The acute influence of sucrose consumption with and without vitamin C co-ingestion on microvascular reactivity in healthy young adults

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Title: The acute influence of sucrose consumption with and without vitamin C co-ingestion on microvascular reactivity in healthy young adults

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References: 42

HIGHLIGHTS

- Microvascular function is known to be altered by an oral glucose tolerance test
- Sucrose, not glucose, better reflects habitual sugar intake
- Consumption of 50 g of sucrose did not acutely influence microvascular function
- The microvascular response was unaltered by the co-ingestion of vitamin C
ABSTRACT

Background: Sugar sweetened beverages (SSB) are a major source of dietary sugar and a public health concern. Glucose consumption acutely influences microvascular reactivity in healthy adults, possibly via oxidative stress. The purpose of this study was to observe the acute influence of a more relevant dose of sucrose on microvascular reactivity, and to identify whether this response is influenced by the amount of vitamin C typically contained in SSB. Methods: Thirteen ostensibly healthy adults (8 male, 5 female) performed three 1-day trials in a randomized order; the consumption of 300 ml water (control; CON), or 300 ml water with 50 g sucrose (SUGAR) or 50 g sucrose with 160 mg of vitamin C (VITC). Near infrared spectroscopy was used to determine peak reactive hyperaemia (PRH), the rate of desaturation (Slope 1) and reperfusion (Slope 2), and the total area under the reperfusion curve versus time (TRH) following 5 min of forearm cuff occlusion before and 30, 60, 90 and 120 min after test drink consumption. Results: SUGAR and VITC significantly increased the total area under the curve versus time for plasma glucose (P<0.05 for both). No changes in microvascular reactivity were observed between trials, although VITC increased Slope 1 compared to both SUGAR and CON 30 and 60 min post drink (P<0.05 for both). Conclusion: The consumption of a sugar load representative of commercially available SSB did not influence microvascular reactivity. The co-ingestion of Vitamin C also failed to influence microvascular reactivity, but did increase the rate of oxygen extraction.
INTRODUCTION

Postprandial hyperglycaemia is an independent risk factor for cardiovascular disease (Coutinho et al. 1999), and one which may be more powerful than glucose concentrations determined in the fasted state (Leiter et al. 2005; Tominaga et al. 1999). The acute hyperglycaemic response following a sugar bolus is also known to transiently impair vascular endothelial function (Loader et al. 2017), and this is implicated in the progression of atherosclerosis and cardiovascular disease (Mah and Bruno 2012). Given that cardiovascular diseases are a leading cause of global mortality and morbidity (WHO 2017), furthering our understanding of the deleterious effects of exposure to periods of hyperglycaemia on vascular function is a pertinent public health question.

Two recent studies have utilised near-infrared spectroscopy (NIRS) to quantify the hyperaemic response in the microvasculature following limb occlusion, and demonstrated that a standard oral glucose tolerance test (75g of glucose) can acutely alter microvascular function in healthy young adults (Soares et al. 2018; Soares et al. 2017). This is conceptually important, as the earliest detectable changes in endothelial function associated with the metabolic syndrome may present within the capillary beds, rather than conduit arteries (Pinkney et al. 1997). Furthermore, post-occlusive microvascular reactivity has been shown to be more strongly related to cardiovascular risk factor status (Gayda et al. 2015), and better predict future cardiovascular disease risk (Anderson et al. 2011), than macrovascular reactivity (flow mediated dilation; FMD) in healthy adults. However, a single meal rarely contains 75 g of glucose – either in isolation or in total – which means that the aforementioned studies (Soares et al. 2018; Soares et al. 2017) have limited real-world application.

A major source of dietary sugar is the habitual consumption of sugar-sweetened beverages (SSB) (Guthrie and Morton 2000), with recent data indicating that young adults consume an average of 1.7 servings per day (Singh et al. 2015). This translates to ~50 g of sucrose, or ~25 g of glucose with ~25 g of fructose (Walker et al. 2014). Given the widespread popularity of SSB, and the known association between SSB consumption and cardiometabolic disease (Malik et al. 2010), it is important to establish the vascular response to this more relevant dose. Furthermore, the metabolism of fructose is markedly different to glucose (Tappy et al. 2010), and the consumption of 75 g of glucose, but not fructose, has been shown to acutely impair FMD in healthy men (Mah et al. 2011). Currently, the microvascular response to a typical SSB is largely unexplored, although it has been demonstrated that a commercially available SSB (72g of sugar) impairs microvascular function 30 min post drink (Loader et al. 2017). However, the specific content of glucose and fructose was not defined in that study, and the time course of the postprandial changes in microvascular function following SSB consumption have not yet been described.

Data are available which demonstrate that the acute vascular impairment observed following a glucose load is related to oxidative stress (Ceriello et al. 2002; Du et al. 1999), and that this can be ablated with co-ingestion of antioxidants, including vitamin C (Title et al. 2000). The vitamin C content of popular SSB are often advertised by manufacturers, and one third of consumers may actively look for “vitamin C” or “antioxidant” marketing claims when purchasing SSB (Munsell et al. 2016). However, whilst the typical vitamin C content of popular SSB may exceed current dietary reference intakes (Levine et al. 1999), this is far lower than the 2000 mg previously demonstrated to protect against hyperglycaemia-induced vascular impairment (Title et al. 2000).
Given the above, the purpose of this study was to observe the acute microvascular response in healthy young adults to 50 g of sucrose, with and without 160 mg of vitamin C, which is more reflective of commercially available SSB.

METHODS

Ethical Approval

This study was approved by the Sport and Health Sciences Ethics Committee at the University of Exeter (reference number 2017/M/05) and complied with the guidelines established in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to commencement of the study.

Participants

A sample size calculation was performed a priori based upon the repeatability of the NIRS technique (McLay et al. 2015), and the magnitude of the change in microvascular function observed approximately 30 min after the consumption of a commercially available SSB (Loader et al. 2017). Subsequently, thirteen adults (5 female) volunteered to take part in this study (Table 1). Exclusion criteria included the presence of known cardiometabolic disease and the use of any medication or substance known to impact vascular function. Participants were familiarised to all measures prior to study commencement in order to minimise any potential effect of protocol anxiety on the post occlusive hyperaemic response (Dyson et al. 2006), and were asked to avoid strenuous exercise and alcohol consumption during the preceding 24 hours (Thijssen et al. 2011). Females completed all trials in the second week of the menstrual cycle in order to control for any potential changes in vascular reactivity (Williams et al. 2001).

Experimental Protocol

Following a ~ 10 hour overnight fast, participants reported to the laboratory at 08:00 and rested in the supine position for 15 min before providing a baseline capillary blood sample and measure of vascular function. Participants then consumed, within 10 min, one of three test drinks in a randomised order; 1) 300 ml of water (control; CON), 2) 300 ml of water with 50 g sucrose (SUC), or 3) 300 ml of water with 50g sucrose and 160 mg vitamin C (VITC). The content of the test drinks were designed to replicate popular SSB, and the drinks were administered in a double blind fashion. Capillary blood samples were then collected (10, 20, 30, 60, 90 and 120 min post) post drink consumption. Microvascular reactivity was reassessed 30, 60, 90 and 120 min after the drink, so that blood flow could return to the physiological baseline (McLay et al. 2015). All procedures were performed in a darkened, light- and temperature-controlled (24°C) laboratory, and participants remained at rest between measures.

Plasma Glucose and Lactate Concentrations

Capillary blood samples were collected into heparin-fluoride coated Microvette CB 300 tubes and centrifuged immediately for 10 min at 16,000g. Plasma was then extracted from the sample and analysed for [glucose] and [lactate] (YSI 2500 Lactate Analyser, YSI, UK). The total (TAUC) and
incremental (IAUC) area under the curve analyses for [glucose] and [lactate] were performed using the pre-drink (0 min) capillary sample as the baseline (GraphPad Prism, San Diego, CA).

**Microvascular reactivity**

Post-occlusive microvascular reactivity was quantified using NIRS (NIRO-300, Hamamatsu Photonics K. K., Japan) following 5 min of limb occlusion via rapid pneumatic cuff inflation (Hokanson, Bellevue, USA), as described by McClay et al. (Mclay et al. 2015). This NIRS system has four laser diodes which emit light at different wavelengths (776, 826, 845 and 905 nm) and a black rubber probe housing which ensures a constant emitter-detector distance of 4 cm. The cuff was secured to the proximal third of the forearm, and the NIRS probe was positioned approximately 5 cm distal to the cuff at a reproducible point which was free from obvious tendons, veins, freckles or scars. In accordance with the manufacturer’s guidelines, probe was secured to the skin using a transparent sticker in order to negate any movement caused by cuff inflation and deflation. An opaque elastic tensor bandage was also loosely wrapped around the probe to further minimise any movement and block any extraneous light.

The post-occlusive microvascular reactivity protocol involved 1 min of baseline measures, 5 min of cuff occlusion (220 mmHg) and 3 min of recovery post cuff deflation. Oxygenated (HbO$_2$) and deoxygenated (HHb) haemoglobin were continuously determined throughout the protocol at a frequency of 1 Hz. Tissue oxygen saturation (StO$_2$) was estimated as [HbO$_2$]/([HbO$_2$ + HHb]) and expressed as a percentage. Baseline perfusion was defined as the average StO$_2$ during the 1 min prior to occlusion. Muscle oxygen consumption was derived using the StO$_2$ slope during the first 180 s of occlusion (Slope 1) (Soares et al. 2019a). The rate of reperfusion (Slope 2) was calculated as the upslope in StO$_2$ 10 s after cuff release. When determined in this manner, Slope 2 has been shown to be highly correlated with established methods of arterial endothelial function (McLay et al. 2015; Soares et al. 2019b), and is sensitive to changes in vascular reactivity following an oral glucose tolerance test (Soares et al. 2017). Peak StO$_2$ was calculated as the greatest StO$_2$ value attained after cuff release and expressed as a percentage increase from baseline perfusion (peak reactive hyperaemia; PRH). Total reactive hyperaemia (TRH) was determined as the incremental area under the 3 min reperfusion curve versus time above baseline StO$_2$ adjusted to the time taken for StO$_2$ to return to pre-occlusion values.

**Statistical analyses**

Data were analysed using SPSS version 24.0 (IBM, USA) and are presented as mean ± standard deviation. Microvascular outcomes met the assumption of normal distribution. Analysis of microvascular outcomes, plasma [glucose] and [lactate] were performed using a repeated measures analysis of variance (ANOVA), with time and trial (CON, SUC, VITC) as the main effects. Neither the inclusion of sex or body mass into the ANOVA revealed a significant interaction effect for any outcome, so male and female data are pooled (n=13). Changes in TAUC and IAUC for plasma [glucose] and [lactate] were analysed using a one-way ANOVA. Homogeneity of variance was assessed using Mauchly’s test of sphericity, and adjusted using the Greenhouse-Geisser correction factor if violated. Pairwise comparisons between means were interpreted using the P value and the 95% confidence intervals (CI), and standardized effect sizes (ES) were used to document the magnitude of the effect using the following thresholds: small (0.2-0.49), moderate (0.5-0.79) and large (≥0.8) (Cohen 1988).
RESULTS

Plasma Glucose and Lactate Concentrations

There were no differences between trials for fasted plasma [glucose] ($P=0.29$). Mean plasma [glucose] over time are presented in Figure 1A. There was a time by trial interaction for plasma [glucose] ($P<0.001$). Plasma [glucose] was greater in SUC and VITC compared to water 10, 20 and 30 min post drink ($P<0.001$ and $ES=2.40$ for all). Plasma [glucose] was greater 20 min post drink in VITC compared to SUC ($P=0.045$, 95% CI 0.01 to 1.02, $ES=0.49$). Plasma [glucose] was not different 60 min post drink between VITC and CON ($P=0.88$, 95% CI -0.42 to 0.36, $ES=0.05$), but remained elevated in SUC compared to CON ($P=0.03$, 95% CI 0.10 to 1.45, $ES=0.93$). There were no differences in plasma [glucose] between trials 90 and 120 min post drink ($P>0.13$ for all).

Compared to CON, TAUC-glucose was greater in SUC ($P<0.001$, 95% CI 95.5 to 166.4, $ES=2.21$) and VITC ($P<0.001$, 95% CI 78.5 to 141.6, $ES=1.92$), with no differences between SUC and VITC ($P=0.21$, 95% CI -13.8 to 55.6, $ES=0.35$). Compared to CON, IAUC-glucose was greater in SUC ($P=0.03$, 95% CI 39.0 to 148.3, $ES=1.73$) and VITC ($P=0.001$, 95% CI 42.5 to 138.9, $ES=1.83$), with no differences between SUC and VITC ($P=0.81$, 95% CI -23.4 to 29.3, $ES=0.07$).

There were no differences between trials for fasted plasma [lactate] ($P=0.23$). Mean plasma [lactate] over time are presented in Figure 1B. There was a time by trial interaction for plasma [lactate] ($P<0.001$). Plasma [lactate] was greater in SUC and VITC compared to water 10, 20, 30, 40, 60 and 90 min post drink ($P<0.01$ and $ES>1.21$ for all). Plasma [lactate] was never different between SUC and VITC at any time point ($P>0.19$ and $ES<0.52$ for all).

Compared to CON, TAUC-lactate was greater in SUC ($P<0.001$, 95% CI 88.7 to 186.2, $ES=1.94$) and VITC ($P<0.001$, 95% CI 110.4 to 185.2, $ES=2.75$), with no differences between SUC and VITC ($P=0.70$, 95% CI -66.7 to 46.1, $ES=0.14$). Compared to CON, IAUC-glucose was greater in SUC ($P<0.001$, 95% CI 82.1 to 163.8, $ES=2.59$) and VITC ($P<0.001$, 95% CI 79.8 to 161.1, $ES=2.50$), with no differences between SUC and VITC ($P=0.91$, 95% CI -52.7 to 47.7, $ES=0.04$).

Post-occlusive reactive hyperaemia

Parameters of microvascular reactivity are presented in Figure 2. There was no main effect for trial ($P=0.54$), time ($P=0.39$) or time by trial interaction ($P=0.35$) for baseline StO2. A time by trial interaction effect was observed for the Slope 1 outcome ($P<0.01$). Specifically, VITC Slope 1 was greater than CON 30 min ($P=0.001$, 95% CI 0.03 to 0.07, $ES=0.87$) and 60 min ($P=0.001$, 95% CI 0.02 to 0.05, $ES=0.65$) post drink. VITC Slope 1 was also greater than SUC at these time points ($P=0.04$, 95% CI 0.003 to 0.08, $ES=0.77$, and $P=0.02$, 95% CI 0.01 to 0.04, $ES=0.55$, respectively). A small, but not statistically significant, difference was observed between SUC Slope 1 and CON ($P=0.08$, 95% CI 0.00 to 0.04, $ES=0.36$) and VITC ($P=0.07$, 95% CI 0.00 to 0.04, $ES=0.43$) at 90 min.

There was no main effect for trial ($P=0.16$), time ($P=0.79$) or time by trial interaction ($P=0.55$) for PRH (Figure 2A). There was no main effect for trial ($P=0.47$), time ($P=0.82$) or time by trial interaction ($P=0.30$) for the Slope 2 outcome (Figure 2B). There was no main effect for trial ($P=0.39$), time ($P=0.15$) or time by trial interaction ($P=0.18$) for TRH.
DISCUSSION

This is the first study to characterise the acute microvascular response to a sugar bolus which is reflective of a typical SSB, and also to determine whether any changes in microvascular reactivity are related to the vitamin C content of the drink. The key finding of this investigation is that the consumption of 50 g of sucrose, with or without 160 mg of vitamin C, does not influence post-occlusive microvascular reactivity in healthy young adults.

Presently, only two studies have characterised the Slope 2 response to a sugar load, and both reported an increase in the rate of reperfusion post occlusion 90 min after consumption of 75 g of glucose (Soares et al. 2018; Soares et al. 2017). The disparity between these findings and our own is likely explained by the differences in sugar moiety (sucrose; equal parts glucose and fructose) and quantity (50 g in total). Insulin is a potent, endothelial-dependent vasodilator (Steinberg et al. 1994) which increases capillary perfusion (Vincent et al. 2002), and these vasoactive responses are observed in the microvasculature during glucose-mediated hyperinsulinaemia (Vollenweider et al. 1993). Although the aforementioned studies did not measure insulin, it is likely that the increase in the post-occlusive reperfusion rate observed 90 min post glucose consumption (Soares et al. 2018; Soares et al. 2017) is, at least in part, related to this mechanism. In comparison fructose is not an insulin secretagogue and does not increase blood flow (Vollenweider et al. 1993). Given that 25 g of orally administered glucose is likely to provide a far lower hyperinsulinaemic response than 75 g (Tillil et al. 1988), the sugar bolus adopted in our current investigation is both quantitatively and qualitatively different, and unique compared to existing work.

The finding that 50 g of sucrose did not influence TRH is also of interest, as the previously observed impairment in this outcome (Soares et al. 2018; Soares et al. 2017) has been attributed to the increase in oxidative stress observed following an oral glucose challenge (Ceriello et al. 1998) and SSB (Loader et al. 2017). Indeed, the co-ingestion of antioxidants has been shown to protect against the fall in arterial reactivity (FMD) following an oral glucose tolerance test in healthy adults (Title et al. 2000). Whilst it is recognised that a change in hyperglycaemic redox state is not a consistent finding in healthy adults (Ma et al. 2005), it has also been demonstrated that only glucose, but not fructose, ingestion acutely increases oxidative stress and attenuates FMD in young healthy men (Mah et al. 2011). Thus, it is possible that the 50 g of sucrose consumed in the present study did not sufficiently challenge redox state in our population, although further data are required to confirm this. We were also not able to discern any notable microvascular benefit of the co-ingestion of vitamin C with sucrose. Whilst this study did not include a fourth trial to specifically isolate the effect of 160 mg vitamin C on microvascular reactivity, this finding is in line with other data which demonstrates that 500 - 1000 mg of vitamin C does not acutely influence vascular reactivity in healthy adults (Eskurza et al. 2004; Heitzer et al. 1996). However, we are the first to document that the co-ingestion of vitamin C with sucrose may alter the Slope 1 response, and this manipulation of metabolic rate could conceivably confer a benefit to glycaemic control. Indeed it has previously been observed that vitamin C may play a role in glucose disposal (Paolisso et al. 1994). Although only subtle differences in postprandial [glucose] were observed between the two sucrose trials at the 30 min time point in our study, this may be related to the comparatively low glucose content (25 g) of these drinks. The moderate effect size observed here is an interesting finding which warrants further research, particularly with the added insight of determining changes in [insulin] or adopting a larger glucose bolus.
This study controlled for potential confounders of post-occlusive hyperaemia (including laboratory temperature, menstrual cycle, fasted state, prior exercise, time of day, protocol-anxiety and extraneous light (Cracowski et al. 2006; McLay et al. 2015; Thijssen et al. 2011)). Furthermore, we utilised a technique which is purported to be less operator dependent and more reliable than FMD (McLay et al. 2016) and sensitive to changes following the consumption 75 g of glucose in healthy adults (Soares et al. 2017). Given this methodological rigour, our data add to the extant literature (Soares et al. 2018; Soares et al. 2017), and collectively these data suggest that higher doses of sugar may be necessary for changes in postprandial microvascular reactivity, and that these changes are likely related to glucose, rather than fructose, consumption. However, this requires further investigation.

There are many strengths to this study design, including the prescription of a test drink which better reflects habitual sugar exposure than the standardised oral glucose tolerance test, a double-blind and counterbalanced design, and the control of potential confounders which are important when performing vascular research. However, these data should be interpreted in light of some limitations. Firstly, despite following best practice (Cracowski et al. 2006; McLay et al. 2015; Thijssen et al. 2011), it is important to note that the present study determined microvascular function in the forearm, and most previous postprandial studies utilising NIRS studied changes in the tibialis anterior (Soares et al. 2018; Soares et al. 2017). This is relevant as the hyperaemic response following forearm occlusion may approximately triple that observed in the lower limb (Parker et al. 2014; Soares et al. 2019a), which might explain the near three-fold greater Slope 2 values witnessed in this study compared to others (McLay et al. 2015; McLay et al. 2016; Soares et al. 2018; Soares et al. 2017). Furthermore, acute changes in microvascular reactivity in the lower leg may not correlate with changes at the forearm (Restaino et al. 2015).

Whilst it remains to be seen if our findings also extend to the lower limb, one recent study has shown that the Slope 2 outcome is altered at the forearm by a glucose challenge in healthy adults (Soares et al. 2019a). Whilst the NIRS device utilised by these authors differ slightly in wavelength and device-emitter distance, it seems unlikely that this entirely explains our findings. Indeed, the data presented here are of a similar order of magnitude, and we also observed a small (although not significant) increase in the Slope 1 response only 90 min after 50 g sucrose consumption (Soares et al. 2019a), which is probably reflective of only a 25 g, not 75 g, dose of glucose in the present trial. It is therefore plausible that this discrepancy reflects a different vascular response to the consumption of sucrose in our study compared to glucose (Soares et al. 2019a). However, it was beyond the scope of this study to include such a trial in order to make this comparison, and this remains a pertinent future research question.

Secondly, whilst we detail the changes in plasma [glucose] and [lactate], it was beyond the scope of this study to measure [insulin] or provide insight regarding redox state. Given the pertinent nature of this research question, we believe that this warrants further study. However, given that we did not observe an impairment in microvascular reactivity following sucrose consumption, such further investigations should also observe whether the co-ingestion of Vitamin C can ameliorate the known impairment observed following 75 g of glucose consumption (Soares et al. 2019a). Finally, the amount of test drink consumed was not related to body mass, which ranged from 56.0 – 99.2 kg, although only one participant was of overweight status. However, this was a deliberate attempt to
reflect sugar exposure via SSB consumption and, given that no influence of weight was observed on the postprandial response, is unlikely to have influenced our interpretation of this data.

CONCLUSION

A novel strength of the present study is that the test drinks reflected the sugar (25 g of glucose and 25 g of fructose) and vitamin C (160 mg) content of commercially available, and popular (Singh et al. 2015), SSB, rather than the typical challenge of 75 g of glucose or supraphysiological doses of antioxidants (Title et al. 2000) which grossly exceed current reference nutrient intakes (Levine et al. 1999). Thus, these findings are more reflective of a real world setting, which is not offered by other data in this field. Collectively, our data suggest that consuming the type and amount of sugar typically present in SSB does not acutely influence microvascular function in ostensibly healthy young adults, and that the co-ingestion of vitamin C does not modulate this postprandial response. Further studies are warranted to replicate these findings, and to observe whether the microvascular response is altered in the presence of other typical behaviours (i.e. a “stacking” effect when this sugar load is consumed with a meal) or whether the inclusion of stimulants present in popular “energy drinks” influence the postprandial microvascular response.
Table 1: Participant characteristics (n=13)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
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<tr>
<td>Age (y)</td>
<td>22.9 ± 1.6</td>
</tr>
<tr>
<td>Male:Female</td>
<td>8:5</td>
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<tr>
<td>Height (m)</td>
<td>1.73 ± 0.09</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>70.8 ± 10.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 8.4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121 ± 8</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>67 ± 7</td>
</tr>
</tbody>
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BMI, body mass index; BP, blood pressure.
Figure 1. Mean plasma [glucose] (A) and [lactate] (B) for the control (○), sugar (▲) and sugar with vitamin C (■) drinks. Error bars represent the standard deviation. The test drink is represented by the black rectangle. *P<0.05 for sugar and sugar with vitamin C compared to control; †P<0.05 for sugar compared to sugar and vitamin C, #P<0.05 for sugar compared to control.
Figure 2. Mean deoxygenation (Slope 1; A), reperfusion (Slope 2; B), peak reactive hyperaemia (PRH; C), and total reactive hyperaemia (TRH; D) for the control (○), sugar (▲) and sugar with vitamin C (■) drinks. Error bars represent the standard deviation. The test drink is represented by the black rectangle. StO₂ = tissue oxygen saturation. Statistical significance between trials is denoted by * (sugar with vitamin C vs sugar) and ** (sugar with vitamin C vs control).
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COMPETING INTERESTS

The authors have no competing interests to disclose.

AUTHOR CONTRIBUTIONS

All work was completed at the University of Exeter. SW and BB conceived and designed the study. SW and OS completed data collection for the study. All authors carried out data analysis and interpretation, and all authors critically reviewed the manuscript and approved the final draft as submitted. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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