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Dose-dependent effect of dobutamine on chemoreflex activity in healthy volunteers

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Aims
β-adrenergic agonists increase peripheral chemoreceptor sensitivity in humans. We tested the hypothesis that β_1-agonist-related increase in peripheral chemoreflex sensitivity is selective and dose-dependent.

Methods
Using a double-blind, placebo-controlled, randomized, crossover study, we examined the effects of dobutamine (n = 17 healthy subjects) at perfusion rates of 2.5 μg kg^{-1} min^{-1} (D2.5) and 7.5 μg kg^{-1} min^{-1} (D7.5) on ventilation, haemodynamics and sympathetic nerve activity during normoxia, isocapnic hypoxia, posthypoxic maximal voluntary end-expiratory apnoea, hyperoxic hypercapnia and cold pressor test (CPT). We analysed the effect of pretreatment with atenolol on dobutamine-evoked chemosensitivity.

Results
Dobutamine dose-dependently increased ventilation (placebo 6.7 ± 0.5 *vs.* D2.5 7.8 ± 0.4 *vs.* D7.5 8.7 ± 0.4 l min^{-1}, $P < 0.005$) during normoxia, enhanced the ventilatory (placebo 14.4 ± 0.6 *vs.* D2.5 17.3 ± 0.8 *vs.* D7.5 22.5 ± 1.9 l min^{-1}, $P < 0.0001$) and sympathetic (placebo +215 ± 31 *vs.* D2.5 +285 ± 19 *vs.* D7.5 +395 ± 50% of baseline, $P < 0.03$) responses at the fifth minute of isocapnic hypoxia and enhanced the sympathetic response to apnoea performed after hypoxia (increase after 5 min of hypoxia: +290 ± 43% for placebo *vs.* +360 ± 21% for D2.5 *vs.* 537 ± 69% for D7.5, $P < 0.05$). No differences were observed between dobutamine and placebo in the responses to hyperoxic hypercapnia and CPT. Atenolol inhibited the dobutamine-related hyperventilation and apnoea shortening during normoxia and hypoxia.

Conclusion
Dobutamine enhances peripheral chemosensitivity at low infusion rates selectively and in a dose-dependent manner. There is a β_1 adrenoceptor component in dobutamine-evoked increase in peripheral chemosensititivity; however, a contribution of additional adrenoceptor subtypes cannot be excluded.

Introduction

Dobutamine, a primarily β-adrenergic agonist, is indicated for the short-term treatment of cardiac failure and is also frequently administered in the intensive care unit [1]. Moreover, this widely prescribed agent is used as a diagnostic tool during stress echocardiography for the diagnosis of coronary artery disease and the prediction of cardiac events [2]. The rate of infusion required to increase cardiac output is typically between 2.5 and 10 μg kg^{-1} per min, although higher infusion rates are occasionally required.

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Dobutamine's actions on cardiovascular parameters are well established [3]. However, the pharmacological modulation of chemoreflex sensitivity by dobutamine is less well known. We have recently shown that the increases in blood pressure during 5 μg kg^{-1} min^{-1} of dobutamine did not prevent a rise in peripheral chemoreflex sensitivity in healthy subjects [4]. Whether these effects are dose-dependent is not known. Most studies investigating pharmacological modulation of chemoreflex activity have used a single drug dose [5] or dosages below those used clinically, thus limiting the ability to extrapolate the results to daily clinical practice. Moreover, single-dose experiments do not provide insight into the selectivity and specificity of, in this case, β-agonists on chemoreceptor adrenoceptors.

The peripheral chemoreceptors are located in the carotid and aortic bodies and respond to a reduction in arterial oxygen content by an increase in ventilation and sympathetic nerve activity directed to muscle blood vessels (muscle sympathetic nerve activity, MSNA) [6]. The chemoreflex system is rich in receptors, triggering biological responses from various endogenous substances, among them β-adrenergic receptors [6]. The arterial baroreceptors, situated in the aortic and carotid arteries, are also able to modulate chemoreceptor sensitivity. Hence, baroreflex activation, through a rise in systemic blood pressure, restricts the ventilatory and MSNA responses to peripheral chemoreflex activation [7]. While larger doses of dobutamine may result in more marked β-adrenergic stimulation and chemoreflex enhancement, larger increases in blood pressure could also hamper peripheral chemoreflex response to hypoxia. However, larger doses of dobutamine could also activate α-adrenergic receptors, which increase chemoreflex sensitivity [8]. Moreover, carotid chemoreceptors have shown marked sensitivity to β-adrenergic stimulation in more basic studies [9, 10].

We therefore decided to test primarily the hypothesis that effects of dobutamine on chemoreflex sensitivity are dose dependent; that these effects are mediated by β_1-receptor activation was our second hypothesis. These results could be of importance in allowing extrapolation of our findings to the clinical setting.

Methods

We examined the effects of dobutamine on ventilation, haemodynamics and MSNA during normoxia and isocapnic hypoxia (10% O_2–90% N_2) in a randomized, crossover, double-blind, dose ranging, placebo-controlled study. Because hyperventilation stimulates pulmonary stretch afferents, which inhibit sympathetic nerve activity [11], we also studied the sympathetic nerve response during voluntary end-expiratory apnoea. In addition, we assessed the influence of dobutamine on the ventilatory and sympathetic responses to the cold pressor test (CPT) to ensure that the changes observed were not simply due to nonspecific enhancement of responses to excitatory stimuli by dobutamine [12, 13]. Finally, study of the effects of dobutamine during hypercapnic hyperoxia excluded an influence on central chemoreceptors [14–18].

Subjects

Seventeen healthy subjects (all men, age 26 years, range 20–30 years) with normal physical examination and on no medication were enrolled in the study. The Ethics Committee approved the study protocol and informed written consent was obtained from each subject.

Measurements

We obtained continuous recordings of minute ventilation (pneumotacometer), end-tidal PCO_2 (Normocap; Datex, Sheffield, UK), O_2 saturation (Nellcor N-100 C pulse oximeter, Pleasanton, CA, USA) and electrocardiogram (Siemens Medical, ECG Monitoring, Erlangen, Germany). Mean arterial blood pressure (MABP; Physiocontrol Colin BP-880 sphygmomanometer) was measured every 3 min during normoxia and every minute during hypoxia, hypercapnia and the CPT. MSNA was recorded continuously using multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head of all subjects [19].

Protocols

The protocol used to test the chemoreflex responses was identical to that used in previous studies [13, 16, 19]. Subjects breathed across a low-resistance mouthpiece with a nose clip to ensure exclusive mouth breathing during all the sequences.

Infusions of dobutamine [2.5 μg kg^{-1} min^{-1} (D2.5) and 7.5 μg kg^{-1} min^{-1} (D7.5) in 5% glucose solution] and placebo (identical volumes of 5% glucose solution) were prepared by a research nurse. Each infusion received a random code. The investigators were unaware of the content of each infusion. An antecubital vein cannulation was realized. We used a randomized, double-blind, crossover study design, randomizing the order of the placebo and the dobutamine infusions as well as the order of the breathing sequences. A recovery period of 20 min was allowed between infusions and between the two sequences of gas mixture exposure.

Effect of dobutamine during normoxia and isocapnic hypoxia Ten minutes after the initiation of the dobutamine or placebo infusion, measurements were taken

during a 5-min baseline period of room air breathing and during a period of 5 min of exposure to isocapnic hypoxia (10% O_2 in 90% N_2, with CO_2 titrated to maintain isocapnia, $n = 17$).

Effect of dobutamine during posthypoxic apnoeas Maximal voluntary end-expiratory apnoeas were performed at baseline and at the end of the 5th minute of hypoxia to eliminate the inhibitory influence of ventilation on sympathetic nerve traffic ($n = 17$) [4, 20].

Effect of dobutamine and atenolol during normoxia, isocapnic hypoxia and posthypoxic apnoeas In a group of five subjects, we analysed peripheral chemoreflex activation by continuous recording of blood pressure, heart rate, oxygen saturation, minute ventilation and electrocardiogram during 5 min of normoxia and during 5 min of isocapnic hypoxia. This recording was realized: (i) before and after a 15-min bolus of saline to exclude possible effects on recorded parameters of both the infusion and the time; (ii) after 15 min of intravenous dobutamine perfusion at a rate of 7.5 μg kg^{-1} min^{-1} (effect of dobutamine alone). This sequence was followed by a wash-out period of 25 min; (iii) after subjects were given atenolol intravenously (mean dose 0.053 mg kg^{-1}). The dose of the drug was tailored to reach a decrease in heart rate of 15% (effects of atenolol alone); (iv) after 15 min of dobutamine infused at a rate of 7.5 μg kg^{-1} min^{-1}, while subjects had already received atenolol, to study the effect of blocking dobutamine action on peripheral chemoreceptors (combined effect of dobutamine and atenolol).

Effect of dobutamine during hyperoxic hypercapnia After a 5-min baseline period of room air breathing, nine subjects were exposed to hyperoxic hypercapnia (7% CO_2 in 93% O_2) for 5 min.

Effect of dobutamine on CPT Seven subjects also underwent a 2-min CPT after a recovery period of 15 min following the last sequence of gas mixture exposure.

Data analysis

Sympathetic bursts were identified by careful inspection of the mean voltage neurogram [21]. The amplitude of each burst was determined and sympathetic activity was calculated as bursts per minute and multiplied by mean burst amplitude (in arbitrary units). The sympathetic and heart rate responses to the apnoeas were calculated during the entire apnoea period, divided by the duration of the apnoea in seconds, and subsequently multiplied by 60 to express the response in change per minute [13, 15, 22, 23].

Changes in SNA during hypoxia, hypercapnia and CPT were expressed as percentage change from baseline. Relative increases in sympathetic activity were expressed as percent increases from the five preceding minutes for the apnoeas during normoxia and from the 5th minute of hypoxic breathing for the apnoeas during hypoxia. This best reflects the dynamic nature of the sympathetic responses while taking into account spontaneous fluctuations in activity.

We could not find an adequate sympathetic nerve recording site or lost the sympathetic nerve recording during one of either of the dobutamine or placebo sessions in several subjects. We completed technically excellent studies examining the effects of dobutamine and placebo on the sympathetic nerve response to hypoxia in 11 subjects and on the responses to hypercapnia in nine subjects. SNA recordings were obtained during the CPT in seven subjects.

Statistical analysis

Results are expressed as means ± SD. A multiple ANOVA for repeated measurements with adjustment for baseline values and Bonferroni's correction determined whether dobutamine affected the cardiovascular and ventilatory responses to hypoxia, hypercapnia and the CPT compared with the changes occurring during the infusion of placebo. The same test was applied for comparison of the same parameters in subjects pretreated with atenolol. Other comparisons were performed with Student's paired *t*-tests (two-tailed). Significance was assumed at $P < 0.05$.

Results

Effects of dobutamine during normoxia

Dobutamine increased minute ventilation, oxygen saturation, MABP and heart rate (Table 1), but did not change end-tidal PCO_2 during room air breathing. Dobutamine decreased MSNA significantly on a dose-dependent basis.

Effects of dobutamine during isocapnic hypoxia

Dobutamine markedly increased the ventilatory (14.4 ± 0.6 *vs.* 17.3 ± 0.8 *vs.* 22.52 ± 1.9 l min^{-1} at the fifth minute of hypoxia, $P < 0.0001$ by ANOVA, placebo *vs.* D 2.5 μg kg^{-1} min^{-1} *vs.* D 7.5 μg kg^{-1} min^{-1}; Figure 1) and the MSNA responses to hypoxia ($+215 \pm 31\%$ *vs.* $+285 \pm 19\%$ *vs.* $+395 \pm 50\%$ at the fifth minute of hypoxia, $P < 0.03$ by ANOVA, placebo *vs.* D 2.5 μg kg^{-1} min^{-1} *vs.* D 7.5 μg kg^{-1} min^{-1}; Figure 2). MABP remained dose-dependently higher during dobutamine administration (87 ± 3 *vs.* 93 ± 2 *vs.* 98 ± 2 mmHg,

Table 1
Effects of dobutamine during normoxia

	Normoxia			
	Placebo	D2.5	D7.5	*P*-values (ANOVA)
Minute ventilation, l min^{-1}	6.7 ± 0.5	7.8 ± 0.4†	8.7 ± 0.4*	<0.005
MABP, mmHg	86 ± 3	93 ± 2†	103 ± 3**	<0.001
HR, beats min^{-1}	69 ± 4	72 ± 4	76 ± 5	>0.05
PCO_2, mmHg	38 ± 0.5	37 ± 0.3	38 ± 0.2	>0.05
Sa O_2, %	97.1 ± 0.1	97.4 ± 0.1†	98.0 ± 0.2*	<0.01
Δ MSNA, %	0	24 ± 5	37 ± 6 *	<0.05

Results are expressed as means ± SD; n = *17 subjects except for muscle sympathetic nerve activity (MSNA) measurements, where results are expressed as the percent decrease from the placebo value (*n = *11 subjects). MABP, Mean arterial blood pressure; HR, heart rate; Sa $O_{2,\%}$, arterial O_2 saturation.*†P < *0.05;* ††P < *0.01 for D2.5 vs. placebo.* *P < *0.05 and* **P < *0.01 for D7.5 vs. D2.5.*

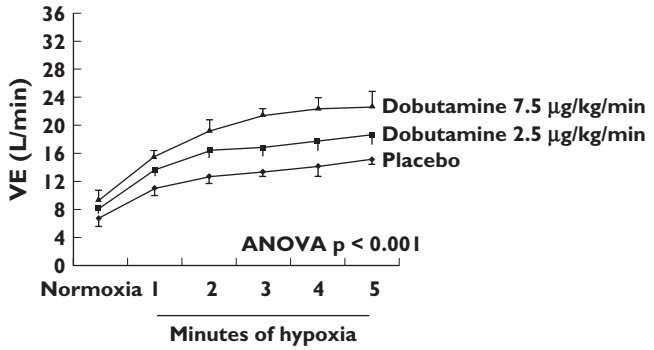

Figure 1
Ventilatory response to 5 min of isocapnic hypoxia in 17 subjects. Dobutamine increased the ventilatory response to hypoxia compared with placebo in a dose-dependent fashion

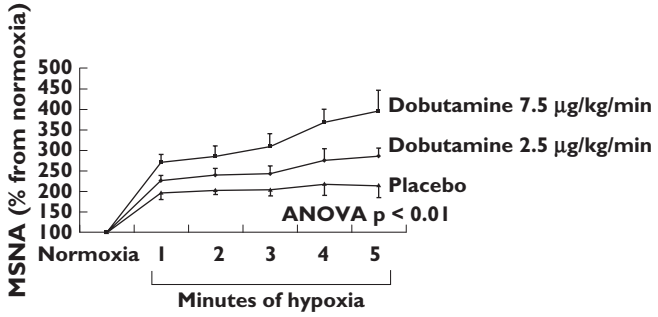

Figure 2
Muscle sympathetic nerve activity (MSNA) in response to 5 min of isocapnic hypoxia in 11 subjects. Dobutamine dose-dependently increased the sympathetic nerve response to hypoxia compared with placebo

$P = 0.01$ for placebo *vs.* D 2.5 µg kg^{-1} min^{-1} *vs.* D 7.5 µg kg^{-1} min^{-1}). Dobutamine did not change the fall in oxygen saturation (86 ± 2% *vs.* 89 ± 2% *vs.* 90 ± 2% for placebo *vs.* D 2.5 µg kg^{-1} min^{-1} *vs.* D 7.5 µg kg^{-1} min^{-1}) but increased the heart rate (80 ± 5 beats min^{-1} *vs.* 82 ± 8 beats min^{-1} *vs.* 94 ± 6 beats min^{-1} for placebo *vs.* D 2.5 µg kg^{-1} min^{-1} *vs.* D 7.5 µg kg^{-1} min^{-1}) in response to hypoxia. The addition of CO_2 maintained isocapnia (37.9 mmHg *vs.* 37.5 mmHg *vs.* 37.6 mmHg for placebo *vs.* D 2.5 µg kg^{-1} min^{-1} *vs.* D 7.5 µg kg^{-1} min^{-1}) during hypoxia.

Effects of dobutamine on end-expiratory apnoeas

Apnoeas with dobutamine were always shorter than those with placebo, both after normoxia and after hypoxia (Table 2). Shortening of apnoea duration was related to increase in dobutamine dose in both conditions (i.e. normoxia and hypoxia). Sympathetic activation during the apnoea performed after hypoxia was expressed as the relative change from a heightened sympathetic drive induced by 5 min of sustained hypoxia. Dobutamine dose-dependently enhanced the MSNA response to the apnoea after the fifth minute of hypoxia despite the shorter duration and a lesser reduction in oxygen saturation at the end of the apnoea (Figure 3).

Effects of atenolol on dobutamine-induced modifications (n = 5)

Analysis of recorded parameters showed no differences before and after a 15-min bolus of saline, thus excluding possible effects on recorded parameters of both the

Table 2
Effect of dobutamine on apnoeas during normoxia and hypoxia

	Normoxia				Hypoxia			
	Placebo	D2.5	D7.5	*P* (ANOVA)	Placebo	D2.5	D7.5	*P* (ANOVA)
Duration, s	43 ± 3	35 ± 2†	28 ± 3*	<0.05	21 ± 2	17 ± 1†	15 ± 1*	<0.01
ΔMSNA, %	251 ± 34	372 ± 50†	585 ± 101*	<0.05	290 ± 43	360 ± 21†	537 ± 69*	<0.05
Sa O_2,%	93 ± 0.8	95 ± 2	95 ± 1	NS	76 ± 2	82 ± 3†	88 ± 2*	<0.01
HR, beats min^{-1}	69 ± 2	70 ± 4	76 ± 3*	<0.05	83 ± 6	92 ± 5	98 ± 3*	<0.05

Results are expressed as mean ± SD; n = *17 subjects except for muscle sympathetic nerve activity (MSNA) measurements, where* n = *11 subjects. DMSNA, Changes in MSNA; MABP, mean arterial blood pressure; HR, heart rate; Sa O_2 %, arterial O_2 saturation.*†P < *0.05 for D2.5 vs. placebo; *P < 0.05 for D7.5 vs. D2.5.*

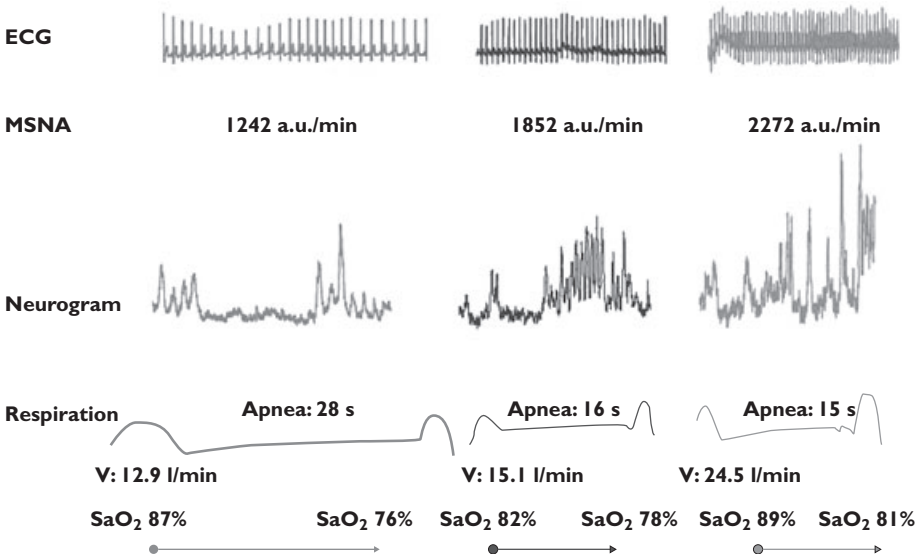

Figure 3
Apnoeas performed in one subject after the fifth minute of isocapnic hypoxia during infusions of placebo (red), dobutamine at 2.5 μg kg^{-1} min^{-1} (blue) and dobutamine at 7.5 μg kg^{-1} min^{-1} (green). The recording shows electrocardiographic activity (ECG), sympathetic nerve activity (MSNA and neurogram) and respiratory activity (Respiration) during the apnoea. Both VE and arterial oxygen saturation (SaO_2) are dose-dependently higher with dobutamine than with placebo at the last minute of hypoxia preceding the apnoea. The sympathetic nerve response to the apnoea is markedly increased during dobutamine infusion despite the shorter apnoea duration and lesser reduction in SaO_2

infusion and time atenolol inhibits dobutamine-related increase in minute ventilation at the 5th minute of normoxia and hypoxia. The shortening of apnoea duration related to dobutamine during normoxia and hypoxia was blunted when atenolol was combined with dobutamine. During hypoxia, the lesser fall in oxygen saturation after end expiratory apnoea observed with dobutamine was reduced after atenolol administration (Table 3).

Effects of dobutamine during hyperoxic hypercapnia (n = 9)

MABP remained dose-dependently higher during dobutamine administration (82 ± 3 *vs.* 96 ± 2 *vs.* 102 ± 3 mmHg for placebo *vs.* D 2.5 μg kg^{-1} min^{-1} *vs.* D 7.5 μg kg^{-1} min^{-1} for placebo, $P = 0.002$). Dobutamine did not influence the ventilatory and sympathetic responses to hyperoxic hypercapnia ($P = 0.11$). Heart rate and oxygen saturation were identical with both infusions ($P > 0.05$). The increase in end-tidal PCO_2 was similar with dobutamine and placebo ($P = 0.08$).

Effects of dobutamine during CPT (n = 7)

Dobutamine did not affect the ventilatory, heart rate or MABP responses to the CPT ($P > 0.4$ by ANOVA). Dobutamine did not affect the MSNA response to CPT in the seven subjects in whom SNA recordings were obtained ($P = 0.58$).

Discussion

The novel finding of this double-blind, randomized, placebo-controlled, crossover study is that β_1-adrenergic

Table 3
Effect of dobutamine and a β-blocker (atenolol) on ventilation and apnoeas during normoxia and hypoxia

	Normoxia				Hypoxia			
	Placebo	D7.5	D7.5 + atenolol	*P* (ANOVA)	Placebo	D7.5	D7.5 + atenolol	*p* (ANOVA)
Minute ventilation, l min^{-1}	7.1 ± 0.6 (NS)	8.1 ± 0.8†	7.5 ± 0.6*	<0.05	9 ± 0.5 (NS)	11.2 ± 1†	9.7 ± 1.5*	<0.01
Duration of apnoea, s	34 ± 3	22 ± 3†	25 ± 5	<0.01	17 ± 2 (NS)	12 ± 1†	15*	<0.05
Sa O_2 after apnoea, %	92.2 ± 0.5‡	94.2 ± 1	94.8 ± 0,6	<0.05	63 ± 1 (NS)	71 ± 2†	68 ± 2	<0.05

Results are expressed as mean ± SD; n *= 5 subjects; Sa* O_2*, %, arterial* O_2 *saturation; NS, not significant between placebo and D7.5 + atenolol.* †P *< 0.05 for D7.5* vs. *placebo;* *P *< 0.05 for D7.5* vs. *D7.5 + atenolol;* ‡P *< 0.05 for placebo* vs. *D7.5 + atenolol.*

agonism enhances arterial chemoreflex sensitivity directly and dose dependently in healthy subjects.

This is supported by the following findings: first, dobutamine dose-dependently increased the ventilatory and sympathetic responses to isocapnic hypoxia in our subjects. Second, dobutamine attenuated the duration of the apnoeas and blunted the level of hypoxia that could be maintained during the apnoeas. This is evident from the lesser falls in oxygen saturation during the apnoeas performed under hypoxic conditions while subjects received dobutamine. Apnoeas performed during both normoxia and hypoxia were also shorter with dobutamine. The enhanced sympathetic response to peripheral chemoreflex activation during dobutamine was especially marked during the end-expiratory apnoeas. This enhanced sympathetic response was manifest during apnoeas performed during both normoxia and hypoxia, was dose-dependent and was observed despite the shorter apnoea duration and the attenuated reduction in oxygen saturation. Third, dobutamine also dose-dependently increased ventilation during normoxia. Peripheral arterial chemoreceptors have a significant physiological activity in normoxia, the so-called 'resting drive' [24]. This 'resting' chemoreflex activity was probably enhanced by dobutamine in the presence of normal levels of oxygen saturation. Finally, dobutamine effects on minute ventilation and on length of end-expiratory apnoeas are reversed when pretreatment by a selective β_1-blocker, atenolol, is given (Table 3).

We have previously reported [4] that 5 μg kg^{-1} min^{-1} of dobutamine specifically enhanced the peripheral chemoreceptors because it did not affect ventilation and sympathetic activity when peripheral chemoreceptors were inhibited by 93% O_2 and the central chemoreceptors were activated by 7% CO_2. Moreover, this dose of dobutamine did not enhance the ventilatory response to the CPT, a nonspecific ventilatory and sympathetic excitatory stimulus [12, 13].

A new contribution of our study is that it offers further insight into the role of β_1- rather than β_2- and/or α_1-receptors on peripheral chemoreflex control. Dobutamine is a selective β_1-adrenergic agonist but also has weak β_2 and α_1 activity. At higher doses, dobutamine, like any other drug, loses its selectivity. However, peripheral chemoreflex sensitization was already evident at low doses of 2.5 μg kg^{-1} min^{-1} of dobutamine, when the effects of dobutamine are very selective for the α_1-adrenergic pathway. Experimental pharmacological data indicate that chemoreceptor cells possess receptors for major neurotransmitters. Adrenergic agonists and antagonists modulate basal- and hypoxia-induced activation of peripheral chemoreceptors measured by neurotransmitter release in the synaptic cleft (dopamine, cathecholamines) [25]. β- and α-adrenoceptors have been identified on chemoreceptor cell membranes and have a specific excitatory influence on chemoreflex afferent activity in animals [26] and humans [27]. Our results emphasize that the excitatory effects of sympathomimetic agonists are selectively mediated by β_1-receptors because: (i) they are seen at low doses of dobutamine (2.5 μg kg^{-1} min^{-1}), known to stimulate β_1-receptors directly without stimulating α_1- or β_2-adrenoreceptors, and (ii) effects are blunted when a selective β_1 blocker is added to dobutamine infusion.

Higher doses of dobutamine (7.5 μg kg^{-1} min^{-1}) are less selective. As a result, enhancement of the chemoreflex response to hypoxia at larger doses of dobutamine could be related to both α and β stimulation. α-adrenergic agonist infusion tends to restrict chemoreflex activation through blood pressure-related baroreflex activation [7]. Thus, β-adrenergic stimula-

tion may remain the main pathway responsible for chemoreflex activation at larger doses of dobutamine. Clinical pharmacology studies have shown that isoprotenerol, a nonspecific β-adrenergic agonist, as well as norepinephrine, enhances the ventilatory response to hypoxia in humans [26]. Fenoterol, a selective β_2 agonist, has also been shown to stimulate both peripheral and central ventilatory chemosensitivity [5]. Thus, our study highlights the importance of β_1-adrenergic activation in the increase in peripheral chemoreflex sensitivity, but does not exclude the possibility that β_2-adrenergic stimulation participated in the effects we observed at larger doses of dobutamine. Despite these limitations, reversal of some of the dobutamine effects by a β_1 blocker, atenolol, strengthens the observation that there is a β_1-adrenoceptor component in dobutamine-evoked increases in peripheral chemosensitivity; however, contribution of additional adrenoceptor subtypes cannot be excluded.

A direct stimulation of the respiratory centre by dobutamine cannot be excluded. However, injection of norepinephrine into the internal carotid artery beyond the carotid chemoreceptors produces only a slight increase in ventilation in man [27]. Moreover, dobutamine enhanced only the ventilatory and sympathetic response to hypoxia, and did not affect the responses of two other conditions associated with an increase in ventilation and MSNA. The absence of any effect of different doses of dobutamine on the response to hypercapnia and to the CPT argues against a nonspecific excitatory effect on the central nervous system. Moreover, it is also unlikely that variations in respiration could be secondary to an entrainment phenomenon; we did not observe that variations in one signal were transmitted to a second parallel system during hypercapnia and the CPT.

Dobutamine increased the sympathetic nerve response during hypoxia, but not the response in heart rate. This could be explained by baroreflex-related limitations in the rise in heart rate in response to the increases in arterial blood pressure [28]. Furthermore, the primary response to hypoxia is bradycardia [29]. Baroreflex activation is a powerful inhibitor of the peripheral chemoreflex. Our observation of a dose-dependent enhanced ventilatory and sympathetic response to hypoxia, despite a dose-dependent rise in blood pressure, further argues in favour of the importance of chemoreflex sensitivity enhancement with dobutamine.

Finally, some studies in normal subjects receiving dobutamine have reported a reduction in sympathetic activity and an increase in parasympathetic activity due to stimulation of ventricular mechanoreceptors and arterial baroreceptors. We have no data about contractility in this study.

Conclusion

Our study shows that dobutamine dose-dependently enhances peripheral chemosensitivity mainly through β_1-adrenergic stimulation.

Conflict of interest

None declared.

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