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The effects of dopamine on the respiratory system:

Friend or foe?

Agnieszka Ciarka¹, Jean-Louis Vincent², Philippe van de Borne¹

¹Cardiology Department, and ²Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Belgium

Corresponding author:

Agnieszka Ciarka
Cardiology Department
Erasme Hospital
808 Route de Lennik
1070 Brussels
Belgium
Ph: 0032/2/5553275
Fax: 0032/2/5556813
e-mail: aciarka@ulb.ac.be
Dopamine (DA) is an immediate precursor of noradrenaline that has stimulatory or inhibitory effects on a variety of adrenergic receptors. DA is primarily used in the management of circulatory shock for its combined vasopressor and inotropic effects, but it may also exert significant effects on the respiratory system. Although the respiratory effects of intravenous DA attract less attention than its hemodynamic effects, there is evidence that DA affects ventilation, pulmonary circulation, bronchial diameter, neuromodulation of sensory pulmonary nerves and lung water clearance. Through these complex mechanisms, DA may exert beneficial as well as detrimental effects on respiration.

DA may have beneficial effects on the respiratory system by decreasing oedema formation and improving respiratory muscle function, but can also have deleterious effects, by inhibiting ventilation. Hence, DA may be beneficial in lung oedema, but harmful in cases of difficult weaning from mechanical ventilation. DA should be used with caution in patients with heart failure during weaning from mechanical respiration, however, critically ill patients with chronic obstructive pulmonary disease (COPD) do not show this negative effect of DA on ventilatory drive.
Introduction

Dopamine (DA) is an immediate metabolic precursor of noradrenaline and adrenaline [1]. It has an intrinsic capacity to activate peripheral adrenergic and dopaminergic receptors [1]. In physiologic conditions, DA increases cardiac output and aortic pressure, reduces renal vascular resistance and increases glomerular filtration rate and urinary output [2]. At low doses (5 µg/kg/min), which do not have important hemodynamic effects, DA causes modest diuresis [3]. DA is used in patients suffering from circulatory shock (primarily septic and cardiogenic) [4], for its combined inotropic and vasopressor effects. Although the dopaminergic actions may theoretically be beneficial for renal function, the renal protective effects of DA are seriously questioned and there is ongoing discussion about the place of DA in the intensive care unit [5].

DA can exert various effects on the respiratory system (Table 1). First, DA has an established role in the control of ventilation. Dopaminergic receptors are located pre- and postsynaptically on the carotid glomus cells [6] and high concentrations of DA have been measured in the carotid bodies [7]. DA inhibits the chemosensory discharge rate in various animal species and there is clearcut evidence from animal and human studies that low dose DA infusion decreases the ventilatory response to hypoxia [8-15]. Second, DA provokes a reduction in arterial oxygen saturation at a given alveolar oxygen tension by impairing regional ventilation/perfusion matching in the lung [16]. When administered to patients with circulatory failure, DA may be deleterious for ventilation and pulmonary gas exchange, especially in hypoxemic patients with compromised respiratory function [17]. Third, DA can also reduce pulmonary vascular resistance, resulting in a decrease in pulmonary hypertension [18-22]. Fourth, DA may promote lung oedema clearance by activation of epithelial Na+/K+-ATPase [23-27] and epithelial sodium channels [28]. Fifth, DA is involved in the regulation of airway diameter [29-31] and in neuromodulation of pulmonary sensory nerves [32, 33].

These effects have primarily been tested in animal studies. There is some clinical evidence that dopamine may improve respiratory muscle function in respiratory failure [34]. A randomised, placebo-controlled human study, based on the observation that DA receptor activation inhibits rapidly adapting stretch receptors in the lungs, gave disappointing results. Indeed, the DA-2 and beta2 adrenergic
receptor agonist, sibenadet, did not alleviate breathlessness, cough or excess sputum in patients with chronic obstructive pulmonary disease (COPD) [35, 36]. This paper focuses on the effects of DA on the respiratory system, to evaluate whether DA can be safely used in acutely ill patients with respiratory failure.

Clinical pharmacology

DA exerts complex actions on peripheral and central adrenergic and dopaminergic receptors [37]. In the peripheral nervous system, DA is present in postganglionic sympathetic nerve endings and is an immediate precursor of noradrenaline. Intravenous DA does not cross the brain-blood barrier, so that it does not have central effects.

The different pharmacological actions of DA are effected through dose-dependent activation of α-adrenergic, β-adrenergic and dopaminergic receptors. Activation of β₁, β₂, and α₁ adrenergic receptors in the heart results in an increase in heart rate and contractility, while activation of presynaptic α₂ receptors has an inhibitory effect on further release of noradrenaline from nerve terminals. In the vasculature, the activation of postsynaptic α₁ and α₂ receptors mediates vasoconstriction, while β₂ receptors mediate vasodilatation. Peripheral DA receptors belong to two classes. The DA-1 receptors activate adenyl cyclase, with a consequent increase in intracellular cAMP, while DA-2 receptors inhibit adenyl cyclase and result in activation of K⁺ channels, inhibition of Ca²⁺ channels, and the exchange of phosphatidyl inositol. DA-1 receptors provoke renal, coronary, and mesenteric vasodilatation and a natriuretic response. Stimulation of DA-2 receptors is associated with noradrenaline release from sympathetic nerve endings and inhibition of prolactin release.

DA influences these receptors in a dose dependent manner. Low doses of DA (1-2 µg/kg/min) act primarily on the DA-1 receptors, resulting in selective vasodilatation in the renal, mesenteric, cerebral, and coronary beds. Vasodilatation can be balanced by an increase in stroke volume, so that arterial pressure remains relatively stable. Higher doses (2-5 µg/kg/min) activate not only the dopaminergic but also the β-adrenergic receptors, resulting in increased cardiac output, due to combined increases in stroke volume and heart rate [38]. Doses of 5-10 µg/kg/min have predominant β-adrenergic effects and start to have α-adrenergic effects, resulting in combined increases in cardiac
output and blood pressure. Higher doses (10-20 µg/kg/min) provoke a predominantly α-adrenergic activation, with vasoconstriction and increased systemic vascular resistance. The dose-dependent effects of DA are, however, not entirely predictable because of significant interindividual variability in enzymatic DA inactivation. In practical terms, DA should be titrated to a desired physiologic effect, because weight-based administration of DA can achieve quite different concentrations among individuals [39].

Although the respiratory effects of intravenous DA have attracted less attention than its hemodynamic actions, there is evidence that DA affects ventilation [16, 40-47], pulmonary circulation [18-22], bronchial diameter [29-31], neuromodulation of sensory pulmonary nerves [32, 33], and lung water clearance [23-28]. The exact mechanisms of certain pulmonary actions of DA are not entirely understood. Recently, DA-2 and DA-1 receptors were identified in the lung arteries. Interestingly, these receptors were found within the tunica adventitia in human pulmonary arteries and within the tunica media of large and medium sized intrapulmonary arteries of the rabbit [48-53]. No dopaminergic receptor has been found in the bronchial tree yet, despite the described bronchodilating action of DA in healthy subjects during histamine administration [31]. Studies on mechanisms of lung water clearance have shown that in alveolar cells, DA increases the activity of basolateral Na-K-ATPase and the activity of epithelial sodium channels [24, 28]. DA-1 and DA-2 receptors have been found in the carotid bodies of experimental animals [54, 55], providing an argument for a modulatory role of DA in the control of ventilation.

**Clinical use**

DA is primarily used for its vasopressor and inotropic actions in the management of critically ill patients with circulatory failure [4, 56]. By combined beta-adrenergic and dopaminergic effects, low doses of DA (typically <5 µg/kg/min) can decrease renal vascular resistance, increase renal blood flow, glomerular filtration rate and sodium excretion in animals and healthy humans [2]. However, the renal protective effects of DA have not been demonstrated in critically ill humans and randomised control trials did not provide direct proof that DA confers protection from renal dysfunction in critically ill patients at risk of renal failure[5]. Furthermore, the place of DA as a therapeutic agent is
debated [57, 58], with many clinicians preferring the use of noradrenaline with or without dobutamine in the treatment of shock states [59].

DA is not used clinically for its effects on respiration. Nevertheless, it does exert effects on the respiratory system, including depression of ventilatory drive, change in bronchial diameter, and increase in lung water clearance, which will be discussed further.

THE EFFECTS OF DOPAMINE ON RESPIRATORY FUNCTION

Effects on respiration

Respiration is largely regulated by chemoreflex mechanisms [60]. Peripheral chemoreceptors located in the carotid bodies respond primarily to hypoxia and provoke an increase in sympathetic nerve activity [61] and ventilation [62]. Human and animal type I cells (glomus cells) of the carotid bodies contain abundant quantities of DA [63-67], with a 5 to 1 ratio of DA to noradrenaline [68]. DA intervenes in the regulation of respiration not only at the level of the carotid bodies, but it is also present in the neurons of the nucleus tractus solitarius, where afferents from the carotid bodies end [55, 69]. Hypoxia increases carotid body tyrosine hydroxylase activity [70], resulting in increased DA synthesis [71] and release [8], which suggests that DA can play a role in the regulation of ventilation. In addition, many studies in animals and healthy humans have demonstrated that low dose DA is associated with decreased carotid sinus drive and diminished ventilatory response to hypoxia. In healthy subjects, low dose DA blunts the ventilatory response to isocapnic [14, 15] and hypercapnic [13] hypoxia, an effect which is abolished by the dopaminergic receptor blocker, haloperidol [72].

These effects of DA on respiration can be detrimental in seriously ill patients with limited breathing reserve. This detrimental effect has been shown in patients with heart failure, where low dose DA decreased minute ventilation by more than 1 L/min during normoxic breathing; this did not occur in age-matched control subjects[17]. Heart failure patients often have only mild arterial blood oxygen desaturation as a result of low cardiac output and pulmonary vascular congestion. DA also impairs regional ventilation/perfusion matching in the lungs [73]. Thus, there are two synergistic
mechanisms which can affect ventilation in heart failure: first, direct impairment of gas exchange [73], and second, impaired compensatory ventilation [17]. Both mechanisms can be counterbalanced by the administration of supplemental oxygen [74] so that these effects of DA would not have important consequences, especially in mechanically ventilated patients. Sleep disordered breathing, frequently observed in patients with heart failure [75, 76], could be another factor contributing to the detrimental actions of DA in these patients. During sleep, central and obstructive apnoeas decrease arterial oxygen saturation and this may play a pivotal role in the genesis of cardiac arrhythmias. Both hypoxia and hypercapnia activate chemoreceptors [77] and induce short lasting arousals that terminate obstructive apnoeas. Chemoreflex inhibition by DA could be particularly deleterious in this condition, as end-apnoeic desaturations, combined with potential DA arrhythmogenicity, could promote life-threatening arrhythmias.

In patients with heart failure, DA may have dual effects during weaning from mechanical ventilation. Patients receiving DA would experience reduced discomfort associated with hypoxia, but DA would further decrease ventilatory drive and diminish arterial blood oxygen saturation[17], with the potential danger of precipitating respiratory failure and problems during weaning from mechanical ventilation.

We recently investigated the possible impact of DA on weaning from mechanical ventilation in patients with COPD [78]: we observed that DA did not attenuate ventilation and had no effect on arterial blood gases [78]. This discrepancy between patients with COPD and those with heart failure may be explained by differences in the peripheral chemoreceptor drive for ventilation, which is reduced [79, 80] in COPD patients and heightened in patients with heart failure [81]. We speculate that the low peripheral chemoreceptor drive cannot be further inhibited in COPD, and therefore DA cannot further decrease ventilatory drive in these patients.

Effects on the respiratory muscles

Improvement in blood flow can increase the force of contraction of the respiratory muscles, and an early study suggested that DA may improve diaphragmatic function in COPD patients [34].
Effects on the pulmonary circulation

DA can reduce pulmonary vascular tone and thus decrease pulmonary hypertension [18-22]. This has been shown in patients with COPD [82]. Several mechanisms have been proposed. First, DA-1 receptors are present in the tunica intima and media of large and medium pulmonary arteries, while DA-2 receptors are found in the adventitia of extrapulmonary arteries and in medium and large intrapulmonary arteries. All these findings were made using histochemical techniques [49-53], while in situ hybridisation further confirms the presence of DA-1 receptors in the tunica media of the aorta and the pulmonary artery [48]. Second, dopaminergic receptors may also induce vasodilation through relaxation of the pulmonary endothelium.

Effects on extravascular lung water

Pulmonary oedema can be viewed as an imbalance between the biological mechanisms that drive water into the alveolar space and the forces assuring its removal. It can result from a change in the hydrostatic and/or oncotic pressure gradients across the pulmonary circulation or from increased alveolar permeability.

Several studies have reported that DA can increase lung oedema clearance by increasing active sodium transport (via epithelial Na/K-ATP-ase stimulation). In rats, experiments with DA were performed using three different models of pulmonary oedema (hyperoxia, mechanical ventilation with high tidal volume, and increase in hydrostatic pressure). DA increased lung oedema clearance in rats breathing room air and rats exposed to 100 % oxygen (such exposure to oxygen results in severe lung injury and death due to respiratory failure) [26]. Moreover, rat alveolar type II cells incubated with DA present abundant quantities of the alpha1 subunit protein of Na K-ATPase in the basolateral membranes, indicating that DA may recruit Na pumps from intracellular pools [26]. In line with this hypothesis, colchicine, which inhibits the microtubular transport system, blocks the stimulatory effect of DA on active Na+ transport [26]. The same effect of DA on lung oedema clearance was observed in an isolated perfused lung rat model, where ouabain, a specific inhibitor of Na K-ATP-ase, abolished
the dose dependent increase in liquid clearance exerted by DA [23]. Furthermore, it was demonstrated that the lung oedema clearance was mediated by D1 receptor activation [24].

Sznajder and co-workers developed an animal model of lung oedema, induced by mechanical ventilation with high tidal volume, with resulting impairment of active Na+ transport and lung liquid clearance [25]. In this model, DA increased alveolar fluid reabsorption in nonventilated control rats by 60 %, rats ventilated with low tidal volume by 55 % and rats ventilated with high tidal volume by 200 % [27]. These effects of DA were abolished by administration of colchicine, which supports previous observations that DA increases Na+-K+-ATPase mobilisation from the intracellular pool [27].

Finally, there are studies on the effects of DA in animal models of hydrostatic pulmonary oedema, where active Na+ transport and alveolar fluid reabsorption are decreased [83]. Similar to other reports on different models of lung oedema, DA increased alveolar fluid reabsorption in isolated rat lungs with increased left atrial pressure, and this effect was abolished by the administration of the specific D1 receptor antagonist, ouabain (a Na K-ATPase inhibitor) and colchicine [84].

In contrast to these studies, Tibayan et al failed to show that DA given intravenously (5-10 µg/kg/min), or intra-alveolarly (10-4 M), affected alveolar liquid clearance [85], while dobutamine increased alveolar liquid clearance by 50 %. Moreover, this effect was abolished by a potent and specific beta 2 receptor blocker [85]. This results are in line with the hypothesis that alveolar epithelial sodium transport is mediated by beta 2 receptor stimulation [85].

Effects on the airways

There is growing evidence that DA is involved in the regulation of airway diameter. The control of the bronchial diameter by the autonomic nervous system is highly complex and involves neural and humoral factors [86]. Adrenergic and cholinergic systems are involved in this regulation, as well as inhibitory and excitatory non-adrenergic, non-cholinergic nerves (i-NANC/e-NANC) [87]. Adrenergic control is carried out by the release of noradrenaline from the nerve endings and by the release of adrenaline from the adrenal medulla. Adrenaline and noradrenaline can produce bronchodilation by the stimulation of β2 adrenergic receptors, but they can also cause bronchoconstriction, by stimulation of α1 and α2 adrenergic receptors, if pathological disturbances
exist in the airways [88]. Non-adrenergic/non-cholinergic nervous control of airway smooth muscle is exerted by neurotransmitters, such as substance P and neurokinin A (contraction of the airway smooth muscle) and neuropeptide Y (relaxation of the neural smooth muscle) [89]. Thus, local reflexes regulate airway diameter through nerves that release neuropeptides as well as by other substances released by epithelial and interstitial cells [90, 91]. Some studies have demonstrated that DA may also exert a modulatory role on airway diameter. DA inhibits the bronchoconstriction produced by increasing doses of histamine, infused or inhaled in healthy subjects as well as in bronchospastic patients (Table 2) [31]. However, DA had no effect on the bronchial tree when administered to subjects with a history of bronchial asthma but no bronchospasm at the time of the investigation (Table 2) [89, 92]. Moreover, the DA2 receptor blocker, metoclopramide, had no effect on asthmatic patients without bronchospasm (Table 2) [89]. One animal study reported that it is possible to inhibit bronchoconstriction induced by electrical field stimulation and this effect may be prevented by blocking DA1 receptors [30].

No DA receptor has yet been identified in the human bronchial tree. However, one recent animal study reported that stimulation of DA2 receptors by a compound similar to DA produces a bronchodilatory effect on the airways in dogs and guinea pigs [29].

Thus, DA could be potentially beneficial in clinical states associated with bronchoconstriction, but further randomised, placebo controlled clinical studies are needed to investigate its potential to alleviate bronchospasm in humans.

DA may also act by neuromodulation of pulmonary sensory nerves. Sensory nerve fibres in the airways control events such as bronchoconstriction, airway plasma leakage and cough [93]. There are two classes of sensory nerve fibres, which control sensory nerve reflexes: myelinated, rapidly adapting stretch receptors (RARs) and non-myelinated, C-fibres [93]. RARs are located along the entire tracheobronchial tree and are activated by chemical (histamine), mechanical, and osmotic stimuli [94]. They elicit defensive actions such as cough, mucus production, and rapid shallow breathing [94]. Activation of myelinated as well as non myelinated fibres, elicits cough, bronchoconstriction and mucus secretion via an afferent central reflex pathway [95, 96].
DA2 receptor mRNA is present in the sensory ganglia of rat airways [33]. It has been demonstrated that DA receptor activation inhibits RAR activation in vivo [32] and inhibits neuropeptide release from the peripheral endings of airway sensory neurons [33]. In dogs pretreated with propranolol and phentolamine (to prevent the β and the α adrenergic effects of DA, respectively), DA infusion inhibited histamine-induced stimulation of RARs [32]. This action was prevented by the DA-2 antagonist, sulpiride [32].

It was, therefore, postulated that DA receptor agonists would alleviate the debilitating symptoms of COPD, and this hypothesis was tested in a randomised, placebo controlled trial, which is discussed later.

**Clinical application in COPD**

Patients with COPD present dyspnoea, cough, and excess sputum production, which decrease their quality of life [97]. The underlying mechanisms are complex, but reflex activation of sensory afferent nerves by irritants, which in the normal organism serves to clear the airways and is an important mechanism of self-defence, is known to induce these symptoms. Since sensory RAR fibres are implicated in the control of cough, bronchospasm and sputum production [94], and DA2 receptors are present in RARs [33], and DA infusion in animal models inhibited histamine-induced activation of RARs [94], it has been suggested that the dual DA-2 and β2 receptor agonist, sibenadet, could have beneficial effects on debilitating symptoms in COPD patients [36, 94]. Although the role of beta2 receptor blockers has been well established in the treatment of COPD, dopamine agonism is a completely new approach in this disease.

An initial study [35] aimed to compare the effects of sibenadet, placebo and common bronchodilator therapies (salbutamol and ipratropium bromide) on key symptoms of COPD evaluated by the Breathlessness, Cough and Sputum Scale (BCSS) [98]. This patient-reported scale is a validated and reliable outcome measure of symptom severity [98]. Early clinical evaluation of sibenadet was very promising [35]. Sibenadet improved the symptoms of breathlessness, cough and sputum in this 28-day trial, while standard bronchodilators provided only limited symptomatic improvement [35]. The positive effects of sibenadet were dose-related, and the dose of 500 µg, delivered in two equal
fractions, proved to have the highest efficacy without compromising safety, and was subsequently used in large scale studies [36].

However, long term studies have not supported a clinical benefit of sibenadet on the symptoms of COPD [36]. The efficacy of sibenadet (at a dose 500 µg) in comparison with placebo was assessed in studies of 3- and 6-month duration. The primary endpoints were defined as changes in BCSS and forced expiratory volume in one second (FEV1) from baseline. Health-related quality of life, perception of treatment efficacy and adverse effects were also recorded. Although there was an immediate reduction in BCSS at the beginning of the study, there was a gradual increase in symptom scores among the patients treated with sibenadet, in comparison to placebo. By the end of the study, the differences in BCSS between the placebo and sibenadet group were not statistically significant. The fact that initial improvements in symptomatology tailed off over time, could reflect a tolerance phenomenon. FEV1 measurement clearly demonstrated a significant improvement in the sibenadet group, which was attributed to the vasodilatatory effects of the drug. However, the magnitude of these increases diminished over time, which could be attributed to tachyphylaxis, a recognised potential effect of regular b2-agonist use. No significant difference between the two groups was detected in the health-related quality of life score, although a higher proportion of investigators and patients rated sibenadet as more effective than placebo. The proportion of patients experiencing at least one exacerbation was similar in placebo and sibenadet groups. There was no difference in the frequency of adverse effects between the placebo and sibenadet groups and a 1-year safety study also demonstrated that sibenadet was well tolerated [99].

Therefore, despite encouraging preclinical and early clinical data, the long-term clinical trial demonstrated that sibenadet does not provide long-term symptomatological benefit. One possible explanation is that early symptomatic benefit was beta2 rather than D2 driven and diminished secondary to tachyphylaxis. Moreover, it is possible that beta2 tachyphylaxis diminished dual beta2/D2 actions and masked such mechanisms as dopamine2 receptor agonism on the cough component [99].

Conclusions
In summary, DA is still used in the intensive care unit for its vasopressor and inotropic effects, combined with dopaminergic effects that may protect renal and splanchnic blood flow. DA can also have both favourable and detrimental effects on pulmonary function. Low dose DA can depress ventilation in patients with heart failure, thus it must be used cautiously in these patients during weaning from mechanical ventilation. However, DA is safe in patients with COPD, because it did not alter ventilation either in patients during weaning, or in hypoxemic, spontaneously breathing COPD patients.

Some anecdotal reports show that DA can improve diaphragmatic function and respiratory muscle contraction, as well as decrease pulmonary hypertension in COPD. Nevertheless, no placebo controlled, randomised trial, has been conducted to confirm these observations.

DA has potentially beneficial effects on the respiratory system, such as an increase in lung oedema clearance or inhibition of bronchoconstriction. However, the impact of DA on lung oedema has not been tested in human studies and clinical trials on the effects of DA on airway diameter have proved disappointing, unless administered during an acute asthmatic exacerbation.

Finally, the dopaminergic receptor agonist, sibenadet, did not induce sustained clinical benefits in patients with COPD, despite evidence from animal studies that DA inhibits sensory nerve fibres (activation of which elicits cough, bronchoconstriction and mucus production).

Thus, despite many years of widespread use, the role of dopaminergic support in respiratory disease remains poorly defined. We lack direct, convincing human studies in favour of DA’s beneficial effects on the respiratory system, but we have evidence of a detrimental impact of low dose DA on ventilation in healthy humans and patients with heart failure. DA should, therefore, be used with caution in critically ill hypoxemic patients during weaning from mechanical ventilation.
Reference List


Table 1. Published beneficial and detrimental effects of dopamine in the respiratory system.

<table>
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<th>Beneficial effects of dopamine</th>
<th>Detrimental effects of dopamine</th>
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<tr>
<td>• decrease in pulmonary vascular resistance and in pulmonary hypertension</td>
<td>• modulation of chemosensitivity and decreased ventilation in hypoxic conditions</td>
</tr>
<tr>
<td>• increase in lung oedema clearance by activation of epithelial ATPase and epithelial sodium channels</td>
<td>• increase in ventilation/perfusion mismatch in the lungs</td>
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<tr>
<td>• improvement of diaphragmatic function in chronic obstructive pulmonary disease</td>
<td></td>
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<tr>
<td>• inhibition of bronchoconstriction during bronchospasm</td>
<td></td>
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<tr>
<td>• inhibition of rapidly adapting stretch receptors in the lung, which control sensory nerve reflexes</td>
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Table 2. Summary of studies on the effects of dopamine (DA) on bronchial diameter. DA was administered either intravenously or by inhalation and the effects were tested in healthy subjects, patients with a past history of asthma, and patients with acute bronchospasm. One study tested effects of the DA receptor blocker, metoclopramide, on bronchial airway diameter. (FVC= forced vital capacity, FEV1= forced expiratory volume in the first second, FEFmax= maximal forced expiratory flow, FEF50= forced expiratory flow at 50 % of vital capacity).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects and patients</th>
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<td>10 subjects with bronchial hyperactivity</td>
<td>DA IV 0.5 µg/kg/min</td>
<td>No effect</td>
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<td></td>
<td>10 healthy subjects</td>
<td>DA IV 0.5 µg/kg/min</td>
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<tr>
<td></td>
<td>10 subjects with asthma without acute bronchospasm</td>
<td>DA inhalation 0.5 µg/kg/min</td>
<td>No changes in respiratory parameters</td>
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<td></td>
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<td>Increased FEV1, FVC, FEFmax, FEF50 in</td>
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