Effect of Selective Denervation of Baroreceptors on Pulmonary Ventilation and Arterial Pressure Lability in Rat

Helder Mauad, Mogens L. Glass, and Benedito H. Machado

Earlier studies report that sinoaortic baroreceptor denervation (SAD) in rats causes moderate elevation of mean arterial pressure along with a marked increase of arterial pressure lability (APL). In this context, we studied the effects of selective aortic denervation (AD) or selective carotid denervation (CD) on the regulation of blood pressure. In addition, we evaluated the effects of selective or total baroreceptor denervation on pulmonary ventilation and ventilation-related changes of arterial pressure. Mean arterial pressure was evaluated by computer-assisted techniques, and ventilation was measured by whole body plethysmography on conscious freely moving rats. With this approach, equal increases of mean arterial pressure were obtained for rats that had undergone AD, CD, and SAD. The APL was higher in SAD rats than in selectively denervated rats. CD and AD rats had an elevated APL relative to sham-operated animals, and its increase was approximately equal for the two selectively denervated groups. Total as well as selective denervation had relatively small effects on ventilation and on the general pattern of breathing. In all groups, this pattern consisted of regular ventilation, periodically interrupted by single deeper breaths. In SAD, AD, and CD animals, these larger tidal volumes were associated with marked transient reductions of mean arterial pressure, whereas small decreases of pressure occurred in sham-operated rats. The results indicate that both groups of baroreceptors must be present to keep mean arterial pressure at its normal level. Moreover, both receptor groups are equally important in reducing APL. Ventilation contributes to generation of APL after total or selective baroreceptor removal. Such ventilation-induced pressure changes are kept at a minimum in baroreceptor-intact rats. (Hypertension 1992;19[suppl II]:II-182-II-186)

The fine regulation of blood pressure in healthy mammals involves fast-responding aortic and carotid baroreceptors that provide information to the central nervous system. Removal of these receptors (sinoaortic deafferentation, SAD) causes moderate elevation of blood pressure accompanied by a marked increase of arterial pressure lability (APL). The generation of this lability is ascribed to a complex of factors that have not been completely evaluated. Earlier studies have not reported on the effects on APL of selective aortic denervation (AD) or selective carotid denervation (CD) of the baroreceptors. In the present study, we sought 1) to assess the effects of selective denervation on mean arterial pressure and its lability, 2) to evaluate the effects of such denervation on the pattern of pulmonary ventilation, and 3) to study the involvement of ventilatory events in the generation of mean APL.

The inclusion of ventilation measurements was motivated by a study reporting CD- and SAD-induced changes in the breathing pattern of infant rats. Moreover, observations by Krieger on rats that had undergone SAD suggested that some changes in mean arterial pressure could be ventilation related. Consequently, the present study focuses on the influences of both selective baroreceptor denervation and of pulmonary ventilation on mean arterial pressure and its lability.

Methods

Male Wistar rats (250–300 g) were instrumented with chronic arterial and venous catheters. To monitor arterial pressure, the abdominal aorta was cannulated via the femoral artery (PE-10 connected to a PE-50, Clay Adams, Parsippany, N.J.). In addition,
the femoral vein was cannulated for drug injection. SAD and selective CD or AD were performed as described by Krieger. With rats under ether anesthesia, a ventral midline incision followed by muscle retraction exposed the vagus, superior cervical ganglion, superior laryngeal nerve, and carotid bifurcation. Selective AD involved resection of the superior cervical ganglion and the superior laryngeal nerve. Selective CD required stripping of all fibers from the carotid sinus and subsequent painting with 10% phenol in ethanol solution to remove all baroreceptor afferents. Complete SAD required a combination of both denervation procedures. To assure complete recovery of rats from anesthesia, a postsurgical period of 24 hours preceded experimentation. The efficacy of SAD was tested just before study. Rats were accepted for study if they presented bradycardia of less than 24 beats per minute in response to an intravenous phenylephrine injection (3–5 μg/kg).

Arterial pressures were monitored with a Statham pressure transducer (P23Db) connected to a four-channel recorder (model 7754A, Hewlett-Packard Co., Palo Alto, Calif.). Mean arterial pressure was obtained from pulse pressure by means of a Bioelectric Amplifier (model 8811A, Hewlett-Packard) with an analog-to-digital interface to a Monydata-XT microcomputer. To obtain APL, sampling of individual pressure points was performed at a frequency of 1 Hz over a period of 30 minutes. APL was expressed as the standard deviation of the mean of all sampling points. Statistical evaluation of APL requires a special approach as applied by Alper et al and Jacob et al, because the standard deviation (the index for measurement of lability) does not fit a normal distribution, which precludes analysis by parametric statistics unless prior transformation is performed. Accordingly, the data were submitted to logarithmic transformation before further analysis. The differences between means of standard deviation were evaluated using the Newman-Keuls test with the level of significance at p<0.05.

Ventilation was measured by means of whole body plethysmography using the approach of Malan, which is based on monitoring of small pressure changes within a closed animal chamber. During inspiration, a gas volume is heated from ambient to body temperature, which increases total pressure within the chamber. Conversely, expiration decreases total pressure. A highly sensitive differential pressure transducer (Statham PM 979) connected to the recorder was applied for these measurements. For further details of the method and calculations, see Malan.

Experiments were performed on three groups of animals: those that had undergone SAD (SAD rats), AD (AD rats), or CD (CD rats). Sham-operated animals were provided separately for each group.

Results

The mean arterial pressures of SAD, AD, and CD rats were virtually the same and significantly elevated when compared with values for sham-operated animals (Figure 1). In SAD rats, APL was three to four times higher than their sham-operated control group and was also significantly higher than the CD and AD groups. Likewise, the lability of the selectively denervated rats was two to three times higher than their sham-operated control animals; however, there was no difference between the CD and AD groups (Figure 2).

Table 1 shows data for the ventilatory patterns in all groups, including controls. The general breathing pattern (frequency and tidal volume) was the same for all groups, with the exception of a reduced minute ventilation that reached significance in SAD rats. Regardless of group, the breathing pattern consisted of regular ventilation interrupted by single much deeper breaths, interposed at intervals of approximately 60–100 seconds (Table 1). In SAD, AD, and
CD rats, these larger tidal volumes were accompanied by transient (no more than 5-seconds duration), abrupt reductions of mean arterial pressure (Figure 3). The degree of such breathing-correlated falls of pressure was the same in all denervated groups, whereas a much smaller reduction occurred in their respective sham-operated control groups.

Discussion

The increase of mean arterial pressure in the SAD group was consistent with earlier data.1-5 Denervation of baroreceptors activates the sympathetic system, which in turn, results in an elevated mean arterial pressure. The pressure may return toward normal levels after a period of several days, even if the sympathetic activity remains higher than normal.1 Likewise, studies on dogs9 and rats4-10 document that the mean arterial pressure of SAD animals is not at a hypertensive level when recordings are performed on a 24-hour basis. An improved regulation of the level of mean arterial pressure in SAD animals may result from an increased role of cardiopulmonary low pressure baroreceptors that, however, are unable to exert the precise moment-to-moment adjustments typical of the arterial baroreceptors.11 Consequently, an increased pressure lability remains even after prolonged periods.

Selective denervation of aortic or carotid baroreceptors produced an increase of mean arterial pressure of the same magnitude as in SAD rats. This indicates that the presence of both sets of baroreceptors is necessary to keep mean arterial pressure at normal levels. Our study used computer-assisted evaluation of mean arterial pressure changes. Earlier work did not apply this technique to assess the effects of selective denervation in rats, so it is difficult to make comparisons with reports on different mammalian species.12

In contrast to the uniform effect of SAD, CD, and AD on mean arterial pressure, selective denervation had a significantly smaller effect in relation to APL. These results indicate that the two sets of barorecept-

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**TABLE 1. Recorded Ventilatory Variables in Rats With Sinoaortic Denervation, Aortic Denervation, and Carotid Denervation**

<table>
<thead>
<tr>
<th>Groups</th>
<th>$f_r$ (min⁻¹)</th>
<th>$V_T$ (ml·kg⁻¹)</th>
<th>$V_I$ (ml·kg⁻¹·min⁻¹)</th>
<th>INT$_{EV}$ (sec)</th>
<th>$V_{EV}$ (ml·kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO (n=6)</td>
<td>119±8</td>
<td>6.9±0.8</td>
<td>787±50</td>
<td>71±8</td>
<td>22.9±0.8</td>
</tr>
<tr>
<td>SAD (n=10)</td>
<td>114±6</td>
<td>5.4±0.4</td>
<td>617±48</td>
<td>89±13</td>
<td>19.8±1.7</td>
</tr>
<tr>
<td>SO (n=6)</td>
<td>107±5</td>
<td>4.9±0.3</td>
<td>524±15</td>
<td>92±11</td>
<td>18.5±1.5</td>
</tr>
<tr>
<td>AD (n=9)</td>
<td>102±4</td>
<td>4.6±0.4</td>
<td>465±35</td>
<td>97±9</td>
<td>14.8±1.0</td>
</tr>
<tr>
<td>SO (n=6)</td>
<td>113±5</td>
<td>4.9±0.5</td>
<td>568±77</td>
<td>80±6</td>
<td>15.5±1.1</td>
</tr>
<tr>
<td>CD (n=13)</td>
<td>108±4</td>
<td>4.3±0.2</td>
<td>467±32</td>
<td>100±11</td>
<td>15.5±0.8</td>
</tr>
</tbody>
</table>

Values are mean±SEM. $f_r$, respiratory frequency; $V_T$, tidal volume; $V_I$, minute ventilation; INT$_{EV}$, interval between large inspiratory event; $V_{EV}$, volume of large inspiration; SO, sham-operated control; SAD, sinoaortic-denervated group; AD, aortic-denervated group; CD, carotid-denervated group.

*p<0.05, Student's t test.*
tors are equally important in stabilizing arterial pressure. In the absence of one set of receptors, the remaining set was partially able to limit pressure lability.

Mean arterial pressure was the same in all three denervated groups, whereas APL was distinctly higher in SAD rats than in selectively denervated rats. This suggests a dissociation between lability and mean arterial pressure, which is consistent with Jacob et al,3 who reported that sustained increases of arterial pressure did not affect lability and concluded that APL is not pressure dependent.

The present data on respiratory frequency, tidal volume, and minute ventilation in normal rats are in complete agreement with the literature.13 The relatively small effect of denervation on the ventilatory pattern after SAD or selective denervation in adult rats gains interest in relation to a recent study by Hofer,6 who investigated CD and SAD in 8- to 10-day-old rats. In that study, both denervations caused abnormal and irregular ventilation characterized by frequent end-expiratory pauses.

In normal as well as in SAD rats, the ventilatory pattern consisted of prolonged (60-100-second) periods of continuous breathing, interrupted by recurring single breaths of an increased volume. These deep breaths caused small transient reductions of arterial pressure in normal rats, whereas SAD animals presented large and abrupt transient falls of mean arterial pressure. Selective denervations also produced large pressure reductions associated with deep breathing. These ventilation-related effects on pressure were of the same magnitude in AD, CD, and SAD animals. Consequently, partial or complete removal of arterial baroreceptors produced the same degree of ventilation-induced imbalance of arterial pressure regulation, which reflects a lack of moment-to-moment buffering of mean arterial pressure.1

Simultaneous ventilatory and circulatory events may originate from central mechanisms. Working on anesthetized, artificially ventilated rats, Cox and Brody14 reported decreases of arterial pressure after microinjection of lidocaine into the ventrolateral portion of the rostral medulla, an essential region for vasomotor tone and regulation of arterial pressure. The magnitude of these depressor events was augmented when tidal volume was increased. Their results indicate an interaction between pulmonary and chest wall afferent information to the central nervous system and regulation of arterial pressure. For a possible anatomic basis of such cardiorespiratory interactions, see Richter and Spyer.15

In conclusion, SAD, CD, and AD produced equal increases of mean arterial pressure, whereas the accompanying increases of APL were larger in SAD rats than in CD and AD animals. Moreover, selectively denervated rats presented a higher degree of APL than sham-operated rats. The results suggest an equal role of aortic and carotid baroreceptors in reducing APL. Large tidal volumes were associated with marked transient decreases of mean arterial pressure in all denervated groups, indicating that ventilation contributes to the generation of APL in the absence of an adequate baroreceptor control.

References

**KEY WORDS** - baroreceptors • sinoaortic denervation • ventilation • respiratory function
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