Hemodynamic effects of blood loss during a passive response to a stressor in the conscious rabbit

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Schadt, James C., and Eileen M. Hasser. Hemodynamic effects of blood loss during a passive response to a stressor in the conscious rabbit. Am J Physiol Regul Integr Comp Physiol 286: R373–R380, 2004. First published October 30, 2003; 10.1152/ajpregu.00351.2003.—In the conscious rabbit, exposure to an air jet stressor increases arterial pressure, heart rate, and cardiac output. During hemorrhage, air jet exposure extends the blood loss necessary to produce hypotension. It is possible that this enhanced defense of arterial pressure is a general characteristic of stressors. However, some stressors such as oscillation (OSC), although they increase arterial pressure, do not change heart rate or cardiac output. The cardiovascular changes during OSC resemble those seen during freezing behavior. In the present study, our hypothesis was that, unlike air jet, OSC would not affect defense of arterial blood pressure during blood loss. Male New Zealand White rabbits were chronically prepared with arterial and venous catheters and Doppler flow probes. We removed venous blood until mean arterial pressure decreased to 40 mmHg. We repeated the experiment in each rabbit on separate days in the presence and absence (SHAM) of OSC. Compared with SHAM, OSC increased arterial pressure 14 ± 1 mmHg, central venous pressure 3.3 ± 0.4 mmHg, and hindquarter blood flow 34 ± 4% while decreasing mesenteric conductance 32 ± 3% and not changing heart rate or cardiac output. During normotensive hemorrhage, OSC enhanced hindquarter and renal vasoconstriction. Contrary to our hypothesis, OSC (23.5 ± 0.6 ml/kg) increased the blood loss necessary to produce hypotension compared with SHAM (16.8 ± 0.6 ml/kg). In nine rabbits, OSC prevented hypotension even after a blood loss of 27 ml/kg. Thus a stressful stimulus that resulted in cardiovascular changes similar to those seen during freezing behavior enhanced defense of arterial pressure during hemorrhage.

In conscious animals, the response to blood loss is biphasic. During the normotensive phase, arterial pressure is well maintained by regional sympathetic vasoconstriction. The hypotensive phase is characterized by a sudden decrease in arterial pressure accompanied by sympathoinhibition and global vasodilation (13). In conscious rabbits, exposure to an air jet stressor increases the blood loss necessary to produce hypotension but does not qualitatively alter the biphasic response to hemorrhage (12).

Exposure to an air jet stressor in the conscious rabbit results in a response similar to a defense reaction with the characteristic increase in heart rate and cardiac output (11). However, the defense reaction is not the only cardiovascular response shown in stressful situations. Some species exhibit what appears to be a more passive response characterized by decreased motor activity and no change or an actual decrease in heart rate and/or cardiac output. This behavior has been referred to as freezing behavior and is seen in many animals, including the woodchuck (18) and the rabbit (17). It is not known how freezing behavior might affect the response to blood loss.

In the present study, we used an oscillation stressor (OSC) in the conscious rabbit to produce a cardiovascular response similar to that seen during freezing behavior (11). Although OSC increases arterial pressure and skeletal muscle blood flow like air jet, it does not increase heart rate or cardiac output (11). Our hypothesis was that OSC would not affect a rabbit’s ability to defend arterial blood pressure during hemorrhage. This study and the earlier reports (11, 12) were done concurrently and, in many cases, used the same rabbits.

METHODS

Preparation. This study was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (DHHS (DHHS) Publication No. (NIH) 85–23, revised 1985, Office of Science Health Reports, DRR/NIH, Bethesda, MD 20205) and was approved by the University of Missouri-Columbia Animal Care and Use Committee. Male New Zealand White rabbits (n = 34), weighing 2.5–3.1 kg [2.76 ± 0.03 (SE) kg], were anesthetized with halothane, and a midline laparotomy was performed. Catheters were implanted in the abdominal aorta and vena cava (2) for recording arterial pressure and withdrawing blood or injecting drugs, respectively. In seven rabbits, a second vena caval catheter (tip in the thoracic cavity) was implanted for measurement of central venous pressure. All rabbits had one or two Doppler flow probes. Probes were placed on the abdominal aorta near the iliac bifurcation (hindquarter blood flow, n = 16); the cranial mesenteric artery (n = 16); the left renal artery (n = 12); and/or the ascending aorta (cardiac output determination, n = 7). For animals in which cardiac output was measured, the ascending aortic flow probe was implanted 2 wk before abdominal surgery (pentobarbital sodium anesthesia and artificial ventilation). Flow probe wires and catheters were exteriorized in the dorsal cervical region. Antibiotics (60,000 IU im; Pen BP-48; Pfizer) were given the day before and the day after surgery. Animals recovered for a minimum of 10 days before the first experiment, and subsequent experiments in the same animal were separated by at least 4 days. We have previously shown that hemodynamic parameters, hematocrit, and body weight (15) as well as the hypotensive blood loss (5) are not altered by repeated hemorrhage experiments separated by an interval of 4 days.

During experiments, the arterial and thoracic venous catheters were connected to pressure transducers (Statham P23Dc). Flow probe wires were connected to flowmeters (Triton model 100). Blood was withdrawn from the abdominal venous catheter into sterile 60-ml syringes using a syringe pump (Sage Instruments model 351). Heart rate (triggered by arterial pressure), pulsatile arterial blood pressure, cen...
tral venous pressure, and pulsatile and mean blood flow velocities were monitored on a chart recorder (Gould model 3800). Pulsatile pressures and flow velocities were also recorded (Neuro-Data model DR-886) on VCR tape and analyzed on- or off-line (RC Electronics). Animals were fasted 15–23 h before experimentation. During experiments, rabbits were placed in a box (33 × 15 × 18 cm, inside dimensions) with a 6-cm-diameter hole in the front. The rabbits were acclimated to the box before experiments. We used OSC as a stressful stimulus. During OSC experiments, the rabbit box was placed on a platform that moved counterclockwise in 2-cm-diameter circles 48 times/min. This stimulus produces cardiovascular changes similar to those observed during freezing behavior (i.e., increased arterial pressure, bradycardia or no change in heart rate, and no change in cardiac output; see Ref. 11).

Experimental protocol. Rabbits were heparinized (sodium heparin; 2000 units iv; Eli Lilly) and allowed 10–30 min to reach a stable cardiovascular baseline. After a 1-min control period, we started OSC or continued with no stimulation (SHAM). OSC or SHAM continued for the remainder of the experiment. After the start of stimulation (2 min), we began removing blood from the abdominal venous catheter at a rate of 8–9 ml/min and continued 5 ml after mean arterial pressure decreased to 40 mmHg. If blood loss reached 27 ml/kg (45% percent of total blood volume) before mean arterial pressure reached 40 mmHg, we stopped blood removal and terminated the experiment. At the conclusion of the experiment, we reinfused the removed blood. The first 50–60% of the shed blood was reinfused at 8–9 ml/min and the last 40–50% at 5–6 ml/min. Each animal was hemorrhaged under both SHAM and OSC conditions, and the order of experiments among rabbits was varied to provide a balanced design.

Analysis of data. Because the blood loss required to reduce arterial pressure varies among rabbits (14), this parameter was normalized to allow statistical comparisons. The hypotensive blood loss, that necessary to decrease mean arterial pressure to 40 mmHg, was set equal to 100%. Because 5 ml of blood were removed after mean arterial pressure reached 40 mmHg, the response to hemorrhage could be compared among animals from 0 to 105% of hypotensive blood loss. Because of the biphasic nature of the cardiovascular changes during blood loss, the statistical analysis was performed separately on the normotensive and hypotensive phases (6). The steep decline in arterial blood pressure begins at 80–85% of the hypotensive blood loss. Thus the normotensive phase extended from 0 to 80% and the hypotensive phase from 85 through 105% of hypotensive blood loss. Hemodynamic changes during blood loss were analyzed by two-way repeated-measures ANOVA. The independent variables were treatment (i.e., OSC or SHAM) and blood loss (i.e., percent of hypotensive blood loss). When the ANOVA demonstrated a significant (P ≤ 0.05) primary effect of treatment or a significant interaction of treatment and blood loss, differences between individual means were assessed by a least-significant difference (LSD) test (19). The dashed lines in Figs. 5–7 enclose parameter values equal to the SHAM ± 1 LSD. Thus OSC data points outside the area enclosed by the dashed lines are significantly different from SHAM (P ≤ 0.05). Data points in the text, Figs. 4–7, and Table 2 are shown as means ± 1 SE (computed from the pooled estimate of the sample variance in the associated ANOVA). Regional blood flows and vascular conductances were normalized to prestressor, baseline levels.

Under the conditions of these experiments (blood loss ≤ 27 ml/kg), 9 of 34 rabbits tested did not become hypotensive during blood loss with OSC. We analyzed results from those 9 rabbits separately from the 25 rabbits that became hypotensive. We compared heart rate and mean arterial pressure between the two groups at the following three times (Table 2): 1) before OSC or SHAM (50-s average immediately before the beginning of the stimulation); 2) during stimulation but before hemorrhage (50-s average during stimulation and immediately before the beginning of the hemorrhage); and 3) at the end of the blood removal (a 6-s average centered on the nadir of arterial blood pressure immediately after mean arterial pressure reached 40 mmHg). These data were analyzed by 2-way repeated-measures ANOVA (see above) with treatment and stage of the experiment as the independent variables (Table 2).

To identify factors associated with enhanced defense of arterial pressure, we examined the correlation between cardiovascular changes resulting from OSC and the associated increase in hypotensive blood loss. We subtracted cardiovascular and hypotensive blood loss values during SHAM from values during OSC. We performed simple linear regression on the resultant differences. Significance of the correlations was assessed by one-way ANOVA.

RESULTS

Effects of OSC on the hemodynamic response to blood loss. Figures 1 and 2 show examples of the hemodynamic response to hemorrhage with no stimulation (SHAM) and during OSC in two rabbits. OSC increased arterial pressure, transiently decreased or did not change heart rate and cardiac output, and increased central venous pressure. OSC-induced changes in

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**Fig. 1.** Original records of the hemodynamic effects of hemorrhage in one rabbit during sham stimulation (SHAM; A) and oscillation (OSC; B). Sensory stimulation began 2 min before hemorrhage. AP, arterial pressure; MAP, mean arterial pressure; HR, heart rate; HQ, hindquarters; REN, renal; CO, cardiac output; FLOW, blood flow velocity.
flow varied among different vascular beds and also among animals within a particular vasculature (Figs. 1–3). OSC increased the hypotensive blood loss (i.e., the blood loss necessary to decrease mean arterial pressure to 40 mmHg). However, it did not alter the fundamental biphasic pattern of arterial pressure maintenance followed by hypotension.

Average changes in mean arterial pressure and heart rate are plotted against the actual blood loss in Fig. 4A. Figure 4B shows the increase in the hypotensive blood loss during OSC (23.5 ± 0.3 ml/kg) compared with SHAM (16.8 ± 0.3 ml/kg) for animals that became hypotensive during OSC (25 of 34).
Fig. 5. Effects of OSC or SHAM on MAP (n = 25; A), HR (n = 25; B), and CVP (n = 6; C) during hemorrhage. Blood loss (x-axis) is normalized to percent of total blood loss (%TOTAL), where the loss required to reduce MAP to 40 mmHg = 100% (i.e., hypotensive blood loss, see METHODS for details). Blood removal began at 0 on the x-axis, and sensory stimulation began 2 min earlier. The pooled estimate of SE (from ANOVA) is plotted on the ends of the curves. Dotted lines are SHAM values ±1 least-significant difference (α = 0.05). During the normotensive phase, there was a significant interaction between blood loss and OSC for MAP, HR, and CVP. During the hypotensive phase, there was a significant interaction between blood loss and OSC for MAP and HR and a significant main effect of blood loss for CVP.

Figures 5–7 show the hemodynamic changes plotted against blood loss normalized to the hypotensive blood loss (see METHODS). The increased blood removal required during OSC (i.e., enhanced defense of arterial pressure) is obvious in Fig. 4, A and B. However, when the response to blood loss is plotted as a percentage of the hypotensive blood loss, the enhanced defense of arterial pressure during OSC is not as apparent (Figs. 5–7).

OSC increased mean arterial pressure (82 ± 1 vs. 68 ± 1 mmHg in SHAM; Figs. 1, 2, 4A, and 5). By the end of the normotensive phase of the response to hemorrhage (80% of the total blood loss), mean arterial pressure was unchanged in the SHAM experiments (66 ± 1 mmHg) but had decreased significantly in the OSC experiments (albeit after a larger blood loss) to 72 ± 1 mmHg. During the hypotensive phase (85–105% of the total blood loss), arterial pressure decreased rapidly to 31 ± 1 and 30 ± 1 mmHg in SHAM and OSC experiments, respectively. This similar nadir was reached despite a significantly greater blood loss during OSC. Although the rate of this decrease was similar, the actual change in arterial pressure during the hypotensive phase was greater with OSC. Thus the change in mean arterial blood pressure during both phases of the response to hemorrhage was modified by OSC. However, the modification was due in part to the OSC-induced increase in arterial pressure before blood loss.

OSC usually resulted in a transient bradycardia (Figs. 1–3). However, average heart rate was not different between OSC and SHAM at the beginning of hemorrhage (143 ± 3 and 149 ± 3 beats/min, respectively, Figs. 4A and 5). In SHAM experiments, heart rate began to increase at the beginning of blood loss. OSC delayed the heart rate increase. Despite this delay and the difference in blood loss, heart rates were similar by the end of the normotensive phase (218 ± 3 and 219 ± 3 beats/min for SHAM and OSC, respectively). Maximum heart rate occurred early in the hypotensive phase and was greater during OSC than during SHAM (251 ± 2 and 239 ± 2 beats/min, respectively). After the maximum was reached, heart rate decreased. Heart rate was greater during OSC (228 ± 2 beats/min) than during SHAM (213 ± 2 beats/min) at the end of hemorrhage. The heart rate response to normotensive and hypotensive blood loss was modified by OSC.

Central venous pressure was increased by OSC compared with SHAM (4.0 ± 0.4 vs. 0.6 ± 0.4 mmHg, respectively; Figs. 2 and 5). However, it decreased more rapidly during
blood loss with OSC than during SHAM. As a result, central venous pressure was similar under the two conditions from 40% through 105% of the hypotensive blood loss. OSC significantly affected the central venous pressure changes during the normotensive phase but not during the hypotensive phase.

Exposure to OSC did not change cardiac output (−5 ± 2% for both SHAM and OSC; Figs. 1 and 6) at the start of hemorrhage. In addition, the decrease in cardiac output over both phases of the response to hemorrhage was similar for SHAM and OSC. However, because blood loss was greater during OSC, OSC actually delayed the decrease in cardiac output (e.g., Fig. 1). OSC decreased total peripheral conductance (−10 ± 3% vs. −1 ± 3% for SHAM), and the difference was maintained through the normotensive phase (Fig. 7). In addition, although total peripheral conductance decreased during the normotensive phase with SHAM stimulation, it did not during OSC. During the hypotensive phase, total peripheral conductance increased to similar levels during OSC or SHAM. Thus OSC resulted in peripheral vasoconstriction and enhanced defense of cardiac output during normotensive hemorrhage.

The OSC-induced changes in hindquarter blood flow (Fig. 6) and conductance (Fig. 7) were quite variable among rabbits. Although the average change in hindquarter flow during OSC was a 36 ± 4% increase, individual changes ranged from a 138% increase to a 33% decrease (e.g., Figs. 1–3). Similarly, although the mean change in hindquarter conductance was a 13 ± 3% increase, individual changes ranged from a 98% increase to a 47% decrease. Normotensive hemorrhage was accompanied by hindquarter vasoconstriction, as indicated by the simultaneous decreases in flow and vascular conductance. The rate of this decrease was greater during OSC (Fig. 6 and 7). Compared with SHAM, OSC almost doubled the slope of the relationship between blood loss and hindquarter blood flow (−2.97 ± 0.64 during OSC and −1.60 ± 0.17 during SHAM). During the hypotensive phase, the continued decrease in hindquarter blood flow (Fig. 6) and the dramatic vasodilation (Fig. 7) were similar for OSC and SHAM. Thus, although OSC increased vasoconstriction in the hindquarter vasculature during maintenance of arterial pressure, the stressor had no effect on the vasodilatory response during the hypotensive phase.

Mesenteric flow was initially reduced by OSC (Figs. 2 and 3). However, this effect was transient. Thus mesenteric flow was statistically similar for the two experiments throughout the normotensive phase. OSC decreased mesenteric conductance significantly at the start of hemorrhage (−30 ± 3% for OSC compared with 3 ± 3% for SHAM; Fig. 7). Mesenteric blood flow and conductance were well maintained during the normotensive phase under either stimulation condition (Figs. 6 and 7). Mesenteric blood flow decreased and mesenteric conductance increased in a statistically similar way during the hypotensive phase with either OSC or SHAM (Figs. 6 and 7). Thus, although OSC caused mesenteric vasoconstriction, it did not qualitatively alter the mesenteric response to hemorrhage.

OSC transiently reduced renal blood flow (Fig. 1), but renal blood flow (Fig. 6) and conductance (Fig. 7) were not different between OSC and SHAM at the start of hemorrhage. However, during OSC but not during SHAM, renal blood flow decreased during the normotensive phase. The result was that renal blood flow and conductance were significantly lower at the end of the normotensive phase during OSC compared with

![Diagram](image-url)

**Fig. 7. Effects of OSC or SHAM on total peripheral (TP) conductance (CON; n = 5; A), HQ CON (n = 13; B), CM CON (n = 13; C), and renal CON (n = 6; D) during hemorrhage. Values for all parameters are shown as percent change from prestressor level. See Fig. 5 and METHODS for other details. During hemorrhage, the stressor had no effect on the vasodilatory response during the hypotensive phase.**

**Table 1. Regression of oscillation-induced changes in hypotensive blood loss (i.e., blood loss to MAP = 40 mmHg) on oscillation-induced changes in hemodynamic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
<th>F(df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>0.52</td>
<td>−0.74</td>
<td>0.76</td>
<td>32.1 (1,23)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HR</td>
<td>−0.05</td>
<td>6.34</td>
<td>0.25</td>
<td>1.51 (1,23)</td>
<td>&lt;0.23</td>
</tr>
<tr>
<td>CVP</td>
<td>2.25</td>
<td>3.37</td>
<td>0.41</td>
<td>0.82 (1,4)</td>
<td>&lt;0.42</td>
</tr>
<tr>
<td>HQ Flow</td>
<td>−0.05</td>
<td>7.32</td>
<td>0.59</td>
<td>5.75 (1,11)</td>
<td>&lt;0.04*</td>
</tr>
<tr>
<td>HQ CON</td>
<td>−0.06</td>
<td>6.41</td>
<td>0.67</td>
<td>8.96 (1,11)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>CM CON</td>
<td>0.06</td>
<td>5.92</td>
<td>0.38</td>
<td>1.87 (1,11)</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>CM CON</td>
<td>0.03</td>
<td>6.02</td>
<td>0.17</td>
<td>0.35 (1,11)</td>
<td>&lt;0.57</td>
</tr>
<tr>
<td>Renal Flow</td>
<td>0.13</td>
<td>6.41</td>
<td>0.46</td>
<td>1.09 (1,4)</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>Renal CON</td>
<td>−0.10</td>
<td>6.09</td>
<td>0.26</td>
<td>0.29 (1,4)</td>
<td>&lt;0.62</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>−0.02</td>
<td>6.58</td>
<td>0.84</td>
<td>7.43 (1,3)</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>TP CON</td>
<td>−0.20</td>
<td>3.75</td>
<td>0.94</td>
<td>21.53 (1,3)</td>
<td>&lt;0.02*</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; HQ, hindquarter; CM, cranial mesenteric; Flow, blood flow velocity; CON, conductance; TP, total peripheral; df, degrees of freedom. *Significant correlation.
SHAM. Thus renal vasoconstriction was evident in the normotensive phase during OSC but not during SHAM. During the hypotensive phase, values for renal blood flow and conductance were decreased by OSC except at the end of blood removal (i.e., 105% in Figs. 6 and 7) when the values for OSC and SHAM were statistically similar.

**OSC-induced hemodynamic changes and the increase in hypotensive blood loss.** The increased blood loss during OSC was positively correlated with the OSC-induced changes in arterial pressure (Table 1). That is to say, the greater the increase in arterial pressure during OSC, the greater the hypotensive blood loss. The OSC-induced increase in hypotensive blood loss was negatively correlated with changes in hindquarter flow and conductance and total peripheral conductance (Table 1). In other words, OSC-induced hindquarter and/or systemic vasoconstriction was associated with an increased ability to maintain arterial pressure.

**Experiments in which OSC prevented the onset of hypotension.** In nine rabbits, OSC prevented (or delayed) the fall in arterial pressure even after a blood loss equal to 27 ml/kg (i.e., ~45% of total blood volume). An example is shown in Fig. 3. Table 2 shows hemodynamic values during the experiments for rabbits that did (n = 25) and did not (n = 9) get hypotensive during OSC. The baseline values for heart rate and arterial blood pressure were similar between the two groups. In addition, the heart rate and arterial pressure response and the hypotensive blood loss during SHAM were similar between the two groups. However, rabbits that did not become hypotensive during OSC had a larger increase in mean arterial pressure and a significant decrease in heart rate in response to the OSC stimulus (Table 2). In eight of the nine rabbits that did not get hypotensive, OSC was stopped after the blood loss maximum was reached. One of these experiments is shown in Fig. 3. In this example, we also measured hindquarter and mesenteric blood flow. After stopping blood withdrawal, turning off OSC (Fig. 3) resulted in an immediate increase in mesenteric flow and conductance. This mesenteric vasodilation was followed closely by hindquarter vasodilation and hypotension. The nadir in arterial pressure (27±1 mmHg) in these rabbits was similar to that reached during their SHAM experiments (28±1 mmHg) as well as SHAM (29±1 mmHg) or OSC (28±1 mmHg) experiments in rabbits that did get hypotensive during OSC (Table 2).

**DISCUSSION**

The defense reaction could be considered the prototypical cardiovascular response to a stressor and is associated with an active response (i.e., fight or flight). It is characterized by increases in arterial blood pressure, heart rate, cardiac output, and skeletal muscle blood flow. In the conscious rabbit, this specialized cardiovascular reaction to a stressor such as air jet (11) modifies the response to hemorrhage and increases the blood loss required to produce hypotension (12). However, the defense reaction is not the only cardiovascular response to a stressful or threatening stimulus. Some animals show another response that is often referred to as freezing. Freezing is associated with decreased motor activity and is often seen in the context of fear-producing situations where hiding and/or increased vigilance are a high priority. Some of the hemodynamic changes during these two different responses to a stressor are similar (e.g., increased arterial pressure and skeletal muscle blood flow). However, the cardiac changes differ. The defense reaction is accompanied by increased heart rate and cardiac output. In contrast, freezing is normally accompanied by a decrease or no change in heart rate and cardiac output (4, 11, 16). Some animals such as the rabbit (11) and the woodchuck (16) may show either response or both responses sequentially (16), depending on the situation. Indeed, in the anesthetized rabbit, studies suggest these two very different responses to stressors may be produced by different brain regions. Cardiovascular changes similar to those seen during freezing and the defense reaction can be produced by electrical stimulation of the medial, lateral hypothalamus, and the dorsomedial, posterior hypothalamus (8a).

We have previously shown that OSC produces a cardiovascular response resembling that seen during freezing behavior (11). That is, OSC increased arterial pressure and hindquarter blood flow but did not increase heart rate or cardiac output. In other words, OSC produced hemodynamic changes suggestive of a more passive response to a stressor (i.e., freezing; see Ref. 11). Our initial hypothesis is that, unlike air jet, OSC would not alter maintenance of arterial pressure during blood loss. Our results are not consistent with this hypothesis. The important new findings were that OSC qualitatively and quantitatively alters the cardiovascular response to blood loss. In addition, like the air jet stressor (12), OSC enhances defense of arterial blood pressure during blood loss. OSC appears to be more effective than air jet in terms of extending maintenance of arterial pressure during blood loss. In our earlier study (12), air jet increased the hypotensive blood loss ~14% (16.9±0.2 and 19.3±0.2 ml/kg for SHAM and air jet, respectively). In the present study, OSC extended the hypotensive blood loss almost 40% (16.8±0.4 and 23.5±0.4 ml/kg for SHAM and OSC, respectively). In nine rabbits, OSC...
actually delayed (or prevented) the onset of hypotension beyond our blood loss maximum of 27 ml/kg (e.g., Fig. 3). In our experience, air jet has never produced this result during hemorrhage. Compared with rabbits that did develop hypotension during hemorrhage in the presence of OSC, these nine rabbits seemed to be at one extreme in terms of their response to a stressor. For example, they had greater increases in mean arterial pressure and sustained decreases in heart rate in response to OSC (Table 2). In addition, they showed a greater increase in heart rate during exposure to the air jet stressor, although they did all develop hypotension during subsequent blood removal (data not shown). Finally, when OSC was turned off after the blood loss limit (27 ml/kg) was reached, mean arterial pressure fell quickly (Fig. 3) to levels similar to rabbits that became hypotensive during OSC (Table 2).

We used simple linear regression to identify oscillation-induced hemodynamic changes that were correlated with the increase in hypotensive blood loss (Table 1). The increase in hypotensive blood loss during oscillation was positively correlated with changes in mean arterial pressure and negatively correlated with changes in hindquarter blood flow and conductance and total peripheral conductance. The positive correlation with arterial pressure is consistent with the results from the rabbits that did not develop hypotension during oscillation (Table 2). These rabbits had a larger increase in arterial pressure during oscillation than the rabbits that did become hypotensive. The negative correlation between blood loss and peripheral vasodilation is also consistent with the arterial pressure-blood loss correlation. Vasodilation or regional increases in blood flow might act to decrease arterial pressure and thus decrease the effects of oscillation on blood loss.

Acccentuated peripheral vasoconstriction before and during hemorrhage is a possible explanation for the enhanced defense of arterial pressure during oscillation. For example, even considering the increase in hypotensive blood loss, hindquarter conductance decreased at a faster rate during hemorrhage in the presence of oscillation. Enhanced vasoconstriction in the renal vasculature may also have contributed. Renal blood flow was significantly decreased at the end of the normotensive phase during OSC but not during SHAM (Fig. 6). It could be argued that the increased blood loss required to produce hypotension during OSC accounted for the enhanced decrease in renal flow. However, renal flow was significantly reduced after a blood loss of 16–17 ml/kg. A similar volume loss during SHAM resulted in hypotension.

During exposure to a stressor, an increase in central blood volume resulting from venoconstriction (8) could delay the onset of the hypotensive phase of hemorrhage. It has been suggested that the onset of hypotension during blood loss is triggered by stimulation of left ventricular receptors due to increased cardiac sympathetic activity and reduced ventricular filling (9). If this is the case, the delayed increase in heart rate with hemorrhage during OSC might reflect a delayed increase in cardiac sympathetic drive and also contribute to maintained cardiac filling. The delayed increase in inotropic stimulation of the heart coupled with increased volume might then delay activation of the ventricular mechanoreceptors and thus delay the onset of the hypotensive phase. Although we did not directly measure venous capacitance or changes in central blood volume, the observed increase in central venous pressure with OSC (Fig. 5) is at least consistent with an increase in central blood volume.

There was a small decrease in mean arterial pressure during normotensive hemorrhage in the oscillation experiments (~12%). However, the bulk of the decrease occurred during the hypotensive phase. Once pressure began to fall, it fell to virtually the same level in both experiments. This is similar to what was observed with air jet (11). In addition, as with air jet, this suggests that the pressor systems activated by oscillation and subsequent hemorrhage were either turned off or ineffective during the hypotensive phase. One possible explanation is a humoral mechanism such as the renin-angiotensin system, which acts in conjunction with the sympathetic nervous system. For example, the renin-angiotensin system might be activated by OSC as a result of the OSC-induced decrease in renal blood flow. If so, the resulting increase in ANG II would potentiate the effects of sympathetic activation during the normotensive phase. However, this mechanism would be less effective during the hypotensive phase when sympathetic activity is significantly reduced.

Although it has been suggested that baroreflex function is compromised during stressful sensory stimulation (4), this does not appear to be true for control of heart rate in conscious rats (3) or rabbits (11). Similar information about baroreflex control of vascular conductance is not available. This information would be especially relevant to this study because baroreflex-mediated vasoconstriction in skeletal muscle is essential to the initial maintenance of arterial pressure during hemorrhage (1, 7, 10, 13). In this study, although we did not evaluate baroreflex sensitivity directly, we did find that oscillation enhanced the relationship between hindquarter vasoconstriction and blood loss. Because this relationship is dependent on the arterial baroreflex, it appears that OSC did not compromise baroreflex-mediated control of skeletal muscle blood flow during hemorrhage.

In conclusion, the oscillation stressor enhanced defense of arterial blood pressure during hemorrhage in conscious rabbits. Skeletal muscle (and perhaps renal) vasoconstriction was enhanced during oscillation. The enhanced ability to defend arterial blood pressure may be because of increased activation of sympathetic nerves and/or a humoral system such as the renin-angiotensin system, which works synergistically with the sympathetic nervous system.

**Perspectives**

Freezing appears to be a somewhat passive response to a stressful sensory stimulus. In fact, it may be better suited than the classic defense reaction as a response to something novel in the environment or during an attempt to “hide” from a predator. The hemodynamic changes may represent readiness for an active response, but at a minimal energy cost to the animal in case the danger does not materialize. In free-ranging woodchucks (16), an acute stressor produces changes in heart rate characteristic of either the defense reaction or freezing, depending on the animal’s location relative to its burrow. Confrontation away from the burrow resulted in tachycardia, whereas animals confronted in their burrow always showed bradycardia. One woodchuck, confronted away from its burrow, initially showed tachycardia and flight. Upon reaching its burrow, the animal exhibited bradycardia.
Although the behavior and hemodynamic responses during freezing and the defense reaction are quite different, the effects of air jet and oscillation on the response to hemorrhage were at least qualitatively similar (12). Both stimuli extended the rabbit’s ability to maintain arterial blood pressure. That is, in the presence of a sensory stressor, the blood loss required to reduce arterial pressure was increased. However, the basic biphasic nature of the response was preserved. In other words, although the transition from vasoconstriction and arterial pressure maintenance to vasodilation and hypotension still occurred in the presence of stress, it occurred after a significantly greater blood loss. The biological advantage of this enhanced defense of arterial pressure during blood loss is not known.

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REFERENCES