Role of the autonomic nervous system in push-pull gravitational stress in anesthetized rats

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Hakeman, Amy L., and Don D. Sheriff. Role of the autonomic nervous system in push-pull gravitational stress in anesthetized rats. J Appl Physiol 94: 709–715, 2003; 10.1152/japplphysiol.00554.2002.—Tolerance to \( 1 \)Gz stress is reduced by preceding exposure to \(-1 \)Gz (push-pull effect). The mechanism(s) responsible for this effect are not fully understood, although the arterial baroreceptor reflexes have been implicated. We investigated the integrative response of the autonomic nervous system by studying responses to gravitational stress before and after autonomic function was inhibited by hexamethonium in 10 isoflurane-anesthetized male and female Sprague-Dawley rats. Animals were restrained supine and subjected to two rotations imposed about the x-axis: 1) a control G profile consisting of rotation from 0 Gz (+1 Gz) to 90° head-up tilt (+1 Gz) for 10 s and 2) a push-pull G profile consisting of rotation from 0 Gz to 90° head-down tilt (−1 Gz) for 2 s immediately preceding 10 s of +1 Gz stress. Eight G profiles consisting of equal numbers of control and push-pull trials were imposed by using a counterbalanced design. We found that hexamethonium lowered baseline arterial pressure and abolished the push-pull effect. The lack of a push-pull effect after autonomic blockade persisted when arterial pressure was restored to baseline levels by phenylephrine infusion. Lowering baseline arterial pressure by sodium nitroprusside infusion or by hemorrhage when autonomic function was intact also abolished the push-pull effect. We conclude that intact autonomic function and a normal baseline arterial pressure are needed for expression of the push-pull effect in anesthetized rats subjected to tilting.

BRIEF EXPOSURE to \(-1 \)Gz (“push”) reduces eye-level blood pressure (ELBP) during subsequent exposure to \(+1 \)Gz (“pull”), termed the “push-pull effect” (3). The push-pull effect is expressed in human subjects when this type of gravitational stress is imposed by aerial combat maneuvering (1), centrifugation (2, 3), or parabolic flight profiles (8). It is also expressed in conscious rats exposed to centrifugation (10) and in anesthetized rats subjected to tilting (7, 10). The axis of rotation appears to be an important factor in humans (4) but not in rats (7), and gender does not appear to be a factor in rats (7).

Although the mechanism(s) responsible for the push-pull effect is not completely understood, it has been speculated that the arterial baroreflexes play a major role (1–4, 6, 10). 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 (9). The cardiopulmonary mechanoreceptor reflexes and/or vestibular-autonomic responses may contribute to the push-pull effect as well. However, other mechanisms such as myogenic vasomotor responses could contribute to and/or cause the push-pull effect. To our knowledge, there has been no direct test of the importance of the autonomic nervous system in causing or contributing to the push-pull effect.

The purpose of the present study was to evaluate the contribution of baroreceptor reflexes to the push-pull effect. Studies were carried out before and after autonomic ganglionic neurotransmission was inhibited with hexamethonium. We hypothesized that treatment with hexamethonium would abolish the push-pull effect. Because hexamethonium inhibits autonomic effector mechanisms, this approach provides an indication of the integrated response of the cardiovascular reflexes from both the high- and low-pressure sides of the circulation as well as the vestibular-autonomic responses in determining the push-pull effect. Because hexamethonium reduces baseline arterial pressure, we also carried out studies before and after autonomic blockade when baseline arterial pressure was manipulated by infusion of vasoactive substances or hemorrhage. Studies were carried out in anesthetized rats subjected to gravitational stress by tilting.

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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 University of Iowa.

Surgical preparation. Eight Sprague-Dawley rats (5 female, 3 male; 270–390 g) were anesthetized with isoflurane and restrained supine on a homeothermically controlled table. The animal’s body temperature was maintained at 37°C. A catheter was implanted in the right carotid artery for arterial pressure measurement and either the left jugular or femoral vein for drug infusion with a syringe pump.

Experimental procedures. For all rotations, the tilt table was oriented such that Earth’s gravity vector was applied across the animal’s y-axis so that $G_y$ gravitational stress could be imposed by manually rotating the table and thus the animal ±90° about the animal’s x-axis (roll rotation). The starting position was 0 $G_y$ (+1 $G_z$). Control gravitational stress consisted of rotating the animal 90° head-up (+1 $G_z$) for 10 s. Push-pull treatment consisted of 10 s of head-up tilt that was immediately preceded by 2 s of 90° head-down tilt (−1 $G_z$). The animal recovered for 50 s in the horizontal (0 $G_z$) position between tilts. Eight $G$ profiles were imposed under each condition in a counterbalanced design to minimize possible time effects of repeated exposure to gravitational stress. A schematic illustration of the experimental protocol is shown in Fig. 1A.

All eight rats were studied under seven different conditions in the same order. First, control studies were performed before administration of drugs. Baseline arterial pressure was then raised by continuous infusion of phenylephrine (20 µg/min), and studies were repeated. The infusion of phenylephrine was stopped, and arterial pressure was allowed to return to baseline. Baseline arterial pressure was then lowered by continuous infusion of sodium nitroprusside (5–20 µg/min), and studies were repeated. The infusion of sodium nitroprusside was stopped, and arterial pressure was allowed to return to baseline. Three to eight milliliters of blood were withdrawn through the arterial catheter to reduce baseline arterial pressure, and studies were repeated. The shed blood was then reinfused, and arterial pressure was allowed to return to baseline. Hexamethonium (10 mg/kg iv) was then injected, and studies were repeated. A supplemental dose of hexamethonium (3.3 mg/kg iv) was then administered, an infusion of phenylephrine (5–40 µg/min) was begun, and studies were repeated. Finally, the rate of phenylephrine infusion was increased to 20–80 µg/min and studies were repeated. Figure 2 shows a schematic illustration of the seven experimental protocols. The time for the entire experiment ranged from 2 to 2.5 h.

Data collection. The arterial catheter was connected to a pressure transducer (PE10 EZ, Ohmeda, Madison, WI) secured at eye level. A length of water-filled tubing connected to a similar pressure transducer was mounted on the table to measure tilt.

Signals were digitized at 1 kHz and stored on the fixed disk of a laboratory microcomputer for subsequent analysis (PONEMAH Physiology Platform, P3, Gould Instruments, Valley View, OH).

Data analysis. Data analysis was performed on 1-s averages of the digitized data. Baseline ELBP was established by calculating the average pressure over the 5 s immediately preceding tilt onset. The magnitude of the ELBP response to the brief −$G_z$ gravitational stress (ΔPush) was calculated as the difference between the peak pressure during the −1 $G_z$ (taken at a time when the animal was stationary) and baseline pressure. The magnitude of the ELBP response to the +1 $G_z$ gravitational stress (ΔPull) for both the control and push-pull $G$ profiles was calculated as the difference between baseline pressure and the pressure observed at second 3 after the onset of head-up tilt. This measure (ΔPull) was used to determine whether a push-pull effect was present or not. The extent of recovery of pressure during the 10 s of head-up tilt (ΔRecovery) was calculated as the difference in arterial pressure between second 3 and second 9 and was used to indicate autonomic reflex compensation during the head-up tilt. Pos-
itive ΔRecovery numbers denote restoration of pressure, whereas negative numbers denote deterioration of arterial pressure from second 3 to second 9. The manner in which these variables were derived is shown schematically in Fig. 1B.

Statistical analysis. The ΔPull value between control and push-pull treatments within each condition (no drug, phenylephrine, sodium nitroprusside, etc.) was compared statistically by performing a paired t-test. Single sample t-tests were performed to determine whether the ΔPush and ΔRecovery values were different from zero. Statistical significance was deemed to exist when P was <0.05. Data are reported as means ± SE.

RESULTS

ELBP during +1 Gz (control) gravitational stress in a single rat is shown in Fig. 3A, top. Pressure initially falls from 109 mmHg at baseline to 71 mmHg at second 3 and then is partially restored to 94 mmHg at second 9 after the onset of tilt. ELBP during push-pull gravitational stress in the same rat is shown in Fig. 3B. From 108 mmHg at baseline, ELBP rises to 119 mmHg during the 2 s of −1 Gz stress and then falls during the subsequent +1 Gz stress to a value (66 mmHg), 4 mmHg lower than seen during control +1 Gz gravitational stress (Fig. 3A). ELBP undergoes restoration to 92 mmHg at second 9. Responses from the same rat after autonomic inhibition are shown in Fig. 3, C and D. During +1 Gz (control) gravitational stress (Fig. 3C), pressure initially falls as when autonomic function is intact but then continues to deteriorate during the 10 s of gravitational stress. During push-pull gravitational stress (Fig. 3D), ELBP rises during the push phase, drops during the initial pull phase, and then continues to deteriorate throughout the 10 s of +1 Gz gravitational stress. Group mean values of ELBP at baseline and at second 3 and second 9 after the onset of +1 Gz gravitational stress are provided in Table 1 for all conditions. Also provided in Table 1 are values representing the magnitude of the rise in ELBP during −1 Gz stress (ΔPush) and the magnitude of the fall in pressure during the initial phase of +1 Gz gravitational stress (ΔPull). Finally, the extent of recovery (or
deterioration) of pressure from second 3 to second 9 during +1 G z gravitational stress (ΔRecovery) for all conditions is provided in Table 1.

Figure 4A shows the group mean response of ELBP during control and push-pull gravitational stress when autonomic function was intact. There was a statistically significant push-pull effect in that the magnitude of the fall in ELBP from baseline (ΔPull) was significantly greater (P < 0.05) during push-pull stress than during control stress (Table 1). Note also that ELBP was partially restored toward baseline during the 10 s of 1 G z stress in both the control and push-pull treatments. The ΔRecovery pressures for both stresses were significantly greater than zero (P < 0.05, Table 1).

Before hexamethonium administration, phenylephrine was infused to raise arterial pressure above control levels. No push-pull effect was seen under this condition (Fig. 4B). Arterial pressure appears to fall throughout the 10 s of +1 G z gravitational stress in both the control and push-pull conditions, but these changes did not achieve statistical significance (P > 0.08).

Also, before hexamethion administration, baseline arterial pressure was reduced to the level later caused by autonomic blockade by nitroprusside infusion and by hemorrhage. As shown in Fig. 4, C and D, the effects of these two interventions were similar in that both abolished the push-pull effect and the partial recovery of pressure normally seen during +1 G z gravitational stress.

The effects of treatment with hexamethionium are shown in Fig. 5A. Inhibition of autonomic function lowered baseline ELBP by ~25 mmHg. Hexamethionium abolished the push-pull effect in that the re-

<table>
<thead>
<tr>
<th>No Drug</th>
<th>Baseline</th>
<th>ΔPush</th>
<th>Second 3</th>
<th>Second 9</th>
<th>ΔPull</th>
<th>ΔRecovery</th>
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<tbody>
<tr>
<td>Control</td>
<td>102 ± 3.2</td>
<td>6 ± 0.5</td>
<td>76 ± 3.3</td>
<td>81 ± 4.1</td>
<td>−25 ± 2.0</td>
<td>4 ± 1.9†</td>
</tr>
<tr>
<td>Push-pull</td>
<td>101 ± 3.2</td>
<td>6 ± 0.5</td>
<td>76 ± 3.3</td>
<td>81 ± 4.0</td>
<td>−28 ± 1.7†</td>
<td>8 ± 2.1†</td>
</tr>
<tr>
<td>PE</td>
<td>101 ± 3.2</td>
<td>6 ± 0.5</td>
<td>76 ± 3.3</td>
<td>81 ± 4.0</td>
<td>−28 ± 1.7†</td>
<td>8 ± 2.1†</td>
</tr>
<tr>
<td>Control</td>
<td>150 ± 6.5</td>
<td>3 ± 0.3 †</td>
<td>137 ± 7.2</td>
<td>134 ± 7.3</td>
<td>−12 ± 1.4</td>
<td>−3 ± 1.6</td>
</tr>
<tr>
<td>Push-pull</td>
<td>150 ± 6.5</td>
<td>3 ± 0.3 †</td>
<td>138 ± 7.9</td>
<td>135 ± 8.1</td>
<td>−12 ± 1.9</td>
<td>−4 ± 1.8</td>
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<tr>
<td>SNP</td>
<td>73 ± 3.4</td>
<td>5 ± 0.3</td>
<td>54 ± 3.6</td>
<td>54 ± 3.0</td>
<td>−20 ± 1.5</td>
<td>0 ± 1.0</td>
</tr>
<tr>
<td>Push-pull</td>
<td>73 ± 3.4</td>
<td>5 ± 0.3</td>
<td>55 ± 3.6</td>
<td>55 ± 3.3</td>
<td>−20 ± 1.3</td>
<td>0 ± 0.5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>79 ± 2.6</td>
<td>4 ± 0.3 †</td>
<td>55 ± 3.3</td>
<td>55 ± 3.6</td>
<td>−24 ± 1.7</td>
<td>0 ± 1.0</td>
</tr>
<tr>
<td>Control</td>
<td>75 ± 4.8</td>
<td>5 ± 0.4 †</td>
<td>63 ± 4.0</td>
<td>60 ± 3.7</td>
<td>−12 ± 1.4</td>
<td>−3 ± 0.7 †</td>
</tr>
<tr>
<td>Push-pull</td>
<td>75 ± 4.8</td>
<td>5 ± 0.4 †</td>
<td>63 ± 3.9</td>
<td>60 ± 3.7</td>
<td>−13 ± 1.2</td>
<td>−3 ± 0.9 †</td>
</tr>
<tr>
<td>Hex</td>
<td>111 ± 5.4</td>
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<td>97 ± 6.2</td>
<td>93 ± 6.2</td>
<td>−14 ± 3.0</td>
<td>−3 ± 1.0 †</td>
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<td>Hex + PE</td>
<td>110 ± 5.4</td>
<td>4 ± 0.7 †</td>
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<td>138 ± 4.6</td>
<td>137 ± 4.9</td>
<td>−9 ± 0.6</td>
<td>−2 ± 0.9</td>
</tr>
<tr>
<td>Push-pull</td>
<td>147 ± 4.7</td>
<td>4 ± 0.6 †</td>
<td>137 ± 4.8</td>
<td>137 ± 4.7</td>
<td>−10 ± 0.5</td>
<td>0 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE (in mmHg); n = 8 rats. PE, phenylephrine; Hex, hexamethonium; +, low-dose; ++, high-dose. * Statistically different (P < 0.05) from control. † Statistically different (P < 0.05) from zero.

Fig. 4. Group mean responses of eye-level blood pressure during control + G z gravitational stress and push-pull gravitational stress imposed by tilting with no drugs (A), phenylephrine (B), sodium nitroprusside (C), and hemorrhage (D). Dashed lines indicate push-pull gravitational stress. Solid lines indicate control (+ G z) tilt. Values are means ± SE; n = 8 rats.
sponses of ELBP during 10 s of +1 Gz gravitational stress for the control and push-pull conditions are essentially superimposed. Hexamethonium also abolished the partial restoration of pressure normally seen over the 10 s of +1 Gz stress. In fact, the ΔRecovery values were significantly less than zero (P < 0.05, Table 1), indicating that pressure further deteriorated over this period.

Phenylephrine was infused after hexamethonium administration to restore baseline arterial pressure to control levels. No push-pull effect was seen under these conditions (Fig. 5B), and pressure deteriorated throughout the 10 s of +1 Gz gravitational stress.

Finally, phenylephrine was infused at a higher rate after hexamethonium administration to raise arterial pressure to the levels achieved by this drug before hexamethionin (Fig. 5C). There was no push-pull effect inasmuch as the magnitudes of the decreases in pressure (ΔPull) were not different. Arterial pressure was stable from second 3 to second 9 during +1 Gz gravitational stress.

**DISCUSSION**

The major findings of this study are twofold. First, the push-pull effect is abolished when autonomic ganglionic neurotransmission is inhibited by hexamethonium. Arterial baroreceptor reflexes are often suggested to contribute to or cause the push-pull effect, and our findings support this supposition. However, because hexamethonium inhibits all autonomic reflexes, it is possible that the cardiopulmonary mechanoreceptor reflexes and/or vestibular-autonomic responses contribute as well. Second, substantially lowering or raising baseline arterial blood pressure also abolishes the push-pull effect, probably by disrupting baroreflex function.

Indirect evidence for the contribution of baroreceptor reflexes in eliciting the push-pull effect is provided in a number of studies. For example, the bradycardia that attends the push occurs more quickly than does the tachycardia that eventually accompanies the subsequent pull (8). As a consequence, heart rate is “too low” early on during +Gz stress when the +Gz stress is preceded by exposure to −Gz (1). Also, Doe et al. (5) imposed rapid, brief alterations in isolated carotid sinus pressure in anesthetized dogs and measured vasmotor responses. They found that the reductions in vascular resistance elicited by increases in carotid sinus pressure were faster and more profound than the vasoconstriction induced by decreases in sinus pressure (5). The relative sluggishness of vasoconstrictor responses could contribute to the exaggerated hypotension early on during +Gz gravitational stress when it follows −Gz stress. Again, 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 gravity is suddenly added to the pressure-reducing effects of the (slowly reversing) baroreceptor-induced bradycardia and peripheral vasodilation. This leads to an unexpectedly large fall in ELBP. Our results indicate that inhibition of autonomic function with hexamethonium likely abolishes the pressure-lowering adjustments initiated during brief −Gz stress and thereby normalizes the fall in arterial pressure that attends +Gz gravitational stress independent of the recent G history. For example, if head-down tilt produced the push-pull effect by altering the mechanical loading of the ventricles or by altering myogenic stimuli, we would expect the push-pull effect to persist across the conditions studied, and this was not the case.

**Responses to +1 Gz gravitational stress.** When autonomic function is intact, arterial pressure initially falls and then undergoes partial restoration from second 3 to second 9 after the onset of +1 Gz gravitational stress under both the control and push-pull conditions. Treatment with hexamethonium reversed this normal recovery of pressure; in fact, pressure falls further from second 3 to second 9. This observation indicates both the efficacy of autonomic inhibition induced by hexamethonium and the importance of the autonomic sys-
tem in producing this recovery. As expected, this lack of recovery persisted when baseline arterial pressure
was manipulated with phenylephrine infusion after treatment with hexamethonium. A lack of recovery of
pressure was also observed in the three conditions in which we altered baseline arterial pressure before
hexamethonium. This lack of recovery of pressure despite intact ganglionic transmission likely stems from
the baroreflex-suppressing effects of these interventions as discussed below. The response of ELBP from second 3 to second 9 of
+1 G gravitational stress followed one of three basic patterns. First, as noted above, pressure was partially
restored toward baseline when autonomic function was intact and no further manipulations were performed.
Second, ELBP remained stable over this period, or third, ELBP fell over this period. By and large, a
consistent finding was that when ELBP fell below ~60 mmHg during head-up tilt, ELBP remained relatively
stable over this period despite being far above 60 mmHg.

Push-pull gravitational stress. Under control condi-
tions, we found a statistically significant push-pull effect in that ΔPull (second 3 ELBP less baseline
ELBP) was significantly greater for push-pull vs. control gravitational stress. The direction and magnitude
of the changes observed are comparable to previously reported values for this species (7, 10) and are in line
with human values (2–4, 6, 8) given the fivefold greater heart-to-eye distance in humans.

We found that hexamethonium abolished the push-
pull effect (Fig. 5A). Thus our hypothesis was an-
swered in the affirmative. However, treatment with hexa-
methonium alone did not specifically test the role of the
autonomic nervous system in producing the push-pull effect because hexamethonium also lowered baseline
arterial pressure. Thus the possibility remained that an unidentified, nonspecific factor associated with a
lower arterial pressure may have abolished the push-pull effect after hexamethonium. To overcome this
limitation, phenylephrine was infused at a dose selected to return arterial pressure to prehexamethonium
levels, and we found that the lack of a push-pull effect persisted. The observation that the push-pull effect was
not restored after restoration of ELBP to control levels provides further support for the autonomic reflexes as
a cause of the push-pull effect. That is, if simply reduc-
ing baseline arterial pressure had abolished the push-
pull effect independent of the other alterations in au-
tonomic function caused by hexamethonium, then restoring arterial pressure with phenylephrine would
be expected to reestablish the push-pull effect. This did not occur. We also raised baseline arterial pressure
further by increasing the rate of infusion of phenylephrine and found the lack of a push-pull effect persisted.
We also sought to test the influence on the push-pull
effect of altering baseline arterial pressure by the in-
fusion of vasoactive substances and by alterations in
circulating blood volume when ganglionic transmission
was intact. We found that lowering baseline ELBP by
nitroprusside infusion or by hemorrhage abolished the
push-pull effect. Also, the push-pull effect was abol-
ished when baseline arterial pressure was elevated by
infusion of phenylephrine. In contrast to the foregoing
argument, these observations could be interpreted as
evidence that altering baseline pressure alone abol-
ishes the push-pull effect by an unidentified, nonspe-
cific mechanism. However, there are two lines of rea-
soning that argue against this possibility, both of
which relate to a possible baroreflex-inhibiting action
of these interventions. The first argument relates to
the sigmoid shape of the characteristic baroreflex
curve. For example, the tendency for phenylephrine
infusion to raise pressure will initially be counteracted
by baroreflex-mediated sympathetic withdrawal. Thus,
in order for phenylephrine infusion to be effective in
raising pressure, it must first overwhelm the arterial
baroreflexes. The opposite argument holds for at-
tempts to lower pressure via nitroprusside infusion or
hemorrhage. Thus one explanation for these results is
that the prevailing arterial pressure was forced out
onto the relatively flat portions of the sigmoid barore-
flex curve so that even though baroreflex function (gan-
glionic transmission) was intact, the reflex was ren-
dered ineffective. That is, the relatively small
alterations in arterial pressure induced by tilting may
have failed to alter baroreceptor firing because pres-
sure was too high in the case of phenylephrine infusion
or too low in the cases of nitroprusside infusion and
hemorrhage. On the other hand, the vestibular-auton-
omic system is presumably unaffected by the changes
in arterial pressure evoked by these interventions.
Thus the lack of a push-pull effect under these condi-
tions argues against the vestibular-autonomic system
playing an important role in producing the push-pull
effect.

The second argument relates to the pharmacological
effects of the vasoactive substances acting at the vas-
cular smooth muscle membrane. In this instance, the
changes in pressure elicited by tilting may have caused
the appropriate changes in baroreceptor firing, but the
resulting physiological alterations in neurotransmitter
release may have failed to alter vascular smooth mus-
cle tone owing to the overwhelming pharmacological
influence of the drug. This phenomenon might also
impair vestibular-autonomic reflexes. In any event, the
observation that the drop in pressure with head-up tilt
during nitroprusside infusion and after hemorrhage
was greater than after hexamethonium when there
could be no neural responses provides further evidence
that these interventions must have greatly impaired
reflex function. Lastly, it should be noted that the
impaired volume status after hemorrhage could have
led to exaggerated reductions in cardiac output with
head-up tilt and this could contribute to the greater pressure fall.

In summary, the push-pull effect is eliminated by administration of hexamethonium, and the lack of a push-pull effect persists when baseline arterial pressure is restored to control levels or higher by phenylephrine infusion. Also, infusion of vasoactive drugs and hemorrhage eliminate the push-pull effect, likely by inhibiting baroreflex function via threshold and saturation phenomena. Thus autonomic reflexes appear to contribute substantially to the production of the push-pull effect in anesthetized rats in which gravitational stress is imposed by tilting.

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REFERENCES