Response time and sensitivity of the ventilatory response to CO₂ in unanesthetized intact dogs: central vs. peripheral chemoreceptors

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We assessed the speed of the ventilatory response to square-wave changes in alveolar PCO₂ and the relative gains of the steady-state ventilatory response to CO₂ of the central chemoreceptors vs. the carotid body chemoreceptors in intact, unanesthetized dogs. We used extracorporeal perfusion of the reversibly isolated carotid sinus to maintain normal tonic activity of the carotid body chemoreceptor while preventing it from sensing systemic changes in CO₂, thereby allowing us to determine the response of the central chemoreceptors alone. We found the following. 1) The ventilatory response of the central chemoreceptors alone is 11.2 (SD = 3.6) s slower than when carotid bodies are allowed to sense CO₂ changes. 2) On average, the central chemoreceptors contribute ~63% of the gain to steady-state increases in CO₂. There was wide dog-to-dog variability in the relative contributions of central vs. carotid body chemoreceptors; the central exceeded the carotid body gain in four of six dogs, but in two dogs carotid body gain exceeded central CO₂ gain. If humans respond similarly to dogs, we propose that the slower response of the central chemoreceptors vs. the carotid chemoreceptors prevents the central chemoreceptors from contributing significantly to ventilatory responses to rapid, transient changes in arterial PCO₂ such as those after periods of hypoventilation or hyperventilation (“ventilatory undershoots or overshoots”) observed during sleep-disordered breathing. However, the greater average responsiveness of the central chemoreceptors to brain hypcapnia in the steady-state suggests that these receptors may contribute significantly to ventilatory overshoots once unstable/periodic breathing is fully established.

carotid body; chemosensitivity; control of breathing; sleep apnea

Recent investigations have reemphasized the need for accurate assessment, in an intact physiological preparation, of both the speed of response and relative gains of the central vs. the peripheral chemoreceptors to changes in arterial PCO₂ (PaCO₂) (3, 5, 21, 24, 31). Despite decades of study, both of these questions remain controversial.

Speed of Response

On the one hand, it is well established that changes in alveolar PCO₂ are reflected in brain extracellular fluid pH within a few seconds, a time course that is consistent with lung to brain circulation time (1, 9, 19, 23, 34). In addition, recent findings have shown that some types of medullary chemosensitive neurons are closely associated with small arteries (3, 24, 31) and would, therefore, be ideally suited to respond rapidly to changes in PaCO₂. On the other hand, recent studies in unanesthetized, carotid body-denervated (CBD) preparations have shown a relatively slow response time on the order of 30–35 s (5, 21).

Sensitivity

Studies using isolation of the central chemoreceptors via pontomedullary perfusion in the anesthetized cat demonstrated that the carotid chemoreceptors accounted for 20–50% of the steady-state ventilatory response to hypercapnia (15). On the other hand, results from awake and anesthetized cats (22, 30) and awake goats (11, 26, 27) suggested that central chemoreceptors were responsible for all of the ventilatory response to hypercapnia. What has been lacking to date is a specific test of the sensitivity of the ventilatory response to CO₂ mediated by the central chemoreceptors in an unanesthetized intact preparation with clear separation of the carotid body and central chemosensors, but in which all essential sensory inputs to the respiratory controller are intact.

Limitations of CBD Studies

A potential major limitation of CBD is the possibility of reduced gain of the central respiratory control system after the denervation, and several studies support this concept. It has recently been shown that hypoxic carotid body stimulation affects the output of putative chemoreceptor neurons in the retrotrapezoid nucleus (14, 20), raising the concern that denervation would remove an important input to the central chemosensor. Other studies have documented functional deficits in medullary raphe and pre-Bötzinger complex after CBD (16, 18).

A second potential limitation of CBD is the well-known change in acid-base status due to the variable but often marked CO₂ retention observed post-CBD (e.g., Refs. 12, 29).

A third major limitation of CBD studies is the concern that there may be time-dependent compensatory changes after denervation. That is, after the initial rise in PaCO₂ after denervation, PaCO₂ may fall and the gain of the ventilatory response to CO₂ may rise gradually over days to weeks presumably due to alterations/upregulation of the central chemoreceptor, central controller, and/or aortic chemoreceptors (2, 17, 25).

Accordingly, we sought to quantify the differences between central and peripheral CO₂ sensitivity and speed of response in the intact, unanesthetized preparation. We utilized extracorporeal perfusion of the vascularity isolated carotid sinus (and, therefore, the carotid body) in the unanesthetized dog to maintain normal blood gases at the carotid body chemorecepto-
tors while isolating it from systemic changes in PCO₂, PO₂, or pH. Thus we could assess the response time and sensitivity of the ventilatory response to hypercapnia when only the central chemoreceptors could sense the hypercapnia and also when the carotid body chemoreceptors were present and providing normal, tonic, afferent output. Our major findings were the following. 1) When acting alone, the central chemoreceptors delayed the ventilatory response to increased Pr_CO₂ by ~11 s, or ~58% slower than the intact animal. 2) The central chemoreceptors alone contribute the majority of the steady-state ventilatory response to CO₂, but the relative contribution of central vs. carotid body chemoreceptors varied markedly among dogs.

**METHODS**

Studies were performed on 12 unanesthetized, female, mixed-breed dogs (20–25 kg). Two series of studies were performed. In one series, six of these dogs were used to address the speed of response of the central chemoreceptors (4 intact, carotid sinus perfused and 2 studied before and after CBD). In the second series, the remaining six dogs were used to address the relative contribution of the central chemoreceptors to the gain of the ventilatory response to hypercapnia. All studies were performed during quiet wakefulness. The dogs were trained to lie quietly in an air-conditioned (19–22°C) sound-attenuated chamber. Throughout all experiments, the dogs’ behavior was monitored by an investigator seated within the chamber and also by closed-circuit television. The Animal Care and Use Committee of The University of Wisconsin-Madison approved the surgical and experimental protocols for this study.

**Chronic Instrumentation**

Our preparation required two surgical procedures performed under general anesthesia and with strict sterile surgical techniques and appropriate postoperative analgesics and antibiotics. In the first procedure, a chronic tracheostomy was created, and a five-lead electroencephalogram-electrooculogram montage was installed. Electroencephalogram leads were tunneled subcutaneously to the cephalad portion of the dog’s back where they were exteriorized.

In the second procedure, the left carotid body was denervated, and the right carotid sinus was equipped with a vascular occluder and catheter to permit extracorporeal perfusion of the reversibly isolated carotid sinus-carotid body (see Carotid Sinus Perfusion below). Indwelling catheters were also placed in the abdominal aorta and abdominal vena cava via branches of the femoral artery and vein, respectively. Catheters were tunneled subcutaneously to the cephalad portion of the dog’s back where they were exteriorized. Dogs recovered for at least 4 days before study. In the two CBD dogs, the second procedure consisted solely of CBD. This was achieved by stripping the adventitia and any surrounding tissue away from all vessels in the carotid sinus region.

**Carotid Sinus Perfusion**

Dogs lay unrestrained on a bed in an air-conditioned, sound-attenuated chamber. The extracorporeal perfusion circuit was primed with ~700 ml of saline, 120 ml of allogenic blood, and 5,000 U of heparin (derived from beef lung) and supplemented with 2,500 U/h. PCO₂, PO₂, and pH in the perfusion circuit were matched to a given dog’s eupneic values by adjustment of the gas concentrations supplying the circuit and by addition of NaHCO₃. The carotid sinus region was perfused at flow rates <100 ml/min, which raised the pressure in the sinus region by <10 mmHg. Before data acquisition, a 30-min period of normal perfusion of the carotid sinus region was used to ensure uniformity between systemic and extracorporeal circuit blood. Intravenous boluses of NaCN (~20 mg/kg) were used to confirm isolation of the carotid sinus during perfusion and also served to confirm denervation of the contralateral carotid body. These techniques have been described in detail in previous publications (6, 32, 33).

**Use of unilateral CBD.** Our method of carotid body perfusion does require unilateral CBD on the nonperfused side. Although the potential effect on the central ventilatory control system mentioned in the introduction is a concern, we think it is probably not significant. There is evidence using this preparation in both the goat (4) and the dog (33) showing that unilateral CBD has little consistent effect on ventilation during control, air-breathing conditions or on ventilatory responses. Apparently, there is sufficient redundancy in the control system to compensate for the loss of one carotid body.

**Experimental Setup and Measurements**

The dogs breathed via an endotracheal tube inserted into the chronic tracheostomy. Airflow was measured with a heated pneumotachograph system (model 3700, Hans Rudolph, Kansas City, MO; model MP-45-14-871, Validyne, Northridge, CA) connected to the endotracheal tube. The pneumotachograph was calibrated before each study with four known flows. One-milliliter arterial or perfusion circuit samples were analyzed for pH, PO₂, and PCO₂ on a blood-gas analyzer (model ABL-505, Radiometer, Copenhagen, Denmark). The blood-gas analyzer was validated daily with dog blood tonometered with three different combinations of PO₂ and PCO₂ covering the range encountered in the experiments. Samples were corrected for both body temperature and systematic errors revealed by tonometry. Ventilation and blood pressure signals were digitized (128-Hz sampling frequency) and stored on the hard disk of a personal computer for subsequent analysis. Key signals were also recorded continuously on a polygraph (Gould ES 2000 or AstroMed K2G). All ventilatory data were analyzed on a breath-by-breath basis by means of custom analysis software developed in our laboratory.

**Experimental Protocol: Response Time Study**

The control protocol consisted of several 1- to 2-min exposures to near-square-wave increases (+10–12 Torr) in Pr_CO₂ (Fig. 1). In this
situation, both carotid body chemoreceptors and central chemoreceptors were exposed to the elevations in PaCO\(_2\) ("CB + Central"). The test protocol consisted of identical CO\(_2\) challenges, but normocapnic, normoxic, and normohydric carotid sinus perfusion was maintained throughout each trial, thus maintaining normal conditions at the carotid body, despite subsequent increases in systemic PaCO\(_2\) ("Central Only"). CBD dogs were assessed similarly, except the comparison was pre- vs. postdenervation.

Experimental Protocol—Relative Sensitivity Study

The control protocol consisted of one to five steady-state CO\(_2\) response tests in dogs surgically prepared for carotid sinus perfusion but in which endogenous perfusion of the carotid sinus with normal systemic blood was permitted to occur (i.e., CB + Central). Each of two to three levels of increased inspired CO\(_2\) fraction in air was presented for ~5 min in random order. The test protocol consisted of CO\(_2\) challenges identical to those used during endogenous perfusion, but normocapnic, normoxic, and normohydric carotid sinus perfusion was maintained throughout each trial, thus maintaining normal conditions at the carotid body, despite subsequent increases in systemic PaCO\(_2\) (i.e., Central Only).

Data Collection and Analysis

**Speed of Response.** We determined the time to the first significant ventilatory response [breath-by-breath minute ventilation (V\(_t\)]. A V\(_t\) response was considered significant if it was three standard deviations greater than the mean of the preceding normocapnic V\(_t\).

**Relative Sensitivity.** Ventilatory data from the last minute of each 5-min interval of air breathing or hypercapnia was averaged to determine the response to the hypercapnic stimulus. Triplicate arterial blood samples were obtained during the last minute to define the PaCO\(_2\) stimulus. Slopes for each condition (i.e., CB + Central, Central Only) were determined by linear regression of the steady-state values. The response slope due to the carotid body chemoreceptors was determined by difference [(CB + Central) – (Central Only)].

**Statistics.** In all studies, an unpaired t-test (assuming unequal variances) was used to compare dog-by-dog comparisons. Paired t-tests were used to assess significance in mean group data. Differences were considered significant if P ≤ 0.05.

**RESULTS**

**Speed of Response**

Table 1 shows that carotid sinus perfusion with blood gases and pH matched to eupneic values in this group of dogs resulted in no significant changes in ventilation, in its components, or in blood gases relative to eupneic, nonperfused control. Thus, as we have previously shown (33), extracorporeal perfusion of the carotid sinus region, by itself, did not affect ventilation.

Figure 1 illustrates the ventilatory responses to a step increase in PetCO\(_2\), in the same representative dog (dog D) during endogenous perfusion (CB + Central) and extracorporeal carotid sinus perfusion (Central Only). Note the rapid response in the endogenous perfusion trial (~6.5 s) and the delayed response (~16.4 s) in the carotid sinus perfusion trial.

Figure 2 illustrates mean breath-by-breath values for all trials in one representative dog (dog C). Note that the mean data are consistent with the example in Fig. 1, namely that central chemoreceptors alone required ~10 s longer to respond to increased PaCO\(_2\), than when both central and carotid body chemoreceptors were exposed to the increased PaCO\(_2\).

The findings are summarized for all four dogs in Fig. 3. Each bar represents the mean of all trials in a given condition (CB + Central vs. Central Only) for one dog. Note that all dogs showed a significantly delayed response when only the central chemoreceptors could sense the increased CO\(_2\) (delay range: +6.2 to +13.9 s; mean 11.2 s i.e., ~58% slower than during endogenous perfusion).

**Relative Sensitivity**

Figure 4 shows the ventilatory response to CO\(_2\) during the first 2 min of a steady-state test when both carotid body and central chemoreceptors sensed the hypercapnia vs. extracorporeal perfusion of the carotid sinus with normal blood gases and pH such that only the central chemoreceptors sensed the hypercapnia. This figure illustrates that the magnitude of the response was reduced when only the central chemoreceptors could respond to the hypercapnia.

Figure 5 shows mean ventilatory responses to CO\(_2\) in three dogs to illustrate the range of slopes encountered in this study. Figure 6 summarizes the slope data for all six dogs. All dogs manifested decreased ventilatory response slopes when only the central chemoreceptors sensed the hypercapnia; however, in two dogs, the decrease was small. On average, the central chemoreceptors accounted for 63% of the ventilatory response slope to hypercapnia; thus 37% was attributable to carotid body chemoreceptors. However, also note the marked heterogeneity among dogs in the relative contributions of central vs. carotid body chemoreceptors to the total response. In four of the dogs, the central contribution exceeded that of the carotid bodies, whereas in the remaining two dogs the carotid body exceeded the central. This figure also illustrates the wide variability in

Table 1. Air-breathing controls: ventilatory components and PetCO\(_2\).  

<table>
<thead>
<tr>
<th></th>
<th>Ti, s</th>
<th>Te, s</th>
<th>f, breath/min</th>
<th>V, liter</th>
<th>V, l/min</th>
<th>PetCO(_2), Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB + Central</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.71</td>
<td>2.39</td>
<td>15.6</td>
<td>0.3</td>
<td>4.59</td>
<td>37.3</td>
</tr>
<tr>
<td>SD</td>
<td>0.50</td>
<td>0.51</td>
<td>3.7</td>
<td>0.04</td>
<td>0.77</td>
<td>2.2</td>
</tr>
<tr>
<td>Range</td>
<td>1.17–2.43</td>
<td>1.7–2.82</td>
<td>11.7–21.1</td>
<td>0.24–0.36</td>
<td>3.52–5.85</td>
<td>34.8–39.9</td>
</tr>
<tr>
<td>Central Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.71</td>
<td>2.22</td>
<td>16.9</td>
<td>0.29</td>
<td>4.75</td>
<td>37.7</td>
</tr>
<tr>
<td>SD</td>
<td>0.59</td>
<td>0.65</td>
<td>6.2</td>
<td>0.02</td>
<td>1.43</td>
<td>1.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.92–2.42</td>
<td>1.3–3.19</td>
<td>11.3–27.8</td>
<td>0.26–0.31</td>
<td>3.0–7.14</td>
<td>35.6–40.0</td>
</tr>
</tbody>
</table>

Values are group means for normal control (carotid body (CB) + Central) and extracorporeal perfusion (Central Only) of the isolated carotid sinus (perfusate with normal arterial pH, P\(_{CO_2}\), and P\(_{O_2}\)), Ti, inspiratory time; Te, expiratory time; f, breathing frequency; V, tidal volume; V, minute ventilation; PetCO\(_2\), end-tidal P\(_{CO_2}\).
response slopes between dogs when both carotid body and central chemoreceptors were exposed to CO₂ and the fact that there was no consistent relationship between the magnitude of these slopes and the slopes of the central response alone or the carotid body response alone.

DISCUSSION

Our study provides two major findings. The first was that the ventilatory response to abrupt increases in PETCO₂ was delayed by \( \sim 11 \) s (i.e., 19.6 s vs. 30.9 s) when only the central chemoreceptors could sense the increase in CO₂ while the carotid body chemoreceptors were present but maintained at normal blood gas values. The second major finding was that the central chemoreceptors account for \( \sim 63\% \) of the steady-state ventilatory sensitivity to hypercapnia. Thus the remainder of the steady-state ventilatory sensitivity to hypercapnia, \( \sim 37\% \), was due to the carotid chemoreceptors. The relative contribution of the central vs. carotid body chemoreceptors to the total CO₂ response was highly variable among dogs.

We propose that the somewhat slower response of the central chemoreceptors vs. the carotid chemoreceptors coupled with the absence of nearly 40% of available CO₂ sensitivity...
prevents the central chemoreceptors from contributing significantly to ventilatory responses to rapid transient changes in PaCO2 such as those after periods of hypoventilation and hyperventilation (“ventilatory undershoots and overshoots”) observed during sleep-disordered breathing (also see Implications For Sleep Apnea below).

Significance of the Unanesthetized, Intact, Carotid Sinus-Perfused Model

We believe that the present study utilizing the unanesthetized, carotid sinus-perfused dog model to isolate the carotid body chemoreceptors from the central chemoreceptors is an important advance in this area over the CBD model. This model, with intact but reversibly isolated carotid bodies, is a more physiological one in three important ways (see the introduction for details). 1) The dogs were unanesthetized; thus the chemo- and mechanoreflexes were not obtunded as is known to occur with anesthesia (e.g., Refs. 7, 13, 28). 2) Tonic carotid body sensory input was preserved, thereby avoiding any potential compensatory changes in the central controller or in central and/or peripheral chemoreceptor sensitivities consequent to CBD. 3) This model does not result in changes in baseline ventilation or acid-base status (e.g., Ref. 29).

Because our model avoids these significant limitations it is, in our view, the best available method for addressing the relative contributions of the peripheral and central chemoreceptors in response to changing PaCO2.

The importance of tonic input from the carotid chemoreceptor to ventilatory responsiveness has been demonstrated by the qualitative differences in the ventilatory response to systemic and cerebral hypoxia between the CBD and the isolated, intact and perfused carotid body preparations. In the awake CBD animal, the ventilatory response to hypoxia is unchanged or slightly reduced, whereas in the intact animal with carotid chemoreceptors maintained normocapnic and normoxic via perfusion, systemic hypoxia causes a dose-dependent, tachypneic hyperventilation, which amounts to about one-third the level of hyperventilation obtained when both carotid bodies and carotid sinus are made hypoxic (6).

Response Time

Our findings in the intact, unanesthetized dog of a substantially longer time to initial ventilatory response following step increases in alveolar PCO2 of the peripheral plus central chemoreceptor vs. central chemoreceptor alone agrees with some, but not all, of the findings reported in CBD animals.

In CBD lambs, Carroll et al. (5) showed a four- to fivefold delay in the initiation of the ventilatory response to increased PCO2 after CBD, and Nakayama et al. (21) reported a doubling of delay time in the appearance of apnea in response to ventilator-induced hypocapnia in sleeping dogs after CBD. In both studies, the absolute response time to the appearance of either increased ventilation or apnea of the denervated preparation was ~30–35 s, in agreement with present observations in the intact, carotid body perfused animal.

On the other hand, there are other CBD preparations (1, 9, 19, 23, 34) that showed extremely fast initial increases in

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![Image](https://via.placeholder.com/150)

Fig. 6. Ventilatory CO2 response slope from all 6 dogs in the CB + Central condition and in the Central Only condition. The carotid body contribution was obtained by difference (CB Only). All dogs showed decreased slopes in the Central Only condition, but in 2 dogs the decrease was small. The mean slope was significantly reduced, showing that the central chemoreceptors contributed ~63% and CBs ~37% of the total steady-state ventilatory response to hypercapnia. Error bars = 1 SD. *Significantly different from CB + Central (P ≤ 0.05).
phrenic nerve responses to large step increases in $\text{PCO}_2$, which were $<10$ s and even faster than the ventilatory responses in our control animals or those of Carroll et al. (5). These investigators also found this initial response to systemic $\text{CO}_2$ occurred very soon after a reduction in medullary surface extracellular fluid pH, which they considered to represent the environment of medullary chemoreceptors.

We have no explanation for these marked differences in response time of the central chemoreceptors between some studies in the denervated preparation and our own studies in the intact, carotid body-perfused animal. These very fast responses would support the concept of a so-called perivascular location of central $\text{CO}_2$ receptors (3, 24, 31), such that they could readily sense changes in $\text{Paco}_2$, whereas our and others’ data showing either a very prolonged delay or long time constant (10) would appear to favor a central site for $\text{CO}_2$ reception that required diffusion from the blood through the interstitial fluid.

### Sensitivity

Our estimate of a greater central contribution to the overall ventilatory gain to steady-state hypercapnia is consistent qualitatively with literature values from both anesthetized (15) and unanesthetized but CBD animals (29). Heeringa et al. (15) used pontomedullary perfusion in anesthetized cats and found that the central chemoreceptors contributed $\sim 52\%$ of the overall $\text{CO}_2$ sensitivity. Rodman et al. (29) used unanesthetized CBD dogs and found that the central chemoreceptors contributed $\sim 60\%$ of the overall ventilatory sensitivity to $\text{CO}_2$ in a hyperoxic background, a value very close to the 63% average found in the present study. A major limitation of all CBD studies, however, is the apparent plasticity of the control system in response to CBD (see Limitations of CBD Studies above) (2, 17, 25). In other words, it was quite likely that the apparent contribution of the central chemoreceptors to the steady-state ventilatory response to $\text{CO}_2$ was dependent on the time that had elapsed between the study and the denervation procedure.

The marked interindividual variability in the ventilatory response to inhaled $\text{CO}_2$ is well documented in humans and animals (12, 29). Our data confirmed this marked individual variability in the unanesthetized dog and also showed that the relative contributions of carotid body and central chemoreceptors to $\text{CO}_2$ responsiveness were equally variable (see Results).

### Implications for Sleep Apnea

How do our findings relate to ventilatory overshoots and undershoots and their repeated occurrence or cycling behavior in the form of periodic breathing, as occurs during sleep in congestive heart failure, in hypoxia, and in patients with central, obstructive, or mixed sleep apneas? Ventilatory overshoots secondary to transient increases in $\text{PA}CO_2$ (and/or decreases in arterial $\text{PO}_2$) normally occur within two to three breaths after an obstructive apnea or a marked hypopnea. In our intact animals, the much faster onset of the hyperpneic response to $\text{CO}_2$, when the carotid chemoreceptors were allowed to sense the hypercapnia, demonstrated that carotid bodies were the primary mediators of at least the initial ventilatory overshoot after an apnea. The carotid body chemoreceptors are also the site of hypoxic-hypercapnic interaction (8) and therefore would provide a substantial ventilatory overshoot in response to asphyxic stimuli present during periods of apnea or hypoventilation.

These data supporting a major role for carotid body chemoreceptors in the genesis of ventilatory overshoots are complemented by our laboratory’s previous carotid body denervated data showing that the peripheral chemoreceptors were essential for those apneas that normally occur in response to a ventilatory overshoot and decreased $\text{PA}CO_2$ (21). Indeed, without the carotid bodies, $\text{PA}CO_2$ had to be lowered more than twice that required in the intact animal to produce an apnea, and these apneas were delayed until long after they normally would have occurred in the intact preparation. These findings in the CBD animal need to be compared with the intact, carotid body-perfused preparation.

Once apnea is initiated, the considerable delay or phase lag between the peripheral and central $\text{CO}_2$ responses will contribute to prolongation of the apnea, a subsequent additional increase in $\text{PA}CO_2$, and reduction in arterial $\text{PO}_2$ leading to a ventilatory overshoot, thereby promoting unstable/periodic breathing. Given the greater average responsiveness of the central chemoreceptors to brain hypercapnia in the steady-state, these receptors would also be expected to contribute significantly to ventilatory overshoots once periodic breathing is fully established.

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