Anesthesiology
71:178–187, 1989

Effects of Clonidine on Anesthetic Drug Requirements and Hemodynamic Response during Aortic Surgery

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The authors studied in a double-blind placebo-controlled study the effects of oral preoperative administration of 5 μg/kg clonidine upon the alfentanil and droperidol requirements, hemodynamic lability, distribution of the values of heart rate and blood pressure, and plasma noradrenaline levels, in two groups of ten normotensive patients undergoing infrarenal aortic surgery. The amounts of alfentanil supplementing a standardized continuous infusion, injected to maintain hemodynamic stability, were statistically identical between the groups ($P = 0.23$). The amount of droperidol, however, was significantly less ($P = 0.004$) in the group of patients that received clonidine. The norepinephrine plasma concentrations, during the entire procedure, were lower ($P = 0.001$) in the clonidine group. The variability of the heart rate, systolic (SBP) and diastolic (DBP) blood pressure recorded every 5 s, and assessed by the calculation of the coefficients of variation for each patient, showed no difference between the clonidine and the placebo group. However, when the values recorded were compared to the preoperative baseline values, and divided into three categories (baseline ± 20%—greater than 20% decrease *vs.* baseline—greater than 20% increase *vs.* baseline), the clonidine group showed a higher frequency of low heart rate and fewer episodes of tachycardia. The frequency of SBP hypertension was lower and of SBP hypotension higher in the clonidine group. After induction of anesthesia, but before surgery, there were more episodes of DBP hypotension in the clonidine group, but during dissection and vascular sutures the placebo group experienced more episodes of DBP hypotension, owing probably to the greater amount of droperidol injected. The authors conclude that the preoperative administration of clonidine decreased the need to supplement anesthetic, and modifies the profile of distribution of heart rate and blood pressure. (Key words: Anesthetics, intravenous: alfentanil. Pharmacology: clonidine. Premedication: clonidine. Sympathetic nervous system, alpha-2 adrenergic agonist: clonidine. Surgery: aortic.)

IN ANIMAL EXPERIMENTS, preanesthetic administration of clonidine decreases the MAC of halothane[1] and exerts an analgesic activity when injected intrathecally[2] or in the epidural space.[3] In human studies, clonidine demonstrated an analgesic activity when injected intrathecally for treatment of chronic pain[4]; it also reduced the amount of anesthetic required to maintain a similar EEG pattern[5,6] or to maintain stable hemodynamic parameters[7]; the variability of hemodynamic variables was also reduced.[6,8] These latter findings would be particularly important in patients with coronary artery disease undergoing cardiac or noncardiac surgery, as perioperative myocardial ischemia is frequently associated with hemodynamic lability.[9–11] However, before general administration of clonidine can be advised, these encouraging results have to be confirmed by double-blind experimental protocols during opioid-based anesthesia, as they have been during isoflurane anesthesia.[8]

The aims of our double-blind placebo-controlled study were to assess if preoperative oral clonidine enhances hemodynamic stability during aortic surgery; if this stability can eventually be obtained while using less anesthetic; and finally, to assess if clonidine modifies the profile of distribution of heart rate and blood pressure.

Methods

This study was approved by the Ethical Committee of the Hospital Erasme, and informed consent was obtained from 20 patients scheduled for elective infrarenal aneurysmectomy. Twenty pillboxes, labelled 1–20, were randomly divided into two groups using a random table; they contained three tablets either of 0.150 mg clonidine per tablet, or identical-looking placebo tablets. These preparations were made by Boehringer-Ingelheim.

Patients with hematologic, renal, or hepatic diseases were excluded from the study. Patients with a heart rate under 50 bpm on the preoperative ECG, with any atrioventricular conduction defect, with a rhythm other than normal sinus, with a history of congestive heart failure or a preoperative left ventricular ejection fraction less than 40%, were also excluded. Patients receiving clonidine, guanfacine, or any beta-adrenergic blocking drugs were excluded. Patients with medically well-controlled hypertension were included, as were patients with stable coronary artery disease.

ANESTHETIC PROTOCOL

Baseline Heart Rate and Systemic Arterial Pressure. Each patient's systolic (SBP) and diastolic (DBP) blood pressure and heart rate were routinely measured twice daily during the three preoperative days on the ward. The baseline

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Received from Erasme University Hospital, Free University of Brussels, Brussels, Belgium. Accepted for publication March 6, 1989. Presented at the 11th Annual Meeting of the Society of Cardiovascular Anesthesiologists, April 16–19, 1989, Seattle, Washington.

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value was defined as the most frequently recorded value, or the lowest value recorded if no stable value could be determined.

Premedication and Clonidine or Placebo Administration. Ninety minutes before arrival in the operating room, patients received premedication with diazepam 10 mg po, morphine 6 mg im, and scopolamine 0.2 mg im. With their premedication, they received 0.3 mg (patient's weight 60–85 kg) or 0.38 mg (weight > 85 kg) of the double-blinded tablets taken in the pillbox corresponding to their rank in the study.

Anesthesia

After arrival in the operating room, electrocardiographic lead CM5 was monitored. Two intravenous catheters, a radial artery catheter and a triple lumen pulmonary artery catheter, were inserted under local anesthesia.

Anesthesia was induced by the injection of 120 $\mu g \cdot kg^{-1}$ alfentanil in 2–5 min. When the patient became unresponsive to verbal commands, 0.1 $mg \cdot kg^{-1}$ pancuronium was injected, and the patient's trachea was intubated after completion of the injection of the 120 $\mu g \cdot kg^{-1}$ alfentanil. Alfentanil administration continued by an infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min and 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remainder of the operation, and postoperatively during at least 2 h or rewarming to 36.5° C. During surgery, the patients lungs were ventilated with an O_2/N_2O mixture (FI_{O_2}: 0.5) and pancuronium bromide was used for muscle relaxation.

Additional Anesthetic Drugs

Each increase of systolic arterial pressure of more than 15 mmHg above the baseline value, or a heart rate greater than 100 bpm in absence of hypovolemia, was controlled by the injection of a bolus dose of 7 $\mu g \cdot kg^{-1}$ alfentanil, repeated if necessary at 2 min intervals, up to five times, to control one episode of increase in blood pressure or tachycardia. If alfentanil was insufficient, droperidol 2.5 $mg \cdot ml^{-1}$ was injected at 2 min intervals, up to 3 ml. If these intravenous drugs did not control the increase in blood pressure or heart rate, enflurane was added in 0.5% increments.

Ringer's Lactate® and a 4.5% protein solution were infused to maintain the pulmonary artery occluded pressure (PAOP) and the central venous pressure (CVP) at the level recorded before induction of anesthesia, and to provide a urine output of 1 $ml \cdot kg^{-1} \cdot h^{-1}$. Furthermore, if systolic blood pressure decreased under 100 mmHg, fluid infusion was increased to raise systolic pressure above 100 mmHg. Just before aortic declamping, fluid was infused to increase the pulmonary artery occluded pressure (PAOP) 3–4 mmHg above the preoperative value to minimize declamping hypotension.[12] Packed red cells were given to maintain hemoglobin concentration above 10 $g \cdot dl^{-1}$.

Hemodynamic Measurements

Heart rate, systolic, diastolic, mean systemic, and pulmonary artery pressure, and mean central venous pressure, were continuously recorded *via* two Siemens Sirecust 400® monitoring systems. Every 5 s, the digital values of all these parameters were recorded and stored on disk using a Siemens Sicomp PC 16–20® computer (IBM PC AT compatible) running under the multitasking operating system Concurrent PC–DOS v 5.0 (Digital Research Inc.). Recording began immediately after insertion of all monitoring catheters, and continued throughout surgical procedure and postoperatively until the end of the protocol.

Measurements of intravascular pressures (including PAOP), cardiac output in triplicate by the thermodilution technique, arterial and mixed venous blood gases, and plasma norepinephrine concentrations, were performed at seven predetermined times: before induction of anesthesia; after induction and tracheal intubation, but before surgery; during dissection immediately before aortic clamping; 5 min after aortic clamping; immediately before aortic declamping; 5 min after aortic declamping; and at the end of surgery during abdominal wall closure. Standard formulae were used for the calculation of the derived parameters.

Norepinephrine Measurements

Ten milliliters of arterial blood samples were drawn and placed in collection tubes containing 20 mg EDTA and 10 mg sodium metabisulfite. The tubes were centrifuged and the plasma removed and frozen until the measurement. Norepinephrine concentration was measured by high performance liquid chromatography with electrochemical detection.[13] The lower limit of detection for norepinephrine in our system is 30 $pg \cdot ml^{-1}$. The intraassay coefficient of variation is 3.3%, and the interassay coefficient of variation is 11%.

Statistical Analysis

As the intensity of the surgical stimulation usually varies widely during the different phases of the procedure, the study was divided into four periods: 1) induction of anesthesia until skin incision, including tracheal intubation; 2) from skin incision until aortic clamping; 3) from aortic clamping until the end of all vascular sutures; and 4) from the end of vascular sutures until the end of surgery.

For each period, and for each individual patient, the mean value (M) and the standard deviation (SD) were computed for heart rate and systemic arterial pressure recorded every 5 s. The coefficients of variation (CV),

TABLE 1. Preoperative Clinical Data (M ± SD)

	Placebo Patients	Clonidine Patients	Differences
Age (year)	65.9 ± 5.9	67.4 ± 4.8	N.S.
Weight (kg)	76 ± 11	67 ± 8	N.S.
Baseline blood pressure (syst/diast)	141 ± 11/82 ± 6	138 ± 11/78 ± 8	N.S.
Baseline heart rate	78.6 ± 5.7	71.6 ± 7.0	N.S.
History of hypertension Yes/No	4/6	4/6	N.S.
History of coronary artery disease Yes/No	4/6	2/8	N.S.
Left ventricular ejection fraction	54.4 ± 11.1	63.8 ± 8.8	N.S.
Number of patients receiving chronic medications			N.S.
Nifedipine	3	2	
Amiodarone	1		
Prazosin	1	1	
Nitrates	2		
Fluid infusion and diuresis (M ± SD)			
Crystalloids ($ml \cdot kg^{-1} \cdot h^{-1}$)	16.7 ± 3.2	17.0 ± 3.4	N.S.
Colloids ($ml \cdot kg^{-1} \cdot h^{-1}$)	3.9 ± 2.6	4.1 ± 1.3	N.S.
Blood (ml)	405 ± 487	756 ± 716	N.S.
Urine output ($ml \cdot kg^{-1} \cdot h^{-1}$)	0.9 ± 0.6	1.1 ± 0.6	N.S.

reflecting the variability of the parameter, were computed as (SD/M) × 100, for each patient during each period.

The two groups, including 10 CV for each parameter during each period, were compared using the Mann-Whitney U test for unpaired data.

However, the CV value gives no indication on the actual value of the parameters. Therefore, the ranges of values were divided into three categories, expressed as a percentage of increase or decrease *versus* the baseline value: baseline ± 20%, decrease greater than 20%, increase greater than 20%. The results for each category are expressed as the percentage of the total number of data for each of the two groups, for the parameter in question, during each period. This distribution in categories was compared between the two groups using the chi-square test.

Because this analysis compares several thousand data for each parameter, even small differences will be statistically significant; therefore, the confidence interval, including the real difference between the two groups, were computed at the 95% confidence level, to allow the clinical significance of the difference to be assessed.[14]

The analysis described was applied to the heart rate, the systolic and diastolic systemic blood pressures recorded every 5 s.

The preoperative clinical data were compared using the Mann-Whitney U test or the Fisher exact test.

The volumes of fluids infused, diuresis, and the length of the time intervals, were compared between the groups using the Mann-Whitney U test.

The amounts of alfentanil and droperidol supplementing the continuous infusion of alfentanil, and the norepinephrine plasma concentration, were compared by a two-way analysis of variance.

The hemodynamic data recorded at the seven predetermined moments were compared between the groups using a multivariate analysis of variance for repeated measures.

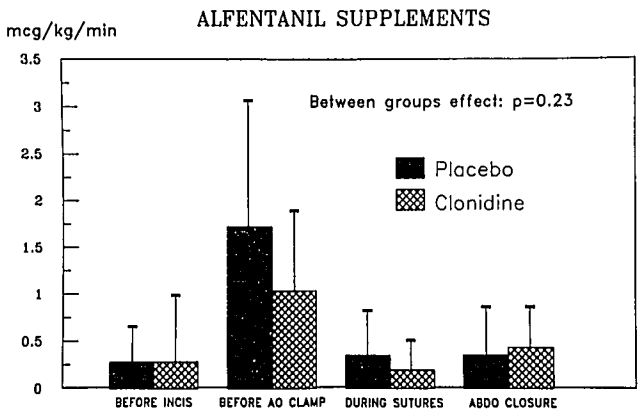

FIG. 1. Mean ± SD doses of alfentanil injected as supplement of the continuous infusion, during each of the four periods.

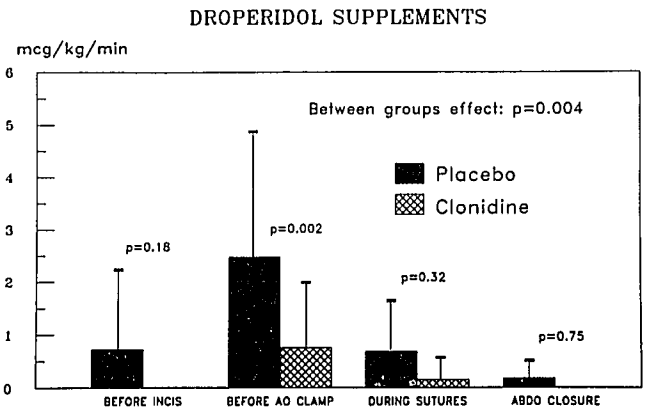

FIG. 2. Mean ± SD doses of droperidol injected to supplement the alfentanil infusion and boluses, during each of the four periods.

All data are given as mean ± SD.

In all tests $P < 0.05$ was considered significant.

The statistical analysis was performed using the software package Systat v 3.0® (Systat, Inc).

Results

The mean dose of clonidine given preoperatively with the premedication was 4.53 ± 0.51 $\mu g \cdot kg^{-1}$ (range: 3.7 to 5.4). There was no significant intergroup difference in preoperative clinical data (table 1), volumes of intravenous fluid infusion and diuresis (table 1), or duration of each time interval. In the operating room, before induction of anesthesia, blood pressure was higher in the placebo group: SBP 151.4 ± 15.1 *versus* 129.1 ± 16.6 ($P = 0.008$) and DBP 75.3 ± 6.8 *versus* 65.8 ± 9.0 ($P = 0.021$).

Drug Requirements

The amount of alfentanil given as bolus injections supplementing the continuous infusion was similar in the two groups (fig. 1).

However, the amount of droperidol injected was significantly less in the clonidine group (fig. 2). The most significant difference between the groups occurred during the interval between skin incision and aortic clamping.

No patient received enflurane during the study.

Hemodynamic Profiles

There was no statistically significant difference between the two groups with respect to cardiac index (CI), stroke index (SI), PAOP, CVP, systemic vascular resistance (SVR), O_2 consumption (V_{O_2}) and mixed venous O_2 saturation (Sv_{O_2}), measured at seven predetermined moments (table 2).

Continuous Recording

Variability of the Parameters (table 3). Comparison of the variability of the parameters, as assessed by the computation of the CV, shows no statistically significant difference between the two groups, during any time interval.

Distribution of the Heart Rate (table 4). Distribution of heart rate was markedly different between the two groups. More than 70% of the data recorded in the clonidine group were in the category of greater-than 20% decrease, during all the periods except for the dissection before aortic clamping. During suturing of the graft, the difference between the two groups tended to decrease. However, bradycardia was more profound in the clonidine group, where 48.1% of the heart rates were slower than a 30% decrease *versus* baseline, as opposed to 22.4% only in the placebo group.

Tachycardia was slightly more frequent in the placebo group during all time intervals, especially before skin in-

TABLE 2. Hemodynamic Data (M ± SD)

	Before Anesthesia	Before Surgery	Before Ao Clamping	5 min After Ao Clamping	Before Ao Declamping	5 min After Declamping	End Surgery	Intergroup Difference
CI ($l \cdot min^{-1} \cdot m^{-2}$)								
Placebo	2.2 ± 0.4	2.3 ± 0.7	2.7 ± 0.8	2.2 ± 0.8	1.7 ± 0.3	2.0 ± 0.3	2.3 ± 0.7	$P = 0.88$
Clonidine	2.1 ± 0.4	2.0 ± 0.4	2.6 ± 1.1	2.1 ± 0.6	1.7 ± 0.4	2.2 ± 0.8	2.3 ± 0.6	N.S.
SI ($ml \cdot beat^{-1} \cdot m^{-2}$)								
Placebo	34.4 ± 6.8	30.2 ± 7.2	36.4 ± 11.5	30.2 ± 8.1	31.0 ± 7.0	31.6 ± 6.4	33.4 ± 7.2	$P = 0.66$
Clonidine	39.9 ± 7.2	34.0 ± 6.4	37.8 ± 8.0	33.7 ± 5.6	34.1 ± 4.6	36.9 ± 7.8	37.9 ± 6.7	N.S.
PAOP (mmHg)								
Placebo	9.5 ± 5.7	9.5 ± 3.3	11.9 ± 4.0	12.2 ± 5.0	13.3 ± 2.7	12.0 ± 2.8	9.3 ± 3.2	$P = 1.00$
Clonidine	9.8 ± 3.2	9.7 ± 1.8	12.1 ± 3.4	12.7 ± 3.9	13.4 ± 3.6	12.3 ± 3.8	9.7 ± 3.2	N.S.
CVP (mmHg)								
Placebo	8.4 ± 2.4	8.9 ± 2.1	11.5 ± 2.8	11.3 ± 2.7	11.9 ± 2.4	11.4 ± 2.2	7.2 ± 3.4	$P = 0.45$
Clonidine	8.7 ± 3.8	9.6 ± 3.8	11.6 ± 3.1	12.2 ± 3.7	13.2 ± 5.2	12.8 ± 4.7	9.0 ± 2.4	N.S.
SVR ($dynes \cdot sec \cdot cm^{-5}$)								
Placebo	1915 ± 543	1857 ± 565	1480 ± 619	2026 ± 775	2060 ± 440	1775 ± 690	1699 ± 533	$P = 0.95$
Clonidine	1694 ± 344	1997 ± 383	1625 ± 788	2126 ± 813	2255 ± 571	1452 ± 717	1752 ± 452	N.S.
V_{O_2} ($ml \cdot min^{-1} \cdot m^{-2}$)								
Placebo	87.5 ± 15.9	78.7 ± 13.9	73.0 ± 16.0	68.1 ± 13.8	73.4 ± 13.0	89.7 ± 16.2	77.2 ± 11.1	$P = 0.42$
Clonidine	91.4 ± 5.2	71.6 ± 8.8	72.0 ± 11.5	63.4 ± 9.8	70.3 ± 6.4	82.0 ± 11.4	72.6 ± 13.1	N.S.
Sv_{O_2} (%)								
Placebo	70.8 ± 5.5	81.9 ± 5.8	81.4 ± 7.6	78.0 ± 10.0	71.8 ± 6.1	70.2 ± 5.4	77.3 ± 6.7	$P = 0.49$
Clonidine	66.1 ± 6.6	79.2 ± 3.4	80.3 ± 6.3	79.1 ± 5.9	71.1 ± 4.0	71.5 ± 8.6	77.8 ± 5.2	N.S.

TABLE 3. Coefficients of Variation (in %) (M ± SD)

	Induction → Incision	Incision → Aortic Clamping	Aortic Clamping → End Vascular Sutures	End Vascular Sutures → End Surgery
Heart rate				
Placebo	11.6 ± 4.7	15.3 ± 6.1	10.2 ± 6.4	9.2 ± 8.4
Clonidine	9.9 ± 5.5	12.6 ± 5.5	8.8 ± 4.9	9.4 ± 4.2
Intergroup Difference	$P = 0.45$ N.S.	$P = 0.33$ N.S.	$P = 0.76$ N.S.	$P = 0.45$ N.S.
Systolic pressure				
Placebo	9.6 ± 5.1	10.9 ± 4.6	9.3 ± 3.7	11.8 ± 4.4
Clonidine	9.4 ± 4.5	11.4 ± 4.5	10.7 ± 5.3	12.1 ± 3.5
Intergroup Difference	$P = 1.00$ N.S.	$P = 0.88$ N.S.	$P = 0.65$ N.S.	$P = 0.85$ N.S.
Diastolic pressure				
Placebo	9.7 ± 3.1	12.6 ± 4.9	7.6 ± 2.3	12.0 ± 4.5
Clonidine	9.3 ± 4.3	12.5 ± 4.8	9.8 ± 5.1	11.4 ± 3.0
Intergroup Difference	$P = 0.60$ N.S.	$P = 1.00$ N.S.	$P = 0.54$ N.S.	$P = 0.64$ N.S.

Intergroup difference assessed by the Mann-Whitney U test. N.S.—no significant difference between placebo and clonidine.

cision. This difference can be attributed to the effects of tracheal intubation; indeed, when the period from induction of anesthesia until 5 min after intubation is considered (table 5), 7% of the heart rates were in the greater than 20% increase category in the placebo group, against 0.6% in the clonidine group.

Distribution of the Systolic Blood Pressure (table 6). Until the end of insertion of the vascular sutures, more than 75% of the values recorded were in the baseline ± 20% category in both groups. However, systolic blood pressure tended to decrease as the procedure went on. Systolic hypertension (greater than 20% increase *vs.* baseline) was more frequent in the placebo group, essentially during the period induction to incision, and particularly during the period centered around endotracheal intubation (table 5, fig. 3), and during the dissection period. Low systolic pressure was much more frequent in the clonidine group.

Distribution of the Diastolic Blood Pressure (table 7). Diastolic hypotension occurred more frequently in the clonidine group before skin incision. During the two following time periods, diastolic pressure values lower than a 20% decrease *versus* baseline were more frequent in the placebo group.

Plasma Norepinephrine Concentration (fig. 4). The norepinephrine plasma concentrations were statistically significantly lower ($P = 0.001$) in the clonidine group. The

TABLE 4. Continuous Recording of Heart Rate

	Percentage of Data Recorded during Each Period			
	Induction → Incision	Incision → Aortic Clamping	Aortic Clamping End Vasc Sutures	End Vasc Sutures → End Surgery
Greater than 20% decrease *vs.* baseline				
Placebo	33.0%	26.8%	60.6%	39.7%
Clonidine	72.1%	50.8%	75.8%	73.8%
Confidence interval for the difference between the two groups (95% level)	37.5–40.7%	22.4–25.4%	13.9–16.4%	32.7–35.6%
Baseline ± 20%				
Placebo	62.7%	61.7%	37.0%	58.6%
Clonidine	27.5%	39.1%	23.2%	24.9%
Confidence interval for the difference between the two groups (95% level)	33.6–36.9%	21.1–24.2%	12.7–15.1%	32.3–35.2%
Greater than 20% increase *vs.* baseline				
Placebo	4.3%	11.4%	2.5%	1.6%
Clonidine	0.3%	10.1%	1.1%	1.4%
Confidence interval for the difference between the two groups (95% level)	3.4–4.4%	0.3–2.2%	0.9–1.6%	0–0.8%
Intergroup difference for the distribution in categories (chi-square test)	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

TABLE 5. Induction of Anesthesia until 5 Min after Intubation

	Distribution of Heart Rate and Blood Pressure (Percentage of Data Recorded)		
	Heart Rate	Systolic Pressure	Diastolic Pressure
Greater than 20% decrease *vs.* baseline			
Placebo	19.2%	8.0%	21.6%
Clonidine	66.4%	12.2%	41.5%
Confidence interval for the difference between the two groups (95% level)	44.9–49.4%	2.5–5.8%	17.4–22.3%
Baseline ± 20%			
Placebo	73.9%	80.2%	75.9%
Clonidine	33.0%	86.6%	55.4%
Confidence interval for the difference between the two groups (95% level)	38.5–43.2%	4.8–8.3%	17.9–23.0%
Greater than 20% increase *vs.* baseline			
Placebo	6.9%	11.7%	2.5%
Clonidine	0.6%	1.2%	3.1%
Confidence interval for the difference between the two groups (95% level)	5.3–7.2%	9.2–11.7%	−0.27–+1.5%
Intergroup difference for the distribution in categories (chi-square test)	$P < 0.001$	$P < 0.001$	$P < 0.001$

difference existed before induction of anesthesia, and remained present during the entire procedure.

Discussion

Thus far, four major published studies have addressed the influence of oral preoperative administration of clonidine on the course of anesthesia, with particular reference to anesthetic drug requirements and the hemodynamic responses to surgery.[5–8] As in this study, two used an opioid-based anesthesia technique.[5,7] However, the first[5] studied only the peri-induction period, and the second[7] included a second administration of clonidine during surgery. Only one of the four studies was double-blinded,[8] and the anesthetic in that study was isoflurane.

During the present double-blinded placebo-controlled study, there was no intergroup difference in the variability of heart rate and blood pressure. This contrasts with the studies of Ghignone *et al.*[6,8] where these parameters were more stable in the clonidine group, as indicated from the computation of the coefficients of variation.

Several elements could account for this difference. First, the initial study[6] by Ghignone *et al.* included only patients with treated hypertension, which was the case in

TABLE 6. Continuous Recording of Systolic Blood Pressure

	Percentage of Data Recorded during Each Period			
	Induction → Incision	Incision → Aortic Clamping	Aortic Clamping End Vasc Sutures	End Vasc Sutures → End Surgery
Greater than 20% decrease *vs.* baseline				
Placebo	9.9%	8.8%	11.4%	22.0%
Clonidine	13.7%	17.8%	21.3%	33.0%
Confidence interval for the difference between the two groups (95% level)	2.7–5.0%	7.9–10.1%	8.8–10.9%	9.6–12.4%
Baseline ± 20%				
Placebo	84.1%	82.3%	83.9%	75.0%
Clonidine	85.0%	80.4%	75.8%	66.0%
Confidence interval for the difference between the two groups (95% level)	−0.4–+2.2%	0.7–3.2%	7.0–9.2%	7.5–10.4%
Greater than 20% increase *vs.* baseline				
Placebo	6.1%	8.9%	4.7%	3.1%
Clonidine	1.3%	1.8%	2.9%	1.0%
Confidence interval for the difference between the two groups (95% level)	4.1–4.5%	6.3–7.8%	1.2–2.3%	1.6–2.5%
Intergroup difference for the distribution in categories (chi-square test)	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

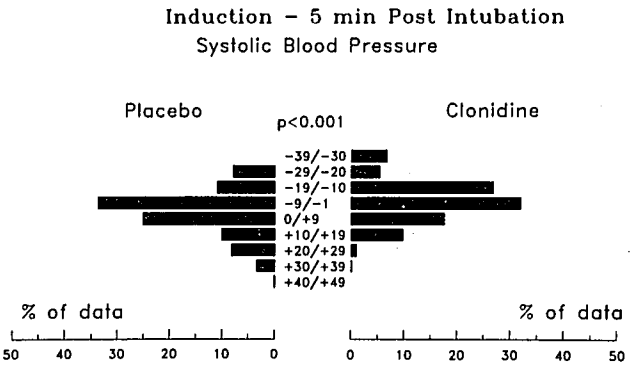

FIG. 3. Detailed distribution in categories representing an increase or decrease of 10% *vs.* the baseline value (=0) of the systolic pressure, during the peri-intubation period.

only 40% of our patients. This could also mean that clonidine is more beneficial if given preoperatively to hypertensive patients, including those under treatment, than if given indiscriminately to all patients with a normal blood pressure. In other words, the increased vascular reactivity to adrenergic stimuli in patients with history of hypertension[15–17] might explain these conflicting results. This hypothesis could not be confirmed by our data, as there was no difference between patients with or without a history of hypertension in the clonidine group; however, the small number of patients makes statistical differences difficult to obtain.

It should also be noted that in the second study by Ghignone *et al.*,[8] only 25% of the patients had preexisting hypertension. Second, the principal anesthetic in Ghignone *et al.* studies[6,8] was isoflurane, in contrast to alfentanil used in this study.

Finally, we recorded all parameters, including blood pressure, much more frequently than Ghignone *et al.*, so that the standard deviations (from which the coefficients of variation are derived) were smaller as the effect of the few more extreme values is reduced when the number of data increases. Indeed, the mean CV in our placebo group, were consistently lower than in the control and placebo groups of the studies by Ghignone *et al.*[6,8]

These are important points to clarify before criteria for the preoperative administration of clonidine are defined.

The lower plasma concentrations of norepinephrine obtained by Flacke *et al.*[7] in clonidine-treated patients have been confirmed in the present study. This can result from a direct effect of clonidine, which reduces norepinephrine release from the central or peripheral terminals when associated with opioids,[18–20] and on descending inhibitory pathways in the spinal cord[20–22] which could result in a greater blunting of the reflex sympathetic stimulation after a nociceptive stimulus.[23] The smaller amount of droperidol injected in the clonidine group possibly played a role, as droperidol induces a moderate increase in plasma norepinephrine.[24]

Heart rate has been shown to correlate with plasma norepinephrine concentrations[25] so that the lower heart rates in the clonidine group are compatible with their lower plasma norepinephrine concentrations. This is confirmed by the significant correlation between the changes in heart rate and the changes in the plasma norepinephrine concentrations (fig. 5) in our patients.

TABLE 7. Continuous Recording of Diastolic Blood Pressure

	Percentage of Data Recorded during Each Period			
	Induction → Incision	Incision → Aortic Clamping	Aortic Clamping End Vasc Sutures	End Vasc Sutures → End Surgery
Greater than 20% decrease *vs.* baseline				
Placebo	28.3%	25.6%	35.2%	33.5%
Clonidine	36.4%	15.2%	29.1%	32.3%
Confidence interval for the difference between the two groups (95% level)	6.4–9.7%	9.2–11.7%	4.8–7.4%	+0.3–−2.7%
Baseline ± 20%				
Placebo	70.4%	70.6%	64.3%	65.0%
Clonidine	57.7%	80.1%	69.5%	64.1%
Confidence interval for the difference between the two groups (95% level)	11.0–14.4%	8.1–10.8%	3.9–6.5%	+0.6–−2.4%
Greater than 20% increase *vs.* baseline				
Placebo	1.3%	3.7%	0.5%	1.5%
Clonidine	5.9%	4.7%	1.4%	3.6%
Confidence interval for the difference between the two groups (95% level)	5.3–4.0%	0.3–1.6%	0.6–1.2%	1.7–2.6%
Intergroup difference for the distribution in categories (chi-square test)	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

In the present study, tachycardia was very uncommon, as the upper limit of 100 bpm was reached in only 0.2% of the recordings in the clonidine group and 1.04% in the placebo group. The heart rate was thus a good marker of the effects obtained by the preoperative administration of clonidine, as very few drug injections were made to control tachycardia alone.

Systolic blood pressure was the principal indicator for drug administration during this study. As the preoperative blood pressures were identical in both groups, and the injection protocol identical, the differences in the profile of distribution of the values can possibly be explained by different reactivity induced by clonidine to the nociceptive stimuli, limiting the increases in systolic blood pressure. A more rapid decrease from a high value toward the baseline target value is also possible if clonidine increased the reactivity to standardized boluses of drugs.

Two hemodynamic parameters, heart rate and systolic blood pressure, were monitored to titrate drug injections and partly fluid infusion. Therefore, the diastolic blood pressure, an important determinant of coronary perfusion, passively fluctuated with the injections of drugs given to control heart rate and systolic pressure. The lower diastolic blood pressures recorded in the clonidine group before incision were probably directly related to the pharmacological action of clonidine. Also, the more frequent diastolic hypotension recorded in the placebo group during dissection and vascular sutures could be the consequence of much greater amounts of droperidol injected.

The hemodynamic parameters recorded only inter-

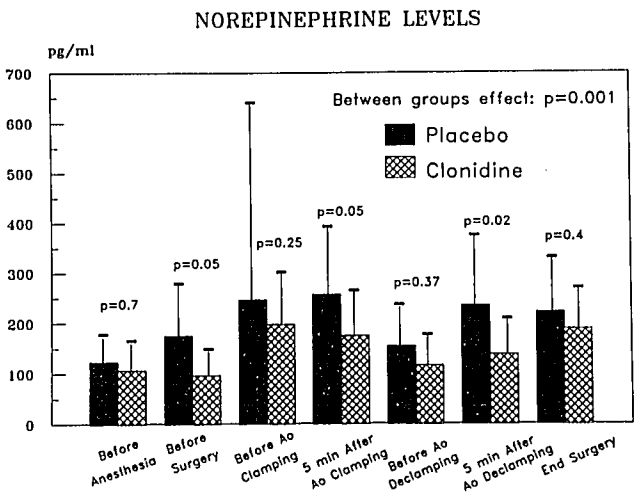

FIG. 4. Mean ± SD for plasma norepinephrine concentration in the two groups, as measured at seven predetermined moments of the procedure.

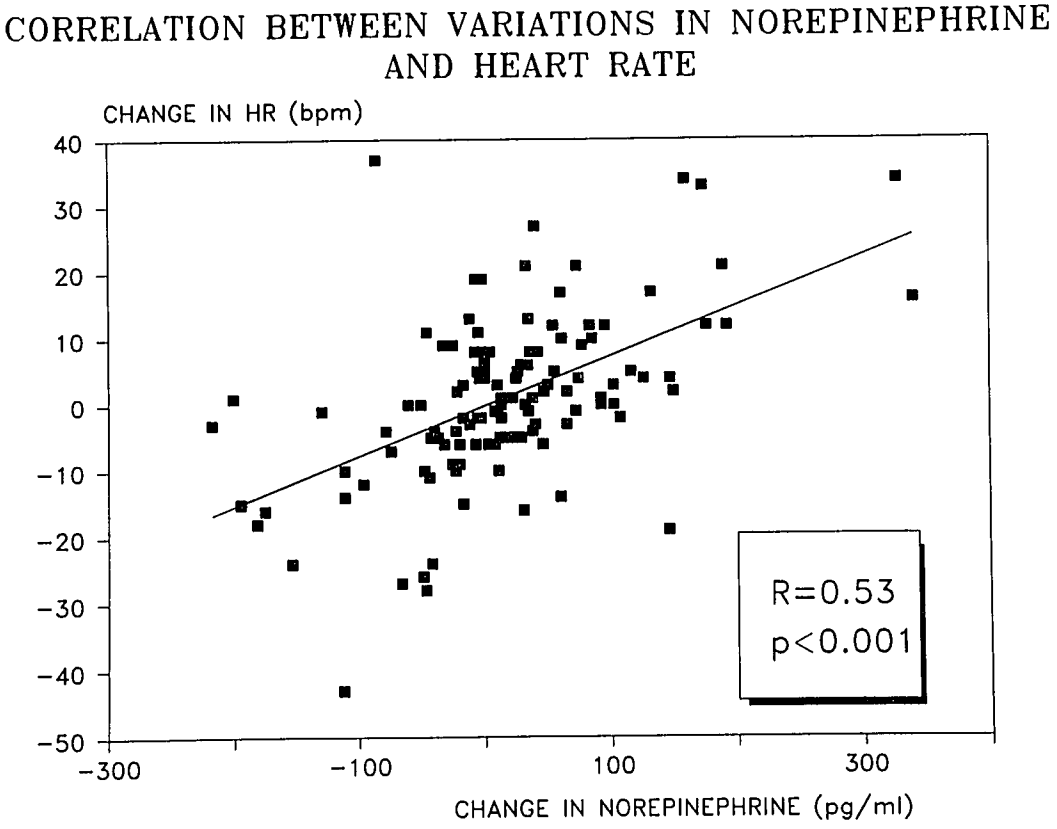

FIG. 5. Correlation between changes in heart rate and changes in plasma norepinephrine concentration, in all patients.

mittently at the seven predetermined moments were identical in the two groups. As there were clear differences when the continuously recorded parameters are examined, this fact probably highlights the limits of intermittent data recording, especially at this very low rate (seven times during a procedure of 3–4 h). However, the absence of significant overall intergroup difference in cardiac output and its derived parameters, is in agreement with the study of Flacke *et al.*[7] during the prebypass period. The similar filling pressures in both groups are consistent with the equal volumes of fluid infused.

In the present study, the sparing effect of clonidine on anesthetic drug consumption was confirmed, although only for droperidol, as there was no statistical difference in the amount of alfentanil used. The maximal amount of alfentanil allowed in the protocol was often reached in both groups, but these additional injections of alfentanil were more often sufficient to control the hemodynamic reactions in the clonidine group. However, the use of droperidol, allowing a more rapid control of the hemodynamic reactivity, could have possibly blunted the sparing effect of clonidine on the alfentanil consumption if the protocol would have allowed further injection of alfentanil before the administration of another drug; this is, of course, speculation, but must remain in mind.

Droperidol was chosen as the primary vasodilator in this study because of its synergic effect with opioids[26]; its partial blocking effect on the baroreceptor reflex,[24] which decreases the reflex tachycardia seen with other vasodilators; and the ability to administer this drug as a bolus, which makes comparison between the two groups easier.

The 45% reduction of fentanyl requirements during the period around tracheal intubation described by Ghignone *et al.*[5] occurred when the maximal effect of oral clonidine is expected (±90–120 min after ingestion).[27–29] In the study using sufentanil,[7] although clonidine was administered twice during the protocol, the sparing effect was effective during the entire study period. The second administration of clonidine, approximately 5 h after the first dose, with probably much of the drug still active,[29] could play an important role in finally determining the importance and the magnitude of the sparing effect. Although this effect appears less important in our present study, these methodological differences make any comparison on the importance of the sparing effect of clonidine particularly difficult.

In conclusion, this double-blind placebo-controlled study shows that in the conditions of this study, clonidine given 90 min before surgery did not decrease the amount of alfentanil, the principal anesthetic drug, when hemodynamic parameters are used as endpoints for dosing, but decreased the need to supplement anesthesia with droperidol. In the present study, the lability of heart rate and blood pressure was not different than that in the placebo group. However, the more frequent low values of heart rate and systolic pressure theoretically allow a more favorable myocardial oxygen supply-and-demand balance. Controlled studies must now be undertaken to test if these theoretical advantages really affect the frequency of myocardial ischemia, and eventually myocardial infarction, during the perioperative period in patients suffering from coronary artery disease, and in general to define more precisely the categories of patients that would benefit from the preoperative administration of clonidine.

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