Differential Baroreflex Control of Heart Rate and Vascular Resistance in Rabbits
Relative Role of Carotid, Aortic, and Cardiopulmonary Baroreceptors

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SUMMARY. We assessed the relative roles of aortic (ABR), carotid sinus (CBR), and vagal cardiopulmonary baroreceptors in the reflex control of heart rate and vascular resistance during changes in arterial blood pressure. Injections of phenylephrine (PE) and nitroglycerin (NG) were given intravenously to anesthetized rabbits (chloralose-urethane). Reflex heart rate responses were impaired significantly by denervation (X) of either CBR or ABR. In contrast, reflex vascular responses in the hindlimb (perfused at constant blood flow) were preserved except for a slight impairment of reflex vasoconstriction after ABRX. Vagotomy with intact CBR and ABR impaired only the reflex bradycardia. After vagotomy, neither CBRX nor ABRX altered significantly the reflex heart rate or vascular responses except, again, for an impairment of reflex vasoconstriction after ABRX. Combined CBRX and ABRX eliminated all reflex responses except for a small bradycardia and a biphasic change in perfusion pressure (constrictor-dilator) during PE. Vagotomy eliminated the bradycardia and the dilator phase; the constrictor phase persisted and was abolished by lumbar sympathectomy. The results indicate that (1) reflex control of heart rate may be impaired when reflex control of hindlimb resistance is preserved; thus reflex changes in heart rate may not be used as a reliable index of the integrity of arterial baroreceptor control of the total circulation; (2) one set of arterial baroreceptors does not compensate for the absence of the other with respect to activation of vagal neurons; in contrast, one set of baroreceptors compensates fully for the absence of the other with respect to inhibition of sympathetic neurons; (3) cardiopulmonary and other baroreceptors contribute minimally to reflex responses only during large PE-induced increases in arterial pressure. (Circ Res 50: 554–565, 1982)

PHENYLEPHRINE (PE) and nitroglycerin (NG) are commonly used to alter arterial pressure in humans and animals, and the corresponding reflex changes in heart rate or pulse interval are used to assess the arterial baroreflexes (Smyth et al., 1969; Eckberg et al., 1971; Randall et al., 1976; Mancia et al., 1978; Tomiyama et al., 1980). Smyth et al. (1969) and Tomiyama et al. (1980) generated a small ramp of pressure and correlated beat-to-beat changes in systolic pressure with pulse interval. Mancia et al. (1978), Korner et al. (1974), and others have used the steady state plateau that develops during an injection, in the hope of obtaining sympathetic as well as vagal components of the baroreflex control of heart rate. This approach to the study of arterial baroreflexes has two limitations. First, since these drugs have powerful vasoactive effects, the technique can be used to provide an assessment only of the reflex control of heart rate, but cannot be used to assess the baroreflex control of the peripheral circulation. These could be important differences in the reflex control of heart rate as opposed to peripheral resistance which would not be evident with this technique. Second, this technique may alter the discharge of cardiovascular mechanoreceptors throughout the circulation and, thus, may not reflect the influence of arterial baroreceptors exclusively. It has been demonstrated that the cardiopulmonary baroreceptors (CPR) with vagal afferents may respond to changes in preload (Thames et al., 1977; Thoren, 1977), afterload (Mark, et al., 1973; Thames et al., 1977), and contractility (Fox et al., 1977; Thoren, 1977), and may be capable of modulating the arterial baroreflex control of heart rate and vascular resistance (Vatner et al., 1975; Mancia et al., 1976). It is possible that hemodynamic changes induced by PE and NG alter the discharge of CPR with afferent vagal fibers and might thus contribute to the observed reflex responses.

The aortic (ABR) and carotid (CBR) baroreceptors may have different relative roles in the control of heart rate, blood pressure, or peripheral vascular resistance (Vatner et al., 1970; Donald and Edis, 1971; Edis, 1971; Abboud et al., 1979). Vatner et al. (1970) suggested from studies in awake dogs that ABR are more effective in controlling heart rate than CBR. In contrast, our work in humans (Abboud et al., 1979) indicates that activation of carotid baroreceptors with neck suction eliminates the reflex tachycardia despite unloading of aortic baroreceptors during systemic hypotension caused by pooling blood in the lower extremities. The work of Itou and Scher (1978, 1979) based on studies with chronic denervation of carotid
sinus or aortic arch in different groups of dogs indicates that reflex changes in heart rate are impaired to a greater extent by denervation (X) of ABR than by CBR. Donald and Edis (1971) and Edis (1971) found that carotid baroreceptors had a lower threshold and a greater gain and total range than had the aortic baroreceptors in regard to control of arterial blood pressure. However, the relative influence of CBR, ABR, and CPBR in mediating reflex heart rate and vascular responses to PE and NG injections has not been systematically evaluated.

These experiments were designed to determine whether interventions that alter arterial baroreflex control of heart rate would alter equally the reflex control of vascular resistance. A second goal was to assess the relative roles of ABR, CBR, and CPBR (vagal afferents) in reflex control of heart rate and vascular resistance during PE and NG. The results indicate that reflex changes in heart rate during PE and NG may not be representative of the arterial baroreflex control of the total circulation. Conclusions concerning the integrity of arterial baroreceptor reflexes based on changes in heart rate with PE or NG should be guarded.

Methods

General Methods and Preparation

Male albino rabbits (New Zealand White) weighing 2-4 kg were anesthetized with intravenous (ear vein) a-chloralose (50 mg/kg) and urethane (500 mg/kg). After tracheal cannulation, the animals were ventilated artificially with a mixture of oxygen and room air. Gallamine triethiodide (2 mg/kg) was administered to permit control of respiration. Supplemental doses of anesthetic and gallamine triethiodide were given as needed.

A catheter was positioned in the aorta via the right axillary artery for measurement of arterial pressure (pulsatile and mean). Heart rate was recorded with a Beckman 9857B cardiotachometer triggered by the arterial pressure pulse. Another catheter positioned in the right axillary vein was used for drug injections. A third catheter was inserted into the right atrium via the right jugular vein for recording central venous pressure. All pressures were measured with Statham pressure transducers (P23dB) and displayed on a Beckman Dynograph recorder. The blood gases and pH were monitored periodically and, when necessary, were corrected by giving 5% sodium bicarbonate or by adjusting the respiratory frequency. The PaO2 of the arterial blood was always found to exceed 200 mm Hg, and PaCO2 and pH were maintained between 25 and 35 mm Hg and between 7.32 and 7.42, respectively. The body temperature was measured from the esophagus and maintained between 36 and 38°C by external warming.

Hindlimb Preparation

The reflex control of vascular resistance was assessed in an isolated hindlimb perfused at constant flow. In brief, the abdomen was opened in the midline and the left iliac artery was ligated. An extracorporeal circuit was used to shunt blood from the abdominal aorta below the renal arteries to the right iliac artery. Collateral circulation to the perfused hindlimb was minimized by ligating vessels in the lower abdomen. A perfusion pressure of less than 15 mm Hg with the extracorporeal circuit occluded indicated insignificant collateral circulation. A delay circuit (30-45 seconds) was included in this extracorporeal circuit to prevent the direct vascular effects of drugs from modifying or obscuring reflex vascular responses. The effect of the delay circuit is illustrated in Figure 1. Sodium heparin (500 U/kg) was given before cannulation of the right iliac artery. Supplemental doses of heparin (200 U) were given every 30 minutes.

The vagal, aortic depressor, and carotid sinus nerves were exposed and looped with fine threads for easy access for subsequent section.

The carotid sinus baroreceptors were denervated by cutting the sinus nerves and stripping the carotid sinus region of all innervation, and were considered denervated when bilateral carotid occlusion failed to alter heart rate and perfusion pressure. However, in eight of 28 animals, small increases in perfusion pressure persisted during bilateral carotid occlusion even though the carotid sinuses had been denervated. In these animals, the influence of residual baroreceptors was minimized by tying off the common carotid arteries. In 14 animals, responses to PE and NG were assessed after sinoaortic denervation (SAD) and vagotomy and after subsequent lumbar sympathectomy.

Protocols

After completion of surgery, a period of 30-60 minutes was allowed for stabilization before beginning the protocols. Phenytoine (PE) (1 mg/ul) and nitroglycerin (NG) (1 mg/ul) were administered intravenously in boluses of 2, 4, 12 μg/kg, and 4, 12, 24 μg/kg, respectively. Each bolus injection of drug was followed by a 0.25-ml saline flush. PE and NG were injected alternately. Injections were separated by at least 5 minutes. Phasic and mean arterial pressure, central venous pressure, heart rate, and hindlimb perfusion pressure were recorded. These responses were examined before and after sequential denervation (X) of the carotid sinus (CBRX) and aortic (ABRX) baroreceptors, and cardiopulmonary receptors with vagal afferents (bilateral vagotomy-BVX). After each denervation, we waited a period of 20 minutes before testing reflex responses to NG and PE to allow for stabilization of arterial pressure, heart rate, and perfusion pressure. This was necessary because the denervations caused abrupt increases in pressures and rate which stabilized gradually over a period of 15-20 minutes. Thus, reflex responses to NG and PE could be determined from a stable baseline. The number of experiments and order of denervation for each group were as follows: Group 1 (n = 8): CBX, ABRX, vagotomy; Group 2 (n = 6): ABRX, CBX, vagotomy; Group 3 (n = 8): vagotomy, CBX, ABRX, Group 4 (n = 6): vagotomy, ABRX, CBX, and Group 5 (n = 6): sham denervations.

Influence of Baseline Resistance and Sympathetic Tone

Denervation of one set of arterial baroreceptors caused increases in baseline vascular resistance and sympathetic tone. To determine if these changes in baseline resistance altered the responsiveness of hindlimb vessels to a given dilator or constrictor stimulus, we injected PE (0.2 and 2 μg) and NG (0.2 and 2 μg) intra-arterially into the circuit perfusing the hindlimb in six rabbits in group 1, before and after CBRX.

The possibility that the increase in baseline sympathetic tone following ABRX or CBX might alter the vascular response to a given change in sympathetic tone was also tested in six additional rabbits. The lumbar sympathetic chain was cut and stimulated electrically (20V, 2 msec) at a baseline frequency of 1 to 3 Hz [mean 1.5 ± 0.3 Hz] to restore perfusion pressure to the level that was present.
before denervation. The frequency of stimulation was then increased or decreased transiently by 1, 2, or 3 Hz for 20 seconds, and the corresponding changes in perfusion pressure were recorded. We then increased baseline frequency of electrical stimulation to 4.0 ± 0.5 Hz in order to increase baseline perfusion pressure to levels similar to those seen after partial baroreceptor denervation. The frequency of stimulation was again increased or decreased transiently by 1, 2, or 3 Hz for 20 seconds from this new baseline level.

Data Analysis

Peak responses of heart rate and perfusion pressure to PE and NG were recorded for statistical analysis. The mean values ± standard error (SE) are presented. The relationship between changes in mean arterial pressure and changes in heart rate or perfusion pressure was assessed by regression analyses. Regression lines for the responses to changes in arterial pressure with both PE and NG were calculated for each rabbit, and the averages of these individual slopes were obtained with each series of drug injections. The slopes of responses to NG and to PE were also analyzed separately. The slopes of all responses to changes in arterial pressure were significant, except after sinoaortic denervation, when responses were either abolished or reduced markedly and were not consistently dose-related. Student’s t-test was used to evaluate the significance of differences in slopes between two series of injections (groups 1 and 2), and an analysis of variance and Duncan’s multiple range test (Steel and Torrie, 1960) were used to evaluate differences between three (groups 3 and 4) or four series (group 5) of injections. Probability levels of less than 0.05 were considered significant.

Results

Reflex Responses to PE and NG with Intact Afferents

Increasing arterial pressure with PE caused reflex bradycardia and vasodilation, and decreasing arterial pressure with NG evoked opposite responses (Figs. 1–3). The direct effects of drugs on vascular smooth muscle did not interfere with the assessment of reflex responses in the hindlimb because they were separated from the reflex effects by the delay circuit (Fig. 1). Changes in central venous pressure following PE or NG were small or zero. As observed in the sham-denervated group (group 5, Table 2), the passage of time, and a moderate increase in baseline perfusion pressure did not alter reflex responses of heart rate and perfusion pressure except during the fourth series of injections when the reflex bradycardia during PE was greater as compared to the first series (Fig. 3).
Immediate Responses to Denervation (Table 1)

Bilateral carotid (CBRX) or bilateral aortic (ABRX) baroreceptor denervation caused significant abrupt increases in arterial pressure, perfusion pressure, and heart rate (Table 1). The heart rate and arterial pressure responses to ABRX and CB RX were similar, as has been reported previously in conscious rabbits (Chalmers et al., 1967). The increases in perfusion and arterial pressures were, on the average, twice as large when the second remaining set of arterial baroreceptors was sectioned than when only one set (either ABR or CBR) was sectioned. (See first vs. second section in groups 1 and 2, and third vs. fourth section in groups 3 and 4.)

Bilateral vagotomy (BVX) in the presence of intact carotid and aortic baroreceptors (first section in groups 3 and 4) caused very small increases in arterial and perfusion pressures, but, when the vagi were cut after sinoaortic denervation (third section in groups 1 and 2), the acute increases in arterial and perfusion pressures were strikingly greater.

Baseline Values 20 Minutes after Selective Denervations (Table 2)

The abrupt increases in heart rate after section of each set of afferents declined back toward control levels within 20 minutes in all groups. The increases in arterial and perfusion pressures after CB RX or ABRX were rapid and stabilized at a level significantly greater than control (Table 2). Section of the remaining set of arterial baroreceptors (i.e., sinoaortic denervation—SAD) caused marked increases in arterial and perfusion pressures which declined to levels that were still significantly higher than those before denervation. However, the increases after bilateral vagotomy were not sustained, even when the sinoaortic nerves had been previously sectioned (groups 1 and 2; fourth vs. third series). Not all the increase in baseline values of perfusion pressure was caused by denervation of afferent nerves since there was a modest but significant increase in resting perfusion pressure in the sham-denervated rabbits over the time period of the experiment (group 5).

Effects of Selective Baroreceptor Denervation on Baroreflex Control of Heart Rate and Resistance

Analysis of Combined Responses to PE and NG after Partial Baroreceptor Denervation

Denervation of one set of afferents (either CB RX or ABRX) caused significant impairment of reflex changes in heart rate, but the reflex vascular responses were preserved (Tables 3 and 4; and Figures 2 and 4).

Reflex Responses to NG and to PE Analyzed Separately (Table 5)

When reflex responses to PE and NG were analyzed separately, the slopes of the heart rate responses to both drugs were consistently and significantly decreased after partial baroreceptor denervation. The slopes of the reflex vasodilator responses to PE were preserved or augmented. The reflex vasoconstrictor

Effect of Selective Denervation on Resting Values of Arterial Pressure, Vascular Resistance, and Heart Rate

There were abrupt increases in arterial pressure, perfusion pressure, and heart rate immediately after section of each set of buffer nerves, which then stabilized gradually over the subsequent 20 minutes. Reflex responses to PE and NG were tested 20 minutes after section of each set of nerves (carotid, aortic, or vagi) when stable levels of pressures and rate were reached.

Effect of Selective Denervation on Resting Values of Arterial Pressure, Vascular Resistance, and Heart Rate
# Table 1

**Acute (maximum) Increases in Mean Arterial Pressure (MAP, mm Hg), Hindlimb Perfusion Pressure (PP, mm Hg), and Heart Rate (HR, beats/min) in Response to Sequential Deafferentation of the Carotid Sinus (CBRX), Aortic (ABRX), and Cardiopulmonary (BVX) Baroreceptors**

<table>
<thead>
<tr>
<th>Sequence of section</th>
<th>First section</th>
<th>Second section</th>
<th>Third section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 8)</td>
<td>CBRX</td>
<td>ABRX</td>
<td>BVX</td>
</tr>
<tr>
<td>MAP</td>
<td>+27 ± 4*</td>
<td>+44 ± 5* †</td>
<td>+41 ± 7*</td>
</tr>
<tr>
<td>PP</td>
<td>+16 ± 2*</td>
<td>+46 ± 3* †</td>
<td>+32 ± 6*</td>
</tr>
<tr>
<td>HR</td>
<td>+9 ± 2*</td>
<td>+10 ± 3*</td>
<td>+5 ± 2*</td>
</tr>
<tr>
<td>Group 2 (n = 6)</td>
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<td>BVX</td>
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<tr>
<td>MAP</td>
<td>+21 ± 4*</td>
<td>+46 ± 6* †</td>
<td>+44 ± 5* †</td>
</tr>
<tr>
<td>PP</td>
<td>+23 ± 3*</td>
<td>+57 ± 12* †</td>
<td>+32 ± 5* †</td>
</tr>
<tr>
<td>HR</td>
<td>+11 ± 5*</td>
<td>+12 ± 5*</td>
<td>+10 ± 4*</td>
</tr>
<tr>
<td>Group 3 (n = 8)</td>
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<td>CBRX</td>
<td>ABRX</td>
</tr>
<tr>
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<td>+6 ± 3*</td>
<td>+25 ± 3* †</td>
<td>+40 ± 4* †</td>
</tr>
<tr>
<td>PP</td>
<td>+9 ± 4*</td>
<td>+17 ± 5*</td>
<td>+55 ± 5* †</td>
</tr>
<tr>
<td>HR</td>
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<td>+18 ± 4*</td>
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<td>Group 4 (n = 6)</td>
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<td>ABRX</td>
<td>CBRX</td>
</tr>
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<td>+23 ± 2* †</td>
<td>+47 ± 7* †</td>
</tr>
<tr>
<td>PP</td>
<td>+1 ± 1</td>
<td>+17 ± 2*</td>
<td>+49 ± 8* †</td>
</tr>
<tr>
<td>HR</td>
<td>+5 ± 2*</td>
<td>+5 ± 3</td>
<td>+23 ± 5* †</td>
</tr>
</tbody>
</table>

* Significant responses to denervation (P < 0.05).
† † Significant differences from values obtained after the first and second sections, respectively (P < 0.05).

# Table 2

**Basal Values of Mean Arterial Pressure (MAP, mm Hg), Perfusion Pressure (PP, mm Hg), and Heart Rate (HR, beats/min)**

<table>
<thead>
<tr>
<th>Series of drug injection</th>
<th>First series</th>
<th>Second series</th>
<th>Third series</th>
<th>Fourth series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 8)</td>
<td>INTACT</td>
<td>CBRX</td>
<td>ABRX</td>
<td>BVX</td>
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<tr>
<td>MAP</td>
<td>79 ± 3</td>
<td>104 ± 4†</td>
<td>126 ± 6†</td>
<td>118 ± 8†</td>
</tr>
<tr>
<td>PP</td>
<td>80 ± 2</td>
<td>98 ± 5†</td>
<td>132 ± 9†</td>
<td>137 ± 10†</td>
</tr>
<tr>
<td>HR</td>
<td>273 ± 7</td>
<td>276 ± 8</td>
<td>270 ± 8</td>
<td>274 ± 13</td>
</tr>
<tr>
<td>Group 2 (n = 6)</td>
<td>INTACT</td>
<td>ABRX</td>
<td>CBRX</td>
<td>BVX</td>
</tr>
<tr>
<td>MAP</td>
<td>80 ± 2</td>
<td>92 ± 3†</td>
<td>114 ± 5†</td>
<td>109 ± 9†</td>
</tr>
<tr>
<td>PP</td>
<td>89 ± 5</td>
<td>122 ± 9†</td>
<td>130 ± 6†</td>
<td>125 ± 11†</td>
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<tr>
<td>HR</td>
<td>264 ± 4</td>
<td>264 ± 12</td>
<td>266 ± 13</td>
<td>271 ± 15</td>
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<td>Group 3 (n = 8)</td>
<td>INTACT</td>
<td>BVX</td>
<td>CBRX</td>
<td>ABRX</td>
</tr>
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<td>MAP</td>
<td>80 ± 2</td>
<td>82 ± 4</td>
<td>106 ± 6†</td>
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</tr>
<tr>
<td>PP</td>
<td>90 ± 3</td>
<td>92 ± 4</td>
<td>110 ± 5†</td>
<td>144 ± 7†</td>
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<tr>
<td>HR</td>
<td>280 ± 10</td>
<td>271 ± 8</td>
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<td>287 ± 10</td>
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<td>81 ± 4</td>
<td>83 ± 4</td>
<td>102 ± 4†</td>
<td>125 ± 9†</td>
</tr>
<tr>
<td>PP</td>
<td>95 ± 1</td>
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<td>111 ± 4†</td>
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<td>HR</td>
<td>289 ± 13</td>
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<td>PP</td>
<td>84 ± 2</td>
<td>95 ± 5</td>
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<tr>
<td>HR</td>
<td>265 ± 13</td>
<td>270 ± 10</td>
<td>263 ± 13</td>
<td>272 ± 12</td>
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</table>

Group 5 was a sham-denervated group subjected to four series of drug injections.
* Before each series of drug injections, when the nerves were intact, and after sequential deafferentation of the carotid sinus (CBRX), aortic (ABRX), and cardiopulmonary baroreceptors (BVX).
† † † Significant differences from basal values before the first, second, and third series of injections, respectively.
### Table 3

Reflex Responses of Heart Rate (ΔHR beats/min) and Perfusion Pressure (ΔAPP mmHg) to Changes in Mean Arterial Pressure (ΔMAP mmHg) before and after Sequential Section of Carotid Sinus (CBRX), Aortic (ABRX) and Cardiopulmonary Baroreceptor Afferents (BVX)

<table>
<thead>
<tr>
<th></th>
<th>Intact afferents</th>
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<th>After ABRX</th>
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<tr>
<td>Phenylephrine</td>
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#### Group 1 (n = 8)

- **AMAP**: -24±2, -20±2, -13±2, 10±1, 18±1, 46±3, -34±3*, -28±3*, -18±3*, 14±3, 25±3, 46±6
- **APP**: 29±3, 23±3, 15±1, -8±2, -15±3, -28±5
- **ΔHR**: 11±2, 8±1, 5±1, -6±1, -13±2, -39±7, 10±3, 6±1, 3±1, -3±1, -9±2, -29±6

#### Group 2 (n = 6)

- **AMAP**: -21±3, -17±3, -7±3, 9±2, 16±3, 36±5
- **APP**: 28±7, 27±5, 13±4, -11±2, -23±4, -3±4
- **ΔHR**: 17±2, 11±3, 6±1, -8±2, -16±3, 47±5

#### After sinoaortic denervation (SAD)

- **Groups 1 and 2 (n = 14)**
  - **AMAP**: -53±3, -50±3, -29±3, 20±5, 31±4, 42±4
  - **APP**: 0±2, 2±2, 9±1, -7±1, -12±1, -28±3
  - **ΔHR**: 17±2, 11±3, 6±1, -8±2, -16±3, 47±5

#### After SAD + BVX

- **Groups 1 and 2 (n = 14)**
  - **AMAP**: -53±3, -50±3, -29±3, 20±5, 31±4, 42±4
  - **APP**: 0±2, 2±2, 9±1, -7±1, -12±1, -28±3
  - **ΔHR**: 17±2, 11±3, 6±1, -8±2, -16±3, 47±5

* Significant differences in ΔMAP (P < 0.05) between "intact" values and values obtained "after CBRX" or "after ABRX" in response to the same doses of nitroglycerin or phenylephrine. After SAD, the ΔPP in response to phenylephrine was biphasic. Significance of difference in the reflex responses of perfusion pressure and heart rate was analyzed by examining the slopes of regressions (see Table 5 and Figure 4).

### Table 4

Reflex Responses in Heart Rate (ΔHR beats/min) and Perfusion Pressure (ΔAPP mmHg) to Changes in Mean Arterial Pressure (ΔMAP mmHg) before and after vagotomy (BVX) Followed by Section of Carotid Sinus (CBRX) or Aortic Baroreceptors (ABRX)

<table>
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<tr>
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</tbody>
</table>

#### Group 3 and 4 (n = 14)

- **ΔMAP**: -23±2, -17±2, -10±1, 9±1, 16±1, 37±2
- **ΔPP**: 23±2, 15±2, 9±1, -8±1, -14±1, -24±2
- **ΔHR**: 16±1, 13±1, 6±1, -8±1, -17±2, -44±6

#### Group 3 (n = 8)

- **ΔMAP**: -33±4†, -25±3†, -12±2, 10±1, 22±3, 37±3
- **ΔPP**: 31±5, 20±3, 11±2, -7±1, -15±3, -25±3
- **ΔHR**: 13±2, 9±1, 4±1, -3±1, -8±1, -18±4

* † Significant differences in ΔMAP (P < 0.05) after CBRX or ABRX compared with "intact" (†) and "after BVX" (*) in response to the same doses of nitroglycerin or phenylephrine. Significance of differences in the reflex responses of perfusion pressure and heart rate was analyzed by examining the slope of regression (see Table 5).

Responses to NG were reduced in some experiments after CBRX and ABRX, but the reductions were more consistent and attained statistical significance only after ABRX.

PE caused similar increases in arterial blood pressure before and after ABRX or CBRX, where NG caused greater hypotension after denervation of either set of afferents (Table 3).
TABLE 5
Regression Coefficients (Slopes) of Reflex Changes in Heart Rate or Perfusion Pressure in Response to Changes in Mean Arterial Pressure (MAP mm Hg) (All Regressions were Negative)

<table>
<thead>
<tr>
<th></th>
<th>Slopes of Δ heart rate (Δbeats/min per Δmm Hg)</th>
<th>Slopes of Δ perfusion pressure (Δmm Hg/Δmm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combined With NG With PE</td>
<td>Combined With NG With PE</td>
</tr>
<tr>
<td>Intact—Groups 1 and 2 (n = 14)</td>
<td>0.89 ± 0.10 0.65 ± 0.10 1.01 ± 0.10</td>
<td>0.85 ± 0.06 1.26 ± 0.10 0.71 ± 0.07</td>
</tr>
<tr>
<td>After CBR†—Group 1 (n = 6)</td>
<td>0.45 ± 0.08* 0.29 ± 0.08* 0.57 ± 0.10*</td>
<td>0.79 ± 0.09 0.93 ± 0.09 0.73 ± 0.12</td>
</tr>
<tr>
<td>After ABR†—Group 2 (n = 6)</td>
<td>0.45 ± 0.03* 0.31 ± 0.18* 0.67 ± 0.09*</td>
<td>0.93 ± 0.11 0.81 ± 0.12* 1.14 ± 0.09</td>
</tr>
<tr>
<td>Intact—Groups 3 and 4 (n = 14)</td>
<td>0.98 ± 0.11 0.75 ± 0.11 1.18 ± 0.12</td>
<td>0.75 ± 0.04 1.04 ± 0.15 0.72 ± 0.06</td>
</tr>
<tr>
<td>After BVX†—Groups 3 and 4 (n = 14)</td>
<td>0.58 ± 0.05* 0.58 ± 0.06 0.59 ± 0.06*</td>
<td>0.95 ± 0.13 1.11 ± 0.16 0.87 ± 0.12</td>
</tr>
<tr>
<td>BVX + CBR†—Group 3 (n = 6)</td>
<td>0.39 ± 0.07 0.40 ± 0.09 0.43 ± 0.07</td>
<td>0.76 ± 0.11 0.93 ± 0.10 0.74 ± 0.15</td>
</tr>
<tr>
<td>BVX + ABR†—Group 4 (n = 8)</td>
<td>0.53 ± 0.07 0.40 ± 0.08 0.62 ± 0.08</td>
<td>0.64 ± 0.10 0.54 ± 0.11 0.80 ± 0.15</td>
</tr>
</tbody>
</table>

Paired comparisons were made within the same groups of animals using an analysis of variance or paired t-test. The absence of symbols indicates that the changes in slopes did not attain statistical significance.
* Significant decreases ($P < 0.05$) between responses obtained before and after denervation of CBR (group 1), ABR (group 2), or BVX (groups 3 and 4).
† Significant differences between responses obtained after BVX and those obtained after BVX + CBR or BVX + ABR.

Effects of Changes in Baseline Resistance on Reflex Vascular Responses

We have interpreted the preservation of reflex vascular responses after either CBR or ABR as indicating preserved baroreflex control of sympathetic outflow to the hindlimb. This interpretation is valid only if increases in basal vasoconstrictor tone (such as those observed after CBRX or ABRX) to the hindlimb circulation do not augment reflex responses in that bed. If increases in basal vasoconstrictor tone did result in augmented responses to changes in sympa-
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baseline vascular resistance increased by 25% over a period of 1–2 hours without denervation of baroreceptors (Table 2: third and fourth series), yet the reflex vasoconstrictor and dilator responses to NG and PE were not altered (Fig. 3).

2. Vasodilator and vasoconstrictor responses to intra-arterial NG and PE were not altered in six rabbits after CBRX. Baseline perfusion pressure increased from 85 ± 2 to 106 ± 5 mm Hg after CBRX. Responses to two doses of NG (0.2 and 2.0 μg) and two doses of PE (0.2 and 2.0 μg) averaged −14 ± 2, −29 ± 2, +3 ± 1, and +27 ± 3 mm Hg, respectively, before CBRX. Corresponding values after CBRX were −10 ± 2, −30 ± 3, +3 ± 1, and +24 ± 3 mm Hg.

3. In another group of six rabbits, the sectioned lumbar sympathetic chain was stimulated either at low frequencies (mean 1.5 ± 0.3 Hz) to cause a perfusion pressure of 84 ± 4 mm Hg, or at high frequencies (4 ± 0.5 Hz) to cause a perfusion pressure of 111 ± 6 mm Hg. These values of perfusion pressure were comparable to those obtained before and after CBRX (group 1) or ABRX (group 2). For a given increase or decrease in frequency of sympathetic stimulation, the change in vascular resistance was either comparable or less at high basal resistance than at low basal resistance (Fig. 5). Thus, an increase in baseline sympathetic tone within the range observed in these experiments does not cause a greater vasoconstriction or vasodilation in response to a given increase or decrease in sympathetic activity.

Responses after Sinoaortic Denervation

Denervation of the remaining arterial baroreceptors in both groups 1 and 2 completed the SAD, and the results from these two groups following SAD (n = 14) were combined for analysis (Table 3; Fig. 4). After SAD, NG-induced hypotension did not result in changes in heart rate or perfusion pressure, but large increases in arterial pressure with PE (+42 ± 4 mm Hg) caused small decreases in heart rate (−7 ± 2 beats/min) and a biphasic change in perfusion pressure (Figs. 4 and 6). Vagotomy eliminated the reflex bradycardia and the vasodilator component (Table 3).

Responses after Vagotomy and Subsequent Partial Baroreceptor Denervation

Vagotomy alone inhibited significantly the reflex bradycardia during PE and tended to reduce the tachycardia during NG; the reflex vascular responses to PE or NG were unchanged (Tables 4 and 5). Denervation of either ABR or CBR in vagotomized animals did not alter significantly the reflex bradycardia or vasodilation during PE. The reflex tachycardia and vasconstriction, however, were reduced in several experiments by ABRX or CBRX, but the reductions did not attain statistical significance except with respect to the vasoconstrictor response after ABRX.

Discussion

The results of these studies allow three conclusions: First, there are major differences in baroreflex control of heart rate and vascular resistance which become apparent after partial denervation of arterial baroreceptor afferents. Second, section of one set of arterial baroreceptors is not compensated for by the remaining set with respect to activation of vagal efferents. In other words, there is no "redundancy" of activation of vagal neurons by aortic and carotid baroreceptors. In contrast, section of one set of afferents is totally...
compensated for by the remaining set with respect to inhibition of sympathetic neurons, i.e., there is marked "redundancy" in the inhibition of sympathetic neurons controlling vascular resistance and heart rate. Third, cardiopulmonary baroreceptors and other baroreceptors besides those in the aorta and carotid sinuses contribute modestly to the reflex responses to PE-induced hypertension.

This discussion will address three points: (1) the possible mechanisms involved in the differential control of heart rate and vascular resistance by arterial baroreceptors and the concept of summation of reflex effects from aortic and carotid baroreceptors; (2) the potential error in interpretation of the reflex vascular responses because of a change in baseline resistance and sympathetic tone after partial baroreceptor denervation; (3) the role of cardiopulmonary and other baroreceptors in these responses.

Mechanisms Involved in Differential Control of Rate and Resistance after Selective Baroreceptor Denervation

Tonic Inhibitory Influence of Carotid and Aortic Baroreceptors

The tonic inhibitory influence of baroreceptors was evaluated from the abrupt responses to acute section of the afferents. The carotid and aortic baroreceptors exerted essentially equivalent tonic inhibitory influences on heart rate, perfusion pressure, and arterial pressure. This was evident from the similar acute increases in rate and pressures in response to ABRX and CBRX (compare groups 1 and 2 in Table 1). Similar hemodynamic changes were noted also by Chalmers et al. (1967) in awake rabbits after aortic nerve section and after carotid sinus nerve section.

The most important finding in this study is that there are major differences in the baroreflex control of heart rate and of vascular resistance in the hindlimb. This was evident from the fact that section of either ABR or CBR impaired significantly the control of heart rate during PE-induced hypertension without interfering with the reflex control of hindlimb resistance (Tables 3–5). This differential influence must be due to the fact that heart rate responses are modulated by vagal as well as sympathetic neurons, whereas vascular responses are regulated predominantly by sympathetic neurons.

Responses to PE-Induced Hypertension

The heart rate responses to PE were impaired after either ABRX or CBRX. When the vagi were sectioned, the addition of CBRX or ABRX did not result in further impairment of the bradycardia during PE. Before vagotomy, the bradycardia was mediated by reciprocal changes in sympathetic and parasympathetic outflow to the heart, but after vagotomy, heart rate changes resulted solely from alterations in sympathetic outflow. The results indicate that, during PE, stimulation of both ABR and CBR is needed for the full stimulation of cardiac vagal motor neurons and vagal efferents, whereas activation of either ABR or CBR can mediate full inhibition of sympathetic neurons to the heart. The same can be said for the baroreflex inhibition of sympathetic outflow to the hindlimb; during PE, the stimulation of either ABR or CBR permitted full control of hindlimb vascular resistance.

The degree to which one set of arterial baroreceptor afferents may compensate for the absence of the other has been addressed previously. Several investigators have studied the individual and combined contributions of the four major afferent baroreceptor nerves (two aortic depressors and two carotid sinus nerves) on arterial pressure and sympathetic tone (Sagawa and Watanabe, 1965; Ninomya and Irisawa, 1969; Kezdi and Geller, 1968; Angell-James and Daly, 1970). When the left and right carotid sinus regions are stimulated in combination, the combined stimulation gives a greater response than when each sinus region is stimulated separately, but the responses of combined stimulation is less than the sum of individual responses. The same was observed in a corresponding comparison between the carotid and aortic baroreceptors (Angell-James and Daly, 1970). It was apparent that a sole remaining receptor area assumes a larger portion of the total control of the vasomotor neurons when the other receptor areas are eliminated. It has been shown (Ninomya and Irisawa, 1969) that during a rise in aortic pressure in the cat, the reflex inhibition of sympathetic activity by either the right or left carotid sinus nerves was increased by 50% after bilateral section of the vagal and aortic nerves. Sagawa and Watanabe (1965) referred to this interaction as "mutual inhibitory addition."

Our results support this concept and provide data which indicate that the extent of "mutual inhibitory addition" varies with respect to the control of vagal and sympathetic neurons by aortic and carotid baroreceptors. We would like to think of this concept in terms of "redundancy" of control of autonomic neurons by the baroreceptor afferents. In contrast to the previous studies, we found that there is "no redundancy" with respect to activation of vagal neurons, but that there is essentially "total redundancy" of the inhibition of sympathetic neurons. Differences in the degree of "redundancy" of control of vagal and sympathetic neurons may be related to the degree of convergency of aortic and carotid baroreceptor afferents on neurons in the central pathways for these reflexes.

Recent studies in dogs by Kendrick et al. (1979) suggest a mutual facilitatory interaction of carotid and aortic baroreflexes in the control of heart rate and a simple algebraic summation of these reflexes in blood pressure control. They showed that combined stimulation of both ipsilateral aortic and carotid sinus nerves resulted in cardiac slowing that was significantly greater than the respective sum of the responses to separate stimulation of these nerves. This observation fits with our results in that both aortic and carotid baroreflexes are needed for full control of heart rate. Our results further indicate that it is the parasympathetic component of the heart rate control-
ling mechanism that requires both sets of arterial baroreceptors. Our results do not suggest a facilitatory interaction of carotid and aortic baroreflexes in the control of heart rate. This difference between our study and that of Kendrick et al. may be due to their use of electric stimulation of aortic and carotid sinus nerves which may have activated chemo- as well as baroreceptor afferent fibers.

From a practical standpoint, our data suggest that altered baroreflex control of heart rate during increases in arterial pressure cannot be taken to indicate abnormal arterial baroreflex control of the total circulation. Recent results by Mancia et al. (1979) in humans with hypertension suggest that a dissociation may be present between heart rate responses and changes in total vascular resistance during the carotid baroreflex.

Responses to NG-Induced Hypotension

After sinoaortic denervation, the reflex responses to NG were abolished (Table 3), suggesting that cardiopulmonary vagal afferents did not mediate these responses. Furthermore, bilateral vagotomy alone had no statistically significant effect on the reflex tachycardia during NG, although the response tended to decrease from a slope of 0.75 ± 0.1 to 0.58 ± 0.06. Thus, tachycardia during NG was mediated mainly by activation of sympathetic efferents, and, to a lesser degree, by inhibition of vagal efferents. The addition of ABRX or CBRX to bilateral vagotomy resulted in further impairment of reflex tachycardia. The reflex tachycardia after both bilateral vagotomy and either ABRX or CBRX (average slopes of 0.40 in Table 3) was significantly less (P < 0.05) than in the "intact" animal (average slope of 0.75), indicating that both aortic and carotid baroreceptors are necessary for the reflex tachycardia during NG.

With respect to activation of sympathetic neurons to the hindlimb during NG-induced hypotension, the absence of CBR did not appear to influence the response, whereas absence of the ABR resulted in significant impairment of the reflex vasoconstriction. This was seen in groups 1 and 2 with intact vagal afferents, as well as groups 3 and 4 with sectioned vagal afferents. It appears that, after section of CBR, the ABR may exert a greater inhibitory influence on the sympathetic outflow to the hindlimb which becomes apparent when the ABR are unloaded during hypotension. The CBR may not exert a similarly greater inhibitory influence when the ABR were denervated.

The hypotensive effect of NG was greater after partial baroreceptor denervation, whereas the hypertensive effect of PE was not augmented. The impairment of reflex bradycardia after ABRX or CBRX may not have been sufficient to influence the pressor response to PE which must depend predominantly on the direct and reflex vascular responses to PE, both of which were preserved. The impairment of reflex tachycardia with NG may have contributed to a limited degree to the greater depressor effect of NG after partial denervation, but inhibition of reflex vasoconstriction was probably an important factor. Although inhibition of reflex vasoconstriction with NG was evident only after ABRX in the hindlimb, a more consistent and possibly more pronounced inhibition may have taken place in other vascular beds after either ABRX or CBRX.

Role of Changes in Baseline Rate, Resistance, or Sympathetic Tone

The differences in the effect of CBRX and ABRX on heart rate and perfusion pressure could be due to the shape of the stimulus-response relationship for baroreflex control of sympathetic outflow to the heart and hindlimb and on the location of the animal in the basal state on the curve for each reflex. The baseline perfusion pressure and vascular resistance of the hindlimb increased and remained elevated after partial arterial baroreceptor denervation, but the increases in heart rate were transient and returned to control values. The differential effect on the reflex control of heart rate and vascular resistance might therefore be attributed to the different influences on baseline parameters.

Myers and Honig (1969) showed that if the initial vascular resistance is high, dilator responses to sympathetic withdrawal increased and constrictor responses to sympathetic augmentation decreased. Such an explanation may account for the lack of evidence of impairment of reflex dilation during phenylephrine after partial denervation, but the same explanation would suggest that reflex vasoconstriction during NG was augmented after partial denervation.

Our results could not be explained on the basis of the passage of time or the increase in baseline resistance. The "time-control" experiments showed that reflex responses of both heart rate and perfusion pressure were not reduced throughout the experiment in sham-denervated animals (Fig. 3). In fact, there was an augmented reflex response of heart rate to PE at the very end of the study.

Another possible explanation for the differential influence of partial arterial baroreceptor denervation on heart rate and hindlimb resistance is that vascular reactivity may have increased as a result of an increase in baseline resistance. Increased reactivity would mask a reduction in reflex control due to interruption of afferent fibers. This is unlikely, since vascular responses to injection of PE and NG directly into the perfusion circuit did not differ significantly before and after CBRX. The most convincing argument against a significant role of an increase in baseline resistance within the ranges observed in this experiment is the fact that changes in sympathetic tone gave comparable or lesser changes in resistance when they were instituted from a higher baseline level of sympathetic activity than from a lower baseline level (Fig. 5). Thus, the preservation of baroreflex control of vascular resistance after partial denervation cannot be explained on the basis of a higher resting resistance.

The differential responses must be due in large part to the fact that heart rate responses are modulated by vagal as well as sympathetic neurons, whereas vas-
cular resistance is predominantly regulated by sympathetic neurons.

In the rabbit, the relative sympathetic influence on heart rate and hindlimb resistance may differ; the effect on heart rate may be limited. Thus, one cannot predict whether identical differential effects on rate and resistance will be noted in other animals that have a different degree of tonic vagal or sympathetic control to the heart. The thrust of this study, however, is the demonstration that, under certain experimental conditions (i.e., partial baroreceptor denervation), reflex vagal control of heart rate with phenylephrine is significantly impaired, whereas reflex sympathetic control of the hindlimb is largely preserved.

**Contribution of CPBR and Other Mechanoreceptors to Reflex Control during PE and NG**

After SAD, reflex bradycardia and vasodilation were observed during PE-induced hypertension, but there were no significant responses to NG-induced hypotension. The reflex bradycardia and vasodilation were abolished by bilateral vagotomy, suggesting that they were mediated through vagal afferents. Activation of mechanoreceptors in the cardiopulmonary region during PE may have triggered this inhibitory reflex after SAD. An important question is whether the CPBR normally contribute to the reflex responses to PE- or NG-induced changes in arterial pressure. If they do, then these interventions may not be used with confidence to assess the status of arterial baroreceptors. In our rabbits with intact arterial baroreflexes, the vagal afferent fibers did not seem necessary for the reflex control of hindlimb resistance vessels (Table 5). The participation of these vagal afferents was significant, however, after SAD (Mancia et al., 1973), and this should be taken into consideration in evaluating the baroreflex control of the peripheral circulation during increases in arterial pressure in pathological states such as hypertension and heart failure where arterial baroreflexes may be impaired (Higgins et al., 1972; Sleight, 1979; Abboud et al., 1981).

Denervation of aortic baroreceptors (ABRX) was performed by sectioning the aortic depressor nerves at the midcervical level. It is possible that some aortic baroreceptor fibers traveling in the cervical vagus in the rabbit (O'Leary et al., 1934) remained intact after SAD, and were responsible for the dilator responses of perfusion pressure to increases in arterial pressure with PE. This seems unlikely since, after SAD, no constrictor and negligible heart rate responses were noted when NG was administered and dilator responses were observed in many experiments after PE administration without concomitant changes in heart rate (Fig. 6). Thus, it is our view that the dilator responses to PE after SAD were mediated by cardiopulmonary baroreceptors with afferent vagal fibers and were eliminated by vagotomy.

The reduced reflex responses of heart rate after vagotomy (CBR and ABR intact) (Table 5) was due to the interruption of the vagal efferent fibers. After SAD (vagi intact), there were no changes in heart rate in response to hypotension and to moderate hypertension (Table 3; Figs. 4 and 6). It may thus be argued that vagal afferents were not importantly involved in reflex responses of heart rate to moderate arterial pressure changes. However, in rabbits with SAD, there were modest decreases in heart rate during large PE-induced increases in arterial pressure (Tables 3 and 5). This modest bradycardia probably resulted from activation of afferent vagal fibers.

Positive feedback excitatory reflexes mediated by spinal afferents have been reported to result from distension of the aorta in conscious dogs (Malliani et al., 1979) or in anesthetized cats (Schwartz et al., 1973; Lioy et al., 1974). This reflex may modulate negative feedback control systems such as arterial and cardiopulmonary baroreflexes (Schwartz et al., 1973). In the present study, we observed transient constrictor responses in hindlimb to PE injection after SAD (bi- phasic responses) and after SAD plus vagotomy (solely constrictor). This response was neurally mediated since it was abolished by lumbar sympathectomy (Fig. 6). The excitatory responses observed in our study differed from those previously reported (Schwartz et al., 1973; Lioy et al., 1974; Malliani et al., 1979). First, the constrictor response was only transient, whether or not vagi were intact and despite sustained elevation of arterial pressure following PE injection (Fig. 6). Second, the reflex had no influence on heart rate (Tables 3 and 4; Fig. 6). Although the afferent pathway mediating this excitatory reflex response was not investigated, we speculate that it was mediated by spinal afferents. Apparently this excitatory reflex was overridden by arterial baroreflexes, since we did not observe such responses when arterial baroreflexes were intact.

**Tonic Influences of Vagal Afferents**

Small responses to vagal section were seen when ABR and CBR were intact. When the vagi were sectioned subsequent to sinoaortic denervation, however, there were large increases in all measured variables, but these increases were not sustained. These findings may indicate that afferent vagal fibers normally exert little tonic inhibitory influence. An alternative interpretation is that the responses to withdrawal of CPBR are effectively buffered by ABR and CBR, although the reverse is not true. A final possibility is that the tonic influence of CPBR might not be easily detected from changes in heart rate, hindlimb perfusion pressure, or arterial pressure, but might be more evident if one examined changes in sympathetic outflow to other beds, such as the kidney (Thoren, 1979). All three of these points may be valid and have been suggested in other published work (Oberg and White, 1970; Mancia et al., 1973; Thoren, 1979).

In conclusion, our data indicate that there are differential effects of partial arterial baroreceptor denervation on the reflex control of heart rate and vascular resistance. Thus, reflex control of heart rate and vas-
cular resistance may be quantitatively dissociated. These differences probably reflect differences in baroreflex control of vagal and sympathetic mechanisms. Arterial baroreflexes account for the majority of responses of heart rate and vascular resistance to PE and NG. Our data also indicate that cardiopulmonary baroreceptors with afferent vagal fibers may contribute to the observed reflex bradycardia and vasodilatation accompanying large increases in arterial pressure. Excitatory reflex responses to raised arterial pressure which we observed may be mediated by spinal afferent fibers.

The use of reflex changes in heart rate with PE and NG as indicators of the arterial baroreceptor reflex control of the total circulation has significant limitations; caution and reservation are required in the interpretation of such results.

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