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Dexmedetomidine as an Anesthetic Adjunct in Coronary Artery Bypass Grafting

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Background: **α_2-Adrenergic agonists decrease sympathetic tone with ensuing attenuation of neuroendocrine and hemodynamic responses to anesthesia and surgery. The effects of dexmedetomidine, a highly specific α_2-adrenergic agonist, on these responses have not been reported in patients undergoing coronary artery bypass grafting.**

Methods: **Eighty patients scheduled for elective coronary artery bypass grafting received, in a double-blind manner, either a saline placebo or a dexmedetomidine infusion, initially 50 $ng \cdot kg^{-1} \cdot min^{-1}$ for 30 min before induction of anesthesia with fentanyl, and then 7 $ng \cdot kg^{-1} \cdot min^{-1}$ until the end of surgery. Filling pressures, blood pressure, and heart rate were controlled by intravenous fluid and by supplemental anesthetics and vasoactive drugs.**

Results: **Compared with placebo, dexmedetomidine decreased plasma norepinephrine concentrations by 90%, attenuated the increase of blood pressure during anesthesia (3 *vs.* 24 mmHg) and surgery (2 *vs.* 14 mmHg), but increased slightly the need for intravenous fluid challenge (29 *vs.* 20 patients) and induced more hypotension during cardiopulmonary bypass (9 *vs.* 0 patients). Dexmedetomidine decreased the incidence of intraoperative (2 *vs.* 13 patients) and postoperative (5 *vs.* 16 patients) tachycardia. Dexmedetomidine also decreased the need for additional doses of fentanyl (3.1 *vs.* 5.4), the increments of enflurane (4.4 vs. 5.6), the need for beta blockers (3 *vs.* 11 patients), and the incidence of fentanyl-induced muscle rigidity (15 *vs.* 33 patients) and postoperative shivering (13 *vs.* 23 patients).**

Conclusions: **Intraoperative intravenous infusion of dexmedetomidine to patients undergoing coronary artery revascularization decreased intraoperative sympathetic tone and attenuated hyperdynamic responses to anesthesia and surgery but increased the propensity toward hypotension. (Key words: Sympathetic nervous system, α_2-adrenergic agonists: dexmedetomidine; catecholamines. Anesthesia: cardiac. Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane. Outcome, cardiac: perioperative myocardial ischemia. Surgery, cardiac: coronary artery bypass grafting. Heart: blood pressure; hypertension. Heart: heart rate.)**

α_2-ADRENERGIC agonists decrease sympathetic tone, induce sedation, and decrease blood pressure and heart rate (HR).[1,2] Perioperative use of clonidine, the most widely studied α_2-adrenergic agonist, has been reported to decrease the hemodynamic responses to noxious stimulation and overall hemodynamic variability,[3–6] the need for anesthetics,[3,7,8] postoperative oxygen consumption,[9,10] and shivering.[3,11] In patients undergoing coronary artery surgery and receiving clonidine as premedication, the need for fentanyl or sufentanil decreased by 20–40% when the opiate was administered according to hemodynamic[3,12,13] or electroencephalographic criteria,[14] and increases in HR and mean arterial blood pressure as a response to intubation and surgical stimulation were attenuated by 5–10 bpm and up to 20 mmHg, respectively. The patients receiving placebo had two- to fivefold increases in plasma epinephrine and norepinephrine concentrations, compared with those who received clonidine.[3,12,13,15] Clonidine has also been reported to decrease the incidence and severity of perioperative myocardial ischemia in patients undergoing coronary artery surgery,[12,13] but others could not show such an effect.[16]

Dexmedetomidine is a more specific and selective α_2 agonist and has a shorter duration of action than clonidine.[17,18] It produces dose-dependent sedation and analgesia.[2,19,20] These properties make it theoreti-

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cally a suitable agent for use as a part of an anesthetic regimen. In patients having noncardiac surgery, perioperative administration of dexmedetomidine decreases the need for anesthetics[21] and induces sympatholysis with ensuing hemodynamic and neuroendocrine stability.[2,3,22] The effects of dexmedetomidine on perioperative hemodynamic responses to painful stimulation, anesthetic requirements, and the incidence of myocardial ischemia in patients undergoing coronary artery bypass grafting (CABG) have not been reported. The primary efficacy hypothesis of the present study was that a continuous intravenous dexmedetomidine infusion given before and during operation will decrease hemodynamic and endocrine (as assessed by plasma catecholamine concentrations) responses to tracheal intubation and surgical stimulation in patients undergoing elective CABG. As secondary efficacy variables, we were also interested in the effects of dexmedetomidine on the occurrence of perioperative myocardial ischemia, fentanyl-induced muscle rigidity, requirements for anesthetics and postoperative analgesics, and on postoperative shivering.

Materials and Methods

Study Design and Patients

All patients referred to the cardiac surgical centers of Turku University Hospital and Helsinki University Hospital for elective CABG between June 1992 and March 1993 were candidates for the study. The inclusion criteria were good left ventricular function, age less than 70 yr, and weight not more than 100 kg. The exclusion criteria were left main coronary artery stenosis greater than 50%, significant valvular dysfunction (over I/IV), severe concurrent systemic disorders (*e.g.*, insulin-dependent diabetes mellitus, insufficient liver or kidney function, respiratory disorder, uncontrolled hypertension), preoperative medication with clonidine or alphamethyl-DOPA, strong susceptibility to allergic reactions, and uninterpretable results of preoperative electrocardiogram (ECG; *e.g.*, left bundle branch block). The study was placebo controlled, double blind, and of parallel-group design. Eighty patients were entered in the study. The randomization (permuted blocks) into dexmedetomidine (DEX, n = 40) and placebo (PLA, n = 40) groups was balanced for each center. Written informed consent was obtained from all patients and the study protocol was approved by the ethics committees at each hospital.

Premedication, Study Drug Infusion, and Induction and Maintenance of Anesthesia

The patients received their regular antianginal medication until surgery. Premedication consisted of scopolamine 5 μg/kg and morphine 0.16 mg/kg given intramuscularly (Scopomorphin; Orion Pharmaceutica, Turku, Finland). After insertion of a pulmonary artery catheter and a radial arterial cannula and a 5-min stabilization period, baseline systolic (SAP) and diastolic (DAP) arterial blood pressure and HR were recorded and baseline blood samples for determination of plasma concentrations of catecholamines (epinephrine and norepinephrine) and dexmedetomidine were drawn. The study drug infusion (dexmedetomidine or saline placebo which were identical in appearance) was then commenced. The infusion rate was set to deliver 50 $ng \cdot kg^{-1} \cdot min^{-1}$ of dexmedetomidine for 30 min before anesthesia was induced and 7 $ng \cdot kg^{-1} \cdot min^{-1}$ thereafter until the end of surgery in the DEX group.

Anesthesia was induced with 30 μg/kg fentanyl given in 5 min. During fentanyl infusion, ventilation was assisted manually with 100% oxygen. If clinically significant, fentanyl-induced chest wall muscle rigidity (based on the anesthesiologist's subjective evaluation as "yes" or "no") developed, 0.1 mg/kg pancuronium was given immediately. Otherwise pancuronium was administered for muscle relaxation 1 min after completion of the fentanyl infusion and after hemodynamic measurements were taken (6 to 8 min after the start of anesthesia induction). The patients were intubated when the hemodynamic measurements were made and muscle relaxation was complete.

After intubation, anesthesia was maintained with a continuous infusion of fentanyl (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and with 0.1% end-tidal enflurane in oxygen and air (40%–60% mixture). The infusion rate of fentanyl was decreased to 0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from the beginning of cardiopulmonary bypass (CPB) to the end of surgery. During CPB, enflurane at 0.5% inspiratory concentration was used. Muscle relaxation was maintained with 2-mg increments of pancuronium. Supplementary anesthetics and other drugs were administered stepwise according to prespecified hemodynamic criteria, as shown in detail in table 1. Any measure taken (an increase or a decrease of enflurane concentration, supplemental fentanyl, diazepam, administration of a fluid challenge, ephedrine, phenylephrine, dopamine, glycopyrrolate, esmolol, or glyceryl trinitrate) while the hemodynamic values were outside the predetermined limits was considered an intervention. Ringer's acetate so-

Table 1. Hemodynamic Criteria and Stepwise Treatment of Deviations

Time	Deviation/Treshold	Treatment
Before CPB	Hypertension	Fentanyl (10 μg/kg) and rate ↑ by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$
	SAP ≥ 20% above BL or SAP >150 mm Hg	−5 min interval before next step
		+ GTN 50 μg/min allowed meanwhile
		Repeat step 1 (5 min interval)
		Repeat step 1 (5 min interval)
		Enflurane ↑ gradually ad 1.5% end-tidal
	Hypotension	↓ or terminate enflurane
	SAP ≥ 30% below BL and < 90 mmHg or SAP < 80 mmHg	Ringer's acetate → CVP within 2 mmHg of BL
		Ephedrine (2.5 mg), allowed two times meanwhile
		Dopamine (5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$)
	Tachycardia (no hypertension)	Esmolol in 0.5-mg/kg increments until effect
	HR > 90 bpm	
	Bradycardia	Glycopyrrolate in 0.2-mg increments
	HR < 40 bpm	
During CPB	Hypertension	Enflurane ↑ gradually add 1.5% end-tidal
	MAP > 80 mm Hg	Diazepam (5-mg increments) until effect
	Hypotension	↓ or terminate enflurane
	MAP < 30 mm Hg	Phenylephrine in 0.2-mg increments until effect
After CBP	Hypertension	Enflurane ↑ gradually add 1.5% end-tidal
	SAP > 130 mm Hg	GTN infusion 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, ↑ until effect
	Hypotension	↓ or terminate enflurane
	SAP < 80 mm Hg or DAP-PCWP < 40 mm Hg	Ringer's acetate → CVP within 2 mmHg of BL
		Ephedrine 2.5 mg, allowed two times meanwhile
		Dopamine 5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$
	Tachycardia (no hypertension)	Esmolol in 0.5-mg/kg increments until effect
	HR > 90 bpm	
	Bradycardia	Glycopyrrolate in 0.2-mg increments
	HR < 40 bpm	

HR = heart rate; BL = baseline; bpm = beats/min; CPB = cardiopulmonary bypass; GTN = glycerol trinitrate; MAP = mean arterial pressure; SAP = systolic arterial pressure; CVP = central venous pressure.

lution was infused at an approximate rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$. The total amount of intravenous fluids given was limited to 1,000 ml before CPB. The end-tidal carbon dioxide and enflurane concentrations were continuously monitored during operation (Capnomac; Datex, Helsinki, Finland). Controlled mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 34 and 45 mmHg (4.5–6.0 kPa).

Cardiopulmonary Bypass

A membrane oxygenator primed with 2,000 ml Ringer's acetate, 100 ml 15% mannitol, and 5,000 IU heparin, and a roller pump were used for CPB. The initial systemic heparin dose was 300 IU/kg. Activated coagulation time (Hemochron 400, Technidyne Co., Edison, NJ) was maintained at >480 s with additional 5000 IU doses of heparin when required. Systemic hypothermia (nasopharyngeal temperature, 28°C), α-stat *p*H management, and a pump flow rate of 2.4 $l \cdot min^{-1} \cdot m^{-2}$ (1.6 $l \cdot min^{-1} \cdot m^{-2}$ during hypothermia) were used. Antegrade cold crystalloid potassium-magnesium cardioplegia solution was given to maintain electromechanical quiescence. Hemoglobin concentration was maintained at more than 70 g/l during CPB and at more than 90 g/l after CPB. After separation from bypass, heparin was neutralized with protamine according to the patient's activated coagulation time. If there was complete atrioventricular block or another type of bradycardia unresponsive to anticholinergic or inotropic medication after aortic unclamping, the heart was paced. The need for pacing was recorded at the following times: 5 min after defibrillation, 30 min after defibrillation, after coming off bypass, and after skin closure. Before weaning from bypass, the surgeon assessed the quality of the anastomoses using a four-grade scale, where 4 = excellent, 3 = good, 2 = fair, and 1 = poor.

Postoperative Procedures

At the end of surgery, the study drug infusion was discontinued and the patient was transferred to the sur-

gical intensive care unit. The lungs were ventilated after operation until stable hemodynamics and clinically adequate recovery from anesthesia and restoration of spontaneous respiration were achieved. Oxycodone was administered intravenously in 3–5-mg increments for pain control. Meperidine was administered in 12.5-mg increments for shivering. Postoperative shivering was recorded as "yes" or "no". Fluid loading and vasoactive medication were administered according to clinical hemodynamic criteria.

Hemodynamic Evaluations

Heart rate, SAP, and DAP were recorded at 1-min intervals from 5 min before induction of anesthesia and until 10 min after intubation, then at 5-min intervals until the end of surgery (except during CPB, when mean radial arterial pressure [MAP] was measured), and at intervals not greater than 1 h after operation until the first postoperative morning. In addition, a set of hemodynamic measurements including SAP, MAP, DAP, HR, mean pulmonary arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output were measured before study drug administration (baseline) and induction of anesthesia; before and 5 min after tracheal intubation; before skin incision; and after sternotomy, termination of CPB, and skin closure. Cardiac index, stroke index and systemic vascular resistance index were derived using standard formulas. The hemodynamic response to tracheal intubation was determined as maximal increases in SAP, DAP, and HR within 10 min after intubation *versus* baseline values. Variability of SAP and HR was assessed as an area under the curve of deviations from the mean value of the given period *versus* time (individual measurement intervals were noted previously). The resulting index was divided by the duration of surgery.

Perioperative Evaluations of Electrocardiograms and Cardiac Enzymes

Each patient was connected to a Holter ECG device (8500 series, Marquette Electronics, Milwaukee, WI) using two bipolar leads (CC_5 and modified CM_5) from at least 8 h before induction of anesthesia until 24 h after operation. All putative ischemic episodes were reviewed independently by one cardiologist blinded to the treatment, the patient's identity, and clinical course. The primary evaluation of the Holter tracing was made using a semiautomatic scanner (Marquette Electronics, Milwaukee, WI). The baseline S-T segment level was defined as the average S-T level over a stable period in the initial parts of the registration with the patient positioned supine. An ischemic episode was defined as a reversible S-T segment deviation of either $\geq$1 mm (0.1 mV) below S-T segment baseline or $\geq$2 mm above S-T segment baseline and lasting for at least 1 min. To be considered reversible, an S-T segment had to return to the baseline value for at least 1 min. The channel representing the greater S-T segment deviation was used in the data analysis. The S-T segment deviation was normally measured 60 ms after the J point, but if the measurement point fell onto the T wave because of tachycardia, the measurement point was set closer to the J point, but not closer than 40 ms. For each ischemic episode, the maximum S-T deviation, its duration, and the area under the S-T deviation $\times$ the time curve (area under the curve) were determined. The total ischemic load was determined as total ischemic minutes/total number of hours monitored.

A 12-lead ECG was obtained before operation, in the morning and evening of first two postoperative days, and at discharge from hospital or 7 days after operation, which ever occurred first. All ECGs were reviewed by an independent cardiologist who was unaware of the treatment and the patient's identity and clinical course. According to the study protocol, all new Q waves and those fulfilling Minnesota code I criteria for a definitive of probable Q-wave infarction[23] were identified. Myocardial infarction was defined as a Q-wave myocardial infarction if new Q waves appeared in the ECG (separately for all Q waves and for those fulfilling Minnesota Code I criteria). A non–Q-wave myocardial infarction was defined as the absence of a Q wave but an elevation of creatine kinase MB isoenzyme activity to >100 U/l at any time before operation or to >70 U/l at any time after the first 12 h after operation.[24]

Assay Methods

Arterial blood samples to determine plasma epinephrine and norepinephrine concentrations were obtained after radial artery catheter placement (baseline), before induction of anesthesia, 5 min after tracheal intubation, 1 min after sternotomy, immediately before aortic declamping, immediately after termination of CPB, at skin closure, 1 and 2 h after completion of surgery, and on the first postoperative morning. Plasma concentrations of norepinephrine and epinephrine were measured using an high-performance liquid chromatography-electrochemical detection assay.[25] Arterial blood samples to determine plasma dexmedetomidine concentrations were obtained after radial artery catheter insertion (baseline), before induction of anesthesia, 5 min after tracheal intubation, 1 min after sternotomy, immedi-

ately after termination of CPB, at skin closure, at 2-h intervals during surgery, 4 h after the start of surgery, and thereafter at 4-h intervals until the first postoperative morning. Plasma dexmedetomidine concentrations were assayed using a gas chromatography-mass spectrometry method (detection limit, 50 pg/ml).[26] A blood sample used to determine serum creatine kinase concentration and its MB subfraction (creatine kinase MB isoenzyme) was obtained before operation, on arrival at the intensive care unit, in the morning and evening of the first two postoperative days, and at discharge from the hospital or 7 days after operation, whichever occurred first.

Statistical Methods

The results are reported as mean values and standard deviations (SD) or as median values with quartile deviations (QD), depending on whether the residual values were normally distributed on the original scale of measurement. The two-sample *t* test and Wilcoxon rank-sum test were used accordingly to compare single end points. Unbalanced two-way analysis of variance for repeated measures with one between-factor (drug) and one within-factor (time) was used for serially measured hemodynamic parameters and catecholamine data. The changes in SAP, DAP, and HR were analyzed independently during the following time periods: (1) the preoperative period (from the start of the study drug infusion until 6 min after anesthesia induction), (2) the intraoperative period (tracheal intubation to 30 min after intubation; skin incision to 25 min after skin incision; first hour of CPB; termination of CPB to 25 min after termination of CPB), and (3) postoperative period (first 14 h after arrival at the intensive care unit). Proportions were compared using the likelihood ratio chi-squared test, or using Fisher's exact test if the expected cell sizes were small. Duration of operation phases, anesthesia and study drug infusion, and characteristics of myocardial ischemia were analyzed using the survival analysis approach and log-rank test. Confidence intervals (95%) were calculated from respective statistical tests for the primary variables. A probability value less than 0.05 was regarded as significant.

Results

The demographic characteristics were similar in both groups with respect to age, weight, height, sex distribution, number of patients with previous myocardial infarction, New York Heart Association classification, and the number of patients taking preoperative beta blocker or calcium antagonist medication. The duration of surgery, CPB, and anesthesia; the number and type of the grafts; and the surgeon's assessment of the function of the grafts were also similar in both groups (table 2). Figure 1 shows the changes in dexmedetomidine plasma concentration.

Table 2. Demographic Characteristics and Operation Data

	DEX	PLA
Weight (kg)	80.3 (13.0)	80.5 (9.0)
Height (cm)	171 (8)	173 (7)
Age (yr)	55.3 (8.6)	55.5 (7.7)
Male/Female (no. of patients)	31/9	36/4
Patients with NYHA class 3 or 4	22	23
Patients with previous MI	18	25
Patients with β blockers	32	32
Patients with calcium antagonists	21	22
Duration of anesthesia (min)*	260 (29)	258 (18)
Duration of surgery (min)*	180 (22)	185 (21)
Duration of CPB (min)*	96 (20)	89 (15)
Distal coronary anastomoses (number)	3.2 (1.0)	3.4 (1.0)
Fair or poor anastomoses (no. of patients)	11	9

Mean values and (SD), *median values (quartile deviation), or number of patients presented. No significant differences (Students *t* test; Wilcoxon rank sum test) were found, DEX = dexmedetomidine; PLA = placebo; MI = myocardial infarction; CBP = cardiopulmonary bypass; NYHA = New York Heart Association.

Changes in Systolic and Diastolic Arterial Blood Pressure and Heart Rate with Time

During the 30-min dexmedetomidine loading period, SAP decreased in the DEX group but stayed at the base-

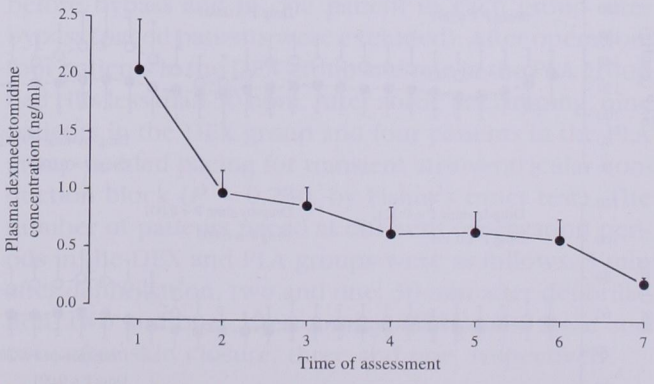

Fig. 1. Mean (SD) dexmedetomidine plasma concentration. Measurements: 1 = before induction of anesthesia; 2 = 5 min after tracheal intubation; 3 = 1 min after sternotomy; 4 = before termination of CPB; 5 = at skin closure; 6 = 4 h after start of surgery; 7 = 4 h after the end of surgery.

line level in the PLA group (fig. 2), and the mean difference between the groups was 15–20 mmHg. There were no significant differences between the groups in HR during this period (fig. 2).

During the 6-min anesthesia induction period, SAP decreased in the PLA group but remained unchanged in the DEX group (fig. 2). During induction of anesthesia, SAP and HR remained significantly higher in the PLA group than in the DEX group (fig. 2). Although SAP and HR increased again in the PLA group after pancuronium was injected (and even further after intubation), these parameters were stable in the DEX group.

In response to tracheal intubation, the maximum mean SAP values were 133 (SD, 26) mmHg in the DEX group and 157 (SD, 26) mmHg in the PLA group, representing a mean increase of 3 mmHg (95% CI, −4 to 11 mmHg) from baseline in the DEX group and of 24 mmHg (95% CI, 17 to 32 mmHg) from baseline in the PLA group ($P < 0.001$, by Student's t test). The corresponding maximum mean HR in response to intubation was 62 (SD, 13) bpm in the DEX group and 80 (SD, 16) bpm in the PLA group, and the mean increase from baseline was 7 bpm (95% CI, −23 to 45 bpm) in the DEX group and 24 bpm (95% CI, −9 to 58 bpm) in the PLA group ($P < 0.001$). During the 30-min period after intubation, SAP and HR decreased in the PLA group but remained stable in the DEX group, and were greater for the PLA, with a maximum intergroup difference of 25 mmHg in SAP and 18 bpm in HR (fig. 2). The response in DAP during this period was similar to that in SAP ($P < 0.001$ for interaction), but the changes were smaller.

In the 25 min after skin incision, there was a significant drug-by-time interaction for SAP, HR (fig. 3), and DAP, with the mean SAP 10 to 25 mmHg higher, HR 5 to 6 bpm higher, and DAP 5 to 10 mmHg higher in the PLA group than in the DEX group. During the first 60 min of CPB, MAP was 6 to 16 mmHg lower in the DEX group than in the PLA group (fig. 4). During the 25 min after termination of CBP, there was a significant interaction for SAP, but the intergroup difference in mean SAP was small (fig. 3), and there were no significant differences in DAP or HR.

After operation, while the patients were in the intensive care unit, the blood pressure response was significantly different in the two groups (fig. 5). Initially SAP and DAP increased in the DEX group during the first hour and remained stable thereafter, at an approximate level of 110 and 60 mmHg, respectively. In the PLA group, SAP and DAP decreased gradually during the first 5 h in the intensive care unit and stayed at an approximate level of 100 and 55 mmHg, respectively. Heart rate increased in both groups during the first hours in the intensive care unit but remained approximately 10 bpm lower in the DEX group than in the PLA group (fig. 5).

Hemodynamic Variability

Intraoperative variability of SAP was significantly less in the DEX group than in the PLA group: 75 (SD, 30) *versus* 89 (SD, 32) mmHg/h (mean difference, 14 mmHg/h; 95% CI, 0–28 mmHg/h; $P = 0.047$, by t test). In addition, postoperative variability of SAP was slightly

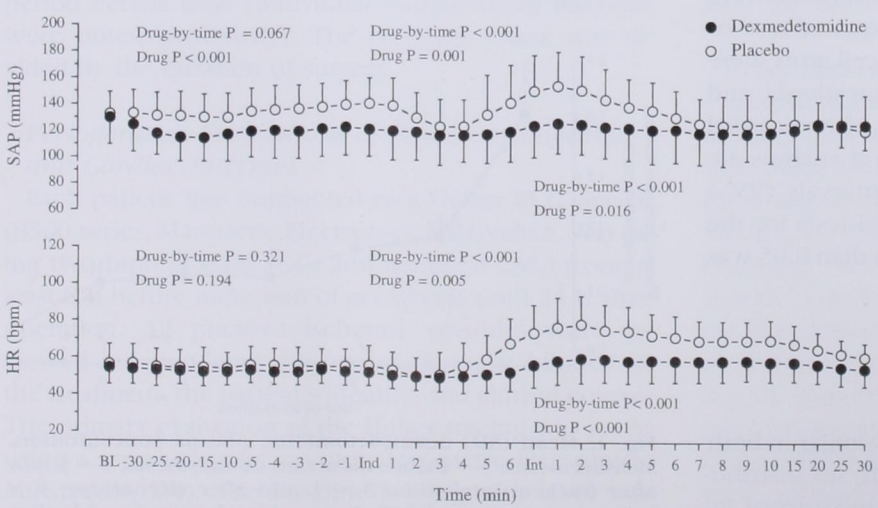

Fig. 2. Mean (SD) systolic blood pressure and heart rate during study drug loading (infusion of 50 $ng \cdot kg^{-1} \cdot min^{-1}$ dexmedetomidine or placebo), anesthesia induction, and intubation periods. After loading, dexmedetomidine infusion was continued with a speed of 7 $ng \cdot kg^{-1} \cdot min^{-1}$ until the end of surgery. BL = baseline measurement before starting study drug infusion; Ind = start of anesthesia induction; Int = tracheal intubation. The changes in SAP and HR were analyzed by repeated-measure analysis of variance, independently during three time periods: (1) study drug loading period (from −30 to −1 min), (2) anesthesia induction (Ind) to 6 min after induction), and (3) tracheal intubation (Int) until 30 min after intubation. Drug-by-time *P*: intergroup difference in response over the time period (interaction). Drug *P*: overall difference in the level between the two groups (drug main effect).

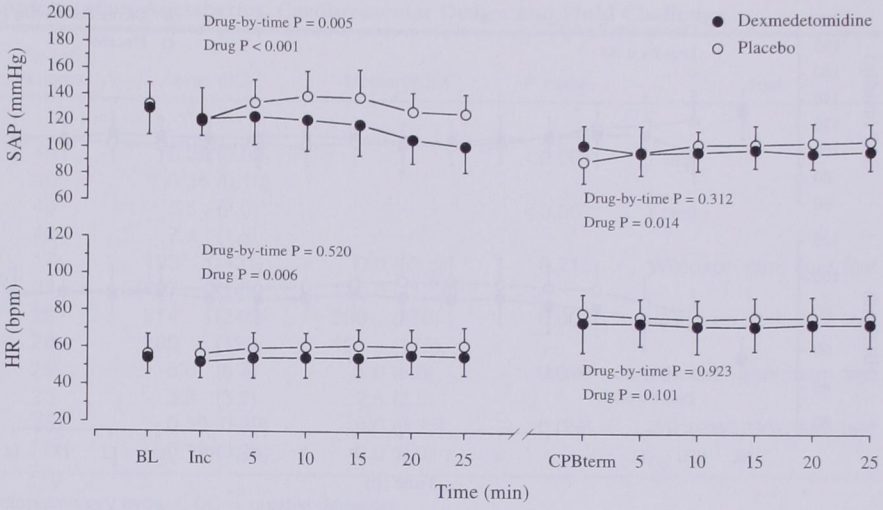

Fig. 3. Mean (SD) systolic blood pressure and heart rate during the first 25 min after skin incision (Inc) and during the first 25 min after termination of the cardiopulmonary bypass (CPBterm). BL = baseline measurement before starting study drug infusion. The changes in systolic arterial blood pressure and heart rate were analyzed by repeated-measure analysis of variance independently during two time periods: (1) from first incision until 25 min after incision and (2) from termination of CPB until 25 min after termination. Drug-by-time *P*: intergroup difference in response over the time period (interaction). Drug *P*: overall difference in the level between the two groups (drug main effect).

less in the DEX group: 14 (SD, 6) *versus* 17 (SD, 8) mmHg/h (mean difference, 4 mmHg/h; 95% CI, 1–7 mmHg/h; $P = 0.016$). No intergroup differences were observed in the variability of HR.

Incidence of Hypotension, Hypertension, Tachycardia, Bradycardia, and Pacing

Using the prespecified criteria (table 1), the incidence of hypotension was similar in both groups during operation before and after CPB, and after operation (table 3). However, in a *post hoc* analysis, more patients in the DEX group (n = 22) had SAP less than 90 mmHg before CPB than did patients in the PLA group (n = 11; $P = 0.022$, by Fisher's exact test), but there was no such difference after CPB (32 and 26 patients, respectively; $P = 0.210$) or after operation (25 and 25 patients, respectively; $P = 1.000$). During CPB, the incidence of hypotension (MAP < 30 mmHg) was higher in the DEX group than in the PLA group (9 *vs.* 0 patients; $P = 0.002$). Before and during CPB, more patients in the PLA group than in the DEX group were hypertensive (table 3), whereas there were no significant differences after CPB or after operation.

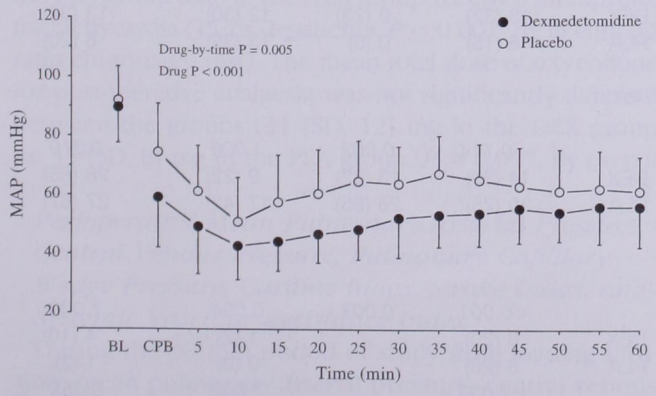

Fig. 4. Mean (SD) values of the mean arterial pressure during the first 60 min of cardiopulmonary bypass. BL = baseline measurement before starting study drug infusion. Drug-by-time *P*: intergroup difference in response during the time period (interaction, repeated-measure analysis of variance). Drug *P*: overall difference in the level between the two groups (drug main effect).

The incidence of tachycardia was significantly greater in the PLA group than in the DEX group before CPB (HR > 90 bpm; table 3) and after operation (HR > 110 bpm). There were no statistically significant differences in the incidence of bradycardia. Heart rate decreased to less than 40 bpm but returned to normal with pharmacologic interventions in eight patients in each group before bypass and in one patient in each group after bypass (paced patients were excluded). After operation, four patients in the DEX group and one in the PLA group had HRs less than 50 bpm. After aortic unclamping, nine patients in the DEX group and four patients in the PLA group needed pacing for transient atrioventricular conduction block ($P = 0.230$, by Fisher's exact test). The number of patients paced at different observation periods in the DEX and PLA groups were as follows: 5 min after defibrillation, two and one; 30 min after defibrillation, two and one; after coming off bypass, three and two; after skin closure, three and one, respectively.

Supplementary Anesthesia and Hemodynamic Interventions

The mean total number of intraoperative interventions required to maintain the hemodynamic parame-

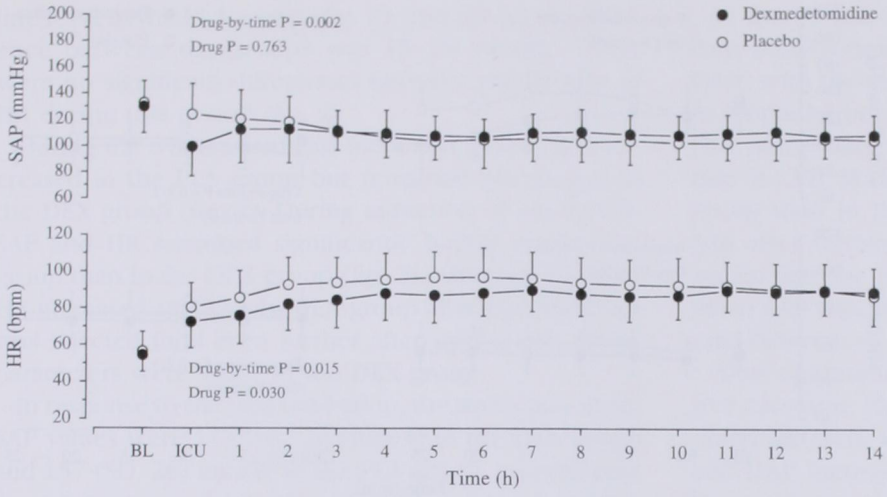

Fig. 5. Mean (SD) systolic blood pressure and heart rate during the first 14 h in the intensive care unit. BL = baseline measurement before starting study drug infusion. Drug-by-time *P*: intergroup difference in response over the time period (interaction, repeated-measure analysis of variance). Drug *P*: overall difference in the level between the two groups (drug main effect).

ters within the predetermined limits was significantly less in the DEX group (n = 18; SD, 7) than in the PLA group (n = 22; SD, 7; $P = 0.016$, by t test), with a mean difference of four interventions (95% CI, 1–7). Table 4 reports the mean or median (or both) total intraoperative doses of supplementary anesthetics, vasoactive drugs, and fluid challenges.

The fentanyl dose was increased more frequently in the PLA group (mean, 5.4 [SD, 1.8] times per patient) than in the DEX group (mean, 3.1 [SD, 1.7] times per patient; $P = 0.000$, by t test), as was the enflurane concentration (mean, 5.6 [SD, 1.9] times per patient in the PLA group *vs.* 4.4 [SD, 1.9] times per patient in the DEX group; $P = 0.004$, by t test). The mean end-tidal enflurane concentration and the cumulative dose of fentanyl to maintain hemodynamic values within predetermined limits were also higher in the PLA group than in the DEX group. A significantly higher proportion of patients in the DEX group than in the PLA group received fluid challenge for hypotension during operation and phenylephrine for hypoten-

Table 3. Incidence of Hypotension, Hypertension, Bradycardia, and Tachycardia

Abnormality	Definition	Group	Before Bypass	During Bypass	After Bypass	Postoperatively
Hypotension	SAP ↓ ≥ 30% and < 90 mmHg or SAP < 80 mmHg before CBP,	DEX	13 (32)	9 (23)	12 (30)	13 (32)
	SAP < 80 mm Hg after CBP and postoperatively,	PLA	6 (15)	0 (0)	13 (32)	8 (20)
	MAP < 30 during bypass					
	Fisher's Exact Test, *P* value		*0.114*	*0.002*	*1.000*	*0.310*
Hypertension	SAP ≥ 20% above BL or SAP > 150 mm Hg before CBP,	DEX	14 (35)	13 (32)	9 (22)	26 (65)
	SAP > 130 mm Hg after CBP and postoperatively,	PLA	30 (75)	26 (65)	17 (42)	27 (67)
	MAP > 80 during CBP					
	Fisher's Exact Test, *P* value		*<0.001*	*0.007*	*0.094*	*1.000*
Bradycardia	HR < 40 bpm intraoperatively,	DEX	8 (20)		1 (2)	4 (10)
	HR < 50 bpm postoperatively	PLA	8 (20)		0 (0)	1 (2)
	Fisher's Exact Test, *P* value		*1.000*		*1.000*	*0.359*
Tachycardia	HR > 90 bpm intraoperatively,	DEX	2 (5)		10 (25)	5 (12)
	HR > 110 bpm postoperatively	PLA	13 (32)		16 (40)	16 (40)
	Fisher's Exact Test, *P* value		*0.003*		*0.232*	*0.010*

No. of patients (%) presented.

DEX = dexmedetomidine; PLA = placebo; CBP = cardiopulmonary bypass; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure.

Table 4. Intraoperative Average Doses of Supplementary Anesthetics, Cardiovascular Drugs, and Fluid Challenge

	Group	No. of Patients	Mean (SD)	Median (QD)	*P* value	Test
End-tidal enflurane concentration (%)	DEX	40	0.26 (0.09)		<0.001	*t* test
	PLA	40	0.35 (0.10)			
Total dose of fentanyl (mg)	DEX	40	5.5 (2.0)		<0.001	*t* test
	PLA	40	7.4 (1.5)			
Glyceryl trinitrate (μg)	DEX	17	193 (431)	0.0 (62.5)	0.215	Wilcoxon rank sum test
	PLA	24	127 (149)	100.0 (112.5)		
Fluid challenge (ml)	DEX	29	374 (346)	250 (250)	0.005	Wilcoxon rank sum test
	PLA	20*	169 (199)	125 (175)		
Ephedrine (mg)	DEX	29	6.6 (6.7)	5.0 (5.0)	0.019	Wilcoxon rank sum test
	PLA	23	3.2 (3.7)	2.5 (2.5)		
Phenylephrine (mg) during CBP	DEX	18	0.19 (0.29)	0.0 (0.15)	0.058	Wilcoxon rank sum test
	PLA	8*	0.12 (0.25)	0.0 (0.0)		

DEX = dexmedetomidine; PLA = placebo; CPB = cardiopulmonary bypass; QD = quartile deviation.

* Significant intergroup difference in incidence; likelihood ratio chi-square test.

sion during CPB (table 4). In addition, the volume of fluid challenge was slightly but significantly higher in the DEX group (table 4). There was no significant difference in the proportion of patients given ephedrine, but the median dose was significantly higher in the patients in the DEX group (table 4). The patients in the PLA group needed esmolol for tachycardia more frequently than did those in the DEX group (11 *vs.* 3 patients; $P = 0.016$). There was no significant difference between the groups in the number of patients needing glyceryl trinitrate or glycopyrrolate, but the DEX group received fewer glyceryl trinitrate doses per patient than did the PLA group patients (mean, 1 [SD, 1.5] *vs.* 2.3 [SD, 2.8]; $P = 0.014$, by *t* test).

After operation, a higher proportion of the patients in the PLA group than in the DEX group received metoprolol for tachycardia (11 *vs.* 1 patients; $P = 0.001$, by likelihood ratio chi-squared test). The mean total dose of oxycodone for postoperative analgesia was not significantly different between the groups (31 [SD, 12] mg in the DEX group *vs.* 35 [SD, 8] mg in the PLA group; $P = 0.077$, by *t* test).

Perioperative Mean Pulmonary Arterial Pressure, Central Venous Pressure, Pulmonary Capillary Wedge Pressure, Cardiac Index, Stroke Index, and Systemic Vascular Resistance Index

During the 30 min period of study drug loading infusion, mean pulmonary arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac index, stroke index, and systemic vascular resistance index stayed approximately at baseline levels in both groups (table 5). During the 6-min induction period before intubation, mean pulmonary arterial pressure, central venous pressure, and pulmonary capillary wedge pressure increased transiently in the PLA group but not in the DEX group. During anesthesia induction and after intubation, cardiac index was significantly increased and systemic vascular resistance index was significantly decreased from baseline in the PLA group but not in the DEX group. During the operation before bypass and after bypass, the changes in all these parameters were similar in both groups.

Catecholamine Response

During the study drug infusion, plasma norepinephrine concentration decreased significantly in the DEX group but not in the PLA group and it stayed significantly lower in the DEX group throughout the surgical procedure (table 6). There was a marked increase in plasma norepinephrine level in the PLA group and a less pronounced increase in the DEX group 2 h after the end of surgery and discontinuation of dexmedetomidine infusion. No significant intergroup differences were observed in changes of plasma epinephrine concentrations.

Perioperative Myocardial Ischemia and Infarction

Altogether 14 DEX patients (38%) and 19 PLA patients (48%) had ischemic S-T segment changes in ECG during the observation period from the start of study drug loading until 24 h after operation ($P = 0.255$, by likelihood ratio chi-squared test). Most of them were in both groups during the first 4 h after operation. Before commencement of the study drug, four patients in DEX group and one patient in the PLA group each had six

Table 5. Perioperative Hemodynamic Data

Parameter	Group	Baseline	Before Induction	Before Intubation	5 min after Intubation	Before Incision	After Sternotomy	End of Bypass	End of Surgery	Drug Main Effect (*P*)	Drug × time interaction (*P*)
SAP (mm Hg)	DEX	130 (20)	119 (19)	125 (23)	119 (23)	124 (25)	123 (23)	99 (14)	100 (12)	0.007	<0.001
	PLA	133 (16)	134 (17)	148 (28)	131 (29)	114 (14)	137 (14)	94 (14)	105 (15)		
MAP (mm Hg)	DEX	90 (12)	83 (15)	89 (12)	86 (18)	89 (20)	90 (18)	73 (12)	74 (10)	<0.063	<0.001
	PLA	92 (11)	92 (11)	104 (20)	91 (18)	82 (9)	99 (10)	69 (11)	78 (12)		
MPAP (mm Hg)	DEX	19 (5)	18 (6)	20 (6)	18 (5)	17 (4)	16 (4)	19 (5)	18 (4)	<0.013	<0.001
	PLA	20 (4)	19 (4)	26 (7)	22 (6)	16 (4)	17 (4)	20 (6)	19 (4)		
HR (bpm)	DEX	54 (9)	53 (7)	57 (11)	58 (11)	53 (9)	54 (9)	76 (14)	74 (14)	<0.001	<0.001
	PLA	56 (11)	55 (10)	73 (15)	71 (13)	57 (7)	60 (8)	78 (10)	77 (12)		
CVP (mm Hg)	DEX	7 (3)	9 (3)	9 (3)	8 (3)	7 (3)	7 (3)	8 (3)	9 (3)	0.360	0.032
	PLA	8 (3)	8 (3)	11 (3)	8 (3)	8 (3)	7 (3)	8 (3)	9 (3)		
PCWP (mm Hg)	DEX	12 (4)	13 (5)	13 (4)	10 (4)	10 (3)	9 (3)	12 (5)	11 (4)	0.665	<0.001
	PLA	12 (4)	12 (3)	16 (6)	10 (4)	9 (3)	10 (3)	13 (5)	11 (4)		
CI ($l \cdot min^{-1} \cdot m^{-2}$)	DEX	2.7 (0.7)	2.4 (0.4)	2.5 (0.7)	2.6 (0.6)	2.3 (0.5)	2.2 (0.5)	2.6 (0.7)	2.5 (0.7)	<0.001	<0.001
	PLA	2.7 (0.5)	2.6 (0.5)	3.4 (0.7)	3.5 (1.0)	2.4 (0.5)	2.5 (0.5)	2.8 (0.7)	2.3 (0.5)		
SI ($ml \cdot beat^{-1} \cdot m^{-2}$)	DEX	49 (9)	46 (7)	43 (8)	44 (7)	44 (7)	41 (7)	35 (9)	34 (8)	0.412	<0.001
	PLA	49 (11)	49 (10)	48 (8)	49 (11)	41 (9)	42 (10)	36 (8)	31 (6)		
SVRI $\cdot 10^3$ ($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	DEX	2.6 (0.6)	2.5 (0.5)	2.7 (0.6)	2.5 (0.7)	3.0 (0.8)	3.1 (0.9)	2.1 (0.7)	2.2 (1.0)	0.087	<0.001
	PLA	2.6 (0.6)	2.6 (0.7)	2.2 (0.5)	2.0 (0.5)	2.6 (0.6)	3.0 (0.7)	1.8 (0.5)	2.5 (0.6)		

Mean values and (SD) presented.

DEX = dexmedetomidine; PLA = placebo; SAP = systolic systemic arterial blood pressure; MAP = mean systemic arterial blood pressure; MPAP = mean pulmonary arterial blood pressure; HR = heart rate; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SI = stroke index; SVRI = systemic vascular resistance index. Significances: analysis of variance for repeated measurements.

episodes of ischemia, and five patients in PLA group each had one episode of ischemia (these episodes were not included in the statistical analysis of perioperative ischemia). From the start of the study drug infusion through anesthesia induction, no patient in the DEX group had ischemia, whereas three in the PLA group had one ischemic episode each. From intubation until the end of the surgery, four DEX patients and six PLA patients had one ischemic episode each. During the first 24 h after operation, 11 DEX patients had 36 ischemic episodes, whereas 12 patients in the PLA group had 46 episodes of ischemia. None of the four patients in the DEX group who had ischemia before starting the study drug infusion had ischemia during any later stage of the study, whereas five patients in the PLA group continued to have ischemia: one during the induction period, two during operation, and four after operation. There were no significant differences between the two treatment

Table 6. Plasma Catecholamine Concentrations

	Group	Baseline	Before Induction	5 min after Intubation	After Sternotomy	End of Bypass	End of Surgery	2 h postoperatively	Drug Main Effect (*P*)	Drug × time interaction (*P*)
Epinephrine ($nmol/ml^{-1}$)	DEX	0.66 (0.64)	0.09 (0.16)	0.11 (0.19)	0.07 (0.12)	0.53 (1.92)	0.54 (2.27)	1.55 (3.83)	0.250	0.347
	PLA	0.42 (0.44)	0.39 (0.43)	0.27 (0.32)	0.21 (0.33)	0.46 (1.89)	0.53 (1.47)	2.59 (4.06)		
Norepinephrine ($nmol \cdot ml^{-1}$)	DEX	1.79 (0.72)	0.20 (0.18)	0.28 (0.34)	0.21 (0.13)	0.59 (0.67)	1.09 (1.76)	2.83 (4.43)	<0.001	<0.001
	PLA	1.73 (0.74)	1.61 (0.68)	2.02 (1.01)	1.23 (0.65)	2.61 (5.39)	2.65 (1.54)	8.44 (8.06)		

Mean values and (SD) presented.

DEX = dexmeditomidine; PLA = placebo.

Table 7. Myocardial Ischemia

Indicator	Group	Mean (SD)	Median (QD)	Range	Log-Rank Test *P* value	Hazard Ratio (95% Confidence Interval)
Number of ischemic episodes	DEX	1.0 (2.1)	0.0 (0.5)	0.0–11.0	0.479	0.90 (0.58–1.39)
	PLA	1.4 (2.5)	0.0 (0.5)	0.0–11.0		
Total ischemic minutes	DEX	8.4 (17.7)	0.0 (3.9)	0.0–68.2	0.335	0.84 (0.54–1.31)
	PLA	14.3 (30.2)	0.0 (7.0)	0.0–147.6		
Area under ST × time curve	DEX	11.1 (28.5)	0.0 (5.3)	0.0–161.3	0.123	0.75 (0.48–1.19)
	PLA	27.3 (60.6)	0.0 (14.3)	0.0–319.7		
Ischemic minutes/hour monitored	DEX	0.27 (0.63)	0.0 (0.1)	0.0–2.8	0.629	0.92 (0.59–1.43)
	PLA	0.34 (0.71)	0.0 (0.2)	0.0–3.4		

Hazard ratio means the likelihood of *not* having the event; i.e. a value of hazard ratio of less than 1 means that the event occurred more often in the PLA group (although the difference was not statistically significant).

DEX = dexmedetomidine; PLA = placebo; QD = quartile deviation.

groups in terms of any of the variables related to the ischemic episodes (table 7). The differences in the incidence of hypotension or tachycardia during any of the observation periods in the patients who had ischemia, and those who did not were small and insignificant.

Eleven patients in the DEX group and seven in the PLA group had a new Q wave on the ECG, but in four DEX patients and in two PLA patients these were seen in only one recording (of five) or they did not meet Minnesota code 1 criteria for a myocardial infarction (table 8). Consequently, six patients in the DEX group and four in the PLA group had a new Q wave that fulfilled the Minnesota code 1 criteria for a perioperative myocardial infarction and, in addition, one patient in each group had a new Q wave that fulfilled the criteria of a probable myocardial infarction. Seven patients in the DEX group and eight patients in the PLA group had a peak creatine kinase MB isoenzyme of >100 IU or >70 IU more than 12 h after operation. Of these patients, three in the DEX group and four in the PLA group also had a new Q wave (two *versus* three of them, respectively, fulfilling the Minnesota code 1 criteria).

Fentanyl-induced Muscle Rigidity, Postoperative Shivering, and Diuresis

Fifteen patients (38%) in the DEX group and 33 patients (82%) in the PLA group had muscle rigidity during

Table 8. New Q Waves and Elevations in Creatine Kinase MB Band

Indicator	Group	No. of Patients (%)	*P*	Statistical Test
New Q wave, all included	DEX	11 (28)	0.280	LR chi-square test
	PLA	7 (18)		
New Q wave, Minnesota criteria*	DEX	7 (18)	0.530	LR chi-square test
	PLA	5 (13)		
CK-MB > 100 IU or > 70 IU > 12 h	DEX	7 (17)	0.774	LR chi-square test
	PLA	8 (20)		
New Q wave, all included, and peak CK-MB > 100 IU or > 70 IU > 12 h	DEX	3 (8)	1.000	Fisher's exact test
	PLA	4 (10)		
New Q wave, Minnesota criteria, and peak CK-MB > 100 IU or > 70 IU > 12 h	DEX	2 (5)	1.000	Fisher's exact test
	PLA	3 (8)		
No Q wave and peak CK-MB > 100 IU or > 70 IU > 12 h	DEX	4 (10)		Not tested
	PLA	4 (10)		

CK-MB = creatinine kinase MB band; DEX = dexmedetomidine; IU = international units; PLA = placebo; LR = likelihood ratio.

* From reference 23.

or immediately after the induction dose of fentanyl ($P < 0.001$, by likelihood ratio chi-squared test). Postoperative shivering occurred more frequently in the PLA group than in the DEX group (23 *vs.* 13 patients; $P = 0.024$, by likelihood ratio chi-squared test). The patients of the DEX group excreted more urine than did the patients of the PLA group both during operation (1,445 [SD, 725] *vs.* 988 [SD, 589] ml; $P = 0.003$, by t test) and during 18 h after operation (4,038 [SD, 1,284] *vs.* 3,528 [SD, 1,000] ml; $P = 0.051$).

Clinical Outcomes

None of the patients died nor had episodes of unstable angina during the first 7 days after operation. One patient in the DEX group had low cardiac output, requiring maximal inotropic support, at the emergence from CPB. One patient in the PLA group had an intraaortic balloon pump inserted on the second postoperative day because of low cardiac output. One patient in the DEX group and three in the PLA group had postoperative radiological signs of congestive heart failure that resolved with pharmacologic treatment. Nine patients in the DEX group and ten in the PLA group had episodes of atrial fibrillation on postoperative days 1 to 6. One patient in each group had a short-lasting episode of ventricular tachycardia. One patient in the PLA group had transitory (postoperative days 1 to 4) weakness of the upper limb. All patients were ambulatory when discharged from the hospital.

Discussion

Hemodynamic Response

This study is the first in which dexmedetomidine was given to patients with documented severe coronary disease who were undergoing coronary bypass operation. The main finding was that dexmedetomidine significantly blunted the responses of SAP and HR to intubation and skin incision, decreased the overall variability of SAP, and decreased the incidence of hypertension and tachycardia both during operation before bypass and after operation. Previously, Flacke *et al.*[3] observed improved hemodynamic stability in patients having CABG who were given clonidine and anesthetized with high-dose sufentanil and supplemental isoflurane, whereas Abi-Jaoude *et al.*[16] did not find any such decrease. A decreased incidence of tachycardia has been a common finding in patients receiving dexmedetomidine and undergoing gynecologic procedures[27–29] or receiving clonidine and undergoing noncardiac surgery.[9,30–32]

In the present study, the intraoperative incidence of bradycardia requiring treatment according to prespecified criteria was not more common in the dexmedetomidine group than in the placebo group, compared with a study of patients having CABG who were premedicated with clonidine, in which four of ten patients received atropine for bradycardia before the start of surgery.[3] However, in another recent study, bradycardia was more common in patients with dexmedetomidine premedication and undergoing abdominal hysterectomy than in patients receiving midazolam premedication.[29] The present study is the first report of patients treated with dexmedetomidine, with most of them receiving long-term β-blocker treatment. With the β-receptors already blocked, additional sympathetic blockade did not appear to decrease the heart rate further. Scopolamine premedication and pancuronium as a muscle relaxant probably also counteracted, in part, the bradycardia-inducing effect of dexmedetomidine during operation.

Administration of clonidine has been associated with an increased incidence of hypotension in studies of patients having noncardiac procedures[31] and CABG.[16] In our study, using prespecified treatment trigger criteria of hypotension, there was no intergroup difference in the incidence of hypotension before or after CPB. However, the volume of fluid challenge needed to maintain adequate filling pressure and to prevent hypotension was slightly greater in the dexmedetomidine group than in the placebo group, and twice as many patients in the dexmedetomidine group than in the placebo group had SAPs less than 90 mmHg before bypass. In addition, 9 of 40 patients receiving dexmedetomidine were hypotensive during CPB in our study, suggesting that the sympathetic blockade by dexmedetomidine adds to the other vasodilative effects of CPB.

Dexmedetomidine prevented the increase in cardiac index and the decrease of systemic vascular resistance index that were observed in the placebo-treated patients during anesthesia induction and intubation. These findings differ from those of studies of patients having CABG and who received clonidine, in which either no effect on cardiac index or SVR was seen,[3,33] or cardiac index was decreased and SVR was increased during induction of anesthesia and intubation.[12,16] These differences may be due to the different α_1/α_2 selectivity or to different routes of administration of dexmedetomidine and clonidine.

Anesthetic Requirement

Some investigators have observed a decreased need for inhalational anesthetics or opioids by administering

clonidine in some studies of patients having noncardiac[14,30,32] and cardiac[3,12] surgical procedures, but other researchers found no such effect.[31,16] The use of dexmedetomidine has been shown to decrease isoflurane requirements to maintain hemodynamic parameters within predetermined limits,[27,29] and to reduce the need for thiopentone[21] and opiates in patients having noncardiac surgery.[28] Salmenperä *et al.*[34] found a fentanyl-sparing effect by dexmedetomidine in the dog. The present study, in which high-dose fentanyl anesthesia was used, showed that a continuous dexmedetomidine infusion reduced the cumulative dose of fentanyl and decreased the mean end-tidal concentration of enflurane used, both given according to prespecified hemodynamic criteria.

Myocardial Ischemia and Infarction

Dorman *et al.*[12] and Quintin *et al.*[13] reported a decreased incidence and severity of ischemic S-T segment changes in patients who were premedicated with clonidine and undergoing CABG, and a similar finding was reported in patients having noncardiac surgery.[32] However, other investigators could not show such an effect.[16] In the present study, the dexmedetomidine infusion was stopped at the end of surgery. The risk for myocardial ischemia was highest in both treatment groups during the first 4 h after operation, at a time when there were increases in plasma catecholamine levels. We could not show any statistical intergroup differences in the incidence or severity of ischemic S-T segment changes in terms of any of the measured variables, but the study included too few patients to make a definitive assessment of the incidence of ischemia.

The criteria to diagnose perioperative myocardial infarction vary considerably.[35,36] In the present study, the incidence of perioperative myocardial infarction was not significantly different for the two treatment groups, regardless of the definition of myocardial infarction used. However, no definitive conclusion of incidence can be made because of the small number of patients. The number of patients with new Q waves (with all Q waves counted) was rather high. However, the incidence of of myocardial infarction based on definitions of diagnostic creatine kinase isoenzyme MB levels combined with either all Q waves (8% in the DEX group and 10% in the PLA group) or new diagnostic Q waves (5% and 8%, respectively) ranged from 4–14%, as reported in the literature.[35,37]

Muscle Rigidity, Postoperative Shivering, and Diuresis

Opioid-induced muscle rigidity is associated with a prompt increase in central venous pressure and mean pulmonary arterial pressure.[38] The proposed mechanisms are hypercapnia-induced pulmonary vasoconstriction and lack of normal cardiovascular compensation of decreased muscle blood flow.[38] Air trapping and increased intrathoracic pressure due to muscle rigidity during manual ventilation using a face mask also could explain increases in filling pressures. In the present study, central venous pressure, mean PAP, and pulmonary capillary wedge pressure increased in the patients in the placebo group after induction of anesthesia before administration of muscle relaxant. Dexmedetomidine decreased the incidence of rigidity (although it did not abolish it entirely), as was expected from experimental observations,[39] and prevented increases in filling pressures.

The incidence of postoperative shivering was decreased among patients given dexmedetomidine. A similar effect has been observed after using clonidine in patients having noncardiac[10,11] and cardiac[3] surgery. Postoperative shivering is potentially harmful because it can increase the systemic oxygen consumption and, consequently, increase cardiac workload.[40,41] The increased workload may lead to myocardial oxygen supply-and-demand imbalance.

α_2-Adrenergic agonists induce diuresis,[42] possibly by attenuating the secretion of antidiuretic hormone or by blocking its effect on the renal tubules, by inhibiting the release of renin, or by releasing atrial natriuretic peptide.[1] In the present study, mean urine output was higher for patients in the dexmedetomidine group, even though more patients in the placebo group received furosemide to promote diuresis. The volume of fluid challenge was slightly higher in the dexmedetomidine group, but the total volume administered during operation was nearly the same in both groups.

Limitations in Interpreting the Results

The sample size of 40 patients in each treatment was too small to evaluate reliably differences between treatment groups for events that have low incidence, such as bradycardia or the need for cardiac pacing. The primary end points of the study were hemodynamic responses to painful stimuli, most importantly to intubation, intraoperative hemodynamic variability, number of interventions to keep the hemodynamic values within predetermined limits, and endocrine response to surgery, and the study was designed accordingly. For

the same reason, the infusion of dexmedetomidine was stopped at the end of surgery, and the postoperative findings can only suggest the effects of dexmedetomidine.

The endocrine response to anesthesia and surgery was evaluated in terms of changes in plasma catecholamine levels. Plasma catecholamine concentrations, however, do not directly measure central sympathetic tone because they reflect only peripheral norepinephrine spillover and not central sympathetic levels, and they vary considerably among patients. Nevertheless, catecholamine concentrations at times of maximum surgical stress and the trends in the (peripheral) concentrations reflect the magnitude of stress reaction.[43]

As secondary efficacy variables, we also wanted to measure myocardial ischemia and infarction in both groups, although the power of the study sample is not large enough to draw conclusions about the eventual effect of dexmedetomidine on myocardial ischemia (either anti- or proischemic) or on the incidence of myocardial infarction. Clearly, further studies in larger patient groups are needed to evaluate this issue.

Another secondary end point, fentanyl-induced muscle rigidity, was quantified by a subjective assessment of the anesthesiologists as "yes" or "no". This subjectivity limits the value of our finding that dexmedetomidine attenuates rigidity.

Conclusions

In patients undergoing coronary bypass surgery under enflurane-supplemented fentanyl anesthesia, intraoperative intravenous infusion of dexmedetomidine decreased the plasma norepinephrine level, blunted blood pressure response to intubation and surgery, decreased the intraoperative and postoperative blood pressure variability and the incidence of tachycardia, but also increased the propensity toward hypotension. Dexmedetomidine decreased the incidence of fentanyl-induced muscle rigidity and postoperative shivering and increased urine output. No decrease in perioperative myocardial ischemia could be demonstrated in this study of a limited number of patients.

References

1. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. ANESTHESIOLOGY 1991; 74:581–605

2. Aantaa R, Scheinin M: Alpha2-adrenergic agents in anaesthesiology. Acta Anaesthesiol Scand 1993; 37:433–48

3. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. ANESTHESIOLOGY 1987; 67:909–17

4. Quintin L, Bonnet F, Macquin I, Szekely B, Becquemin JP, Ghignone M: Aortic surgery: Effect of clonidine on intraoperative catecholaminergic and circulatory stability. Acta Anaesthesiol Scand 1990; 34:132–7

5. Bernard JM, Bourreli B, Hommeril JL, Pinaud M: Effects of oral clonidine premedication and postoperative i.v. infusion on haemodynamic and adrenergic responses during recovery from anaesthesia. Acta Anaesthesiol Scand 1991; 35:54–9

6. Doak GJ, Duke PC: Oral clonidine premedication attenuates the haemodynamic effects associated with ketamine anaesthetic induction in humans. Can J Anaesth 1993; 40:612–18

7. Kaukinen S, Pyykkö K: Potentiation of halothane anaesthesia by clonidine. Acta Anaesthesiol Scand 1979; 23:107–11

8. Bloor BC, Flacke WE: Reduction of halothane anesthetic requirements by clonidine, an alpha2-adrenergic agonist. Anesth Analg 1982; 61:741–5

9. Quintin L, Viale JP, Annat G, Hoen JP, Butin E, Cottet-Emard JM, Levron JC, Bussery D, Motin J: Oxygen uptake after major abdominal surgery: effect of clonidine. ANESTHESIOLOGY 1991; 74:236–41

10. Delaunay L, Bonnet F, Duvaldestin P: Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. Br J Anaesth 1991; 67:397–401

11. Joris J, Banache M, Bonnet F, Sessler DI, Lamy M: Clonidine and ketanserin both are effective treatment for postanesthetic shivering. ANESTHESIOLOGY 1993; 79:532–9

12. Dorman BH, Zucker JR, Verrier ED, Gartman DM, Slachman FN: Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1993; 7:386–95

13. Quintin L, Cicala R, Kent M, Thomsen B: Effect of clonidine on myocardial ischaemia: A double-blind pilot trial (letter). Can J Anaesth 1993; 40:85–6

14. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O: Effects of clonidine on narcotic requirements and hemodynamic response during induction of anesthesia and endotracheal intubation. ANESTHESIOLOGY 1986; 64:36–42

15. Helbo-Hansen S, Fletcher R, Lundberg D, Nordström L, Werner O, Ståhl E, Nordén N: Clonidine and the sympatico-adrenal response to coronary artery by-pass surgery. Acta Anaesthesiol Scand 1986; 30:235–42

16. Abi-Jaoude F, Brusset A, Ceddaha A, Schlumberger S, Raffin L, Dubois C, Guilmet D, Fischler M: Clonidine premedication for coronary artery bypass grafting under high-dose alfentanil anesthesia: Intraoperative and postoperative hemodynamic study. J Cardiothorac Vasc Anesth 1993; 7:35–40

17. Virtanen R, Savola J-M, Nyman L: Characterization of the selectivity, specificity and potency of medetomidine as an alpha2 adrenoceptor agonist. Eur J Pharmacol 1988; 150:9–14

18. Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M: Medetomidine—a novel α_2-adrenoceptor agonist: A review of its pharmacodynamic effects. Prog Neuro-Psychopharmacol Biol Psychiatry 1989; 13:635–51

19. Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M: Hemodynamic and sedative effects of dexmedetomidine in the dog. J Pharmacol Exp Ther 1992; 263:690–7

20. Vickery RG, Sheridan BC, Segal IS, Maze M: Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2-

adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 1988; 67:611–15

21. Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H: Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. ANESTHESIOLOGY 1990; 73:230–5

22. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, Mangano DT: Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. ANESTHESIOLOGY 1995; 82:620–33

23. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram for population studies. A classification system. Circulation 1960; 21:1160–75

24. Guiteras Val P, Pelletier LC, Galinanes Hernandez M, Jais JM, Chaitman B, Dupras G, Solymoss BC: Diagnostic criteria and prognosis of perioperative myocardial infarction following coronary bypass. J Thorac Cardiovasc Surg 1983; 86:878–86

25. Scheinin M, Karhuvaara S, Ojala-Karlsson P, Kallio A, Koulu M: Plasma 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are insensitive indicators of alpha-2-adrenoceptor mediated regulation of norepinephrine release in healthy human volunteers. Life Sci 1991; 49:75–84

26. Vuorilehto L, Salonen JS, Anttila M: Picogram level determination of medetomidine in dog serum by capillary gas chromatography with negative ion chemical ionization mass spectrometry. J Chromatogr 1989; 497:282–7

27. Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K: Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. Anesth Analg 1992; 75:932–9

28. Scheinin H, Jaakola M-L, Sjövall S, Ali-Melkkilä T, Kaukinen S, Turunen J, Kanto J: Intramuscular dexmedetomidine as premedication for general anesthesia. ANESTHESIOLOGY 1993; 78:1065–75

29. Erkola O, Korttila K, Aho M, Haasio J, Aantaa R, Kallio A: Comparison of intramuscular dexmedetomidine and midazolam premedication for elective abdominal hysterectomy. Anesth Analg 1994; 79:646–53

30. Ghignone M, Noe C, Calvillo O, Quintin L: Anesthesia for ophthalmic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthetic requirement. ANESTHESIOLOGY 1988; 68:707–16

31. Engelman E, Lipszyc M, Gilbart E, Van den Linden P, Bellens B, Van Romphey A, de Rood M: Effects of clonidine on anesthetic drug requirement and hemodynamic response during aortic surgery. ANESTHESIOLOGY 1989; 71:178–87

32. Ellis JE, Drijvers G, Pedlow S, Laff SP, Sorrentino MJ, Foss JF, Shah M, Busse JR, Mantha S, McKinsey JF, Osinski J, Thisted RA, Roizen MF: Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. Anesth Analg 1994; 79:1133–40

33. Kulka PJ, Tryba M, Zenz M: Dose-response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. Anesth Analg 1995; 80:263–8

34. Salmenperä MT, Szlam F, Hug CC Jr: Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. ANESTHESIOLOGY 1994; 80:837–46

35. Haagensen R, Steen PA: Perioperative myocardial infarction. Br J Anaesth 1988; 61:24–37

36. Edwards ND, Reilly CS: Detection of perioperative myocardial ischeaemia. Br J Anaesth 1994; 72:104–15

37. The Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Effects of acadesine on the incidence of myocardial infarction and adverse cardiac outcomes after coronary artery bypass graft surgery. ANESTHESIOLOGY 1995; 83:658–73

38. Benthuysen JL, Smith NT, Sanford TJ, Dec-Silver H, Head N: The physiology of narcotic-induced rigidity. ANESTHESIOLOGY 1986; 64:440–2

39. Weinger MB, Segal IS, Maze M: Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. ANESTHESIOLOGY 1989; 71:242–9

40. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. J Cardiothorac Anesth 1987; 1:24–8

41. Frank SM, Fleischer LA, Olson KF, Gorman RB, Higgins MS, Breslow MJ, Sitzman JV, Beattie C: Multivariate determinants of early postoperative oxygen consumption in elderly patients. Effects of shivering, body temperature, and gender. ANESTHESIOLOGY 1995; 83:241–9

42. Hamaya Y, Nishikawa T, Dohi S: Diuretic effect of clonidine during isoflurane, nitrous oxide, and oxygen anesthesia. ANESTHESIOLOGY 1994; 81:811–19

43. Traynor C, Hall GM: Endocrine and metabolic changes during surgery: Anaesthetic implications (review). Br J Anaesth 1981; 53:153–60

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