Face cooling increases blood pressure during central hypovolemia

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ABSTRACT

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. **Purpose** We tested the hypothesis that FC during central hypovolemia induced by lower body negative pressure (LBNP) would increase blood pressure. **Methods** Ten healthy participants (22±2 years, 3 women) completed two randomized LBNP trials on separate days. Trials began with 30 mmHg of LBNP for 6 minutes. Then, a 2.5 L plastic bag of ice water (0±0°C) (LBNP+FC) or thermoneutral water (34±1°C) (LBNP+Sham) was placed on the forehead, eyes, and cheeks during 15 minutes of LBNP at 30 mmHg. **Results** Forehead temperature was lower during LBNP+FC vs. LBNP+Sham with the greatest difference at 21 minutes of LBNP (11.1±1.6 vs. 33.9±1.4°C, $P < 0.001$). Mean arterial pressure was greater during LBNP+FC vs. LBNP+Sham with the greatest difference at 8 minutes of LBNP (98±15 vs. 80±8 mmHg, $P < 0.001$). Cardiac output was higher during LBNP+FC vs. LBNP+Sham with the greatest difference at 18 minutes of LBNP (5.9±1.4 vs. 4.9±1.0 L/min, $P = 0.005$). Forearm cutaneous vascular resistance was greater during LBNP+FC vs. LBNP+Sham with the greatest difference at 15 minutes of LBNP (7.2±3.4 vs. 4.9±2.7 mmHg/PU, $P < 0.001$). **Conclusion** Face cooling during LBNP increases blood pressure through increases in cardiac output and vascular resistance.

KEYWORDS

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

INTRODUCTION

Blood loss and other clinical situations (i.e., postural orthostatic tolerance, sepsis, Dengue fever, etc.) can cause central hypovolemia and lead to cardiovascular decompensation (i.e., inability to maintain blood pressure). Several methods aimed at maintaining blood pressure during central hypovolemia have been investigated in the prehospital setting or in the laboratory. Intravenous saline infusions are common in the prehospital setting to counteract central hypovolemia. However, intravenous saline infusions increase the risk of coagulopathy (38) and necessary blood transfusions (18) in trauma patients. Furthermore, this method requires venous access, which can be difficult to obtain during central hypovolemia (13). Respiratory impedance devices improve blood pressure in a variety of models of central hypovolemia (i.e., large animals, healthy volunteers, and patients) (9-11, 25, 27, 35, 36). However, the patient must have an adequate ventilatory drive for the device to be effective. In this regard, whole-body surface skin cooling has also been used to increase blood pressure during central hypovolemia in humans (12, 14, 30). However, whole-body surface skin cooling is impractical for prehospital use due to its size and the need for a power source to chill and circulate the coolant. Therefore, a practical, prehospital technique is needed to prevent or delay cardiovascular decompensation when patients experience central hypovolemia.

Cooling the forehead and cheeks stimulates the trigeminal nerve which elicits an increase in cardiac parasympathetic activity followed by a rise in sympathetic activity (17). Despite the transient increase in cardiac parasympathetic activity, face cooling causes substantial increases in blood pressure that can be maintained for 15 minutes or

more (37). Therefore, simply cooling the forehead and cheeks might be an effective intervention to maintain or improve blood pressure in individuals during acute periods of central hypovolemia. Two minutes of face cooling during central hypovolemia induced by lower body negative pressure (LBNP) prevents a decrease in mean arterial pressure (8). Therefore, the purpose of our study was to test the hypothesis that cooling the forehead, eyes, and cheeks would raise blood pressure for up to 15 minutes during central hypovolemia in healthy humans.

METHODS

Participants

Ten healthy participants (age: 22 ± 2 years; 3 women; height: 174 ± 10 cm; weight: 73 ± 13 kg) completed the study. Participants self-reported to be free from autonomic, cardiovascular, respiratory, metabolic, or endocrine diseases. All participants self-reported to be non-smokers and were not taking any medications (except oral contraceptives; n = 1). Women were not pregnant (confirmed by a negative urine pregnancy test) and we did not control for menstrual cycle hormones. All participants were fully informed of the experimental procedures and possible risks before giving informed, written consent. The study was approved by the Institutional Review Board at the University at Buffalo and was performed in accordance with the standards set by the latest revision of the Declaration of Helsinki.

Experimental Approach

Participants completed two randomized study visits: one LBNP with face cooling (LBNP+FC) and one LBNP with sham (LBNP+Sham). For both study visits, we asked

participants to report to the temperature controlled (23 ± 1° C, 21 ± 6% relative humidity) laboratory after abstaining from exercise, alcohol, and caffeine for at least 12 hours and food for at least 2 hours. After participants were instrumented, we secured them to the LBNP chamber in the supine position using a neoprene kayak skirt that was sealed at the level of the iliac crest. After a 10-minute rest period, we collected baseline data for an additional 10 minutes. At the end of baseline, 30 mmHg of LBNP commenced for 6 minutes. 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 upwards 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 minutes 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 minutes. After 15 minutes 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 minutes of recovery data.

Instrumentation and Measurements

Height and weight were measured using a stadiometer and scale (Sartorius, Bohemia, NY) prior to the study visits. A 3-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 electrosphygmomanometry (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 minutes of baseline, and every 3 minutes 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 seconds 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 1kHz using a data acquisition system (Biopac MP150, Goleta, CA). Data were analyzed in 1 minute segments at 10 minutes of baseline, at 3 and 6 minutes of LBNP, during each of the first 3 minutes of face cooling or sham, and every 3 minutes thereafter. Recovery data were analyzed in 1 minute segments at the end of the 5-minute 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 (Absolute 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 to those acquired at the 10-minute 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 minutes of LBNP (Figure 1). Forehead skin temperature was lower than baseline and LBNP+Sham throughout the entire face cooling procedure and 5 minutes 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 ($P > 0.068$) (Figure 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 ($P \leq 0.001$) and LBNP+Sham ($P < 0.019$). Mean arterial pressure remained greater than baseline 5 minutes 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 to baseline ($P \leq 0.005$) (Figure 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 ($P \geq 0.123$). During LBNP+FC, systolic blood pressure was greater than LBNP+Sham after 2 minutes 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 ($P = 0.056$) (Figure 2C).

Cardiac responses The heart rate response during LBNP and LBNP+Sham was not different than baseline throughout the protocol ($P > 0.211$) (Figure 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 ($P \geq 0.186$) until 2 minutes ($P = 0.030$), 3 minutes ($P = 0.014$), and 6 minutes ($P = 0.038$) of face cooling.

Stroke volume was lower in both conditions during LBNP alone when compared to baseline ($P \leq 0.001$). Stroke volume remained lower than baseline throughout LBNP+Sham ($P < 0.001$) (Figure 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 minutes of face cooling, stroke volume was greater during LBNP+FC versus LBNP+Sham ($P < 0.001$). Cardiac output was lower than baseline throughout the LBNP+Sham protocol ($P < 0.003$) and only lower in than baseline in LBNP+FC after 2 minutes of face cooling ($P = 0.004$) (Figure 3C). Between conditions, cardiac output was greater in LBNP+FC at several timepoints ($P < 0.007$).

RMSSD was not different between conditions at baseline or during LBNP alone ($P > 0.563$) (Figure 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 minutes of face cooling ($P \leq 0.035$). RMSSD was also greater in LBNP+FC versus 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/ min) than LBNP+FC (5.0 ± 2.5 mL/100 g tissue/ min) 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 versus 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 minutes and throughout the protocol ($P < 0.005$) (Table 1). Fingertip cutaneous blood flow was lower than baseline at 7 minutes of LBNP+FC ($P = 0.007$). Fingertip cutaneous blood flow was greater during LBNP+Sham versus 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 ($P < 0.041$) (Figure 4A). However, during LBNP+FC, total peripheral resistance was greater than baseline starting after the first 2 minutes of face cooling ($P < 0.028$). Total peripheral resistance was greater during LBNP+FC versus LBNP+Sham at 2 minutes of face cooling ($P < 0.008$). We obtained a full data set for only 7 participants for forearm vascular resistance due to technical difficulties. Forearm vascular resistance was greater during LBNP+Sham (34.7 ± 16.3 mmHg/mL/100 g tissue/min) than LBNP+FC (18.1 ± 5.1 mmHg/mL/100 g tissue/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 ($P < 0.004$) (Figure 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 ($P > 0.694$) (Figure 4C). Forearm cutaneous vascular resistance was greater during LBNP+FC after 3 minutes of face cooling and throughout the protocol ($P < 0.021$). Forearm cutaneous vascular resistance was greater than baseline at several time points in LNBP+FC ($P < 0.044$). During LBNP+FC, forearm cutaneous vascular resistance was greater than LBNP+Sham after 3 minutes of face cooling ($P < 0.022$).

During LBNP+Sham, fingertip cutaneous vascular resistance was not different from baseline at any point ($P > 0.915$) (Figure 4D). During LBNP+FC, fingertip cutaneous vascular resistance was greater than baseline at 9 and 12 minutes of face cooling ($P < 0.007$). Between conditions, fingertip cutaneous vascular resistance was greater during LBNP+FC versus 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 minutes 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 two minutes 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 minutes of LBNP+FC when compared to LBNP+Sham (Figure 2A 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 prior to 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 minutes 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 if the increase in blood pressure we observed during LBNP+FC or the timing

277 of the face cooling application during progressive and more severe central hypovolemia
278 will improve LBNP tolerance.

279 Stimulating the trigeminal nerve using face cooling causes a transient increase in
280 cardiac parasympathetic activity that lasts 2-3 minutes (17, 37). However, when facial
281 cooling was applied during LBNP, the increase in cardiac parasympathetic activity
282 above baseline values persisted for 6 minutes (Figure 3D). Moreover, cardiac
283 parasympathetic activity during LBNP+FC was greater that LBNP+Sham for 12 minutes.
284 The increase in cardiac parasympathetic activity decreased heart rate during face
285 cooling (Figure 3A), which most likely allowed for an increase in end diastolic volume (1,
286 47). We speculate that the increase in end diastolic volume during face cooling
287 improved the Frank-Starling relationship that prevented the fall in stroke volume during
288 LBNP+FC (Figure 3B). Although heart rate was lower during LBNP+FC versus
289 LBNP+Sham, the augmented stroke volume during LBNP+FC prevented the fall in
290 cardiac output that was seen during LBNP+Sham. Therefore, the greater cardiac output
291 during LBNP+FC contributed to the increases in both systolic and mean arterial
292 pressure.

293 In addition to augmenting cardiac parasympathetic activity, facial cooling also
294 causes robust increases in sympathetic nerve activity (17, 19, 39) that translate to
295 increased resistance in a variety of vascular beds (5, 16, 17, 20, 29). It is currently not
296 known if sympathetic activity (i.e., muscle or skin sympathetic nerve activity) is
297 increased beyond 3 minutes of face cooling (17, 19, 39). However, our previous study
298 demonstrates that forearm vascular resistance can be augmented for up to 15 minutes
299 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) (Figure 4C & 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 if 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 (i.e., trauma-induced blood loss, sepsis, etc.) 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 quantify cardiovascular fitness or exercise training status in our participants, which have

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 if 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.

Perspectives and Significance

Blood loss is the leading cause of civilian and battlefield trauma deaths (15). Approximately 91% of potentially survivable deaths on the battlefield are blood loss-related (15, 23) and it is estimated that ~25% of these deaths could have been prevented by timely intervention and treatment. These preventable deaths underscore the need for rapid and simple prehospital interventions to maintain or restore blood pressure before and during transport or evacuation (2). This study is the first step towards the possibility of using face cooling to mitigate cardiovascular decompensation during blood loss or other conditions involving central hypovolemia. Combat medics and first responders could carry chemical ice packs in their medic bags and apply them to a patient's forehead following blood loss. However, we believe that using forehead cooling to prevent cardiovascular decompensation is situational. For instance, if active bleeding is occurring, either internal or external, a further increase in blood pressure could augment blood loss and promote cardiovascular decompensation. Therefore, face cooling should only be used after the bleeding is controlled. Furthermore, it is common

for medical personal to allow blood pressure to remain low (i.e. permissive hypotension) prior to the addition of fluid to prevent the rupture of newly formed blood clots (41). It remains to be seen, however, if face cooling can be titrated to maintain blood pressure within acceptable values. This would require an understanding of the dose-response relationship between the magnitudes of face cooling and increases in blood pressure. Moreover, it is also unclear how additional environmental factors that are commonly encountered by military and emergency personnel, such as heat stress, cold stress, hypoxia, and prior exercise influence the pressor response to face cooling during blood loss. In this context, simultaneous stimulation of both the sympathetic and parasympathetic nervous systems (i.e. “autonomic conflict”) due to blood loss and face cooling, respectively, could contribute to an increased risk of cardiac arrhythmias in some patients (3, 40, 44). Consequently, further research is needed to determine if face cooling is feasible for the prevention of cardiovascular decompensation during blood loss, or other central hypovolemic challenges, in a variety of environmental and physiological conditions.

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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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

B.D.J and Z.J.S conception and design of research; B.D.J., J.R.S., S.S., and Z.J.S. performed experiments; B.D.J. analyzed data, B.D.J. and Z.J.S. interpreted results of experiments; B.D.J. prepared figures; B.D.J. 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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Table 1. Change from baseline Forearm Blood Flow, Forearm Cutaneous Blood Flow, and Fingertip Cutaneous Blood Flow during Sham and Face Cooling.

	Delta Forearm Blood Flow (mL/100 g tissue/min) (n = 7)		Forearm Cutaneous Blood Flow (PU) (n = 10)		Fingertip Cutaneous Blood Flow (PU) (n = 10)	
Time (minutes)	Sham	Face Cooling	Sham	Face Cooling	Sham	Face Cooling
Baseline	--	--	23 ± 12	23 ± 14	152 ± 66	190 ± 136
3	-1.3 ± 1.0[B]	-2.3 ± 2.0[B]	23 ± 14	20 ± 17	161 ± 90	158 ± 128
6	-1.1 ± 1.0	-1.8 ± 1.7[B]	21 ± 15	23 ± 26	182 ± 116	181 ± 153
7	--	--	21 ± 15	21 ± 19	174 ± 97	81 ± 51*[B]
8	--	--	24 ± 19	29 ± 24	217 ± 129	155 ± 116
9	-0.9 ± 0.6	-2.0 ± 2.6[B]	25 ± 16	25 ± 22	230 ± 127	174 ± 136
12	--	--	24 ± 22	24 ± 30	250 ± 134[B]	117 ± 79*
15	-0.9 ± 0.8	-2.5 ± 2.5*[B]	23 ± 17	22 ± 28	255 ± 135[B]	115 ± 94*
18	--	--	23 ± 21	26 ± 40	262 ± 119[B]	112 ± 96*
21	-0.9 ± 0.7	-2.6 ± 2.4*[B]	24 ± 15	24 ± 28	282 ± 114[B]	103 ± 64*
Post	-0.4 ± 0.3	0.0 ± 1.3	27 ± 20	28 ± 44	287 ± 61[B]	136 ± 113*

* = Different from Sham ($P < 0.05$).

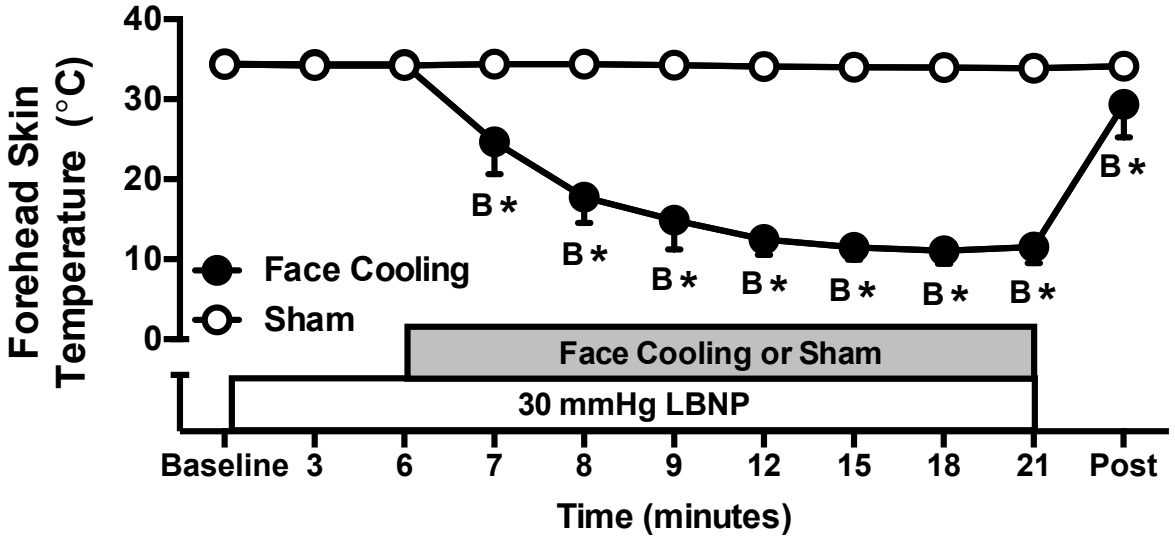
B = Different from Baseline ($P < 0.05$).

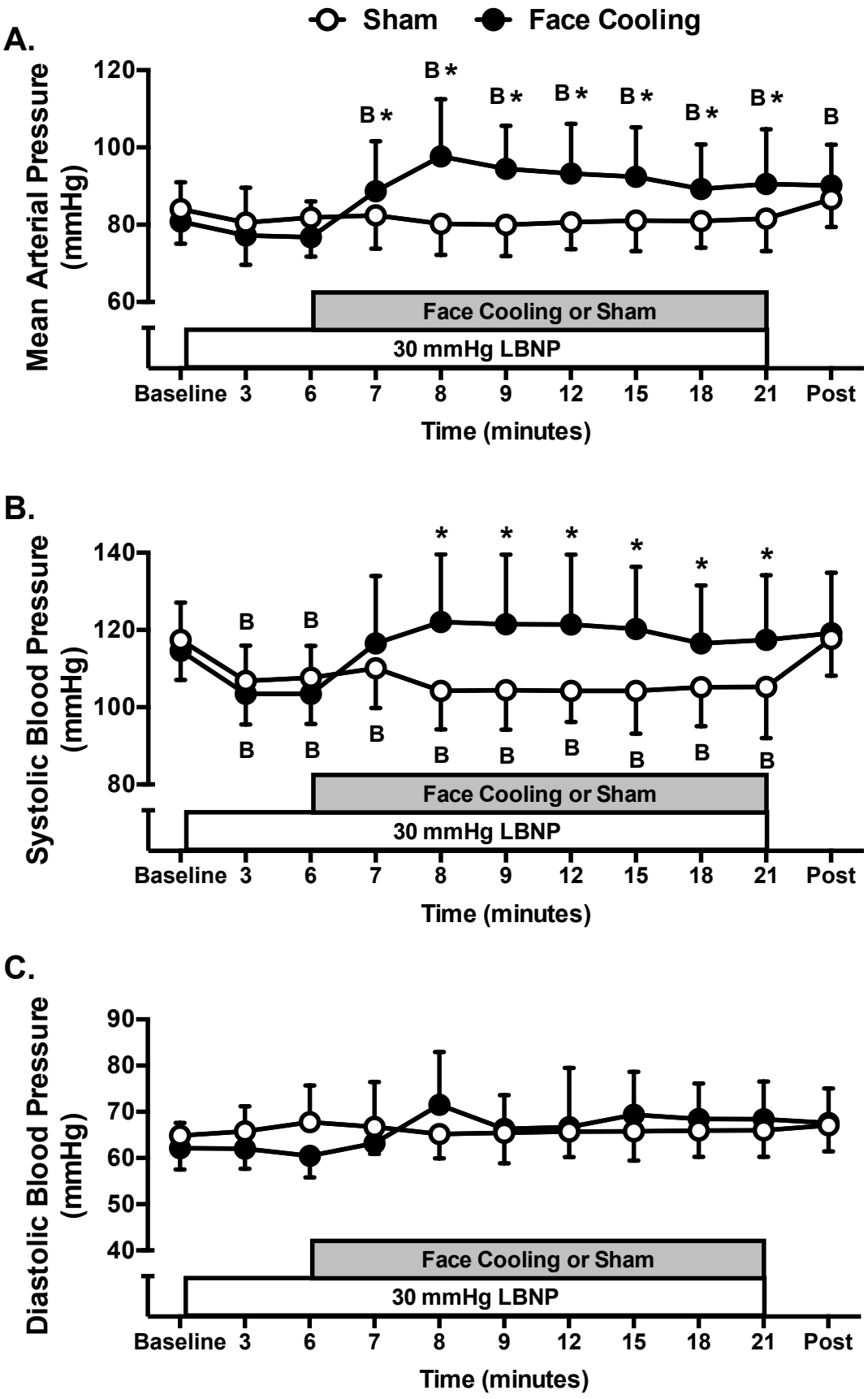
Figure 1. Forehead skin temperature during both protocols. After a 10 minute baseline resting period, 30 mmHg of lower body negative pressure (LBNP) was applied for 21 minutes. After 6 minutes of LBNP, a pliable plastic bag filled with either ice water (Face Cooling) or thermoneutral water (Sham) was applied over the forehead, cheeks, and eyes for 15 minutes (n = 10). Values are expressed as means ± SD. B = different from baseline ($P < 0.001$), * = different from Sham ($P < 0.001$).

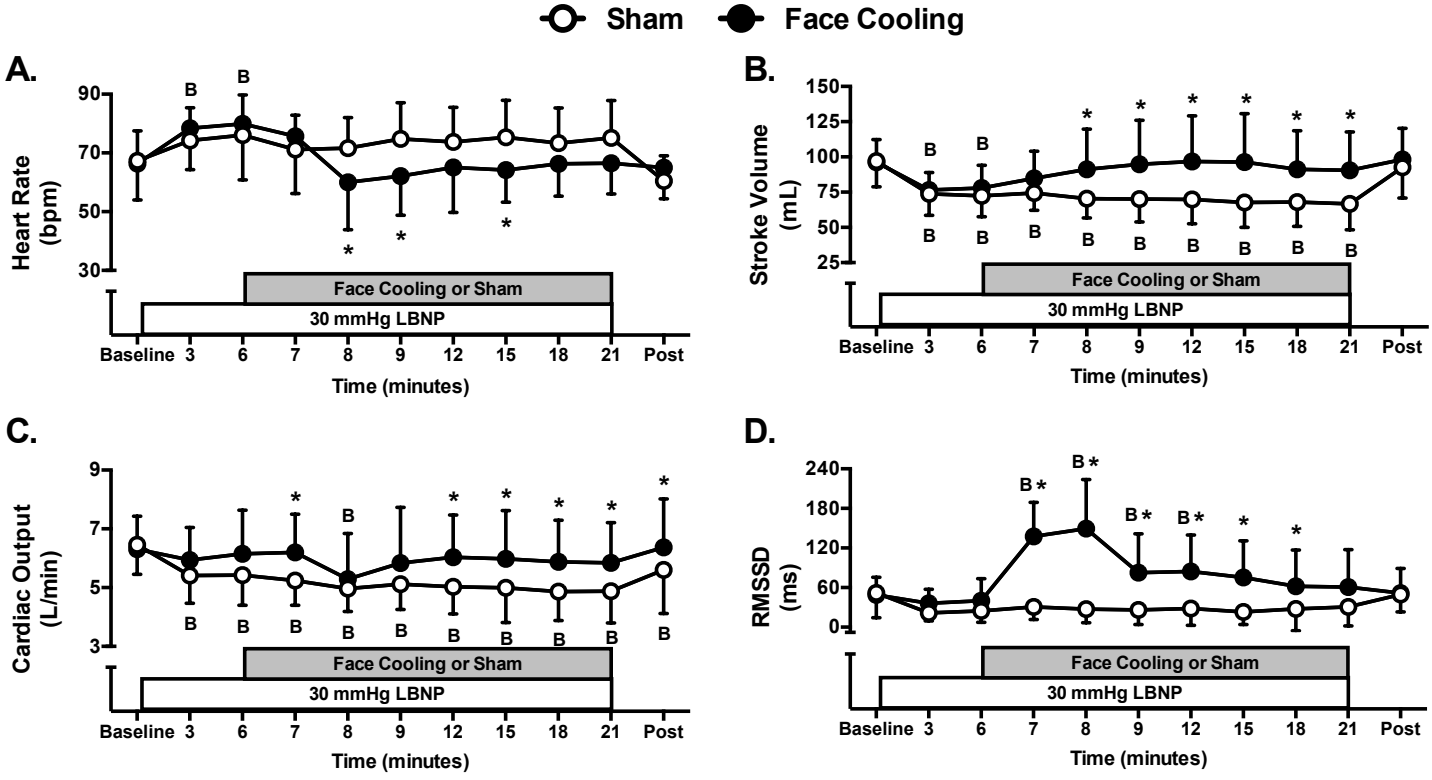
Figure 2. Mean arterial pressure (n = 10) (A), systolic blood pressure (n = 10) (B), and diastolic blood pressure (n = 10) (C) during both protocols. Values are expressed as means ± SD. B = different from baseline ($P < 0.050$), * = different from Sham ($P < 0.050$).

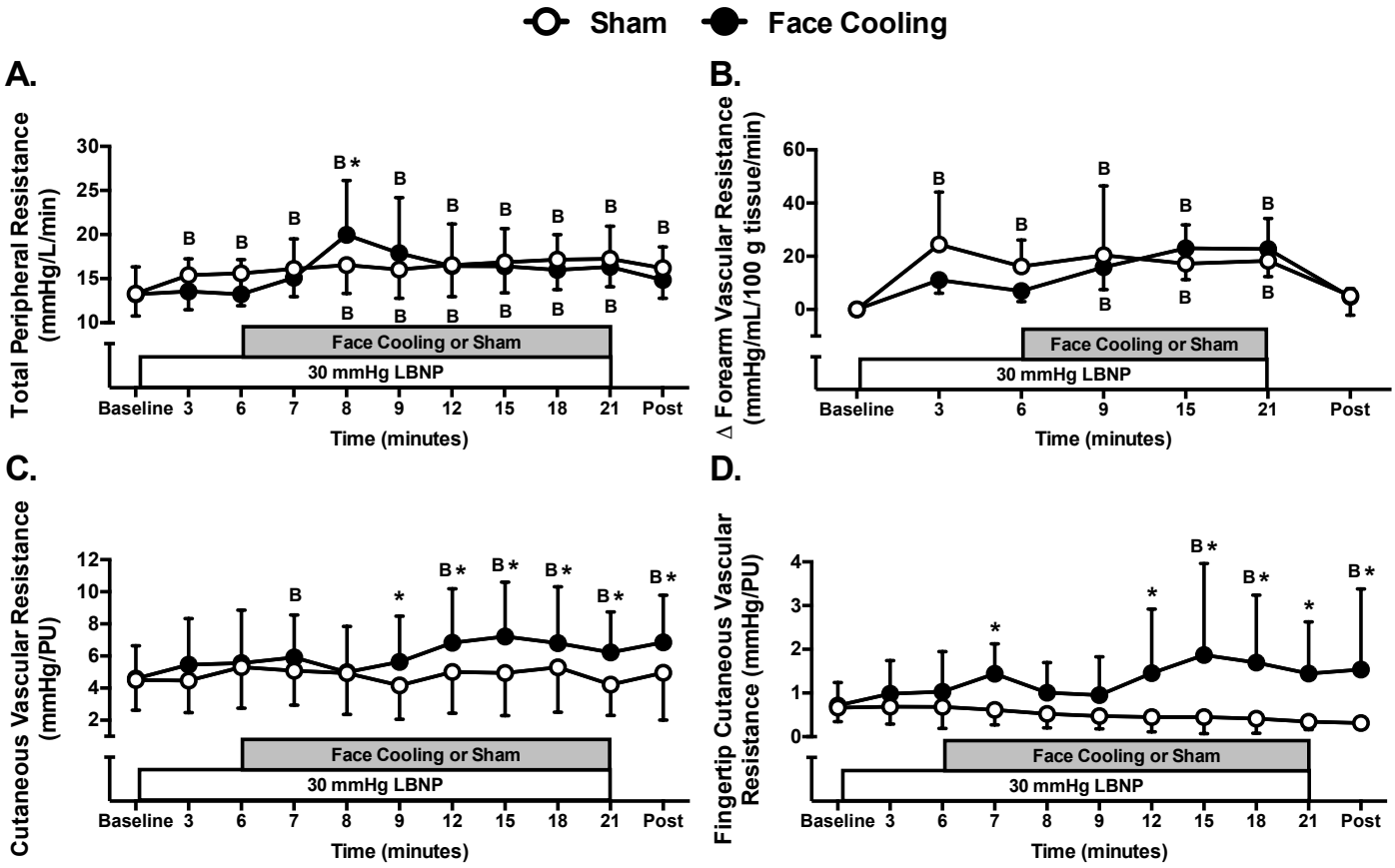
Figure 3. Heart rate (n = 10) (A), stroke volume (n = 10) (B), cardiac output (n = 10) (C), and the root mean square of successive differences of the R-R interval (RMSSD) (n = 10) (D) during both protocols. Values are expressed as means ± SD. B = different from baseline ($P < 0.050$), * = different from Sham ($P < 0.050$).

Figure 4. Total peripheral resistance (n = 10) (A), the change from baseline in forearm vascular resistance (n = 7) (B), forearm cutaneous vascular resistance (n = 10) (C), and fingertip cutaneous vascular resistance (n = 10) (D) during both protocols. Values are expressed as means ± SD. B = different from baseline ($P < 0.050$), * = different from Sham ($P < 0.050$).


Forehead Skin Temperature (°C)
40
30
20
10
0
B *
B *
B *
B *
B *
B *
B *
B *
Face Cooling
Sham
Face Cooling or Sham
30 mmHg LBNP
Baseline
3
6
7
8
9
12
15
18
21
Post
Time (minutes)


A.
Sham
Face Cooling
Mean Arterial Pressure (mmHg)
120
100
80
60
B*
B*
B*
B*
B*
B*
B
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
B.
Systolic Blood Pressure (mmHg)
140
120
100
80
*
B
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
C.
Diastolic Blood Pressure (mmHg)
90
80
70
60
50
40
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)


Sham
Face Cooling
A.
Heart Rate (bpm)
90
70
50
30
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
B.
Stroke Volume (mL)
150
125
100
75
50
25
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
C.
Cardiac Output (L/min)
9
7
5
3
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
D.
RMSSD (ms)
240
180
120
60
0
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)


Sham
Face Cooling
A.
Total Peripheral Resistance (mmHg/L/min)
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
B.
Δ Forearm Vascular Resistance (mmHg/mL/100 g tissue/min)
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 9 15 21 Post
Time (minutes)
C.
Cutaneous Vascular Resistance (mmHg/PU)
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)
D.
Fingertip Cutaneous Vascular Resistance (mmHg/PU)
Face Cooling or Sham
30 mmHg LBNP
Baseline 3 6 7 8 9 12 15 18 21 Post
Time (minutes)