The Role of Cardiac Receptor and Arterial Baroreceptor Reflexes in Control of the Circulation during Acute Change of Blood Volume in the Conscious Rabbit

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SUMMARY. We have studied overall reflex control of the circulation by the arterial baroreceptors and cardiac receptors during acute change of blood volume in seven conscious rabbits. A factorial experimental design allowed analysis of the direction, magnitude, and significance of the reflex effects of independent input from each set of receptors, and the reflex interactions when the inputs were combined. Right atrial pressure, arterial pressure, systemic vascular resistance, cardiac output, and heart rate were measured during acute, graded, isohemic change of blood volume over the range ±27%. This was done with both reflexes present, only the arterial baroreceptor reflex present (intrapercardial 2% procaine), only the cardiac receptor reflex present (surgical baroreceptor denervation), and with both reflexes absent. As blood volume was depleted, the arterial baroreceptor reflex independently increased systemic vascular resistance and sustained arterial pressure, but the cardiac receptor reflex had no significant independent or interactive effects. As blood volume was expanded, each reflex had an independent effect in decreasing systemic vascular resistance and preventing arterial pressure from rising; the cardiac receptor reflex being the more powerful. Their effect in combination on systemic vascular resistance and arterial pressure was only two-fifths of the sum of their independent effects, so that they interacted negatively. In combination, the reflexes supported right atrial pressure during blood loss, despite their negative interaction, but did not significantly affect the relation of cardiac output to blood volume change in either direction. Thus both reflexes have important actions in moderating the overall effects of acute blood volume changes in conscious rabbits, but these are markedly diminished by their interactions. (Circ Res 54: 424-435, 1984)

WE showed recently that, in conscious rabbits, the open-loop gain of the carotid sinus reflex, measured directly, with respect to systemic vascular resistance was depressed by acute blood volume expansion and enhanced by moderate blood loss (Faris et al., 1983). We supposed, as others have done from similar experiments in anesthetized animals (Mancia et al., 1976; Chen et al., 1978, 1979; Thames et al., 1982). However, in conscious animals, division of the cervical vagus nerves causes a more or less gross disturbance of respiration (Widdicombe, 1961), and cold blockade of the vagus nerves is not always fully reversible (Hosomi and Sagawa, 1979), so that it has been difficult to study all permutations of afferent input in the same animal.

The heart contains the set of receptors that is best documented as being sensitive to changes in blood volume (Brown, 1979). Instillation of procaine into the pericardial sac has been shown to block the cardiac afferent (and efferent) nerves reversibly in anesthetized cats (Arndt et al., 1981; Samodelov et al., 1982) and conscious rabbits (Dorward et al., 1983). We have made use of this technique, together with surgical denervation of the arterial baroreceptors, to examine in conscious rabbits the effects of graded expansion and depletion of blood volume under conditions that included all four permutations of the arterial baroreceptor and cardiac receptor input with deletion of the input from vagal cardiopulmonary receptors (Oberg and White, 1970; Pelletier et al., 1971; Mancia et al., 1976; Chen et al., 1978, 1979; Thames et al., 1982). However, in conscious animals, division of the cervical vagus nerves causes a more or less gross disturbance of respiration (Widdicombe, 1961), and cold blockade of the vagus nerves is not always fully reversible (Hosomi and Sagawa, 1979), so that it has been difficult to study all permutations of afferent input in the same animal.
reflexes within each rabbit. Analysis of the results by a factorial method has allowed the combined effects of the two reflexes to be measured, and to be partitioned in terms of the direction, magnitude, and significance of their independent and interactive effects. Our main interest was in the rapid-acting reflex effects of acute change in blood volume on overall systemic vascular resistance.

Methods

Seven rabbits of a cross-bred English strain were used, weighing 2.2–2.8 kg (mean 2.5). Major surgical procedures were performed under halothane anesthesia, after induction with intravenous propanidid and endotracheal intubation. A minimum of 7 days was allowed between the last major surgical procedure and the first experiment, at which time each rabbit was well and gaining weight. The minor surgical procedures on the days of the experiments were performed under local analgesia with 2% procaine HCl. The experiments were conducted in accordance with the Statement by the National Health and Medical Research Council of Australia on Animal Experimentation.

Surgical Procedures

First, an inflatable cuff was placed around the thoracic inferior vena cava via a right thoracotomy. Fourteen to 21 days later, a left thoracotomy was performed. A 1.2-mm o.d. polyvinyl chloride catheter was inserted into the descending thoracic aorta in a downstream direction (Herd and Barger, 1964), and filled with heparin, 2500 IU/ml. The sleeve of pericardium that extends onto the ascending aorta was dissected free from the surrounding tissues, and an electromagnetic flow probe (Biotronex 5050) was applied to the ascending aorta extrapericardially. It was wrapped in fabric to ensure adhesion to the aorta. A fine, saline-filled, catheter was inserted into the pericardial sac (Dorward et al., 1983). The occluded ends of the catheters and the connecting plug for the flow probe were buried subcutaneously.

The first experiment was performed 7–10 days later, and next day a final operation was performed at which the carotid sinuses were denervated and both aortic nerves were divided (Faris et al., 1981a). The second experiment was performed after a further 7–8 days.

Preparations for the Experiments

These were identical for each of the two experiments. Donor blood was used for volume expansion, to avoid the confounding effects of hemodilution (Faris et al., 1981a). On the day before the experiment, the blood volume and hematocrit of the experimental rabbit were determined, and its blood cross-matched against that of a donor rabbit (Faris et al., 1981a). The second experiment was performed after a further 7–8 days.

Blood volume was altered in each of the four conditions, by instilling preservative-free 2% procaine HCl into the pericardial sac as a loading dose of 1 ml followed by 2.5 ml every 15 minutes (Clutton-Brock et al., 1983). These volumes did not restrict cardiac filling, as evaluated by the ascending aortic flow pulse. A mercury-in-silastic strain gauge was placed round the thorax, to provide information about respiration and to detect any movement of the rabbit. All pressures were measured with Statham P23Dc strain gauges, the zero being 50 mm above the floor of the rabbit’s box.

Blood was taken into a polypropylene syringe from the donor rabbit after it had been given 2500 IU heparin, under local analgesia. The experimental rabbit was given heparin 1000 IU/kg, with a further dose of 200 IU/kg hourly. Thirty milliliters of donor blood were mixed with that of the experimental rabbit by repeated infusion and withdrawal; then its arterial hematocrit was measured. The rabbit was allowed to rest for 60 minutes before the experiment started.

Recordings were made on a Grass model 7 polygraph. Mean arterial pressure (MAP), right atrial pressure (RAP), and cardiac output (CO) were obtained by integrating the variables at 5-second intervals. Heart rate (HR) was averaged over the same intervals. Systemic vascular resistance (SVR) was calculated as MAP/CO. Cardiac output and systemic vascular resistance were expressed as indices of body weight (CI and SVRI, respectively).

Drugs

The cardiac nerves were blocked by instilling preservative-free 2% procaine HCl into the pericardial sac as a loading dose of 1 ml followed by 0.25 ml every 15 minutes (Dorward et al., 1983). These volumes did not restrict cardiac filling, as tested at the end of the last experiment when HR had been rendered invariable. The injection of successive 1-ml volumes of isotonic saline into the pericardial sac did not reduce stroke volume or elevate RAP until a total of 4–5 ml had been given.

After the arterial baroreceptor and cardiac receptor afferents had been deleted, the effect of superimposing an autonomic neuroeffector blockade (Ludbrook and Graham, 1983) was tested. First, cardiac autonomic effector blockade was induced by intravenous infusion of dl-propranolol HCl, 4.0 μg/kg per min, after a loading dose of 250 μg/kg, and the intravenous injection of l-scapolamine methyl bromide (methscopolamine), 50 μg/kg. Then autonomic ganglion blockade was effected by giving intravenous pentolinium tartrate, 2.7 ± 0.3 mg/kg.

Protocol

The animals were studied on two separate experimental days. On the 1st day, they were studied before and after cardiac nerve blockade. Thus each animal was studied under the following four conditions: both arterial baroreceptor and cardiac receptor afferents intact (BC), baroreceptor afferents intact but cardiac receptor afferents deleted (B), cardiac receptor afferents intact but baroreceptor afferents deleted (C), and both sets of afferents deleted (O).

Blood volume was altered in each of the four conditions,
as follows. First, it was expanded by infusing 30 ml of blood (12.1 ± 0.3 ml/kg, or 26.5 ± 1.4% of blood volume, in the first experiment; 12.5 ± 0.4 ml/kg, or 28.1 ± 1.5% of blood volume, in the second experiment), in steps of 5 ml. The blood then was withdrawn, and 10 minutes were allowed for the circulatory variables to return to normal. We then depleted blood volume by withdrawing 30 ml of blood in 5-ml steps, then reinfusing the blood. It took 5–10 seconds to infuse or withdraw each 5 ml of blood, and the circulatory variables had reached a steady level after a further 20 seconds. They were recorded over a 10-second control period before each sequence of infusion or bleeding, and over the last 5 seconds of each step. This allowed a generous safety margin beyond the normal response time for the carotid sinus reflex (Faris et al., 1981b).

Criteria for Denervation of the Receptors

The baroreceptor-heart rate reflex was used to test the integrity of the arterial baroreceptors. They were judged to be completely denervated, in condition C, if inflation of the caval cuff which causes MAP to fall by 20–30 mm Hg resulted in a rise in HR of less than 5 beats/min (Blombery and Korner, 1979).

On the basis of our own (Dorward et al., 1983) and others’ (Arndt et al., 1981; Samodelov et al., 1982) experience, it was assumed that—when cardiac efferent neural blockade was complete—all, or most, of the cardiac afferents were also blocked. Two criteria were used to determine that intrapericardial procaine had blocked the cardiac efferent nerves in condition B. The first was that HR should not rise by more than 5 beats/min when the caval cuff was inflated so that MAP was lowered by 20–30 mm Hg (Dorward et al., 1983). The second was that HR should not fall by more than 5 beats/min when 4.5% formalin vapor was presented to the rabbit’s nostrils for 4 seconds (Korner et al., 1979). These tests were performed before, between, and at the end of, the infusion and bleeding sequences. In condition O, the arterial baroreceptors had been denervated, so that only the second criterion could be used.

Autopsy Findings

The rabbit was killed at the end of the second experiment, and an autopsy performed. The flow probe was always firmly bonded to the ascending aorta by fibrous tissue. In every case, the pericardial sac could be inflated with 5 ml of saline without leakage, the lining of the pericardium was glossy, and there was no thrombus in the aorta at the site of the indwelling catheter. The kidneys were examined for macroscopic evidence of embolization from the aortic catheter. A small infarct was found in the renal cortex of one rabbit, but because in every other respect it could not be distinguished from the others, it was not excluded.

Analysis of the Data

The values of the variables for the control periods that preceded the infusion and withdrawal of blood in each state were brought to a common mean, and the values during change in blood volume were adjusted arithmetically to this. Three-way analysis of variance revealed a systematic difference between the two sets of control values only in the case of cardiac index ($F = 4.6; df = 1.55; P < 0.05$) which was, on average, $6.9 ± 1.9$ ml/kg per min (4.5%) lower prior to bleeding than prior to infusion.

The balanced design of the experiment allowed the results to be analyzed by calculating the $F$ statistic in two-way analyses of variance, within which factorial analyses (Snedecor and Cochran, 1980) were used to calculate the direction, magnitude, and significance of the independent effects of the arterial baroreceptor reflex and the cardiac receptor reflex when each was acting on its own, and the effect of interaction between the two reflexes when they were combined. These effects were calculated from the data obtained by the four permutations of afferent input: that is, under conditions BC, B, C, and O. The reflex effect of baroreceptor input was given by $(B - O)$, and that of cardiac receptor input by $(C - O)$. An interaction was judged to be present if the sum of the independent effects of the two inputs differed significantly from their combined effect, $(BC - O)$. Thus the interactive effect was given by $(BC - O) - [(B - O) + (C - O)]$.

This factorial method was used to analyze the effects of the inputs at each of the 13 levels of blood volume. However, we were more interested in whether the reflex effects increased or decreased as the disturbance of blood volume became progressively greater. This was determined as follows. Provided blood volume expansion and reduction were treated separately, the relation of each of the variables to change in blood volume was approximately linear (Fig. 1). Linear regression coefficients ($b$) for the rate of change in each variable with percent change in blood volume were therefore calculated, and factorial analyses on these coefficients were performed.

The variables have been expressed throughout as mean values for the seven rabbits, and between-animal variation is indicated by the standard error of the mean (±).

Results

General

Blood volume prior to the first experiment was $46.4 ± 2.4$ ml/kg, and before the second experiment was $45.0 ± 2.1$ ml/kg. Arterial hematocrit after the admixture of donor blood was $32.6 ± 0.9$% in the first experiment, $34.4 ± 0.5$% in the second. In every rabbit, the criteria set for completeness of arterial baroreceptor denervation and cardiac neural blockade (see Methods) were satisfied. Neither intervention produced detectable effects on the frequency or depth of respiration.

Details of how the cardiovascular variables were affected by change in blood volume, and by the four conditions under which this was observed, are described in the following two sections. In the final section, the calculated independent and interactive effects of the reflexes are presented.

The experiment was designed so that within-animal comparisons could be made, and the results are presented and analyzed accordingly. In fact, for most of the cardiovascular variables, the between-animal variance was small, and was little affected by the changes in blood volume, as indicated by the standard errors of the means (Table 1; Fig. 1). The exceptions were CI and the derived variable SVRI, whose between-animal variances were greater.

Effects of Reflex Status on the Cardiovascular Variables at Normal Blood Volume

These are set out in Table 1. When both reflex pathways were intact, the values of all the cardiovascular variables fell within a normal range for
conscious rabbits (Faris et al., 1981a). There were significant differences among the mean values of each of the variables across the four permutations of afferent input under which they were observed (F always >3.4; df 3.18; P always <0.05). This indicated that, in a general way, the reflexes were influencing the levels of all variables at normal blood volume.

**Table 1**

Effects of Reflex Status on the Values of the Cardiovascular Variables at Normal Blood Volume

<table>
<thead>
<tr>
<th>Reflex Status</th>
<th>RAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>SVRI (x100)</th>
<th>CI (ml/kg per min)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>14 ± 0.4</td>
<td>96 ± 3</td>
<td>63 ± 5</td>
<td>154 ± 12</td>
<td>264 ± 16</td>
</tr>
<tr>
<td>B</td>
<td>1.8 ± 0.3</td>
<td>95 ± 5</td>
<td>66 ± 5</td>
<td>150 ± 12</td>
<td>250 ± 12</td>
</tr>
<tr>
<td>C</td>
<td>1.6 ± 0.4</td>
<td>114 ± 5</td>
<td>73 ± 6</td>
<td>162 ± 11</td>
<td>298 ± 8</td>
</tr>
<tr>
<td>O</td>
<td>2.9 ± 0.4</td>
<td>106 ± 5</td>
<td>80 ± 8</td>
<td>138 ± 9</td>
<td>224 ± 8</td>
</tr>
</tbody>
</table>

Analysis of variance

<table>
<thead>
<tr>
<th>F</th>
<th>&lt;0.001</th>
<th>&lt;0.01</th>
<th>&lt;0.05</th>
<th>&lt;0.05</th>
<th>&lt;0.001</th>
</tr>
</thead>
</table>

**Legend:**
- RAP = right atrial pressure (mm Hg); MAP = mean arterial pressure (mm Hg); SVRI = systemic vascular resistance index (mm Hg/ml/kg per min); CI = cardiac index (ml/kg per min); HR = heart rate (beats/min).
- Values are means ± 1 S.E. for seven rabbits.
- BC = arterial baroreceptor and cardiac receptor reflexes both present.
- B = baroreceptor reflex present, cardiac receptor reflex absent.
- C = cardiac receptor reflex present, baroreceptor reflex absent.
- O = both reflexes absent.

The coordinates intersect at the control values at normal blood volume. The points represent mean values for the seven rabbits. The bars indicate ± 1 S.E.M.
Effects of Change in Blood Volume on the Cardiovascular Variables under the Four Conditions of Afferent Input

These are shown in Figure 1. If blood volume expansion and depletion are considered separately, the mean values of the variables were near-linearly related to change in blood volume. Across the four conditions of afferent input, there were significant differences among the mean slopes of the regressions, both for blood volume expansion and depletion, in the cases of RAP, MAP, SVRI, and HR (F always > 5.0; df 3,18, P always <0.05). This indicated that, in a general way, the reflexes were influencing the rate at which these variables changed as blood volume was progressively altered. In the case of CI, the differences among the mean slopes were not significant, either for blood volume expansion (F = 3.0) or depletion (F = 0.7). This suggested that the reflexes might not have been influencing the rate of change of CI as blood volume was progressively altered.

Right Atrial Pressure

When both reflex pathways were intact (condition BC), the maximum rise and fall of RAP with blood volume expansion and depletion was 3.4 ± 0.5 and 1.9 ± 0.3 mm Hg, respectively. Deletion of both sets of afferents (condition O) increased the rate of fall of RAP as blood volume was depleted (F = 32.2; df 1,18; P < 0.001), but did not significantly affect the rate of rise with blood volume expansion (F = 0.2). This indicated that, in combination, the reflexes acted to restrain the fall of RAP during blood loss but did not affect the rate of rise as blood volume was expanded. Inspection of Figure 1 suggests that there was a contribution from each reflex during blood loss, and also suggests that the contribution of each was greater in the absence (conditions B vs. O; C vs. O) than in the presence (conditions BC vs. C; BC vs. B) of the other.

Mean Arterial Pressure

When both reflex pathways were intact (condition BC), the changes in MAP were small, the maximum rise and fall during blood volume expansion and depletion being 6.9 ± 1.9 and 11.7 ± 2.6 mm Hg, respectively. Deletion of both sets of afferents (condition O) greatly exaggerated the rate of rise and fall of MAP with blood volume change (F = 9.8 and 61.2, respectively; df 1,18; P < 0.01 and 0.001, respectively). This indicated that, in combination, the reflexes acted to moderate the changes in MAP as blood volume was altered progressively in either direction. It is clear from Figure 1 that the arterial baroreceptor reflex was chiefly responsible for this effect during blood loss. During blood volume expansion, the contribution of each reflex appeared to be greater in the absence (conditions B vs. O; C vs. O) than in the presence (conditions BC vs. C; BC vs. B) of the other.

Systemic Vascular Resistance Index

When both reflex pathways were intact (condition BC), there was a steep and progressive rise in SVRI as blood volume was depleted, and a smaller fall as blood volume was expanded. Deletion of both sets of afferents (condition O) caused a reversal of this pattern, so that there was now a steep fall in SVRI as blood volume was depleted, and a rise as it was expanded. Both changes were significant (F = 47.5 and 6.5, respectively; df 1,18, P < 0.001 and 0.05, respectively). This indicated that, in combination, the reflexes acted on SVRI in a way that would moderate the changes in MAP as blood volume was altered progressively in either direction. As in the case of MAP, the arterial baroreceptor reflex appeared to be chiefly responsible for this effect during blood loss. During blood volume expansion, the contribution of each reflex appeared to be greater in the absence (conditions B vs. O; C vs. O) than in the presence (conditions BC vs. C; BC vs. B) of the other.

The relation of SVRI to MAP was also examined (Fig. 2), on the assumption that the progressive deletion of the reflexes had uncovered whole-body autoregulation of SVRI. When both reflex pathways were intact (condition BC), there was an inverse, near-linear association between SVRI and MAP, the slopes of the regressions for blood volume expansion and depletion being indistinguishable (F = 3.7; df 1,6; P > 0.05). Deletion of the arterial baroreceptor afferents (condition C) transformed the association between SVRI and MAP during blood volume depletion into a direct one (F = 6.9; df 1,6; P < 0.05), but did not significantly alter the slope of the inverse.

FIGURE 2. The relation between systemic vascular resistance index (SVRI) and mean arterial pressure (MAP) as blood volume was altered by ±27% in steps of 4.5%. Each point represents the mean value for seven conscious rabbits. Bars indicate ± 1 SEM at normal blood volume. • = both arterial baroreceptor and cardiac receptor reflexes intact. O = arterial baroreceptor reflex deleted. ▲ = both reflexes deleted.

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association during blood volume expansion ($F = 1.8$, df 1.6; $P > 0.05$). When the cardiac receptor afferents were also deleted (condition O), the association between SVRI and MAP became a direct one over the whole range, though the slope of the regression during blood volume expansion was steeper than that during blood volume depletion ($F = 19.4$; df 1.6; $P < 0.01$).

### Heart Rate

When both reflex pathways were intact (condition BC), CI fell to a greater extent during blood volume depletion than it rose during blood volume expansion, the changes being 52 ± 8 and 22 ± 8 ml/kg per min, respectively. Deletion of both sets of afferents (condition O) did not significantly alter the rate of change of CI as blood volume was depleted or expanded ($F = 0.1$ and 2.5 respectively; df 1.18; $P$ always > 0.05). This indicated that, in combination, the reflexes had no significant effect on CI as blood volume was progressively altered. It should be noted that the apparent failure of CI to rise during blood volume expansion in condition O was associated with a higher level of RAP at normal blood volume (Table 1), and a steeper rise of SVRI and MAP as blood volume was expanded (Fig. 1), than under the other conditions of the experiment.

### Cardiac Index

In describing the results, we have placed the greatest emphasis on the effects that became progressively greater or smaller as blood volume was altered. These were calculated from the linear regression coefficients that were used to describe the rate of change of each cardiovascular variable as blood volume was either expanded or depleted. The results of this form of analysis are summarized in Table 1 and Figure 3.

The independent and interactive effects were also calculated on a point-by-point basis for each of the 13 levels of blood volume, and these are also indicated in Figure 3.

### Systemic Vascular Resistance Index

At normal blood volume, the arterial baroreceptor input exerted a tonic effect in depressing SVRI ($F = 7.6$; df 1.18; $P < 0.05$), but there was neither a significant effect of cardiac receptor input nor a significant interaction. As blood volume was depleted, the arterial baroreceptor input exerted a powerful and progressive reflex effect in increasing SVRI, but there was no significant progressive effect of cardiac receptor input, nor was there a significant interaction.

As blood volume was expanded, each input exerted a significant progressive reflex effect, and there was also a progressive and significant interaction. The independent action of each input was to depress SVRI progressively, the effect from the cardiac receptors being greater than that from the arterial baroreceptors as judged by covariant analysis ($F = 14.8$; df 1.6; $P < 0.01$). However, the effect of their interaction was in the opposite direction. Thus, the progressive effect of simultaneous input from both sets of receptors, calculated as $(B - O)$, was only 39% of that which would be predicted from the sum of the independent effects of input from each separate set of receptors, calculated as $[(B - O) + (C - O)]$.

### Mean Arterial Pressure

At normal blood volume, the arterial baroreceptor input exerted a tonic effect in depressing MAP ($F = 5.9$; df 1.18; $P < 0.05$), but there was no significant effect of cardiac receptor input, nor was there a significant interaction. As blood volume was depleted, the arterial baroreceptor input exerted a powerful and progressive effect in preventing MAP from falling, but there was neither a corresponding effect of cardiac receptor input, nor significant interaction. As blood volume was expanded, each input exerted a significant progressive reflex effect, and there...
TABLE 2
Progressive Effects of the Arterial Baroreceptor and Cardiac Reflexes, and of their Interaction, as Blood Volume was Expanded or Depleted

<table>
<thead>
<tr>
<th>Cardiovascular variable</th>
<th>Independent and interactive reflex effects</th>
<th>Blood volume depletion</th>
<th>Blood volume expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B  C  I</td>
<td>B  C  I</td>
<td></td>
</tr>
<tr>
<td>RAP (x10)</td>
<td>-0.46 -0.52 0.40</td>
<td>-0.44 -0.29 0.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001 &lt;0.001 &lt;0.05</td>
<td>&lt;0.01 NS &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>-1.76 -0.18 0.08</td>
<td>-0.49 -0.73 0.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001 NS NS</td>
<td>&lt;0.01 &lt;0.001 &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>SVRI (x100)</td>
<td>-1.44 -0.26 -0.19</td>
<td>-0.48 -0.82 0.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001 NS NS</td>
<td>&lt;0.05 &lt;0.001 &lt;0.05</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>-0.07 0.35 -0.11</td>
<td>0.48 0.92 -0.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS NS NS</td>
<td>NS &lt;0.01 NS</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>-0.21 -0.13 -1.47</td>
<td>0.06 -0.22 -0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS NS NS</td>
<td>NS NS NS</td>
<td></td>
</tr>
</tbody>
</table>

Symbols and units of the cardiovascular variables are as in Table 1. B = independent arterial baroreceptor reflex effect. C = independent cardiac receptor reflex effect. I = interactive effect when both reflexes were combined. E indicates the magnitude of the progressive independent or interactive effect, and is the mean slope of the regression of the effect on the percent change of blood volume. P indicates the significance of the independent or interactive effect, obtained by calculating F by factorial analysis at df 1,18 within a 2-way analysis of variance. NS indicates P > 0.05.

ARTERIAL BARORECEPTOR REFLEX EFFECT CARDIAC RECEPTOR REFLEX EFFECT INTERACTIVE EFFECT

**FIGURE 3.** The average magnitude and direction of the independent effects of the arterial baroreceptor and cardiac receptor reflexes, and the effect of their interaction, as blood volume was altered by ±27% in steps of 4.5% in seven conscious rabbits. The effects were calculated by factorial analysis on the data of Figure 1. Abbreviations as in Figure 1. Each point represents the mean deviation of the variable from its value at normal blood volume that is attributable to the independent or interactive effect of the reflexes. • = significant effect at P = 0.05—0.001. ○ = insignificant effect. The lines indicate a significant effect on the linear rate of change of the variable with change in blood volume, expansion and depletion being analyzed separately *** = P < 0.001. ** = P < 0.01. * = P < 0.05.
was also a progressive and significant interaction. The independent action of each input was to prevent MAP from rising; the effect from the cardiac receptors was greater than that from the arterial baroreceptors as judged by covariance analysis ($F = 8.3; df 1,6; P < 0.05$). However, the effect of their interaction was in the opposite direction. Thus, calculated in the same way as for SVRI, the progressive effect of simultaneous input from both sets of receptors was only 40% of that which would be predicted from the sum of the independent effects of input from each separate set of receptors.

Heart Rate, Cardiac Index, and Right Atrial Pressure

The calculated effects of the inputs on these variables are considered together, because, to a considerable extent, they are interdependent.

Neither input appeared to exert a significant progressive effect on HR as blood volume was altered. In the case of the arterial baroreceptors, this outcome was artefactual because the effect was calculated as the difference between conditions B and O (Fig. 1), and in both these conditions the cardiac efferent nerves were blocked by intrapericardial procaine. Since there was no significant effect of cardiac receptor input, the reflex action of the arterial baroreceptors is most nearly represented by the interactive effect, which was one of progressively elevating HR as blood volume was depleted.

During blood volume depletion, there were no significant independent or interactive effects of the inputs on CI. As blood volume was expanded, the cardiac receptor input appeared to elevate CI progressively. However, this effect was calculated as the difference between conditions C and O (Fig. 1), and may therefore have resulted from blockade of the cardiac efferent nerves in condition O, rather than from deletion of the cardiac receptor afferents.

As described earlier, RAP was supported during blood volume depletion by the combined effect of the two inputs. A significant independent effect from each set of receptors contributed to this, but was opposed by a significant interactive effect. Thus, the progressive effect of simultaneous input from both sets of receptors was only 59% of that which would be predicted from the sum of the independent effects of input from each separate set of receptors.

Discussion

Our principal goal was to quantify the short-term actions and interaction of the arterial baroreceptor and cardiac receptor reflexes in controlling systemic vascular resistance as blood volume was progressively expanded or depleted. This was achieved by making within-animal comparisons of the effects of standardized changes in blood volume under the four conditions that represent all permutations of afferent input from the two sets of receptors. From these comparisons, the reflex effects of input from the arterial baroreceptors and cardiac receptors when each acted independently of the other, and the interactive effects that occurred when both acted together, were calculated. Our analysis of these reflex effects depends on a number of assumptions, which are considered in detail below.

One assumption is that denervation of the receptors was selective, yet division of the carotid sinus nerves denervates chemoreceptors as well as baroreceptors. However, there is evidence that in the rabbit the carotid chemoreceptors do not act tonically on the circulation (Chalmers et al., 1967a) and are not excited until the arterial pressure falls below 20 mm Hg (Ott et al., 1971; Faris et al., 1980), so that it is unlikely that effects attributed to baroreceptor input were confounded by the carotid chemoreceptor reflex. Intrapericardial procaine blocks afferents from the heart and not, for instance, those from the lungs (Arndt et al., 1981), but it also blocks the cardiac efferent nerves, so that it must be assumed that the calculated reflex effects on vascular resistance were unaffected by the abolition of changes in heart rate. This is a fair assumption in the case of the arterial baroreceptor reflex, since we have shown that—in conscious rabbits—the carotid sinus reflex controls arterial pressure by changing vascular resistance rather than cardiac output (Faris et al., 1981b), and that this control is unaffected by drugs that abolish changes in heart rate (Faris et al., 1980). The cardiac receptor reflex effects were examined after barodenervation, which of itself had abolished changes of heart rate as blood volume was altered (Fig. 1).

Another assumption is that 7 days’ denervation of the arterial baroreceptors does not alter the properties of the cardiac receptor reflex, either because of excitation of cardiac receptors from the hemodynamic changes caused by barodenervation, or because of a slow adaptation of the central nervous system to the absence of baroreceptor input. Despite a sustained elevation of arterial pressure after barodenervation, our analysis of the reflexes did not reveal a tonic effect of cardiac receptor input on systemic vascular resistance, and we have shown elsewhere that, in rabbits, there must be a very steep rise in arterial pressure before there are cardiac receptor reflex effects on renal sympathetic nerve activity (Dorward et al., 1983) or heart rate (Ludbrook, in press). If a prolonged absence of baroreceptor input were to cause enhancement of the cardiopulmonary reflexes, as has sometimes been suggested, then our estimates of cardiac receptor reflex effects and interactions might be falsely exaggerated. However, Walgenbach and Donald (1983) have exhaustively reviewed the evidence for such an enhancement, and reached a verdict of not proven.

A further assumption is that the properties of the vasculature were not so altered by receptor denervation as to impair its responsiveness to variations in sympathetic neural drive. Cardiac receptor denervation caused only a small disturbance of systemic vascular resistance, so that the response to variations
in baroreceptor input should not have been impaired on this account. Although baroreceptor denervation significantly raised the resting level of systemic vascular resistance, the rise was less than that which occurred with blood loss when both reflexes were present (Fig. 1), so that a reflex response in either direction should still have been possible. Of more concern is our unexpected finding that deletion of both reflexes caused systemic vascular resistance to fall steadily as blood volume was depleted and to rise steadily as it was expanded (Figs. 1 and 2). It seems likely that whole-body autoregulation of vascular resistance was responsible for this phenomenon, which resembles closely that described in anesthetized dogs (Liedtke et al., 1973) and cats (Borgdorff, 1983), when cardiac output was altered after the arterial baroreceptor and cardiopulmonary afferents had been divided. It is unlikely that some other reflex was uncovered that was responsible for the direct association of vascular resistance and arterial pressure, since ganglion blockade in our experiment caused resistance and pressure to fall, rather than rise, and in Borgdorff’s (1983) study it did not impair autoregulation. This latter observation also suggests that the local autoregulatory mechanisms are overridden, rather than abolished, by the action of the baroreceptor and cardiac receptor reflexes.

Given the foregoing assumptions, our analysis shows that the steep and progressive rise of systemic vascular resistance that occurred as blood volume was depleted was due, almost exclusively, to the independent action of the arterial baroreceptor reflex (Fig. 3). On the other hand, each of the reflexes, when acting independently, was able to lower systemic vascular resistance progressively as blood volume was expanded; the cardiac receptor reflex was the more powerful (Fig. 3). However, their combined effect was only two-fifths of that predicted by the sum of their independent effects (Fig. 3). They can therefore be said to have interacted strongly in a negative, or mutually inhibitory, fashion. There are two pieces of internal evidence that support these conclusions. First, the direction and relative magnitudes of the independent and interactive effects of the reflexes on arterial pressure were identical to those on systemic vascular resistance (Fig. 3). Second, blood loss should unload both the arterial baroreceptors and the cardiac receptors, so that a progressive effect of either reflex should have been evident only if it exerted a tonic effect when blood volume was normal. We found that the arterial baroreceptor reflex exerted a significant tonic depressor effect on systemic vascular resistance, but that the cardiac receptor reflex did not (Fig. 3).

Our findings are novel in several respects. We concerned ourselves with reflexes originating from sensory receptors that were confined to the heart, rather than with those that originate from vagally innervated (Thoren, 1979) or sympathetically innervated (Malliani, 1982) receptors in the general cardiopulmonary area. We did not elicit the cardiac receptor and arterial baroreceptor reflexes by applying discrete mechanical, chemical, or ischemic stimuli to one or other set of receptors, but by applying the same stimulus of acute change in blood volume to both sets. Since the conditions of our experiments included all four permutations of input from the two sets of receptors in the same animal, we were able to employ a factorial method of statistical analysis that maximized the likelihood of detecting reflex effects if they existed, but also minimized the risk of Type 1 error (Snedecor and Cochran, 1980). Finally, our experiment was free from the confounding effects of general anesthesia or artificial ventilation. We are not aware of comparisons of the effects of arterial baroreceptor and cardiac (or cardiopulmonary) receptor reflexes on systemic vascular resistance having been made previously under these circumstances.

Others have compared the effects of arterial baroreceptor and vagal cardiopulmonary receptor reflexes on cardiovascular functions or sympathetic efferent discharge when blood volume is altered, under conditions that have included some (Oberg and White, 1970) or all (Pelletier et al., 1971; Mancia et al., 1976; Chen et al., 1978, 1979; Thames et al., 1982) permutations of the two sets of receptors. It is difficult to compare their results with ours, for a variety of reasons. The species studied usually were dogs or cats, and in only one case were they anesthetized (Hosomi and Sagawa, 1979). In only one instance was the comparison made of the reflex actions of all arterial baroreceptors vs. those of the vagal cardiopulmonary receptors exclusive of the aortic baroreceptors (Thames et al., 1982). A further difficulty is the diverse ways in which the experimental data were analyzed.

The study that resembles ours most in design was made by Thames et al. (1982), who examined the effects of all permutations of the reflexes on the inhibition of renal sympathetic nerve activity caused by volume expansion. The vagal cardiopulmonary receptor reflex acted more powerfully than the arterial baroreceptor reflex, and their interaction was a negative one of the same order of magnitude as we observed in the case of systemic vascular resistance. The studies of blood volume expansion by Mancia et al. (1976) and Chen et al. (1979) differed from ours in design, but can be interpreted as showing that each of the carotid baroreceptor and vagal cardiopulmonary receptor reflexes acted to control arterial pressure, and that they interacted negatively. The impairment by blood volume expansion of open-loop control of systemic vascular resistance by the carotid baroreflex, which we observed in our earlier study of conscious rabbits (Faris et al., 1983), is therefore consistent with there having been an interactive effect from cardiac, or vagal cardiopulmonary, afferents. The importance of our present...
study is that for the first time it has been shown in
a conscious animal that, as blood volume is ex-
expanded, the subset of cardiopulmonary receptors
that lies in the heart can exert an overall reflex effect
in progressively depressing systemic vascular resis-
tance, and that the independent effect of the cardiac
receptor reflex is greater in this respect than the
independent effect of the arterial baroreceptor re-
flex.

We found that, as blood volume was depleted,
only the arterial baroreceptor reflex had an inde-
pendent action in increasing systemic vascular re-
sistance and supporting arterial pressure. Other in-
vestigators have reported that reflexes from vaga
 cardiopulmonary receptors exert effects on car-
diovascular functions when anesthetized animals are
bled, but disagree about the direction of the effects.
Oberg and White (1970) found that, in cats, these
reflexes could support arterial pressure, and Pelletier
et al. (1971) showed in a factorial study of dogs that
they could cause reflex vasoconstriction in the renal
and superior mesenteric beds, although there was a
negative interaction with the carotid baroreceptor
reflex. On the other hand, Chen et al. (1978) found,
in a factorial study of rabbits, that cardiopulmonary
reflexes acted to depress arterial pressure
during hemorrhage, without any interaction with
the arterial baroreceptor reflex. There are several
possible explanations for this discrepancy between
our results and those referred to above. There may
be a qualitative or quantitative difference between
the reflex actions of cardiac receptors alone and
 cardiopulmonary receptors in general, though Chal-
mers et al. (1967b) concluded, as we have done here,
that the short-term support of arterial pressure after
hemorrhage in conscious rabbits was accounted for
almost entirely by the reflex action of the arterial
baroreceptors. In our study, we did not detect a
significant tonic effect of the cardiac receptor reflex
which could be withdrawn when blood volume was
depressed. This may be a peculiarity of conscious
rabbits compared with anesthetized animals of the
same or other species, or it may be a matter of
posture, since in other studies the anesthetized ani-
mal, or the conscious human subject (Zoller et al.,
1972; Johnson et al., 1974; Abboud et al., 1979),
has been recumbent. There is good evidence that, in
anesthetized animals, the output of cardiopulmo-
nary receptor reflexes is not directed uniformly
among the various vascular beds, but influences
predominantly the kidney (Brown, 1979; Thoren,
1979). Moreover, Chalmers et al. (1967c) found,
when studying the effects of hemorrhage on re-
gional vascular resistance in conscious rabbits, that
only in the case of the kidney did vasoconstriction
occur that could not be accounted for by the arterial
baroreceptor reflex. It is quite likely, therefore, that
in our present study a major effect of the cardiac
receptor reflex on the renal vasculature during blood
volume depletion was concealed by the absence of
effects on other vascular beds. In our previous study
(Faris et al., 1983) in which we found that control
of systemic vascular resistance by the carotid baro-
reflex was enhanced by moderate hemorrhage, the
time course of blood volume depletion was slower.
This enhancement may have been due to a periph-
eral or central action of circulating angiotensin II
(Zimmerman, 1981), secondary to reduction in renal
blood pressure or flow, rather than a direct effect of
reduced afferent input from cardiopulmonary recep-
tors.

We have found that the arterial baroreceptor and
cardiac receptor reflexes interact in a negative, or
mutually inhibitory, fashion (Fig. 3), and this has
been a feature of most studies in which the mutual
interaction of arterial baroreceptor and vagal cardio-
pulmonary receptor reflexes have been examined
(Pelletier et al., 1971; Mancia et al., 1976; Chen et
al., 1979; Thames et al., 1982). An exception is the
study of hemorrhage by Hosomi and Sagawa (1979),
in which a strongly positive interaction was reported
between the carotid sinus reflex and vagal cardio-
pulmonary reflexes that included those originating
from the aortic baroreceptors. They analyzed their
results in terms of calculated open-loop gain for
arterial pressure, and this raises the question of
whether control system analysis is appropriate in
the case of cardiopulmonary receptor reflexes, when
the receptors do not sense arterial pressure directly,
if at all.

Our experiment also showed that there were sig-
nificant actions and interactions of the reflexes on
the relation of right atrial pressure to blood volume
(Fig. 3). Those that occurred, as blood volume was
expanded, are of little consequence, because the
combination of both reflexes exerted no net effect.
However, during blood volume depletion, they com-
bined to support right atrial pressure. We hesitate to
ascribe this to a reflex effect on systemic vascular
compliance, even though there is evidence that both
the arterial baroreceptors (Kirchheim, 1976) and car-
diopulmonary receptors (Thoren, 1979) can act re-
flexly on capacity vessels. This is because there were
changes in other factors that may have influenced
the relation of right atrial pressure to blood volume,
such as the resting level of right atrial pressure and
comcomitant changes in cardiac output and arterial
pressure.

The combination of the two reflexes exerted no
significant effect on cardiac output as blood volume
was altered. The lack of an independent effect of
the arterial baroreceptor reflex on cardiac output
under these closed-loop conditions (Fig. 3) confirms
our previous findings made under open-loop con-
ditions in conscious rabbits (Faris et al., 1981b).
However, the cardiac receptor reflex did appear to
have the independent effect of progressively in-
creasing cardiac output, by increasing stroke vol-
ume, as blood volume was expanded (Fig. 3). The
true basis for this effect is not clear, but it stems
from the failure of cardiac output to increase as blood volume was expanded after both reflexes had been deleted (Fig. 1). This, in turn, may merely be the result of a combination of factors: the high level of central venous pressure and low level of heart rate at normal blood volume, the progressive increase in systemic vascular resistance and arterial pressure as blood volume was expanded—suggesting that there was an increase in left ventricular afterload, and the possible adverse effects of cardiac sympathetic efferent nerve blockade on ventricular contractility.

The effect of intrapericardial procaine in blocking the cardiac efferent nerves invalidates factorial analysis as a means for detecting the independent and interactive effects of the reflexes on heart rate. However the fact that deletion of the arterial baroreceptors virtually abolished all changes in heart rate as blood volume was altered suggests that any effect of the cardiac receptor reflex would have been small.

The results of our experiment describe the global actions and interactions of reflexes that originate from two populations of receptors. In the case of the arterial baroreceptors the differences among subpopulations of receptors appear to be quantitative rather than qualitative (Brown, 1980; Yao and Thoren, 1983). However, cardiac receptors can be subdivided according to their anatomical location, their sensitivity to mechanical or chemical stimuli, their innervation by medullated or nonmedullated fibers, and according to whether the afferents enter the central nervous system via the vagus or sympathetic nerves (Brown, 1979). Under the conditions of our experiment, any or all of these subsets of cardiac receptors may have contributed to the effects we observed when blood volume was altered, although the direction of these effects makes it likely that they originated from vagally innervated (Thoren, 1979), rather than from sympathetically innervated (Malliani, 1982) receptors. We have reported the effects of the reflexes on systemic vascular resistance without knowing whether these were mediated by neural or neurohumoral mechanisms, although the rapidity with which we altered blood volume was intended to emphasize the former. Though we found that the reflexes interacted, the locus of the interaction may have been at any level from the first synapse of their respective afferents in the brainstem to the vascular smooth muscle itself. Nevertheless, the very similar direction and magnitude of the interaction found in the study by Thames et al. (1982) suggests that at least part of the interaction that we observed took place within the nervous system. Despite the uncertainties about the receptor and effector mechanisms responsible for the independent effects of the reflexes, and the basis for their interactions, we believe that our factorial experimental design has an advantage over the reductionist approach, in that it provides a description of how two major reflexes act and interact to determine their combined effect when a disturbance, such as change in blood volume, is imposed on the conscious animal.

We are grateful to Anne Day and Margaret Sutcliffe for technical and secretarial assistance, and to Professor P.1. Korner for his helpful criticism.

Supported by the National Health and Medical Research Council of Australia.

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Received May 31, 1983; accepted for publication February 1, 1984.

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INDEX TERMS: Baroreceptor reflex • Blood volume • Cardiac receptor • Rabbit • Vascular resistance
The role of cardiac receptor and arterial baroreceptor reflexes in control of the circulation during acute change of blood volume in the conscious rabbit.

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doi: 10.1161/01.RES.54.4.424

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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