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Lower body negative pressure protects brain perfusion in aviation gravitational stress induced by push–pull manoeuvre

Changyang Xing[1,2], Xinpei Wang[1], Yuan Gao[1], Jiaxin Zhang[1], Yunnan Liu[2], Yitong Guo[2], Chen Wang[2], Yang Feng[2], Yujia Lei[2], Xing Zhang[1], Jia Li[1], Wendong Hu[1], Shu Zhang[1], Lijun Yuan[2] and Feng Gao[1]

[1] *School of Aerospace Medicine, Fourth Military Medical University, Xi'an 710032, China*
[2] *Department of Ultrasound Diagnostics, Tangdu Hospital, Fourth Military Medical University, Xi'an 710038, China*

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Key points

- Rapid alterations of gravitational stress during high-performance aircraft push–pull manoeuvres induce dramatic shifts in volume and pressure within the circulation system, which may result in loss of consciousness due to the rapid and significant reduction in cerebral perfusion. There are still no specific and effective countermeasures so far.
- We found that lower body negative pressure (LBNP), applied prior to and during −Gz and released at the subsequent transition to +Gz, could effectively counteract gravitational haemodynamic stress induced by a simulated push–pull manoeuvre and improve cerebral diastolic perfusion in human subjects.
- We developed a LBNP strategy that effectively protects cerebral perfusion at rapid −Gz to +Gz transitions via improving cerebral blood flow and blood pressure during push–pull manoeuvres and highlight the importance of the timing of the intervention.
- Our findings provide a systemic link of integrated responses between the peripheral and cerebral haemodynamic changes during push–pull manoeuvres.

Abstract The acute negative (−Gz) to positive (+Gz) gravity stress during high-performance aircraft push–pull manoeuvres dramatically reduces transient cerebral perfusion, which may lead to loss of vision or even consciousness. The aim of this study was to explore a specific and effective counteractive strategy. Twenty-three healthy young male volunteers (age 21 ± 1 year) were subjected to tilting-simulated push–pull manoeuvres. Lower body negative pressure (LBNP) of −40 mmHg was applied prior to and during −Gz stress (−0.50 or −0.87 Gz) and released at the subsequent transition to +1.00 Gz stress. Beat-to-beat cerebral and systemic haemodynamics were continuously recorded during the simulated push–pull manoeuvre in LBNP bouts and

Changyang Xing completed his MD in 2011 and received his PhD in Medical Imaging in 2017 at the Fourth Military Medical University, China. He is currently working as a Postdoc at the School of Aerospace Medicine supported by the National Postdoctoral Program for Innovative Talents, and also as a doctor at the Department of Ultrasound Diagnostics, Tangdu Hospital, Fourth Military Medical University. His research focuses on cardio- and cerebrovascular ultrasound diagnosis in clinical and aerospace medicine. **Xinpei Wang** received her MD in 2018 and is now a postgraduate in the School of Aerospace Medicine, Fourth Military Medical University. She is currently focusing on investigating the impacts and the underlying mechanism of microgravity on the cardiovascular system, with an interest in developing countermeasures for cardiovascular health in long-term space flight.

C. Xing and X. Wang contributed equally to this work.

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corresponding control bouts. During the rapid gravitational transition from −Gz to +Gz, the mean cerebral blood flow velocity decreased significantly in control bouts, while it increased in LBNP bouts (control *vs.* LBNP bouts, -6.6 ± 4.6 *vs.* 5.1 ± 6.8 cm s^{-1} for −0.50 Gz, and -7.4 ± 4.8 *vs.* 3.4 ± 4.6 cm s^{-1} for −0.87 Gz, $P < 0.01$), which was attributed mainly to the elevation of diastolic flow. The LBNP bouts showed much smaller reduction of mean arterial blood pressure at the brain level than control bouts (control bouts *vs.* LBNP bouts, -38 ± 12 *vs.* -23 ± 10 mmHg for −0.50 to +1.00 Gz, and -62 ± 16 *vs.* -43 ± 11 mmHg for −0.87 to +1.00 Gz, $P < 0.01$). LBNP applied at −Gz and released at subsequent +Gz had biphasic counteractive effects against the gravitational responses to the push–pull manoeuvre. These data demonstrate that this LBNP strategy could effectively protect cerebral perfusion with dominant improvement of diastolic flow during push–pull manoeuvres.

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Corresponding author F. Gao: School of Aerospace Medicine, Fourth Military Medical University, 169 Changlexi Road, Xi'an 710032, China. Email: fgao@fmmu.edu.cn

Introduction

Rapid alterations of the gravitational gradient in the body can induce dramatic shifts in volume and pressure within the cardio- and cerebrovascular system, which may result in dizziness or even loss of consciousness due to a significant decrease in cerebral perfusion (Scott *et al.* 2007; Sheriff *et al.* 2007). The push–pull manoeuvre (PPM) is a common flying manoeuvre for pilots of high-performance aircraft, and is composed of a brief exposure to negative gravity along the long (z) axis of the body (−Gz) by pushing on the control stick to unload the aircraft and a following positive gravity (+Gz) by pulling on the control stick (Banks *et al.* 1994, 1995). The prior −Gz stress reduced physiological tolerance during subsequent +Gz stress, as evidenced by a greater reduction in mean arterial blood pressure (MAP) than normal 1 G gravitational stress transiting to +Gz acceleration (Banks *et al.* 1994; Goodman *et al.* 2000; Hakeman *et al.* 2003). This push–pull effect may account for the increased risk for loss of consciousness in pilots during manoeuvres (Michaud & Lyons, 1998; Michaud *et al.* 1998).

Current countermeasures to gravitational stress during high-performance aircraft manoeuvres, including an anti-gravity suit and an anti-gravity straining manoeuvre, are all targeted at the +Gz stress. The anti-gravity suit aims at increasing the venous return from the lower body to the heart, which would aggravate the 'push' effect when applied during the PPM (Fraser *et al.* 1994; Scott *et al.* 2007). The anti-gravity straining manoeuvre is a coordinated manoeuvre combining a thoracoabdominal Valsalva-like strain and a peripheral musculoskeletal isometric strain, which increases both the blood pressure and the venous return (Latham *et al.* 1991). When performed under air combat conditions, it requires additional effort and concentration, which is very stressful for pilots. The increased venous return from the legs also has a negative effect on the −Gz haemodynamics during the PPM. Until now, there are still no effective and specific protective measures for the PPM.

Although the mechanism of the push–pull effect has not been fully elucidated, it has been proven that the sympathetic nervous system neither contributes to nor guards against the push–pull effect as demonstrated in a vasomotor blunting experiment using clonidine, an α_2-adrenergic agonist that works primarily by centrally inhibiting sympathetic function independent of its sedative effects (Sheriff *et al.* 2010). Our previous study also demonstrated that the cerebral autoregulation that remained intact during −Gz (head down tilt, HDT) responded rapidly and appropriately in a transition to +Gz (head up tilt, HUT) (Yang *et al.* 2015). Through the quantitative analysis of leg blood flow and an autonomic inhabitation study, Sheriff *et al.* demonstrated that the great fall in MAP at eye level was largely attributed to the exaggerated change in leg blood flow during a tilting-simulated PPM (Sheriff *et al.* 2007; Wong & Sheriff, 2008). Thus, the leg blood flow might be an effective target for cerebral perfusion protection during the PPM.

Lower body negative pressure (LBNP) has long been used to counteract the blood redistribution caused by microgravity (Campbell & Charles, 2015). LBNP can cause blood to pool in the legs without impairing arterial blood pressure in the brain or stimulating carotid baroreceptors (Musgrave *et al.* 1969; Vukasovic *et al.* 1990; Guo *et al.* 2006). Therefore, LBNP may serve as an ideal method to counteract the blood redistribution between legs and upper body and the corresponding haemodynamic changes caused by the PPM and thus protect the brain perfusion. In the present study, we found that LBNP applied prior to and during the 'push' phase (upright and HDT), and then released at the subsequent 'pull' phase (HUT) could counteract the cardio- and cerebrovascular haemodynamic responses at the transition from −Gz to +Gz stress and protect brain perfusion during the PPM.

Methods

Ethical approval

The study conformed to the standards set by the latest *Declaration of Helsinki*, except for registration in a database, and was approved by the Ethics Committee of The Fourth Military Medical University. All participants gave their written informed consent.

Subjects

Twenty-three healthy young male volunteers (age 21 ± 1 years, height 173 ± 2 cm, weight 68 ± 4 kg), all non-smokers with no history of fainting and/or cardiac arrhythmia and not taking any cardiovascular medication, were recruited. The subjects abstained from caffeinated beverages, alcohol and vigorous exercise at least 24 h before the study and a light meal was eaten 2 h before. Subjects were familiarized with the measurement and study procedures. All subjects were undergraduates from the School of Aerospace Medicine of our university, who had experienced both the tilting test and LBNP one or two times in class several weeks before the study.

Experimental protocol

Measurements were performed with subjects in positions following an experimental protocol on a computer-controlled tilt table whose transition speed was set as 45° s^{-1}. Shoulder blocks and a wide abdominal belt were fixed and adjusted well to prevent the body from moving during rapid position transition. Following instrumentation, the lower body was positioned inside the LBNP chamber and sealed at the level of the iliac crest. The LBNP chamber was designed with a −30 mmHg s^{-1} increasing rate of negative pressure and the capability for transient release. Two straps were used to fix the LBNP chamber to the tilt table. A saddle was supplied to prevent the downward shift of body during HUT to minimize skeletal muscle pump effects. During the experiment, subjects were coached to avoid leg tensing to cause muscle contraction.

Before actual testing, familiarization was provided at −60° HDT for 15 s with a rapid transition to 90° HUT, which minimized psychological responses to the posture change. It appears that the potential influence of this familiarization procedure on the baroreflex-related responses during the following experimental bouts was minor according to a previous report of repeated baroreflex sensitivity measurements during tilt tests (Reynolds *et al.* 2016). No further familiarization of LBNP was performed before the trial as they had already experienced the same level of LBNP (−40 mmHg) as in present study in class several weeks before. As illustrated in Fig. 1, a design of HUT–HDT–HUT was used to simulate PPM. The angle of HUT was set as 90° (1 G). Two different angles of HDT (−30°, −0.50 G and −60°, −0.87 G) were imposed to test the impact of varying levels of 'push' effect. Another two bouts with LBNP were performed just after their corresponding control bouts. Thus, each bout consisted of 5 min HUT with or without additional 60 s LBNP, followed by 15 s HDT with or without LBNP in the meantime, then another 60 s HUT.

Data acquisition and processing

Heart rate (HR) was measured by a three-lead ECG (Dual Bio/Stim, ML408, ADInstruments, Bella

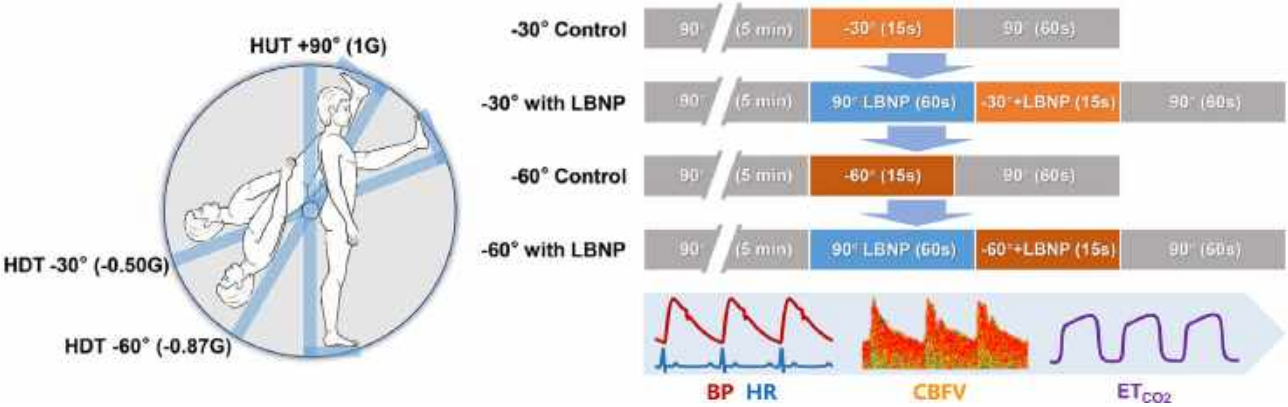

Figure 1. Schema of the study design
A total of four bouts of HUT–HDT–HUT with or without LBNP were performed. Each control bout was followed by a corresponding LBNP bout with −40 mmHg LBNP for 60 s imposed in addition to the baseline 5 min HUT and during HDT. The durations and tilt angles of each phase were as shown for the four bouts. Two different angles of HDT (−30° and −60°) were imposed to simulate varying levels of −Gz stress. Beat-to-beat cerebral and systemic haemodynamics were continuously monitored and measured. BP, blood pressure; CBFV, cerebral blood flow velocity; ET_{CO_2}, end-tidal CO_2; HDT, head down tilt; HR, heart rate; HUT, head up tilt; LBNP, lower body negative pressure.

Vista, NSW, Australia). Beat-to-beat arterial blood pressure was measured non-invasively using finger-cuff plethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands), and height-corrected to the heart. An estimate of cardiac output (CO) was obtained from the finger arterial pulse wave with the Modelflow algorithm that incorporates age, sex, height and weight as the factors to estimate stroke volume (SV) (Langewouters *et al.* 1984). Total peripheral resistance index (TPRi) was calculated beat-by-beat as the ratio between MAP and CO. All signals were outputted at 1000 Hz from PowerLab (ADInstruments) and recorded onto a computer running LabChart 7 for future analysis.

The cerebral blood flow velocity (CBFV) was continuously measured in the middle cerebral artery (MCA) using a transcranial Doppler (EMS-9 PB, Delica, Shenzhen, China). A 2 MHz Doppler probe was placed over the temporal window using headgear (Delica) and fixed at a constant angle and depth where the optimal CBFV signal was obtained as previously described (Xing *et al.* 2017). Blood pressure at the level of the MCA was estimated by subtracting the hydrostatic column between the level of the heart and the insonation point of the transcranial Doppler probe. The cerebrovascular resistance index (CVRi) was calculated as MAP at the level of the MCA (MAP_{MCA}) divided by mean CBFV ($CBFV_m$). Systolic CBFV ($CBFV_s$) and diastolic CBFV ($CBFV_d$) were used to calculate pulsatility index (PI), as ($CBFV_s$ – $CBFV_d$/$CBFV_m$) (Xing *et al.* 2019).

Breath-to-breath CO_2 was sampled through a nasal cannula and analysed by an infrared-based carbon dioxide measurement module (CO2100C, Biopac Systems, Goleta, CA, USA). Before the trial, participants were instructed to breathe only through their noses with the nasal cannula. It was emphasized that participants should keep their mouth closed throughout the protocol and not switch types of breathing between postures. During the protocol, an experimental assistant was also appointed to monitor the breathing of participants. End-tidal CO_2 (ET_{CO_2}) values were converted to mmHg based on atmospheric temperature and pressure.

For control bouts, baseline HUT data were obtained from the fifth minute measurements of the beginning 5 min HUT. The 15 s of HDT data were divided into three segments every 5 s. The first 20 s of the second HUT data was divided into four segments every 5 s, and later 40 s was divided to two segments every 20 s. For LBNP bouts, the additional 60 s data LBNP in HUT was divided to three segments every 20 s. Those specific blocks of time were chosen based on our previous study on the PPM (Yang *et al.* 2015) and observation of the original data recordings, to better reflect the rapid haemodynamic changes during the protocol as well as to facilitate data analyses.

Statistical analysis

An *a priori* sample size calculation determined that a minimum of 10 participants would provide sufficient power ($\beta = 0.80$) to detect a difference of 10 ± 10% for change in $CBFV_m$ and MAP_{MCA} during tilt tests or LBNP (Sheriff *et al.* 2007; Yang *et al.* 2015; Bronzwaer *et al.* 2017), with a two-sided α of 0.05. One-way repeated measures ANOVA was used for single time point comparisons of the cerebral and systemic haemodynamics among the four bouts. When a significant effect was observed, a *post hoc* paired Student's *t* test with a Sidak correction was performed in the following comparisons: control *vs.* LBNP during −30° bouts; control *vs.* LBNP during −60° bouts; −30° *vs.* −60° during control bouts; −30° *vs.* −60° during LBNP bouts. Statistical power analyses of *post hoc* comparisons were performed using G∗power 3.1 (program written by Franz Faul, Universität Kiel, Germany). To identify the protective effect of LBNP, data of the last 5 s of HDT and first 5 s of the following HUT from control and corresponding LBNP bouts were analysed by *a priori* two-way repeated measures ANOVA with LBNP and PPM as main factors. Also, *a priori* two-way repeated measures ANOVA with HDT angles and PPM as main factors for control bouts or LBNP bouts were also performed. All data are reported as means ± SD. Data were analysed with SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined by a two-tailed test with $P < 0.05$.

Results

The study design is illustrated in Fig. 1. The cerebral and systemic haemodynamic trajectories of simulated PPM for control and LBNP bouts with different HDT angles are depicted in Figs 2 and 3. The average statistical power for *post hoc* analysis of the paired comparisons with significant differences at each single time point was 0.936 (0.784∼1.000). Detailed phase-to-phase comparisons between control and LBNP bouts were as follows.

Impact of LBNP in the upright posture

There were no differences in baseline HUT haemodynamic variables among all bouts. No significant differences were found between the two LBNP bouts during HUT+LBNP. Data for the baseline HUT+LBNP phase from the −30° HDT LBNP bouts are reported in Table 1. $CBFV_m$ decreased with LBNP. Blood pressures were maintained during LBNP, except that the systolic blood pressure (SBP) fell by 4.1% after 40 s. Thus, CVRi was elevated. No significant changes of PI were found during HUT and HUT+LBNP. ET_{CO_2} was decreased in response to LBNP. HR was elevated and SV was reduced, while no significant

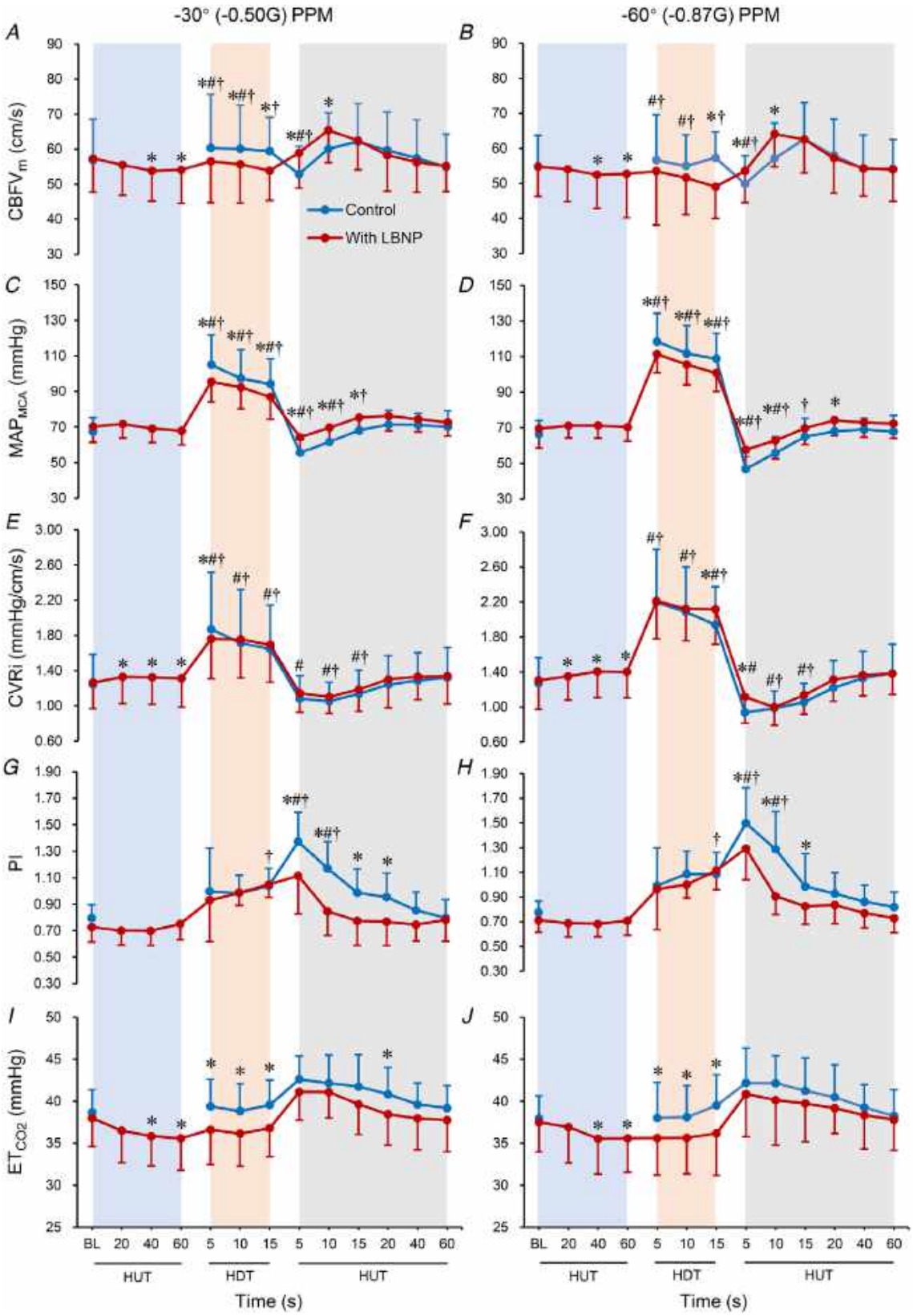

Figure 2. Cerebral haemodynamic changes during control and LBNP bouts
The blue lines represent control bouts and the red lines represent the corresponding LBNP bouts. One-way repeated measures ANOVA was used for single time point comparisons of the cerebral and systemic haemodynamics among

change of CO was observed with LBNP. TPRi increased significantly during LBNP.

Impact of LBNP in −Gz stress

As shown in Fig. 2, $CBFV_m$ and MAP_{MCA} were significantly lower in the LBNP bout than in control bouts during −30° HDT. No significant differences of CVRi or PI were observed between the two bouts (Fig. 2). The ET_{CO_2} was reduced with LBNP. Similar differences of these cerebral haemodynamics between the LBNP and control bouts during −60° HDT were also observed, except that the difference of $CBFV_m$ did not reach the significance level until 11–15 s. Also, the LBNP bouts showed higher CVRi than the control during 11–15 s.

As shown in Fig. 3, HR was higher and SV was lower in the LBNP bout than its control during −30° HDT, while TPRi and CO were not significantly different. During −60° HDT, HR and SV were similar between the LBNP and its control bout, except that SV was higher in the control bout at the first 5 s. Thus, the CO of the control bout was also higher than that of the LBNP bout at 5 s. No significant difference was found for TPRi. These results suggested that LBNP counteracted the blood shift caused by HDT (Hinghofer-Szalkay *et al.* 2004; Petersen *et al.* 2019) and dampened the increase of SV and MAP at the brain and heart levels. Also, the counteractive effect of LBNP against −Gz on HR and SV vanished after 5 s with the increase of −Gz (−0.50 to −0.87 G).

In the comparison between different HDT angles, $CBFV_m$ was decreased, MAP_{MCA} was increased and CVRi was thus increased in −60° HDT compared with −30° HDT during both LBNP and control bouts. ET_{CO_2} was similar between these two angles during both control and LBNP bouts ($P = 0.060$, 0.307, 0.938 for control bouts, and 0.174, 0.549, 0.994 for LBNP bouts, corresponding paired comparisons at 5, 10 and 15 s, respectively). For control bouts, HR was similar between −30° and −60° HDT, whereas HR was significantly higher in −30° than in −60° HDT with LBNP. SV was higher in the middle segment of −30° HDT than −60° HDT during control bouts, but lower in the first segment of −30° HDT than −60° HDT during LBNP bouts. TPRi was increased and CO was decreased at 6–15 s of −60° HDT compared with −30° HDT.

Impact of prior LBNP in the rapid −Gz to +Gz transitions

As the loss of consciousness in pilots during a PPM generally happens just after the rapid transition from −Gz to +Gz, the rapid HDT to HUT transition was the key period of the present simulated PPM. During the dramatic MAP_{MAC} and CBFV reduction, cerebral and systemic haemodynamic variables were compared at the end of HDT and beginning of HUT. Interactions between LBNP and PPM at different HDT angles were analysed (Table 2). The $CBFV_m$ decreased significantly during this transition in control bouts, while it increased in LBNP bouts ($\Delta CBFV_m$, control bouts *vs.* LBNP bouts, -6.6 ± 4.6 *vs.* 5.1 ± 6.8 cm s^{-1} for −30° HDT–HUT, and -7.4 ± 4.8 *vs.* 3.4 ± 4.6 cm s^{-1} for −60° HDT–HUT, all $P < 0.05$, Figs 2 and 4). The MAP_{MCA} dropped significantly in all bouts, among which LBNP bouts showed much smaller reduction of MAP_{MCA} than control bouts (ΔMAP_{MCA}, control bouts *vs.* LBNP bouts, -38 ± 12 *vs.* -23 ± 10 mmHg for −30° HDT–HUT, and -62 ± 16 *vs.* -43 ± 11 mmHg for −60° HDT–HUT, all $P < 0.001$). PI demonstrated a smaller increase in LBNP bouts than in control bouts. Significant reduction of CVRi and elevation of ET_{CO_2} were also observed, while no significant effects of LBNP × PPM interaction were found.

HR increased in response to a HDT–HUT transition in all bouts, among which the −30° HDT LBNP bout showed a smaller increase of HR than the control bout (ΔHR, control bouts *vs.* LBNP bouts, 17 ± 9 *vs.* 12 ± 7 bpm, $P = 0.046$). The MAP fell during both control bouts and rose during the −30° HDT LBNP bout, but it remained unchanged during the −60° HDT LBNP bout. TPRi reduced significantly in control bouts and the −60° HDT LBNP bout, whereas it remained relatively stable in the −30° HDT LBNP bout. SV was raised significantly in all bouts. CO increases were smaller in LBNP bouts than in control bouts.

The angle of HDT did not cause significant differences of $CBFV_m$ reduction in control bouts or increase in LBNP bouts. However, greater MAP_{MCA} reduction was observed in −60° HDT–HUT in contrast with −30° HDT–HUT for both control bouts and LBNP bouts. The reduction of CVRi and increase of PI were significantly larger during −60° HDT–HUT. The increases of ET_{CO_2} during the transition were similar between −60° HDT–HUT and

the four bouts. When significant effect was observed, the *post hoc* paired *t* test with a Sidak correction was performed in the following comparisons: control *vs.* LBNP during −30° bouts, control *vs.* LBNP during −60° bouts, −30° *vs.* −60° during control bouts, −30° *vs.* −60° during LBNP bouts. All data are presented as means ± SD ($n = 23$). $P < 0.05$, *Control *vs.* corresponding LBNP bout (the LBNP data during the first HUT stage were compared with baseline HUT), #−30° HDT control bout *vs.* −60° HDT control bout, †−30° HDT LBNP bout *vs.* −60° HDT LBNP bout. BL, baseline; $CBFV_m$, mean cerebral blood flow velocity; CVRi, cerebrovascular resistance index; ET_{CO_2}, end-tidal CO_2; HDT, head down tilt; HUT, head up tilt; LBNP, lower body negative pressure; MAP_{MCA}, mean arterial pressure at the level of middle cerebral artery; PI, pulsatility index.

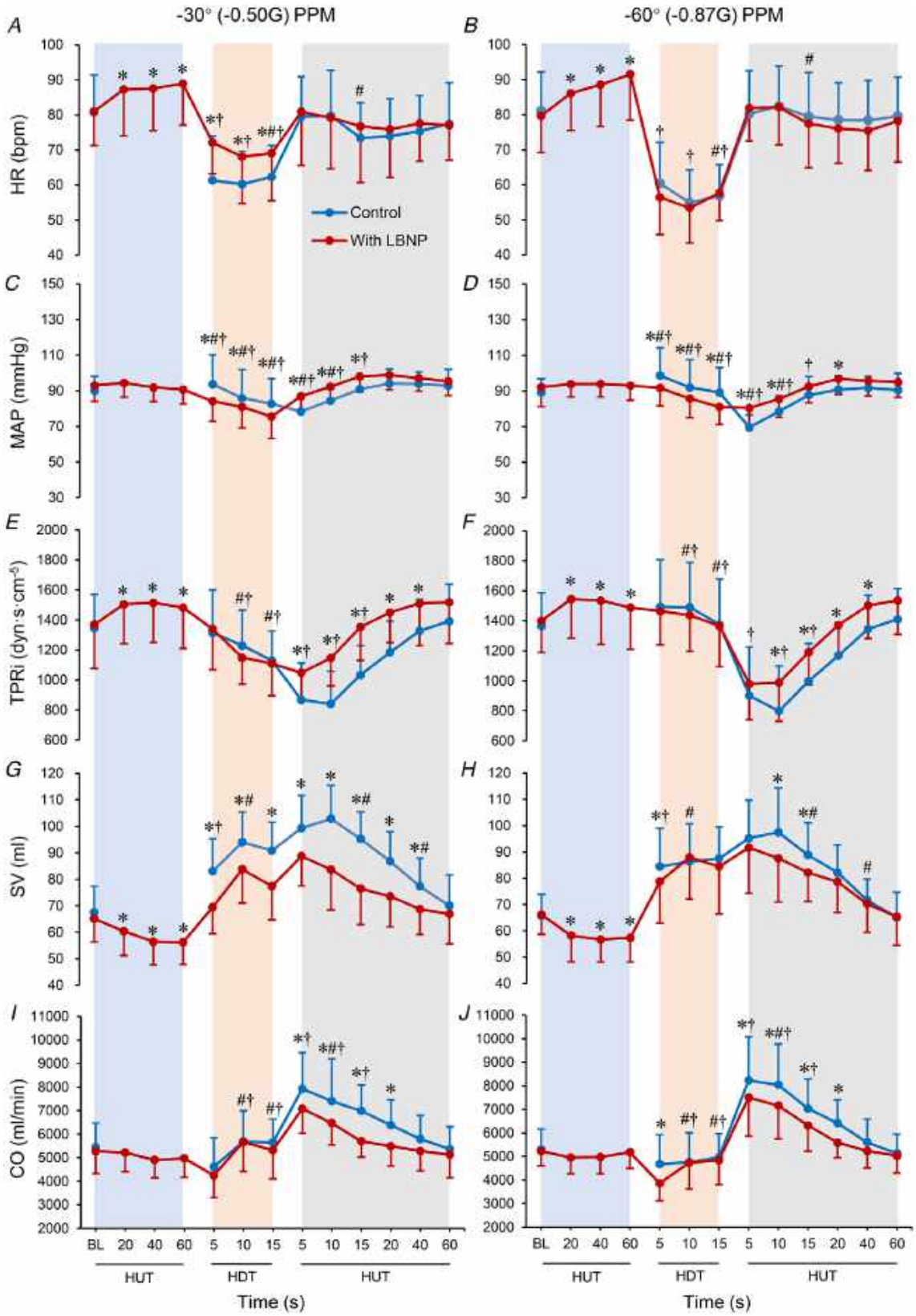

Figure 3. Systemic haemodynamic changes during control and LBNP bouts
The blue lines represent control bouts and the red lines represent the corresponding LBNP bouts. One-way repeated measures ANOVA was used for single time point comparisons of the cerebral and systemic haemodynamics among

Table 1. Impact of LBNP in the upright posture

	Baseline upright	Upright+LBNP		
	60 s	20 s	40 s	60 s
$CBFV_m$ (cm s^{-1})	57.3 ± 9.6	55.5 ± 8.7	53.8 ± 8.6*	54.1 ± 9.5*
$CBFV_s$ (cm s^{-1})	85.0 ± 13.4	81.4 ± 12.5*	78.8 ± 12.2*	80.6 ± 12.0*
$CBFV_d$ (cm s^{-1})	43.5 ± 8.3	42.6 ± 7.3	41.3 ± 7.3*	40.8 ± 8.5*
PI	0.73 ± 0.11	0.70 ± 0.11	0.70 ± 0.11	0.74 ± 0.12
MAP_{MCA} (mmHg)	70 ± 9	72 ± 8	69 ± 8	68 ± 8
SBP_{MCA} (mmHg)	98 ± 10	99 ± 9	95 ± 10	94 ± 9*
DBP_{MCA} (mmHg)	56 ± 9	58 ± 8	56 ± 7	55 ± 8
CVRi (mmHg cm^{-1} s^{-1})	1.26 ± 0.30	1.33 ± 0.30*	1.32 ± 0.30*	1.31 ± 0.32*
ET_{CO_2} (mmHg)	38.0 ± 3.4	36.5 ± 3.8	35.8 ± 3.5*	35.6 ± 3.8*
HR (bpm)	81 ± 10	87 ± 13*	88 ± 12*	89 ± 12*
MAP (mmHg)	93 ± 9	94 ± 8	92 ± 8	91 ± 8
SBP (mmHg)	121 ± 10	122 ± 10	118 ± 10	116 ± 9*
DBP (mmHg)	79 ± 9	81 ± 8	79 ± 7	78 ± 8
TPRi (dyn s cm^{-5})	1370 ± 293	1505 ± 262*	1515 ± 264*	1483 ± 273*
SV (ml)	65 ± 9	60 ± 9*	56 ± 9*	56 ± 8*
CO (ml min^{-1})	5272 ± 937	5214 ± 805	4903 ± 763	4973 ± 803

One-way repeated measures ANOVA was used for the comparisons of the cerebral and systemic haemodynamics among different time points. When significant effect was observed, a *post hoc* paired *t* test with a Sidak correction was performed between data at baseline and following LBNP time points. All data are presented as means ± SD ($n = 23$). *$P < 0.05$ *vs.* baseline. $CBFV_d$, diastolic cerebral blood flow velocity; $CBFV_m$, mean cerebral blood flow velocity; $CBFV_s$, systolic cerebral blood flow velocity; CO, cardiac output; CVRi, cerebrovascular resistance index; DBP, diastolic blood pressure; DBP_{MCA}, diastolic blood pressure at the level of middle cerebral artery; ET_{CO_2}, end-tidal CO_2; HR, heart rate; LBNP, lower body negative pressure; MAP, mean arterial pressure; MAP_{MCA}, mean arterial pressure at the level of middle cerebral artery; PI, Pulsatility index; SBP, systolic blood pressure; SBP_{MCA}, systolic blood pressure at the level of middle cerebral artery; SV, stroke volume; TPRi, total peripheral resistance index.

corresponding −30° HDT–HUT bouts. The HR response was significantly greater in −60° HDT–HUT. Significant interactions of angle × PPM for MAP were found between both the control bouts and the LBNP bouts (ΔMAP, −30° *vs.* −60° HDT–HUT, −5 ± 12 *vs.* −20 ± 15 mmHg for control bouts, $P = 0.001$, and 11 ± 10 *vs.* −1 ± 11 mmHg for LBNP bouts, $P < 0.001$). The TPRi response was significantly greater in −60° HDT–HUT in either control or LBNP bouts. Similar increases of SV were observed between −30° and −60° HDT–HUT. CO increases were significantly larger in −60° HDT–HUT than in −30° HDT–HUT.

Impact of prior LBNP in the recovery after simulated PPM

In order to explore the effect of prior LBNP at −Gz on the following recovery time course at +Gz, haemodynamic data were compared at each time segment. During HUT following −30° HDT, $CBFV_m$ was higher in a LBNP bout within the first 10 s, and then returned to the same level at 15 s as the control bout. MAP_{MCA} was also higher with prior LBNP. The CVRi response to HUT of both LBNP and control bouts showed similar time courses, while PI remained lower in a LBNP bout than in its control bout during the first 20 s. Although ET_{CO_2} seemed higher in the LBNP bout, the differences were not significant except for the period of 16–20 s. Similar differences of these cerebral haemodynamics between LBNP and control bouts during HUT after −60° HDT were also observed, except that a LBNP bout showed higher CVRi than control at the first 5 s (Fig. 2).

As to the systemic haemodynamics, HR was not significantly different between LBNP and control bouts during HUT after prior −30° HDT. SV remained higher and TPRi was lower in the control bouts than in LBNP

the four bouts. When significant effect was observed, a *post hoc* paired *t* test with a Sidak correction was performed in the following comparisons: control *vs.* LBNP during −30° bouts, control *vs.* LBNP during −60° bouts, −30° *vs.* −60° during control bouts, −30° *vs.* −60° during LBNP bouts. All data are presented as means ± SD ($n = 23$). $P < 0.05$, *Control *vs.* corresponding LBNP bout (the LBNP data during first HUT stage were compared with baseline HUT), #−30° HDT control bout *vs.* −60° HDT control bout, †−30° HDT LBNP bout *vs.* −60° HDT LBNP bout. BL, baseline; CO, cardiac output: HDT, head down tilt; HR, heart rate; HUT, head up tilt; LBNP, lower body negative pressure; MAP, mean arterial pressure; SV, stroke volume; TPRi, total peripheral resistance index.

Table 2. Cerebral and systemic haemodynamics during the rapid −Gz to +Gz transitions

		−30° (−0.50 G) PPM		−60° (−0.87 G) PPM		*P* for interactions			
		HDT end	HUT begin	HDT end	HUT begin	LBNP × PPM (−0.50 G)	LBNP × PPM (−0.87 G)	Angle × PPM (Control)	Angle × PPM (LBNP)
$CBFV_m$ (cm s^{-1})	Control	59.5 ± 9.6	52.9 ± 8.0†	57.3 ± 7.5	49.9 ± 8.1$^{\dagger,\#}$	<0.001	<0.001	0.497	0.086
	LBNP	53.9 ± 8.5*	58.9 ± 10.1*,†	50.3 ± 9.0$^{*,\#}$	53.6 ± 9.0$^{*,\dagger,\#}$				
MAP_{MCA} (mmHg)	Control	94 ± 14	56 ± 7†	109 ± 14$^{\#}$	47 ± 7$^{\dagger,\#}$	<0.001	<0.001	<0.001	<0.001
	LBNP	87 ± 12*	64 ± 8*,†	101 ± 10$^{*,\#}$	58 ± 10$^{*,\dagger,\#}$				
CVRi (mmHg cm^{-1} s^{-1})	Control	1.64 ± 0.50	1.08 ± 0.26†	1.94 ± 0.44$^{\#}$	0.94 ± 0.17$^{\dagger,\#}$	0.392	0.831	<0.001	<0.001
	LBNP	1.69 ± 0.42	1.14 ± 0.22*,†	2.12 ± 0.40$^{*,\#}$	1.12 ± 0.30*,†				
PI	Control	1.04 ± 0.13	1.37 ± 0.22†	1.09 ± 0.17	1.50 ± 0.29$^{\dagger,\#}$	<0.001	0.010	0.220	0.085
	LBNP	1.05 ± 0.10	1.11 ± 0.29*	1.11 ± 0.15$^{\#}$	1.29 ± 0.25$^{*,\dagger,\#}$				
ET_{CO_2} (mmHg)	Control	39.6 ± 2.9	42.6 ± 2.8†	39.5 ± 3.6	42.2 ± 4.1†	0.365	0.067	0.882	0.739
	LBNP	36.8 ± 3.4*	41.1 ± 3.4†	36.2 ± 5.0*	40.9 ± 6.1†				
HR (bpm)	Control	62 ± 9	80 ± 11†	57 ± 9$^{\#}$	80 ± 12†	0.046	0.852	0.015	0.001
	LBNP	69 ± 13*	81 ± 15†	58 ± 8$^{\#}$	82 ± 9†				
MAP (mmHg)	Control	83 ± 14	78 ± 7	89 ± 14$^{\#}$	70 ± 7$^{\dagger,\#}$	<0.001	<0.001	<0.001	0.001
	LBNP	76 ± 12*	87 ± 8*,†	81 ± 10$^{*,\#}$	80 ± 10$^{*,\#}$				
TPRi (dyn s cm^{-5})	Control	1131 ± 196	869 ± 245†	1375 ± 303$^{\#}$	901 ± 295†	<0.001	0.044	0.017	<0.001
	LBNP	1111 ± 214	1049 ± 174*	1364 ± 269$^{\#}$	941 ± 240$^{\dagger,\#}$				
SV (ml)	Control	91 ± 11	99 ± 12†	87 ± 12	95 ± 15†	0.620	0.889	0.810	0.818
	LBNP	77 ± 13*	89 ± 11*,†	84 ± 18	92 ± 17†				
CO (ml min^{-1})	Control	5645 ± 991	7923 ± 1346†	4963 ± 1003$^{\#}$	8231 ± 1454†	0.059	0.878	0.047	<0.001
	LBNP	5315 ± 1204	7078 ± 1037*,†	4837 ± 1031$^{\#}$	7503 ± 1442$^{\dagger,\#}$				

Data of the last 5 s of HDT and first 5 s of the following HUT from control and corresponding LBNP bouts were analysed by *a priori* two-way repeated measures ANOVA with LBNP and PPM as main factors. *A priori* two-way repeated measures ANOVA with HDT angles and PPM as main factors for control bouts or LBNP bouts were also performed. All data are presented as means ± SD ($n = 23$). $P < 0.05$, **vs*. Control; †*vs*. HDT end; #*vs*. −30° (−0.50 G). $CBFV_m$, mean cerebral blood flow velocity; CO, cardiac output; CVRi, cerebrovascular resistance index; ET_{CO_2}, end-tidal CO_2; HDT end, the last 5 s of head down tilt; HR, heart rate; HUT begin, the first 5 s of head up tilt; LBNP, lower body negative pressure; MAP, mean arterial pressure; MAP_{MCA}, mean arterial pressure at the level of middle cerebral artery; PI, Pulsatility index; PPM, 'push–pull' manoeuvre; SV, stroke volume; TPRi, total peripheral resistance index.

bouts within 40 s. CO remained lower in LBNP bouts within the first 20 s. Similar differences of these systemic haemodynamics between LBNP and control bouts during HUT after −60° HDT were also observed, except that significant differences of SV were only detected at 6–15 s, and that no significant difference of TPRi was found at the first 5 s (Fig. 3).

For comparison between different prior HDT angles, LBNP bouts and control bouts showed similar time courses of cerebral haemodynamic differences. $CBFV_m$ was decreased at the first 5 s, MAP_{MCA} was decreased within the first 10 s (or 15 s), and CVRi was also decreased during 1–15 s (or 6–15 s) in HUT after prior −60° HDT compared with −30° HDT during control bouts (or LBNP bouts). The ET_{CO_2} was similar between these two angles in both control and LBNP bouts (all $P > 0.1$ for corresponding paired comparisons at 5–60 s between angles). The HR response to HUT was quite similar after −30° and −60° HDT for both LBNP bouts and control bouts, except that HR was significantly higher after −60° HDT than after −30° HDT at 15 s during control bouts. SV was higher at 15 and 40 s of HUT after 30° HDT than after −60° HDT during control bouts, while no significant differences were found between the two LBNP bouts. TPRi was higher and CO was lower at the first 15 s of HUT after −30° HDT than after −60° HDT during LBNP bouts.

All the cerebral and systemic haemodynamic variables recovered to the baseline upright level within 60 s.

Discussion

The aim of this study was to explore an effective and specific LBNP-based counteractive strategy to protect cerebral perfusion during PPM. Here we found that LBNP applied prior to and during –Gz followed by release at the subsequent transition to +Gz exerted biphasic counteractive effects against the gravitational responses to simulated PPM. The LBNP strategy we developed could effectively reverse the reduction of cerebral blood flow and

blunt the drop of arterial blood pressure, which was mainly attributable to the protection of diastolic cerebral blood flow and pressure during simulated PPM. These findings also highlight the integrated response between systemic and cerebral haemodynamic changes during PPM.

The great fall of MAP_{MCA} and cerebral blood flow at the transition from 'pull' (−Gz) to 'push' (+Gz) was the direct reason for loss of vision or consciousness during PPM (Scott *et al.* 2007). LBNP applied prior to –Gz increased $CBFV_m$ and diminished the drop of MAP_{MCA} compared with control bouts. This is mainly because the blood that accumulated in the legs by prior LBNP impeded the tendency of blood to shift to the lower body. In control bouts, the reduced filling in leg veins caused by HDT would be expected to persist early on during the subsequent HUT (owing to the venous valves) (Sheriff *et al.* 2007). Therefore, the pressure gradient between the upper body and legs during the early HUT was enlarged, resulting in the greater increase of leg blood flow and fall in MAP_{MCA} (Sheriff *et al.* 2007). Our design of applying LBNP at HDT and releasing it at HUT just counteracted this change of blood flow in the leg at both phases. With the application of LBNP, the heart–leg pressure gradient lessened, which in turn facilitated the increased SV distributing to the brain. The increased cerebral blood flow caused by prior LBNP in comparison with control lasted for 10 s and then went back to a similar level, which might be mainly attributed to the elevated MAP_{MCA}, since no significant difference of ET_{CO_2} was found and SV and CO began to reduce just after the first 5 s. After that, the cerebral blood flow in both control and LBNP bouts shared a similar recovery time course.

LBNP bouts showed improved blood pressure control during the rapid gravitational transitions, as indicated by the increased or preserved MAP in LBNP bouts compared with control bouts. A previous report regarding PPM suggested that the activation of cardiopulmonary and/or arterial baroreceptors by −Gz stress during the 'push' stage initiated peripheral vasodilatation, which could delay the appropriate vasoconstrictor response at the following 'pull' stage (Goodman & LeSage, 2002). The application of LBNP during HDT unloaded the pressure and volume stimulations to baroreceptors, thereby improving the peripheral vascular response, which enabled a better blood pressure control (Ogoh *et al.* 2002). On the other hand, the release of LBNP at the transition may also directly impede the blood shift towards legs caused by HUT, thus maintaining the blood pressure at a higher level. Similarly, the increased leg vascular resistance by LBNP release could alter total peripheral resistance (as shown by TPRi) since this region constituted a sizable fraction (20%) of the total peripheral resistance (Sheriff *et al.* 2007). Our observation of an earlier recovery of TPRi in LBNP bouts than control bouts after transition was

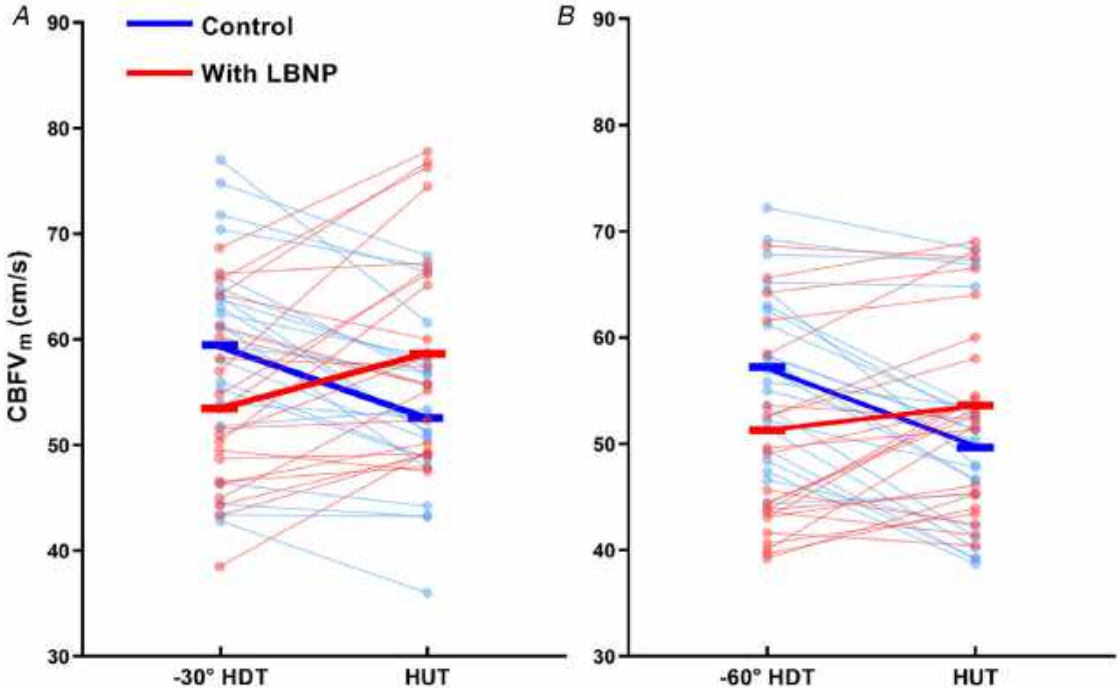

Figure 4. Individual values of MCA blood velocity during the rapid HDT to HUT transition
The blue circles and lines represent control bouts and the red circles and lines represent the corresponding LBNP bouts. Data were from the last 5 s of HDT and first 5 s of the following HUT ($n = 23$). The continuous line in each column represents the mean value. $CBFV_m$, mean cerebral blood flow velocity; HDT, head down tilt; HUT, head up tilt; LBNP, lower body negative pressure; MCA, middle cerebral artery.

in line with the more rapid central control of baroreflex mentioned above. Furthermore, the vascular myogenic response *per se* might also account for the different TPRi response between LBNP and control bouts. The myogenic relaxation of leg vasculature induced by cephalad blood shift of the lower body during HDT is a potential contributor to the increase in leg vascular conductance (or decrease in leg vascular resistance) during a following HUT due to the venoarteriolar response in control bouts (Henriksen *et al.* 1983; Jepsen & Gaehtgens, 1995), which might be attenuated by LBNP during HDT. The lower SV in LBNP bouts than in control bouts during HDT was attributable to the reduction of central circulation caused by LBNP (Goswami *et al.* 2019). The control and LBNP bouts showed similar initial SV responses to the rapid −Gz to +Gz transition. Two underlying mechanisms might account for this initial SV increase: the discharged blood volume from the apical regions of lungs to the heart, and/or the increased left ventricular filling due to the fall in right atrial pressure via ventricular interdependence (Sheriff *et al.* 2007, 2010; Xing *et al.* 2013). SV continued to rise from 5 to 10 s in control bouts, while it declined just after 5 s in LBNP bouts following the rapid −Gz to +Gz transition. Therefore, it is likely that LBNP decreased the restoration of blood volume in the lungs caused by HDT.

Another interesting finding was the different PI responses to rapid −Gz to +Gz transition between control bouts and LBNP bouts. The significantly higher increase of pulsatility in control bouts was owing to the obvious reduction of diastolic flow (Fig. 5), which was also observed in clinical syncope (Jorgensen *et al.* 1993; Van Lieshout *et al.* 2003). The decrease of diastolic flow in control bouts might relate to the markedly larger drop of DBP_{MCA} than SBP_{MCA} ($\%\Delta DBP_{MCA}$ *vs.* $\%\Delta SBP_{MCA}$, 51% *vs.* 28% for −30° HDT–HUT, 69% *vs.* 39% for −60° HDT–HUT, Table 3). In contrast, the diastolic flow and pressure were well protected by the LBNP counteractive strategy as shown in Fig. 5 and Table 3. The 10–15 s adjustment of $CBFV_m$ and MAP after the rapid HDT–HUT transition is consistent with the responses from the sit–stand model of dynamic autoregulatory stimuli (Claassen *et al.* 2009). During the following 15–20 s, PI remained lower in LBNP bouts than in control bouts due to an improvement of $CBFV_d$ and a small reduction in $CBFV_s$, suggesting an increase in brain vasculature compliance. A transition from dynamic autoregulation during immediate posture changes to overall cephalad blood shift following LBNP release might cause cerebral vascular dilatation, contributing to the improvement in cerebrovascular compliance.

Although the LBNP strategy developed in this study showed protective effects on the cerebral perfusion during simulated PPM as increased $CBFV_m$ and a smaller drop of MAP_{MCA} with both prior −Gz stresses (−0.50 and −0.87 Gz), it seems that the efficacy of the current LBNP of −40 mmHg attenuated with the increase of −Gz stress at 'push' phase. During HDT, the counteractive effect of LBNP against −Gz on HR and SV vanished after 5 s with

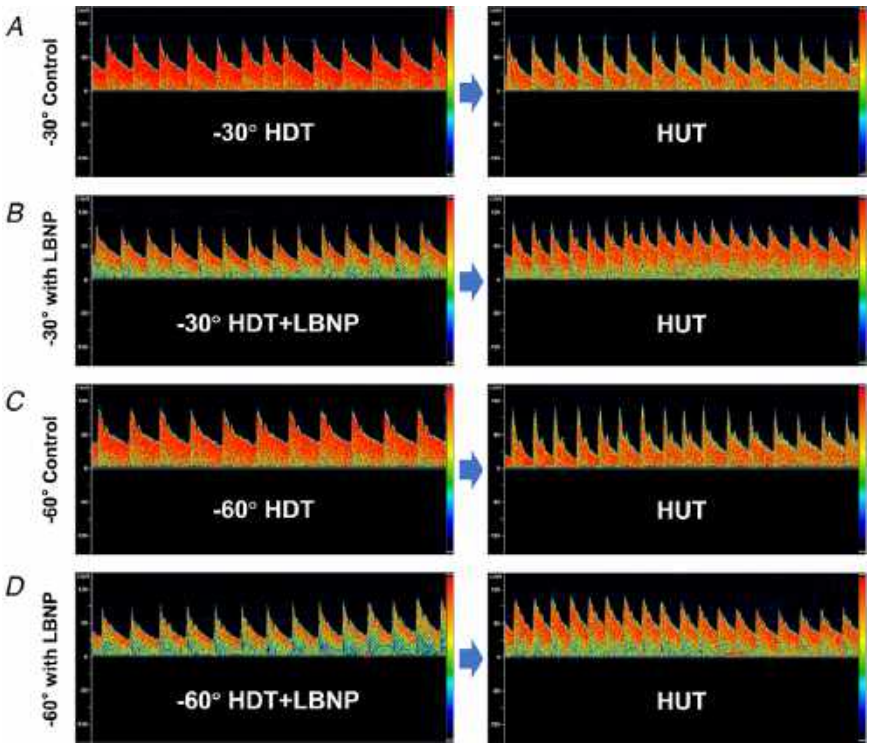

Figure 5. Representative transcranial Doppler records of cerebral blood flow during the rapid HDT to HUT transition
The duration of each record is 15 s. HDT, head down tilt; HUT, head up tilt; LBNP, lower body negative pressure.

Table 3. Systolic and diastolic haemodynamics during the rapid −Gz to +Gz transitions

		−30° (−0.50 G) PPM		−60° (−0.87 G) PPM		*P* for interactions			
		HDT end	HUT begin	HDT end	HUT begin	LBNP × PPM (−0.50G)	LBNP × PPM (−0.87G)	Angle × PPM (Control)	Angle × PPM (LBNP)
$CBFV_s$ (cm s^{-1})	Control	100.9 ± 16.7	100.9 ± 13.2	99.2 ± 15.6	99.5 ± 13.7	<0.001	<0.001	0.906	0.528
	LBNP	91.9 ± 14.9*	101.6 ± 12.7†	85.5 ± 14.4$^{*,\#}$	98.6 ± 14.7†				
$CBFV_d$ (cm s^{-1})	Control	38.8 ± 7.0	29.0 ± 7.2†	36.4 ± 5.3$^{\#}$	25.1 ± 8.1$^{\dagger,\#}$	<0.001	<0.001	0.333	0.127
	LBNP	34.8 ± 5.6*	37.5 ± 8.2*,†	30.9 ± 7.1$^{*,\#}$	31.0 ± 7.9$^{*,\#}$				
SBP_{MCA} (mmHg)	Control	125 ± 12	90 ± 7†	137 ± 11$^{\#}$	83 ± 9$^{\dagger,\#}$	<0.001	0.001	<0.001	<0.001
	LBNP	113 ± 12*	96 ± 10*,†	128 ± 14$^{*,\#}$	91 ± 12$^{*,\dagger,\#}$				
DBP_{MCA} (mmHg)	Control	78 ± 17	38 ± 8†	95 ± 17$^{\#}$	29 ± 7$^{\dagger,\#}$	<0.001	<0.001	<0.001	<0.001
	LBNP	74 ± 14*	49 ± 8*,†	87 ± 10$^{*,\#}$	41 ± 10$^{*,\dagger,\#}$				
SBP (mmHg)	Control	114 ± 12	114 ± 9	118 ± 11	105 ± 9$^{\dagger,\#}$	<0.001	0.001	<0.001	0.003
	LBNP	101 ± 12*	118 ± 11*,†	108 ± 13$^{*,\#}$	114 ± 12$^{*,\dagger,\#}$				
DBP (mmHg)	Control	68 ± 16	60 ± 8†	75 ± 17$^{\#}$	52 ± 8$^{\dagger,\#}$	<0.001	<0.001	<0.001	0.001
	LBNP	63 ± 13*	71 ± 8*,†	68 ± 9$^{*,\#}$	64 ± 10$^{*,\#}$				

Data of the last 5 s of HDT and first 5 s of the following HUT from control and corresponding LBNP bouts were analysed by *a priori* two-way repeated measures ANOVA with LBNP and PPM as main factors. *A priori* two-way repeated measures ANOVA with HDT angles and PPM as main factors for control bouts or LBNP bouts were also performed. All data are presented as means ± SD ($n = 23$). $P < 0.05$, **vs.* Control; †*vs.* HDT end; #*vs.* −30° (−0.50 G). $CBFV_d$, diastolic cerebral blood flow velocity; $CBFV_s$, systolic cerebral blood flow velocity; DBP, diastolic blood pressure; DBP_{MCA}, diastolic blood pressure at the level of middle cerebral artery; HDT end, the last 5 s of head down tilt; HUT begin, the first 5 s of head up tilt; LBNP, lower body negative pressure; PPM, 'push–pull' manoeuvre; SBP, systolic blood pressure; SBP_{MCA}, systolic blood pressure at the level of middle cerebral artery.

the increase of −Gz. The improvement of MAP and TPRi responses to the gravitational change by LBNP was smaller in the −0.87 Gz bout than in the −0.50 Gz bout. At the following HDT–HUT transition, no differences of HR changes were found between control and LBNP bouts with prior −0.87 Gz stress. Furthermore, during the recovery phase, the counteractive effects of prior LBNP were also attenuated following prior −0.87 Gz compared with −0.50 Gz, evidenced by lower initial $CBFV_m$, MAP and peripheral resistance, but higher PI. Thus, the protective effect of our LBNP strategy attenuated with the increase of −Gz stress at 'push' phase during the whole process of PPM, including the −Gz phase, rapid gravitational transition and the +Gz recovery. These findings highlighted the necessity for using different levels of LBNP to counteract the haemodynamic change during PPM with different −Gz.

Limitations

There are several limitations in the present study that should be acknowledged. First, although the measurement of MCA blood velocity by transcranial Doppler has been suggested as a valid method to estimate changes of cerebral perfusion (Willie *et al.* 2012), it was still limited in reflecting volumetric cerebral blood flow for lack of diameter measurement as opposed to the ultrasound Doppler measures from extracranial arteries (Liu *et al.* 2013). Second, the Modelflow technique has been reported to overestimate SV and underestimate total peripheral resistance during LBNP and HUT in women as compared with pulsed Doppler ultrasound measurements (Dyson *et al.* 2010), which might also apply in this study. Third, we used a uniform protocol in which all bouts were performed in the same order without randomization or counterbalancing in this study. Although the control bouts at different tilting angles showed concordant results with our previous report of a randomized design (Yang *et al.* 2015), there might be a potential ordering effect. Finally, the responses observed in a supine position during the tilt tests in the present study should have a similar pattern to those in a seated position during aircraft manoeuvres, except that the haemodynamic changes might be larger in a seated position according to the previous report regarding the cardiovascular responses to gravitational stress in seated and supine positions (Arvedsen *et al.* 2015).

Perspectives

The LBNP countermeasures, if integrated into the current anti-gravity suit with improved design of automatic gravity sensor and response system, could effectively protect brain perfusion of pilots against gravitational stress during aviation manoeuvres such as PPM. The anti-gravity suit could be designed with two layers for the lower body, with the inner layer for LBNP and the outer layer for traditional inflation. The inner LBNP layer should be cushioned with an airtight rubber surrounding at the level

of iliac crest. LBNP should be applied automatically, since a −Gz acceleration is detected by the gravity sensor on the aircraft, and released immediately at +Gz acceleration, followed by graded inflation of outer layers after +2.0 or +3.0 Gz (Scott *et al.* 2007). Furthermore, if ET_{CO_2} could be raised through the pilot ventilation system during LBNP, a greater protective effect might be expected.

Conclusion

LBNP applied prior to and during –Gz followed by release at the subsequent transition to +Gz could specifically and effectively counteract gravitational stress induced by simulated PPM. This LBNP counteractive strategy protects against the reduction of cerebral blood flow and arterial blood pressure, with a dominant diastolic protection. LBNP level should vary with −Gz stress to guarantee a better protection against PPM-induced aviation gravitational stress.

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Additional information

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Author contributions

C.X. designed and performed research, analysed data and wrote the paper. X.W. performed research, and helped with data analysis and manuscript preparation. Y.G. helped with research design and data analysis, and contributed analytic tools. J.Z., Y.L., Y.G., C.W., Y.F. and Y.L. performed research. X.Z., J.L., W.H., S.Z. and L.Y. helped with data interpretation and manuscript preparation. F.G. helped with research design, data collection and manuscript preparation. All authors have read and approved the final version of this manuscript and 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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Keywords

aviation, cerebral blood flow, gravity, lower body negative pressure, push-pull maneuver, tilt

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Statistical Summary Document