Effect of carotid or aortic baroreceptor denervation on arterial pressure during hemorrhage in conscious dogs

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Thrasher, Terry N., and Cassandra Shifflett. Effect of carotid or aortic baroreceptor denervation on arterial pressure during hemorrhage in dogs. Am J Physiol Regulatory Integrative Comp Physiol 280: R1642–R1649, 2001.—We studied the effect of chronically denervating arterial or aortic baroreceptors (ABR; n = 6) or carotid baroreceptors (CBR; n = 7) on mean arterial pressure (MAP) and heart rate (HR) responses to hemorrhage in the dog. Neither denervation had a significant effect on basal MAP, the variability (standard deviation) of MAP, or resting HR. However, the breakpoint of MAP (defined as the volume of blood removed when MAP fell more than 10% below control and declined monotonically thereafter) was significantly reduced in dogs with only ABR functional (12.4 ± 1.4 ml/kg) compared with the volume in the intact condition (18.9 ± 1.8 ml/kg). In contrast, there was no difference in the breakpoint of the MAP at any time during hemorrhage in dogs with both CBR functional compared with their intact responses. In a different group of dogs (n = 6), responses were determined with both CBR operating and again after unilateral denervation, leaving only one CBR functional. Basal MAP and the variability of MAP were not altered in dogs with only 1 CBR functional, but the breakpoint (11.7 ± 1.4 ml/kg) during hemorrhage was significantly different compared with responses to two CBR (21.2 ± 2.3 ml/kg), and MAP fell to much lower levels. These results indicate that the CBR can compensate fully for loss of ABR during hemorrhage but not vice versa; and bilateral CBR inputs are required for normal responses to hemorrhage.

blood pressure; hypovolemia; blood volume; ventricular receptors; arterial baroreceptors

PREVIOUS STUDIES HAVE EXAMINED the effect of acutely blocking either carotid baroreceptor (CBR) or aortic baroreceptor (ABR) afferents on the ability to maintain mean arterial pressure (MAP) during hemorrhage. Compared with intact responses (i.e., both sets of receptors functional), removal of either set of baroreceptors results in a greater fall in MAP in anesthetized dogs (7, 11) and rabbits (9). Typically, the effect of removing CBRs has a greater effect compared with loss of ABRs, although Edis (7) observed only a small effect of removing the ABR. Hosomi and Sagaawa (10) studied responses to rapid loss of 10% of blood volume in conscious dogs in four experimental conditions: intact, during acute vagal cold block, 24–48 h after CBR denervation, and during acute vagal cold block 24–48 h after CBR denervation. They reported much larger decreases in MAP with only one set of baroreceptors functional compared with intact responses. Thus acutely removing either set of baroreceptors results in attenuated reflex control of MAP in response to blood loss.

Many anesthetic agents are known to alter either sympathetic or parasympathetic tone as well as altering basal MAP and heart rate (HR) (3). Furthermore, acute loss of afferent input from either CBR or ABR results in an increase in basal MAP and HR, caused at least in part by increased sympathetic outflow (6, 10). Thus the role of CBR and ABR in the reflex responses to hypovolemia deduced from acute preparations may differ significantly from the responses following adaptation to chronic loss of baroreceptor input. Surprisingly, there appear to be no studies that examined the effect of chronic loss of either set of baroreceptors on responses to hemorrhage. Therefore, the principal goal of this study was to determine the effect of chronic denervation of either ABR or CBR on MAP and HR responses to continuous hemorrhage in conscious dogs. We also compared MAP and HR responses to hemorrhage in dogs with both CBR (2CBR) functional and again after unilateral denervation of one set of CBR (1CBR).

METHODS

General. Experiments were performed on 19 adult mongrel dogs (14 male and 5 female) weighing between 19 and 32 kg. Nine dogs were pound source, adult mongrels that were conditioned for at least 30 days before use to ensure a good state of health. The other 10 dogs were farm-raised, purpose-bred mongrels (Butler Farms, Clyde, NY). The age of the purpose-bred dogs during experimentation ranged from 12 to 24 mo. There was no difference in resting MAP between the pound source and the purpose-bred animals, but, for unknown reasons, resting HR averaged ~20 beats/min higher in the purpose-bred dogs. All dogs were housed in a room maintained at 22 ± 2°C and 70% humidity with a 12:12-h light-dark cycle. Each day between 1600 and 1800, the dogs were administered oral prophylactic antibiotic treatment (400 mg sulfamethoxazole plus 80 mg trimethoprim) and fed a mixture of dry chow and canned food sufficient to maintain...

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a constant body weight. The food was always consumed within 10 min of presentation, and sodium intake on this diet averaged 2–3 meq·kg⁻¹·day⁻¹. Water was available ad libitum.

Patency and sterility of the vascular catheters were maintained by filling them with a mixture of heparin (1,000 U/ml; Elkins-Sinn, Cherry Hill, NJ) and penicillin G potassium (20,000 U/ml; Eli Lilly, Indianapolis, IN), which was replaced a minimum of every 72 h. To ensure that the dogs were free of infection throughout all aspects of the study, rectal temperatures were taken on a weekly basis and on the morning before experiments. Rectal temperatures were always below 39°C, indicating that the dogs were free of infection throughout the duration of the study.

**Surgical procedures.** In all surgical procedures, the dogs were sedated with acepromazine (0.2 mg/kg iv; Tech America, Elwood, KS) and anesthetized with pentobarbital sodium (25 mg/kg iv; Fort Dodge Laboratories, Fort Dodge, IA). In procedures involving thoracotomies, analgesia was provided with either oxymorphone (0.2 mg/kg sc; Numorphan, Dupont Pharmaceuticals) as required or a patch (Duragesic, Janssen Pharmaceuticals). During the postoperative periods following major surgical procedures, the dogs were treated with enrofloxacin (2.5 mg/kg; Baytril, Mobay, Shawnee, KS) twice daily to provide antibacterial coverage.

In some dogs (n = 13), the first procedure was to implant catheters in the abdominal aorta and vena cava via the femoral artery and vein. The catheters were tunnelled subcutaneously to exit between the shoulder blades and were protected by placement in a pouch sewn to the underside of a nylon jacket (Alice King Chatham Medical Arts, Los Angeles, CA). After experimentation in the intact condition, additional surgical procedures were performed to either remove the ABR (n = 6, 2 pound source and 4 purpose bred) or the CBR (n = 7, all pound source). The ABRs were denervated via a left thoracotomy at the fourth intercostal space. All visible nerves in the region of the arch were cut, and the adventitia of the aorta was stripped beginning at the origin of the carotid proximal to the lingual artery. The adventitia between the cranial thyroid artery and the lingual artery was stripped and painted with 5% phenol in ethanol bilaterally. The adventitia between the cranial thyroid artery and the lingual artery was stripped and painted with 5% phenol in ethanol bilaterally. This was reestablished to insure complete expansion of the lungs. The CBRs were denervated via a ventral midline incision. The internal carotid arteries were ligated and cut together with all other vessels originating from the external carotid proximal to the lingual artery. The adventitia between the cranial thyroid artery and the lingual artery was stripped and painted with 5% phenol in ethanol bilaterally. Subsequently, the ABRs were denervated in five of these dogs to produce sinoaortic denervation (SAD). In a separate group of six dogs (all purpose bred), the first surgical procedure was to denervate the ABR as above and implant catheters in the femoral artery and vein. After the recovery, responses to hemorrhage were determined with 2CBR functional. Subsequently, the carotid sinus was denervated on one side leaving these animals with 1CBR functional.

**Experimental protocols.** Experiments were conducted between 0800 and 1300 in a quiet room with the dog in a sling (Alice King Chatham Medical Arts), which provided support but minimal restraint. At each stage of the surgical preparation, MAP and HR were measured for 60–120 min at various times after surgery to determine if and when MAP and pressure variability (defined as the standard deviation of the MAP) returned to normal levels. Some dogs with only 1CBR functional required 3 wk of recovery before MAP and pressure variability had returned to predeneration levels. To standardize experimental conditions, all tests of responses to hemorrhage were conducted at least 3 wk after any surgical procedure to denervate baroreceptors. Furthermore, in some animals, the hemorrhage was repeated 6 to 12 wk following denervation to ensure that additional time for recovery did not alter the response.

On the day of an experiment, the dog was transported to the laboratory in a cart and allowed to settle for 30 min before beginning the protocol. The protocol began with a 20-min control period, followed by a hemorrhage with blood removed continuously at 1 ml·kg⁻¹·min⁻¹ via the venous catheter. The blood was collected in a sterile bag with heparin added as anticoagulant (1,000 U/100 ml blood) and was returned to the dog 30 min after completing the experiment. On a different day, a control experiment was conducted that was identical in duration, but no hemorrhage was performed.

**Effectiveness of carotid, aortic, and combined SAD denervation.** The effectiveness of carotid sinus denervation was determined at surgery by measuring the responses to carotid occlusion. After denervation, there was no change in HR in response to carotid occlusion, and the increase in MAP never exceeded 5 mmHg. We were unable to devise a simple method of testing the completeness of aortic denervation alone. However, in the five dogs that later underwent CBR denervation, tests of responses in the SAD condition indicated that both ABRs and CBRs were destroyed. These tests included measuring HR responses to bolus administration of nitroglycerine (NG; 15 μg/kg; American Critical Care, McGaw Park, IL) and phenylephrine (PE; 5 μg/kg; Winthrop-Breon Laboratories, New York, NY). HR responses reported below are based on a 10-s sample corresponding to the peak of the change in MAP. In the intact condition, PE increased MAP 34 ± 3 mmHg and HR decreased 27 ± 2 beats/min, whereas NG decreased MAP 29 ± 3 mmHg and HR increased 56 ± 9 beats/min. After SAD, PE increased MAP 49 ± 8 mmHg with no change in HR (0.4 ± 3.7 beats/min), and NG decreased MAP 50 ± 5 mmHg with no change in HR (1.2 ± 1.1 beats/min).

**Methods of measurement.** Arterial pressures were measured using Cobe transducers and recorded on a Grass model 7d polygraph. The pressure transducers were adjusted to heart level for each dog. Each analog signal from the polygraph was sampled at 100 Hz and digitized using a Biopac Systems data-acquisition system (BIOPAC Systems, Santa Barbara, CA). The data were saved on disc for subsequent analysis. Note that the MAP referred to in RESULTS is equivalent to the average or electronically damped pressure signal, not calculated MAP.

**Data analysis.** A two-factor ANOVA with repeated measures on both treatment (intact vs. ABR only, intact vs. 2CBR only, and 2CBR vs. 1CBR) and hemorrhage volume was used to analyze the experimental data (24). Differences were considered significant if P < 0.05. Note that group changes in MAP and HR during hemorrhage are displayed in the figures as a percentage of control (the average MAP and HR over the 10 min preceding the hemorrhage), but the statistical analysis was performed on the raw data. When a significant interaction between factors was detected, the differences in MAP were compared at each level of hemorrhage using Newman-Keuls test (25). The paired t-test (two-tailed, P < 0.05) was used to determine if the denervations altered
baseline levels of MAP, HR, or the standard deviations describing the individual variability in MAP and HR. Data enumerated in the text are means ± 1 SE.

We have defined the term “breakpoint” of good MAP maintenance to be the volume of blood removed at which MAP falls more than 10% below the control mean and never recovers. The rationale for this approach is as follows. In the time control experiments, MAP (60-s bins) never deviated more than 10% above or below the average MAP in 9 of 13 intact dogs. In 2 of 13 dogs, MAP averaged more that 10% above control for 1 min each but never fell 10% below control. In 1 of 13 dogs, MAP was 10% above control for 1 min and 10% below control for 1 min. In the final dog, MAP averaged 10% below control for 7 min, all in the first 10 min of the experiment, and 10% above control for 8 min, all in the final 10 min of the experiment; a pattern that was consistent and due to increasing restlessness in the sling as time passed. Thus, in 12 of 13 resting dogs, deviations in MAP of more than 10% above or below control lasting more than 1 min are rare.

The criteria of a fall in MAP greater than 10% of control with no recovery is an objective method to determine the point at which an individual dog can no longer maintain MAP at control levels. The paired t-test was used to determine if denervation altered the breakpoint in the denervated condition compared with the control response.

RESULTS

Effect of removing carotid sinus baroreceptors. The average values for MAP, HR, and the standard deviations describing these variables during the 60-min time control experiments are shown in Table 1. There was no effect of removing carotid sinus baroreceptors on either basal MAP, MAP variability, or HR. However, the variability of HR was different (P < 0.05) with only ABR functional. In the SAD condition (n = 5), MAP was not different from the intact condition, but HR and the variability in both MAP and HR were significantly different.

The absolute values for MAP and HR during hemorrhage in a representative dog are shown in Fig. 1. In the intact condition, MAP was maintained within 10% of control through 18 ml/kg of blood loss and then MAP plummeted, hence a breakpoint of 19 ml/kg. The increase in HR as hemorrhage progressed also reached a peak at the 18-ml/kg level of hemorrhage and then declined toward control levels at 30 ml/kg of blood loss. When the hemorrhage was repeated with only ABR functional, MAP was maintained within 10% of control until blood loss exceeded 13 ml/kg, after which MAP declined rapidly. HR increased during hemorrhage, peaking near the breakpoint, but the increase was not as large as observed in the intact condition. In both the intact and ABR conditions, MAP fell to the same level at the end of hemorrhage.

The group changes in MAP and HR (expressed as a % of control) in response to hemorrhage in the intact and ABR only conditions (n = 7) and the SAD condition (n = 5) are shown in Fig. 2. Comparison of the MAP in the intact and ABR only conditions by ANOVA indicated significant main effects of both treatment (i.e., denervation) and hemorrhage and a significant interaction between the two factors (all P < 0.02). With only

Table 1. Effect of carotid or aortic baroreceptor denervation on hemodynamic variables in the time control experiment

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP</th>
<th>SD of MAP</th>
<th>HR</th>
<th>SD of HR</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Group 1</strong> (n = 7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intact</td>
<td>101 ± 3</td>
<td>4.8 ± 0.7</td>
<td>59 ± 4</td>
<td>6.7 ± 0.9</td>
</tr>
<tr>
<td>ABR only</td>
<td>102 ± 3</td>
<td>5.5 ± 0.8</td>
<td>65 ± 5</td>
<td>8.5 ± 1.0*</td>
</tr>
<tr>
<td>SAD (n = 5)</td>
<td>111 ± 11</td>
<td>12.9 ± 1.2*</td>
<td>85 ± 10*</td>
<td>8.3 ± 0.4*</td>
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<tr>
<td><strong>Group 2</strong> (n = 6)</td>
<td></td>
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</tr>
<tr>
<td>Intact</td>
<td>107 ± 4</td>
<td>3.3 ± 0.4</td>
<td>88 ± 10</td>
<td>6.1 ± 1.4</td>
</tr>
<tr>
<td>2CBR</td>
<td>106 ± 4</td>
<td>5.0 ± 1.1</td>
<td>89 ± 6</td>
<td>7.8 ± 1.1</td>
</tr>
<tr>
<td>SAD (n = 6)</td>
<td></td>
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</tr>
<tr>
<td>2CBR</td>
<td>104 ± 3</td>
<td>5.6 ± 0.7</td>
<td>89 ± 4</td>
<td>6.9 ± 0.6</td>
</tr>
<tr>
<td>1CBR</td>
<td>100 ± 2</td>
<td>5.5 ± 0.6</td>
<td>83 ± 8</td>
<td>5.3 ± 0.7</td>
</tr>
</tbody>
</table>

Values for mean arterial pressure (MAP) and heart rate (HR) are the average (±1 SE) over the 60-min time control. Values for standard deviation (SD) of MAP and HR are the means of the individual SD. *Different from intact (P < 0.05). ABR, aortic baroreceptor; SAD, sinoaortic denervation; 2CBR, both carotid baroreceptors; 1CBR, one set of CBR.
ABR functional, MAP was significantly different compared with the intact response at hemorrhage volumes of 12 through 19 ml/kg. The average of the individual breakpoints in the intact condition was 18.9 ± 1.8 ml/kg compared with 12.4 ± 1.4 ml/kg in the ABR only condition (\( P < 0.01 \)). There was no increase in HR in the SAD condition in response to hemorrhage as would be expected.

**Effect of removing ABRs.** The average values for MAP, HR, and the standard deviations describing these variables in the time control experiment in the intact and 2CBR only conditions are shown in Table 1. There were no significant differences between the intact and 2CBR conditions for any measured variable.

The changes in MAP and HR (expressed as a % of control) during hemorrhage in the intact and 2CBR conditions are shown in Fig. 3. Statistical analysis of MAP responses indicated a significant effect of hemorrhage but no effect of denervation and no denervation × hemorrhage interaction. The failure of the ANOVA to detect an effect of denervation may be related to the high degree of variability in HR during hemorrhage. HR increased in all dogs before the breakpoint and then declined as the hemorrhage progressed. Because the breakpoints of the individual dogs in the intact condition varied from 13 to 29 ml/kg and 6 to 18 ml/kg in the ABR condition, HR was declining in some while increasing in others at the same level of hemorrhage. If the HR is compared over the 2-min period before the breakpoint, the increase was 63 ± 11 beats/min in the intact condition and 32 ± 11 beats/min in the ABR only condition, and the difference was significant (\( P < 0.01 \)). There was no increase in HR in the SAD condition in response to hemorrhage as would be expected.

Comparison of the HR responses in the intact and ABR only conditions indicated a significant effect of hemorrhage but no effect of denervation and no denervation × hemorrhage interaction. The failure of the ANOVA to detect an effect of denervation may be related to the high degree of variability in HR during hemorrhage. HR increased in all dogs before the breakpoint and then declined as the hemorrhage progressed. Because the breakpoints of the individual dogs in the intact condition varied from 13 to 29 ml/kg and 6 to 18 ml/kg in the ABR condition, HR was declining in some while increasing in others at the same level of hemorrhage. If the HR is compared over the 2-min period before the breakpoint, the increase was 63 ± 11 beats/min in the intact condition and 32 ± 11 beats/min in the ABR only condition, and the difference was significant (\( P < 0.01 \)). There was no increase in HR in the SAD condition in response to hemorrhage as would be expected.

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tion × hemorrhage interaction. The volume of blood removed at the breakpoint of good pressure maintenance averaged 23.3 ± 2.1 ml/kg in the intact condition and 22.5 ± 2.3 ml/kg in the 2CBR condition, and the difference was not significant.

Two-factor analysis of the HR responses indicated a significant effect of hemorrhage but no effect of denervation and no denervation × hemorrhage interaction. Reanalyzing the data using a single-factor, repeated-measures ANOVA detected significant overall changes in HR in response to hemorrhage in both the intact and 2CBR (both P < 0.02) conditions. However, post hoc analysis failed to identify means during the hemorrhage that differed from the control HR. Again, this is most likely due to the large variability in individual HRs as a function of hemorrhage volume. That is, HR was increasing in some dogs and decreasing in others at the same volume of blood loss as noted previously. However, the change in HR over the 2 min preceding the breakpoint of each individual dog averaged 47 ± 10 beats/min and 44 ± 4 beats/min in the intact and 2CBR conditions, respectively. These increases were significantly different from control (P < 0.01) and did not differ from each other.

**Effect of removing aortic plus baroreceptors in one carotid sinus.** The average values for MAP, HR, and the standard deviations describing these variables in the time control experiments in the 2CBR and 1CBR conditions are shown in Table 1. There were no statistically significant differences between the two conditions for any measured variable.

The changes in MAP and HR (as a % of control) during hemorrhage in the 2CBR and 1CBR conditions are shown in Fig. 4. For comparison, the responses of the SAD dogs from Fig. 2 are also shown. Two-factor, repeated-measures analysis of MAP responses indicated significant effects of denervation, hemorrhage, and the denervation × hemorrhage interaction (all P < 0.01). The volume of blood removed at the breakpoint of good pressure maintenance was 21.2 ± 2.3 ml/kg in the 2CBR condition and 11.7 ± 1.4 ml/kg in the 1CBR condition, and this difference was significant (P < 0.01). The MAP in the 1CBR condition was significantly different (P < 0.01) from the 2CBR beginning at 10 ml/kg of blood loss through the end of hemorrhage. The hemorrhage was terminated at 25 ml/kg in the 1CBR condition because MAP had fallen below 50 mmHg in three of six dogs. In three dogs with only 1CBR functional, the hemorrhage was repeated 6–12 wk later to determine if additional time for recovery altered the response. There was no change in the MAP responses to hemorrhage after allowing 6–12 wk of additional time for recovery.

Analysis of the HR responses indicated no significant effect of denervation, hemorrhage, or a denervation × hemorrhage interaction. The HR data were reanalyzed using a single-factor, repeated-measures ANOVA to determine if HR changed in either the 2CBR or 1CBR conditions. No significant changes occurred during hemorrhage in either condition. However, the increase in HR over the 2 min preceding the breakpoint in each individual dog was 33 ± 5 beats/min and 22 ± 8 beats/min in the 2CBR and 1CBR conditions, respectively. These increases were both significant (P < 0.05) with respect to the control HR and did not differ significantly from each other (P = 0.29).

**DISCUSSION**

This study examined the role of baroreceptors in the carotid sinus and the aortic arch in the defense of MAP during hemorrhage in conscious dogs. To put the results into context, it is necessary to review the current view of responses to hemorrhage. The classical view of responses to hemorrhage, based largely on observations in anesthetized animals, is that sympathetic outflow increases initially in response to unloading cardiopulmonary receptors and is augmented secondarily by unloading of arterial baroreceptors as arterial pressure...
gradually declines (3). More recent observations based on responses in conscious animals have indicated a different pattern of events. Schadt and Ludbrook (19) have characterized responses to hemorrhage as consisting of two distinct phases in conscious rabbits, dogs, and humans. The first or sympathoexcitatory phase (phase I) is characterized by steady decreases in cardiac output that are matched by increases in systemic vascular resistance resulting in maintenance of MAP at control levels. The second or sympathoinhibitory phase (phase II) appears abruptly when 25–35% of blood volume has been removed and is characterized by a marked decrease in sympathetic outflow and a decline in HR leading to a precipitous fall in MAP. The increase in peripheral resistance and HR in phase I appears to be accounted for by the unloading of arterial baroreceptors in dogs (20, 22). Arterial baroreceptors also appear to be of primary importance in the rabbit (12, 13), although one study proposed a contribution from cardiopulmonary afferents (5). The receptor(s) that triggers the sympathoinhibitory phase is not known with certainty, but its effect is reversed by administration of naloxone, an opioid antagonist; within minutes after being injected with naloxone, the phase II response is converted back to the characteristics of phase I (19). Thus the fall in MAP during hemorrhage is not due to inadequate buffering power but to a separate mechanism, presumably acting at a critical synapse in the medullary circuitry subserving the baroreceptor reflex.

The transition from phase I to phase II is usually defined as an abrupt reduction in sympathetic nerve activity or increase in vascular conductance (19). We did not measure either of these variables. However, the breakpoint in MAP, which marks the transition from good MAP maintenance during phase I to the precipitous fall in pressure during phase II, correlates precisely with the decline in sympathetic activity (1, 12, 13). Thus comparison of breakpoints before and after denervation together with comparison of the actual decreases in MAP provide two means to evaluate the relative importance of ABR and CBR in the defense of MAP during progressive hemorrhage.

The results obtained in this study show that denervation of the ABR had no effect on the breakpoint in MAP during hemorrhage compared with the intact response. Thus the changes in MAP during hemorrhage in the intact condition and with only CBR functional were superimposable (Fig. 3). In contrast, denervating the CBR resulted in the appearance of the breakpoint at a smaller volume of blood loss (34% less on average) compared with the intact response (Fig. 2). It should be noted that until the breakpoint was reached in each dog, there was no difference between the maintenance of MAP in the intact and ABR conditions (Figs. 1 and 2). Therefore, ABRs acting alone were able to maintain MAP at control levels in response to developing hypovolemia. O’Leary and Scher (16) determined the buffering power of ABR 9 days after denervation of CBR in conscious dogs. They caused a step decrease in cardiac output by cardiac pacing and measured the reflexly mediated restoration of MAP. The results indicated no reduction in buffering power in the ABR only condition compared with the intact response. These results show that ABR signals are sufficient to compensate for loss of CBR input within the range of cardiac outputs tested and are in agreement with our results.

The earlier appearance of the breakpoint in the ABR condition resulted in a significant difference in MAP relative to the intact state (Fig. 2). However, once the breakpoint was reached in the intact condition, the difference in MAP disappeared and the absolute declines in MAP at the end of hemorrhage were identical in both conditions. This suggests that sympathetic vasoconstrictor drive was reduced to a similar degree during the sympathoinhibitory phase of hemorrhage. Thus we conclude that the main effect of removing the CBR was to allow the appearance of phase II to occur at smaller hemorrhage volumes. In contrast, in the SAD condition, MAP declined from the beginning of the hemorrhage and resulted in much greater decreases in MAP for the same volume of blood loss (Fig. 2).

Why phase II appeared at a lesser degree of hypovolemia with only ABR operating is not clear from the data obtained in this study. It has been reported that the threshold of ABR is higher compared with the threshold of CBR in the dog (17). This observation has led to the suggestion that ABRs in dogs act mainly to buffer increases in MAP and not decreases (17). However, a later study by Coleridge et al. (4) examined a sample of 35 ABRs all of which were active at a resting pressure of 100 mmHg (average firing rate 14.8 ± 1.3 impulses/s). The receptors responded appropriately to both increases and decreases in aortic pressure, although most were silent when pressure was reduced to 80 mmHg. Taken together, these results indicate that at a normal resting pressure in a conscious dog, a larger portion of the afferent baroreceptor activity arises from receptors in the carotid sinus. However, because MAP and pressure variability were normal after removal of CBRs, central adaptation to the reduced baroreceptor input must have occurred because it is unlikely that the threshold of the ABR changed. Therefore, during hemorrhage with only ABR functional, the absolute number of impulses should have decreased more rapidly as blood was removed compared with the intact condition. Unfortunately, this line of reasoning appears to end in a contradiction. If the only baroreceptor input became silent at a smaller hemorrhage volume, sympathetic outflow should have been at maximal levels, and yet MAP declined much earlier in response to hemorrhage.

A number of authors has assumed that activation of ventricular receptors with vagal afferents is the trigger that initiates the phase II response (5, 23). Oberg and Thoren (15) observed that rapid bleeding or occluding both the superior and inferior vena cavae led to a dramatic fall in MAP and a sudden increase in activity of a population of ventricular receptors in anesthetized cats. They proposed that ventricular muscle contracting at small volumes under intense sympathetic stim-
ulation would cause distortion of the ventricular walls leading to stimulation of mechanoreceptors and reflex suppression of sympathetic outflow, presumably as a protective mechanism. Burke and Dorward (1) reported that administration of procaine into the pericardial sac prevented the appearance of phase II in response to hemorrhage in conscious rabbits, lending support for the idea of cardiac receptor involvement. Similarly, vagotomy relieves the marked inhibition of renal nerve activity in anesthetized rats hemorrhaged to a MAP of 50 mmHg (21). However, vagotomy does not prevent hemorrhage-induced suppression of renal nerve activity in conscious dogs (14). And more recently, Evans et al. (8) observed that vagotomy delayed but did not prevent the appearance of phase II in conscious rabbits made hypovolemic by caval constriction. These results suggest the signal that triggers phase II may not arise solely from ventricular receptors or travel exclusively as vagal afferents.

There is no sympathoexcitatory phase in response to hemorrhage following SAD (19, 20, 22 and Fig. 2), thus MAP begins to decline almost immediately. Consequently, there is no discernable appearance of phase II in SAD animals. However, there is indirect evidence that the receptors that trigger phase II are still stimulated during hypovolemia in SAD animals. For example, Schadt and Gaddis (18) compared the responses to naloxone in intact and SAD rabbits bled to a MAP of 34 mmHg. The rabbits were then injected with naloxone, and MAP increased to control levels within 2 min in the intact rabbits as expected. Surprisingly, MAP increased much higher in response to naloxone in the SAD rabbits. Because naloxone has no effect on MAP in euvolemic animals, this observation suggests that the same sympatoexcitatory mechanism was activated in the SAD condition. The results also indicate that baroreceptor-mediated increases in sympathetic outflow are not a prerequisite to activation of receptors that initiate phase II. Thus these results argue against the mechanism proposed by Oberg and Thoren (15) for activation of ventricular receptors, because it is unlikely that sympathetic outflow increased in the SAD rabbits.

Additional evidence has been reported by Chen et al. (2). They observed that the decreases in MAP in response to hemorrhage volumes of 10, 20, and 30 ml in anesthetized rabbits were attenuated when the hemorrhage was repeated following vagotomy. Furthermore, similar volumes of hemorrhage caused greater falls in MAP in SAD rabbits, and vagotomy again attenuated the responses. Finally, in rabbits made hypotensive by a 20-ml hemorrhage, subsequent vagotomy caused an increase in MAP, and the effect was greater in SAD rabbits. These results are compatible with the hypothesis that an unidentified group of receptors with vagal afferents is stimulated during progressive blood loss and that the increase in firing results in inhibition of sympathetic outflow. Again, it is unlikely that these receptors are similar to the ventricular receptors identified by Oberg and Thoren (15) as the response they described was a sudden burst of activity only after massive blood loss.

Although speculative, if one assumes that there is a population of receptors that inhibit sympathetic outflow and are stimulated by graded hypovolemia, one could hypothesize that the switch from phase I to phase II occurs when input from these receptors becomes dominant to the excitatory effect of decreasing baroreceptor impulses. This mechanism provides a simple explanation for the earlier appearance of phase II in dogs with only ABR functional. Because the total firing from ABRs at a normal MAP is less than in the intact condition, during hemorrhage the point at which impulses from inhibitory receptors exceed the reduction in baroreceptor firing is reduced accordingly. On the other hand, the reduction in impulse traffic after removing ABRs is likely to be small because CBRs provide the dominant baroreceptor input at normal resting MAP in dogs (17). Therefore, there should be little change in the breakpoint leading to phase II in dogs with 2CBR functional compared with the intact condition, and the data support this prediction.

A similar argument could explain the early appearance of phase II during hemorrhage in dogs with only 1CBR functional compared with their responses with 2CBR operating. However, this was not the only difference between the two conditions. The absolute magnitude of the decrease in MAP in dogs with only 1CBR was larger compared with their responses with 2CBR functional. At the 25-ml/kg level of hemorrhage, actual MAP in the 2CBR and 1CBR conditions was 72 ± 7 and 55 ± 4 mmHg, respectively (P < 0.01). In contrast, at the same level of hemorrhage, actual MAP in the intact vs. ABR conditions was 61 ± 7 and 62 ± 4 mmHg, respectively. The greater fall in MAP in the 1CBR condition at the same level of blood loss indicates that some other aspect of reflex control was altered in this condition. It is worth noting that the dogs with only 1CBR functional had the same resting MAP and pressure variability compared with control values with 2CBR functional. This suggests that significant reorganization of baroreflex pathways must have occurred. Nevertheless, the challenge of hypovolemia reveals that the adaptation to loss of baroreceptor input is incomplete.

In summary, the results of this study indicate that the baroreceptors are not equivalent with respect to defending MAP during hypovolemia. Chronic removal of ABRs had no effect on the maintenance of MAP compared with intact responses. In contrast, removal of 2CBR led to a fall in MAP at a hemorrhage volume of 12 ml/kg compared with a fall in MAP at 19 ml/kg with all baroreceptors functional. Thus input from 2CBR was sufficient to drive a normal response to hemorrhage in the absence of input from ABRs but not the converse. The fall in MAP during hemorrhage also occurred earlier in dogs with only 1CBR operating, and the absolute magnitude of the decrease was greater compared with responses with 2CBR functional. Thus it would appear that bilateral inputs are required to
The notion of sympathoexcitatory and inhibitory phases during hemorrhage is relatively recent (19). The fact that arterial baroreceptors mediate most, if not all, of the sympathoexcitatory phase is not surprising, and the response clearly has adaptive advantage for an organism. The sympathoinhibitory phase is much more mysterious, both in terms of the receptors that initiate it and in terms of the adaptive advantage. Because the response has been identified in rats, rabbits, dogs, goats, and human subjects undergoing hypovolemia, it should be obvious that evolution has distributed the mechanism widely and retained it as a functional response to hemorrhage. Therefore, it is surprising that there is a paucity of studies focused on the stimulus that initiates the response and just exactly what benefit the response confers on an organism. At a time when many consider the basics of organismic physiology to be generally understood, the sympathoinhibitory response to hypovolemia is not.

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REFERENCES