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Systemically Administered α_2-Agonist-induced Peripheral Vasoconstriction in Humans

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Background: **α_2-Adrenoceptors mediate both sympatholytic and vasoconstrictive hemodynamic effects. The goal of this study was to profile the peripheral vasoconstrictive effects of a selective α_2-adrenoceptor agonist in isolation from the sympatholytic effects it also induces.**

Methods: **The authors administered increasing plasma target concentrations of dexmedetomidine (0.075, 0.15, 0.3, and 0.6 ng/mL) or saline placebo to healthy young volunteers in whom the sympatholytic effects of the drug were attenuated in one of two ways: general anesthesia (propofol–alfentanil–nitrous oxide) or axillary brachial plexus block. Measurements were made of finger blood volume (an indicator of vasoconstriction) by photoplethysmographic determination of light transmitted through a finger (LTF) and hemodynamic variables. Measurements made before and during the four steps of infusion were compared by repeated-measures ANOVA.**

Results: **In anesthetized volunteers, all concentrations of dexmedetomidine increased LTF (vasoconstriction) and systolic blood pressure ($P < 0.001$ for both), whereas placebo did not. In awake volunteers, all concentrations decreased systolic blood pressure ($P < 0.001$). Concentrations of 0.15, 0.3, and 0.6 ng/mL decreased LTF (vasodilation) in the neurally intact hand; in contrast, the same concentrations increased LTF (vasoconstriction) in the sympathectomized hand ($P < 0.001$ for both).**

Conclusions: **The results of this study are the first to characterize the lower end of the dose–response curve for vasoconstriction induced by dexmedetomidine. By denervating the vascular bed of interest or by decreasing sympathetic nervous system activity, the authors were able to observe vasoconstriction induced by a systemically administered α_2-agonist with minimal interference from the sympatholytic effects of the drug.**

ACTIVATION of α_2-adrenoceptors mediates several different cardiovascular effects.[1–3] In humans, three subtypes have been identified: α_{2a}, α_{2b}, and α_{2c}.[4] Recent evidence suggests that α_2-agonists induce sympatholytic effects through α_{2a}-adrenoceptors in the central nervous system.[5] Evidence also suggests that α_2-agonists induce vasoconstrictive effects through α_{2b}-adrenoceptors in peripheral vascular smooth muscle.[6] Whereas study of the effects of α_2-agonists on hemodynamics is relatively simple, specific study of the vasomotor effects mediated by α_2-adrenoceptors *in vivo* has been complicated by the fact that all currently available α_2-agonists produce both vasoconstrictive and sympatholytic effects simultaneously.

Dexmedetomidine is the most selective α_2-adrenoceptor agonist available clinically.[7] The vasoconstrictive effects of this drug, in isolation from its concurrent sympatholytic effects, have not yet been quantified in humans. The ability to characterize the vasoconstrictive effects of α_2-agonists would be useful in studying their hemodynamic profiles, their interaction with other vasoactive drugs, and the specific function and vascular distribution of α_2-adrenoceptors.

Our goal was to characterize the peripheral vasoconstrictive effects of dexmedetomidine in isolation from its concurrent sympatholytic effects. A wide range of steady-state concentrations of dexmedetomidine were given to healthy young volunteers in whom sympatholytic effects of the drug were eliminated by either administration of general anesthesia or sympathetic denervation of one arm.

Materials and Methods

With approval from the Institutional Review Board of the University of California, San Francisco, and written informed consent, we enrolled 26 volunteers into one of two studies. We excluded individuals who had a history of cardiac, pulmonary, hepatic, or renal disease or of alcohol or drug abuse; those taking prescription medications; those more than 45 yr old; and those weighing more than 130% of normal. In study 1, volunteers were given general anesthesia; in study 2, volunteers had axillary brachial plexus block and were awake.

Preliminary Preparations Common to Both Studies

During the study, subjects rested in the supine position. On the morning of study, a catheter was inserted into a vein of the left foot to permit administration of intravenous fluids and study drug. Lactated Ringer's solution (7 mL/kg) was administered before the study, and 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$ was administered thereafter until the end of the study. After production of local anesthesia with lidocaine, a cannula was placed into the radial artery of the right arm to permit continuous measurement of arterial blood pressure. Monitors for measurement of blood volume (by photoplethysmography) and temperature in the finger were attached to the hands as described below (see section on photoelectric plethysmography). To minimize locally mediated vasomotor activity in response to changes in body temperature, subjects were covered with blankets during the study.

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Study 1: General Anesthesia

Study 1 randomly compared the effects of four progressively increasing intravenous doses of dexmedetomidine (n = 8) or equal volumes of saline placebo (n = 8) in eight male and eight female volunteers given general anesthesia. On the study day, subjects breathed 100% oxygen during induction of general anesthesia with intravenous alfentanil (30 μg/kg) and propofol (3 mg/kg). Administration of rocuronium (600 μg/kg) facilitated tracheal intubation. Anesthesia was then maintained with 70% nitrous oxide in oxygen and intravenous infusion of propofol (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and alfentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for the duration of the study. Ventilation was adjusted to keep the end-tidal concentration of carbon dioxide at 35 to 40 mmHg. During anesthesia, use of forced air warming kept esophageal temperatures at 36 to 37°C.

Once blood pressure and HR varied less than 5% over a 5-min period (approximately 30 min after induction of anesthesia), we obtained baseline measurements of hemodynamic variables, finger blood volume (by photoplethysmography), and temperature. We then determined hemodynamic and vasomotor responses before and during four progressively increasing intravenous doses of dexmedetomidine (Abbott Laboratories Inc., North Chicago, IL) or saline placebo.

Study 2: Axillary Brachial Plexus Block

Study 2 compared the effects of four progressively increasing intravenous doses of dexmedetomidine (n = 10) in a neurally innervated right hand *versus* a neurally denervated left hand in eight male and two female awake volunteers.

Approximately 15 min after application of all monitors, we obtained measurements of hemodynamic variables, finger blood volume (by photoplethysmography), and finger temperature. The sympathetic fibers of the left arm were then blocked by administration of 30 ml of 1% mepivacaine for production of an axillary perivascular brachial plexus block. Successful block was confirmed approximately 25 min later by testing motor and sensory function of the left hand. Thirty minutes after production of axillary block, baseline measurements of hemodynamic variables, finger blood volume, and finger temperature were obtained. We then determined hemodynamic and vasomotor responses before and during four progressively increasing intravenous doses of dexmedetomidine.

Fifteen minutes after the end of infusion of dexmedetomidine, we again verified motor and sensory block of the left hand. Data for subjects who had inadequate block were excluded from analysis.

Dexmedetomidine Infusion

A computer-controlled infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA) was used to infuse dexmedetomidine (4 μg/mL) to target plasma concentrations of 0.075, 0.15, 0.3, and 0.6 ng/mL. The duration of each infusion step was 15 min. The pump was controlled by STANPUMP software (obtained from Steven Shafer, MD, Professor, Department of Anesthesia, Stanford University, Palo Alto, CA), which adjusted and recorded the rate of infusion every 10 s on the basis of currently available pharmacokinetic data for dexmedetomidine (*i.e.*, a central volume of distribution of 0.427 l/kg and absorption and elimination rate constants of k_{10} = 0.0212 min^{-1}, k_{12} = 0.0744 min^{-1}, and k_{21} = 0.0264 min^{-1}).

Photoelectric Plethysmography

Blood volume in the finger was assessed by photoelectric plethysmography, which measures infrared light transmitted through a fingertip (LTF). The absolute level of transmitted light was determined by pulse oximeter (Nellcor N200; Nellcor Inc., Hayward, CA), for which we placed a sensor (Nellcor D25; Nellcor Inc., Pleasanton, CA) on the ring finger of the right hand (study 1) or both hands (study 2).

The pulse oximeter consists of two parts, a sensor and a monitor. The sensor, which is applied to the tip of a finger, contains a low-voltage, low-intensity light-emitting diode that is supplied with constant drive current and emits infrared light (approximately 920 nm). When light from the light-emitting diode is transmitted through the finger, a portion of the light is absorbed by the finger. A detector photodiode in the sensor receives light and generates an electrical current proportional to the amount of light received.[8] A microprocessor-based monitor processes the measurements. Data on electrical current thus generated were transmitted to a computer, sampled every 10 s, and recorded. This measurement of current (in nanoamperes) served as the qualitative measure of blood volume and, hence, vasoconstriction in the fingertip.

Hemodynamic Variables and Hemoglobin Oxygen Saturation

Systolic (SBP), diastolic, and mean arterial blood pressures were measured continuously (Propaq 106; Protocol Systems, Beaverton, OR) *via* the radial artery cannula, which was connected to a Transpac II transducer (Abbott Laboratories). Hemoglobin oxygen saturation (Spo_2) and heart rate (HR) were measured noninvasively with a pulse oximeter (Propaq 106) with the probe placed on a distal phalanx. Data for hemodynamic variables and Spo_2 were recorded at 10-s intervals by an automated data-acquisition system.

Finger Temperature

Finger temperature was recorded bilaterally from thermocouples that were attached to the pulp of the ring finger of the right hand (study 1) or both hands (study 2) and connected to Iso-Thermax thermometers (Colum-

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Table 1. Transmitted Light through a Fingertip, Hemodynamic Variables, and Temperature during Infusions of Dexmedetomidine or Placebo in Volunteers Given General Anesthesia

	Plasma Target Concentration of Dexmedetomidine, ng/ml					
	0	0.075	0.15	0.3	0.6	ANOVA *P*
LTF, %						
Dexmedetomidine	0	2.1 ± 2.2†	6.1 ± 4.6†	12.0 ± 7.2*†	19.2 ± 9.4*†	<0.001
Peak LTF values	0	6.2 ± 3.8*†	10.4 ± 6.0*†	20.1 ± 10.2*†	30.4 ± 12.2*†	<0.001
Placebo	0	−0.6 ± 1.6	−1.9 ± 2.2	−2.3 ± 3.2*	−2.5 ± 3.5*	<0.05
SBP, mmHg						
Dexmedetomidine	87 ± 10.7	87 ± 11.0	86 ± 13.8	91 ± 13.9*	103 ± 15.0*†	<0.001
Peak SBP values	87 ± 10.7	98 ± 14.0*†	97 ± 14.1*†	100 ± 17.3*†	108 ± 17.2*†	<0.001
Placebo	87 ± 8.5	85 ± 9.0	83 ± 8.4	84 ± 8.2	85 ± 9.8	NS
HR, bpm						
Dexmedetomidine	61 ± 10.2	58 ± 10.2	58 ± 9.2	59 ± 8.9	58 ± 10.0	NS
Placebo	59 ± 6.3	56 ± 6.0	56 ± 7.0*	56 ± 6.2*	56 ± 5.6	<0.05
Temperature, finger, °C						
Dexmedetomidine	35.3 ± 0.6	35.4 ± 0.5	35.4 ± 0.5	35.5 ± 0.5*	35.5 ± 0.5*	<0.05
Placebo	34.8 ± 0.3	34.9 ± 0.4	34.9 ± 0.3	35.0 ± 0.3	35.1 ± 0.4*	<0.05
Temperature, esophageal, °C						
Dexmedetomidine	36.5 ± 0.4	36.5 ± 0.3	36.5 ± 0.3	36.6 ± 0.3*	36.7 ± 0.3*	<0.001
Placebo	36.3 ± 0.3	36.3 ± 0.3	36.4 ± 0.3	36.4 ± 0.3*	36.4 ± 0.3*	<0.05

Data are expressed as mean ± SD.

* $P < 0.05$ *vs.* postanesthesia value (0 ng/ml). † $P < 0.05$ *vs.* placebo.

LTF = light transmitted through finger; HR = heart rate; SBP = systolic blood pressure.

bus Instruments Corp., Columbus, OH). The thermometers have an accuracy of 0.1°C. Finger temperature was recorded before anesthesia or axillary block, immediately before infusion of dexmedetomidine or placebo (baseline), and at the end of each infusion step.

Statistics

Data are reported as mean ± SD, with a value of $P < 0.05$ signifying statistical significance. For analysis, data for blood pressure, HR, and LTF were reduced to 1-min median values. Baseline values for continuously measured variables (SBP, HR, LTF) were defined as the median value over a period of 2 min before infusion of dexmedetomidine or placebo. We determined the values present at the end of each step increase in dexmedetomidine infusion. Because every step produced an initial rapid change in LTF and/or SBP, we also determined peak values during each infusion step. We used repeated-measures ANOVA followed by Dunnett's *post hoc* test to determine the effect of dexmedetomidine or placebo on SBP, HR, LTF, and finger temperature. For study 1, values obtained with dexmedetomidine and placebo were compared by use of an unpaired Student *t* test with Bonferroni correction for multiple comparisons. For study 2, values obtained from the right and left hands were compared by use of a paired Student *t* test with Bonferroni correction for multiple comparisons. Linear least-squares regression was used to correlate changes in SBP with changes in LTF in anesthetized volunteers.

Results

Study 1 volunteers were 26 ± 4 yr old, 171 ± 12 cm tall, and 65 ± 11 kg in weight. Study 2 volunteers were 24 ± 2 yr old, 168 ± 11 cm tall, and 63 ± 13 kg in weight.

The cumulative doses of dexmedetomidine administered at the end of each of the four infusion steps were 0.07 ± 0.01, 0.17 ± 0.01, 0.37 ± 0.01, and 0.75 ± 0.01 μg/kg for study 1 and 0.07 ± 0.01, 0.18 ± 0.01, 0.37 ± 0.01, and 0.76 ± 0.01 μg/kg for study 2.

Study 1: General Anesthesia

Table 1 shows the values for LTF, hemodynamic variables, and esophageal and finger temperatures during infusions of dexmedetomidine and placebo in volunteers given general anesthesia.

At all target concentrations of dexmedetomidine, LTF was significantly ($P < 0.001$) higher than values before dexmedetomidine; the maximum increase occurred from 9,829 ± 2,209 to 12,754 ± 2,955 nA (30 ± 12%) at the concentration of 0.6 ng/mL (fig. 1). At the third and fourth infusion steps of placebo, LTF values were slightly ($P = 0.03$) lower than values before infusion. The LTF values obtained at the end of each infusion step with dexmedetomidine and placebo differed significantly at all target concentrations.

At all target concentrations of dexmedetomidine, SBP (maximum values) was higher ($P < 0.001$) than values before infusion; the maximum increase occurred from 87 ± 11 to 108 ± 17 mmHg (table 1, fig. 1). Placebo had no effect on SBP. Increases in SBP correlated with increases in LTF with dexmedetomidine ($r = 0.44$, $P < 0.0001$) but not with placebo.

Dexmedetomidine had no effect on HR. Placebo decreased HR slightly ($P = 0.02$) (table 1). HR values did

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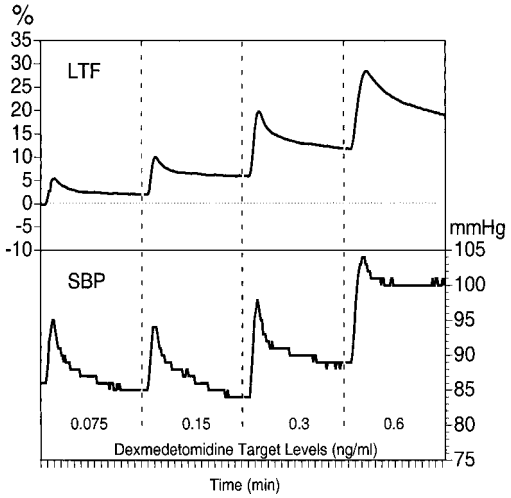

Fig. 1. Percent change in transmitted light through a fingertip (*LTF*) and change in systolic blood pressure (*SBP*) during stepwise infusion of dexmedetomidine in volunteers given general anesthesia. Data are expressed as mean values from all subjects. An increase in transmitted light represents a decrease in finger blood volume (vasoconstriction). The *vertical lines* mark the beginning of each step increase in the infusion of dexmedetomidine.

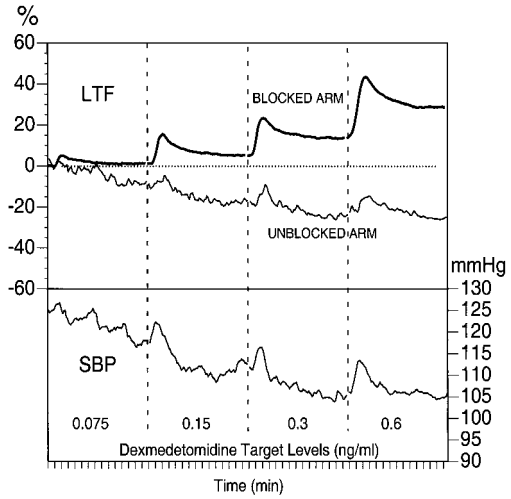

Fig. 2. Percent change in transmitted light through a fingertip (*LTF*) of the blocked arm (*thick line*) and the unblocked arm (*thin line*), and change in systolic blood pressure (*SBP*) during stepwise infusion of dexmedetomidine in awake volunteers given axillary brachial plexus block of the left arm. Data are expressed as mean values from all subjects. An increase in transmitted light represents a decrease in finger blood volume (vasoconstriction). The *vertical lines* mark the beginning of each step increase in the infusion of dexmedetomidine.

not differ in volunteers given dexmedetomidine or placebo.

During infusions of study drugs, esophageal and finger temperatures increased an average of 0.1 and 0.2°C, respectively (table 1), in both groups.

Study 2: Axillary Brachial Plexus Block

Table 2 shows values for LTF, hemodynamic variables, and finger temperatures during infusions of dexmedetomidine in awake volunteers given axillary brachial plexus block. Data for two male volunteers were excluded from analysis because of inadequate motor block at the end of the study.

At concentrations of 0.15, 0.3, and 0.6 ng/mL, LTF was significantly ($P < 0.001$) lower (vasodilation) in the neurally intact right hand than before infusion; the maximum decrease occurred from 5,843 ± 2,306 to 4,266 ± 1,585 nA (−26 ± 27%) (table 2, fig. 2). In contrast, in the sympathectomized left hand, at all concentrations except 0.075 ng/mL, LTF was significantly ($P < 0.001$) higher than before infusion; the maximum increase occurred from 4,475 ± 1,754 to 6,353 ± 2,443 nA (45 ± 24%) (fig. 2). At all concentrations except 0.075 ng/mL, the maximum changes in LTF in the right *versus* the left hand differed significantly during each infusion step (table 2).

In awake volunteers, dexmedetomidine decreased SBP ($P < 0.001$) from 127 ± 14 to 105 ± 4 mmHg (table 2). The decrease was significant for all target concentrations relative to control values before infusion.

Table 2. Transmitted Light through a Fingertip, Hemodynamic Variables, and Temperature during Infusions of Dexmedetomidine or Placebo in Awake Volunteers Given Axillary Brachial Plexus Block

	Plasma Target Concentration of Dexmedetomidine, ng/ml					
	0	0.075	0.15	0.3	0.6	ANOVA *P*
LTF, %						
Blocked hand	0	1 ± 4	6 ± 7†	16 ± 11*†	28 ± 15*†	<0.001
Peak LTF values	0	6 ± 7	17 ± 19*	25 ± 16*	45 ± 24*	<0.001
Unblocked hand	0	−7 ± 16	−18 ± 15*	−24 ± 14*	−26 ± 17*	<0.001
SBP, mmHg	127 ± 14	119 ± 10*	113 ± 12*	106 ± 10*	105 ± 4*	<0.001
HR, bpm	62 ± 9	60 ± 7	61 ± 8	60 ± 7	57 ± 5*	<0.05
Temperature, finger, °C						
Blocked hand	35.6 ± 0.6†	35.6 ± 0.5†	35.5 ± 0.6†	35.4 ± 0.6*	35.3 ± 0.7*	<0.001
Unblocked hand	30.7 ± 3.8	32.1 ± 3.6	33.8 ± 2.2*	34.9 ± 0.4*	35.0 ± 0.5*	<0.001

Data are expressed as mean ± SD.

* $P < 0.05$ *vs.* postblock value (0 ng/ml). † $P < 0.05$ *vs.* unblocked hand.

LTF = light transmitted through finger; SBP = systolic blood pressure; HR = heart rate.

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Dexmedetomidine decreased HR ($P = 0.03$) from 62 ± 9 to 57 ± 5 mmHg. The decrease was significant only for the 0.6 ng/mL target concentration (table 2).

Axillary block increased temperature in the left hand from 31.0 ± 4.5 to 35.6 ± 0.6°C ($P = 0.03$) but had no effect on the temperature of the right hand. During infusion of dexmedetomidine, finger temperature of the right hand increased ($P < 0.001$) from 30.7 ± 3.8 to 35.0 ± 0.5°C.

Discussion

We used a wide range of steady-state concentrations of dexmedetomidine to characterize the peripheral vasoconstriction mediated by α_2-adrenoceptors *in vivo*. In both of our studies, dexmedetomidine, the most selective α_2-agonist available clinically, induced peripheral vasoconstriction in a dose-dependent manner. Vasoconstriction was already apparent at the 0.075-ng/mL plasma concentration of dexmedetomidine, a concentration approximately 5 to 15 times lower than the clinically recommended plasma target concentration of 0.4 to 1.2 ng/mL.

Our results are the first to characterize the lower end of the dose–response curve for vasoconstriction induced by dexmedetomidine. In this study, the plasma target concentrations of dexmedetomidine ranged from subtherapeutic to therapeutic. Study of the high end of the dose–response curve in humans is limited by the side effects of administering high concentrations of α_2-agonist, primarily profound vasoconstriction. This was demonstrated by Ebert *et al.*,[9] who administered consecutively increasing doses of dexmedetomidine to young healthy volunteers. At and above a plasma dexmedetomidine concentration of 1.9 ng/mL, systemic and pulmonary vascular resistances increased significantly above baseline values, and cardiac output decreased.

Although dexmedetomidine induced peripheral vasoconstriction in both of our studies, the hemodynamic effects differed. In awake volunteers with an intact cardiovascular regulatory system and normal sympathetic nervous system tone, consecutively increasing doses of dexmedetomidine decreased blood pressure. In contrast, in anesthetized subjects with reduced sympathetic nervous system tone, consecutively increasing doses of dexmedetomidine increased blood pressure. These differing effects on blood pressure are consistent with known effects of α_2-agonists: a centrally mediated decrease in blood pressure and peripherally mediated vasoconstriction.[10]

The finding that dexmedetomidine caused vasodilation in the neurally intact hand, as indicated by measurement of LTF, is consistent with previous results we obtained using an identical clonidine protocol targeting 0.3- to 2.25-ng/ml plasma clonidine concentrations in a similar volunteer study population.[11] Also consistent with previous work is our present finding that dexmedetomidine increased vasoconstriction in the sympathetically denervated hand and in anesthetized subjects.[11,12] However, in both of our studies, dexmedetomidine (which has a 10 times greater selectivity ratio of α_2 to α_1 than clonidine) was two to three times more potent in inducing vasoconstriction than clonidine had been in our earlier studies.[11,12]

The rapid changes in transmitted light and blood pressure values approximately 60 s after the start of infusion of dexmedetomidine support the hypothesis that dexmedetomidine-induced vasoconstriction is mediated peripherally by vascular smooth muscle. The shape of the LTF curve over time (rapid increase followed by a slow decline) is identical to that found in previous studies with clonidine.[11,12] The reason for the slow decline in LTF values over time is not known, but differences in the design of the two studies may help to eliminate some possible causes. For example, the divergent blood pressure effects between the two studies suggest that peripheral vasoconstriction was not caused by direct or indirect (reflex) changes in blood pressure. The similar shape of the LTF curve with both clonidine and dexmedetomidine, with almost identical study designs, further suggests that these findings are not a result of pharmacokinetic factors. Thus, we are left to consider that the slow decline in LTF is caused by either receptor desensitization or endothelium-derived vasodilatory mediators.

Study of physiologic functions mediated by α_2-adrenoceptor subtypes in humans has been limited by lack of clinically available subtype-selective α_2-agonists and antagonists. In addition, *in vivo* study of vascular α_2-adrenoceptor function (vasoconstriction) has been limited by the simultaneous central sympatholytic effects of the clinically available non–subtype-selective α_2-agonists. Because systemic administration of α_2-agonists is accompanied by reduction in sympathetic nervous system activity, to date, postjunctional α_2-adrenoceptor function has been studied almost exclusively in awake subjects by infusion of α_2-agonist into the brachial artery of the forearm.[13–15] However, these studies are limited by the simultaneous effects of the study drugs on presynaptic and postsynaptic α_2-adrenoceptors, potentially resulting in divergent peripheral vasomotor effects. Furthermore, local drug administration will not allow study of α_2-adrenoceptor–induced vasoconstriction of many other vascular beds of interest. Conversely, our experimental designs should allow future studies of α_2-adrenoceptor–induced vasoconstriction of other vascular beds of interest.

Both of our experimental designs have advantages and disadvantages for the study of systemically administered α_2-agonists *in vivo*. The advantages of studying awake volunteers given axillary brachial plexus block include complete sympathectomy of one arm, an intact cardio-

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vascular regulatory system, and normal blood pressure at the beginning of the study. However, the disadvantages include a predictable decrease in the concentration of circulating catecholamines and blood pressure induced by the α_2-agonist.[16] In contrast, general anesthesia incurs minimal changes in the already low concentrations of circulating catecholamines, and general anesthesia–induced sympathectomy allows for study of increases in blood pressure induced by the α_2-agonist.[12,17] The limitations include potentially confounding vasomotor effects of the anesthetics themselves and abnormally low blood pressure and vasodilatory state at baseline.

Blood vessels have a mixed population of postsynaptic α_1- and α_2-adrenoceptors. There appears to be an inverse relationship between arterial diameter and the presence of α_2-adrenoceptors. Large arteries have both α_1- and α_2-adrenoceptors, whereas α_2-adrenoceptors are more prominent in small arteries and veins.[18] The prominence of α_2-adrenoceptors in the distal vasculature makes an *in vivo* study of vascular α_2-adrenoceptor function feasible in distal phalanxes (fingers). In contrast, *in vitro* studies are complicated by the small size of the blood vessels of interest.

In animals, the peripheral vasoconstriction induced by α_2-agonists seems to be mediated by the α_{2b} subtype.[6] If this is also true for humans, our experimental methods would allow *in vivo* study of peripheral α_{2b}-adrenoceptors. This would be particularly important because vascular α_2-adrenoceptor distribution in different human vascular beds is not known. The ability to study systemically administered vasoconstriction induced by an α_2-agonist *in vivo* may help to define the functional role of α_{2b}-adrenoceptors in vascular smooth muscle, to screen for subtype-specific α_2-agonists, and to define the role of α_{2b}-adrenoceptors in various disease states.

Our study has several limitations. We did not measure the plasma concentrations of dexmedetomidine directly but instead used pharmacokinetic data to simulate the concentrations. Our method of quantifying vasoconstriction (photoplethysmography) is limited by the inability of this technology to differentiate between arterial and venous vasoconstriction. Although distribution of postsynaptic vascular smooth muscle α_2-adrenoceptor in different human vascular beds is not known, animal data suggest that α_2-agonists induce vasoconstriction in almost all vascular beds.[19] However, we studied changes only in blood volume of the finger and therefore cannot comment on other vascular beds.

In these studies of peripheral vasoconstriction induced by an α_2-agonist, we eliminated the sympatholytic effects of the agonist by either sympathetic denervation of one arm (brachial plexus block) or attenuation of sympathetic nervous system activity (general anesthesia). We demonstrated that denervation of the vascular bed of interest allows for observation of vasoconstriction induced by an α_2-agonist with minimal interference from the sympatholytic effects of that agent.

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