

## Reduced Narcotic Requirement by Clonidine with Improved Hemodynamic and Adrenergic Stability in Patients Undergoing Coronary Bypass Surgery

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The authors examined the effect of clonidine, a preferential  $\alpha_2$ -adrenergic agonist, upon narcotic requirements, hemodynamics, and adrenergic responses during the perioperative period in patients undergoing CABG surgery. Anesthesia was provided by sufentanil supplemented with isoflurane; sodium nitroprusside was given as needed for hemodynamic control. Ten patients received oral clonidine preoperatively at the time of premedication, and again intraoperatively by nasogastric tube. Another group of ten untreated patients were otherwise managed identically. Intergroup differences in required anesthetic and vasoactive drug doses and recovery times were measured and evaluated, as well as hemodynamics and plasma catecholamines prior to induction, after intubation, and at intervals intra- and postoperatively. Patients who received clonidine required less diazepam prior to induction, and received 40% less sufentanil during the anesthetic period, than did untreated controls. More control patients required the addition of isoflurane to prevent hypertension. Mean blood pressures and heart rates were elevated at many sampling points in patients not treated with clonidine. Four of the clonidine-treated group required atropine for treatment of bradycardia in the pre-incision period. Plasma catecholamines were significantly lower throughout most of the study period in patients treated with clonidine. After cardiopulmonary bypass and postoperatively, cardiac outputs were significantly higher in the treated group. Patients who had received clonidine were extubated significantly earlier, and fewer of them shivered postoperatively. We conclude that perioperative treatment with clonidine reduced narcotic and anesthetic requirements, improved hemodynamics, reduced plasma catecholamines, and shortened the

period of postoperative ventilation in patients undergoing coronary artery surgery. (Key words: Anesthetics, intravenous: sufentanil. Anesthetics, volatile: isoflurane. Pharmacology: clonidine. Premedication: clonidine. Surgery: cardiac. Sympathetic nervous system, alpha adrenergic agonist: clonidine. Sympathetic nervous system: catecholamines.)

A MAJOR GOAL OF ANESTHESIA in patients undergoing cardiac surgery is to produce an anesthetic state sufficient to assure attenuation of the hemodynamic and autonomic responses to noxious stimuli, while still preserving adequate circulatory function. Factors which tend to compromise this goal are the following: 1) patients with coronary artery disease are particularly prone to have hyperdynamic cardiovascular responses;<sup>1-5</sup> 2) perioperative hypertension occurs commonly in patients with a history of hypertension;<sup>6</sup> and 3) patients with heart failure are known to have increased vascular resistance and higher levels of circulating norepinephrine.<sup>7</sup>

Episodes of hypertension and tachycardia, accompanied by undesirable elevations in sympathetic activity and myocardial oxygen demand, are common occurrences during anesthesia and surgery in patients undergoing coronary artery bypass grafting (CABG). These episodes have been shown to occur both at the time of tracheal intubation,<sup>1</sup> and intermittently during the operation, especially in response to the stimuli of incision, sternotomy,<sup>2,8,9</sup> cardiopulmonary bypass,<sup>10,11</sup> and aortic-cross clamping.<sup>12</sup> Moreover, in the immediate postoperative period, hypertension and elevated plasma catecholamines have been reported in from 35-58% of patients who have undergone myocardial revascularization procedures.<sup>3,6,13</sup> In an effort to prevent hyperdynamic and/or adrenergic events, anesthesiologists have utilized ever higher doses of narcotics, but have met with only partial success,<sup>4,8,10,14-16</sup> at the price of prolonged, obligatory, postoperative ventilation.<sup>4,15</sup> Nitroprusside and other peripherally acting vasodilators have been used to control blood pressure, but the resulting reflex baroreceptor activation causes a still greater increase in central sympathetic outflow, reflected in elevated plasma catecholamine concentrations, and manifested as tachycardia and increased myocardial contractility.<sup>17-19</sup> This further increases the discrepancy between myocardial oxygen supply and demand.<sup>8,9,14</sup>

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Moreover, sympathetic activity to the heart may be additionally enhanced in situations (*e.g.*, coronary occlusion) in which myocardial ischemia is already present.<sup>20</sup> Control of the beta-adrenergic component of this by the addition of a beta-adrenergic blocking agent has been advocated; however, this may result in unopposed alpha-adrenergic activity, thus leading to coronary vasoconstriction and further decrease in blood flow to the myocardium.<sup>21,22</sup> Clonidine, a centrally acting preferential alpha<sub>2</sub>-adrenergic agonist, reduces both elevated blood pressure and heart rate by bringing about a balanced reduction in sympathetic outflow from the central nervous system.<sup>23</sup> This agent has been found to prevent reflex sympathetic activation in response to vasodilators in patients<sup>19</sup> and animals.<sup>17</sup> Furthermore, clonidine has been shown to potentiate halothane anesthesia.<sup>24</sup> Finally, several investigators have reported central interactions of clonidine and narcotic analgesics.<sup>25-28</sup> For these reasons, we embarked upon the present investigation to examine the effects of clonidine upon 1) the incidence and magnitude of hyperadrenergic reactions during the perioperative period in patients undergoing coronary artery bypass surgery; 2) intraoperative narcotic requirements; 3) recovery from anesthesia; and 4) incidence of adverse effects.

### Methods

After approval of the study protocol by the UCLA Human Subjects Protection Committee, patients scheduled to undergo elective primary coronary artery bypass grafting by the same surgeon were identified on the day before surgery. The patients were assigned randomly (coin toss) to either a group treated with clonidine, or to a control group. At the time of the pre-anesthetic visit, 20 patients gave written informed consent to participate as a subject in the study group to which they had been randomly assigned. Only patients with good left ventricular function (ejection fraction > 45% at cardiac catheterization) were included, and no patients were accepted who had previously received clonidine therapy. Management of the two study groups was identical, except for the administration of two doses of clonidine to patients in the treated group. According to body size, these patients received either 200 µg or 300 µg of clonidine p.o. 90 min prior to coming to the operating room. A second dose of 200 or 300 µg of clonidine was dissolved in 20 ml of normal saline, and administered *via* nasogastric tube approximately 5 h after the first dose, to permit absorption prior to the initiation of cardiopulmonary bypass and hypothermia. In both groups, chronic cardiac medications were contin-

ued until the morning of surgery, the last dose being given 90 min prior to coming to the operating room. At this time, lorazepam premedication, 0.05 mg/kg p.o. (maximum dose 4 mg), was also administered.

A Swan-Ganz catheter had been placed in all patients on the evening prior to surgery. Prior to induction of anesthesia, ECG leads were applied and cannulae were inserted into the radial artery and a peripheral vein under local anesthesia. If, in the opinion of both the attending anesthesiologist and the cardiac anesthesia fellow, the patient appeared in any way apprehensive or anxious upon arrival in the operating room and/or during placement of catheters, small incremental doses of diazepam were given intravenously until sedation was judged adequate. A nitroglycerin infusion (0.5 µg · kg<sup>-1</sup> · min<sup>-1</sup>) was started, and control measurements were made. Patients were given oxygen to breathe, and pancuronium 15 µg/kg was administered. Five minutes later, anesthesia was induced with sufentanil, administered at <0.5 µg · kg<sup>-1</sup> · min<sup>-1</sup> until the patient became unresponsive to vigorous voice command and tactile stimuli. Pancuronium (0.1 mg/kg) was given iv, intubation was carried out, and patients were ventilated to normocarbica with 100% oxygen.

For maintenance of anesthesia, additional sufentanil, up to a maximal dose of 15 µg/kg, was given as necessary to maintain heart rate and mean arterial blood pressure within 15% of baseline preoperative levels (the baseline values were established by taking the lowest heart rate and blood pressure recorded for a given patient either at the time of the preoperative visit, at the time of insertion of the Swan-Ganz catheter, or just prior to anesthetic induction). If the desired control of the cardiovascular system could not be attained with 15 µg/kg sufentanil, isoflurane up to 1 MAC (1.2% end tidal) was added. If blood pressure remained elevated even with isoflurane, an infusion of sodium nitroprusside was begun. Hypotension (systolic blood pressure less than 90 mmHg) was treated with phenylephrine. If bradycardia (heart rate less than 50 bpm) occurred, atropine was given in 0.4-mg increments. Additional doses of muscle relaxant were used as needed.

During extracorporeal circulation, moderate hypothermia (core temperature close to 28° C), hemodilution (hemoglobin about 7 gm%), and pump flows of 1.5 (during hypothermia) to 2.5 l · min<sup>-1</sup> · m<sup>-2</sup> (after re-warming) were used. During and after cardiopulmonary bypass, indications for sufentanil, isoflurane, and nitroprusside were as above. Nitroglycerin was discontinued at the onset of bypass, and none was given thereafter. Following cardiopulmonary bypass, nifedipine was given to patients who had been receiving chronic calcium channel blocker therapy. At the end of the

operation, patients were transferred to the surgical intensive care unit (ICU), where they were ventilated with 100% oxygen and given nitroprusside, if needed, for blood pressure control.

Arterial, pulmonary arterial, and central venous pressures; ECG (leads II and V-6); and heart rate were measured and recorded continuously from before induction until the end of the third hour in the ICU. End tidal gases were monitored continuously from induction until the end of surgery, and blood was drawn intermittently as necessary for determination of blood gas tensions.

Duplicate thermodilution cardiac outputs were measured and recorded, systemic vascular resistance was calculated (pump flow was used for this calculation during cardiopulmonary bypass), and arterial blood samples were drawn for the determination of plasma catecholamines at the following times: 1) just prior to induction of anesthesia; 2) 1–2 min after tracheal intubation; 3) 1–2 min after incision; 4) 1–5 min post-sternotomy (at peak blood pressure increase); 5) 15 min after start of cardiopulmonary bypass; 6) just before removal of aortic cross-clamp; 7) 2 min post-removal of aortic cross-clamp; 8) just prior to discontinuing cardiopulmonary bypass; 9) 15 min after discontinuing CPB; 10) during placement of sternal wires; 11) upon arrival in the ICU; 12) after 1 h in the ICU; 13) after 2 h, and 14) after 3 h.

Plasma catecholamines were determined by a previously described<sup>29</sup> and verified<sup>30</sup> high-performance liquid chromatography method.

Doses of diazepam necessary prior to induction; doses of sufentanil given pre-intubation, pre-incision, pre-bypass, and for the entire case; and incidence of use of isoflurane in the pre-, intra-, and post-pump periods were noted. Records were also kept of the amount of fluid administered and of the doses required of nitroprusside and other vasoactive drugs. The incidence of shivering in the ICU, and the times from the end of operation until the patients would respond to and carry out simple verbal commands, and until they were extubated, were noted and recorded. Criteria for extubation were those in standard use in the surgical ICU and consist briefly of the following: stable hemodynamics, no evidence of bleeding, and maintenance of satisfactory arterial blood gases for 1 h while inspiring 40% oxygen by t-tube.

Results are reported as mean values  $\pm$  standard error of the mean. Plasma norepinephrine (NE) and epinephrine (EPI) levels were normalized through log conversion prior to statistical testing. Intergroup comparison of demographics, drug doses, fluids, times, hemodynamic variables, and catecholamines were made by

TABLE 1. Mean Values  $\pm$  SEM

	Control Patients	Clonidine Patients
Age (yr)	65 $\pm$ 2	58 $\pm$ 3
Sex (m/f)	7/3	8/2
Weight (kg)	74 $\pm$ 3	80 $\pm$ 6
BSA (meters <sup>2</sup> )	1.8 $\pm$ 0.04	1.9 $\pm$ 0.09
Blood pressure		
At pre-op visit (sys/dias)	132 $\pm$ 4/73 $\pm$ 3	124 $\pm$ 4/71 $\pm$ 2
At Swan-Ganz catheter Insertion (mean)	107 $\pm$ 5	98 $\pm$ 5
Number of patients who received internal mammary graft	7	10
Number of patients on chronic medications		
Beta-adrenergic antagonists	4	3
Ca <sup>++</sup> channel blocking agents	7	8

means of Student's *t* test for unpaired data. Incidence of shivering and isoflurane use was compared by the Fisher exact probability test. Statistical comparisons within groups were tested using analysis of variance for repeated measures followed by the Bonferroni inequality correction for *t* test. A value of *P* < 0.05 was used as the criterion for statistical significance.

## Results

The mean doses of clonidine given to the treated patients were the following: 3.42  $\pm$  0.21  $\mu$ g/kg as pre-medication, and 3.11  $\pm$  0.4  $\mu$ g/kg just prior to cardiopulmonary bypass.

## DEMOGRAPHICS

There were no significant intergroup differences in patients' ages, weights, sex, body surface area, or in the number of saphenous vein or internal mammary artery grafts performed (table 1). Although six control patients, as opposed to two patients in the clonidine group, stated that they had been hypertensive at some time in the past, no differences in blood pressure were found between the two groups at the time of the preoperative visit by the anesthesiologist or at the time of insertion of the pulmonary artery catheter the evening before surgery. Similar numbers in each group were receiving chronic therapy with beta-adrenergic antagonists and/or calcium channel blocking agents.

Times from the start of induction until intubation (11  $\pm$  0.2 min for all patients), until incision (42  $\pm$  2 min), and until the institution of cardiopulmonary bypass

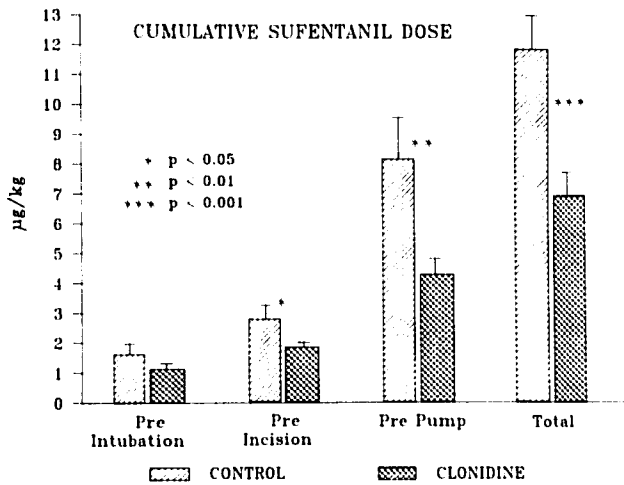


FIG. 1. Mean cumulative sufentanil doses are shown for the periods prior to intubation, prior to incision, prior to cardiopulmonary bypass, and for the entire anesthetic period.

(136 ± 11 min) did not differ between groups, nor did total surgery time (6.06 ± 0.2 h). Amounts of fluids and blood products administered before, during, and after the cardiopulmonary bypass did not differ significantly between groups.

ANESTHETIC DRUG DOSES

The sedative effect of clonidine was obvious when compared to the control group ( $P < 0.01$ ), as eight out of the ten patients in the clonidine group were noticeably sleepy upon arrival in the operating area, remained calm during placement of intravascular catheters, and, therefore, did not require the addition of diazepam. The other two patients in the clonidine group each re-

ceived 5 mg of diazepam intravenously; therefore, the mean dose for the group was  $1 \pm 0.7$  mg. This was in distinct contrast to the control patients, nine out of ten of whom arrived wide awake, and were sufficiently anxious so that they required immediate additional sedation. The mean dose of diazepam given to the control patients was  $8 \pm 2$  mg ( $P < 0.01$ ).

Sufentanil doses are shown in figure 1. Patients who had received clonidine required less sufentanil at all time periods than did the control patients: pre-intubation  $1.2 \pm 0.2$  µg/kg versus  $1.7 \pm 0.3$  µg/kg (NS); pre-incision  $1.9 \pm 0.2$  µg/kg versus  $2.8 \pm 0.4$  µg/kg ( $P < 0.05$ ); pre-cardiopulmonary bypass  $4.3 \pm 0.5$  µg/kg versus  $8.2 \pm 0.4$  µg/kg ( $P < 0.01$ ). The total doses of sufentanil were  $7.0 \pm 0.8$  µg/kg versus  $11.9 \pm 1.1$  µg/kg ( $P < 0.001$ ) for the treated and control groups, respectively. In five control patients, persistent hypertension during the pre-bypass period, even after the administration of 15 µg/kg sufentanil, necessitated the addition of isoflurane, whereas no patients in the clonidine group required this inhalation agent before bypass ( $P < 0.05$ ). During cardiopulmonary bypass, isoflurane was given to six and four patients in the control and clonidine groups, respectively (N.S.); after bypass, four control and no clonidine-treated patients received isoflurane ( $P < 0.05$ ).

POSTOPERATIVE COURSE

The time from the end of surgery until the patients were responsive to verbal command was the same in the two groups, but patients who had received clonidine could be extubated significantly sooner (fig. 2). During the period of observation in the intensive care unit, shivering occurred in seven control patients and in two patients in the clonidine-group ( $P < 0.05$ ) (fig. 2), although core temperature upon admission to the ICU was not different ( $36.3 \pm 0.3^\circ\text{C}$  for controls and  $36.2 \pm 0.4^\circ\text{C}$  for the clonidine group).

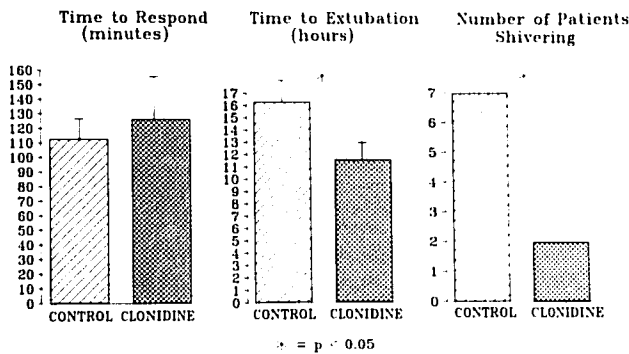


FIG. 2. This figure illustrates the mean times from the end of operation until the patients responded to commands (left side), and until they were extubated (center). In addition, the number of patients in each group who shivered postoperatively is shown (right side).

VASOACTIVE DRUGS

No patient in either group received positive inotropic drugs before or after cardiopulmonary bypass. Small doses of phenylephrine for support of blood pressure in the pre-bypass period were given to one control patient (total dose 100 µg) and to one patient in the clonidine group (170 µg). This agent was again employed in eight control and nine clonidine-treated patients during bypass in the rewarming period; mean doses were  $738 \pm 274$  µg and  $610 \pm 252$  µg, respectively (N.S.).

In the pre-incision period, atropine was administered to four patients in the clonidine group for control of bradycardia. All four of these patients were on chronic

therapy with diltiazem, and had received it at the time of premedication. Two patients had also received propranolol. A total dose of 1.2 mg atropine was given to one patient; the other three received 0.4 mg each. In one of the latter patients, a heart rate of 45 bpm was accompanied by a mean arterial pressure of 57 mmHg, which recovered to 75 mmHg as the heart rate rose. The other patients were not hypotensive when they received atropine. No patients in the control group required atropine, although the same number were receiving chronic medication (table 1).

There was no significant difference between groups in the amount of nifedipine given in the post-bypass or ICU periods. Intraoperatively, no sodium nitroprusside was required in either group before or after cardiopulmonary bypass. Only small amounts of sodium nitroprusside (mean dose for all patients  $144 \pm 108 \mu\text{g}$  total) were required during cardiopulmonary bypass, with no difference between groups. Postoperatively, four patients in the clonidine group received a mean dose of  $85 \pm 24 \mu\text{g}/\text{kg}$  nitroprusside, and none of these required it beyond the third hour in the ICU. Three control patients received a mean dose of  $85 \pm 37 \mu\text{g}/\text{kg}$  during the first 3 h. Two additional control patients required very large doses of nitroprusside over a longer time period: 8.2 mg/kg over 33 h, and 1.8 mg/kg over 38 h.

### HEMODYNAMICS

Patients in the control group had significantly higher mean arterial blood pressures and heart rates upon arrival in the operating suite than patients who had received clonidine. The control group values remained higher even after the administration of diazepam (fig. 3). During anesthetic induction, there was a greater fall in blood pressure in the control patients ( $P < 0.05$ ); hence, post-intubation blood pressures were the same in the two groups. However, skin incision and sternotomy caused blood pressure to rise to significantly higher levels in controls than in patients treated with clonidine, in spite of attempts to control this according to the study protocol. During and after cardiopulmonary bypass, mean blood pressure was the same in both groups until the third hour postoperatively, when it was again higher in control patients. The nearly identical blood pressure values reflect simply how well this parameter was controlled by sufentanil, isoflurane, and/or nitroprusside according to the study protocol (see Methods). In spite of atropine (see above), relative bradycardia in the patients receiving clonidine persisted until after sternotomy, but there were no clinically significant intergroup differences in mean heart rate after that time.

Both the stimulus of sternotomy and that secondary to insertion of sternal wires during chest closure caused

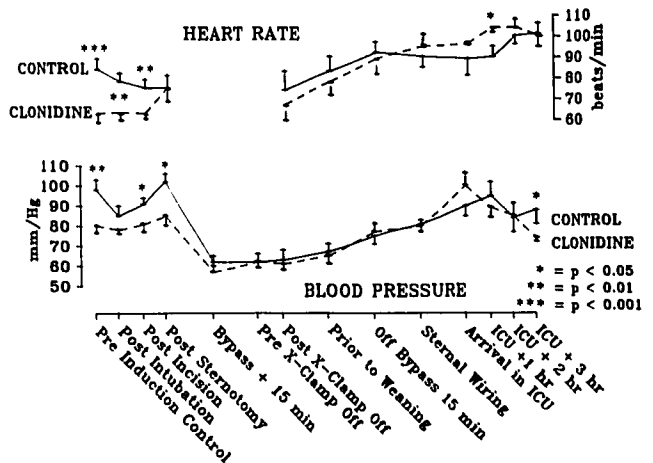


FIG. 3. The mean values ( $\pm$ SEM) for heart rate (right ordinate) and for mean arterial blood pressure (left ordinate) are shown for the two groups at the sampling periods indicated on the abscissa. In this and the following slides, the control group is represented by the solid line and the clonidine group by the dashed line. At most points prior to cardiopulmonary bypass, both mean blood pressure and heart rate were greater in control patients than in those who received clonidine.

a marked rise in systemic vascular resistance in the control patients, but not in those who had received clonidine (fig. 4). After chest closure, there was a trend toward a lower mean systemic vascular resistance in the clonidine-treated group throughout the rest of the study period.

Cardiac outputs (fig. 4) were not statistically significantly different until the time of chest closure. However, from this point on and throughout the ICU pe-

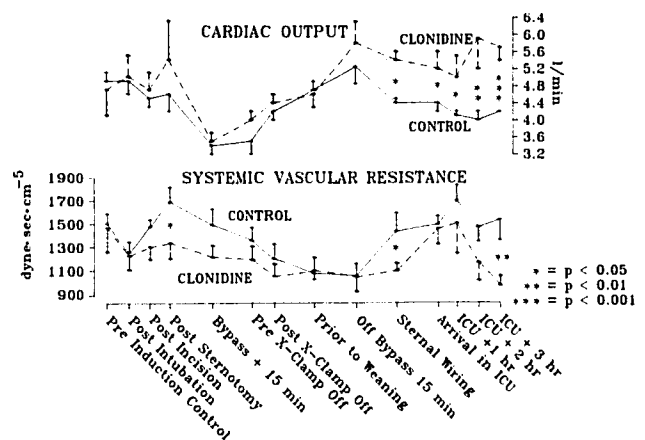


FIG. 4. Mean values for cardiac output (right ordinate) and calculated systemic vascular resistance (left ordinate) are shown for the two groups. Post-bypass, cardiac output was consistently higher in the clonidine group. Systemic resistance was significantly greater in control patients at the stressful times of sternotomy and sternal wiring, and again at the end of the third hour in the ICU.

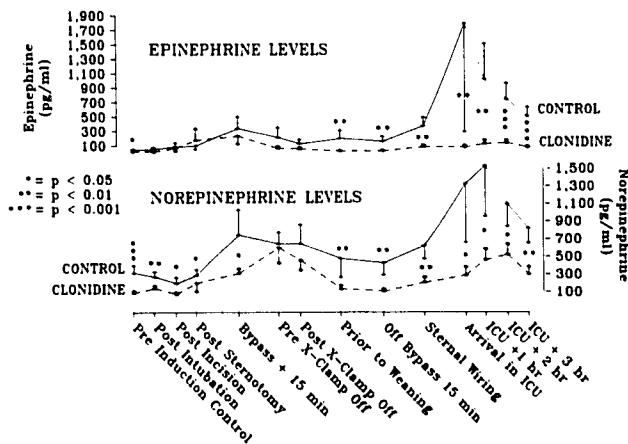


FIG. 5. Mean values for plasma epinephrine (left ordinate) and norepinephrine (right ordinate) in the two groups of patients. At most sampling times, these were significantly lower in the clonidine group.

riod, cardiac outputs were significantly higher in patients who had received clonidine.

#### PLASMA CATECHOLAMINES

Prior to induction, mean NE and EPI levels were higher in the control group than in patients who had received clonidine (fig. 5), and NE remained lower in the clonidine group until after the start of cardiopulmonary bypass. Although both catecholamines had risen in both groups after 15 min on bypass, NE was still significantly higher in the control group. This intergroup difference disappeared after aortic cross clamping. However, except for the times just before and just after removal of the aortic cross clamp, both NE and EPI remained consistently higher, throughout cardiopulmonary bypass and afterwards, in the control than in the clonidine group (fig. 5).

#### Discussion

In a recent study, Slogoff and Keats<sup>31</sup> noted that there was a strong relationship of both perioperative myocardial ischemia and postoperative myocardial infarction with anesthetic and surgical events known to produce intense sympathetic stimulation, with or without hemodynamic abnormalities. Thus, it is logical to look for methods to reduce sympathetic stimulation *per se*. In this investigation, clonidine was used to attenuate sympathetic activity in patients with good left ventricular function during and after coronary bypass surgery. Although the number of patients studied was small, significant intergroup differences were found in plasma catecholamine levels, in hemodynamic function, in requirements for sedative, narcotic, and anesthetic drugs, and in time to extubation.

The principal limitation of the study design is its non-blinded nature. However, the objective quantitative hemodynamic criteria for the administration of sufentanil, isoflurane, and nitroprusside were formulated with this deficiency in mind. An exception to this objectivity was the determination of the dose of diazepam in the pre-induction period, which was done subjectively according to the best judgment of the anesthesiologists. In fact, there was an obvious difference in the preoperative state of sedation of the two sets of patients. In addition, if bias had occurred at this point, the patients pretreated with clonidine would have received a lower dose of diazepam, *i.e.*, would have been relatively underdosed. This would have made the possibility of hemodynamic breakthrough in the prebypass period more likely in the clonidine than in the control group. In fact, the opposite occurred.

No anesthetic technique or pharmacological intervention examined thus far has been shown to be capable of significantly reducing the incidence of hypertension, tachycardia, and elevated plasma catecholamines associated with coronary artery surgery without resulting in undesirable effects. Fentanyl, used in moderate doses, did not always prevent hemodynamic breakthrough and myocardial ischemia with painful stimuli, such as sternotomy,<sup>8,9,14</sup> higher doses of narcotics were ineffective in preventing hyperdynamic, adrenergic, and hypermetabolic consequences during or after cardiopulmonary bypass,<sup>4,11,32</sup> and resulted in prolonged postoperative respiratory depression.<sup>15,16</sup>

The plasma levels of epinephrine reached during cardiopulmonary bypass<sup>10-12</sup> (and postoperatively, as demonstrated by this study) are comparable to those seen in acute myocardial infarction,<sup>33</sup> and the norepinephrine response is comparable to that of strenuous exercise.<sup>34</sup> In the present investigation, as in those reported previously by others, peak intraoperative plasma concentrations of NE and EPI occurred at the time of removal of the aortic cross-clamp. This is a critical period for the heart; the sudden reperfusion of an ischemic myocardium, depleted of energy stores, with blood rich in catecholamines is potentially harmful.<sup>10,35,36</sup>

Clonidine is a centrally acting antihypertensive agent which modulates final efferent activity in sympathetic vasomotor neurones, allowing the preservation of sympathetically mediated reflex control of blood pressure.<sup>37</sup> The hemodynamic consequences of this central action are somewhat dependent on the level of pre-existing sympathetic tone, but generally are manifested by a decreased heart rate, cardiac output, and systemic vascular resistance, leading to a "balanced" reduction in blood pressure. Blood flow to vital organs is maintained.<sup>28</sup> Although there are some peripheral effects of clonidine, its predominant action is central.

Rebound phenomena, or untoward hemodynamic events after the sudden withdrawal of chronic clonidine therapy, occur only after 6–30 days of clonidine treatment,<sup>38</sup> a period considerably longer than that of this study.

Inhibition of adrenergic transmitter release differs from competitive beta-adrenergic antagonism because it reduces both alpha- and beta-adrenergic activity in concert. This may be the reason for the reported efficacy of clonidine in preventing sympathetically induced genesis and aggravation of post-stenotic myocardial ischemia,<sup>20</sup> in the treatment of chronic angina pectoris,<sup>39</sup> and in relieving pain in acute myocardial infarction.<sup>40</sup> The increase in vagal tone by clonidine and the associated reduction in heart rate increase diastolic perfusion and favorably affect myocardial oxygen supply-demand ratio.

These same pharmacological characteristics may also result in undesirable effects. We observed bradycardia in four of the clonidine-treated patients during the preincision period when stimulation was absent. This parasympathetic overactivity was easily corrected by atropine. However, in patients in whom sympathetic activity is essential for maintenance of circulatory function (e.g., congestive heart failure, valvular disease), withdrawal of central sympathetic output by clonidine may be deleterious.

If it had been possible to individually titrate clonidine by intravenous administration, such situations as bradycardia might have been avoided. Parenteral clonidine, which would have eliminated problems of bioavailability, is not available in this country. However, we decided to do this study with oral clonidine because the drug has been reported to be rapidly and almost completely absorbed after oral administration in normal volunteers (bioavailability of over 80%), with peak plasma levels occurring in 60–90 min,<sup>41</sup> and with an elimination half-life of approximately 12 h. However, we do not know the magnitude and time course of plasma clonidine levels in our patients as we were not able to measure them. Efficiency of absorption and resulting blood levels after the second dose of clonidine, given before cardiopulmonary bypass and hypothermia, may have been erratic. Thus, knowledge of clonidine blood levels would have been especially informative, and it was during bypass, and in the post-bypass and postoperative periods, when more exact dosing (or titration) might have provided better control of sympathetically mediated hemodynamic functions (figs. 3–5).

The importance of the immediate postoperative period as an additional time of stress has been emphasized previously by others.<sup>3,6,13</sup> In the present study, this is evident in the postoperative elevation of plasma catecholamines levels in the control patients and in their

attenuation by clonidine pre-treatment. Walsh *et al.*<sup>16</sup> have noted that even the continued administration of fentanyl, for 12–18 h after surgery, failed to prevent postoperative endocrine and metabolic effects. Recently, however, Glass *et al.*<sup>††</sup> have demonstrated the beneficial effect of stress reduction by postoperative epidural analgesia.

Ghignone *et al.*<sup>27</sup> studied the effect of clonidine on fentanyl requirement during the induction and intubation periods in patients anesthetized for coronary artery bypass surgery. They found that the clonidine decreased fentanyl requirements by 45%, a figure comparable to the 40% reduction of sufentanil dose that we found. However, these investigators used an EEG endpoint for narcotic dosing, as compared to the hemodynamic parameters utilized in this study. In spite of this difference in endpoint, and the different opioid analgesic used, the magnitude of the narcotic "saving" by clonidine was similar.

In the present investigation, the significant reduction in frequency of administration and of dose requirement of diazepam in the clonidine group may be attributed to both the sedative and anxiolytic effects<sup>‡‡</sup> of clonidine; however, because of the limitation of the study design, no distinction could be made between these effects. The reduction in dosage of sufentanil, primarily (fig. 1), and possibly that of diazepam, could account for the shorter time to extubation (fig 2).

Acute clonidine administration has been shown to reduce halothane anesthetic requirement in dogs by as much as 50%, and this effect was reversible by tolazoline, an alpha adrenergic antagonist.<sup>24</sup> In this study, clonidine reduced the required dose of the narcotic. This suggests that clonidine's ability to reduce anesthetic requirement is not specific to either the halogenated or narcotic anesthetics and involves an adrenergic receptor. Clonidine itself has been shown to have analgesic properties in animal models<sup>42,43</sup> and in humans.<sup>44</sup> It is unlikely, however, that the reduction in anesthetic requirement is solely through this mechanism, as higher doses of clonidine than those used here are generally required to demonstrate its analgesic properties.

Other interactions between preferential alpha<sub>2</sub>-adrenergic agonists and the opiate system have been noted. Clonidine has been reported effective in stabilizing the untoward autonomic effects during opiate withdrawal<sup>28</sup> and during administration of naloxone.<sup>26</sup> Conversely, the antihypertensive actions of clonidine have

†† Glass DD: personal communication

‡‡ Kruse H, Dunn RW, Theurer KL, Novick WJ, Shearman GT: Attenuation of conflict-induced suppression by clonidine: Indication of anxiolytic activity. *Drug Development Research* 1:137–143, 1981

been reported to be reversed by naloxone.<sup>26</sup> In addition, release of immunoreactive beta-endorphin by clonidine has been demonstrated, suggesting that central alpha-adrenergic stimulation involves the release of beta-endorphin-like material from the brain.<sup>45</sup>

In spite of control measures prescribed by the study protocol, blood pressures were higher in the control than in the clonidine group in the period prior to cardiopulmonary bypass. After this time, there were no longer any intergroup differences in pressure. However, in order to achieve this, more sufentanil was given to the control patients, and the incidence of isoflurane use intraoperatively was greater than in the clonidine group. In the ICU period, when anesthetic agents were no longer used to control blood pressure, two patients in the control group, neither with a preoperative history of hypertension, required extremely high doses of nitroprusside.

Clonidine-treated patients were found to shiver significantly less often when compared to the control group. Although the cause of the lower incidence of shivering in the clonidine patients is unclear, central adrenergic receptors are known to be involved in temperature regulation. For example, it is known that, in virtually all species, the central administration of norepinephrine brings about a fall in core temperature, unaccompanied by shivering, *via* an increase in cutaneous blood flow and a reduction in heat production by a lowering of basal metabolism.<sup>46</sup> Perhaps the central alpha<sub>2</sub>-adrenergic effects of clonidine are similar to those of the neurotransmitter. As catecholamines do not cross the blood brain barrier, the increased plasma concentrations in the control patients were irrelevant in this regard.

In a study of patients who experienced hypertension following myocardial revascularization surgery, Fouad *et al.*<sup>47</sup> reported that the hemodynamic pattern was that of an increased systemic vascular resistance accompanied by increased plasma catecholamines, a finding confirmed by others.<sup>6,13</sup> In the present study, we saw the same pattern in the control patients. In this group, the higher systemic vascular resistance, once again associated with significantly more evidence of hyperadrenergic function, apparently hampered cardiac performance. Mean cardiac output in this control group was significantly less than the mean in the clonidine-treated patients (fig. 4).

In summary, clonidine, given prior to and during coronary artery surgery, decreased anesthetic drug requirements and improved the hemodynamic status. This was achieved by marked attenuation of undesirable hyperdynamic, adrenergic events intraoperatively, which resulted in more favorable hemodynamics, lower plasma catecholamines, and higher cardiac outputs. In

the postoperative period, patients who received clonidine were extubated sooner, shivered less, and again exhibited lower sympathetic tone, and higher cardiac outputs. Control of the adrenergic nervous system with clonidine seemed to provide important anesthetic advantages for these patients with ischemic heart disease, with a low incidence of easily treatable hypotension or bradycardia.

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