Cardiopulmonary control in sleeping Sprague-Dawley rats treated with hydralazine

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Carley, David W., Sinisa M. Trbovic, Alex Bozanich, and Miodrag Radulovacki. Cardiopulmonary control in sleeping Sprague-Dawley rats treated with hydralazine. J. Appl. Physiol. 83(6): 1954–1961, 1997.—To test the hypothesis that hydralazine can suppress spontaneous sleep-related central apnea, respiratory pattern, blood pressure, and heart period were monitored in Sprague-Dawley rats. In random order and on separate days, rats were recorded after intraperitoneal injection of 1) saline or 2) 2 mg/kg hydralazine. Normalized minute ventilation (NVI) declined significantly with transitions from wake to non-rapid-eye-movement (NREM) sleep (−5.1%; P = 0.01) and rapid-eye-movement (REM) sleep (−4.2%; P = 0.022). Hydralazine stimulated respiration (NVI increased by 21%; P < 0.03) and eliminated the effect of state on NVI. Blood pressure decreased by 17% after hydralazine, and the correlation between fluctuations in mean blood pressure and NVI changed from strongly positive during control recordings to weakly negative after hydralazine (P < 0.0001 for each). Postsigh and spontaneous apneas were reduced during NREM and REM sleep after hydralazine (P < 0.05 for each). This suppression was strongly correlated with the reduction in blood pressure and with the degree of respiratory stimulation. We conclude that mild hydralazine-induced hypotension leads to respiratory stimulation and apnea suppression.

baroreflex; sleep; hypotension; respiration; telemetry; apnea

ANATOMICAL AND FUNCTIONAL EVIDENCE suggests a close interdependence among the respiratory network, the central autonomic network, and the hypnogenic neurons of the brain stem and midbrain (10, 13). Accordingly, stimulation of peripheral chemoreceptors leads not only to increased minute ventilation (V̇I) but also to a generalized increase in sympathetic motor activity (25, 26). Along the same lines, stimulation of baroreceptors produces not only bradycardia and vasodilation but also decreased V̇I and suppression of respiratory reflexes (8). Comorbidity can also occur in clinical derangements of these systems. For example, sleep-related apnea causes profound disruption of sleep architecture and cardiovascular homeostasis (9). The prevalence of hypertension is increased among patients with sleep apnea (15), and the prevalence of sleep apnea is increased among patients with hypertension (7). Moreover, treatment of sleep apnea by continuous positive airway pressure can improve sleep consolidation and reduce hypertension (11) while treatment of hypertension by angiotensin-converting enzyme inhibitors has been shown in some cases to improve sleep apnea (12).

Several investigators have reported that spontaneous central apneas are expressed during all stages of sleep, at rates of 2 to 20 apneas/h, by several strains of rat (3, 14, 21, 28). We have further demonstrated that the apnea index is increased by 300% in spontaneously hypertensive rats with respect to normotensive strain controls and that normalizing blood pressure by hydralazine in spontaneously hypertensive rats significantly reduces apnea expression (3). In the present study, we employed telemetric blood pressure (BP) monitoring and single-chamber plethysmography to examine relationships among BP, heart period (HP), breath V̇I, and apnea expression. Furthermore, we tested the hypothesis that systemically administered hydralazine would suppress apnea expression in normotensive Sprague-Dawley rats.

METHODS

Ten adult (weighing 200–300 g) male Sprague-Dawley rats were included in this study. As previously described (3), rats were anesthetized (ketamine, 80 mg/kg ip and acetylpromazine, 2 mg/kg ip), and a surgical incision of the scalp was made to allow bilateral implantation of stainless steel screws into the frontal and parietal bones of the skull for electroencephalogram (EEG) recording. Bilateral wire electrodes were placed into the nuchal muscles for electromyogram (EMG) recording. The EEG and EMG leads were soldered to a miniature connector and fixed to the skull with cranioplastic cement. The skin was then sutured, and the rats were allowed at least 7 days for surgical recovery.

A second surgery was then performed for implantation of a telemetric BP monitor (TA11PA-C40; Data Sciences International, St. Paul, MN). The abdomen was shaved, scrubbed with iodine, and rinsed with alcohol and saline. A 4- to 6-cm midline abdominal incision was made to allow visualization of the area from the bifurcation of the aorta to the renal arteries. The aorta was dissected free, and the tip of the BP catheter was introduced via a longitudinal incision made by using a 21-gauge needle. The puncture was sealed with cellulose fabric and tissue adhesive, and the transmitter was attached to the abdominal wall with 3–0 silk suture. The incision was closed in layers, and rats were again allowed a 1-wk recovery period. Throughout the surgical and experimental period, rats were maintained on a 12:12-h light-dark cycle in a fixed environment at 20°C with 40% humidity. Food and water were available ad libitum.

Before shipping, each implant was calibrated at the factory (Data Sciences International), and calibration factors (offset and scale) were provided. Before implantation, each calibration was rechecked by progressively submerging the transmitter in a calibrated water column to a final depth of 100 cm. Adjustments to the calibration factors were made as appropriate, but in no case was the required adjustment >1%.

Respirations were recorded by placing each rat inside a single-chamber plethysmograph (PLYUN1R/U; Buxco Electronics, Sharon, CT; dimensions 6 in. width × 10 in. length × 6 in. height). Thermal fluctuations associated with tidal
respiration induce changes in pressure within the plethysmograph that, under appropriate conditions, are proportional to tidal volume (5, 6). Plethysmograph pressure was transduced by using a Validyne DP45–14 differential pressure transducer (∆±2 cmH2O). Plethysmograph pressure was referenced to a low-pass filtered (5 s time constant) version of itself to minimize the effects of any drift in temperature or ambient pressure during a recording. To minimize any possible artifact related to asymmetry or nonuniformity of pressure within the rectangular chamber, the transducer was mounted to and centered on the lid of the plethysmograph.

The plethysmograph chamber was flushed with room air at a constant regulated flow rate of 2 l/min. This flow was approximately one order of magnitude greater than the rat's Vi and was thus sufficient to ensure that carbon dioxide rebreathing did not occur (22). The room and box temperature were measured and maintained at 20 ± 0.5°C throughout. Animal core temperature was not continuously monitored, but individual measurements at ambient temperature = 20°C revealed a mean (±SD) of 37.28 ± 1.02°C for nine animals. From these values, tidal volume was calibrated by using the formula of Epstein et al. (6). Ambient temperature and pressure were measured immediately before each recording, and between-study calibrations were performed for repeated measurements in individual animals. Vi was defined as the product of breath inspiratory tidal volume and breath respiratory rate (RR).

EEG and EMG activities were carried from the connector plug on the rat head by a cable and passed through a sealed port in the plethysmograph. EEG, EMG, respirations, and BP were continuously digitized (100 samples·s⁻¹·channel⁻¹), displayed on a computer monitor (Experimenter's Workbench; Datawave Systems, Longmont, CO) and stored on disk. All signals were low-pass filtered (50 Hz corner frequency, 6-pole Butterworth filter) to prevent aliasing.

All polygraphic recordings were 6 h in length and were made between 1000 and 1600. Each rat was recorded twice in random order, once after injection with saline (1 ml/kg ip) and once after injection with hydralazine (2 mg/kg in a volume of 1 ml/kg ip). Recordings for an individual animal were separated by at least 3 days.

Polygraphic recordings of sleep and wakefulness (W) were assessed by computer algorithm by using the bifrontal EEG and nuchal EMG signals on 10-s epochs (2). This software discriminates W as a high-frequency, low-amplitude EEG with concomitant high EMG tone; non-rapid-eye-movement (NREM) sleep by increased spindles and theta EEG, together with decreased EMG; and rapid-eye-movement (REM) sleep by a low ratio of delta to theta band EEG activity and an absence of EMG tone. This automated scoring system has been extensively validated by Benington et al. (2), who demonstrated an overall accuracy of >90% vs. visual scoring. Sleep efficiency was measured as percentage of the total recorded epochs staged as sleep.

Throughout each 6-h recording, each beat was detected by an adaptive threshold algorithm (DataWave Systems), and the values of mean BP (MBP) and pulse interval, which served as an estimate of HP, were extracted. Normalized MBP (NBP) was also computed by dividing the value for each beat by the mean value recorded throughout the 6-h control (saline injection) recording for that animal during W stage.

A similar algorithm was employed to measure RR and Vi for each breath. Normalized RR (NRR) and Vi (NVI) were computed by dividing the appropriate value for each breath by the mean value recorded during W throughout the 6-h control recording for that animal. These normalized measurements facilitated examination of the effects of sleep and hydralazine administration on respiratory pattern. Sleep apneas, defined as cessation of respiratory effort for at least 2.5 s, were scored for each recording session and were associated with the stage in which they occurred; W, NREM, or REM sleep. The duration requirement of 2.5 s was arbitrarily chosen but it reflects at least 2 "missed" breaths, as we have previously described (3, 4, 16). The events detected represent central apneas, because decreased ventilation associated with obstructed or occluded airways would generate an increased plethysmographic signal rather than a pause. We characterized apneas as a posterior or spontaneous according to the presence or absence of a preceding inspiration at least 150% larger than the average amplitude during regular breathing. Apnea index, defined as apneas per hour in stage, was separately determined for NREM and REM sleep. The major effects of recording hour, sleep state, and hydralazine administration were assessed by using separate one-way analyses of variance (ANOVAs) with repeated measures. Interaction terms were evaluated using multi-way ANOVAs. Multiple comparisons between means were controlled by

![Fig. 1. Mean blood pressure (MBP) during wakefulness (W), non-rapid-eye-movement (NREM), and rapid-eye-movement (REM) sleep. Data are pooled for 10 animals, and each point reflects mean ± SE for each hour of recording (time) for control (C; ○) and hydralazine (HY; □) conditions. There is no significant effect of recording hour (circadian effect) during control recordings for any sleep stage (P > 0.2 for each stage by analysis of variance (ANOVA), with recording hour as a repeated measure). By contrast, in W and NREM, HY leads to maximal hypotension during the 1st 2 h, followed by a sustained plateau for the final 4 h [⁎ P < 0.05 vs. hours 3 through 6, with multiple contrasts controlled by Fisher's paired least significant difference (PLSD)].](image-url)
using the Fisher’s paired least significant difference (PLSD) or by use of specific paired t-tests, as indicated.

RESULTS

Effects of sleep and hydralazine on cardiovascular variables. Figure 1 depicts the hour-by-hour measurements of MBP throughout the 1000 to 1600 recording interval for all 10 animals pooled. During control recordings, there was no change in MBP over time in any sleep stage (P > 0.2 for each; ANOVA with time as a repeated measure). Similar results were observed for HP (P > 0.4; data not shown). In contrast, after hydralazine injection, a nadir occurred in MBP during the first 2 h, followed by a plateau that was sustained throughout the remainder of the recording (P < 0.0001 for main effect of recording hour; P < 0.05 for all contrasts between first 2 and final 4 h of recording). HP exhibited an inverse effect, with maximal values during the first 2 h (P < 0.0001). Because a cardiovascular steady state was not achieved until 2 h after hydralazine injection, all summary data and statistical evaluations presented below are derived from the final 4 h of each recording except as noted.

The effects of sleep state on MBP and HP are illustrated in Fig. 2 and Table 1. Figure 2 illustrates the successive decreases in MBP with transitions from W to NREM and REM sleep, respectively. Despite the significant interanimal variability in baseline BP, MBP consistently decreased during sleep and reached its lowest levels during REM sleep (P < 0.0001 by ANOVA, with sleep state as a repeated measure). Table 1 describes the inverse significant (P < 0.0007) changes in HP, which was longest in REM and shortest in W.

Hydralazine administration lowered MBP in every animal during all sleep stages by an average of 17% (P < 0.0001 by ANOVA; see Fig. 2). In addition, the sleep-state dependencies of MBP and HP were eliminated by hydralazine (P > 0.2 for each; see Fig. 2, Table 1).

Effects of sleep and hydralazine on respiratory pattern. Figure 3 presents group mean data for NV˙I hour by hour throughout the 6-h recording period. The significant increase in NV˙I (P < 0.01) after hydralazine administration was also observed in NRR (P < 0.05, data not shown). As for MBP, no significant time dependence was observed for either variable during the final 4 h of recording.

Figure 4 depicts, in the group mean data derived from the final 4 h of each recording, the effects of behavioral state and hydralazine treatment on NRR and NV˙I. Two-way ANOVA, by using injection type [control (saline) vs. hydralazine] and behavioral state as repeated measures within each animal, revealed a significant effect of hydralazine on NRR and NV˙I (P = 0.0032 for NRR; P = 0.03 for NV˙I). Individual contrasts, controlled for multiple comparisons by Fisher’s PLSD, demonstrated that NRR and NV˙I were higher after hydralazine injection than after saline injection in each of the three behavioral states tested (P < 0.01 for each). Paired t-tests indicated that significant declines in NV˙I observed with transitions from W to NREM (P = 0.02) and from NREM to REM (P = 0.01) were eliminated by hydralazine administration and were not observed in NRR during either recording condition.

Absolute values for RR are presented in Table 2. As in Fig. 4, the increase in RR after hydralazine administration is evident in all behavioral states (P < 0.01 for each, by Fisher’s PLSD). Despite the hydralazine-related decreases in breath duration, apnea (breath duration > 2.5 s) corresponded to approximately four
“missed” breaths during NREM and REM and during control and hydralazine recordings.

Effects of hydralazine on cardiopulmonary integration. Figure 5 demonstrates the average relationship between NVI and NBP for each animal during the final 4 h of recording. Solid symbols reflect behavior after hydralazine administration; open symbols indicate observations during control recordings. Because of the normalization employed, the values of NBP and NVI during W in control recordings are identical (1.0) for all animals. This baseline state is indicated by a single open circle at the intersection of the dashed lines. Figure 5 illustrates that, although the group MBP decreased and the group mean NVI increased after hydralazine, the change in BP was much more consistent. The solid symbols (hydralazine) are almost completely segregated from the open symbols (control) in terms of NBP. Figure 5 also indicates that the reduction in BP associated with sleep during control recordings was associated with decreased NVI. This sleep-related decrease in NVI was also observed after hydralazine administration, unless BP decreased by at least 15-20% from control.

Figure 6 exemplifies the dynamic relationships among BP, Vi, and behavioral state. The left and right panels present the control and hydralazine recordings, respectively, from a single animal. Although sleep state has a significant effect on both BP and Vi, it is evident that these variables are dynamically regulated and can demonstrate considerable variability even within individual behavioral states. Moreover, fluctuations in BP and Vi appear to be closely coupled, with a strong positive linear correlation coefficient of 0.64 during the control recording depicted in Fig. 6. Hydralazine administration not only leads to significant hypotension, shifting this relationship to the left, but the nature of the coupling is reversed, leading to a negative correlation coefficient of −0.42. This negative correlation is also observed even if the first 2 h of the hydralazine recording are excluded. In most individual animals, these relationships (positive correlation during control recording but negative correlation during hydralazine recording) could be observed separately in W and NREM sleep.

Table 3 provides the average slope of the Vi/BP relationship for each behavioral state in each recording condition. Post hoc contrasts (Fisher’s PLSD) confirmed the significant slope reversal with hydralazine administration (P < 0.0001). One-sample t-tests demonstrated that the average slope of Vi/BP was significantly greater than zero (P < 0.001 for each) during W, NREM, and REM of control recordings, whereas this slope was significantly less than zero (P < 0.05 for each) during W and NREM of hydralazine recordings. The mean slope during REM in hydralazine recordings was not different from zero.

Effects of hydralazine on sleep-related apnea. Hydralazine administration was associated with consistent but not uniform decreases in the expression of sleep-related apnea. Figure 7 shows that during NREM sleep spontaneous apnea index was decreased in 7 of 10 animals and postsigh apnea index was decreased in 8 of 10 animals after hydralazine administration. The effects during REM sleep were similar; spontaneous apnea index decreased in 7 of 10 animals, whereas postsigh apnea index decreased in 10 of 10 animals. In all cases, paired t-tests demonstrated these decreases to be significant (P < 0.05 in each case) for the group data. The decreased postsigh apnea indexes did not result from a decrease in sighs. Parallel analyses of the numbers of sighs per hour revealed no significant effects of hydralazine during NREM or REM sleep (P > 0.2 for each). Because the effect of hydralazine on apnea expression was not uniform in magnitude or even sign, we sought

| Table 2. Effects of sleep state and hydralazine on respiratory rate (l/min) |
|---------------------------------|-----------------|---|
| Control | Hydralazine | P |
| W | 125.5 ± 12.4 | 147.9 ± 15.1 | 0.01 |
| NREM | 115.1 ± 12.5 | 132.9 ± 12.4 | 0.01 |
| REM | 117.3 ± 6.9 | 127.0 ± 5.2 | 0.01 |

Values are means ± SE.
to correlate the change in apnea index with the changes in MBP and NV\dot{I}\] after hydralazine administration.

A consistent correlation was observed between changes in NV\dot{I}\] and changes in apnea expression, as depicted in Fig. 8. Straight-line segments relate the control and hydralazine recordings from individual animals. This relationship is seen most clearly in Fig. 8A, left but it is consistent with all four panels: during NREM, NV\dot{I}\] typically fell below 0.75 to 0.85, and apnea expression was significant; when hydralazine increased NV\dot{I}\] above 1.2 to 1.3, significant apnea expression was not observed. The range of NV\dot{I}\] between 0.75 and 1.3 was transitional, and a wide range of apnea expression was observed. Note □ and ◦ in Fig. 8A, left, which correspond to the same symbols in Fig. 7A, left. In these two animals, hydralazine administration was paradoxically associated with a decrease in NV\dot{I}\], and apnea expression was increased.

Table 4 summarizes the sleep-wake architecture during control and hydralazine recordings. Hydralazine administration was associated with no change in the volume of NREM sleep (\(P = 0.95\)) and a 47% decrease in REM sleep volume (\(P < 0.0001\)).

**DISCUSSION**

This study demonstrates in Sprague-Dawley rats that transitions from W to NREM and REM sleep are associated with progressive decreases in V\dot{I}\] (Fig. 4) and increases in apnea expression (Fig. 7). The 15–25% decrease in V\dot{I}\] with sleep onset is associated with significant apnea expression, whereas increasing V\dot{I}\] by 25% via hydralazine administration is associated with near-total apnea suppression (Fig. 8). Hydralazine administration also reverses the positive correlation between fluctuations in MBP and NV\dot{I}\] observed at baseline (Fig. 6, Table 3).

Sleep is associated with characteristic changes in respiratory and cardiovascular regulation and, possibly, cardiopulmonary interactions. NREM sleep onset is associated with small but reproducible decreases in V\dot{I}\] and BP in most mammalian species, including humans (19). The present study confirms progressive decreases in NV\dot{I}\], MBP, and heart rate during NREM and REM sleep, respectively, in Sprague-Dawley rats.
It has been shown in humans that NREM sleep is associated with increased sensitivity of baroreflexes that may contribute to the observed decrease in BP (20, 23). Augmented baroreflexes during sleep may also contribute to the well-documented decreases in ventilation and chemoreflex sensitivity (19).

It has long been appreciated that baroreflexes and respiratory chemoreflexes can be mutually inhibitory (18). The general response to chemoreceptor stimulation includes increased $V_\text{I}$ and vasoconstriction in several vascular beds. Conversely, arterial baroreceptor stimulation leads to reduced ventilation and vasodilation. Heistad et al. (8) demonstrated in dogs that activation of baroreceptors inhibited the ventilatory and vasoconstrictor responses to peripheral chemoreceptor stimulation. Somers and co-workers (24, 26, 27) showed that the sympathetic motor response to hypoxia, but not hypercapnia or cold challenge, is inhibited by baroreceptor stimulation. Also, small reductions in arterial BP in awake dogs lead to significant stimulation of ventilation (17), presumably by reducing baroreceptor stimulation. However, the ventilatory baroreflex in the rat may differ from that in other animals, including dogs. A recent study of conscious Sprague-Dawley rats failed to reproduce ventilatory depression after arginine vasopressin infusion (30), which had been demonstrated previously in conscious dogs (17). The authors concluded that the ventilatory baroreflex may adapt more quickly in rats than in dogs. In contrast to these findings, we recently demonstrated that administration of protoveratrin A and B at doses known to stimulate baroreflexes produced bradycardia and ventilatory depression for at least 6 h during W and sleep in Sprague-Dawley rats (29).

In the present study, hydralazine yielded hypotension (MBP decreased by 17%, $P < 0.0001$), tachycardia (HP decreased by 6%, $P < 0.05$), and increased $V_\text{I}$ ($P = 0.03$). This constellation of responses is consistent with disinhibition of respiratory drive and sinoatrial node activity by reduced baroreceptor activity after hydralazine administration. It is noteworthy that during hydralazine-induced hypotension, the sleep-state dependencies of NV$\,V_\text{I}$, MBP, and HP were eliminated. It may be that, during hypotension, modulation of baroreflexes by changes among behavioral states was insufficient to significantly alter average baroreceptor activity.

Whereas hydralazine-induced hypotension would be expected to reduce baroreceptor afferent firing, the short-term fluctuations in MBP and NV$\,V_\text{I}$ suggest that these afferents retained an active inhibitory role on NV$\,V_\text{I}$ after hydralazine administration. Figure 5 illustrates that a weak negative correlation existed between fluctuations in MBP and NV$\,V_\text{I}$ during hydralazine-induced hypotension, even when only the final 4 h of recording were considered. In contrast, during control recordings, NV$\,V_\text{I}$ and MBP demonstrated a strong positive correlation. These relationships suggest that during control recordings MBP and NV$\,V_\text{I}$ are primarily determined by fluctuations among behavioral states; with the greatest NV$\,V_\text{I}$, MBP, and heart rate during W.

### Table 3. State and hydralazine effects on $V_\text{I}$/MBP (ml·min$^{-1}$·mmHg$^{-1}$)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hydralazine</th>
<th>$P$</th>
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<tbody>
<tr>
<td>W</td>
<td>7.8±1.7</td>
<td>−1.9±.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NREM</td>
<td>7.1±1.4</td>
<td>−1.5±.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>REM</td>
<td>6.2±2.2</td>
<td>−.4±.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. $V_\text{I}$, minute ventilation; MBP, mean blood pressure. All control slopes were significantly greater than 0 ($P < 0.001$ by one-sample $t$-test). After hydralazine administration, slopes were significantly less than zero during W and NREM ($P < 0.05$, one-sample $t$-test); during REM the slope was not different from zero. NS, not significant.

It has been shown in humans that NREM sleep is associated with increased sensitivity of baroreflexes that may contribute to the observed decrease in BP (20, 23). Augmented baroreflexes during sleep may also contribute to the well-documented decreases in ventilation and chemoreflex sensitivity (19).

Values are means ± SE. $V_\text{I}$, minute ventilation; MBP, mean blood pressure. All control slopes were significantly greater than 0 ($P < 0.001$ by one-sample $t$-test). After hydralazine administration, slopes were significantly less than zero during W and NREM ($P < 0.05$, one-sample $t$-test); during REM the slope was not different from zero. NS, not significant.

![Fig. 7. Expression of spontaneous (left) and post-sigh (right) apneas per hour of NREM (A) and REM (B) sleep. Straight line segments connect control and HY (A) and REM (B) sleep.](http://jap.physiology.org/DownloadedFrom)
Conversely, during hypotension the relationship between MBP and NV˙I is reversed.

During hydralazine-induced hypotension spontaneous and postsigh apneas were suppressed during NREM and REM sleep. Three possible mechanisms must be considered: 1) disinhibition of ventilation secondary to reduced baroreceptor activation, 2) nonspecific effects due to hypotension and possible cranial hypoperfusion, and 3) direct central nervous system action of hydralazine. The most likely explanation is disinhibition of respiratory drive. During all states, hydralazine administration was associated with hypotension in every animal and with increased V˙I in most animals, compared with control recordings. This is consistent with disinhibition secondary to decreased baroreceptor stimulation. Nonspecific circulatory effects on respiratory drive cannot be ruled out, however. Although unlikely during the moderate hypotension observed in the present study, compromised oxygen delivery to the brain could offset or negate the respiratory stimulation resulting from baroreceptor inhibition. Indeed, despite significant hypotension, two animals exhibited no change or a decrease in NV˙I after hydralazine administration. Hypotension-induced general depression of the central nervous system may have contributed to this effect. This would, however, be unexpected, as hydralazine is not normally associated with decreased cerebral perfusion (1).

Hydralazine is believed to exert its primary effects on the circulatory system. Preferential arteriolar dilation results from altered calcium metabolism within smooth muscle cells. In concert with this effect, heart rate, stroke volume, and cardiac output typically increase (1). Although administered peripherally, some metabolites of hydralazine are known to cross the blood-brain barrier. Direct central effects of these metabolites on respiration cannot, therefore, be excluded. Also, hydralazine potentiates the production of nitric oxide within the vasculature. Nitric oxide can freely diffuse across the blood-brain barrier, and it is possible that increased brain stem interstitial nitric oxide concentrations contributed to the observed respiratory stimulation after hydralazine administration.

Whatever the mechanisms, changes in apnea expression during sleep and after hydralazine administration correlated with changes in integrated respiratory drive, as estimated by NV˙I (Fig. 8). During sleep in most control recordings, NV˙I dropped by 15–30% with respect to quiet W state, and significant apnea expression was observed. When NV˙I did not drop with sleep onset (NV˙I remained ≥1), apnea expression remained low. In most animals, hydralazine administration was associated with NV˙I = 1.25 and with minimal apnea expression. In two animals (◊ and □ symbols in Figs. 7 and 8), hydralazine was not associated with increased V˙I, and apnea expression was not suppressed. We have previously demonstrated that respiratory stimulation by inspired hypercapnia or hypoxia also leads to apnea suppression in Sprague-Dawley rats (5). Taken together with the present study, these observations suggest that integrated respiratory drive is an important factor that determines the likelihood of apnea expression during sleep in the rat. In this interpretation, sustained states of decreased drive render the respira-

Table 4. Effects of hydralazine on sleep/wake states

<table>
<thead>
<tr>
<th>Condition</th>
<th>NREM, min</th>
<th>REM, min</th>
<th>Sleep Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>218.8 ± 15.1</td>
<td>33.5 ± 2.2</td>
<td>252.3 ± 15.2</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>220.3 ± 14.9</td>
<td>17.6 ± 1.8</td>
<td>237.9 ± 13.7</td>
</tr>
<tr>
<td>P</td>
<td>0.95</td>
<td>0.0001</td>
<td>0.49</td>
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Values are means ± SE.
tory network more vulnerable to apnea expression, whereas interventions or conditions that increase the baseline respiratory drive diminish apnea expression with respect to control conditions.

In summary, the present study demonstrates in Sprague-Dawley rats that NREM and REM sleep are associated with progressive decreases in BP, heart rate, and Vi, as has been observed in humans. Hydralazine induces hypotension, tachycardia, increased V˙I, and suppression of apnea. These findings suggest that sleep-related apnea is promoted by sustained states of decreased respiratory drive.

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