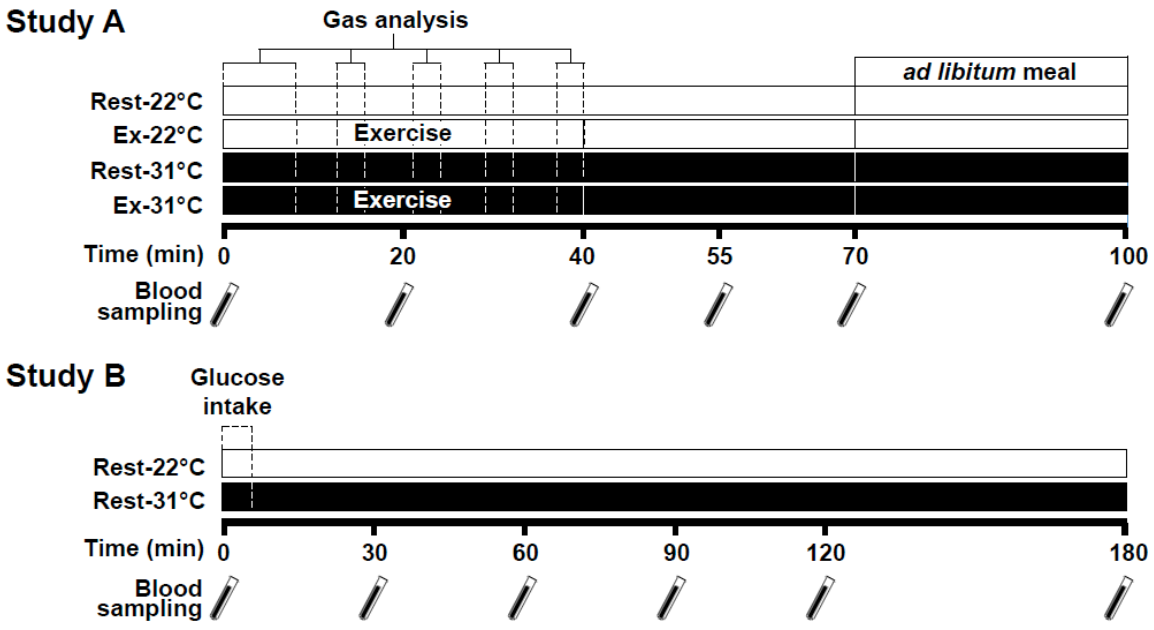
	Study A (N=10)		Study B (N=12)	
	mean	**SD**	**mean**	**SD**
Age (years)	20.9	1.7	20.4	2.0
Height (m)	1.80	0.06	1.79	0.07
Body Mass (kg)	69.2	7.1	74.4	8.1
Fat mass (%)	7.2	5.3	10.1	6.0
V'O2max (mL/min/kg)	47.1	7.4	-	-

TABLE 2: Indicators of the metabolic and cardiovascular load during the experimental sessions in study A.

		rest-22°C		rest-31°C		ex-22°C		ex-31°C	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate (bpm)	T40	57.1	3.4	62.6†	4.8	148.5**	12.2	166.6$^{\dagger\dagger **}$	14.9
V'O2 (L/min)	T40	0.24	0.05	0.25	0.04	2.04**	0.14	1.98**	0.13
Respiratory exchange ratio	T40	0.84	0.08	0.77†	0.07	0.98**	0.03	1.00**	0.05
Energy expenditure (kcal)		45.2	6.4	46.4	6.4	396.8**	23.5	384.9**	26.0

540 : the same environmental temperature) † and ††: $P < 0.05$ and $P < 0.01$ for the difference with the 22°C condition (at the same level of metabolic activity).

FIGURE 1: Schematic representation of the study design.



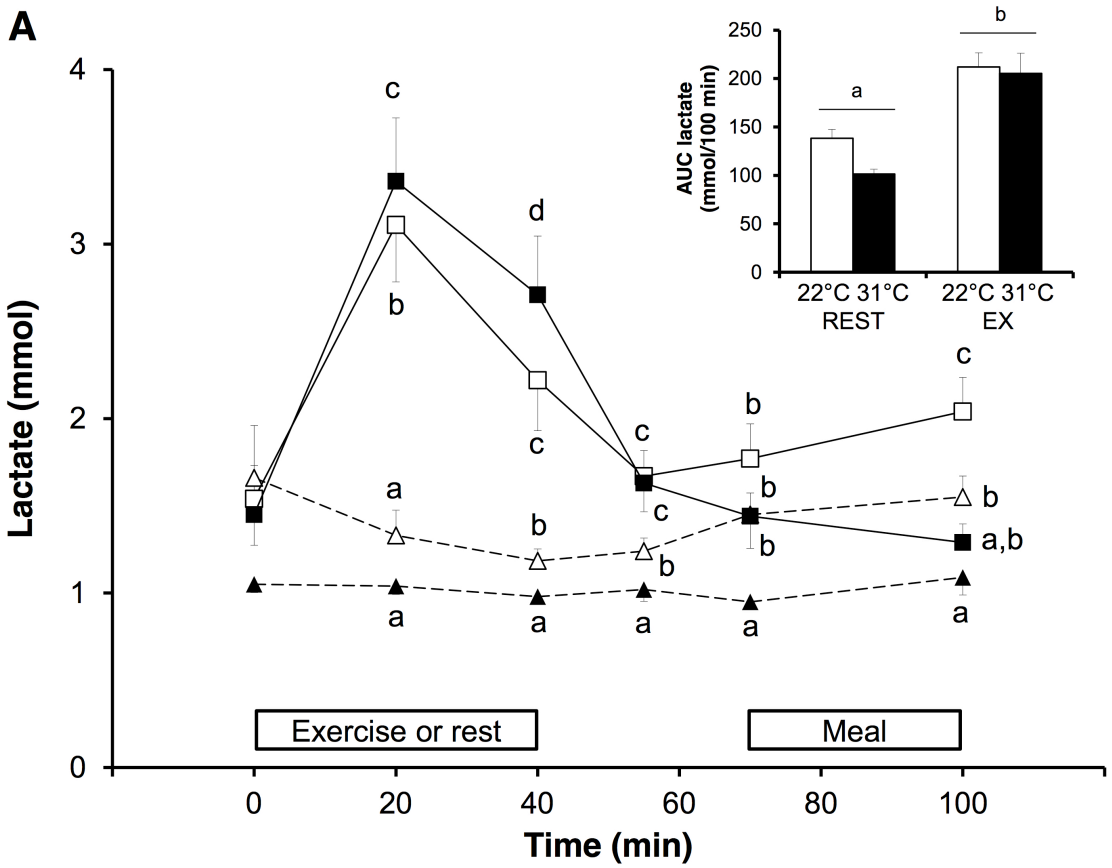
545 ture (white triangles), rest session at 31°C (black triangles), exercise session at 22°C (white squares, and exercise session at 31°C (black squares). Means in the same column with different letters are different (one-way ANOVA for condition effect, Tukey's post hoc, P < 0.05). Non significant P are not reported. N=10.

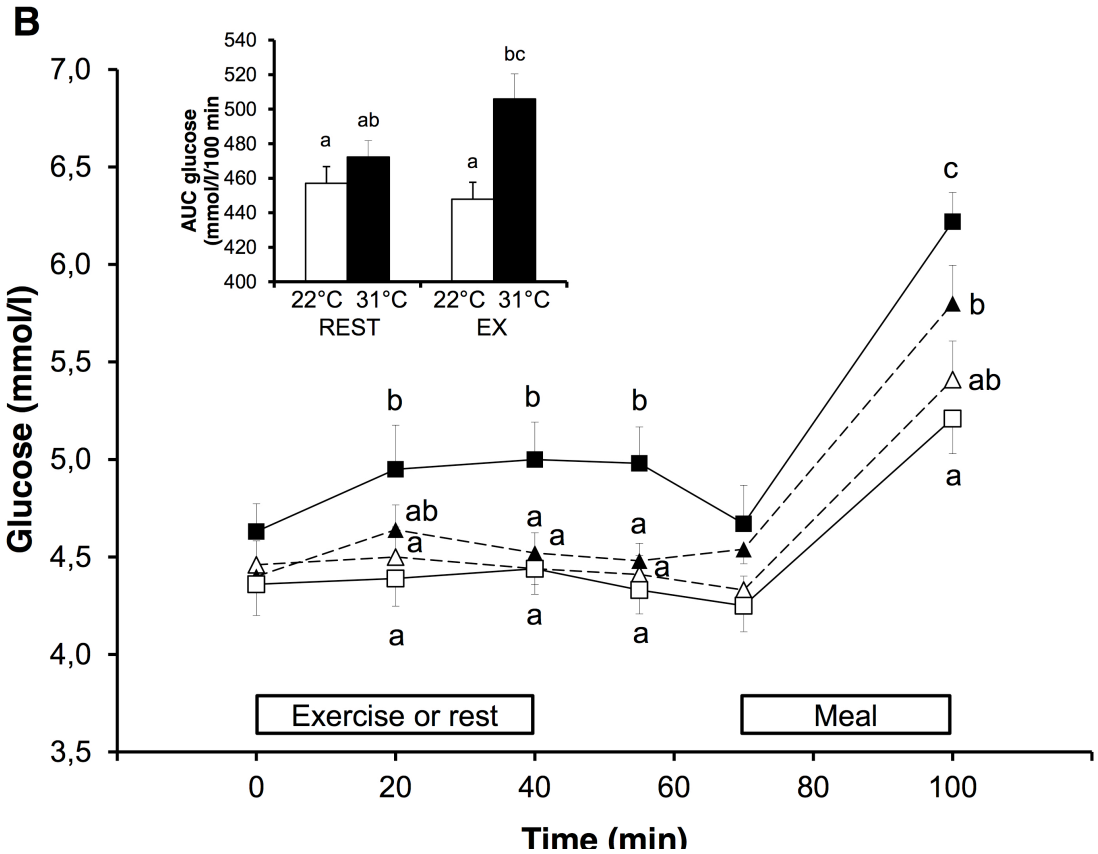
550 < 0.0001; metabolic level-by-time P < 0.0001; temperature-by-time P = 0.009; metabolic level x time x temperature P = 0.017.

B. Serum glucose. Time P < 0.0001; temperature P < 0.0001; metabolic level-by-temperature P = 0.024; temperature x time P = 0.012.

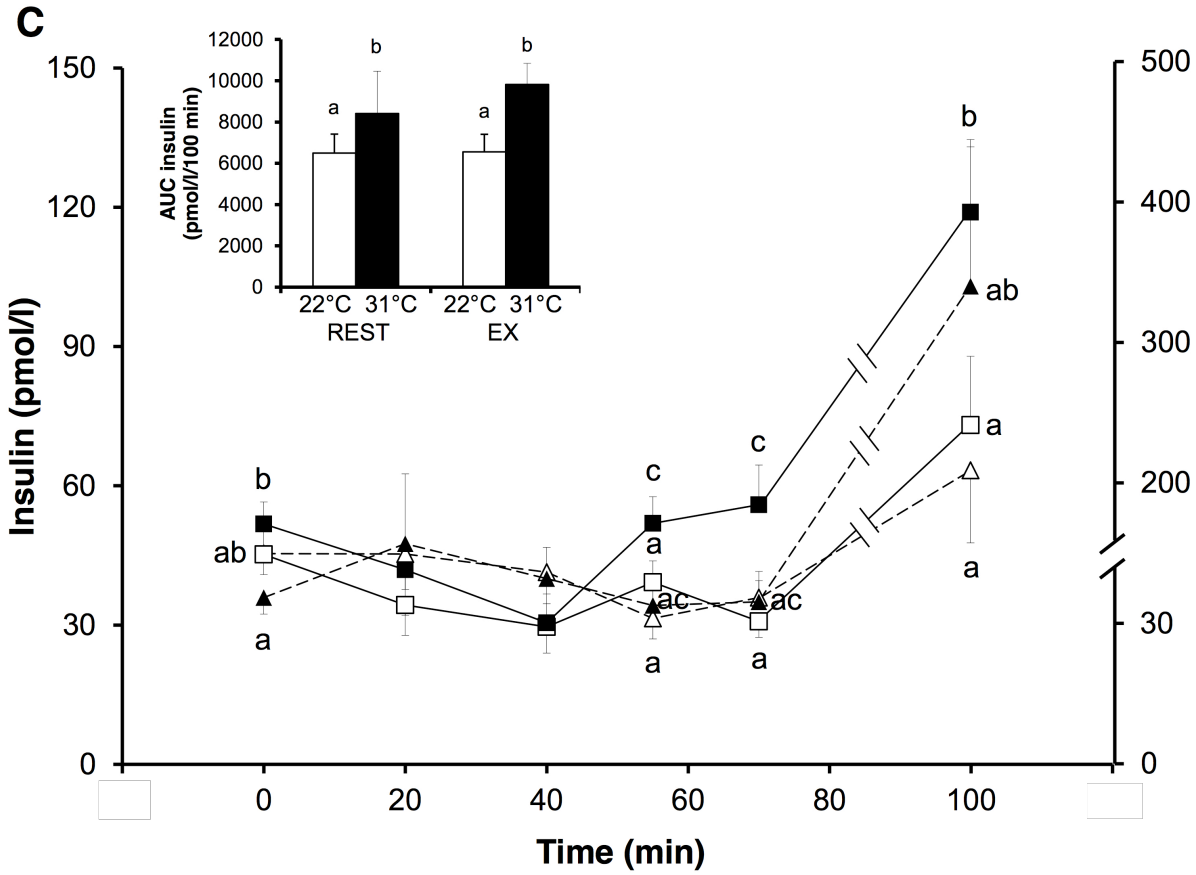
555 = 0.007.

D. Serum cortisol. Metabolic level P = 0.016; metabolic level-by-time P = 0.003.




B
Glucose (mmol/l)
Time (min)
Exercise or rest
Meal
AUC glucose (mmol/l/100 min
22°C 31°C
REST
22°C 31°C
EX

560


C
Insulin (pmol/l)
Time (min)
AUC insulin (pmol/l/100 min)
22°C 31°C
REST
22°C 31°C
EX

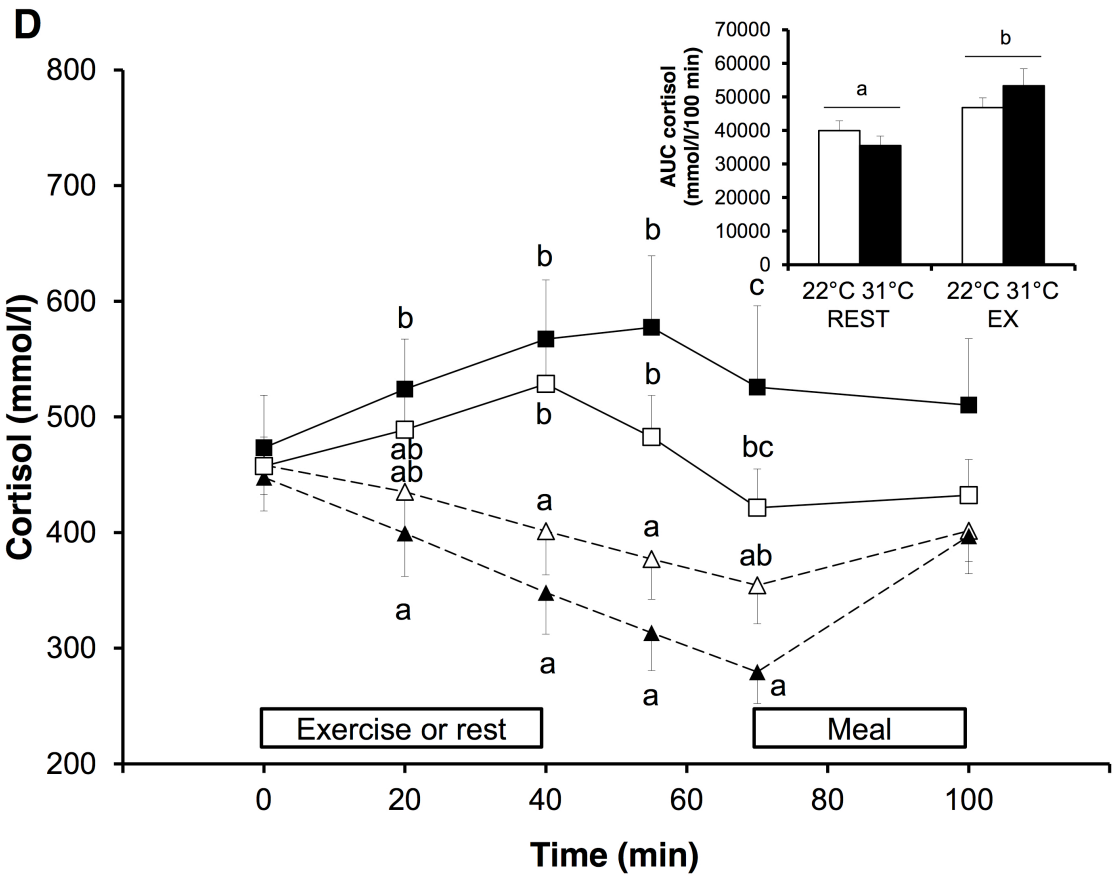
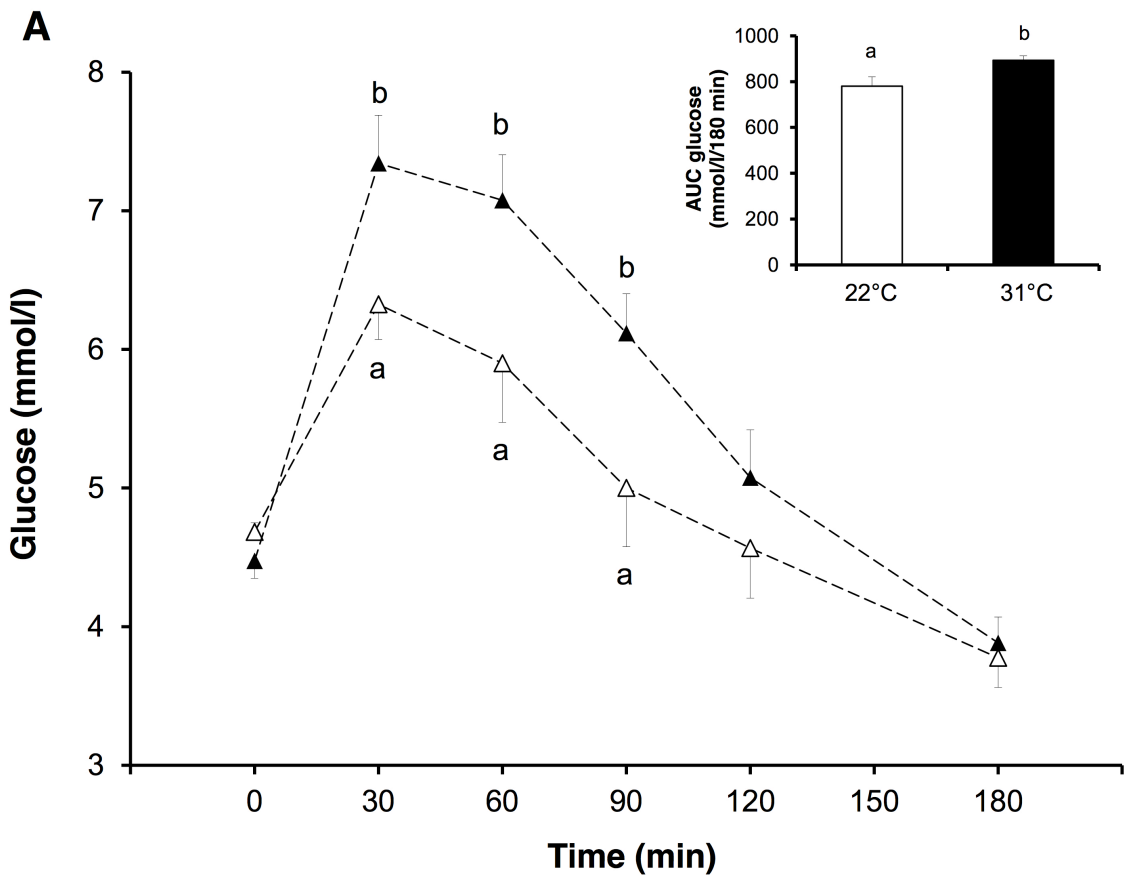


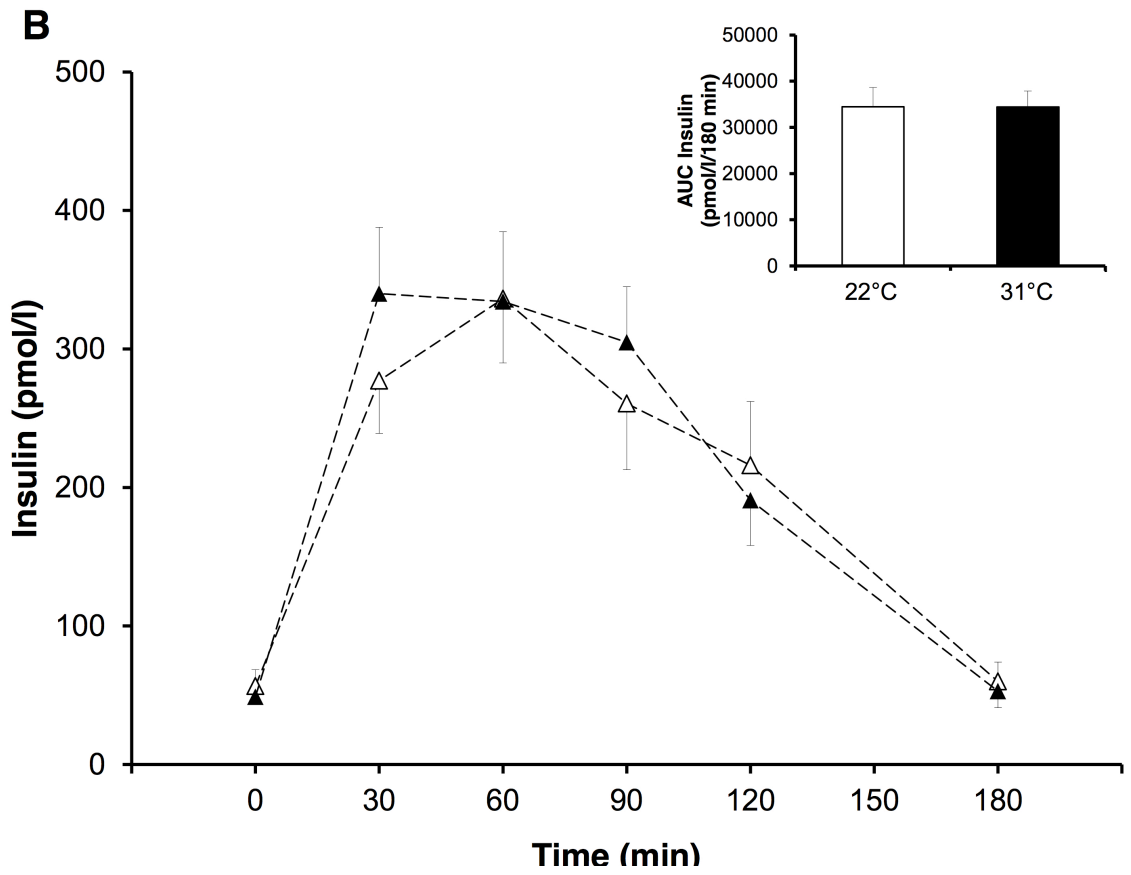
FIGURE 3: Metabolic responses during the oral glucose tolerance test performed at 22°C (white triangles) and 31°C (black triangles) ambient temperature. N=12.

565 = 0.030.

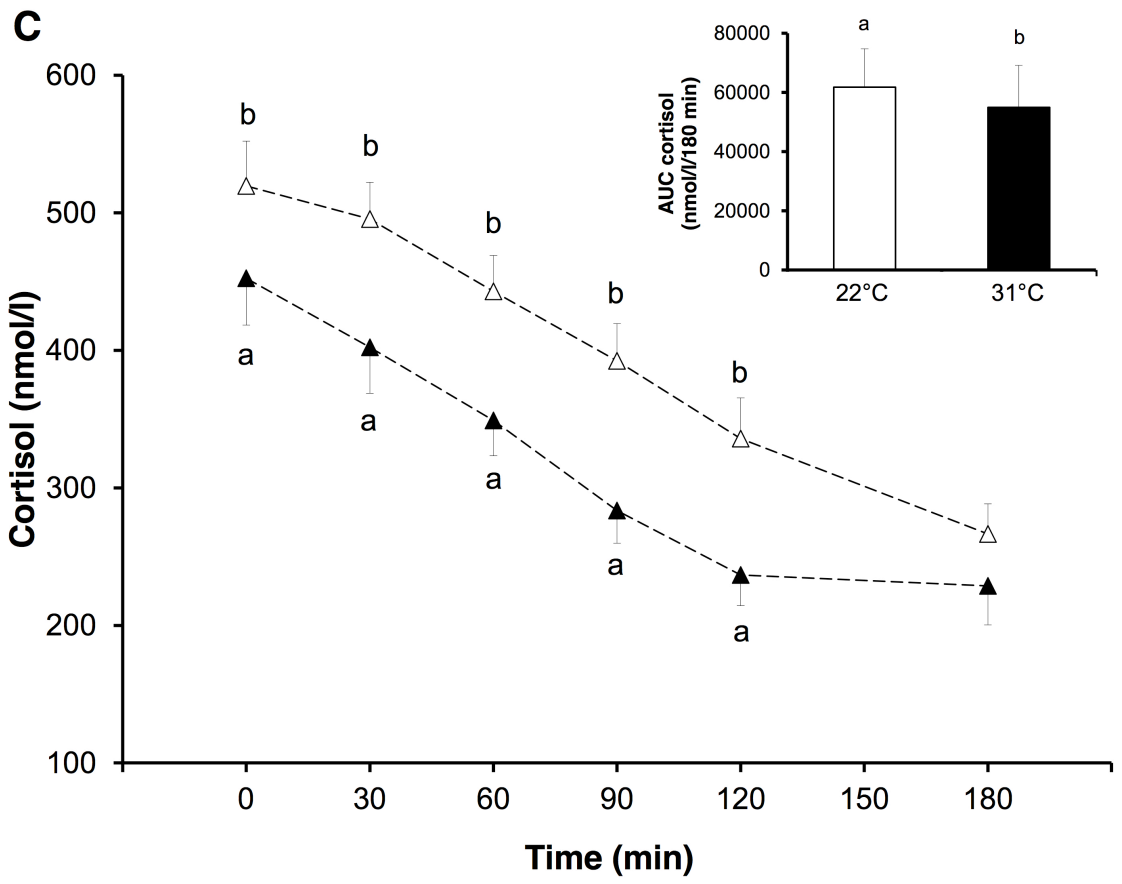
B. Serum insulin. Time P < 0.0001.

C. Serum cortisol. Time *P* < 0.0001; temperature *P* = 0.001; temperature-by-time *P* = 0.046.


A
Glucose (mmol/l)
Time (min)
b
b
b
a
a
a
AUC glucose (mmol/l/180 min)
a
b
22°C
31°C


B
Insulin (pmol/l)
Time (min)
AUC Insulin (pmol/l/180 min)
22°C
31°C

570


C
Cortisol (nmol/l)
600
500
400
300
200
100
0
30
60
90
120
150
180
Time (min)
b
b
b
b
b
a
a
a
a
a
AUC cortisol (nmol/l/180 min)
80000
60000
40000
20000
0
a
b
22°C
31°C