RESEARCH ARTICLE | Exploiting Environmental Factors to Improve Health and Performance

Face cooling increases blood pressure during central hypovolemia

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Johnson BD, Sackett JR, Sarker S, Schlader ZJ. Face cooling increases blood pressure during central hypovolemia. Am J Physiol Regul Integr Comp Physiol 313: R594–R600, 2017. First published August 30, 2017; doi:10.1152/ajpregu.00253.2017.—A reduction in central blood volume can lead to cardiovascular decompensation (i.e., failure to maintain blood pressure). Cooling the forehead and cheeks using ice water raises blood pressure. Therefore, face cooling (FC) could be used to mitigate decreases in blood pressure during central hypovolemia. We tested the hypothesis that FC during central hypovolemia induced by lower-body negative pressure (LBNP) would increase blood pressure. Ten healthy participants (22 ± 2 yr; three women, seven men) completed two randomized LBNP trials on separate days. Trials began with 30 mmHg of LBNP for 6 min. Then, a 2.5-liter plastic bag of ice water (0 ± 0°C) (LBNP + FC) or thermonutral water (34 ± 1°C) (LBNP + Sham) was placed on the forehead, eyes, and cheeks during 15 min of LBNP at 30 mmHg. Forehead temperature was lower during LBNP + FC than LBNP + Sham, with the greatest difference at 21 min of LBNP (11.1 ± 1.6 vs. 33.9 ± 1.4°C, P < 0.001). Mean arterial pressure was greater during LBNP + FC than LBNP + Sham, with the greatest difference at 8 min of LBNP (98 ± 15 vs. 80 ± 8 mmHg, P < 0.001). Cardiac output was higher during LBNP + FC than LBNP + Sham with the greatest difference at 18 min of LBNP (5.9 ± 1.4 vs. 4.9 ± 1.0 liter/min, P = 0.005). Forearm cutaneous vascular resistance was greater during LBNP + FC than LBNP + Sham, with the greatest difference at 15 min of LBNP (7.2 ± 3.4 vs. 4.9 ± 2.7 mmHg/perfusion units, P < 0.001). Face cooling during LBNP increases blood pressure through increases in cardiac output and vascular resistance.

Blood loss; central hypovolemia; human dive reflex; cardiovascular decompensation

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...ber in the supine position using a neoprene kayak skirt that was sealed at the level of the iliac crest. After a 10-min rest period, we collected baseline data for an additional 10 min. At the end of baseline, 30 mmHg of LBNP commenced for 6 min. This represents a moderate level of LBNP that elicits central hypovolemia (e.g., ~6.8 mmHg reduction in central venous pressure) and hemodynamic responses that are associated with upward of 1,000 ml of blood loss in humans (21). Then, we placed a pliable plastic bag filled with ice water (LBNP+FC) or thermoneutral water (LBNP+Sham) on the forehead, eyes, and cheeks for the next 15 min, while 30 mmHg of LBNP was maintained. The volume of water in the plastic bag was 2.5 liters in both trials, and the bags were agitated every 3 min. After 15 min of face cooling or sham, LBNP was terminated, the plastic bag was removed, and water temperature was measured using a thermocouple (Omega Engineering, Stanford, CT; face cooling: 0 ± 0°C; sham: 34 ± 1°C). After the termination of face cooling or sham, participants remained supine, and we collected 5 min of recovery data.

Instrumentation and measurements. Height and weight were measured using a stadiometer and scale (Sartorius, Bohemia, NY) before the study visits. A three-lead electrocardiogram (DA100C, Biopac Systems, Goleta, CA) was used to continuously record heart rate, and the Penaz method was used to collect beat-to-beat blood pressure (Finometer Pro; FMS, Amsterdam, The Netherlands). Beat-to-beat blood pressure was intermittently confirmed using auscultation of the brachial artery via electrophysgmonanometry (Tango M2; SunTech, Raleigh, NC), and no corrections were needed. Stroke volume was calculated via ModelFlow using the blood pressure waveform (46). Laser-Doppler flowmetry (Periflux System 5010; Perimed, Stockholm, Sweden) was used to measure skin blood flow on the dorsal side of the left forearm and the pad of the left-hand index finger. Skin blood flow was measured on the fingertip to provide an index of reflex cutaneous vasoconstriction because only cutaneous vasoconstrictor nerves innervate glabrous skin (22). Both laser-Doppler probes were inserted into thin plastic holders that were adhered to the skin using porous tape. Participants were also instructed to keep their left arm and hand still throughout the protocol. Forearm blood flow was measured in the right arm using venous occlusion plethysmography (48) at 10 min of baseline and every 3 min during LBNP. A strain gauge was placed around the largest circumference of the forearm, and pressure cuffs were secured around the upper arm proximal to the elbow and around the wrist. The wrist cuff was inflated to 250 mmHg, and the upper arm cuff cycled between 0 mmHg and 50 mmHg every 8 s during each measurement period. Forearm blood flow was calculated for each cycle using the slope of the increase in forearm circumference determined by the strain gauge and the average of six cycles at each measurement period was used for statistical analyses (49). A thermocouple (Omega Engineering, Stanford, CT) was adhered to the forehead using permeable tape (Transpore, 3M, St. Paul, MN) to continuously measure forehead skin temperature.

Data analyses. We recorded data continuously at 1 kHz using a data acquisition system (Biopac MP150, Goleta, CA). Data were analyzed in 1-min segments at 10 min of baseline, at 3 and 6 min of LBNP, during each of the first 3 min of face cooling or sham, and every 3 min thereafter. Recovery data were analyzed in 1-min segments at the end of the 5-min recovery period (Post). We calculated the R-R intervals from the electrocardiogram during each data analysis time point. All R-waves were visually inspected for ectopic beats and manually edited where needed (37). These analyses were used to estimate changes in short-term cardiac parasympathetic activity using the root mean square of successive differences in R-R intervals (RMSSD) using WinCPRS software (Absoloute Aliens, Turku, Finland) (17, 34, 37). Cardiac output was calculated as the product of heart rate and stroke volume, and total peripheral resistance was calculated as the quotient of mean arterial pressure and cardiac output. Cutaneous, fingertip, and forearm vascular resistances were calculated as the quotient of mean arterial pressure and skin and forearm blood flow, respectively.

**Statistical analyses.** Two-way repeated-measures ANOVA were used to compare responses between LBNP+FC and LBNP+Sham (condition effect) and within experimental conditions (time effect). We used the Holm-Sidak post hoc procedure to determine where differences existed if the ANOVA revealed a significant interaction or main effect. Data over time were compared with those acquired at the 10-min baseline. All data were assessed for approximation to a normal distribution and sphericity, and no corrections were made. Statistical analyses were performed using Prism software (version 6, GraphPad Software, La Jolla, CA). Data are reported as means ± SD, and P values are reported.

**RESULTS**

**Forehead skin temperature.** There were no differences between conditions in forehead skin temperature at baseline or during the first 6 min of LBNP (Fig. 1). Forehead skin temperature was lower than baseline and LBNP+Sham throughout the entire face cooling procedure and 5 min after the cooling stimulus had been removed (P < 0.001).

**Blood pressure.** There were no differences in mean arterial pressure between conditions at baseline or during LBNP alone (P > 0.068) (Fig. 2A). During LBNP alone, mean arterial pressure was not different from baseline in either condition (P > 0.107). Throughout LBNP+FC, mean arterial pressure was greater than baseline (P ≤ 0.001) and LBNP+Sham (P < 0.019). Mean arterial pressure remained greater than baseline 5 min after LBNP+FC (P < 0.001). We did not observe any change from baseline in mean arterial pressure during LBNP+Sham (P > 0.454). During LBNP alone, systolic blood pressure was lower in both conditions compared with baseline (P ≤ 0.005) (Fig. 2B). Throughout LBNP+Sham, systolic blood pressure remained lower than baseline (P < 0.035). However, systolic blood pressure returned to baseline values during LBNP+FC (P ≥ 0.123). During LBNP+FC, systolic blood pressure was greater than LBNP+Sham after 2 min of face cooling and remained greater throughout face cooling (P < 0.002). Diastolic blood pressure was not different between conditions (condition effect: P = 0.991), nor was there an effect of time (P = 0.379) or interaction (P = 0.056) (Fig. 2C).

**Cardiac responses.** The heart rate response during LBNP and LBNP+Sham was not different than baseline throughout the protocol (P > 0.211) (Fig. 3A). Heart rate during LBNP...
alone was greater than baseline during the LBNP+FC protocol ($P < 0.020$), but it returned to baseline values during face cooling ($P > 0.129$). There were no differences in heart rate between the conditions ($P = 0.186$) until 2 min ($P = 0.030$), 3 min ($P = 0.014$), and 6 min ($P = 0.038$) of face cooling.

Stroke volume was lower in both conditions during LBNP alone when compared with baseline ($P \leq 0.001$). Stroke volume remained lower than baseline throughout LBNP+Sham ($P < 0.001$) (Fig. 3B). However, stroke volume was restored to baseline values during LBNP+FC ($P > 0.108$). Between conditions, stroke volume was not different during baseline, LBNP alone, or the first minute of face cooling ($P > 0.121$). After 2 min of face cooling, stroke volume was greater during LBNP+FC than LBNP+Sham ($P < 0.001$). Cardiac output was lower than baseline throughout the LBNP+Sham protocol ($P < 0.003$) and only lower than baseline in LBNP+FC after 2 min of face cooling ($P = 0.004$) (Fig. 3C).

Between conditions, cardiac output was greater in LBNP+FC at several time points ($P < 0.007$).

RMSSD was not different between conditions at baseline or during LBNP alone ($P > 0.563$) (Fig. 3D). During the LBNP+Sham protocol, there were no significant changes in RMSSD from baseline ($P > 0.113$). During LBNP+FC, RMSSD was greater than baseline during the first 6 min of face cooling ($P \leq 0.035$). RMSSD was also greater in LBNP+FC than LBNP+Sham from minutes 7 to 18 ($P < 0.026$).

**Blood flow.** Forearm blood flow was lower during LBNP+Sham (2.9 ± 1.3 ml·100 g tissue$^{-1}$·min$^{-1}$) than LBNP+FC (5.0 ± 2.5 ml·100 g tissue$^{-1}$·min$^{-1}$) at baseline ($P < 0.005$); therefore, we analyzed changes from baseline forearm blood flow. The change in forearm blood flow during LBNP+Sham was lower than baseline at minute 3 only ($P < 0.050$) (Table 1). The change in forearm blood flow during LBNP+FC was lower than baseline throughout the protocol ($P < 0.002$). The change in forearm blood flow was greater at minutes 15 and 21 during LBNP+FC than LBNP+Sham ($P < 0.007$).

Forearm cutaneous blood flow was not statistically different between conditions ($P = 0.855$) or throughout the protocols ($P = 0.601$), nor was there a significant interaction effect ($P = 0.881$) (Table 1).

Fingertip cutaneous blood flow was greater than baseline during LBNP+Sham after 12 min and throughout the protocol ($P < 0.005$) (Table 1). Fingertip cutaneous blood flow was lower than baseline at 7 min of LBNP+FC ($P = 0.007$). Fingertip cutaneous blood flow was greater during LBNP+Sham than LBNP+FC at minute 7 and from minute 12 to the end of the protocols ($P < 0.020$).

**Vascular resistance.** During LBNP+Sham, total peripheral resistance was greater than baseline throughout the protocol ($P < 0.041$) (Fig. 4A). However, during LBNP+FC, total peripheral resistance was greater than baseline starting after the first 2 min of face cooling ($P < 0.028$). Total peripheral resistance was greater during LBNP+FC than LBNP+Sham at 2 min of face cooling ($P < 0.008$). We obtained a full data set for only seven participants for forearm vascular resistance due to technical difficulties. Forearm vascular resistance was greater during LBNP+Sham (34.7 ± 16.3 mmHg·ml$^{-1}$·100 g tissue$^{-1}$·min) than LBNP+FC (18.1 ± 5.1 mmHg·ml$^{-1}$·100 g tissue$^{-1}$·min) at baseline ($P < 0.005$); therefore, we analyzed changes from baseline forearm vascular resistance. The change in forearm vascular resistance in LBNP+Sham was greater than baseline throughout the protocol ($P < 0.004$) (Fig. 4B). In LBNP+FC, the change in forearm vascular resistance was greater than baseline only during face cooling ($P < 0.010$). There were no differences in the change from baseline forearm vascular resistance between LBNP+Sham and LBNP+FC ($P \geq 0.060$).

During LBNP+Sham, forearm cutaneous vascular resistance did not change from baseline ($P > 0.694$) (Fig. 4C). Forearm cutaneous vascular resistance was greater during LBNP+FC after 3 min of face cooling and throughout the protocol ($P < 0.021$). Forearm cutaneous vascular resistance was greater than baseline at several time points in LBNP+FC ($P < 0.044$). During LBNP+FC, forearm cutaneous vascular resistance was greater than LBNP+Sham after 3 min of face cooling ($P < 0.022$).

During LBNP+Sham, fingertip cutaneous vascular resistance was not different from baseline at any point ($P > 0.915$).
During LBNP + FC, fingertip cutaneous vascular resistance was greater than baseline at 9 and 12 min of face cooling ($P < 0.007$). Between conditions, fingertip cutaneous vascular resistance was greater during LBNP + FC than LBNP + Sham at minutes 7, 12, 15, 18, 21, and Post ($P < 0.025$).

**DISCUSSION**

The main finding of this study is that face cooling facilitated a rapid increase in mean arterial pressure that was sustained throughout 15 min of 30 mmHg of LBNP. The increase in mean arterial pressure during face cooling was accomplished by a combination of increases in cardiac output and skin vascular resistance. These findings indicate that face cooling is able to augment mean arterial pressure during a central hypovolemic challenge, which suggests that this technique could be employed as a tool to prevent or delay cardiovascular decompensation during central hypovolemia.

Face cooling during 2 min of 30 mmHg of LBNP has been shown to prevent mean arterial pressure from decreasing by ~8 mmHg in healthy participants (8). However, we observed substantial increases in mean and systolic blood pressure throughout 15 min of LBNP + FC when compared with LBNP + Sham (Fig. 2, A and B). Whole body surface skin cooling increases mean arterial pressure by ~7–8 mmHg during 30 mmHg (14, 30), 40 mmHg (12, 14), and 50 mmHg (14, 31) of LBNP. Inspiratory threshold devices increase mean arterial pressure by 22–28 mmHg during LBNP (11, 35, 36). In this context, it is thought that raising blood pressure during moderate levels of LBNP would help stabilize hemodynamics during more severe central hypovolemia and improve LBNP tolerance. However, evidence to support this idea is not entirely clear and could be dependent on the method and/or timing of increasing mean arterial pressure. For instance, the application of whole body surface skin cooling before and during progressive LBNP improves LBNP tolerance by ~34% (14). Using an inspiratory threshold device throughout progressive LBNP also improves tolerance by 12–23% (11, 35, 36), whereas applying whole body surface skin cooling after 10 min of 30 mmHg of LBNP followed by progressive LBNP with continued whole body surface skin cooling does not improve LBNP tolerance (30). It is currently not known whether the increase in blood pressure we observed during LBNP + FC or the timing of the face cooling application during progressive and more severe central hypovolemia will improve LBNP tolerance.

**Table 1. Change from baseline forearm blood flow, forearm cutaneous blood flow, and fingertip cutaneous blood flow during sham and face cooling**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Δ Forearm Blood Flow, ml·100 g tissue⁻¹·min⁻¹ (n = 7)</th>
<th>Forearm Cutaneous Blood Flow, PU (n = 10)</th>
<th>Fingertip Cutaneous Blood Flow, PU (n = 10)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$-1.3 ± 1.0^{B}$</td>
<td>23 ± 12</td>
<td>152 ± 66</td>
</tr>
<tr>
<td>6</td>
<td>$-1.1 ± 1.0$</td>
<td>23 ± 14</td>
<td>161 ± 90</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>20 ± 17</td>
<td>158 ± 128</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>21 ± 15</td>
<td>182 ± 116</td>
</tr>
<tr>
<td>9</td>
<td>$-0.9 ± 0.6$</td>
<td>21 ± 15</td>
<td>174 ± 97</td>
</tr>
<tr>
<td>12</td>
<td>$-0.9 ± 0.8$</td>
<td>24 ± 22</td>
<td>81 ± 51^{A}</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>25 ± 16</td>
<td>217 ± 129</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>25 ± 22</td>
<td>155 ± 116</td>
</tr>
<tr>
<td>21</td>
<td>$-0.9 ± 0.7$</td>
<td>24 ± 22</td>
<td>230 ± 127</td>
</tr>
<tr>
<td>Post</td>
<td>$-0.4 ± 0.3$</td>
<td>24 ± 21</td>
<td>250 ± 134^{B}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0 ± 1.3</td>
<td>117 ± 79^{*}</td>
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Values are means ± SD. PU, perfusion units. *Significantly different Sham ($P < 0.05$). ^Significantly different from baseline ($P < 0.05$).
Stimulating the trigeminal nerve using face cooling causes a transient increase in cardiac parasympathetic activity that lasts 2–3 min (17, 37). However, when facial cooling was applied during LBNP, the increase in cardiac parasympathetic activity above baseline values persisted for 6 min (Fig. 3D). Moreover, cardiac parasympathetic activity during LBNP+FC was greater than LBNP+Sham for 12 min. The increase in cardiac parasympathetic activity decreased heart rate during face cooling (Fig. 3A), which most likely allowed for an increase in end-diastolic volume (1, 47). We speculate that the increase in end-diastolic volume during face cooling improved the Frank-Starling relationship that prevented the fall in stroke volume during LBNP+FC (Fig. 3B). Although heart rate was lower during LBNP+FC than LBNP+Sham, the augmented stroke volume during LBNP+FC prevented the fall in cardiac output that was seen during LBNP+Sham. Therefore, the greater cardiac output during LBNP+FC contributed to the increases in both systolic and mean arterial pressure.

In addition to augmenting cardiac parasympathetic activity, facial cooling also causes robust increases in sympathetic nerve activity (17, 19, 39) that translate to increased resistance in a variety of vascular beds (5, 16, 17, 20, 29). It is currently not known whether sympathetic activity (i.e., muscle or skin sympathetic nerve activity) is increased beyond 3 min of face cooling (17, 19, 39). However, our previous study demonstrates that forearm vascular resistance can be augmented for up to 15 min during face cooling (37), which suggests that sympathetic activity is elevated throughout the duration of face cooling. Although we did not observe further sustained increases in total peripheral resistance and forearm vascular resistance during LBNP+FC, we did observe increases in forearm and fingertip cutaneous vascular resistance, which primarily occurred during the latter portions of LBNP+FC (minute 9 through Post, and minute 7 and minutes 12 through Post, respectively) (Fig. 4, C and D). These results indicate that skin sympathetic vasoconstrictor nerve activity is likely increased during LBNP+FC. Furthermore, we speculate that the increases in skin vascular resistance offset a potential reduction in vascular resistance to vital organs during LBNP+FC, which resulted in no differences in total peripheral resistance between LBNP+FC and LBNP+Sham. However, additional work is needed to discern whether increases in skin vascular resistance during LBNP+FC cause a redistribution of blood flow to mitigate decreases in central blood volume.

**Experimental considerations.** Our study has several limitations worth noting. First, we did not take participants to LBNP tolerance. This would have provided valuable applied information regarding the capability of face cooling to prevent or delay cardiovascular decompensation during severe central hypovolemia (i.e., blood loss). Nonetheless, we have provided evidence that face cooling during a constant moderate level of LBNP increases blood pressure. Second, we did not control for menstrual cycle hormones. Because the timing of hypotensive states (e.g., trauma-induced blood loss, and sepsis) is unpredictable, we chose not to control for menstrual cycle hormones despite their influence on blood pressure regulation (28) and sympathetic responses to LBNP (7, 45). Third, we did not quantitate cardiovascular fitness or exercise training status in our participants, which has been shown to influence hemodynamic responses to LBNP (24, 26, 32, 33, 42). Fourth, blood loss is commonly associated with hypothermia (6), which can lead to coagulopathy (4). However, we currently do not know whether face cooling influences coagulopathy in hypothermic trauma patients. Finally, we did not clamp respiratory rate or tidal volume between conditions, which could have influenced our measure of cardiac parasympathetic activity (i.e., RMSSD) (43). Currently, the interaction between face cooling and LBNP on ventilatory pattern and stability is not known.

**Conclusions.** We have demonstrated that face cooling during moderate LBNP increases mean arterial pressure throughout the duration of face cooling. The increase in mean arterial pressure during LBNP was accomplished by increases in both cardiac output and skin vascular resistance. Moreover, the application of face cooling during LBNP provoked temporal increases in cardiac parasympathetic activity and sympathetic activity, both of which contributed to the increase in mean arterial pressure.
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B.D.J. and Z.J.S. drafted manuscript; B.D.J., J.R.S., S.S., and Z.J.S. edited and revised manuscript; B.D.J., J.R.S., S.S., and Z.J.S. approved final version of manuscript.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

B.D.J. and Z.J.S. conceived and designed research; B.D.J., J.R.S., S.S., and Z.J.S. performed experiments; B.D.J. and Z.J.S. analyzed data; B.D.J. and Z.J.S. interpreted results of experiments; B.D.J. and Z.J.S. prepared figures; B.D.J. and Z.J.S. drafted manuscript; B.D.J., J.R.S., S.S., and Z.J.S. edited and revised manuscript; B.D.J., J.R.S., S.S., and Z.J.S. approved final version of manuscript.

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