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Effects of Low and High Plasma Concentrations of Dexmedetomidine on Myocardial Perfusion and Cardiac Function in Healthy Male Subjects

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Background: **Dexmedetomidine, a selective α_2-adrenoceptor agonist, has counteracting effects on the cardiovascular system. It mediates sympatholysis by activating α_2 adrenoceptors in the central and peripheral nervous system, and vasoconstriction and vasorelaxation by activating postsynaptic α_2 adrenoceptors in blood vessels. The goal of this study was to determine the effects of therapeutic and high concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy subjects.**

Methods: **The authors studied 12 healthy young men. Myocardial blood flow (assessed with positron emission tomography), myocardial function (by echocardiography), and hemodynamic data were collected before and during low (measured mean plasma concentration, 0.5 ng/ml) and high (5 ng/ml) plasma concentrations of dexmedetomidine.**

Results: **The low concentration of dexmedetomidine reduced myocardial perfusion (mean difference, −27% from baseline [95% confidence interval, −31 to −23%], $P < 0.001$) in parallel with a reduction in myocardial oxygen demand (estimated by the rate–pressure product (−23% [−28 to −18%], $P < 0.001$). The high dexmedetomidine plasma concentration did not further attenuate myocardial perfusion (−3% [−12 to +6%] from low dexmedetomidine, $P > 0.05$; −29% [−39 to −18%] from baseline, $P < 0.001$) or statistically significantly affect the rate–pressure product (+5% [0 to +10%], $P > 0.05$). Systolic myocardial function was attenuated by sympatholysis during the low infusion rate and was further attenuated by a combination of the sustained sympatholysis and increased afterload during the high infusion rate.**

Conclusions: **In healthy subjects, plasma concentrations of dexmedetomidine that significantly exceed the recommended therapeutic level do not seriously attenuate myocardial perfusion below the level that is observed with usual therapeutic concentrations and do not induce evident myocardial ischemia.**

α_2-ADRENOCEPTOR agonists mediate their cardiovascular effects through activation of receptors in the central and peripheral nervous system and through activation of postsynaptic receptors in target organs. Activation of presynaptic α_2 adrenoceptors on sympathetic nerves and the central nervous system induces sympatholysis, whereas activation of vascular postsynaptic receptors causes both vasoconstriction[1] (through activation of α_2 adrenoceptors on vascular smooth muscle cells) and vasodilatation (through activation of α_2 adrenoceptors on endothelial cells).[2] Because of these counteracting mechanisms, the overall effect of α_2 adrenoceptor activation on organ blood flow is complex, and difficult to predict— especially in organs that are under major influence of the autonomic nervous system, such as the heart. The classic cardiovascular response in mammalians to systemic infusion of therapeutic doses of an α_2-adrenoceptor agonist, such as clonidine, is biphasic with an initial short-term increase in blood pressure (BP) followed by a long-lasting decrease in BP and heart rate (HR).[3] The initial response is presumably a result of activation of vascular postsynaptic α_2 adrenoceptors, later masked by sympatholysis.

Current information on the direct effects of α_2-adrenoceptor activation on human coronary artery blood flow has been derived from patients with chest pain undergoing diagnostic left-side catheterization. Indolfi *et al.*[4] and Baumgart *et al.*[5] reported that direct infusion of BHT-933 (azepexole, an α_2-adrenoceptor agonist) into the coronary vasculature attenuates coronary blood flow. This effect is augmented by atherosclerosis and is associated with a significant increase in myocardial lactate production.[5]

Dexmedetomidine, a selective and potent α_2-adrenoceptor agonist, was approved by the US Food and Drug Administration in 1999 for sedation of patients hospitalized in intensive care settings, and since then, a growing number of research articles have emerged reporting other possible indications, such as regional[6] and general[7] anesthesia. Dexmedetomidine induces nearly complete sympatholysis already at low concentrations, and continuous and linear increases in its postsynaptic effects can be observed with increasing concentrations.[8] Despite its increased clinical use, many times in critically ill patients, the effect of dexmedetomidine on myocardial

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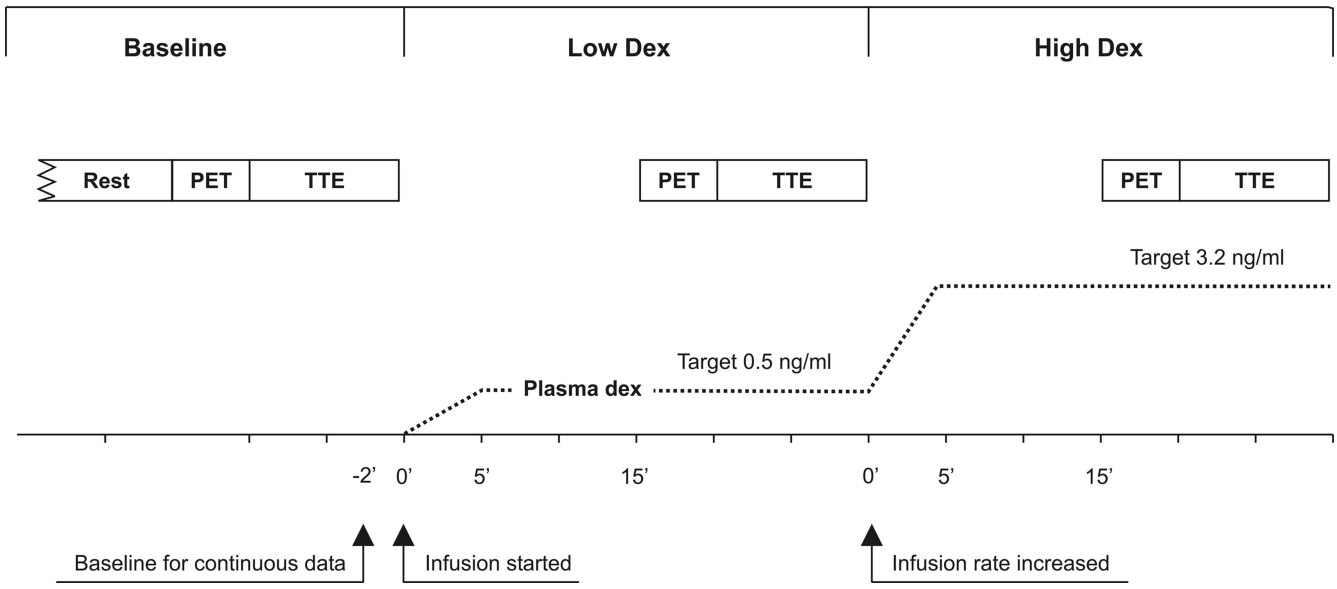

Fig. 1. Outline of the study design. After at least 30 min of rest, baseline measurements were obtained. The Low Dex phase started with the infusion of dexmedetomidine (Dex) to target a plasma concentration of 0.5 ng/ml. After completion of the positron emission tomography (PET) and transthoracic echocardiography (TTE) measurements, High Dex was started by increasing the rate of infusion of dexmedetomidine to target a plasma concentration of 3.2 ng/ml. The infusion of the PET tracer was started exactly 15 min after the infusion of dexmedetomidine was initiated or increased. The PET measurements were followed by the TTE measurements.

blood flow (MBF) has not been yet investigated, and its effect on myocardial function has been limited to studies of cardiac output (CO). This study was designed to investigate the effects of low and high steady state plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy young subjects.

Materials and Methods

Study Population

The study was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the ethics committee of the Southwestern Health Care District, Turku, Finland. All subjects gave their written informed consent.

We studied 12 nonsmoking healthy male volunteers aged 20–28 y (mean, 24 y) with a body mass index of 19 to 27 kg/m^2 (mean, 24 kg/m^2). The health of the volunteers was assessed by medical history, physical examination, 12-lead electrocardiogram, bicycle maximal exercise test, blood cell count, and urine drug screening. Because studies in transgenic mice have suggested that α_2-adrenoceptor–mediated vasoconstriction is mediated by the α_{2B}-adrenoceptor subtype,[3] and because it has been demonstrated that an insertion/deletion polymorphism in the human α_{2B} adrenoceptor is associated with modified receptor desensitization,[9] we also screened the volunteers for this genetic polymorphism and selected 6 subjects from each homozygous genotype to prevent genetic bias.

Study Protocol

In the current study, we collected data before infusion of dexmedetomidine (Baseline) and during low and high plasma concentrations of dexmedetomidine. Based on the results of Ebert *et al.*,[8] we chose target plasma concentrations of 0.5 ng/ml for the low-dose phase (Low Dex) and 3.2 ng/ml for the high-dose phase (High Dex). The recommended therapeutic concentration range of dexmedetomidine is 0.4–1.2 ng/ml (Precedex® SPC; Abbott Laboratories, Abbott Park, IL).

Experiments were conducted during morning hours after an 8-h fast. Subjects abstained from alcohol for 48 h or more, from caffeine for 12 h or more, and from heavy exercise for 24 h or more. After stabilization for at least 30 min, baseline measurements were obtained in the following order: blood sampling for determination of epinephrine, norepinephrine, and dexmedetomidine concentrations in plasma; positron emission tomography (PET) measurements; transthoracic echocardiography (TTE) measurements; and a second blood sampling. After the baseline measurements, Low Dex was started. Thirteen minutes after the initiation of the infusion, blood samples were drawn, and exactly 15 min from the initiation of the drug infusion, PET scanning was started. Data collection for this phase was completed with TTE measurements and blood sampling (30 min from the beginning of the drug infusion). This sequence was then repeated with High Dex. The study design is summarized in figure 1.

Dexmedetomidine Infusion

A Harvard 22 syringe pump (Harvard Apparatus, Holliston, MA) connected to a computer running STAN-

PUMP software‡‡ was used. Dexmedetomidine (Precedex®) was administered intravenously as a target-controlled infusion aiming at pseudo–steady state plasma drug concentrations of 0.5 ng/ml (in Low Dex) and 3.2 ng/ml (in High Dex). We used the same pharmacokinetic parameters of dexmedetomidine as Talke *et al.*[1] and set the maximum infusion rate to 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Approximately 5 min was thus required to reach the targeted plasma concentration of 3.2 ng/ml.

Hemodynamic Measurements

Two veins in the right forearm were cannulated for infusion of dexmedetomidine and the PET tracer. A 20-gauge catheter was inserted into the left radial artery for BP monitoring (Truwave PX-600F 3X; Edwards Lifesciences LLC, Irvine, CA) and blood sampling. A fiberoptic pulmonary artery flotation catheter (Swan-Ganz CCOmbo, CCO/SVO2, Catheter model 744HF75, 7.5 French; Edwards Lifesciences LLC) was introduced into a pulmonary artery during pressure monitoring *via* an 8.5-French introducer inserted into the right internal jugular or the left subclavian vein. The catheter was connected to an Edwards Vigilance® Monitor (Edwards Lifesciences LLC) for monitoring of CO and mixed venous oxygen saturation and was used for infusion of lactated Ringer's solution (5 ml/min). Data from the Vigilance® monitor was stored on a personal computer using Vigilance Monitor Driver 2.1 program (Technical Services Division, Department of Medical Physics, Royal Perth Hospital, Perth, Australia). Systemic vascular resistance was calculated as 80 × mean systemic arterial BP × CO^{-1}.

The electrocardiographic electrodes, pulse oximeter probe, and blood pressure transducers from the radial and pulmonary arteries and the central vein were connected to an S/5 patient monitoring system (Datex-Ohmeda, Helsinki, Finland). For data acquisition, the monitor was connected to a personal computer running S/5 Collect software (version 4; Datex-Ohmeda).

Respiratory rate was measured with a PowerLab system (PowerLab/4SP and Chart version 5.02; ADInstruments, Castle Hill, New South Wales, Australia) using a nasal air temperature probe (model MLT415, connected to a thermistor pod model ML309; ADInstruments).

Measurement of Myocardial Blood Flow

Myocardial blood flow was measured with ^{15}O-labeled water and a GE Advance PET scanner (General Electric, Milwaukee, WI). ^{15}O-labeled water was injected as an intravenous bolus over 20 s (infused mean [SD] doses during Baseline, Low Dex, and High Dex were 991 [141], 968 [102], and 956 [89] MBq), and acquisition of serial transaxial tomographic images of the heart was performed during approximately 5 min (14 × 5, 3 × 10, 3 × 20, and 4 × 30 s frames). All data were corrected for dead time, decay, and measured photon attenuation.[10]

The acquired data sets were processed by factor analysis to enable accurate localization of myocardial tissue. Four representative midventricular slices were chosen from the acquired transaxial images for quantitative analysis. Regions of interest that were first defined on images taken at Baseline were used to analyze the images taken during Low and High Dex. Time–activity curves of myocardial tissue were created based on these regions of interest. The researcher who analyzed the PET images was blind to the study design and protocol.

The methods used to calculate values of regional MBF (expressed in milliliters per gram of tissue per minute) have been previously described.[11,12] Coronary vascular resistance (CVR) was calculated by dividing mean systemic arterial BP with MBF.

Echocardiography

The subjects were studied in the supine position. Measurements were performed with an Acuson Sequoia C 512 (Acuson Inc., Mountain View, CA) instrument with a 3.5-MHz transducer and recorded in digital mode. Standard and modified subcostal, apical, and parasternal imaging windows were used. Results are the averages of the three measurements.

Early (E′) and late (A′) myocardial relaxation velocities were measured using tissue Doppler imaging with 8 mm gate basally in the lateral wall. Peak velocity of early filling (E) was measured with pulsed-wave Doppler with 5 mm gate at the level of the mitral leaflets in the four-chamber view. Longitudinal contraction of the left and right ventricle was measured as displacement of the lateral atrial valve annulus in M-mode using the apical imaging window. The ratios of E′ to A′ and E to E′ were used to assess parameters of myocardial relaxation. The ratio between the preejection period to the left ventricular ejection time (the contractility index, preejection period divided by the left ventricle ejection time) was measured using phonocardiography and pulsed-wave Doppler–derived outflow of the left ventricle. Ejection fraction and left ventricular diameter were based on M-mode measurements. Stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral of the left ventricular outflow measured approximately 5 mm from the aortic valve. CO (stroke volume × HR) was calculated as the mean of the CO measured in the right and the left ventricles.

Assessment of Myocardial Ischemia

Myocardial ischemia was assessed during and after the experimental sessions using electrocardiography and TTE. The 12-lead electrocardiogram was monitored for changes during the session, and the recordings were

‡‡ Available at: http://anesthesia.stanford.edu/pkpd. Accessed May 18, 2006.

later reexamined after the experimental session was over. An ischemic episode was defined as an ST-segment deviation of greater than or equal to 1 mm (0.1 mV) below the ST-segment baseline or greater than or equal to 2 mm above ST-segment baseline and lasting for at least 1 min. The motion of the ventricle walls was followed during the study session using TTE, and the saved echocardiography data were later analyzed according to a five-point scale that defines the severity and the extent (by standard 16 area segmentation) of wall motion abnormality.[13]

Analytic Laboratory Methods

Concentrations of dexmedetomidine in plasma were determined using reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection (PE Sciex API365 instrument; PE Sciex, Foster City, CA). The method was modified from a recently published procedure.[14] The lower limit of reliable quantitation of the assay was 0.1 ng/ml. The within- and between-run precision of the assay (coefficient of variation) was within 8% in the relevant concentration range. Epinephrine and norepinephrine concentrations were determined using high-performance liquid chromatography with coulometric electrochemical detection (Coulochem 5100A; ESA Inc., Bedford, MA).

Data Handling and Statistical Analysis

Means are presented with either 95% confidence intervals or SDs. For analyses of the effects of dexmedetomidine at discrete time points, BP, CO, HR, respiratory rate, and mixed venous oxygen saturation were reduced from continuous 10-s measurements to 1-min median values that corresponded with the noncontinuous measurements (PET, TTE, and blood tests). Statistical significance was assessed with paired-samples *t* test, or with repeated-measures analysis of variance with Tukey *post hoc* test. Multivariate correlates of MBF were assessed by multivariate stepwise linear regression modeling (forward manner, $P < 0.05$ to enter, $P \geq 0.10$ to remove). Variables of interest were first assessed with the Pearson bivariate correlation, and those that were correlated with MBF with $P < 0.1$ were inserted into the multivariate regression model. For presentation of relative changes in systemic mean arterial pressure, HR, CO, systemic vascular resistance, and rate–pressure product (RPP), the median of 1-min continuous measurement that started 2 min before the initiation of dexmedetomidine infusion (fig. 1) was determined as baseline (100%). Statistical analyses were performed with SPSS for Windows (version 12.0.1; Chicago, IL) and with GraphPad Prism for Windows (version 4.03; GraphPad Software, San Diego, CA).

Table 1. Target and Actual Plasma Concentrations of Dexmedetomidine during the Study

Target plasma concentration, ng/ml	Expected plasma concentration,[5] ng/ml	Time from initiation of the infusion phase, min	Measured plasma concentration, ng/ml
0.5	0.7	13	0.4 (0.1)
		30	0.5 (0.1)
3.2	5.1	13	5.1 (1.0)
		30	4.8 (1.1)

Plasma concentrations (ng/ml) are presented as mean (SD).

Results

All experimental sessions were completed as planned. All subjects fell asleep before the measurements of the High Dex phase started, reflecting the sedative action of the drug. Plasma dexmedetomidine concentrations were measured 13 min and 30 min after the beginning of both infusion steps and were similar to what was expected based on the findings of Ebert *et al.*[8] (table 1). The α_{2B}-adrenoceptor ins/del gene polymorphism did not have a statistically significant effect on MBF or CVR at baseline or during the two infusion phases (data not shown). All results are therefore presented for the entire study population.

Plasma levels of epinephrine and norepinephrine decreased on the average by approximately 70% during Low Dex, and only slight further decreases were noted during High Dex (fig. 2). Dexmedetomidine had a biphasic effect on hemodynamics expressed by reduced blood pressures and HR during Low Dex, and substantial increases in blood pressures (systemic, pulmonary, and venous) and peripheral vascular resistance with corresponding decreases in HR, mixed venous oxygen saturation, and CO during High Dex (figs. 3 and 4 and table 2).

As assessed with ^{15}O-labeled water and PET, dexmedetomidine had significant effects on MBF and CVR. The low dexmedetomidine concentration produced a 22% increase in CVR and a 27% reduction in MBF. The high dexmedetomidine concentration did not affect MBF in terms of population mean; however, great variability was observed in the subjects' responses in this phase (fig. 5). CVR was further increased during the High Dex infusion phase (fig. 5). The only variable that was significantly correlated with the change in MBF after the increase in the dexmedetomidine infusion rate was the difference in RPP between Low and High Dex phases; increased RPP was associated with increased MBF and *vice versa* ($r^2 = 0.45$, $P = 0.017$) (fig. 5). No signs of myocardial ischemia (as assessed by electrocardiography and TTE) were observed throughout the study.

Dexmedetomidine had only small effects on systolic myocardial function. Compared with baseline, changes in ejection fraction, contractility index (preejection period divided by the left ventricle ejection time), and displacements of the mitral and tricuspid valve annuli

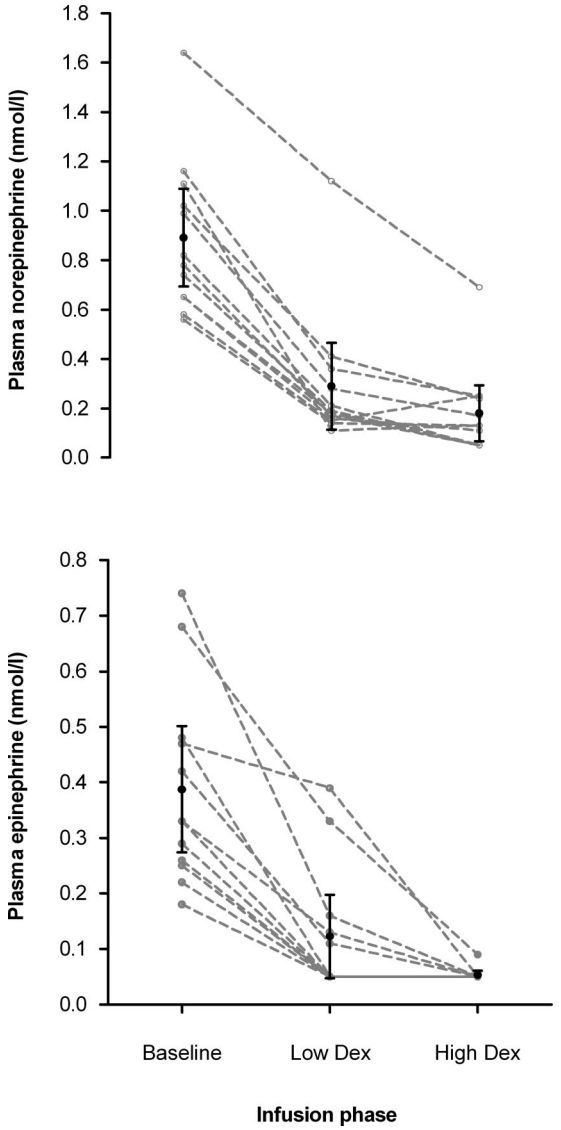

Fig. 2. Plasma norepinephrine and epinephrine levels during low (mean 0.5 ng/ml) and high (mean 5 ng/ml) plasma levels of dexmedetomidine (Dex). Data are presented for each individual subject, and as mean and SD of all subjects.

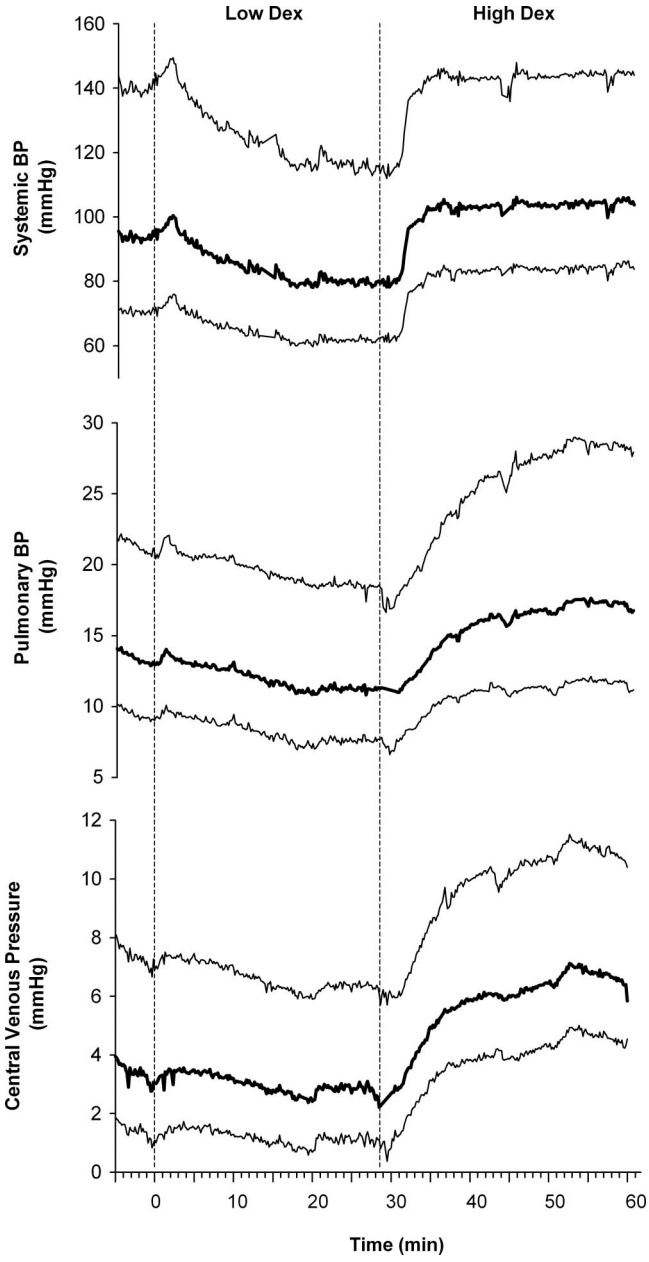

Fig. 3. Systemic, pulmonary, and central venous blood pressures (BPs) during low (mean, 0.5 ng/ml) and high (mean, 5 ng/ml) plasma levels of dexmedetomidine (Dex). *Upper* and *lower thinner lines* represent systolic and diastolic pressures. *Thicker lines* represent mean pressure ([systolic − diastolic BP]/3 + diastolic BP). Data are mean of all subjects (systemic BP, n = 12; central venous pressure and pulmonary BP, n = 11).

indicated slightly depressed myocardial function during both phases. Dexmedetomidine had no notable effects on the diastolic functions of the heart (table 3). The effects of dexmedetomidine on the cardiovascular system are summarized in figure 6.

Discussion

Despite the growing interest in the clinical uses of dexmedetomidine in both low and high concentrations, its effects on myocardial perfusion and cardiac function have not been fully explored. In the current study, we investigated the effects of therapeutic and high concentrations of dexmedetomidine on hemodynamics and myocardial perfusion and cardiac function in healthy male volunteers.

Our results suggest that therapeutic plasma concentrations of dexmedetomidine diminish MBF, and that this can be attributed to sympatholytic myocardial depression that was parallel with reductions in plasma catecholamines, HR, and BP. During high dexmedetomidine plasma concentrations, mean MBF did not change significantly from Low Dex; however, the variability between the subjects was increased to a great degree. Other relevant responses in this infusion phase included

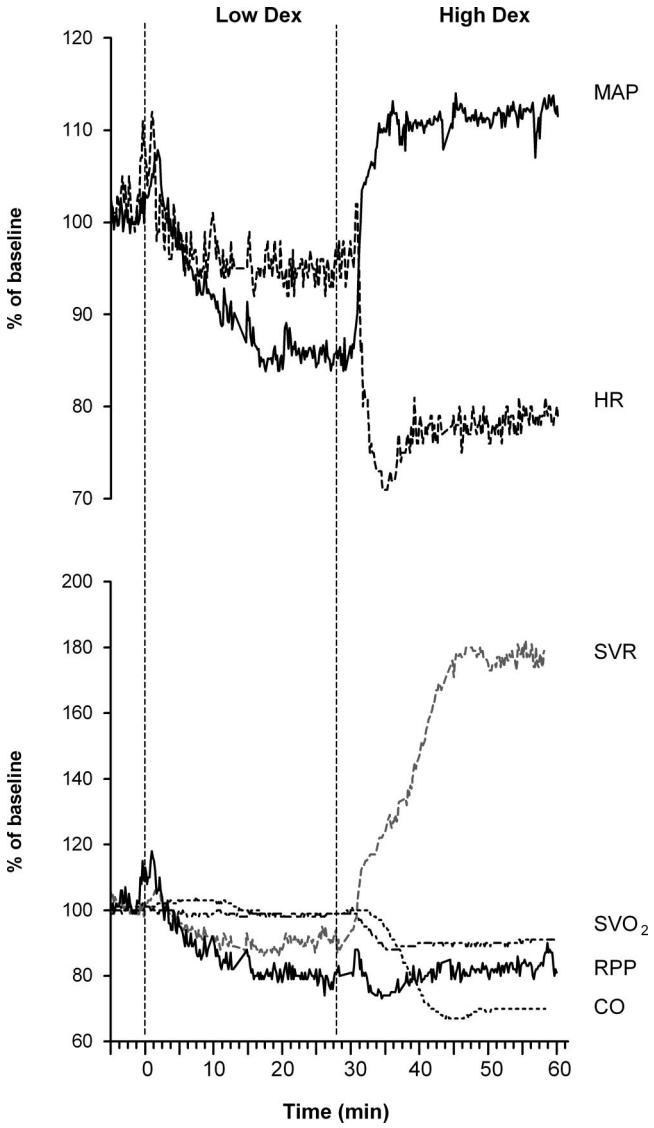

Fig. 4. Continuous effects of dexmedetomidine (Dex) on the cardiovascular system. Data are presented as percent of baseline (time-point numerical values are presented in table 2). Systemic vascular resistance (SVR) was calculated as the mean arterial pressure (MAP) divided by the cardiac output (CO). HR = heart rate; RPP = rate–pressure product; Svo_2 = mixed venous oxygen saturation.

reductions in HR, stroke volume, and ejection fraction and significant increases in BP.

As expected,[8] systemic vascular resistance responded to the low and high concentrations of dexmedetomidine in a biphasic manner. The decrease in systemic vascular resistance during Low Dex was presumably a result of activation of α_2 adrenoceptors in the central and peripheral nervous system that led to marked sympatholysis, counteracted by only a small effect of postsynaptic vasoconstriction. Because nearly complete sympatholysis was achieved already with the lower plasma concentration, the higher concentration of dexmedetomidine had only minor additional sympatholytic effects (approximately 10%, judging by the levels of plasma catecholamines) but induced considerable additional vasoconstriction that led to the increased vascular resistance and BP.

Systemic infusion of dexmedetomidine confers complex direct and indirect cardiovascular responses that affect myocardial perfusion. Direct effects of the drug on the central[1] and peripheral[15] nervous system result in sympatholysis, whereas direct activation of vascular postsynaptic α_2 adrenoceptors results in constriction[1,5] and nitric oxide– and adenosine triphosphate–dependent potassium channel–dependent dilatation.[2,16,17] Indirect mechanisms that are involved in the control of myocardial perfusion during dexmedetomidine infusion include vascular myogenic responses that correspond to the changes in the perfusion pressure, blood flow–dependent dilatation, and local metabolic regulation; these are tightly coupled with myocardial work. The effects of dexmedetomidine on release of catecholamines, preload and afterload, and HR are key determinants of myocardial work. Therefore, the results of the current study describe the overall effects of dexmedetomidine on myocardial perfusion and cardiac function, including the direct drug effects and the corresponding regulatory responses.

The current study demonstrates that systemic infusion of dexmedetomidine to healthy subjects in concentrations that are achieved at steady state with approximately three times the maximum recommended infusion rate induces variable effects on myocardial perfusion. Between Low and High Dex, MBF was either significantly increased (three subjects) or decreased (five subjects) or remained mainly unchanged (four subjects) (fig. 5). To identify factors that modulate MBF during infusion of dexmedetomidine, we searched our database for variables that correlated with the change in MBF between the infusion phases. The only variable that statistically significantly was associated with the change in MBF was the change in RPP during the two infusion phases (r^2 = 0.45). Therefore, our data suggest that in healthy subjects that are infused with dexmedetomidine at high rates, MBF seems to be largely matched with myocardial work, without clinically significant mismatch of oxygen demand and supply (*i.e.*, ischemia), as assessed by electrocardiography and TTE. The echocardiographic method especially is considered very sensitive and specific in diagnosis of myocardial ischemia,[18] and both methods are used routinely in clinical settings. The statistical model suggests that RPP determines approximately 45% of the variability in MBF. Other factors that affect MBF either had too small effect to be detected (low power) or were not recorded in this study.

Ex vivo and *in vivo* studies with animals and humans have shown that postsynaptic α_2-adrenoceptor activation induces coronary constriction.[4,5,19,20] It has also been demonstrated that impaired endothelial function aggravates the constrictive response to an α_2-adrenocep-

Table 2. Effects of Dexmedetomidine on Hemodynamics and Related Variables

	Baseline	Low Dex *vs.* Baseline	High Dex *vs.* Baseline	Low Dex *vs.* High Dex
Myocardial blood flow, ml · g^{-1} · min^{-1}	0.86 (0.16)	−0.23 [−0.33 to −0.13]‡	−0.26 [−0.37 to −0.16]‡	−0.03 [−0.14 to 0.07] NS
Coronary resistance, mmHg · g · min · ml^{-1}	83 (13)	+16 [2 to 30]*	+58 [44 to 72]‡	+43 [29 to 57]‡
Systolic systemic BP, mmHg	140 (18)	−25 [−33 to −17]‡	+5 [−4 to 13] NS	+30 [22 to 38]‡
Diastolic systemic BP, mmHg	70 (6)	−10 [−14 to −6]‡	+14 [10 to 18]‡	+24 [20 to 28]‡
Systolic pulmonary BP,§ mmHg	20 (4)	−3 [−6 to 0]*	+7 [5 to 10]‡	+10 [8 to 12]‡
Diastolic pulmonary BP,§ mmHg	9 (2)	−2 [−3 to −1]†	+1 [0 to 2]*	+4 [3 to 5]‡
Systolic central venous pressure,§ mmHg	8 (2)	−1 [−2 to 0]†	+3 [2 to 4]‡	+4 [3 to 5]‡
Diastolic central venous pressure,§ mmHg	2 (2)	−1 [−1 to 0]*	+3 [2 to 3]‡	+3 [3 to 4]‡
Systemic vascular resistance, dyn · s · cm^{-5}	1,014 (258)	−139 [−300 to 22] NS	+595 [434 to 756]‡	+735 [574 to 896]‡
Rate–pressure product, mmHg/min	9,342 (2,088)	−2,261 [−3,195 to −1,327]‡	−1,852 [−2,786 to −918]‡	+408 [−526 to 1,342] NS
Central venous oxygen saturation,§ %	77 (4)	−1 [−4 to 1] NS	−7 [−9 to −5]‡	−6 [−8 to −3]‡
Heart rate, beats/min	66 (10)	−4 [−8 to 0]*	−14 [−18 to −10]‡	−10 [−14 to −6]‡
Respiratory rate, breaths/min	14 (3)	0 [−2 to 2] NS	+5 [3 to 7]‡	+5 [3 to 7]‡
Cardiac output (Vigilance®), l/min	7.1 (1.6)	−0.2 [−1.2 to 0.8] NS	−2.2 [−3.2 to −1.2]‡	−2.0 [−3.0 to −1.0]‡
Cardiac output (TTE), l/min	5.4 (1.2)	−0.4 [−0.9 to 0.1] NS	−1.7 [−2.2 to −1.2]‡	−1.3 [−1.8 to −0.8]‡
Stroke volume (TTE), ml	78 (14)	−2 [−8 to 4] NS	−11 [−17 to −5]‡	−9 [−15 to −3]†

Low Dex and High Dex correspond to target plasma concentrations of 0.5 and 3.2 ng/ml, respectively. Data at baseline are presented as mean (SD). Data in the other columns are presented as difference between the means [95% confidence interval]. The corresponding *P* value is from repeated-measures analysis of variance with Tukey multiple-comparisons *post hoc* test. Overall *P* value for all tests was less than 0.001. n = 12 or 11 (marked with §). Time-point data are 1-min medians extracted from continuous data (except for the measurements by positron emission tomography and transthoracic echocardiography [TTE]).

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

BP = blood pressure; NS = not significant ($P > 0.05$).

tor agonist in coronaries of animals[20] and humans.[5] The latter effect of postsynaptic α_2 adrenoceptors on vessel tone may have great significance in the extrapolation of the results of the current study into clinical settings. In the current study, MBF seemed to be primarily matched with myocardial work, and although CVR was significantly increased between the infusion phases (fig. 5), MBF was increased or remained unchanged in more than half of the subjects, and there were no signs of myocardial ischemia in any of the subjects. However, the apparent function of α_2 adrenoceptors in the endothelium suggests that systemic infusion of dexmedetomidine at

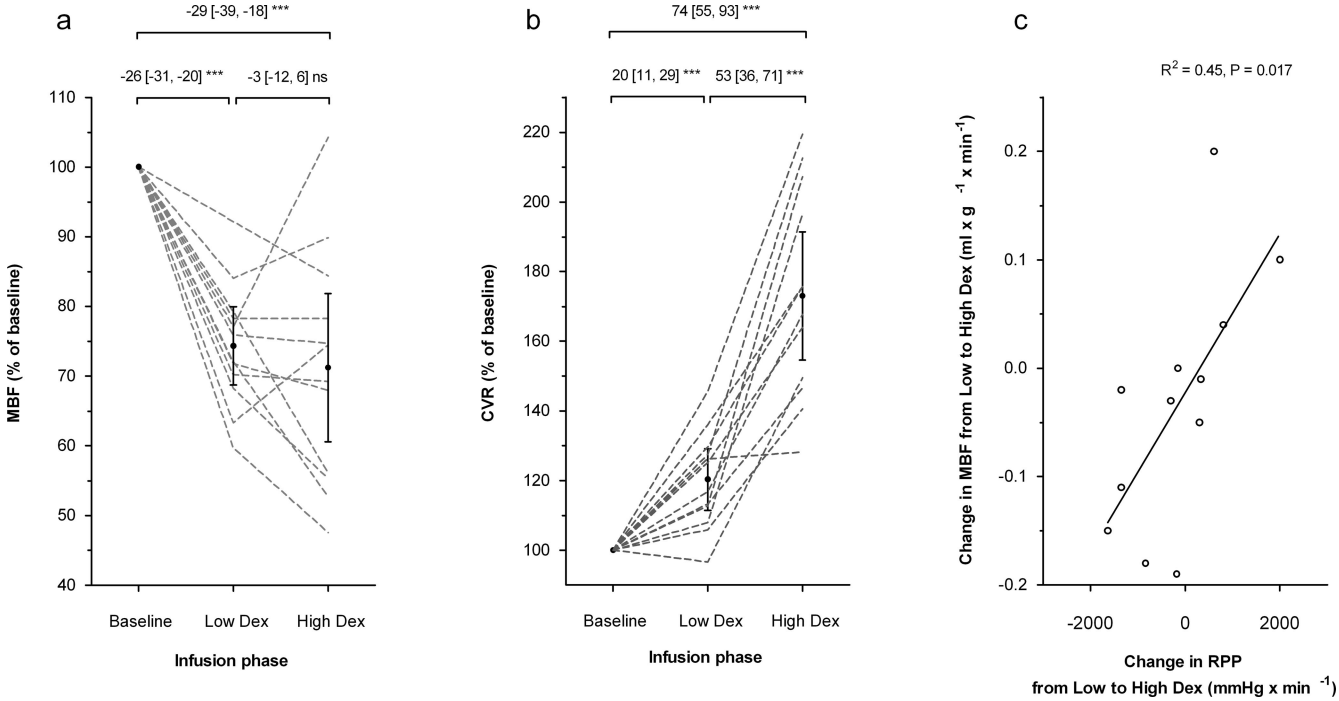

Fig. 5. Effects of low and high plasma concentrations of dexmedetomidine (Dex) on myocardial blood flow (MBF; *A*) and coronary vascular resistance (CVR; *B*), and the relations between the change in rate–pressure product (RPP) and MBF during the two infusion phases (*C*). Effects of dexmedetomidine on MBF and CVR are presented for individual subjects and the mean and their 95% confidence intervals of all subjects (presented as percent of baseline). Differences between means, their 95% confidence intervals, and the corresponding *P* values are from paired *t* tests. Changes in RPP between the Low and High Dex phases were associated with the corresponding changes in MBF. The regression line, r^2, and the corresponding *P* value are from a linear regression model. *** $P < 0.001$. NS = not significant ($P > 0.05$).

Table 3. Effects of Dexmedetomidine on Myocardial Function

	Baseline	Low Dex *vs.* Baseline	High Dex *vs.* Baseline	High Dex *vs.* Low Dex	Overall *P*
Diastolic function					
E′/A′§	2.0 (0.5)	+0.2 [−0.3 to 0.7] NS	+0.1 [−0.4 to 0.6] NS	−0.1 [−0.6 to 0.4] NS	0.66
E/E′§	3.1 (0.6)	−0.4 [−0.9 to 0.1] NS	−0.5 [−1.0, 0] NS	−0.0 [−0.5 to 0.5] NS	0.054
Systolic function					
TDI lateral wall, m/s	0.19 (0.04)	+0.02 [−0.02 to 0.06] NS	−0.00 [−0.04 to 0.04] NS	−0.03 [−0.07 to 0.01] NS	0.14
M-mode MV lateral annulus, cm	1.5 (0.3)	−0.1 [−0.2 to 0] NS	−0.2 [−0.3 to −0.1]‡	−0.1 [−0.2 to 0] NS	<0.001
M-mode TCV lateral annulus, cm	2.4 (0.3)	−0.3 [−0.5 to −0.1]†	−0.3 [−0.5 to 0.1]†	−0.0 [−0.2 to 0.2] NS	0.001
PEP/LVET	0.33 (0.06)	+0.07 [0.01 to 0.13]†	+0.10 [0.04 to 0.16]‡	+0.02 [−0.04 to 0.08] NS	<0.001
Ejection fraction, %	64 (9)	−2 [−7 to 3] NS	−8 [−10 to −6]†	−6 [−8 to −4]*	0.004
Left ventricle diameter,§ cm	5.4 (0.4)	0.0 [−0.2 to 0.2] NS	+0.2 [0 to 0.4] NS	+0.2 [0 to 0.4]*	0.019

Low Dex and High Dex correspond to dexmedetomidine target plasma concentrations of 0.5 and 3.2 ng/ml, respectively. Data at baseline are presented as mean (SD). Data in the other columns are presented as difference between the means [95% confidence interval]. The corresponding *P* values are from repeated-measures analysis of variance with Tukey multiple-comparisons *post hoc* test. n = 12 or 11 (marked with §).

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ (figure 1).

A′ = late diastolic blood flow velocity through the mitral valve annulus; E = peak velocity of early filling; E′ = early diastolic blood flow velocity through the mitral valve annulus; MV = mitral valve; NS = not significant ($P > 0.05$); PEP = time from the Q wave in the electrocardiogram to the second heart sound minus left ventricular ejection time; LVET = left ventricular ejection time; TCV = tricuspid valve; TDI = tissue Doppler imaging.

high rates to patients with impaired endothelial function, such as older patients[21] and patients with vascular diseases (*e.g.*, coronary artery disease,[22] diabetes[23]), may have deleterious effects on myocardial (and possibly other organ) perfusion.

The results of our echocardiography measurements propose that dexmedetomidine induces myocardial depression that is similar to the effect of treatment with β blockers, and that this effect is achieved already at therapeutic concentrations. A previous study on isolated dog heart has shown that dexmedetomidine does not have direct effects on cardiac function.[24] Therefore, a probable explanation for this observation is the reduction in release of catecholamines and therefore reduction in myocardial inotropy. Contractility (denoted by preejection period divided by the left ventricle ejection time; positive changes mean less contractility), contraction (denoted by the movement of the lateral annuli), and ejection fraction were reduced during High Dex compared with Baseline; however, the differences between the Low and the High Dex phases were relatively small and may be largely explained by the increased afterload during this phase.

We conclude that in healthy subjects, dexmedetomidine plasma concentrations that correspond to the recommended infusion rates reduce MBF by sympatholysis and reduction in cardiac work, and that high concentrations of dexmedetomidine that correspond with concentrations that are achieved at steady state with approximately three times the maximum recommended infusion rate do not further reduce MBF and do not induce clinically evident mismatch between cardiac oxygen demand and supply. Because of the apparent significance of the vascular endothelium for the overall response of

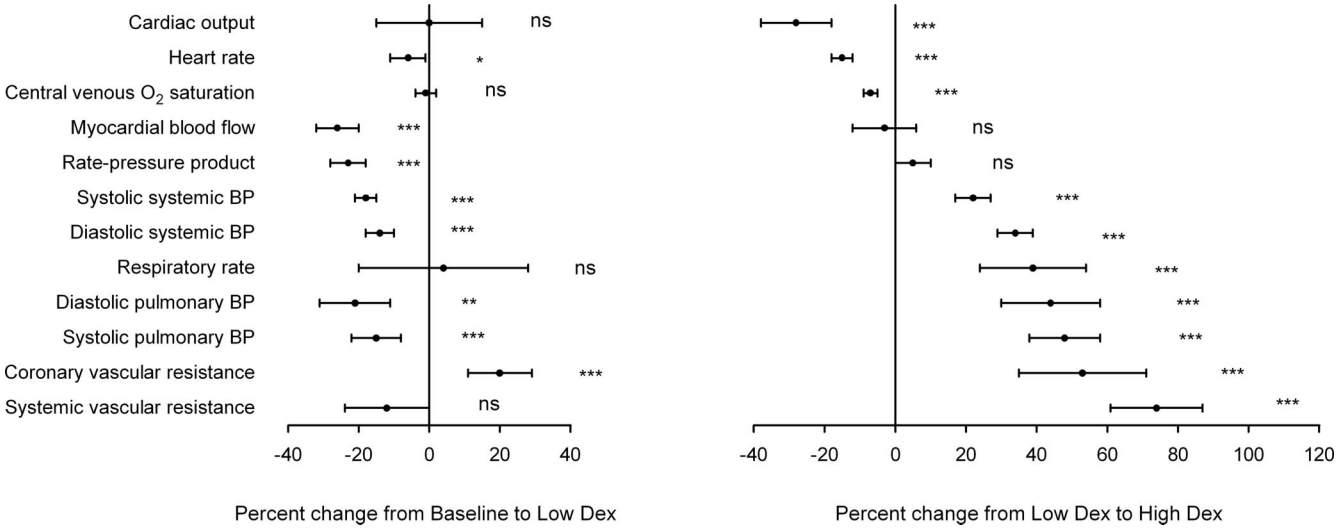

Fig. 6. Summary of the effects of dexmedetomidine (Dex) on the cardiovascular system. The data are differences between means and their 95% confidence intervals between Low Dex (mean plasma dexmedetomidine, 0.5 ng/ml) and Baseline (plasma dexmedetomidine 0 ng/ml) and between High Dex (mean plasma dexmedetomidine, 5 ng/ml) and Low Dex. *P* values are from paired *t* tests. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. BP = blood pressure; NS = not significant ($P > 0.05$).

arteries to α_2-adrenoceptor activation, an extrapolation of the results of this study on healthy subjects to older patients with possible coronary artery disease should be exercised with great caution. A study to explore the effects of low and high concentrations of dexmedetomidine in patients with impaired coronary endothelial function is required.

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