Effects of nitric oxide synthase inhibition on dexmedetomidine-
induced vasoconstriction in healthy human volunteers

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Background. This study aimed to assess the contribution of endothelial nitric oxide synthesis to the net responses of human peripheral blood vessels in vivo to the selective \( \alpha_2 \)-adrenoceptor agonist dexmedetomidine.

Methods. Two groups of healthy young men were studied. In the first experiment, after brachial plexus block, the responses of digital arteries to systemically administered dexmedetomidine (target plasma concentration 1.2 ng ml\(^{-1}\)) were studied using a photoplethysmograph (\( n=10 \)) during i.a. infusions of saline and the nitric oxide synthase (NOS) inhibitor NG-monomethyl-L-arginine (L-NMMA) (8 \( \mu \)mol min\(^{-1}\)). In a separate experiment, after pre-treatment with acetyl-salicylic acid, responses to increasing doses of dexmedetomidine (0.01–164 ng min\(^{-1}\)) in the presence and absence of L-NMMA were compared in dorsal hand veins (DHV) (\( n=10 \)) using linear variable differential transformers.

Results. L-NMMA significantly augmented dexmedetomidine-induced vasoconstriction of digital arteries as assessed by an increase in light transmission through a finger and by a decrease in finger temperature. The mean (95% confidence interval) extent of the additional effect of L-NMMA over the constrictor effect of dexmedetomidine alone was 19\% (14–24\%) (\( P<0.0001 \)). In DHV, L-NMMA had variable effects on the dexmedetomidine-constriction dose–response curve. In three subjects, the curve was shifted significantly to the left (with a >10-fold difference in ED\(_{50}\)), but ED\(_{50}\) was only marginally affected by L-NMMA in the other subjects (difference in ED\(_{50}\) < five-fold).

Conclusions. The endothelial NOS enzyme has a significant role in opposing the vasoconstrictor action of dexmedetomidine at drug concentrations within the therapeutic range.


Keywords: muscle vascular, pharmacology, responses; pharmacology, dexmedetomidine, nitric oxide; sympathetic nervous system, dexmedetomidine

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The sympathetic nervous system plays a central role in regulation of organ blood flow, primarily through regulating the release of epinephrine and norepinephrine, which act on \( \alpha_1 \)-, \( \alpha_2 \)-, and \( \beta_2 \)-adrenoceptors in arteries and veins. \( \alpha_2 \)-Adrenoceptors modulate organ blood flow in a complex manner. Activation of presynaptic \( \alpha_2 \)-adrenoceptors on sympathetic nerves and in the central nervous system induces sympatholysis, whereas activation of vascular postsynaptic receptors causes both vasoconstriction (through activation of \( \alpha_2 \)-adrenoceptors on vascular smooth muscle cells) and vasodilatation (through activation of \( \alpha_2 \)-adrenoceptors on endothelial cells).\(^2\) Because of these counteracting mechanisms, the overall effects of \( \alpha_2 \)-adrenoceptor activation on organ blood flow are difficult to predict.

Dexmedetomidine (Precedex\textsuperscript{\textregistered}, Hospira, Lake Forest, IL, USA) is a selective and potent \( \alpha_2 \)-adrenoceptor agonist, which is used for sedation in the intensive care
unit and as an adjunct to regional and general anaesthesia. At low doses, dexmedetomidine induces nearly complete sympatholysis, but continuous and linear increases in its postsynaptic effects (e.g. increased systemic vascular resistance) are observed with increasing doses. We recently studied the effects of dexmedetomidine on myocardial blood flow and found that in spite of significant peripheral vasoconstriction, high dexmedetomidine concentrations do not induce myocardial ischaemia in healthy subjects. One possible explanation for this is that the balance between direct smooth muscle-dependent vasoconstriction and endothelium-dependent vasodilatation by α2-adrenoceptors may vary in different organs.

Recent studies using pharmacological inhibition of nitric oxide synthase (NOS) with N5-monomethyl-L-arginine (L-NMMA) have suggested that α2-adrenoceptor agonist-induced vasoconstriction is opposed by α2-adrenoceptor-mediated nitric oxide release from endothelial cells *in vivo* in humans. The current study was designed to test the hypothesis that inhibition of NOS increases α2-adrenoceptor agonist-induced arterial and venous constriction in healthy humans.

**Methods**

The study was performed in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and was approved by the Ethics committee of the Southwest Finland Hospital District, Turku, Finland. All subjects gave their written informed consent.

We conducted two separate experiments in healthy young men; constriction responses of digital arteries to dexmedetomidine with and without NOS inhibition were studied using photoplethysmography, and the responses of dorsal hand veins (DHV) to dexmedetomidine with and without NOS inhibition were studied using the linear variable differential transformer method.

**Study population**

Non-smoking male Caucasian subjects were eligible for the study if they were aged 18–45 yr and were in good general health as assessed by medical history, physical examination, 12-lead ECG, blood cell count, serum lipid concentrations, and urine drug screening. Twenty-one volunteers were recruited. Subjects in the finger blood flow experiment (n=11) had a mean age of 26 yr (range 21–36 yr) and a mean BMI of 24 kg m⁻² (range 18–27 kg m⁻²). Subjects in the DHV experiment (n=10) had a mean age of 27 yr (range 21–40 yr) and a mean BMI of 24 kg m⁻² (range 20–30 kg m⁻²). The number of subjects in the finger blood flow experiment was calculated to provide about 90% power to detect a difference of 10% in light transmission through a finger (LTF) between before and after infusion of L-NMMA, using the previously observed variability in LTF in anaesthetized subjects infused with dexmedetomidine to a target plasma concentration of 0.6 ng ml⁻¹. In the DHV experiment, 10 subjects were calculated to provide about 80% power to detect a one log unit difference in the ED50 of dexmedetomidine between the DHV response with and without L-NMMA using the within-group standard deviation of the ED50 of the response to dexmedetomidine as previously reported. We expected less variability in the response to dexmedetomidine because of the within-subject paired study design. In both calculations, a type I error probability of 0.05 for a two-sided test was used.

**Study protocols**

Subjects were instructed to abstain from alcohol for ≥48 h, from caffeine for ≥12 h, and from heavy exercise for ≥24 h. All experiments were carried out in a quiet, temperature-controlled room [mean (SD) T=23.3 (0.3)°C] with the subjects in the supine position.

**Finger blood flow experiment**

Responses of digital arteries to i.a. (brachial) L-NMMA infusion were studied with photoplethysmography during systemic dexmedetomidine (dexmedetomidine session) or saline (saline session) infusion. The order of these two sessions was randomized and sessions were separated by a minimum of 7 days. Different hands were studied in each session to avoid repeated brachial artery cannulation. A venous catheter was placed into a dorsal vein on the non-studied hand. LTF and skin temperature sensors (see below) were placed on the distal phalanx of the index and middle fingers of the studied hand, respectively. During the study, the subject’s hand was elevated (flexed at the elbow) to ~5 cm above the heart to minimize resting venous tone and facilitate emptying of the hand veins. To induce sympathectomy of the studied hand, a brachial plexus block was performed with mepivacaine 1% (35 ml) administered using a 23 G bevel B needle, the axillary approach, and a paraesthesia technique. After success of the block was confirmed (assessed by motor function, skin sensation, finger temperature, and changes in the photoplethysmography signal), a 22 G catheter was inserted into the brachial artery of the studied arm (or in three cases into the radial artery) for infusion of L-NMMA, measurement of arterial pressure (see below), and for arterial blood sampling.

Thirty minutes after the induction of brachial block, an i.v. infusion of either dexmedetomidine or saline was started and continued for 50 min. Dexmedetomidine (Precedex®) was administered i.v. as a target-controlled infusion aiming at pseudo-steady-state plasma drug concentrations of 1.2 ng ml⁻¹. A Harvard 22 syringe pump (Harvard Apparatus, Holliston, MA, USA) connected to a computer running STANPUMP software was used with the pharmacokinetic parameters of dexmedetomidine as described previously and with the maximum infusion rate...
set to 0.3 \mu g \text{kg}^{-1} \text{min}^{-1}. With these parameters, we expected to reach the target plasma concentration of 1.2 ng ml\(^{-1}\) within 3 min. The total dexmedetomidine dose was 2.1 \mu g \text{kg}^{-1}.

Thirty minutes after the beginning of the i.v. dexmedetomidine or saline infusion, an i.a. infusion (1 ml min\(^{-1}\), Perfusor ED2, B. Braun, Melsungen, Germany) of saline (for 5 min), followed by l-NMMA (8 \mu mol min\(^{-1}\) for 5 min) was started.

Arterial samples for measurement of plasma dexmedetomidine, epinephrine, and norepinephrine concentrations were collected before the i.v. dexmedetomidine or saline infusion, 2 min before the beginning of the i.a. saline infusion, and at the end of the dexmedetomidine infusion. The study design is illustrated in Figure 1A.

**Dorsal hand vein experiment**

DHV responses to increasing doses of dexmedetomidine in the presence or absence of l-NMMA were measured simultaneously in both hands. Acetylsalicylic acid (500 mg p.o.) was given to the subjects about 1 h before the session started to inhibit \(\alpha_2\)-adrenoceptor-induced production of prostanoids. Skin temperature sensors (see below) were placed on the middle finger of both hands, and a 22 G catheter was inserted into a radial artery for arterial pressure measurement and for arterial sampling. A suitable vein on the dorsum of each hand was cannulated with a 24 G catheter, and infusions of normal saline were initiated. Veins with no tributaries over a segment of 2–3 cm and neither over- nor under-crossed by other veins within about the same distance were considered suitable. Constant infusion rates of 0.3 ml min\(^{-1}\) were maintained throughout the session.

Diameters of the veins were measured by the linear variable differential transformer technique.\(^{12}\) It has been demonstrated that \(\alpha\)-adrenoceptor responsiveness is similar in both hands when this method is used.\(^{13}\) Low-pressure tourniquets were placed on each upper arm (Automatic Low-Pressure Tourniquet, Stille Surgical Ab, Solna, Sweden), and the pressure regulator set to 45 mm Hg. This tourniquet system allows rapid simultaneous inflation of both cuffs to exactly the same pressure. With the aid of a tripod, a measurement transducer (type CD-375-100, connected to an LVC-2500 signal conditioner, Macro Sensors, Penmauken, NJ, USA) was placed over the studied vein with the central movable core resting on the summit of the vein about 10 mm proximally from the tip of the 24 G catheter. The tripod position was then secured with tape. The subject’s arms were placed on padded supports and elevated to the same level above the heart, at 25° above horizontal. Linear variable differential transformer outputs from both hands were recorded (PowerLab/4SP and Chart version 5.5.1 software package, AD Instruments, Castle Hill, NSW, Australia) at a frequency of 100 Hz.

Twenty minutes after completion of all preparations, the tourniquets were inflated for 2 min at 3 min intervals until reproducible plateau distensions were attained. After this,
a minimum of 30 min from the beginning of the session, the tourniquets were inflated for 3 min, and baseline measurements were taken. After releasing the pressure from the tourniquets, an infusion of L-NMMA (dose rate of 0.5 μmol min⁻¹) was started into one DHV at a constant infusion volume rate of 0.1 ml min⁻¹ (a total infusion rate of 0.3 ml min⁻¹ into the vein was maintained with saline until the infusion of dexmedetomidine was started) (Module PDS, Fresenius Vial). Whereas the saline infusion was continued into the other DHV. These infusions of L-NMMA and saline were maintained until the end of the session.

Seven minutes after the initiation of the L-NMMA infusion, the tourniquets were inflated for 3 min. After vein distension recording and release of the tourniquets, dexmedetomidine was administered into the investigated veins of both hands at eight increasing dose rates ranging from 0.01 to 164 ng min⁻¹, with a constant infusion volume rate of 0.2 ml min⁻¹ (Module PDS, Fresenius Vial). Turnover time between the infusion steps was a few seconds. Each of the eight infusion phases lasted 5 min, with the tourniquets inflated for the last 3 min of each phase. The study design is illustrated in Figure 1b.

**Haemodynamic and temperature measurements**

Probes for photoplethysmography (Oximeter Sensor OxyTip+ OXY-AF, GE Healthcare, Helsinki, Finland) and skin temperature (400 series, GE Healthcare), arterial pressure transducers (Truwave PX-600F 3X, Edwards Lifesciences LLC, Irvine, CA, USA), and ECG electrodes were connected to two patient monitoring systems (Datex-Ohmeda S/5 Anaesthesia Monitor with E-PRESTN haemodynamic module, GE Healthcare) that were connected to a personal computer furnished with a S/5 iServer 4.2 network package and two data acquisition software packages (S/5 iCollect version 5.0, GE Healthcare). The iCollect systems were set to collect composite photoplethysmographic waveform data from both patient monitors at a frequency of 100 Hz, and to collect finger temperature, heart rate (HR), and diastolic and systolic arterial pressure data every 10 s.

Photoelectric plethysmography measures the total infrared LTF. This measurement served as a measure of blood volume in the finger and, hence, vasoconstriction in the finger. Increases in LTF due to increased infrared light transmission thus reflect peripheral vasoconstriction.

**Analytical laboratory methods**

Concentrations of dexmedetomidine in plasma were determined using reversed-phase high performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS; Applied Biosystems/MDS SCIEX API 4000 instrument, Foster City, CA, USA). The lower limit of reliable quantification of the assay was 0.02 ng ml⁻¹. The within- and between-run precision of the assay (coefficient of variation) was within 8% in the relevant concentration range. Epinephrine and norepinephrine concentrations in plasma were determined using high performance liquid chromatography with coulometric electrochemical detection (Coulochem 5100A, ESA Inc., Bedford, MA, USA).15

**Data handling and statistical analysis**

**Finger blood flow experiment**

The effects of L-NMMA on peripheral vasoconstriction in the presence and absence of dexmedetomidine were assessed by two methods. In the first method, the area under the photoplethysmographic time–response curve (AUC) was calculated during the 5 min i.a. saline and L-NMMA infusions. The baseline for AUC was defined as the value at the start of the segment. Net effects of L-NMMA on digital vasoconstriction for each session (saline and dexmedetomidine) were calculated by subtracting the AUC during the saline infusion from the AUC during the L-NMMA infusion.

In the second method, the relative significance of nitric oxide production on finger blood vessel tone in the presence and absence of dexmedetomidine was evaluated. We calculated 1 min means of LTF for three segments: just before initiation of i.v. dexmedetomidine infusion (baseline), at the end of the i.a. saline infusion (100% of response to dexmedetomidine), and at the highest response to L-NMMA.

**Dorsal hand vein experiment**

Responses of DHV to L-NMMA and dexmedetomidine were analysed by calculating the AUC of the linear variable differential transformer data. The AUC was calculated for the last 3 min of each infusion phase, with the value at the time when cuff inflation was turned on defined as baseline. Integral data were then transformed into per cent, with 100% defined as the AUC of the phase just before the first dexmedetomidine infusion was started (7–10 min, Fig. 1b). The effect of L-NMMA alone on vein distension was analysed by comparing the AUC of the phase just before time 0 and the next phase (i.e. the phase before dexmedetomidine infusion).

**Assessment of haemodynamic and temperature responses**

The systemic cardiovascular and temperature effects of the treatments were compared using the 2 min mean values of mean arterial pressure and HR before and after the drug treatments. In the finger blood flow experiment, the values were extracted from 26 to 28 min and from 42 to 44 min, and in the DHV experiment from −2 to 0 min and from 50 to 52 min (Fig. 1).

**Data presentation and statistical analysis**

Data are presented as mean (95% confidence intervals) or mean (SD). Statistical significance was assessed using a paired t-test, and with one sample t-test from a theoretical
value (zero). Differences in norepinephrine and epinephrine concentrations between three phases of the finger blood flow experiment were analysed with repeated measures ANOVA. In the DHV experiment, dexmedetomidine ED$_{50}$ was determined using a sigmoidal dose–response model with variable slope. Models were accepted only when the goodness of fit ($R^2$) was $>0.95$.

Statistical analyses were performed with SPSS for Windows (version 12.0.1, Chicago, IL, USA) and with GraphPad Prism for Windows (version 4.03, GraphPad Software, San Diego, CA, USA).

**Results**

**Finger blood flow experiment**

One subject developed local anaesthetic toxicity during induction of brachial plexus block and was excluded from the analysis. In all subjects, shortly after induction of the brachial block, a significant decrease in LTF (vasodilation) was observed with a corresponding increase in the fingertip temperature that remained stable throughout the session with only small decreases at the beginning of the dexmedetomidine infusion, and during arterial infusion of L-NMMA. Shortly after the initiation of the i.v. dexmedetomidine infusion, the mean arterial pressure increased for a few minutes, and then returned to baseline levels. The dexmedetomidine infusion induced a significant reduction in HR. All subjects fell asleep before the arterial saline infusion started. Arterial pressure and HR remained stable during the i.v. saline session.

L-NMMA had an effect on LTF and finger temperature only in the presence of dexmedetomidine. L-NMMA induced an increase in LTF (vasoconstriction) in every subject during the dexmedetomidine infusion. The mean (95% CI) difference in AUC between LTF in the dexmedetomidine and the saline session was 26 (17–35) units (95% CI) difference in AUC between LTF in the dexmedetomidine infusion. The mean induced an increase in LTF (vasoconstriction) in every subject during the dexmedetomidine infusion. The mean change 0 (saline) was 26 (20–32) units min. In the saline session, the mean maximum increase in LTF values during i.a. L-NMMA infusion was 19% (14–24) ($P<0.0001$) during the dexmedetomidine infusion (Fig. 2). The mean maximum increase in LTF values during i.a. L-NMMA infusion was 19% (14–24) ($P<0.0001$) during the dexmedetomidine infusion (Fig. 3). In contrast, there were no statistically significant changes in LTF values during i.a. L-NMMA infusion during the saline session.

The mean difference in fingertip temperature between the i.a. infusion of saline and L-NMMA within the dexmedetomidine session was $-0.20^\circ C$ ($-0.32$ to $-0.08$), reflecting drug-induced reduction in blood flow. The corresponding result in the saline session was $0.03^\circ C$ (0–0.05). The mean difference between the sessions was $-0.23^\circ C$ ($-0.36$ to $-0.09$) ($P=0.0048$). Fingertip temperature data are presented in Figure 4.

Dexmedetomidine decreased plasma norepinephrine and epinephrine concentrations. The mean differences from baseline (before dexmedetomidine infusion) until the end of the infusion were $-0.65$ nmol litre$^{-1}$ ($-0.93$ to $-0.38$) ($P<0.001$) and $-0.15$ nmol litre$^{-1}$ ($-0.22$ to $-0.08$) ($P<0.001$) for norepinephrine and epinephrine, respectively. Mean (sd) plasma dexmedetomidine concentrations were 1.76 (0.25) ng ml$^{-1}$ at 25 min after the initiation of the dexmedetomidine infusion and 1.77 (0.29) ng ml$^{-1}$ at the end of the session.

**Dorsal hand vein experiment**

All sessions ($n=10$) were completed successfully. No statistically significant changes were observed between the linear variable differential transformer readings taken before and during the L-NMMA alone infusion. There were no statistically significant changes in arterial pressure or HR during the sessions. Dose–response curves for dexmedetomidine infusions of all subjects are presented in Figure 5. The sigmoidal model could not be successfully fitted to three of the individual data sets—all of these acquired from hands that were infused with saline and dexmedetomidine (Subjects 5, 6, and 9 in Fig. 5). These subjects were therefore excluded from the analysis of the effect of L-NMMA on the response to dexmedetomidine. The calculated ED$_{50}$ values of dexmedetomidine were not significantly different in the absence or presence of L-NMMA ($n=7$). The mean difference in log ED$_{50}$ between the control and the L-NMMA hands was $-0.02$ ($-0.53$ to $0.48$) ($P=0.91$). The range of individual dexmedetomidine ED$_{50}$ estimates in the control hand ($n=7$) was

![Fig 2 Responses to i.a. infusion of L-NMMA in the absence (saline session) or presence of dexmedetomidine (dex session). Data points are results of subtraction of the area under the time–response curve during 5 min i.a. saline infusion from the area under the curve during 5 min i.a. L-NMMA. Dex, dexmedetomidine.](image-url)
Norepinephrine and epinephrine plasma concentrations before baseline (time point 10 min, Fig. 1B) and at the end of the session were similar [mean differences \( -0.14 \text{ nmol litre}^{-1} \) (-0.32 to 0.04) and \( -0.04 \text{ nmol litre}^{-1} \) (-0.15 to 0.06) respectively]. The mean (sd) plasma concentration of dexmedetomidine at the end of the session was 0.09 ng ml\(^{-1}\) (0.05).

**Discussion**

The main finding of this study is that NOS inhibition by \( L\)-NMMA significantly increases dexmedetomidine-induced constriction of small arteries *in vivo* in humans, suggesting that there is a significant endothelial nitric oxide component in the action of dexmedetomidine on the peripheral circulation. This effect of \( L\)-NMMA on responses of finger blood flow to dexmedetomidine was demonstrated in all subjects participating in this experiment, with only minimal between-subject variability. We also found that the effect of \( L\)-NMMA on DHV responses to dexmedetomidine varies greatly between the subjects. Among the 10 subjects who participated in the DHV experiment, \( L\)-NMMA quite markedly shifted the dose–response curve of dexmedetomidine for constriction to the left in three subjects (ED50 reduced by at least 10-fold), whereas in seven subjects, the effect of \( L\)-NMMA on the dexmedetomidine ED50 was modest (<five-fold difference in ED50). Activation of NOS by \( \alpha_2\)-adrenoceptor agonists has been shown in several animal models. In isolated canine coronary
and cerebral arteries, Coughlan and colleagues\textsuperscript{16} demonstrated that NOS inhibition enhances dexmedetomidine-induced constriction of coronary arteries, but with no effect on cerebral arteries. The lack of effect of NOS inhibition on $\alpha_2$-adrenoceptor-induced constriction of cerebral arteries has been confirmed.\textsuperscript{17} 

Two previous \textit{in vivo} studies have investigated the effect of nitric oxide synthesis inhibition on responses of blood vessels to $\alpha_2$-adrenoceptor agonists in healthy

\textit{Fig 5} Plots from all subjects of DHV responses to eight graded doses of dexmedetomidine in the presence and absence of L-NMMA. Responses are presented as per cent of the last venous distension before dexmedetomidine infusion (time $-3$ to 0 in Fig. 1A). Dex, dexmedetomidine.
Dexmedetomidine and human endothelium

The results of the current finger blood flow experiments show that the actions of dexmedetomidine on small arteries include a significant component of NOS activation. When this component is eliminated, the constrictive effect of the drug is augmented. The existence of this component was demonstrated in the current study at plasma concentrations of dexmedetomidine that are only slightly above the recommended therapeutic range, and that are regularly encountered in clinical practice.

The effects of NOS inhibition on dexmedetomidine-induced constriction of human DHV have not been studied previously, though one study suggested that clonidine-induced venoconstriction is not potentiated by methylene blue, an inhibitor of NOS. However, a component of azepexole-induced dilatation of DHV was observed in a study of healthy females aged >30 yr. In the current study of young males, we observed more than 10-fold shifts of the dexmedetomidine-induced constriction curve to the left (i.e. increased potency of dexmedetomidine to induce constriction) during inhibition of NOS in three out of 10 subjects, but only minor effects in the other seven subjects, and it may be that females aged >30 have a larger dilatation component than younger women and men. We observed great inter-individual variability in the ED$_{50}$ of dexmedetomidine-induced constriction, which is consistent with other studies, though the reason for this variability is unknown.

Activation of α$_2$-adrenoceptors has been shown modulating blood vessel tone also through regulation of production of prostanoids in vivo in humans. As changes in prostanoid production may have been a confounding variable in our experiment, we attempted to eliminate it as much as possible in the DHV experiment by using acetyl-salicylic acid (aspirin). This inhibits the actions of both cyclooxygenase 1 and 2 and so inhibits the formation of all prostaglandins including prostaglandins F2, E2, I2 and thromboxane A2. However, since we did not measure local prostanoid levels, we cannot be sure that we inhibited blood vessel prostanoid production completely.

In the current study, we investigated responses of small digital arteries and DHV to dexmedetomidine. These peripheral blood vessels are often used to monitor human blood vessel responses in vivo. These vessels are not isolated from the complex feedback mechanisms of the cardiovascular system, but still represent feasible approaches to study human blood vessels. Axillary brachial plexus block resulted in abolishment of autonomic nervous system regulation of finger blood flow. Our study is also limited by our assumption that the LTF measurements reflect only changes in arterial blood vessel volume. Because these measurements can also be affected by changes in venous blood vessel volume, we elevated the subject’s hand. This position minimizes resting venous tone and facilitates emptying of the hand veins. Despite the usefulness of these models, results of studies on these peripheral vessels do not necessarily apply to other types of blood vessels, and therefore caution should be exercised before their extrapolation to the entire circulation or to other vascular beds.

In both experiments, the volunteers served as their own controls. In an effort to reduce the variation in the responses of DHV to dexmedetomidine, we studied both hands simultaneously. Clearly, the highest dexmedetomidine dose rate we used in the hand vein experiment was not sufficient to induce maximal constriction in all subjects. This dose was selected based on the results of previous studies, and resulted in low systemic drug exposure, but higher dose rates would have been required to obtain full dose–response curves.

In summary, these data demonstrate that dexmedetomidine, when infused in clinically relevant doses, has a significant component of vasodilatation through activation of endothelial NOS, in addition to peripheral vasoconstriction, and when the endothelial component of the blood vessel response to dexmedetomidine is inhibited, peripheral vasoconstriction is augmented. It is therefore plausible that when infused to patients with impaired endothelial...
function, such as patients with diabetes or atherosclerosis, dexmedetomidine may induce greater increases in peripheral resistance compared with patients with a healthy vascular endothelium. Additional studies are required to investigate the clinical implications of these observations.

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