Mechanisms of ventilatory inhibition by exogenous dopamine in cats

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Loos, N., P. Haouzi, and F. Marchal. Mechanisms of ventilatory inhibition by exogenous dopamine in cats. J. Appl. Physiol. 84(4): 1131–1137, 1998.—Intravenous injection of dopamine (DA) has consistently been shown to depress minute ventilation (Ve). Whereas at low dosage (≤10 µg/kg) this effect may be accounted for by inhibition of the carotid sinus nerve chemosensory discharge (CSNCD), other mechanisms appear to be involved with large dosage (≥50 µg/kg). The purpose of this study was to elucidate the mechanisms of DA-induced Ve depression. The effects of intravenous injection of DA doses ranging from 1 to 200 µg/kg were studied in 18 anesthetized cats. DA was injected during air and O2 breathing, after α-adrenergic blockade by phenoxybenzamine and after baro- and chemodenervation. Ve and CSNCD were also simultaneously recorded on four occasions. In contrast to that with use of low-dose DA, Ve depression induced by high-dose DA was dissociated from CSNCD, persisted during 100% O2 breathing, and was significantly correlated with the rise in arterial blood pressure. Although blunted, Ve depression was still present after complete chemo- and barodenervation but was suppressed by blocking of the concomitant vasoconstriction with phenoxybenzamine. It is concluded that reflexes of circulatory origin contribute to the Ve depression induced by large-dose DA, in addition to its effects on arterial chemoreceptors. The contribution of baroreceptor stimulation and peripheral vasoconstriction is discussed.

DOPAMINE (DA) is routinely administered to patients with cardiocirculatory failure. Dosage regimens are used to induce either pure dopaminergic or dopaminergic and adrenergic effect (15). The latter effect includes prominent peripheral vasoconstriction and increased arterial blood pressure (ABP). Although the circulatory effects of DA are carefully monitored, little attention is usually given to its potential effects on ventilatory control. However, there is evidence that DA depresses ventilation in a number of mammalian species (1, 26, 35), including healthy humans (33). DA has long been shown to inhibit the chemosensory discharge from the carotid sinus nerve (CSN) (2), a mechanism that is believed to account for hypoventilation. However, some intriguing facts indicate that this may not be the only mechanism. Hypoventilation has been reported after large doses of DA during 100% O2 breathing while the CSN discharge was almost nil (35), after bilateral section of the CSNs in cats (26, 35), or after resection of the carotid bodies in goats (1). Also, DA has occasionally been reported to excite chemosensory discharge (21, 24, 27, 34), an observation that is difficult to reconcile with the depressant ventilatory effect. DA does not cross the blood-brain barrier (3, 6), and the mechanisms that may account for the ventilatory depression have not been elucidated. They could be related to the vascular effects of DA. Indeed, it has been reported that the magnitude of the ventilatory response to carotid chemoreceptor stimulation was dependent on the degree of baroreceptor stimulation in dogs (14) and cats (9). Furthermore, the stimulation of the carotid sinus baroreceptors by increasing the intracarotid pressure in vagotomized dogs was found to decrease ventilation (4). On the other hand, more recent studies suggested that distending the peripheral circulation, particularly in muscles, could represent an important source of ventilatory drive (13). The mechanism involves type III–IV somatic afferents, which have long been shown to trigger ventilatory reflexes (19, 25). The mechanosensitive fibers ending close to the vascular network could be stimulated by vascular distension, thus linking ventilation to the degree of peripheral perfusion. Taken in this context, the vasoconstriction resulting from the adrenergic stimulation by large-dose DA could also contribute to depression of ventilation.

The purpose of this study was to examine the mechanisms of the ventilatory effects of DA and to test the hypothesis that the hypertension and/or vasoconstriction induced by large-dose DA determines the magnitude of the ventilatory response.

MATERIALS AND METHODS

Anesthesia and General Preparation

Experiments were performed in 18 adult cats weighing 2.5–4.0 kg. Sedation was obtained with an intramuscular injection of ketamine (25 mg/kg) or xylazine (10 mg/kg), and anesthesia was induced with a mixture of chloralose (40 mg/kg) and Urethane (250 mg/kg), administered through a saphenous vein. The animals were placed supine on a heating pad, and body temperature was measured with a rectal probe (Digi-Sense thermocouple) and maintained between 37.5 and 38.5°C.

Indwelling catheters were inserted into a femoral vein for drug injection and into a femoral artery to monitor ABP by using a P23 Db Statham pressure transducer and to sample arterial blood for blood-gas measurements (Radiometer, ABL 330). The cervical trachea was dissected, cannulated, and connected to a Fleisch no. 0 pneumotachograph attached to a differential pressure transducer (Validyne MP45, ±2 hPa) to measure ventilatory flow, which was electronically integrated to volume. At the end of the experiment, the cats were euthanized by an intravenous lethal dose of pentobarbital.

Protocol

DA injection. Fresh DA solutions were prepared daily from dopamine chloride (DA, Nativelle) diluted to normal saline to achieve doses ranging from 1 to 200 µg/kg in a total volume of 1 ml. The drug was injected slowly into the catheter, the volume of which was 1.2 ml. After a control period of at least 1 min of regular breathing and stable blood
pressure, the catheter was flushed with 2 ml normal saline, beginning at the end of an expiration.

Responses to DA in air and O₂ breathing. In eight cats, one CNS was dissected, severed, and prepared for recording of the carotid chemosensory discharge, as previously described (23). The ventilatory and ABP responses to DA were studied by using the following doses: 1, 50, 100, and 200 µg/kg while the animal was breathing room air or 100% O₂.

α-Blockade. Phenoxybenzamine, an irreversible blocker of α₁- and α₂-adrenergic receptors (dibenzyline, SmithKline Beecham) was diluted to normal saline and administered by slow intravenous injection, under monitoring of ABP in 12 cats. The dose ranged from 5 to 10 mg/kg. α-Blockade was considered effective when the hypertensive response to an intravenous injection of 20–50 µg epinephrine (Aguetant) was replaced by a decrease in ABP. Series DA injections (1, 100, and 200 µg/kg) were performed before and after α-blockade, as described above. Seven cats were studied in these conditions, two of which were also included in the prior experiment. The effect of α-blockade was also tested after baro- and chemodenervation, as described below.

Nerve sections. Five cats were studied as follows. The areas of the carotid bifurcations were dissected on both sides. CSNs and vagi were first exposed before control studies, during which the preparation was kept under warm isotonic saline solution. CNSs were then severed distal to their junction with the nodose ganglion, the aortic nerves were selectively cut. Otherwise, a vagotomy was performed. The ventilatory response to an intravenous injection of 25 µg/kg sodium cyanide was tested to attest the effectiveness of the chemodenervation.

DA (100 and 200 µg/kg) was successively injected 1) as a control, 2) after denervation, and 3) after α-blockade by phenoxybenzamine administered as described above. Arterial blood gases were checked during long-lasting experiments, and pH was maintained by using sodium bicarbonate.

Data Analysis

Tidal volume (VT), ABP, the action potentials from the CNS, and the corresponding frequency discharge were recorded on a chart recorder (Gould TA 4000). Ventilation, ABP, and the CNS frequency discharge were also digitized at 20 Hz by using an analog-to-digital converter (MacLabs 8) and a computer (Macintosh IIIs, Chart 8 software). Volume signal and mean ABP (MABP) were processed in either of the following ways. 1) Minute ventilation (Ve) was computed from the digitized VT signal over the 30-s period before (baseline) and after the onset of DA injection (post-DA), and MABP was averaged over each epoch. The differences between post-DA and baseline ventilation (ΔVe) and MABP (ΔMABP) were calculated. 2) To describe the relationship between CNS chemosensory discharge and ventilation and to characterize the effects of α-blockade on the ventilatory response to DA with better time resolution, the data were transferred off-line to text files. After an electronic drift in the VT signal was eliminated, the amplitude and duration of each cycle (Fr) were calculated on a breath-by-breath basis, so as to obtain ventilation as VT · 60/TT. The baseline was computed as the mean of 5–10 ventilatory cycles before DA. The breath with the lowest Ve after DA was taken as the nadir of the response. Time to reach this value and time required for Ve to return to baseline were calculated. MABP or discharge frequency from the CNS was averaged during the corresponding ventilatory cycle, and the time course of response was similarly calculated.

Baseline and post-DA Ve and MABP were compared by using an analysis of variance for repeated measures, and linear correlation was used as necessary. Significant differences were considered at P < 0.05. Data are expressed as means ± SE.

RESULTS

Responses to DA During Air and 100% O₂ Breathing

Ventilatory and ABP responses to different DA doses were studied in eight cats during air and O₂ breathing. Figure 1 shows mean Ve before and after each dose. After 1 µg/kg DA, the decrease in Ve was significant in air (−67.3 ± 18.3 ml/min, P < 0.05) but not in O₂ (−7.1 ± 18.7 ml/min). In contrast, Ve decreased significantly after doses of from 50 to 200 µg/kg, both in air and O₂ (P < 0.05). The magnitude of ΔVe also increased with increasing doses: after 50, 100, and 200 µg/kg DA, ΔVe was −105.7 ± 32.4, −174.9 ± 39.0, and −281.4 ± 51.5 ml/min, respectively, in air and −87.9 ± 12.2, −167.8 ± 60.8, and −234.0 ± 75.0 ml/min, respectively, in O₂.

MABP is also shown in Fig. 1. It can be seen that there was no significant change in MABP after 1 µg/kg DA. In contrast, MABP increased significantly (P < 0.05) after 50 µg/kg (+18.0 ± 7.8 mmHg in air and +22.7 ± 14 mmHg in O₂), 100 µg/kg (+36.3 ± 5.6 mmHg in air and +45.2 ± 10.9 mmHg in O₂), or 200 µg/kg DA (+46.3 ± 13.8 mmHg in air and +47.1 ± 18.1 mmHg in O₂). Figure 2 illustrates the relationship between ΔVe and ΔMABP induced by DA doses ranging from 50 to 200 µg/kg. The correlation is significant so...
that the larger the increase in blood pressure, the larger the decrease in $\dot{V}E$ ($r = -0.65$, $P < 0.01$).

Pattern of Carotid Chemosensory and Ventilatory Responses to DA

Simultaneous recording was possible in four fiber preparations recorded in three cats. An example is shown in Fig. 3. After a low-dose DA injection, the chemosensory activity was completely stopped for $\sim 5$ s, and $\dot{V}E$ decreased for three ventilatory cycles. Both events were tightly linked: the decrease in $\dot{V}E$ occurred within one ventilatory cycle of cessation of the chemosensory discharge, and the return of $\dot{V}E$ to baseline was within two ventilatory cycles of reonset of the chemosensory discharge (Fig. 3A). The pattern was clearly different after the high-dose DA (100 $\mu$g/kg). In this case, the inhibition of the chemosensory discharge was followed by a period of stimulation, which could be explained by a rise in arterial $P_{CO_2}$ ($P_{ACO_2}$) and a decrease in arterial $P_{O_2}$ ($P_{AO_2}$), as shown below. Ventilation was depressed for a prolonged period of time despite the clear increase in chemosensory discharge (Fig. 3B).

After low-dose DA, the mean chemosensory discharge in the four preparations was silenced for $6.7 \pm 1.0$ s into the injection period and returned to control $42.7 \pm 3.8$ s thereafter. After 100–200 $\mu$g/kg DA, the discharge was silenced for $7.2 \pm 0.3$ s into the injection and was back to control after $22.6 \pm 5.5$ s. The relationship between $\dot{V}E$ and chemosensory discharge after a small and a large dose of DA is illustrated in Fig. 3, inset. $\dot{V}E$ followed the chemosensory discharge after the small-dose DA but was clearly dissociated from the chemosensory discharge after the large one. The mean correlation coefficients between $\dot{V}E$ and chemosensory discharge after DA were $0.58 \pm 0.05$ for the small and $0.12 \pm 0.05$ for the large doses. The latter value reflects the hysteresis observed between $\dot{V}E$ and chemosensory discharge.

Effects of $\alpha$-Adrenoreceptor Blockade

Seven cats were studied. The injection of phenoxybenzamine was found to be associated with a significant decrease in MABP, from $115.6 \pm 6.5$ to $87.8 \pm 9.3$ mmHg ($P < 0.01$), and a significant increase in $\dot{V}E$, from $768.8 \pm 82.6$ to $865.9 \pm 70.5$ ml/min ($P < 0.03$).

The effects of phenoxybenzamine on the ventilatory response to small- and high-dose DA are summarized in Fig. 4. After the control injection of 1 $\mu$g/kg DA, $\dot{V}E$ decreased by $232.9 \pm 45.8$ ml/min, $11.0 \pm 1.9$ s into the injection, and was back to baseline after $24.6 \pm 3.9$ s.
The pattern of response was unaltered by phenoxybenzamine: V˙E decreased by 277.5 ± 23.6 ml/min, 10.0 ± 1.5 s into DA injection, and was back to baseline 23.5 ± 1.5 s thereafter. MABP did not change significantly after 1 µg/kg DA: +5.9 ± 1.9 mmHg before and +7.5 ± 2.9 mmHg after phenoxybenzamine. More prominent V˙E changes were observed after 100 and 200 µg/kg DA. Moreover, the amplitude and timing of V˙E responses and the amplitude of MABP response to 100 and 200 µg/kg DA were significantly altered by phenoxybenzamine (P < 0.01). In response to 100 µg/kg DA, V˙E dropped by 498.0 ± 71.2 ml/min at 14.5 ± 1.7 s and returned to baseline 49.7 ± 8.8 s later, whereas MABP rose by 29.7 ± 12.1 mmHg. After phenoxybenzamine, V˙E dropped by 393.0 ± 73.9 ml/min at 11.5 ± 2.1 s and returned to baseline 24.8 ± 6.1 s later, whereas MABP changed by 1.2 ± 2.4 mmHg. A similar effect was seen in the response to 200 µg/kg DA. Control and phenoxybenzamine peak decreases in V˙E were 577.3 ± 102.7 and 304.6 ± 88.3 ml/min at 17.4 ± 3.1 and 11.5 ± 2.4 s, respectively, whereas delays to recovery were 79.9 ± 14.4 and 34.7 ± 9.4 s and changes in MABP were 43.7 ± 11.6 and 1.1 ± 1.1 mmHg, respectively. For clarity, V˙E responses to 100 and 200 µg/kg DA were pooled in Fig. 4 because neither the amplitude nor the delay to peak V˙E responses was different between the two doses. Only the delay in V˙E recovery was significantly longer with 200 µg/kg DA compared with 100 µg/kg DA (P < 0.02). In summary, after phenoxybenzamine, the ventilatory response to 100–200 µg/kg DA very much resembled that to 1 µg/kg DA.}

Nerve Section Experiments

Figure 5 illustrates the main results of these experiments. As expected, V˙E was significantly depressed by control injections of 100 and 200 µg/kg DA; changes in V˙E during the 30-s period into DA were, respectively, −243.8 ± 50.0 and −291.3 ± 72.7 ml/min (P < 0.001). Although the magnitude of the response decreased after complete baro- and chemodenervation, V˙E was still significantly inhibited after both doses, changing −51.6 ± 39.1 and −123.6 ± 34.8 ml/min, respectively (P < 0.01). The average changes in MABP were highly significant (P < 0.001) for 100 µg/kg and 200 µg/kg DA in both control conditions (+39.1 ± 3.8 and +50.1 ± 4.9 mmHg, respectively) and after chemo- and barodenervation (+23.1 ± 14.4 and +46.9 ± 5.3 mmHg, respectively).

The injection of phenoxybenzamine was associated with a significant decrease in MABP, from 132.5 ± 13.9 to 69.2 ± 6.5 mmHg (P < 0.02), and a significant increase in V˙E, from 521.8 to 554 ± 61.5 ml/min (P < 0.01). In response to DA, however, V˙E did not change significantly, +20.6 ± 16.5 ml/min with 100 µg/kg and −0.5 ± 13.8 ml/min with 200 µg/kg, whereas MABP decreased significantly in response to either 100 µg/kg (−16.2 ± 9.6 mmHg) or 200 µg/kg DA (−13.8 ± 5.5 mmHg, P < 0.03). Altogether, the data indicate that chemo- and barodenervation decreased but did not abolish the ventilatory response to DA, whereas phenoxybenzamine injected thereafter suppressed the response.

Arterial Blood Gases

In 14 cats, arterial pH, PaO2, and PaCO2 measured in air at the beginning of the experiment were 7.29 ± 0.02, 94.9 ± 3.4 Torr, and 37.1 ± 1.9 Torr, respectively. In five cats breathing O2, those values were 7.26 ± 0.02, 427.6 ± 29.7 Torr, and 41.6 ± 4.0 Torr, respectively. Finally, measurements were performed in eight cats immediately before and 20–30 s into the injection of large-dose DA while ventilation was still depressed. Arterial pH, PaO2, and PaCO2, were found to change significantly, from 7.31 ± 0.02 to 7.23 ± 0.01, 99.3 ± 4.7 to 80.8 ± 4.2 Torr, and 34.2 ± 2.0 to 43.1 ± 1.9 Torr, respectively (P < 0.05).
DISCUSSION

The present study shows that DA depresses ventilation by different mechanisms. At low dose, DA is devoid of adrenergic effect, and the inhibition of the carotid chemoreceptor activity appears to be the main mechanism of the observed ventilatory depression. Altogether, ventilatory depression lasts a short time, and there is no evidence of change in ABP. This study adds to the well-documented evidence that low-dose DA transiently suppresses ventilation. In addition, we have described the dose-dependent relationship between carotid chemosensory discharge and ventilation after DA injection. The breath-by-breath analysis of the relationship between ventilation and CSN chemosensory discharge shows that ventilatory depression follows the decrease in chemosensory discharge within two respiratory cycles. A very similar relationship between ventilation and CSN chemosensory discharge was demonstrated during O2 tests in the pioneer work of Leitner et al. (22). The demonstration that ventilatory depression by small-dose DA is suppressed by 100% O2 breathing, shown in the present study and in a previous study (35), also favors the mechanism of carotid chemoreceptor inhibition. DA D2 receptors are located on the carotid body type I cell that is connected to afferent endings from the CSN. Because of their presynaptic location and evidence for DA synthesis by the type I cell, these receptors are believed to function as autoreceptors, regulating DA release and synthesis. The selective stimulation of these D2 receptors is thought to inhibit the chemosensory discharge (8).

Large doses of DA were associated with very different patterns of ventilatory response. Ventilation was depressed well beyond the short-lasting cessation of chemosensory discharge, at a time when chemoreceptor activity was already above control (Fig. 3). Indeed, it is worth noting that, despite an average decrease in Pao2 and a 10 Torr increase in PCO2, 30 s into DA injection ventilation was depressed for up to at least 1 min, and the concomitant rise in chemosensory discharge was clearly ineffective in restoring ventilation. Moreover, large-dose DA also induced a significant ventilatory depression during O2 breathing, a further indication that suppressing the carotid chemosensory discharge was not the determinant mechanism to this hypoventilation. Similar conclusions can be drawn from other studies dealing with the effects of DA on the arterial chemoreflex. For example, Zapata and Zuazo (35) demonstrated that intracarotid injection of DA induced a rapid decrease in both VT and breathing frequency in cats. This response was abolished after sectioning of the ipsilateral carotid nerve. However, the ventilatory depression provoked by an intravenous injection of 20 µg/kg DA did not change after bilateral carotid neuromuscular stimulation (35). Similar findings were reported by Nishimoto (26) in the same species, in which bilateral section of the CSNs diminished but did not abolish the hypoventilation induced by intravenous infusion of 10 µg·kg⁻¹·min⁻¹ DA. A non-chemoreceptor-related mechanism must therefore be proposed to account for part of the “high-dose” DA-induced ventilatory depression. The present study brings definitive evidence for such a dual mechanism to the ventilatory effect of DA.

The significant correlation between the increase in blood pressure and the decrease in ventilation suggests the possibility of a link between respiratory and circulatory events. Various sites of the cardiovascular system primarily devoted to the control of circulation, i.e., the arterial baroreceptors (4, 14) and the receptors located in the heart (17) or the pulmonary circulation (18), contribute to the regulation of breathing (32). Such a circulatory-ventilatory coupling relies on the existence of direct synaptic connections between neurons involved in regulation of breathing and circulation at the brain-stem level, like in the nucleus tractus solitarii (29), a major relay for cardiovascular and respiratory afferents. Exogenous DA has a variety of cardiovascular dose-dependent effects. With infusion at a dosage above 10–20 µg·kg⁻¹·min⁻¹, both a β- and an α-mimetic effect are obtained, consisting of a rise in cardiac output and peripheral resistance, leading to an increase in systemic blood pressure. Such circulatory changes could have affected the level of ventilation. An increase in cardiac output could have stimulated mechanoreceptors located in the right heart (10) and thus triggered ventilatory responses (17). The afferent arm of this reflex travels through the vagus and/or sympathetic nerve (10). However, this mechanism should, if anything, stimulate rather than inhibit breathing during DA infusion. A similar effect is expected from stimulation of mechanoreceptors located in the pulmonary circulation because distending the pulmonary artery and its main branches appears to increase ventilation (18). In contrast, stimulation of mechanoreceptors located in the left ventricle can depress ventilation, a response that persists after bilateral destruction of the stellate ganglia but is suppressed by vagotomy (20). It is unlikely that the conditions required to trigger this hypoventilation, i.e., an acute and dramatic distension of the left ventricle, could result from DA injection. Lung receptors, mostly those with unmyelinated fibers, have long been shown to respond to local circulatory changes (5) and can produce rapid shallow breathing and apnea. However, it is difficult to predict whether C fibers could have been stimulated through a possible increase and/or redistribution of intrapulmonary blood flow during DA injection. Moreover, in no instance did the observed changes in breathing pattern provoked by DA resemble that occurring with pulmonary C-fiber stimulation. Finally, the persisting ventilatory depression after vagotomy is a strong argument to a non-vagally mediated reduction in breathing, independent therefore of the mechanoreceptors located in the left heart or the lungs.

In contrast, it has long been recognized that ventilation can be decreased through the arterial baroreflex when ABP rises. The precise characteristics of this baroreceptor-mediated effect on ventilation have been described by using the isolated carotid sinus preparation in vagotomized dogs. Brunner et al. (4) have found...
that the slope of the relationship between the decrease in ventilation and the increase in carotid sinus pressure averaged 0.65 ml·min⁻¹·kg⁻¹·mmHg⁻¹ when intra-

sinus pressure was increased 100 mmHg above normal resting level. Beyond this value, the slope appeared to flatten, resulting in a pseudosigmoidal shape over the whole range of intrasinus pressure studied (4). The gain of ventilatory-to-blood pressure change depends on many factors, including the level of chemoreceptor activity and the integrity of vagal feedback loops. This aspect is obvious in the study by Heistad et al. (14), in which a fivefold potentiation of the slope of the relationship between carotid perfusion pressure and V\(\dot{E}\) was observed after vagotomy. It becomes therefore impossible to evaluate the contribution of vagally mediated information to the observed ventilatory inhibition of breathing by cutting the vagi because the interaction between vagal and other inputs to the brain-stem respiratory neurons is simply not that expected from a linear function. Similarly, the gain of the relationship between ventilation and carotid sinus pressure (0.24 ml·min⁻¹·kg⁻¹·mmHg⁻¹) reported by Heistad et al. increased 5 to 10 times during arterial chemoreceptor stimulation by nicotine. The inverse relationship between systemic blood pressure and ventilatory changes reported in the present study in intact animal displayed a much higher slope (1.5 ml·min⁻¹·kg⁻¹·mmHg⁻¹) than in any study in which discrete pressure changes were applied at the level of the baroreceptors (4, 14). Importantly, the gain was still \(\sim 1\) ml·min⁻¹·kg⁻¹·mmHg⁻¹ during 100% \(\text{O}_2\) breathing, a condition in which the ventilatory component of the arterial baroreflex is expected to be dramatically blunted (14). More importantly, after complete barodenervation, the gain of the ventilatory response (0.8 ml·min⁻¹·kg⁻¹·mmHg⁻¹) was still above that reported for the relationship between intrasinus pressure and ventilation in dogs (4). In other words, although complete barodenervation blunted the magnitude of DA-induced hypover-
vilation, the ventilatory depression remained and was only abolished after \(\alpha\)-blockade.

It remains unclear what other structure could be involved to account for the \(\dot{V}\)\(\dot{e}\) inhibition after section of sinus and aortic nerves because the arterial baroreceptors are not operative anymore, but the ventilatory depression to DA remains. A central mechanism is unlikely to explain the depressant effect of DA on ventilation after arterial baro- and chemodenervation because DA does not cross the blood-brain barrier. Moreover, DA acting on the central nervous system should, if anything, produce an opposite effect on ventilation because the DA-receptor blocker haloperidol acts centrally to inhibit ventilation (16, 28). Furthermore, any reduction in cerebral blood flow, which is likely to occur during high-dose DA injection, will yield a rise in ventilation through local accumulation of \(\text{CO}_2\) (6).

We have recently reported that high-dose DA injected into the isolated hindlimb circulation of an anesthe-
tized sheep after injection of a vasodilatory agent can produce a ventilatory depression despite the lack of increase in systemic blood pressure and therefore the lack of involvement of any of the known receptors located in the central circulation (12). It was therefore postulated that the status of the peripheral circulation could be sensed by slow-conducting afferent fibers and contributes to control breathing. Indeed, stimulation of group III and IV muscle receptors evokes strong cardiac and ventilatory responses (25). They are found close to or within the adventitia of arterioles and venules (30, 31). Many receptors respond to low-threshold mecha-
nical stimuli (19) and could plausibly encode the disten-
sion of the peripheral vascular network. High-dose DA could therefore inhibit ventilation by reducing peripheral blood flow the same as after occlusion of the arterial supply to the hindlimb circulation (11). This inhibitory effect on ventilation does not depend on arterial baro- and/or chemoreceptors and is expected to disappear with blockade of the vasoconstriction, as observed in this study.

It is concluded that the depression of ventilation by DA is explained by a depression of the arterial chemore-
ceptor discharge at low (dopaminergic) doses. The increase in blood pressure as well as the vasoconstric-
tion resulting from the adrenergic effect are likely to contribute to the ventilatory inhibition observed with large doses. The clinical relevance of these mechanisms must be considered because DA is usually administered to patients with low blood pressure and probably a dramatic decrease in peripheral vascular conductance. The above concept implies that infusion of an agent that would further reduce peripheral perfusion could plausibly lead to hypoventilation, independent of, or in addition to, the effect of reloading the arterial baroreceptors. Although the ventilatory effects of DA under experimental conditions have been described for sev-
eral years, there is precious little clinical data in subjects with circulatory failure. Such studies may be of importance in improving the management of those patients.

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