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Effect of α_{2B}-Adrenoceptor Polymorphism on Peripheral Vasoconstriction in Healthy Volunteers

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Background: **Alpha-2B adrenoceptor is the vasoconstrictive subtype in the mouse. Human α_{2B}-AR deletion (D) allele has been associated with loss of short-term agonist-promoted receptor desensitization, which may lead to increased vasoconstriction on α_2 activation. The goal of this study was to test the hypothesis that α_{2B}-adrenoceptor activation induces enhanced vasoconstriction in carriers of the DD genotype, compared with carriers of the insertion/insertion (II) genotype.**

Methods: **The authors administered increasing doses of dexmedetomidine (targeting plasma concentrations of 0.15, 0.3, 0.6, and 1.2 ng/ml) to 16 healthy young volunteers (8 carrying the α_{2B} DD genotype, 8 carrying the II genotype) in whom sympatholytic effects of the drug were attenuated by general anesthesia. Measurements were made of finger blood volume (an indicator of vasoconstriction) by photoplethysmographic determination of light transmitted through a finger, finger blood flow by venous occlusion plethysmography, and hemodynamic variables.**

Results: **All concentration of dexmedetomidine increased light transmitted through the finger (vasoconstriction) and systolic blood pressure and decreased heart rate in both groups ($P < 0.001$ for all). Dexmedetomidine reduced finger arterial inflow only in the DD group ($P < 0.001$). Dexmedetomidine had no effect on finger venous outflow or venous capacitance. There were no significant differences between the II and DD groups in any of the variables.**

Conclusions: **The results of this study confirm the α_2 agonist induced vasomotor and hemodynamic effects in peripheral vasculature. However, the results do not support the hypothesis that α_{2B}-adrenoceptor polymorphism has an effect on peripheral vasoconstriction in humans.**

ALPHA-2 adrenoceptors mediate multiple cardiovascular effects such as bradycardia, hypotension and vasoconstriction.[1,2] Human α_2 adrenoceptors can be classified into three subtypes: α_{2A}, α_{2B}, and α_{2C}.[3] Studies with mice suggest that α_2 agonist–induced increase in blood pressure is mediated *via* stimulation of postsynaptic vascular α_{2B} adrenoceptor.[4] An insertion/deletion variation of three glutamate residues was recently identified in the human α_{2B}-adrenoceptor gene. Small *et al.* reported that in *in vitro* studies, when compared with the insertion (I) variant, the deletion variant (D) had normal ligand binding, underwent only 56% of agonist promoted phosphorylation, and had a complete loss of short-term agonist-promoted receptor desensitization.[5] Reduced desensitization of these receptors suggests that individuals with the DD genotype may have increased vasoconstriction in response to prolonged α_2-agonist exposure.

In a study on 912 middle-aged men, Snapir *et al.*[6] found that those with the DD genotype had 2.2 times the risk to experience an acute coronary event, defined as a definite or possible myocardial infarction or ischemic cardiac arrest. The authors proposed that the mechanism for the increased cardiac mortality in individuals with DD genotype may be due to augmented coronary vasoconstriction of small coronary arteries and increased cardiac workload due to increased peripheral resistance. The association between the α_{2B} DD genotype and increased risk for acute myocardial infarction and sudden cardiac death was recently confirmed by the same group in another independent study population. In an autopsy material of 700 out-of-hospital deaths of Finnish men aged 33–70 yr, the odds ratios for sudden cardiac death and death from acute myocardial infarction were 2.1.[7]

Based on the evidence that α_2 adrenoceptors mediate coronary vasoconstriction in humans and the recent reports that there is an association of α_{2B}-adrenoceptor DD genotype with an increase risk for acute myocardial events, we hypothesize that individuals with the D variant are prone to increased vasoconstriction, and this may explain, in part, the increased incidence of cardiovascular pathologies in these individuals.[6] This hypothesis is further supported by studies that show α_{2B} receptor–mediated peripheral vasoconstriction in mice and the lack of receptor desensitization of the D variant of the human α_{2B} receptor *in vitro*.[4,5] Therefore, the primary objective of this study was to test the hypothesis that α_{2B} adrenoceptor activation induces enhanced vasoconstriction in individuals with the DD genotype, compared with individuals with the II genotype.

Materials and Methods

With approval from the Institutional Review Board of the University of California, San Francisco, and written informed consent, we enrolled 153 volunteers. We excluded individuals who had a history of cardiac, pulmonary, hepatic, or renal disease or a history of alcohol or drug abuse; those taking prescription medications; those aged older than 45 yr; and those weighing more than 130% of their expected weight.

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Subjects for the study were selected according to their α_{2B}-adrenoceptor insertion/deletion genotyping results. Genotyping data were available for 152 of the 153 screened subjects (99.3%). Of the 152 subjects, 63 (42%) carried the II genotype, 14 (9%) carried the DD genotype, and 75 (49%) were heterozygous. Sixteen healthy subjects (8 carrying the DD genotype, 8 carrying the II genotype) completed the study. DNA for genotyping was extracted from peripheral blood using standard methods. The method used to identify the subjects' genotype of the α_{2B}-adrenoceptor insertion/deletion polymorphism was based on polymerase chain reaction amplification and DNA electrophoresis and has been described elsewhere.[6] Genotyping and selection of the subjects for the study were done at the University of Turku, Finland. The investigators at University of California, San Francisco, conducting the study were blinded to the genotype until completion of the study.

Preliminary Preparations

During the study, subjects rested supine on a padded operating room table. On the day of study, a catheter was inserted into a vein of the left foot to permit administration of intravenous fluids, anesthetics, and the 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 placement of local anesthesia with lidocaine, a cannula was placed into the radial artery of the left arm to permit continuous measurement of arterial blood pressure. Monitors for measurement of blood volume (by photoplethysmography), blood flow (by strain gauge plethysmography), and temperature in the finger were attached to the hands as described below (see Photoelectric Plethysmography, Mercury-in-Silastic Strain Gauge Plethysmography, and Finger Temperature). Subjects were covered with blankets during the study.

General Study Design

This study randomly compared the effects of four progressively increasing intravenous doses of dexmedetomidine in 8 volunteers with the α_{2B} DD and 8 volunteers with the α_{2B} II genotypes given general anesthesia. General anesthesia was used to eliminate α_2 agonist–induced sympatholytic effects to allow the study of α_2 agonist–induced vasoconstrictive effects.[2]

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 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) and alfentanil (0.5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) for the duration of the study. Ventilation was adjusted to keep the end-tidal concentration of carbon dioxide at 35–40 mmHg. During anesthesia, use of forced air warming kept esophageal temperatures at 36°–37°C.

When blood pressure and heart rate varied less than 5% over a 5-min period (approximately 30 min after induction of anesthesia), baseline measurements of hemodynamic variables, finger blood volume (by photoplethysmography), finger blood flow (by strain gauge plethysmography), and temperature were obtained. Hemodynamic and vasomotor responses before, during, and for 20 min after four progressively increasing intravenous doses of dexmedetomidine (dexmedetomidine; Abbott Laboratories Inc., North Chicago, IL) were determined.

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 0.15, 0.3, 0.6, and 1.2 ng/ml. The duration of the first three infusion steps was 15 min. The duration of the last infusion step was 30 min. The pump was controlled by STANPUMP** software, which adjusted and recorded the rate of infusion every 10 s, based on 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 using 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 left hand.

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. A microprocessor-based monitor processes the measurements.[8] 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.

** STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd. Accessed September 20, 1999.

Mercury-in-Silastic Strain Gauge Plethysmography

Finger arterial inflow, venous outflow, and venous capacitance were measured using venous occlusion plethysmography by abruptly stopping venous outflow for 1 min with a proximal cuff inflated to above venous pressure (40 mmHg).[9] The volume change in the finger was determined by mercury strain gauge plethysmograph with electrical calibration (Hokanson EC6; Hokanson, Inc., Bellevue, WA) for which a sensor on the ring finger of the right hand was placed. An E20 Rapid Cuff Inflator (Hokanson, Inc.) with a finger cuff placed at the base of the ring finger was used to abruptly stop venous outflow. During the study, the subject's right hand was elevated (flexed at the elbow) approximately 10 cm above the heart. This position minimizes resting venous tone and facilitates emptying of the hand veins.

Strain gauge plethysmography data were continuously recorded using a Gould EasyGraf TA240 recorder (Gould Electronics Inc., Eastlake, OH). Finger blood flow measurements were done before volunteers were anesthetized (in triplicate); immediately before dexmedetomidine infusion (in triplicate); at 3 min and every 5 min from the beginning of each infusion step; and at 5, 10, 15, and 20 min after the end of dexmedetomidine infusion.

Finger arterial inflow after rapid occlusion of the cuff was recorded at a paper speed of 5 cm/s. Analysis was performed using a slope drawn at the best-fit tangent to the peaks of the first few pulses. The slope of this line indicates the rate of volume change per unit time, which is caused by arterial inflow. Finger venous outflow was derived from a tangent line that represents the vertical drop in the volume graph from the excursion line and drawn at 0.5 and 2 s after the release of the venous occlusion pressure. Venous capacitance was measured as the vertical distance (in mm) representing the maximum increase in finger volume graph during the 1-min venous occlusion period.

Hemodynamic Variables and Hemoglobin Oxygen Saturation

Systolic (SBP) and diastolic 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 and heart rate (HR) were measured noninvasively using a pulse oximeter (Propaq 106; Protocol Systems) with the probe placed on a distal phalanx. Data for hemodynamic variables and hemoglobin oxygen saturation 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 both hands and connected to Iso-Thermax thermometers (Columbus Instruments Corp., Columbus, OH). The thermometers have an accuracy of 0.1°C. Finger temperature was recorded before anesthesia, immediately before infusion of dexmedetomidine (baseline), and at the end of each infusion step.

Statistics

The primary endpoint was defined as the peak percent increase in LTF values from baseline values during the last 30-min dexmedetomidine infusion step. Sample size estimation for this study was performed using data from our previous study.[2] We hypothesized the increase in LTF values would be 15% higher in subjects with the DD genotype compared with subjects with the II genotype. Our sample size analysis indicated that 16 subjects (8 in each group) would provide an 80% chance (power = 0.8) to identify a statistically significant difference between the two groups at a two-tailed α level of 0.05.

Data are reported as mean ± SD, with $P < 0.05$ 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 2 min before infusion of dexmedetomidine. We determined the values present at the end of each step increase in dexmedetomidine infusion and at 5, 10, 15, and 20 min after the end of dexmedetomidine infusion. Because every step produced an initial rapid change in LTF, SBP, and HR, peak values during each infusion step were also determined. Plethysmographic measurements during dexmedetomidine infusion are expressed as percent changes in relation to baseline values recorded immediately before dexmedetomidine infusion. Repeated-measures analysis of variance followed by the Dunnett *post hoc* test to determine the effect of dexmedetomidine and discontinuation of dexmedetomidine administration on SBP, HR, LTF, finger blood flow, and finger temperature was used. Values obtained from volunteers with the DD and II genotypes were compared using an unpaired Student *t* test with Bonferroni correction for multiple comparisons.

Results

Demographic and screening blood pressure and heart rate information for the 16 subjects is listed in table 1. There were no statistically significant differences in demographics or screening hemodynamics between subjects with the DD and II genotypes. The cumulative doses of dexmedetomidine administered at the end of each of the four infusion steps were 0.15 ± 0.01, 0.36 ± 0.01, 0.77 ± 0.01, and 1.93 ± 0.02 μg/kg. Oxygen saturation values were at or above 96% in all subjects during the study.

Table 2 shows the values for LTF, hemodynamic variables, and esophageal and finger (left hand) tempera-

Table 1. Volunteer Demographics and Screening Hemodynamics

	Genotype	
	II	DD
Age, yr	28 ± 7	23 ± 3
Height, cm	176 ± 9	171 ± 14
Weight, kg	71 ± 12	65 ± 15
BMI, kg/m^2	22 ± 2	23 ± 3
Sex, M/F	6/2	4/4
Screening HR, beats/min	74 ± 6	74 ± 3
Screening SBP, mmHg	118 ± 10	122 ± 9

Data are expressed as mean ± SD or number of subjects. There were no statistically significant differences.

BMI = body mass index; HR = heart rate; SBP = systolic blood pressure.

tures before, during, and 20 min after infusion of dexmedetomidine in volunteers with II and DD genotypes.

Induction of anesthesia decreased LTF values (vasodilation) significantly ($P < 0.005$) in both groups (28 ± 13 and 22 ± 9% for the II and DD groups respectively; P = not significant). In both groups, at all target concentrations of dexmedetomidine, LTF was significantly ($P < 0.001$) higher (vasoconstriction) than values before dexmedetomidine. The maximum increase was 46 ± 12% for the II group and 35 ± 16% for the DD group (table 1 and fig. 1). Maximum LTF values during each infusion step and LTF values obtained at the end of each infusion step did not differ between the genotype groups. LTF values decreased significantly ($P < 0.001$) in both groups during the first 20 min after dexmedetomidine infusion, with no differences between the genotype groups.

At all target concentrations of dexmedetomidine, in both groups, maximum SBP values were higher ($P < 0.001$) than values before infusion. The maximum increase occurred from 78 ± 5 to 115 ± 10 mmHg for the II group and from 82 ± 12 to 124 ± 14 mmHg for the DD group (table 1 and fig. 1). Maximum SBP values during each infusion step and SBP values obtained at the end of each infusion step did not differ between the groups. SBP values decreased significantly ($P < 0.001$) in both groups during the first 20 min after dexmedetomidine infusion, with no differences between the groups.

Induction of anesthesia reduced HR (from 60 ± 9 beats/min to 55 ± 6 beats/min) in the DD group but not in the II group (from 60 ± 6 to 61 ± 6 beats/min; $P < 0.04$). HR did not differ between the groups after induction of anesthesia. Dexmedetomidine decreased HR ($P < 0.001$) in both groups (table 1 and fig. 1). Minimum HR values during each infusion step did not differ between the groups. HR values increased significantly ($P < 0.001$) in both groups during the first 20 min after dexmedetomidine infusion, with no differences between the groups.

Induction of anesthesia increased finger arterial inflow significantly in both groups ($P = 0.03$ for both). Dexmedetomidine infusion decreased arterial inflow only in the DD group ($P < 0.001$), but there were no significant differences between the groups (table 3).

Table 2. Transmitted Light through a Fingertip, Hemodynamic Variables, and Temperature During Infusions of Dexmedetomidine

	Plasma Target Concentration of Dexmedetomidine					
	0 ng/ml	0.15 ng/ml	0.3 ng/ml	0.6 ng/ml	1.2 ng/ml	20 min After
LTF, %						
II genotype	0	5 ± 5*	16 ± 7*	26 ± 8*	28 ± 9*	11 ± 8†
(peak LTF values)		10 ± 3*	22 ± 9*	39 ± 11*	46 ± 12*	
DD genotype	0	4 ± 4*	13 ± 8*	20 ± 10*	22 ± 13*	10 ± 9†
(peak LTF values)		8 ± 5*	19 ± 9*	31 ± 14*	35 ± 16*	
SBP, mmHg						
II genotype	78 ± 5	82 ± 6	88 ± 8*	99 ± 8*	115 ± 10*	108 ± 9†
(peak SBP values)		94 ± 6*	96 ± 7*	104 ± 9*	113 ± 10*	
DD genotype	82 ± 12	86 ± 11*	94 ± 12*	107 ± 12*	123 ± 13*	111 ± 13†
(peak SBP values)		101 ± 10*	102 ± 10*	110 ± 11*	124 ± 14*	
HR, beats/min						
II genotype	61 ± 6	58 ± 7*	57 ± 7*	55 ± 6*	54 ± 5*	59 ± 6†
(minimum HR values)		55 ± 6*	54 ± 7*	52 ± 6*	50 ± 5*	
DD genotype	55 ± 6	53 ± 6	52 ± 5	51 ± 5*	51 ± 5*	54 ± 5†
(minimum HR values)		49 ± 6*	48 ± 6*	46 ± 5*	46 ± 6*	
Temperature, finger, °C						
II genotype	34.4 ± 0.8	34.8 ± 1.0	34.5 ± 0.9	34.5 ± 1.0	34.4 ± 1.2	
DD genotype	35.3 ± 0.4	35.4 ± 0.4	35.3 ± 0.4	35.3 ± 0.5	35.4 ± 0.5	
Temperature, esophageal, °C						
II genotype	36.1 ± 0.2	36.3 ± 0.2*	36.3 ± 0.2*	36.4 ± 0.2*	36.5 ± 0.2*	
DD genotype	36.3 ± 0.3	36.4 ± 0.3	36.4 ± 0.3	36.6 ± 0.5*	36.5 ± 0.4*	

Data are expressed as mean ± SD. There were no statistically significant differences between the II and DD genotype groups.

* $P < 0.05$ *vs.* baseline value (0 ng/ml). † $P < 0.05$ *vs.* 1.2 ng/ml.

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

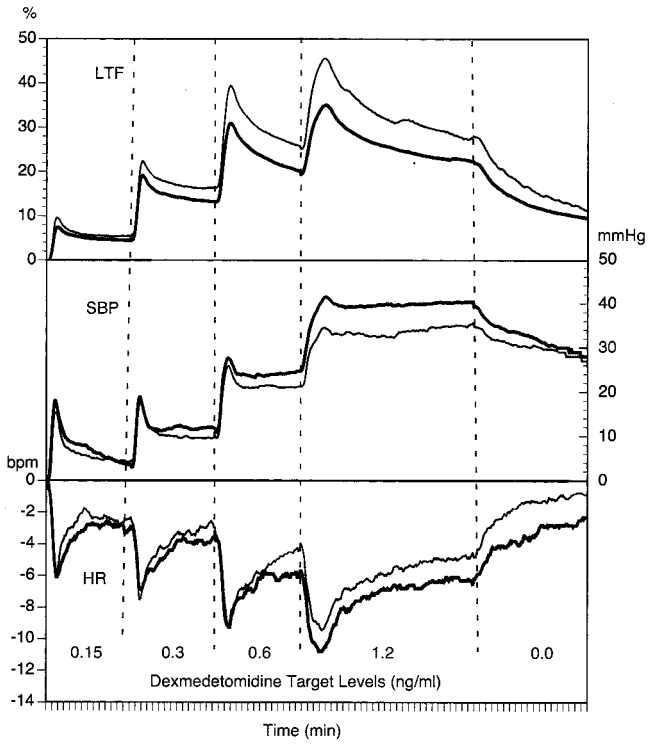

Fig. 1. Percent change in transmitted light through a fingertip (LTF), change in systolic blood pressure (SBP), and change in heart rate (HR) in volunteers with the II (*thin line*) and DD (*thick line*) genotypes during and for 20 min after administration of dexmedetomidine. Data are expressed as mean 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 and end in the infusion of dexmedetomidine.

Dexmedetomidine had no effect on venous outflow in either group (table 3). Venous outflow increased significantly ($P < 0.005$) in both groups during the first 20 min after dexmedetomidine infusion, with no differences between the groups.

Dexmedetomidine had no effect on venous capacitance in either group as measured by venous occlusion plethysmography, nor were there any difference between the groups (table 3).

Discussion

We used a wide range of steady state concentrations of dexmedetomidine to study the peripheral vasoconstriction mediated by α_2 adrenoceptors in two groups of young healthy volunteers who carried one of the homozygous genotypes of the α_{2B}-adrenoceptor insertion/deletion polymorphism. Although our results add significantly to the existing literature on α_2 agonist–induced peripheral vasoconstriction, our results did not support our hypothesis that the DD genotype is associated with enhanced vasoconstriction compared with the I/I genotype.

The hemodynamic and LTF data in the current study are almost identical to those from our previous study with dexmedetomidine.[2] In the current study, the highest targeted dexmedetomidine plasma concentration was twice as high (1.2 ng/ml) as in the previous study. In both studies, with each step increase in dexmedetomidine infusion, there was an initial increase in LTF, followed by a gradual decline. Blood pressure data displayed similar changes with the lower dexmedetomidine doses. However, at the 0.6-ng/ml targeted dexmedetomidine plasma concentration, the initial increase in blood pressure was followed by only minimal decline (fig. 1), and at the 1.2-ng/ml targeted dexmedetomidine plasma concentration, blood pressure did not decrease significantly after the initial increase. The different patterns in the blood pressure and LFT responses seen with higher dexmedetomidine doses are possibly a reflection of α_2-adrenoceptor stimulation of multiple vascular beds having an effect on systemic vascular resistance and

Table 3. Venous Occlusion Plethysmography Data during the First 3 min and at the End of Infusions of Dexmedetomidine

	Plasma Target Concentration of Dexmedetomidine					
	0 ng/ml	0.15 ng/ml	0.3 ng/ml	0.6 ng/ml	1.2 ng/ml	20 min After
Arterial inflow, Δ%						
II genotype	0	−18 ± 40	24 ± 83	7 ± 68	11 ± 125	113 ± 311
(3-min values)		17 ± 36	67 ± 261	−21 ± 68	−11 ± 101	
DD genotype	0	−8 ± 61	−14 ± 51	−11 ± 80	−28 ± 36	7 ± 74
(3-min values)		−10 ± 35	−45 ± 23*	−48 ± 31*	−46 ± 37*	
Venous outflow, Δ%						
II genotype	0	13 ± 19	2 ± 20	3 ± 24	−6 ± 22	7 ± 20†
(3-min values)		5 ± 14	3 ± 17	−4 ± 22	−6 ± 28	
DD genotype	0	−3 ± 13	2 ± 20	−9 ± 15	−3 ± 45	11 ± 40†
(3-min values)		5 ± 39	1 ± 23	0 ± 29	4 ± 71	
Venous capacitance, Δ%						
II genotype	0	3 ± 9	2 ± 10	5 ± 21	1 ± 24	11 ± 24
(3-min values)		0 ± 19	9 ± 11	10 ± 22	4 ± 22	
DD genotype	0	6 ± 9	4 ± 10	−2 ± 15	−7 ± 19	8 ± 22
(3-min values)		7 ± 9	12 ± 16	7 ± 16	−5 ± 17	

Data are expressed as mean ± SD.

* $P < 0.05$ *vs.* baseline value (0 ng/ml). † $P < 0.05$ *vs.* 1.2 ng/ml.

blood pressure, whereas the LTF data reflect vasomotor changes only in the fingertip. These data suggest that radial artery blood pressure reflects complex α_2-adrenoceptor responses in multiple tissues and that this complex response does not represent accurately vasoconstriction in all peripheral vascular beds, such as the fingertip.

Alpha-2 adrenoceptors are located in peripheral arteries and veins.[10] Because the LTF data cannot differentiate between arterial or venous constriction, the venous occlusion plethysmography data adds to our understanding of the contribution of arteries and veins to α_2 agonist–induced vasoconstriction in the finger. Our finger venous occlusion plethysmography data demonstrate α_2 agonist–induced arterial constriction with no significant effect on veins. The arterial inflow data do not suggest as consistent (large variability and no significant difference in the II group) a vasoconstrictive response as the LTF data do. This could be in part because of the different sites of measurement and the fact that there seems to be an inverse relation between arterial diameter and presence of α_2 adrenoceptors.[11] Fingertip LTF measurements are thought to be mainly a reflection of small distal arterioles and arteriovenous canals, whereas the finger venous occlusion plethysmography measurement includes also larger digital arteries.

Blood vessels have a mixed population of postsynaptic α_1 and α_2 adrenoceptors.[10] Both are located throughout the vasculature and mediate vasoconstriction when stimulated. Large arteries have both α_1 and α_2 adrenoceptors, whereas α_2 adrenoceptors are more prominent in small arteries and veins.[11] Prominence of α_2 adrenoceptors in the distal vasculature makes an *in vivo* study of α_{2B}-adrenoceptor function feasible in distal phalanxes. In contrast, *in vitro* studies are complicated by the small size of the blood vessels of interest. Although the increased incidence of acute myocardial events with subjects with the α_{2B} DD genotype was assumed to be linked to enhanced vasoconstriction of endocardial blood vessels, we chose to study α_2 agonist–induced vasoconstriction in the distal phalanx because it is much more feasible than the study of distal coronary arteries and because there are no data to suggest that the mechanism of α_2 agonist–induced vasoconstriction differs in different vascular beds. Although the presence of α_2 adrenoceptors has been demonstrated in human finger and coronary vasculature, the distribution (large arteries, small arteries, veins) and density of α_2 adrenoceptors and their subtypes in different human vascular beds are not known. Based on our results, we cannot rule out that α_{2B} adrenoceptor activation in coronary arteries would have enhanced vasoconstriction in individuals with the DD genotype compared with individuals with the II genotype.

We used dexmedetomidine because it is the most selective clinically available α_2 agonist. Dexmedetomidine is highly lipid soluble and reaches the central and peripheral effect sites within minutes after administration. As a non–subtype-selective α_2 agonist, dexmedetomidine activates all three α_2-adrenoceptor subtypes. Our study could be improved by using an α_{2B}-selective agonist; however, this type of drug is not available for clinical use.

The *in vitro* data show that compared to the α_{2B} I variant, the D variant has normal ligand binding, undergoes only 56% of agonist-promoted phosphorylation, and has a complete loss of short-term agonist-promoted receptor desensitization.[5] These data suggest that *in vivo* activation of the D receptor would result in enhanced vasoconstriction. Because there are no data to suggest whether this enhanced activity might cause *in vivo* a more potent or a more prolonged vasoconstrictive response, we chose our dexmedetomidine dosing to cover a wide range of target plasma concentrations as well as to provide a prolonged (1 h 15 min) exposure to dexmedetomidine and to continue our study of the hemodynamic and LTF responses for 20 min after dexmedetomidine infusion. However, during stress, local endogenous release of α_2 agonist may result in much higher tissue agonist concentrations than those in our study, and we cannot rule out that this may result in a difference between the II and DD genotypes in the vasoconstrictive response, nor would it be feasible for us to administer much higher dexmedetomidine doses to healthy volunteers (profound vasoconstriction).

Our hypothesis was based on a finding in mice that α_{2B} adrenoceptors are responsible for α_2 agonist–induced increases in blood pressure.[5] Although physiologic functions associated with receptor subtypes seem to be similar between species, there are exceptions. A recent report suggests that in humans the α_{2C} adrenoceptor might be responsible for peripheral vasoconstriction.[12] Validation of these data and ruling out the role of α_{2B} adrenoceptors in vascular smooth muscle contraction in humans would explain the results of the current study.

One plausible explanation for enhanced vasoconstriction in subjects with the α_{2B} DD genotype and lack of our ability to observe this effect is that a specific combination of genotypes would be needed to produce the enhanced vasoconstrictive effect on α_2-adrenoceptor activation. This possibility is consistent with our unpublished clinical observation that some patients (1–3%) have an exacerbated increase in blood pressure in response to α_2-adrenoceptor activation (dexmedetomidine and mivazerol).

Our sample size calculation was based on our primary endpoint, which was peak percent increase in LTF values from baseline values during the last 30-min dexmedetomidine infusion step. Therefore, this study may have been underpowered for several other variables, such as venous occlusion plethysmography data, that did not reach statistical significance. We studied only young

healthy subjects. Therefore, we cannot comment on the effect of α_{2B}-adrenoceptor polymorphism on older individuals. Our study is also limited by not being able to assess the effect of sex on the effect of α_{2B}-adrenoceptor polymorphism on peripheral vasoconstriction.

We studied the hemodynamic and LTF responses of subjects with α_{2B} II and DD genotypes during exposure to a nonselective α_2 agonist and found no differences in the responses between the groups. Our failure to observe any differences may be explained in part by (1) α_{2B} adrenoceptors not being involved in peripheral vasoconstriction in humans, (2) α_{2B} D variant receptor displaying no desensitization *in vitro* but behaving as the I variant receptor *in vivo*, (3) not having used a high enough α_2-agonist dose, or (4) the potential enhanced vasoconstriction being caused by a specific combination of different genotypes.

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