Hypotensive effect of push-pull gravitational stress occurs after autonomic blockade

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Sheriff, Don D. Hypotensive effect of push-pull gravitational stress occurs after autonomic blockade. J Appl Physiol 95: 167–171, 2003; 10.1152/japplphysiol.00165.2003.—The “push-pull” effect denotes the reduced tolerance to $+G_z$ (hypergravity) when $+G_z$ stress is preceded by exposure to hypogravity, i.e., fractional, zero, or negative $G_z$. Previous studies have implicated autonomic reflexes as a mechanism contributing to the push-pull effect. The purpose of this study was to test the hypothesis that nonautonomic mechanisms can cause a push-pull effect, by using eye-level blood pressure as a measure of $G$ tolerance. The approach was to impose control (30 s of 30° head-up tilt) and push-pull (30 s of 30° head-up tilt immediately preceded by 10 s of −15° head-down tilt) gravitational stress after administration of hexamethonium (10 mg/kg) to inhibit autonomic ganglionic neurotransmission in four dogs. The animals were chronically instrumented with arterial and venous catheters, an ascending aortic blood flow transducer, ventricular pacing electrodes, and atioventricular block. The animals were paced at 75 beats/min throughout the experiment. The animals were sedated with acepromazine and lightly restrained in lateral recumbency on a tilt table. After the onset of head-up tilt, the magnitude of the fall in eye-level blood pressure from baseline was $-27.6 \pm 2.3$ and $-37.9 \pm 2.7$ mmHg for the control and push-pull trials, respectively ($P < 0.05$). Cardiac output fell similarly in both conditions. Thus a push-pull effect attributable to a rise in total vascular conductance occurs when autonomic function is inhibited.

arterial blood pressure; tilt; orthostatic stress; atioventricular block; dog

RELATIVE BRIEF EXPOSURE TO less than $+1 G$ along the long (z) axis of the body (e.g., microgravity, 0 $G_z$ or negative $G_z$) reduces $G_z$ tolerance during subsequent exposure to positive $G_z$ stress. This pattern of $G$ stress occurs in the flying environment when a pilot first pushes on the control stick to unload the aircraft to zero or negative $G$ and then subsequently pulls on the control stick, thereby imposing high positive $G_z$ stress. For this reason, the phenomenon of reduced $G_z$ tolerance after brief exposure to hypogravity has been termed the “push-pull effect” (2). The reduction in $G_z$ tolerance is associated with an exaggerated reduction in eye-level blood pressure (ELBP) in response to $+G_z$ (2, 7–11), and this hypotension is graded to the magnitude of the “push” stimulus (8). The push-pull effect has been demonstrated in human subjects (1–3) as well as in both conscious (1) and anesthetized (8–11) rats. The axis of rotation appears to be an important factor in human subjects (3) but not in rats (9), and gender does not appear to be a factor in rats (9). Moreover, similar alterations in regional hydrostatic pressure occur during common everyday movements such as bending over to pick an object up, and thus these studies relate to the dizziness, and possible loss of consciousness, that can accompany “standing up too quickly.”

Although the mechanism(s) responsible for the push-pull effect is incompletely understood, it has been speculated that the arterial baroreflexes play a role (3, 5, 6, 8–11). Support for this hypothesis stems from the observation that peripheral vasoconstriction to head-up tilt is impaired by prior head-down tilt (7). Further support for this hypothesis stems from the observation that inhibition of autonomic ganglionic neurotransmission eliminates the push-pull effect in rats (10) and that the magnitude of the push-pull effect is coupled to the magnitude of the carotid hypertension that occurs during the push phase of push-pull gravitational stress (8). However, nonautonomic mechanisms could be activated differently during control and push-pull gravitational stress. For example, differences in the regional hydrostatic component of arterial blood pressure could elicit myogenic vasomotor responses (4) that could contribute to the push-pull effect. Also, tilt-induced differences in regional venous pressures could transiently alter the effective regional arterial-venous pressure gradient for blood flow, and this could contribute to the push-pull effect. The purpose of the present study was to test the hypothesis that a nonautonomic mechanism(s) can produce a push-pull effect. If the hypothesis were answered in the affirmative, the study was also designed to test whether the mechanism producing a nonautonomic push-pull effect was of central or peripheral origin, i.e., whether it was due to a difference in cardiac output and/or total vascular conductance.

METHODS

The following procedures meet National Institutes of Health guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee of The Uni-
versity of Iowa. Experiments were carried out using four mongrel hound-type dogs (19–23 kg body wt) (Oak Hill Genetics, Ewing, IL). The length from the right atrium to the eyes ranged from 28 to 35 cm, and the trunk length (right atrium to base of tail) ranged from 46 to 50 cm.

**Surgical preparation.** The animals were prepared in the following series of aseptic surgical procedures as described previously (15). A right thoracotomy was performed, a blood flow transducer (Transonic, Ithaca, NY) was placed on the ascending aorta, and pacing leads were sutured to the apex of the left ventricle. A skin patch delivering 50 µg/h of fentanyl was placed on the dog for 72 h after surgery to control postoperative pain. In a final procedure, 1) a catheter was inserted into a side branch of the femoral artery and advanced into the abdominal aorta, 2) a catheter was inserted into a side branch of the femoral vein and advanced into the caval-right atrial junction. A skin patch delivering 25 µg/h of fentanyl was placed on the dog for 72 h after surgery to control postoperative pain. The animals were treated with cephazolin (1 g iv) immediately before each surgical procedure and with cephalin (500 mg po bid) for 1 wk postoperatively. The animals were allowed at least 1 wk for recovery between surgical procedures. All experiments were performed after the animals had recovered from the surgery and were afebrile, active, and of good appetite. A pacemaker carried by the dog paced the heart at 70 beats/min between experiments.

**Experimental procedures.** The animals were sedated with acepromazine (20–30 mg iv) in order that the results would not be complicated by the cardiovascular consequences associated with excitement and/or muscular straining associated with tilting. The animals were treated with hexamethonium (10 mg/kg iv), a dose previously shown to provide effective inhibition of autonomic ganglionic neurotransmission (12, 13). The animals were lightly restrained on a padded tilt table. For all rotations, the tilt table was oriented such that Earth’s gravity vector was applied across the animal’s y-axis so that Gz gravitational stress could be imposed by manually rotating the table and thus the animal about the animal’s z-axis (roll rotation). The starting position was 0 Gz (+1 or −1 Gz). The control treatment consisted of rotating the animal 30° head up (+0.50 Gz) for 30 s. The push-pull treatment consisted of 30 s of head-up tilt that was immediately preceded by 10 s of 15° head-down tilt (−0.26 Gz). Movement times were 1 s (0.5 g/s). Each animal was subjected to a control trial, a push-pull trial, and a second control trial. This counterbalanced design is illustrated in Fig. 1A and was selected to minimize possible time effects of repeated exposure to gravitational stress. The animal recovered for at least 1 min in the horizontal (0 Gz) position between trials.

**Data collection.** The arterial catheter and the jugular catheters were connected to pressure transducers (PE10 EZ, Ohmeda, Madison, WI) secured at the level of the right atrium and the degree of tilt. Baseline ELBP was established by calculating the average pressure over the 20 s immediately preceding tilt onset. The magnitude of the response of ELBP to −Gz stress (ΔPush) was calculated as the difference between pressure averaged over the period from 4 to 6 s before the transition from −Gz to +Gz, and baseline pressure. The magnitude of the response of ELBP to +Gz stress (ΔPull) was calculated as the difference between baseline pressure and the pressure averaged over the period from 6 to 8 s after the onset of head-up tilt. The manner in which ΔPush and ΔPull were derived is shown schematically in Fig. 1B. Data from the two control trials within each dog were averaged together such that each dog only contributed once to the group mean data and to the statistical analysis for each condition.

**Statistical analysis.** Baseline, ΔPush, and ΔPull values between control and push-pull trials were compared statistically by paired *t*-tests. Data are presented as means ± SE.

### RESULTS

An illustrative example of the hemodynamic response to control and push-pull gravitational stress from a single dog after autonomic inhibition by hexamethonium is shown in Fig. 2. Head-down tilt raised heart-level arterial pressure and right atrial pressure. Arterial pressure fell to a greater extent during head-up tilt in the push-pull trial (Fig. 2E) than in the control trial (Fig. 2A).

The hemodynamic responses to control and push-pull gravitational stress, averaged from four dogs after autonomic inhibition by hexamethonium, are shown in Fig. 3. Responses are similar to those seen in Fig. 1. Head-down tilt raised heart-level arterial pressure and right atrial pressure. Both heart-level arterial pressure (solid lines) and ELBP (dashed lines) fell to a greater extent during head-up tilt in the push-pull trial (thick lines) than in the control trial (thin lines). Right atrial pressure and cardiac output fell similarly during head-up tilt in the control and push-pull trials. Cardiac output (and thus stroke volume because heart rate was constant) fell similarly in the control and push-pull trials. Total vascular conductance rose during head-
down tilt and remained elevated during the subsequent head-up tilt in the push-pull trial. Total vascular conductance was little altered in the control trials. The baseline, \( \Delta \)Push, and \( \Delta \)Pull values are presented in Table 1. The values of \( \Delta \)Push for ELBP \( (P < 0.01) \), right atrial pressure \( (P < 0.01) \), and total vascular conductance \( (P < 0.05) \) were significantly greater during push-pull than during control gravitational stress. The values of \( \Delta \)Pull for ELBP \( (P < 0.05) \) and total vascular conductance \( (P < 0.05) \) were significantly greater during push-pull than during control gravitational stress.

**DISCUSSION**

The major new findings of this study are that a push-pull effect can be produced by a nonautonomic mechanism(s) and that this effect is attributable to peripheral vascular factors. When autonomic function is intact, these factors likely contribute to the push-pull effect in addition to the contributions made by the autonomic nervous system.

Although the mechanism(s) responsible for the push-pull effect are incompletely understood, it has been speculated that the arterial baroreflexes play a major role. The thinking is that the rise in carotid distending pressure imposed during the push activates the carotid sinus baroreceptors, which in turn slow the heart and initiate peripheral vasodilation in an effort to restore carotid pressure back toward its baseline value. These blood pressure-lowering responses, initiated during the push, persist during the early phase of the subsequent pull. At this time, the mechanical reduction in carotid artery pressure produced by the alteration in acceleration is suddenly added to the pressure-reducing effects of the (slowly reversing) baroreceptor-induced bradycardia and peripheral vasodilation. This can lead to an unexpectedly large fall in cerebral perfusion pressure and loss of consciousness in extreme conditions. The cardiopulmonary mechanoreceptor reflexes and/or vestibular-autonomic responses (3) may contribute to the push-pull effect as well. However, other mechanisms such as myogenic vasomotor responses could contribute and/or cause the push-pull effect. To our knowledge, there has been no direct test of the importance of local, periph-
eral vascular factors in causing or contributing to the push-pull effect.

In rats, the magnitude of the exaggerated fall in ELBP induced by push-pull gravitational stress is graded to the magnitude of carotid hypertension imposed during the push (8), and the push-pull effect is eliminated by autonomic blockade (10). Both of these observations provide support for the importance of baroreflexes in contributing to the push-pull effect, and the observation that autonomic blockade eliminates the push-pull effect suggests that the entire response can be explained by autonomic mechanisms in this species. However, we reasoned that local, peripheral vascular factors might play a more important role in a larger species in which the regional alterations in the hydrostatic component of blood pressure induced by tilting are much larger. That is, the changes in regional pressure that occur in rats when they are tilted may simply be too small to elicit functionally important alterations in myogenic stimuli or regional venous pressures. This idea is supported by studies in which the region pressure changes associated with push-pull gravitational stress were simulated in rats by terminal aortic vascular occlusion (8). Terminal aortic occlusion raises upper body arterial pressure similar to the rise seen during head-down tilt. Importantly, terminal aortic occlusion induces an exaggerated fall in lower body arterial pressure compared with head-down tilt. That is, it causes lower body arterial pressure to fall to an extent that would be expected to occur in human legs when humans are subjected to head-down tilt. Brief terminal aortic occlusion in rats treated with hexamethonium induced a push-pull like hypotension (8). This finding indicates that reductions in lower body pressure that are larger than those imposed by tilting in this small species activate local regulatory mechanisms in a manner that produces a push-pull effect. Thus, to better test the importance of local, peripheral vascular factors in contributing to the push-pull effect in humans (and other relatively large species), experiments would be better carried out in a species larger than rats. Dogs were selected for the present study because 1) they are far larger than rats and thus develop much greater changes in regional pressure during tilting, and 2) they can have a trunk length equal to or larger than most humans. Hearts were paced at a constant rate to prevent the tilt-induced changes in right atrial changes from altering rate (13).

![Graphs showing cardiovascular responses to control and push-pull gravitational stress](image)

**Table 1. Hemodynamic response to control and push-pull gravitational stress in dogs during constant-rate ventricular pacing after autonomic blockade**

<table>
<thead>
<tr>
<th></th>
<th>ELBP, mmHg</th>
<th>Pra, mmHg</th>
<th>CO, l/min</th>
<th>TVC, ml·min⁻¹·mmHg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>84.9 ± 10.2</td>
<td>1.8 ± 1.3</td>
<td>3.23 ± 0.50</td>
<td>37.5 ± 3.8</td>
</tr>
<tr>
<td>Push</td>
<td>87.2 ± 10.7</td>
<td>2.9 ± 1.6</td>
<td>3.21 ± 0.50</td>
<td>36.8 ± 3.5</td>
</tr>
<tr>
<td><strong>ΔPush</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.3 ± 3.5</td>
<td>-0.1 ± 0.8</td>
<td>0.04 ± 0.08</td>
<td>-0.2 ± 0.2</td>
</tr>
<tr>
<td>Push</td>
<td>12.7 ± 2.3</td>
<td>-0.1 ± 0.9</td>
<td>0.08 ± 0.05</td>
<td>1.8 ± 0.4*</td>
</tr>
<tr>
<td><strong>ΔPull</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-27.6 ± 2.3</td>
<td>-8.6 ± 1.2</td>
<td>-0.26 ± 0.08</td>
<td>-3.8 ± 1.3</td>
</tr>
<tr>
<td>Push</td>
<td>-37.9 ± 2.7</td>
<td>-8.4 ± 1.6</td>
<td>-0.04 ± 0.09</td>
<td>2.7 ± 1.6*</td>
</tr>
</tbody>
</table>

Values are means ± SE for 4 dogs. ELBP, eye-level blood pressure; Pra, right atrial pressure; CO, cardiac output; TVC, total vascular conductance; ΔPush, magnitude of the response of ELBP to -Gx stress; ΔPull, magnitude of the response of ELBP to +Gx stress. *Statistically different from control, P < 0.05.
because the expected changes would be in the opposite direction to those normally induced by the autonomic adjustments to push-pull gravitational stress (6).

In contrast to rats, we found that a push-pull effect occurred in dogs when autonomic function was blocked. The fall in ELBP during head-up tilt when head-up tilt was immediately preceded by head-down tilt exceeded by 10 mmHg the fall seen in control conditions. The decreases in stroke volume and thus cardiac output were similar between control and push-pull gravitational stress. Thus different alterations in the loading conditions of the heart between control and push-pull gravitational stress do not appear to account for the push-pull effect. Rather, the push-pull effect appears to be entirely attributable to differences in calculated total vascular conductance under the conditions of the present experiments. The difference in calculated conductance could in turn be due to changes in arteriolar diameter and/or to differences in regional venous pressures that act in a manner that mimics an alteration in true conductance (12). For example, the fall in lower body arterial pressure that occurs during head-down tilt could elicit myogenic relaxation and an increase in arteriolar caliber that persists early on during the subsequent head-up tilt. This relaxation would be lacking in the control trials. Alternatively, head-down tilt also reduces lower body venous blood pressure (and blood volume). This reduction in the pressure in the small veins in the lower body (the effective back pressure governing arterial inflow to the lower body) would be expected to persist early on during the subsequent head-up tilt because of the venous valves. Thus, compared with control, there would be a relatively greater arterio-venous pressure gradient driving flow into the lower body during the head-up tilt phase of push-pull gravitational stress, and this could lead to an increase in arterial inflow to the lower body in the absence of locally produced changes in vessel diameters. This greater pressure gradient would persist until the veins are refilled. An increase in arterial inflow to the lower body stemming from such an increase in the local arterio-venous pressure gradient would manifest itself as an increase in calculated total vascular conductance when right atrial pressure is assumed to constitute the back pressure for perfusion. Finally, greater filling of the lower body arterial system when head-up tilt follows head-down tilt could also contribute to the greater hypotension. Although blood flow to the lower body may be reduced during head-down tilt, metabolic vasodilation appears to be too slow to contribute to the push-pull effect (14). Further investigation is required to determine the relative importance of these factors.

The hemodynamic responses that would result during the gravitational stresses employed in the present study when autonomic function is intact are unknown, but presumably the push-pull effect would be larger. We selected to first evaluate the passive (hydraulic) or nonautonomic consequences of tilting because we sought to avoid the nonspecific reactions to tilting of human subjects (15) or unweighting of rats (16).

**Summary.** A push-pull effect attributable to peripheral vascular factors occurs in conscious dogs after autonomic blockade. In addition to the autonomic factors, the nonautonomic factors appear to contribute importantly to the push-pull effect in relatively large species such as dogs and humans.

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**REFERENCES**


