Consequences of peripheral chemoreflex inhibition with low-dose dopamine in humans

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Key points

- Low-dose dopamine reduces the ventilatory response to acute hypoxia both in animal and in human studies.
- In this study we show that low-dose dopamine also attenuates the haemodynamic responses (tachycardia, hypertension) to acute hypoxia in healthy humans.
- Moreover, we found that dopamine withdrawal results in a temporary increase in minute ventilation.
- The magnitude of the increase in minute ventilation after dopamine withdrawal correlates with the degree of ventilatory response to acute hypoxia and depends on the duration of dopamine administration.
- Dopamine may provide a novel method for assessing differences in the level of peripheral chemoreceptor activity, which has important clinical implications given the recently reported pathological role of the carotid body in cardiovascular diseases in animals and humans.

Abstract Low-dose dopamine inhibits peripheral chemoreceptors and attenuates the hypoxic ventilatory response (HVR) in humans. However, it is unknown: (1) whether it also modulates the haemodynamic reactions to acute hypoxia, (2) whether it also modulates cardiac baroreflex sensitivity (BRS) and (3) if there is any effect of dopamine withdrawal. We performed a double-blind, placebo-controlled study on 11 healthy male volunteers. At sea level over 2 days every subject was administered low-dose dopamine ($2 \ \mu g \ kg^{-1} \ min^{-1}$) or saline infusion, during which we assessed both ventilatory and haemodynamic responses to acute hypoxia. Separately, we evaluated effects of initiation and withdrawal of each infusion and BRS. The initiation of dopamine infusion did not affect minute ventilation (MV) or mean blood pressure (MAP), but increased both heart rate (HR) and cardiac output. Concomitantly, it decreased systemic vascular resistance. Dopamine blunted the ventilatory, MAP and HR reactions (hypertension, tachycardia) to acute hypoxia. Dopamine attenuated cardiac BRS to falling blood pressure. Dopamine withdrawal evoked an increase in MV. The magnitude of the increment in MV due to dopamine withdrawal correlated with the size of the HVR and depended on the duration of dopamine administration. The ventilatory reaction to dopamine withdrawal constitutes a novel index of peripheral chemoreceptor function.

Abbreviations   BR, breathing rate; BRS, baroreflex sensitivity; CB, carotid body; CO, cardiac output; CSN, carotid sinus nerve; GC1, type I glomus cell; HF, high frequency band; HR, heart rate; HRV, heart rate variability; HVR, hypoxic ventilatory response; IQR, interquartile range; LF, low frequency band; MAP, mean arterial pressure; MV, minute ventilation; RR interval, R wave to R wave interval; SEM, standard error of the mean; SBP, systolic blood pressure; S_{pO_2}, blood oxygen saturation; SVR, systemic vascular resistance; TV, tidal volume.

Introduction

Dopamine is an endogenous catecholamine that is often used in clinical practice (Giamouzis *et al.* 2010; Rafouli-Stergiou *et al.* 2012), although the clinical benefits of its administration have increasingly been questioned (Friedrich *et al.* 2005; Chen *et al.* 2013). Dopamine at low dose exerts its action by stimulating dopamine receptors dispersed widely within the human body (Hussain & Lokhandwala, 2003). Dopamine receptors also play an integral role in the functioning of peripheral chemo-receptors (located in the carotid and aortic bodies; González *et al.* 1995), which are responsible for the regulation of partial pressures of oxygen and carbon dioxide in the bloodstream (O'Regan & Majcherczyk, 1982). Dopamine has been reported to inhibit afferent signalling from the peripheral chemoreceptors in human patients (van de Borne *et al.* 1998).

The haemodynamic and ventilatory responses to hypo-xia are closely related, which is particularly well seen in patients with heart failure (Niewinski *et al.* 2013*a*). As low-dose dopamine attenuates the ventilatory reaction to acute hypoxia (i.e. peripheral chemosensitivity; van de Borne *et al.* 1998), it could be speculated that it would also affect the reflex haemodynamic responses to hypo-xia. Such an analysis might be facilitated by the use of the recently developed methodology for studying peri-pheral chemoreceptor sensitivity (Niewinski *et al.* 2013*a*). If proven correct, it would add to the ongoing discussion on the benefits and perils of the use of dopamine in critical care settings (Rafouli-Stergiou *et al.* 2012).

Thus far, the effects of dopamine infusion on ventilation have been assessed shortly after its initiation (Welsh *et al.* 1978; van de Borne *et al.* 1998). It is unknown whether dopamine withdrawal after prolonged administration would cause any discernible change in the ventilatory or haemodynamic parameters. If a relationship between these parameters and the level of peripheral chemosensitivity could be demonstrated, then reaction to dopamine withdrawal may become a clinically useful and novel index of peripheral chemoreceptor function.

It has been postulated that the response from peripheral chemoreceptors can be evoked not only by acute hypoxia (Chua & Coats, 1995) but might also be tonically aroused during normoxia (Abdala *et al.* 2012; Sinski *et al.* 2012;

McBryde *et al.* 2013). This was recently demonstrated in an animal model of heart failure (Del Rio *et al.* 2013; Schultz *et al.* 2013), in which carotid body denervation resulted in marked improvement in autonomic indices, including a significant decrease in directly measured sympathetic tone (Marcus *et al.* 2013). Yet, it is unknown if such tonic peripheral chemoreceptor activation is correlated with the acute response to hypoxia (i.e. reflex chemo-sensitivity). Low-dose dopamine infusion may facilitate this comparison by inhibition of the tonic activation arising from the peripheral chemoreceptors without inter-fering with acute hypoxic testing (i.e. assessment of reflex chemosensitivity). Such an evaluation would not be possible using pure oxygen, which is the standard method for assessing the tonic level of peripheral chemoreceptor activation.

As the inverse relationship between peripheral chemo-sensitivity and cardiac barosensitivity (BRS) has been shown in both animal and human studies (Marshall, 1981; Somers *et al.* 1991; Ponikowski *et al.* 1997; Despas *et al.* 2012), it could be hypothesized that low-dose dopamine-induced inhibition of peripheral chemoreceptors would lead to improvements in BRS. To address the above issues, we performed a double-blind cross-over placebo-controlled study in which we compared ventilatory, haemodynamic and BRS indices in response to low-dose dopamine *versus* saline infusions in a group of young healthy male volunteers.

Methods

Studied population

After obtaining local Institutional Ethics Committee (Komisja Bioetyczna, Wroclaw Medical University) approval, 11 healthy, non-smoking male volunteers, age 23–40 years (median 26 years), were enrolled into the study. All subjects gave informed consent. The study was performed in accordance with the latest review of the Helsinki Declaration.

Study participants were asked to have a light break-fast and avoid caffeine intake for at least 12 h prior to the examination. During two consecutive days of the study, each subject underwent one infusion per day. All tests followed the same protocol, with the only difference

being the intravenous solution used: a low-dose infusion of dopamine ($2\ \mu g\ kg^{-1}\ min^{-1}$) or an identical volume of normal sterile saline (0.9%) infusion (placebo). The sequence of the administered solutions was randomized and blinded to the researchers (and subjects) performing the testing and calculating the results. A venous catheter was placed into the cephalic vein and primed with saline before connecting to the infusion pump (AP-14; Ascor, Warsaw, Poland).

Measurements

Subjects were examined in the supine position at an ambient temperature of 22°C. A one-way open breathing circuit (Hans Rudolph, Inc., Shawnee, KS, USA) was used during the study. The inhale arm of the circuit served to administer room air or 100% nitrogen gas. Gas switching was controlled silently using a high-pressure electric valve. The exhale arm was connected via a $1000\ l\ min^{-1}$ flowhead (MLT3000L; ADInstruments, Sydney, Australia) to a differential pressure transducer (FE141 Spirometer; ADInstruments) for the measurement of breathing rate (BR), tidal volume (TV) and minute ventilation (MV). Heart rate (HR), mean blood pressure (MAP), cardiac output (CO) and systemic vascular resistance (SVR) were continuously and non-invasively recorded using a NexFin device (BMEYE B.V., Amsterdam, Netherlands). A pulse oximeter (Radical-7; Masimo Corp., Irvine, CA, USA) with a lightweight ear clip was used to evaluate blood oxygen saturation (S_{pO_2}). All data were collected at a sampling rate of 1 kHz (16-bit resolution) using PowerLab 16/30 (ADInstruments) and recorded on a laptop computer (Dell Inc., Round Rock, TX, USA).

Study protocol

During the entire experiment we measured the following parameters continuously: BR, TV, MV, S_{pO_2}, MAP, HR, CO, SVR and the electrocardiogram. The first 5 min of the study protocol was ignored but allowed the subject familiarization with the equipment and environment. The next 10 min of the testing were defined as *baseline recording before infusion*. Next, an infusion of the previously randomized solution began and the following 15 min was defined as *recording during infusion*. Subsequently, an assessment of peripheral chemoreceptor sensitivity to intermittent hypoxia was performed using the transient hypoxia method (see below). This phase took approximately 40 min. Ten minutes following the last nitrogen administration (time period defined as *baseline prior to infusion withdrawal*), the intravenous infusion was stopped and the last 10 min was recorded (defined as *recording after infusion withdrawal*). The influence of the infusion on the measured parameters was assessed

by comparing averaged data from the last 4 min of *baseline recording before infusion* and from the last 4 min of *recording during infusion*. For assessment of the effects of the infusion withdrawal we took 4 min immediately preceding and following the infusion termination (Fig. 1*A*). Additionally, the assessment of the ventilatory reaction to dopamine withdrawal was performed in two subjects using two different durations of dopamine administration (15 and 60 min).

Assessment of peripheral chemosensitivity

Peripheral chemoreceptor sensitivity to intermittent hypoxia (hypoxic ventilatory response, HVR) was estimated using the transient hypoxia method (Chua & Coats, 1995). Briefly, subjects were silently switched to breathing with pure nitrogen gas for 10–45 s. This procedure was repeated 5–8 times per study participant, achieving falls in S_{pO_2} of 99–65%. After each administration of nitrogen subjects were allowed to rest for 5 min breathing room air to allow for the measured parameters to return to baseline levels. The lengths of nitrogen administration were randomized. MV was calculated from breathing rate and tidal volume. Each ventilatory response was calculated as an average from the three largest consecutive breaths following the end of nitrogen administration. HVR was used as a measure of peripheral chemosensitivity and expressed as the slope of the linear regression describing the relationship between the single ventilatory responses and the associated nadirs of S_{pO_2}, including the baseline values of MV and S_{pO_2}. The baseline values of MV and S_{pO_2} were averaged from the 90 s period prior to each gas administration.

Assessment of haemodynamic response

The haemodynamic response to hypoxia was assessed over the same time course as HVR. The peak HR and peak MAP responses following nitrogen gas administrations were plotted against the corresponding S_{pO_2} nadirs. The slopes of regression functions describing these relationships were defined as HR slope and MAP slope and reflected the magnitude of the haemodynamic responses to acute hypoxia (Niewinski *et al.* 2013*a*).

Assessment of baroreflex sensitivity

Cardiac BRS was assessed using the sequence method (Parati *et al.* 1988). Systolic blood pressure (SBP) and R wave to R wave (RR) intervals from 5 min preceding the initiation of the infusion and first nitrogen gas administration (separately for the dopamine and placebo solutions) were used to calculate BRS separately to rising and falling SBP. BRS assessment was based

on the analysis of brief (usually lasting for 3–5 cardiac cycles), spontaneous fluctuations in SBP (rises and falls) and corresponding changes in RR intervals. To improve the robustness of the assessment, we decided to report BRS results only for the recordings with more than five sequences, which was possible in 8 out of 11 subjects.

Assessment of heart rate variability

RR intervals taken from 5 min preceding the initiation of the infusion and first nitrogen gas administration (separately for the dopamine and placebo solutions) were analysed with the spectral method (Malliani *et al.* 1991; using fast Fourier transformation and Hanning windowing) for calculation of the power within the low frequency band (LF, 0.04–0.15 Hz), high frequency band (HF, 0.15–0.40 Hz) and LF/HF ratio. To assess the relative predominance of these components of heart rate variability (HRV), normalized units (n.u.) were used. All premature beats seen during the analysis were corrected by interpolation with previous and following beats.

Data and statistical analysis

Statistica 10 (StatSoft Inc., Tulsa, OK, USA), LabChart Pro (ADInstruments), Nevrocard (Nevrokard Kiauta d.o.o., Izola, Slovenia) and MATLAB (MathWorks, Natick, MA, USA) were used to analyse the data. The statistical comparisons were evaluated using the Wilcoxon matched pairs test. Correlations were calculated using Spearman rank method. Variables are shown as mean and standard error of the mean (SEM), or as median and interquartile range (IQR) where appropriate. A *P* value < 0.05 is considered statistically significant.

Results

Baseline characteristics in dopamine and placebo arm

The comparison between *baseline recording before infusion* values of BR, TV, MV, MAP, S_{pO_2}, HR, CO and SVR in the placebo and dopamine arms revealed no significant differences (for more details see Table 1). This indicates no changes in the conditions between the two infusions.

Table 1. Median (IQR) values of measured parameters during baseline recording before saline and dopamine infusions

	Baseline before saline infusion	Baseline before dopamine infusion
Breathing rate (breaths min^{-1})	14.3 (10.8–16.5)	14.5 (11.4–15.1)
Minute ventilation (l min^{-1})	10.2 (8.8–11.4)	9.9 (7.9–11.5)
Mean arterial pressure (mmHg)	91.7 (85.7–97.8)	95.3 (90.5–102.6)
S_{pO_2} (%)	95.8 (95.4–97.6)	96.4 (95.6–97.5)
Heart rate (b.p.m.)	66.1 (56.3–70.6)	66.8 (52.6–73.2)
Cardiac output (l min^{-1})	7.2 (6.3–7.5)	7.7 (6.1–8.5)
Systemic vascular resistance (dyn s cm^{-5})	1095.2 (919.4–1197.1)	1052.1 (944.6–1095.7)

Effects of infusion initiation/termination

Administration of low-dose dopamine did not influence BR, TV, MV or MAP, but increased both HR (66.8 (52.6–73.2) *vs.* 71.11 (54.0–82.6) b.p.m., *P* = 0.008) and CO (7.7 (6.1–8.5) *vs.* 8.5 (7.8–10.3) l min^{-1}; *P* = 0.003) and decreased SVR (1052.1 (944.6–1095.7) *vs.* 923.3 (857.1–1006.8) dyn s cm^{-5} *P* = 0.007). By contrast, no significant changes were observed after initiation of the saline infusion (Fig. 2). There was no correlation between changes in the measured parameters (before and during dopamine infusion) and HVR measured during placebo infusion (n.s. for all).

The termination of low-dose dopamine caused a significant transient increase in MV (9.1 (8.6–12.2) *vs.* 11.7 (9.6–12.9) l min^{-1}; *P* = 0.006). The rise in MV was most prominent after 131 s (118–139) following withdrawal of the infusion. The magnitude of this augmentation of MV post-dopamine infusion correlated with HVR measured during saline infusion (i.e. level of peripheral chemosensitivity) (*r* = 0.61, *P* < 0.05). Increased MV resulted from an augmentation of TV (0.75 l (0.56–0.88) *vs.* 0.81 l (0.63–1.06), *P* = 0.003) with no significant change in BR (13.7 (11.3–15.4) *vs.* 12.8 (12–15.4) breaths min^{-1}, *P* = 0,18). We also did not observe
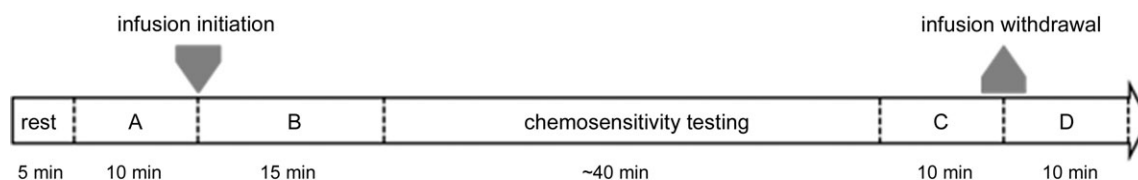

Figure 1. Schematic diagram of the study protocol
A, baseline recording before infusion; *B*, recording during infusion; *C*, baseline prior to infusion withdrawal; *D*, recording after infusion withdrawal.
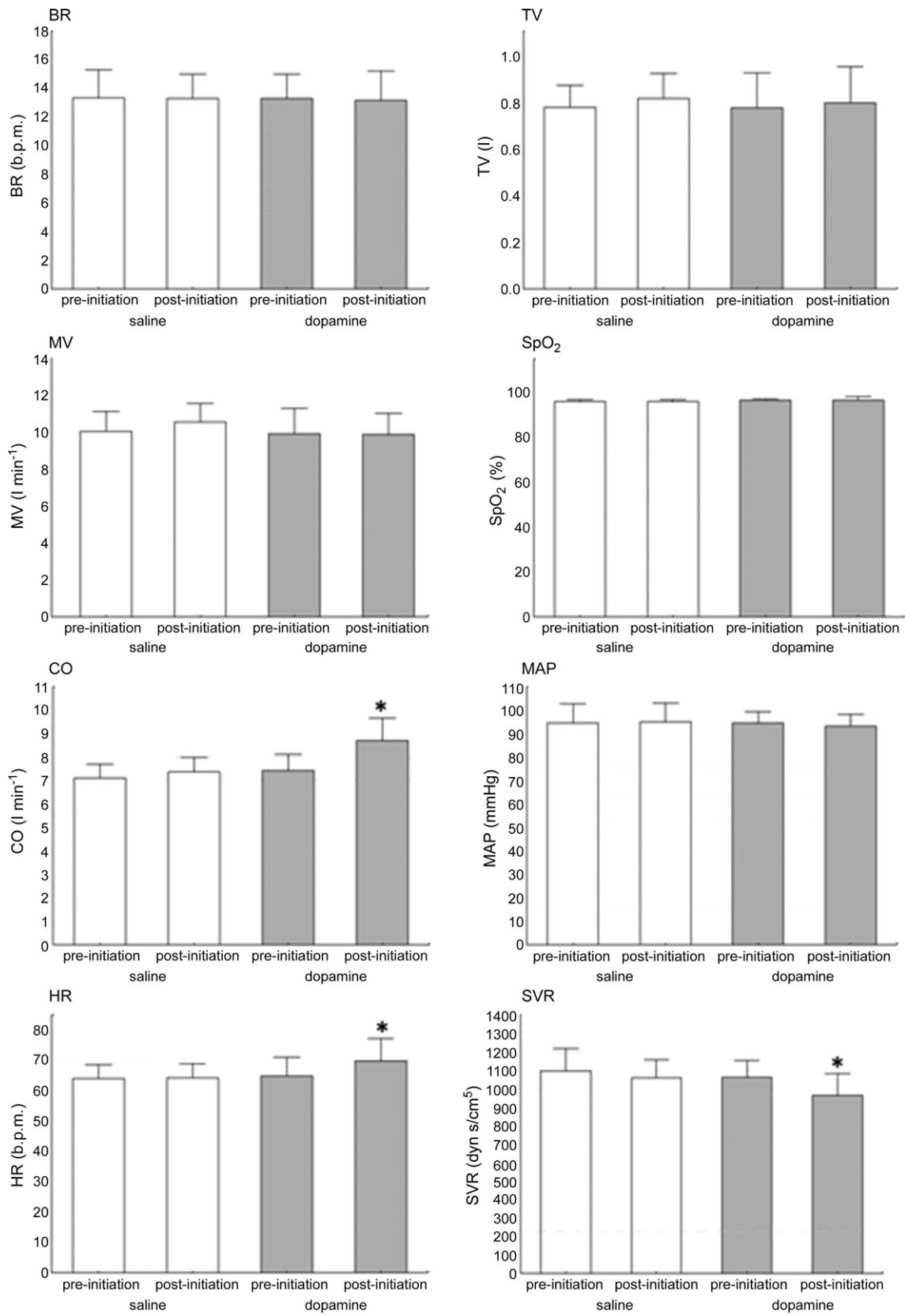
Figure 2. Effects of saline infusion initiation compared with dopamine infusion initiation on BR, TV, MV, S_{pO_2}, CO, MAP, HR and SVR

Open columns, saline infusion initiation; shaded columns, dopamine infusion initiation. *$P < 0.05$.

significant changes in the haemodynamic parameters recorded (HR, MAP, CO, SVR) following dopamine withdrawal (n.s. for all). Detailed haemodynamic data for dopamine and placebo withdrawal are provided in online supplementary material. In contrast to dopamine infusion, the discontinuation of the placebo infusion did not cause significant changes in any of the measured parameters (n.s. for all; Fig. 3).
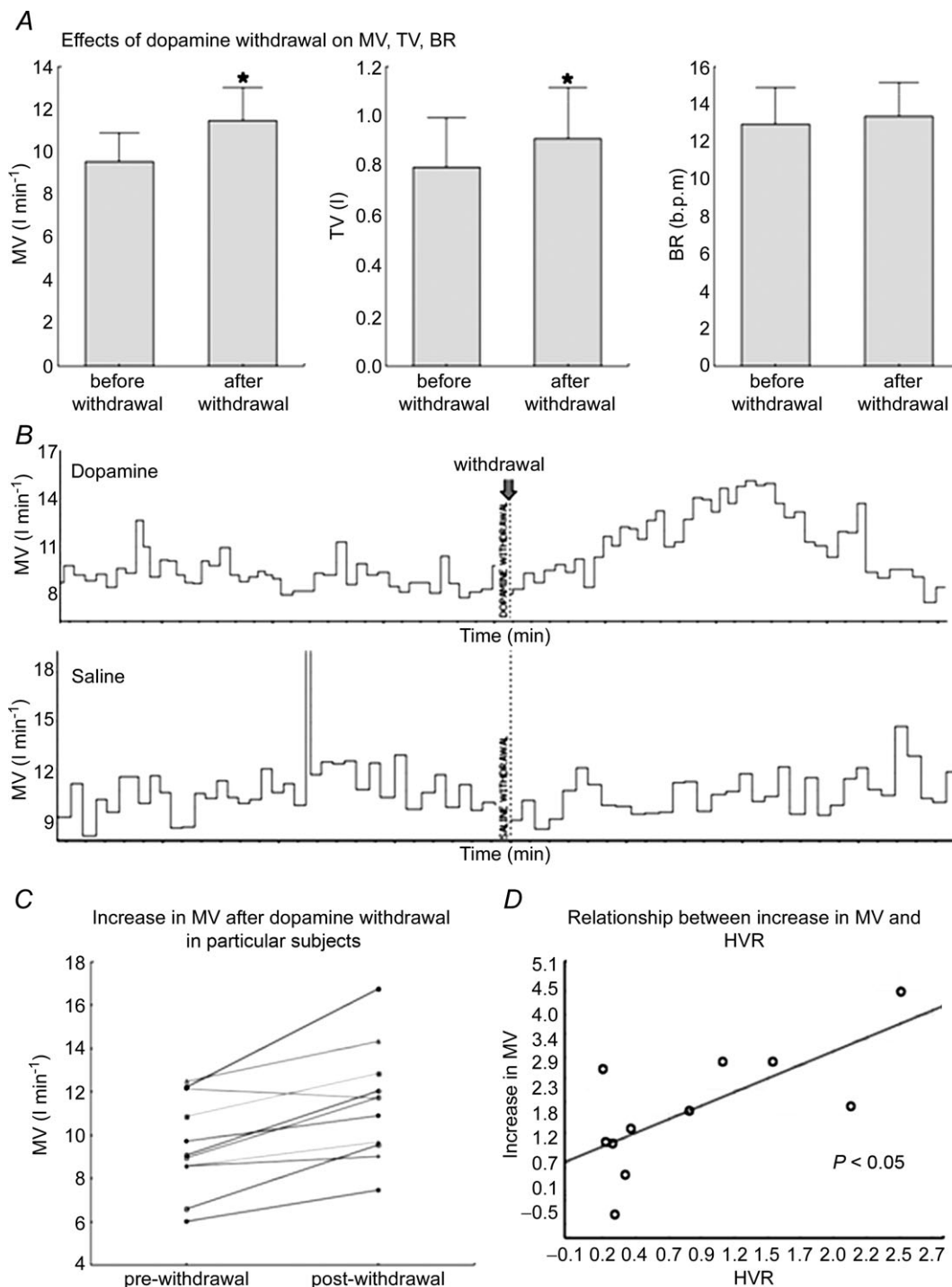

Figure 3. Analysis of dopamine withdrawal
A, effects of dopamine infusion withdrawal on ventilatory parameters. *B*, example showing the effects of dopamine and placebo withdrawal on MV. *C*, an increase in MV after dopamine withdrawal presented as individual data. *D*, correlation between an increase in MV after dopamine withdrawal and hypoxic ventilatory response (HVR). *$*P < 0.05$.

Effects of dopamine on peripheral chemosensitivity, baroreflex and heart rate variability

The infusion of low-dose dopamine reduced significantly the chemoreflex-evoked ventilatory (HVR) and MAP (MAP slope) responses to hypoxia (0.40 (0.26–1.49) vs. 0.16 (0.02–0.24) l min^{-1}/S_{pO_2}, $P = 0.003$; 0.49 (0.37–0.8) vs. 0.41 (0.27–0.45) mmHg/S_{pO_2}, $P = 0.03$; saline vs. dopamine, respectively). The infusion of low-dose dopamine also reduced the HR response to hypoxia (HR slope), although this did not quite reach statistical significance (0.56 (0.46–0.64) vs. 0.44 (0.29–0.54) b.p.m./S_{pO_2}, $P = 0.06$; Figs 4 and 5).

Cardiac BRS to falling SBP was significantly decreased after the initiation of the low-dose dopamine infusion compared with placebo (Table 2). Interestingly, no change in cardiac BRS was found for rising SBP (Table 2). BRS was not calculated in three subjects due to an insufficient number of adequate HR/SBP sequences.

We found no change in LF and HF power of HRV and in LF/HF ratio after the initiation of low-dose dopamine infusion (36 (22–46) vs. 40 (16–54) n.u.; 60 (49–72) vs. 57 (44–80) n.u.; and 1.19 (0.31–0.93) vs. 1.16 (0.20–1.25), respectively, n.s. for all).

Correlations within the indices of peripheral chemosensitivity and barosensitivity

The HVR during the saline infusion correlated with HR slope ($r = 0.63$, $P = 0.04$) and showed a trend to correlate with MAP slope ($r = 0.55$, $P = 0.08$). We found no correlation between cardiac BRS to rising and falling SBP during both the dopamine ($r = 0.57$, n.s.) and the placebo infusion ($r = 0.19$, n.s.).

Relationship between duration of dopamine administration and ventilatory response to dopamine withdrawal

Based on the data obtained from two subjects we found that the magnitude of the ventilatory reaction to the
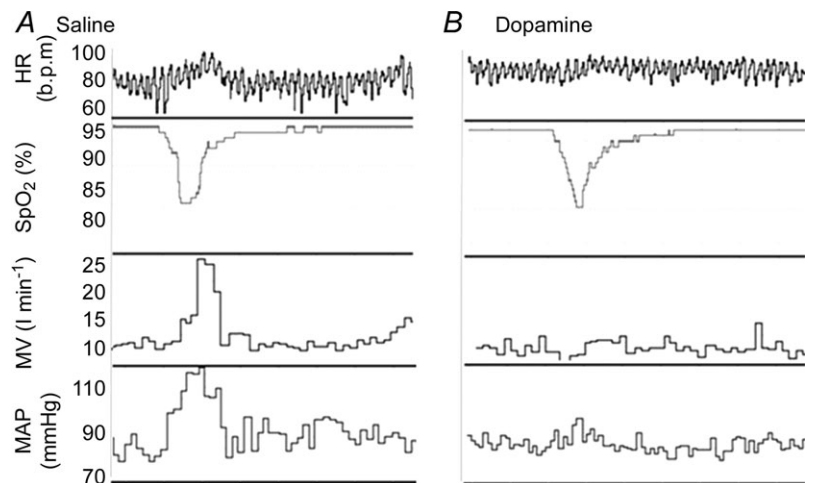

Figure 4. Effect of dopamine on hypoxic responses
Example of the raw data showing the ventilatory and haemodynamic responses to hypoxia during (A) saline and (B) dopamine infusion.
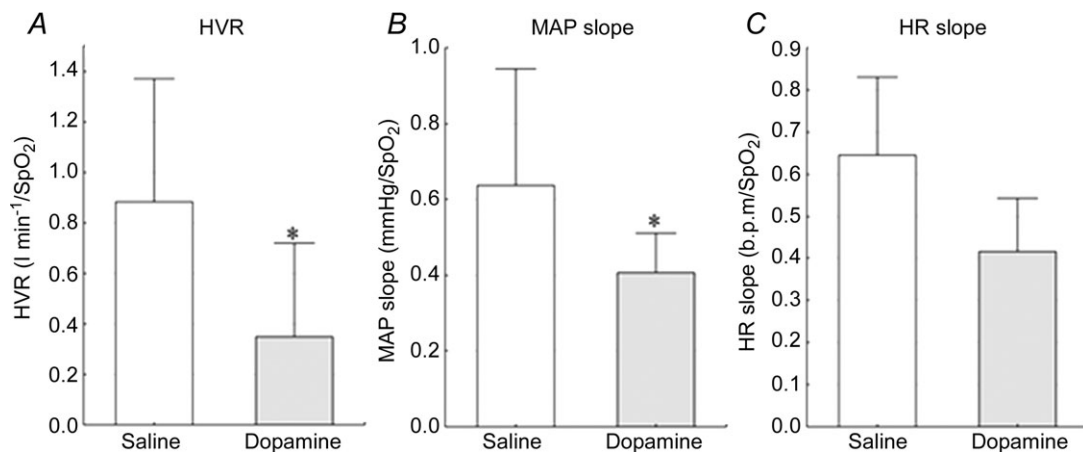

Figure 5. Changes in hypoxic responses on dopamine
Influence of dopamine on the ventilatory (A) and haemodynamic (B and C) responses to hypoxia. *$P < 0.05$

Table 2. Effects of low-dose dopamine and placebo infusions on cardiac barosensitivity (BRS)

	BRS to rising SBP (ms mmHg^{-1})		BRS to falling SBP (ms mmHg^{-1})	
	Before infusion	On infusion	Before infusion	On infusion
Placebo infusion	16.07	14.65	17.5	16.43
	(12.81–18.38)	(13.83–16.36)	(13.69–19.26)	(13.91–18.11)
Dopamine infusion	17.33	16.5	18.54	13.42
	(14.5–21.11)	(13.52–19.09)	(16.16–19.81)	(12.24–16.34)*

Values are given as medians and interquartile ranges. See text for details.
*$P < 0.05$ for before infusion *vs.* on infusion.

Table 3. Effect of the duration of dopamine infusion on the ventilatory reaction to dopamine withdrawal

Measured parameter	Duration of dopamine infusion (min)	Change after dopamine withdrawal (%)	
		Subject A	Subject B
Minute ventilation	15	+11	+10
	60	+19	+50
Tidal volume	15	+11	−1
	60	+36	+60
Breathing rate	15	+1	+19
	60	−14	−7

Note that the pronounced increase in minute ventilation observed with long administration is mainly driven by an increment in tidal volume. Subject A has hypoxic ventilatory response of 0.2 l min^{-1}/S_{pO_2} and subject B of 1.1 l min^{-1}/S_{pO_2}.

dopamine withdrawal depended on the duration of dopamine administration. The infusions lasting for 60 min resulted in greater ventilatory reactions than the infusions administered for 15 min. This increment in the ventilatory reaction was driven by an increase in TV but not in BR (Table 3).

Discussion

This randomized, double-blind, placebo-controlled study revealed that low-dose dopamine infusion attenuated both the ventilatory reaction and the haemodynamic (HR and MAP) response to acute hypoxia. The second novel finding was an excitatory effect of dopamine withdrawal on MV. The magnitude of this increase in MV correlated with HVR as measured during saline infusion. Finally, we found that the decrease in peripheral chemosensitivity caused by the dopamine administration was accompanied by a decrease in cardiac BRS to falling blood pressure but not to baroreceptor loading.

Ventilatory effects of low-dose dopamine administration

There are two chemosensitive areas in humans – a central site localized at or near the ventral surface of the medulla (Caruana-Montaldo *et al.* 2000), which is sensitive to hypercapnia, and peripheral regions localized to the carotid (CB) and aortic bodies, which are excited by both hypercapnia and hypoxia (O'Regan & Majcherczyk, 1982). Intravenous dopamine is believed to depress the peripheral chemoreceptors only. This theory was confirmed by Welsh *et al.* (1978), who revealed that dopamine does not change the hypercapnic ventilatory response. This might be related to the fact that dopamine does not cross the blood–brain barrier (Pardridge, 2005).

The influence of exogenously administered low-dose dopamine on the ventilatory response during hypoxia and the molecular mechanism of action have been described previously (Welsh *et al.* 1978; Ward & Bellville, 1982; Bascom *et al.* 1991; González *et al.* 1995; van de Borne *et al.* 1998; Iturriaga & Alcayaga, 2004). Dopamine infused at low dose binds mostly to type 2 receptors (D_2) on type I glomus cells (GC1) due to much higher affinity as compared with D_1 receptors (Lehmann *et al.* 1983). Activation of D_2 receptors leads to a reduction in the release of neurotransmitters from GC1 and therefore to a decrease in the discharge rate of the carotid sinus nerve (CSN) in response to hypoxia (González *et al.* 1995). In contrast, dopamine infused at a high dose activates both D_1 and D_2 receptors and results in an increase in CSN discharge rate and MV both in normoxic and in hypoxic conditions (Welsh *et al.* 1978; González *et al.* 1995), probably due to activation of the postsynaptic D_1 receptors, which overcomes the inhibitory effect of D_2 stimulation. We propose that D_1 receptors are unlikely to become activated during the low-dose infusion used in our study. This is consistent with seeing a marked decrease in HVR without a significant change in normoxic MV with low-dose dopamine.

Dopamine-related changes in haemodynamic responses to acute hypoxia

The ventilatory response is not the sole consequence of the hypoxic activation of the peripheral chemoreceptors. The acute excitation of the carotid and aortic bodies leads also to an increase in HR and blood pressure (Kumar, 2009). Therefore, blockade of the peripheral chemoreceptors by low-dose dopamine infusion may also blunt the haemodynamic response. Previous studies describe only the respiratory part of the hypoxic response during dopamine administration. In our study, however, we assessed both ventilatory and haemodynamic changes simultaneously with accompanying intermittent decreases of S_{pO_2}. Using this method we revealed that the reduction in HVR caused by the dopamine infusion is accompanied by reductions in the MAP and HR responses to hypoxia (hypertension, tachycardia), although the HR response did not quite reach statistical significance ($P = 0.06$). However, this decrease was seen consistently despite an increased HR resulting from the dopamine infusion itself. As HVR showed positive correlations with both the HR and the MAP slopes, we suggest that all these reflex components can be down-modulated by a dopaminergic mechanism at the level of the peripheral chemoreceptor. While we assume that this interruption is caused by dopamine acting at the receptor level, it is difficult to speculate at which stage any divergence of the ventilatory and haemodynamic signals takes place. Some authors suggest that it is within the CB, where different populations of glomus cells might be responsible for ventilatory *versus* sympathetic control (Paton *et al.* 2013). On the other hand, the central site of termination of peripheral chemoreceptor afferents within the nucleus tractus solitarii could also be responsible for a differential modulation of respiratory and cardio-vascular/sympathetic reactions to hypoxia (Sapru, 1996; Paton, 1998a,b). However, a recent study performed in humans after CB resection suggested that the dissociation between ventilatory, cardiac and blood pressure responses to hypoxia might be related to different function of carotid *versus* aortic bodies (Niewinski *et al.* 2013b).

Apart from the sympathetic nervous system one must acknowledge the Hering–Breuer reflex and its influence on the HR and MAP responses to hypoxia. This reflex originating from the pulmonary stretch receptors and stimulated by hyperventilation leads to tachycardia and vasodilatation (Ursino & Magosso, 2000; Kumar, 2009). It is possible that the dopamine infusion influences the haemodynamic response by diminishing the ventilatory response to hypoxia and hence suppresses the role of the Hering–Breuer reflex. While this might assist in explaining the reduction in HR slope, it is not in concordance with the MAP slope decrease. As cardiac BRS to rising blood pressure did not change after initiation of the dopamine infusion, we believe that the influence of the baroreflex on

the magnitude of the haemodynamic responses to hypoxia in our study is negligible. A final issue is that the hypoxic stimulus is likely to have a direct inhibitory effect on the cardiac pacemaker cells (Marshall & Metcalfe, 1988) and vascular smooth muscle tone (Umbrello *et al.* 2013) – this might lead to a generalized underestimation of the haemodynamic responses during both the dopamine and the placebo infusions.

We recently found that CB denervation in human patients results in the dissociation of BP *versus* HR responses to hypoxia (Niewinski *et al.* 2013b). It is also well known that the aortic bodies are reactive to dopamine agonists and antagonists (Smatresk & Lahiri, 1982). In this context, the reductions in both MAP and HR slopes seen in our study suggest that dopamine exerts its haemodynamic actions not only through the carotid bodies but also through the aortic bodies. In contrast, the ventilatory response in humans is solely mediated by the carotid bodies (Kumar, 2009).

Comparison with previous studies

The effects of the initiation of low-dose dopamine (2–5 μg kg^{-1} min^{-1}) on normoxic MV, HR and MAP in healthy humans have been described previously. van de Borne *et al.* (1998) reported no changes in both MV and MAP but increased HR, while Welsh *et al.* (1978) described a significant decrease in MV but no changes in MAP and HR. Our observations are concordant with those made by van de Borne, which are consistent with the proposed mode of action of dopamine discussed above. Of interest, none of these studies evaluated the influence of low-dose dopamine on SVR, which is positively affected by high doses of the drug (>10 μg kg^{-1} min^{-1}; Stetson & Reading, 1977). In our study, low-dose dopamine caused vasodilatation as proven by drop in SVR, which was balanced by a concomitant increase in CO, thus resulting in relatively stable blood pressure. Discrepancies in the cited studies can be most likely attributed to the differences in the dopamine dosing, relatively low numbers of studied subjects and often subtle dopamine-related changes in MV seen in healthy humans.

Effects of dopamine on tonic and acute components of peripheral chemoreflex

Our study provides insight into the issue of sensitivity and tonicity of the peripheral chemoreflex. The dopamine infusion is expected to eliminate any tonic aspect of peripheral chemoreflex drive as with hyperoxia (Sinski *et al.* 2012). Both methods have side effects, including tachycardia and hypertension for dopamine and hyperoxia, respectively, that may influence findings and interpretations. However, it is only the low-dose dopamine

method that enables a concomitant study of the acute hypoxic response, and thus assessment of both ventilatory and haemodynamic components of reflex chemosensitivity. In our study, we did not find a significant relationship between HVR and MV changes after initiation of the dopamine infusion (index of tonic activation). This is consistent with the notion that reflex sensitivity of the peripheral chemoreceptors is not necessarily related to its tonic activation (Paton *et al.* 2013). On the other hand, we did not notice a significant change in MV after the initiation of dopamine infusion, which could be related to the very low level (or absence) of any tonic activity in healthy individuals (Stickland *et al.* 2008). A significant decrease in sympathetic tone was seen after CB denervation in the animal model (Marcus *et al.* 2013). However, the animals studied developed a high level of sympathetic drive and increased chemosensitivity to hypoxia and hypercapnia at baseline due to introduction of heart failure state (Del Rio *et al.* 2013).

Despite the lack of significant changes in MV after dopamine initiation, we observed a significant drop in SVR. One could hypothesize that this fall is not only due to the direct influence of dopamine on several subtypes of dopamine receptors present in peripheral vasculature (Polakowski *et al.* 2004; Armando *et al.* 2011), but can also arise from inhibition of the haemodynamic arm of the peripheral chemoreflex. Therefore, a reduction of SVR could be related to modulation of the sympathetic tone to blood vessels by chemoreceptor deactivation, as shown by Sinski *et al.* (2012). Admittedly, van de Borne *et al.* (1998) did not observe a significant decrease in sympathetic nerve activity during normoxic dopamine infusion in healthy individuals, but during hypoxic state noted the lack of expected sympathoactivation. HRV analysis performed in our study showed no significant changes in indices of sympathetic/parasympathetic activity (LF power, HF power, LF/HF ratio) after initiation of dopamine infusion. However, we regard these results as inconclusive because of a possible direct influence of dopamine on sinus node β-receptors (Endoh, 1975). A more complete picture would be expected to be obtained from subjects with presumably high chemosensitivity and tonic activity, e.g. patients with congestive heart failure (Niewinski *et al.* 2013*a*) or possibly hypertension (McBryde *et al.* 2013).

Dopamine withdrawal

While the results of the initiation of low-dose dopamine infusion have been described previously (Welsh *et al.* 1978; Bascom *et al.* 1991; van de Borne *et al.* 1998), the effects of its withdrawal have not been reported so far. In the present study, withdrawal of the prolonged dopamine infusion (lasting nearly 60 min) resulted in a significant temporary rise in MV. The magnitude of this increase correlated with the level of HVR measured during the placebo infusion (i.e. chemosensitivity), suggesting a similar mechanism was involved. While we can only speculate as to the mechanism of this phenomenon, we hypothesize that the withdrawal reaction could be caused by the sudden release of the excitatory neurotransmitters accumulating in GC1 cells. Neurotransmitters of the CB are constantly synthesized in GC1 cells and stored in vesicles in the cytoplasm (Gonzalez *et al.* 1994). Activation of D_2 receptors on GC1 cells causes hyperpolarization as calcium currents are blocked (Carroll *et al.* 2005). This minimizes the release of CB neurotransmitters (González *et al.* 1995). It could be expected that the neuroactive substances accumulate in the GC1 cells and when the inhibiting effect of dopamine subsides the release rate of these neurotransmitters rises temporarily, increasing the discharge rate in the CSN and resulting in a hyperventilatory response (Fig. 3). This concept is further supported by the fact that the magnitude of the ventilatory response to dopamine withdrawal depends on the duration of dopamine administration (see Table 3). As individuals with sensitized peripheral chemoreceptors are also expected to have a higher rate of neurotransmitter synthesis (Soulier *et al.* 1997; Wang *et al.* 1998), the response to the withdrawal of dopamine infusion could be more pronounced in these individuals, which is reflected in our study by the positive correlation between HVR and the magnitude of the MV response to dopamine withdrawal. No such relationship was found for the haemodynamic components of the withdrawal reaction. This could be due to the postulated heterogeneity of the glomus cells (Paton *et al.* 2013) and/or neurotransmitters responsible for ventilatory and haemodynamic arms of the peripheral chemoreflex. Another possibility for the lack of concomitant ventilatory and haemodynamic responses to dopamine withdrawal could be related to the differential action of dopamine on carotid *versus* aortic chemoreceptors. However, a recent study has suggested the existence of contrasting patterns of response to hypoxia between carotid and aortic bodies (Niewinski *et al.* 2013*b*).

Dopamine and baroreflex sensitivity

The sequential method used in our study (Parati *et al.* 1988), which is based on the analysis of very brief and spontaneous fluctuations in blood pressure, allowed for BRS assessment despite unchanged averaged MAP observed during dopamine infusion. The inverse relationship between peripheral chemosensitivity and BRS has already been shown in both healthy and congestive heart failure subjects (Somers *et al.* 1991; Ponikowski *et al.* 1997). It was also shown that the transient blockade of the peripheral chemoreceptors with hyperoxia temporarily increased BRS (Ponikowski *et al.* 1997). Therefore, attenuation of peripheral chemoreceptor activity by

low-dose dopamine infusion should enhance BRS. In our study, however, we found a decrease in cardiac BRS but only to falling SBP. Since cardiac BRS to rising BP is controlled mostly by the parasympathetic system whereas the cardiac BRS to falling BP involves activation of the cardiac sympathetic system (La Rovere *et al.* 2008), it could be speculated that dopamine administration modulated predominantly the sympathetic component of the autonomic system. This distinction is further supported by the lack of a correlation between cardiac BRS to rising and falling blood pressure. Thus, the attenuation of cardiac BRS could be related to cardiac sympathoinhibition attributed to: (1) dopamine itself (Mannelli *et al.* 1997; Kaya *et al.* 2003) or (2) a dopamine-mediated decrease in chemoreceptor activity (Ciarka *et al.* 2005; Sinski *et al.* 2012). On the other hand, the observed decrease in cardiac BRS could simply be an effect of increased HR (Ward *et al.* 2006) secondary to the dopamine infusion and movement to the non-linear portion of the baroreflex function curve. Our findings differ from those of Somers *et al.* (1991), possibly because we did not assess sympathetic tone after simultaneous activation of baroreceptors and chemoreceptors, but rather looked at spontaneous cardiac BRS in response to chemoreflex modulation. It is also difficult to compare our data with the results obtained by Ponikowski *et al.* (1997), as we used different methodology to assess cardiac baroreflex and did so not in heart failure patients but in young, healthy subjects with presumably no impairment of baroreflex function. Thus, the effect of dopamine on cardiac BRS using the sequence method remains inconclusive.

Study limitations

As expected, some systemic actions of low-dose dopamine were observed (increase in HR and cardiac output). These changes might to some extent influence HR responses (tachycardia) to acute hypoxia and hence the measurement of HR slope during dopamine infusion. Isocapnia was not maintained during evaluation of the ventilatory and haemodynamic responses to hypoxia. However, such a poikilocapnic approach has been previously validated and proven to be clinically useful in healthy humans and patients with systolic heart failure (Chua & Coats, 1995; Niewinski *et al.* 2013*a*).

Conclusions

We present novel phenomena related to the dopamine-induced inhibition of the peripheral chemo-receptors. First, we found that low-dose dopamine reduces both the ventilatory and the HR/MAP reactions to hypoxia, which could be of particular importance, especially in critically ill patients in whom dopamine is still used. In the event of acute respiratory failure (leading to hypoxia) such patients might be lacking the compensatory effects of tachycardia and hypertension. On the other hand, decreased afterload and HR responses to hypoxia might lead to improvements in stroke volume and diastolic coronary perfusion, respectively, which might benefit some of the dopamine-treated patients. However, as recently shown (Chen *et al.* 2013) administration of low-dose dopamine had no impact on diuresis, renal function and prognosis in decompensated heart failure patients with renal dysfunction.

Moreover, we found a decrease in cardiac BRS that might be related to the modulation of the sympathetic system. Finally, we describe a positive ventilatory reaction to dopamine withdrawal, which could serve as a novel index of the degree of peripheral chemoreceptor activity between individuals.

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Additional information

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

The experiments were performed in the Laboratory for Applied Cardiovascular Research at the Department of Cardiology, 4th Military Hospital, Wroclaw, Poland. P.N.: conception and design of the experiments, collection, analysis and interpretation of data, drafting the article. S.T.: conception and design of the experiments, collection, analysis and interpretation of data, drafting the article. W.B.: data interpretation and analysis, revision of the manuscript. J.F.R.P.: data interpretation and analysis, revision of the manuscript. Piotr Ponikowski: conception and design of the experiments, drafting the article, revision of the manuscript. All authors approved the final version of the manuscript. All persons designated as authors qualify for authorship. All those who qualify for authorship are listed.

Translational perspective

The efficacy of low-dose dopamine in the treatment of critically ill patients remains an unresolved issue. Randomized clinical trials performed mostly in acute heart failure patients have provided conflicting and rather discouraging results. While low-dose dopamine exerts some diuretic and minor inotropic properties, these struggle to translate into clinically meaningful benefits. An influence of low-dose dopamine on peripheral chemoreceptors is rarely appreciated among clinicians. In our study we showed that such intervention through the inhibition of chemoreceptive cell function results in diminished ventilatory and haemodynamic responses to acute hypoxia. This could be of importance in severely ill patients in whom compensatory reactions to hypoxia (hyperventilation, tachycardia and hypertension) are necessary for adequate tissue perfusion. Similarly, low-dose dopamine, could complicate the process of weaning from mechanical ventilation by inducing a state of inappropriate sensing of hypoxia.

On the other hand, recent studies have suggested that denervation of the CB results in favourable modulation of autonomic tone in animal models of hypertension and heart failure. Our findings might support this approach by showing a significant decrease in systemic vascular resistance with a corresponding drop in peripheral chemosensitivity. However, a direct vasodilatory effect of low-dose dopamine administration cannot be excluded.