Midodrine as a Countermeasure to Orthostatic Hypotension Immediately after Space Shuttle Landing

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ABSTRACT

Midodrine prevents post-space flight orthostatic intolerance when testing is conducted in a controlled laboratory setting within 2-4 hours after Space Shuttle landing. It is unknown if midodrine is as effective during re-entry and immediately following landing. **METHODS**: Cardiovascular responses to 10 minutes of 80° head-up tilt in five male astronauts were compared before and immediately after Space Shuttle missions. Pre-flight tests were conducted in the Johnson Space Center Cardiovascular Laboratory without midodrine. Post-flight testing was performed in the Crew Transport Vehicle on the Space Shuttle runway within 60 minutes of landing; midodrine was self-administered before re-entry. Survival analysis was performed (Gehan-Breslow test) to compare presyncope rates pre- to post-flight. Cardiovascular responses (last minute standing minus supine) to tilt before and after space flight were compared using paired t-tests. **RESULTS**: Midodrine did not prevent post-flight orthostatic hypotension in two of the five astronauts, but the rate of presyncope across the group did not increase ($p=0.17$) from pre- to post-flight. Also, although the change in heart rate from supine to the last minute of standing was not affected by space flight, systolic blood pressure decreased more ($p=0.05$) and diastolic blood pressure tended to decrease ($p=0.08$) after space flight. **CONCLUSIONS**: Accurate interpretation of the current results requires that similar data be collected in control subjects (without midodrine) on the CTV. However, drug interaction concerns with commonly used anti-emetics and potentiation of prolonged QTc intervals observed in long duration astronauts make the routine use of midodrine for immediate post-flight orthostatic hypotension unlikely.

INTRODUCTION

Following space flight, the capability to remain upright (standing) may be compromised by an inability to maintain adequate arterial pressure and cerebral perfusion. This condition, termed orthostatic or postural hypotension, may result in presyncope (lightheadedness) or syncope (loss of consciousness) during re-entry or egress from the space vehicle and for several days after landing. A significant number of astronauts experience post-flight orthostatic hypotension, and its severity and incidence increases as the length of microgravity exposure is extended. Approximately 20% of short-duration and 80% of long-duration crewmembers experience presyncope during testing on landing day (15). We expect that orthostatic hypotension also will be a significant concern following exploration class space flight missions when medical assistance will be limited or even unavailable. The development of an effective countermeasure may be critical to the success of these missions, and post-flight orthostatic hypotension is listed as a high priority in the HHC Integrated Research Plan (Gap CV3).

To date, the potential countermeasures that have been tested (e.g., lower body negative pressure, fluid loading, Florinef, exercise) have not eliminated post-flight orthostatic hypotension. Midodrine is a selective alpha-1 adrenergic agonist which is used clinically to treat orthostatic hypotension. It is almost completely absorbed after oral administration and is hydrolyzed enzymatically to its active metabolite, desglymidodrine, which has a bioavailability of 93% (11; 13);(14). Midodrine acts by increasing vasoconstriction and decreases peripheral venous capacity, prevents blood pooling, and increases total peripheral resistance (14), but does not pass the blood-brain barrier and

therefore has no central stimulant effects (13). The effects of midodrine may be particularly protective of orthostatic tolerance in astronauts who become presyncopal on landing day due to inadequate release of norepinephrine (9).

Midodrine as a countermeasure to orthostatic intolerance was evaluated in two phases. In Phase I, 10 mg of midodrine was given orally to astronauts two hours after the landing of a Space Shuttle mission and one hour prior to an 80° head-up tilt test administered in NASA's data collection facility at the landing site. In five male astronauts, heart rate during upright tilt was not significantly elevated compared to preflight with midodrine administration. Other hemodynamic responses to tilt were not different than pre-flight, and no crewmember experienced hypertension after consuming this adrenergic agonist. Importantly, heart rate was significantly greater in these crewmembers following a previous mission of similar duration when they had not taken the drug (17). Additionally, orthostatic intolerance was prevented in one female crewmember during tilt after taking midodrine following a Space Shuttle mission even though she had become presyncopal during a stand test of similar duration following a previous Space Shuttle flight (18).

In Phase II, midodrine was administered to crewmembers in the manner in which it might be used routinely following space flight. Midodrine was administered to five male astronauts one hour before landing, near the time of firing the Shuttle main engines to decelerate the Orbiter and begin its descent. The peak therapeutic effect of midodrine occurs approximately one hour after ingestion (18);(10);(25), making it particularly attractive as landing day countermeasure, such that its peak effect is close to the time of

the maximum gravitational forces during landing (17). The purpose of this report is to summarize the preliminary findings from Phase II of this countermeasure evaluation. The strength of this study is that crewmembers participated in the post-flight tilt test of orthostatic tolerance within 30 minutes after wheelstop such that their physical status more closely represented their condition during re-entry and immediately upon landing.

METHODS

Overall Protocol

Eight crewmembers volunteered to participate in this countermeasure evaluation. Three subjects withdrew from participation following the collection of pre-flight data. Two subjects were waived from participation: one demonstrated a prolonged QTc interval on an electrocardiogram during in-flight screening and one experienced significant neurovestibular disturbances on landing day. One crewmember voluntarily withdrew from participation following the pre-flight midodrine tolerance test.

In the course of this study, countermeasure subjects participated in a familiarization session and drug tolerance test, an 80° head-up tilt test without medications approximately 10 days before launch (L-10), and the tilt test protocol within 60 minutes of Shuttle landing (R+0). Protocols were reviewed and approved by the Committee for the Protection of Human Subjects at NASA-Johnson Space Center (JSC). Subjects received verbal and written explanation of all procedures and signed statements of informed consent prior to participation.

Preflight Activities

Approximately 90 days before the scheduled launch date, subjects were briefed on test protocols and procedures. Afterwards, crewmembers participated in a midodrine tolerance test. A 12-lead electrocardiogram was first obtained to insure that the crewmember's QTc interval was within acceptable limits for ingestion of midodrine (<0.45 sec for men, <0.47 sec for women). Once verified, the crewmember's baseline systolic (SBP) and diastolic blood pressure (DBP) was measured. Following the ingestion of 10 mg midodrine, blood pressure was monitored at regular intervals during normal activities for four hours by trained personnel using a manual sphygmomanometer. Crewmembers were requested to report any unusual experiences or symptoms during this four-hour monitoring period and completed an activity log.

Approximately 10 days before launch (L-10), crewmembers participated in a tilt test in the JSC Cardiovascular Laboratory. Six minutes of supine data were collected prior to tilting the subjects to 80° head-up tilt using an automatic tilt table. The subjects remained in this position for 10 minutes, or until symptoms of orthostatic hypotension (SBP<70 mmHg, sudden drop in heart rate>15 beats·min^{-1}, sudden drop in SBP> 25 mmHg, sudden drop in DBP>15 mmHg, bradyarrythmia) and/or presyncope occurred (severe nausea, clammy skin, perfuse sweating, pallor, light-headedness, dizziness, or tingling). Subjects were discouraged from movement, muscle contractions, talking (except to report symptoms), and were encouraged to breathe normally. Subjects were returned to the supine posture upon termination of the test protocol.

Subjects were instrumented to measure ECG (Escort II, MDE, Arleta, CA) for heart rate (HR) and rhythm, beat-to-beat blood pressure in the finger (Finapres 2300 blood pressure monitor, Ohmeda, Englewood, CO), and blood pressure each minute in the brachial artery (Dinamap XL Vital Signs Monitor, GE Medical Systems Information Technologies, Milwaukee, WI). Two-dimensional echocardiography was used to obtain the aortic annulus diameter from the parasternal long axis during supine rest prior to data collection. Ascending aortic blood velocity time integral was measured each beat during rest and tilt from pulse wave Doppler measurements made at the suprasternal notch using a 2 MHz probe (Biosound MyLab 30, Esoate, Indianapolis, IN) (3). Images were digitally stored for offline analysis. Images from three cardiac cycles collected at a time corresponding to the heart rate and blood pressure data were independently analyzed by two experienced sonographers. Sonographers were blinded to the test conditions during the analyses. Stroke volume (SV=annulus diameter x velocity time integral), cardiac output (CO=stroke volume x heart rate) and total peripheral resistance (TPR=mean arterial pressure/cardiac output) were calculated.

In Flight Activities

Crewmembers participated in their scheduled in-flight activities without restriction for the duration of their Shuttle mission. After the decision for deorbit burn was confirmed on the scheduled landing day, crewmembers donned the Advanced Crew Escape Suit (ACES) and ingested 10 mg of midodrine approximately one hour prior to the scheduled landing time. The midodrine pill and a cue card with medication instructions were stowed previously in the astronaut's ACES for their convenience. Crewmembers

participated in the standard oral fluid loading protocol (equivalent to isotonic saline at a rate of 15 $ml \cdot kg^{-1}$ within two hours of landing (18)) and inflated their antigravity suits during re-entry and landing.

Post-flight Activities

Post-flight testing on landing day (R+0) was conducted on the Shuttle runway at either Kennedy Space Center, FL, or Dryden Flight Research Center, CA, in NASA's Crew Transport Vehicle (CTV), a modified airport "people mover" used to transport the crewmembers from the Space Shuttle to the data collection facility. After Shuttle wheel stop, the CTV approached the Orbiter with the rest of the NASA convoy, and the Shuttle hatch was opened within ~20 min. After a brief medical check by the NASA Flight Surgeons, the crewmembers exited the Orbiter with the midodrine test subjects exiting first. The crewmember doffed their ACES within 5 min and participated in the same tilt test protocol as during the pre-flight assessment.

Statistical Analyses

Hemodynamic and heart rate data were collected during the tilt test. The last minute of supine data was used as baseline. Standing values represent the data at the end of the tilt test: either after 10 minutes of tilt or when symptoms of orthostatic hypotension (presyncope) intervened.

Survival analysis was performed using the Gehan-Breslow test to compare the rate of presyncope during tilt at L-10 in the JSC Cardiovascular Laboratory and during tilt on

R+0 when testing was performed on the CTV. Because of the small number of subjects in this study, inferential statistics should be viewed with caution. Paired t-tests were conducted to determine whether there was a significant change in the heart rate and hemodynamic variables from supine to the last minute of tilt within each day. Then, paired t-tests were performed to compare the heart rate and hemodynamic responses (last minute standing minus supine) to tilt before and after space flight. Heart rate and blood pressure data were available for all five subjects on L-10 and R+0. However, SV, CO, and TPR data were not available for two subjects on R+0. Therefore, no inferential statistics were performed with these data.

Mean differences were considered significant if $p \leq 0.05$. Statistical analysis was performed using the software package SigmaPlot for Windows, version 11.0 (Systat Software, Inc.). Data are presented as means ± SEM.

RESULTS

On L-10, all five subjects completed the full 10 minutes of 80° head-up tilt in the laboratory without developing signs or symptoms of presyncope. When testing was performed in the CTV on R+0, only three of the five crewmembers completed the full 10 minutes of tilt. In this small group of subjects, the rate at which pre-syncope developed was not different (p=0.17) between testing in the laboratory on L-10 and testing on the CTV on R+0 (**FIGURE 1**).

INSERT FIGURE 1 HERE

HR increased from supine to tilt (**TABLE I**) both on L-10 (20±2 beats•min^{-1}, p<0.001) and on R+0 (25±9 beats•min^{-1}, p=0.05), but the change in HR from supine to tilt was not different from L-10 to R+0 (p=0.55, **FIGURE 2**). In contrast, SBP did not significantly change from supine to tilt either on L-10 (+3±5 mmHg, p=0.62) or on R+0 (-27±15 mmHg, p=0.15); however, the change in SBP from supine to tilt was different from L-10 to R+0 (p=0.05). DBP increased from supine to tilt on L-10 (+7±2 mmHg, p=0.03), but DBP did not change from supine to tilt on R+0 (-12±8 mmHg, p=0.21). Similar to SBP, the change in DBP from supine to tilt tended to be different on R+0 than L-10 than on L-10 (p=0.08).

Supine and tilt echocardiographic data were not statistically tested but are displayed in **Table I**.

INSERT TABLE I HERE

INSERT FGURE 2 HERE

DISCUSSION

This study represents the conclusion of Phase II of testing of midodrine as a pharmacological countermeasure to post-space flight orthostatic intolerance. The unique aspects of this investigation were that (a) this was the first time that a medication had been administered immediately prior to Space Shuttle re-entry and landing to protect

against orthostatic intolerance and (b) this was the first time that tilt tests were conducted on the CTV as an opportunity to examine orthostatic responses immediately after landing. In these five crewmembers, the rate of presyncope was not increased from pre-flight without midodrine to post-flight with midodrine. However, although the HR response to tilt was not changed from pre- to post-flight, midodrine did not prevent a drop in a blood pressure after space flight. Unfortunately, because of the unique operational aspects of this study, there were no control data (without midodrine) collected on the CTV to which comparisons could be made and conclusions drawn.

Post-flight orthostatic hypotension is one of the consequences of cardiovascular adaptations to microgravity that negatively impacts crew safety (1);(2);(6);(7);(9). Some crewmembers are so affected that they require assistance when exiting the Shuttle. Susceptibility to orthostatic hypotension is individual, with some astronauts experiencing severe symptoms, while others are less affected (8). Presyncopal astronauts, who exhibit severe orthostatic hypotension, have significantly lower standing plasma norepinephrine levels and total peripheral resistance than their crew mates who do not become presyncopal (9). These symptoms resemble those seen in patients with orthostatic hypotension due to autonomic dysfunction (9);(13).

Midodrine has proven to be a very safe and effective therapy for orthostatic hypotension due to autonomic dysfunction (5); (11);(13);(14);(20);(22);(24). In a randomized, double-blind, multicenter study with 171 patients with neurogenic orthostatic hypotension, Midodrine (10 mg dose, 3 times per day) resulted in substantial increases in

standing systolic blood pressure (increase of 22 mm Hg) with corresponding reductions in subjective symptoms such as lightheadedness over patients given placebo (13). In a second study, midodrine improved the following orthostatic hypotension symptoms: dizziness/lightheadedness, weakness/fatigue, syncope, low energy level, impaired ability to stand, and feelings of depression (11). The usual dose of midodrine is 5-10 mg orally three times a day (22);(24). When given to healthy subjects, midodrine only modestly increases supine and standing arterial pressure (increases less than 10 mm Hg) and decreases heart rate (less than 10 bpm) (5);(14).

The National Space Biomedical Research Institute's Cardiovascular Alterations Team conducted a two-week head-down bed-rest study (an analogue of space-flight) in normal human volunteers to simulate the effects of weightlessness on the cardiovascular system (19). They tested midodrine as a countermeasure for the post-bedrest orthostatic hypotension commonly observed during tilt testing. Five mg of midodrine significantly increased blood pressure and reduced fainting during post-bed rest tilt tests. The investigators concluded that midodrine might be an effective countermeasure for the prevention of orthostatic intolerance in astronauts following spaceflight.

For these reasons, we evaluated midodrine as a countermeasure to orthostatic intolerance after space flight. Because there were concerns about the safety of performing these studies in astronauts during re-entry and landing, the implementation took place in two phases. In Phase I, midodrine was administered to crewmembers after space flight, and testing was conducted in the controlled environment of the laboratory at the landing sites.

The primary finding of this experiment was that orthostatic responses in five male crewmembers after a Space Shuttle mission were not different than that which they experienced pre-flight. Additionally, their post-flight HR response with midodrine was less than the post-flight HR response following a previous Space Shuttle mission, and midodrine did not cause hypertension (17). Further, the administration of midodrine appeared to have prevented orthostatic intolerance after an 11-day mission in one female astronaut who had become presyncopal during a tilt test administered following a previous flight of nine days (18).

However, the second phase of this study examined the efficacy of midodrine immediately upon landing, in a less controlled and more provocative environment, onboard the CTV. This type of operationally-relevant environment was necessary to determine the true efficacy of midodrine as a countermeasure to immediate post-spaceflight orthostatic hypotension. The actual effectiveness of midodrine in this environment is unknown; it is not known how a crewmember would react to an orthostatic challenge immediately after landing without a countermeasure. Temperatures onboard the CTV were above 80°F in some cases, and the rocking of the vehicle further confounded the results of the tilt test. For example, elevated body temperature, secondary to increased ambient temperature (21) and impaired thermoregulation after space flight (4);(12), will result in decreased orthostatic tolerance (23). The most similar control group, astronauts tested in the baseline data collection facility after spaceflight, has two to four hours of upright ambulation in which to re-acclimate to Earth's gravity environment. Furthermore, these

crewmembers have the opportunity to eat and consume additional fluids before testing in a laboratory setting.

Hazards of Use of Midodrine

There is no central nervous system or cardiac stimulation with midodrine. The most frequent side-effect is pilomotor reactions (skin crawling sensation) in <8% of patients. Other less frequently reported side-effects are nausea, heartburn, dizziness, restlessness, and reflex bradycardia. Some reflex bradycardia may occur when BP is increased. Risk mitigation steps involve a drug tolerance test for each individual before its use during space flight, which we conducted for this experiment. Possible drug interactions also include the following: alpha- or beta-adrenergic agonists or blocking agents, especially digitalis glycosides; sodium-retaining corticosteroids; or vasoconstricting medications. Subjects were instructed not to take any of these drugs with midodrine before (drug tolerance test) and after space flight (landing day).

In addition, a drug interaction may exist with promethazine. There is the potential that midodrine and promethazine will interact when given together. In subjects that have received both of these medicines, in a previous study performed by our laboratory, we noted changes in mood and increased restlessness (16). The subjects described feelings of "anxiety", "aggressiveness", "claustrophobia", and a "need to constantly shift about". These changes in mood and restlessness were noticed about 10 minutes after subjects received an intravenous dose of promethazine and had been given midodrine one hour prior. Symptoms resolved within 30 to 45 minutes, and no lasting effects in mood or

restlessness were reported or observed in these subjects. If midodrine were to be eventually used as part of the preventive care in subjects known to have a propensity towards orthostatic hypotension, it could not be administered in those crewmembers in whom promethazine was administered before landing, while in the CTV or at the baseline data collection facility. Based upon our previous experiences in the laboratory, we recommend that no promethazine may be administered within 70 hours prior to midodrine ingestion or within 4 hours following midodrine ingestion.

Summary

Midodrine appears to prevent orthostatic intolerance in test subjects after bed rest and in astronauts following space flight when testing is conducted in a controlled, laboratory setting within 2-4 hours after landing. It is unclear at this time whether similar effects can expected during re-entry and immediately following landing, particularly in warmer environments and/or when the crewmembers are still wearing the ACES. Accurate interpretation of the current data require similar data be collected in control subjects (without midodrine) on the CTV. However, concerns with drug interactions with commonly used commonly used anti-emetics and prolonged QTc intervals observed in long duration astronauts make the routine use of midodrine unlikely and reliance upon lower body compression garments preferential.

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FIGURE LEGENDS

FIGURE 1. The probability of completing a 10-minute 80° head-up tilt test in the laboratory before space flight (L-10, solid line) was not different ($p=0.17$) than the probability of completing a tilt test on landing day (R+0, dashed line) in the Crew Transport Vehicle in five astronauts.

FIGURE 2. Change in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) from last minute of supine rest to the last minute of tilt in the laboratory before flight (L-10) and on landing day (R+0) in the Crew Transport Vehicle. *Significantly different than L-10 ($p<0.05$).

FIGURE 1

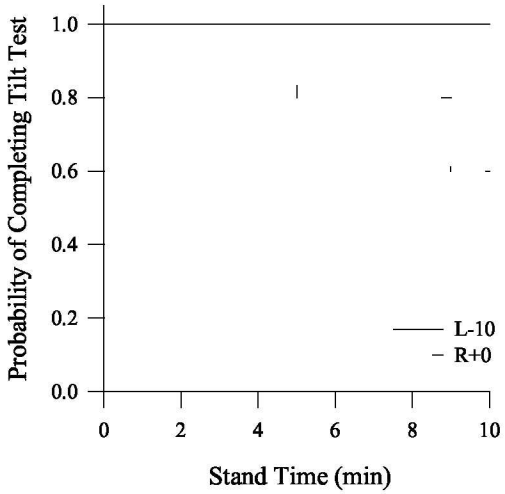
Probability of Completing Tilt Test
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Stand Time (min)
L-10
R+0

FIGURE 2

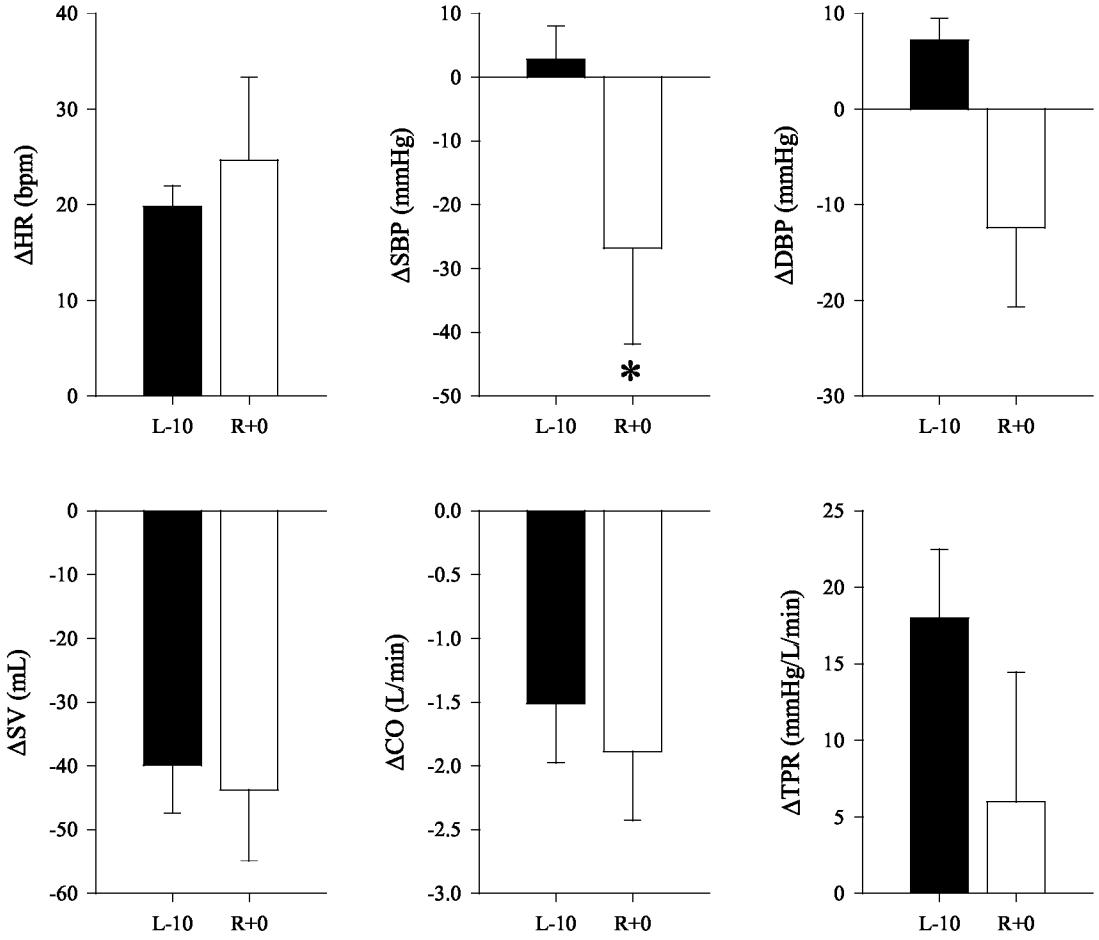
ΔHR (bpm)
40
30
20
10
0
L-10
R+0
ΔSBP (mmHg)
10
0
-10
-20
-30
-40
-50
*
L-10
R+0
ΔDBP (mmHg)
10
0
-10
-20
-30
L-10
R+0
ΔSV (mL)
0
-10
-20
-30
-40
-50
-60
L-10
R+0
ΔCO (L/min)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
L-10
R+0
ΔTPR (mmHg/L/min)
25
20
15
10
5
0
L-10
R+0

Table I. Hemodynamic variables during the last minute of supine rest and at tilt test termination. *Significantly different than supine.

	L-10		R+0	
	Supine	Tilt	Supine	Tilt
Heart Rate (beats•min^{-1}, n=5)	54±3	74±3*	58±2	82±8*
Systolic Pressure (mmHg, n=5)	121±6	124±7	131±2	104±15
Diastolic Pressure (mmHg, n=5)	67±4	74±4*	76±2	64±8
Stroke Volume (ml, n=3)	69±6	29±4	73±7	29±6
Cardiac Output (L•min^{-1}, n=3)	3.8±0.6	2.3±0.4	4.3±0.5	2.4±0.1
Total Peripheral Resistance (mmHg•L^{-1}•min^{-1}, n=3)	24.9±3.6	42.9±6.1	22.5±2.8	28.5±5.7