Cardiac Baroreflex during the Postoperative Period in Patients with Hypertension

Effect of Clonidine

Joel L. Parlow, M.D., F.R.C.P.C.,* Gérard Bégou, M.D.,† Pierre Sagnard, M.D.,† Jean Marie Cottet-Emard, Ph.D.,‡ Jean Claude Levron, Ph.D.,§ Guy Annat, M.D., Ph.D.,|| François Bonnet, M.D.,# Marco Ghignone, M.D., F.R.C.P.C.,** Richard Hughson, Ph.D.,|| Jean-Paul Viale, M.D., Ph.D.,†† Luc Quentin, M.D., Ph.D.‡‡

Background: Patients with essential hypertension show altered baroreflex control of heart rate, and during the perioperative period they demonstrate increased circulatory instability. Clonidine has been shown to reduce perioperative circulatory instability. This study documents changes in measures of heart rate control after surgery in patients with essential hypertension and determines the effects of clonidine on postoperative heart rate control in these patients.

Methods: Using a randomized double-blind placebo-controlled design, 20 patients with essential hypertension (systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg for ≥1 yr) were assigned to receive clonidine (or placebo), 6 μg/kg orally 120 min before anesthesia and 3 μg/kg intravenously over 60 min before the end of surgery. The spontaneous baroreflex (“sequence”) technique and analysis of heart rate variability were used to quantify control of heart rate at baseline, before induction of anesthesia, and 1 and 3 h postoperatively.

Results: Baroreflex slope and heart rate variability were reduced postoperatively in patients given placebo but not those given clonidine. Clonidine resulted in greater postoperative baroreflex slope and power at all frequency ranges compared with placebo (4.9 ± 2.9 vs. 2.2 ± 2.1 ms/mmHg for baroreflex slope, 354 ± 685 vs. 30 ± 37 ms²/Hz for high frequency variability). Clonidine also resulted in lower concentrations of catecholamine, decreased mean heart rate and blood pressure, and decreased perioperative tachycardia and hypertension.

Conclusions: Patients with hypertension exhibit reduced heart rate control during the recovery period after elective surgery. Clonidine prevents this reduction in heart rate control. This may represent a basis for the improved circulatory stability seen with perioperative administration of clonidine. (Key words: α₂ Agonists; anesthesia; emergence; heart rate; hypertension; surgery; variability.)

PATIENTS with preexisting hypertension appear to be at increased risk of perioperative circulatory instability.¹ ² This may be related in part to a baseline alteration of the control of heart rate mediated by the autonomic nervous system compared with normotensive individuals. This is reflected by decreased sensitivity of the arterial baroreceptor–heart rate reflex, i.e., the cardiac baroreflex, and reduced cyclic change of heart rate over time, i.e., heart rate variability.³ ⁵ During the period after surgery, sensitivity of the cardiac baroreflex is blunted only transiently in healthy patients after minor procedures.⁶ By contrast, cardiac baroreflex sensitivity has not previously

* Anesthetist, Department of Anesthesia, Queen’s University.
† Anesthetist, Department of Anesthesia, Hôpital Edouard Herriot.
‡ Assistant Professor, Department of Physiology, School of Medicine.
§ Head, Pharmacokinetics, Janssen, France.
|| Professor of Physiology, Department of Physiology, School of Medicine.
# Professor of Anesthesia, Department of Pharmacology, School of Medicine.
** Anesthetist, Department of Physiology, School of Medicine.
†† Professor of Anesthesia, Department of Anesthesia, Hôpital Edouard Herriot.
‡‡ Department of Physiology, School of Medicine, and Department of Anesthesia, CHU Nord, St Etienne, Lyon, France.

Received from the Department of Anesthesia, Queen’s University, Kingston, Ontario, Canada; the Department of Anesthesia, Hôpital Edouard Herriot, Lyon, France; and the Department of Physiology, School of Medicine, Lyon, France. Submitted for publication November 3, 1997. Accepted for publication November 10, 1998. Supported in part by Fondation de France, INSERM CN 91 48, MEBR 1896,CNRS 5578, and the Janssen Fellowship of the Canadian Anesthetists’ Society, Glaxo-Wellcome, Roche.

Address reprint requests to Dr. Quentin, Physiology, School of Medicine, 69375 Lyon 08, France. Address electronic mail to: quentin@univ-lyon1.fr

Anesthesiology, V 90, No 3, Mar 1999
Table 1. Perioperative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>P Value</th>
<th>Clonidine (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>73 ± 16</td>
<td>ns</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67 ± 11</td>
<td>ns</td>
<td>67 ± 5</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>8 ± 7</td>
<td>ns</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>Maximum systolic blood pressure (mmHg)</td>
<td>204 ± 17</td>
<td>ns</td>
<td>204 ± 26</td>
</tr>
<tr>
<td>Ward systolic blood pressure (mmHg)</td>
<td>161 ± 24</td>
<td>ns</td>
<td>153 ± 15</td>
</tr>
<tr>
<td>Ward diastolic blood pressure (mmHg)</td>
<td>91 ± 9</td>
<td>ns</td>
<td>86 ± 12</td>
</tr>
<tr>
<td>Ward heart rate (bpm)</td>
<td>81 ± 8</td>
<td>ns</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Procedure (intestinal/orthopedic)</td>
<td>7 ± 3</td>
<td>ns</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>214 ± 52</td>
<td></td>
<td>181 ± 63</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>173 ± 44</td>
<td></td>
<td>148 ± 70</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>37 ± 35</td>
<td></td>
<td>46 ± 34</td>
</tr>
<tr>
<td>Net perioperative fluid balance (ml)</td>
<td>+800</td>
<td></td>
<td>-525</td>
</tr>
<tr>
<td>Postoperative respiratory rate (min⁻¹) : R1/R3</td>
<td>16 ± 4/15/4</td>
<td>ns</td>
<td>15 ± 3/16 ± 3</td>
</tr>
<tr>
<td>Postoperative Pco₂ (mmHg):R1/R3</td>
<td>23 ± 12</td>
<td>ns</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Nicardipine requirements postoperatively (mg)</td>
<td>5.8 ± 6.5 (n = 6)</td>
<td>0.04</td>
<td>0.3 ± 0.8 (n = 1)</td>
</tr>
</tbody>
</table>

Values are mean ± SD; Ward measurements represent the mean of three values taken after admission.

R1 = 1 h, R3 = 3 h following end of anesthesia.

been studied after more extensive surgery or in surgical patients with concomitant essential hypertension.

The α₂-adrenoceptor agonist clonidine has been shown to increase perioperative circulatory stability in patients with preexisting hypertension. The explanation for the improved circulatory stability has not been explored but may relate to the central inhibition of sympathetic nervous system influence on the heart and vasculature. In addition, an enhancement of parasympathetic control of heart rate after administration of clonidine has been shown indirectly. Clonidine also has been shown to increase cardiac baroreflex sensitivity in hypertensive individuals and thus may act by enhancing the role of heart rate changes in stabilizing blood pressure. The current study was designed to test the hypotheses that, in a group of patients with essential hypertension, (1) the sensitivity of the cardiac baroreflex is reduced postoperatively compared with preoperative measurements, and (2) perioperative administration of clonidine prevents this postoperative reduction in cardiac baroreflex sensitivity. The techniques of spontaneous baroreflex analysis (‘sequence’ technique) and power spectral analysis of the interval between each successive pair of R waves on the electrocardiogram were used to quantify changes in heart rate control.

Materials and Methods

Patient Population and Research Design

A randomized double-blind placebo-controlled prospective study design was used. After the Ethics Committee of the Hospices Civils de Lyon approved the study and written informed consent was obtained, 20 patients > 50 yr old who were scheduled for elective intestinal or orthopedic surgery (table 1) expected to last a minimum of 2 h were included. All patients had a diagnosis of essential hypertension for > 1 yr as defined by a systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure > 95 mmHg on at least three occasions over the previous year. All patients were treated chronically for hypertension by their usual physicians. Patients were excluded if they had a history of diabetes mellitus, autonomic dysfunction, stroke, congestive heart failure, or cardiac rhythm other than sinus. Patients receiving β-blockers or centrally acting antihypertensive agents (clonidine, methyl dopa, rilmeline) had these medications discontinued gradually, and they were replaced with nifedipine during the week before surgery. Thus, no patients received such medications within 48 h of surgery. Other medications, including nifedipine, were continued to the morning of surgery. Patients were randomized by the hospital pharmacy to receive either clonidine (Boehringer-Ingelheim) or an identical placebo drug (saline or inert tablet) in a double-blind manner, with the randomization code held by the pharmacist until the end of the study. Patients received clonidine 6 μg/kg (or placebo) orally 120 min before induction of anesthesia and 3 μg/kg (or placebo) as an intravenous infusion over the final hour of surgery. This regimen has been shown in previous work to maintain stable concentrations of clonidine reliably during the first three postoperative hours and takes into...
account a terminal elimination half-life of clonidine of 20-25 h.17

Anesthetic Protocol

For consistency, all anesthetic and fluid management was performed by two anesthetists according to a prescribed protocol. Central venous and intraarterial pressures, electrocardiogram, respiratory rate, oxygen saturation, and nasopharyngeal temperature were monitored perioperatively. End-tidal carbon dioxide tension (Capnomac, Datex, Helsinki, Finland) was monitored while patients were intubated. Two intravenous catheters were inserted for lactated Ringer's infusion. After having preoperative intravenous fluids commencing the night before surgery (20 ml/kg over 12 h), a preinduction bolus dose of 15 ml/kg was given over 30-45 min. The anesthetic protocol has been detailed previously.9 Anesthesia was induced with midazolam 75 μg/kg, alfentanil 20 μg/kg, and lidocaine 1.5 mg/kg. Atracurium 500 μg/kg was given for muscle relaxation. Anesthesia was maintained with nitrous oxide 70% in oxygen adjusted to maintain oxygen saturation > 95%, isoflurane titrated to blood pressure goals, and infusion of atracurium 500 μg·kg⁻¹·h⁻¹ and alfentanil 0.25 μg·kg⁻¹·min⁻¹ until wound closure was commenced. Maintenance fluid requirements and evaporative and blood losses were replaced with appropriate volumes of lactated Ringer's solution or packed erythrocytes to maintain hemoglobin of ≥100 g/l. Patients were mechanically ventilated to an end-tidal carbon dioxide tension of 35 mmHg. Temperature was maintained at > 36°C using a fluid warmer and a warming mattress and blanket.

Heart rate and blood pressure were continuously monitored throughout the perioperatve period by a dedicated observer involved only in administering the study protocol. All episodes of circulatory derangements lasting longer than 2 min were identified, and the number and total duration were recorded intraoperatively and postoperatively. Circulatory derangements were defined and treated according to the following protocol. Hypertension (defined as SBP > 170 mmHg) was treated with isoflurane (0.25% increments) twice at 1-min intervals if required up to 2%. Tachycardia (defined as heart rate > 90 beats/min) was treated with bolus doses of alfentanil 0.5 mg, to be repeated twice if necessary at 2-min intervals, then by increasing the rate of alfentanil infusion to 0.5 μg·kg⁻¹·min⁻¹ if needed. Hypotension (defined as SBP < 90 mmHg) was treated by reducing the concentration of isoflurane and head down tilt followed by 250-ml bolus doses of lactated Ringer's solution over 5 min followed by phenylephrine 100 μg if the patient was unresponsive. Bradycardia (defined as heart rate < 40 beats/min associated with hypotension) was treated with atropine 1 mg repeated once if necessary. At skin closure, morphine 150 μg/kg was administered subcutaneously. Neuromuscular function was allowed to recover spontaneously, and patients were extubated in the recovery area when awake and able to maintain a 5-s head lift and adequate oxygen saturation and end-tidal carbon dioxide. Postoperatively, analgesia was provided with propacetamol 2 g and ketoprofen 200 mg both given intravenously. Morphine was administered according to patient request or obvious discomfort. Circulatory derangements were treated per the intraoperative protocol except that hypertension was treated with infusion of nicardipine and tachycardia with additional morphine or fluid bolus infusions as appropriate. Fluids were administered to maintain central venous pressure at baseline values in a semirecumbent position during spontaneous ventilation and to ensure a diuresis of ≥1 ml·kg⁻¹·h⁻¹.

Data Collection

In addition to monitoring for hemodynamic derangements, data were collected for subsequent analysis of baroreflex and heart rate variability parameters at four intervals: baseline on the day before surgery, 90 min after administration of the study drug before induction of anesthesia, and 1 (R1) and 5 (R5) h after the end of anesthesia (defined as the time of withdrawal of nitrous oxide) during spontaneous ventilation. At each study interval on the day of surgery, a 20-min recording of electrocardiogram (Physio Control VSM1, Redmond, WA) and radial arterial blood pressure waveforms were made onto magnetic tape (Store 4S; Racal Dana, Southampton, UK) after appropriate calibration. The electrocardiogram lead was selected to give the highest signal to noise ratio. To avoid an extra day of arterial cannulation, blood pressure recorded on the day before surgery was obtained noninvasively on a beat-by-beat basis using the Finapres 2300 (Ohmeda, Madison, WI). This apparatus has been shown to reliably track intravascular pressures during a variety of tests of autonomic function.18,19 All electrocardiogram and blood pressure signals were digitized off-line at a sampling rate of 1.000 Hz using a 12-bit analog-digital converter (DAS 16G; Metabyte, Taunton, MA). During digitization, the interval between each successive pair of R waves on the electrocardiogram (RR interval) was measured, as well as SBP and diastolic blood pressure. Digital files were thus
generated, each line consisting of values of SBP, diastolic blood pressure, and RR interval for every heartbeat. These files were used for the calculation of spontaneous baroreflex sensitivity and power spectral analysis of heart rate (see data analysis).

Venous blood samples were collected at each of the four study intervals in chilled syringes. Samples were centrifuged (+4°C, 3,000 rpm, 10 min) to allow immediate separation of plasma and stored at −80°C until the time of analysis. Concentrations of adrenaline and noradrenaline were obtained by high-performance liquid chromatography and clonidine and alfentanil by radioimmunoassay, according to methodology previously validated. Arterial blood gases were analyzed at the R1 and R3 postoperative study periods.

**Data Analysis**

The primary end points of the study were cardiac baroreflex sensitivity and RR interval power. The technique of spontaneous baroreflex analysis was used to calculate sensitivity of the cardiac baroreflex during spontaneous fluctuations of blood pressure and heart rate. The computer software examined each 20-min data recording to select all sequences of three or more successive heartbeats in which there were concordant increases or decreases in SBP and RR interval. A linear regression was applied to each of the sequences, and an average regression slope was calculated for the sequences detected during each recording period. The slope of this regression (expressed as ms/mmHg) represents the mean cardiac baroreflex sensitivity for that time period and has been shown to reflect values obtained at the resting blood pressure using the vasoactive drug method.

Details of the method of spectral analysis of RR interval variability have been published previously. From each study period, an artifact-free stationary time series of 512 consecutive RR intervals (representing ~8-10 min) was selected. A fast Fourier transformation was applied to the tachogram to calculate the amplitude of variations of RR intervals as a function of frequency (power spectral analysis: RR interval power [units of ms²/Hz] as a function of frequency [Hz]). The RR interval power is calculated as the integration of the area under the curve over any given frequency range and represents an index of the frequency-specific degree of RR interval variability. Spectral power was calculated over the total frequency range (0.00–0.50 Hz), as well as the low (0.00–0.15 Hz) and high (0.15–0.50 Hz) frequency ranges.

**Statistical Analysis**

Demographic data and number and total duration of episodes of circulatory derangements and treatments were analyzed using Student’s t test or chi-square analysis as appropriate. Parametric data were analyzed using two-way repeated measures analysis of variance (ANOVA) with study period as the repeated variable and drug group as the nonrepeated variable. When significant (P < 0.05), Tukey’s test was performed post hoc for between-group comparison. Log transformation was used for non-normally distributed data before performing ANOVA. Data are presented as mean ± SD.

**Results**

**Perioperative Characteristics**

Ten patients were randomized to each group. One patient in the clonidine group exhibited persistent frequent ventricular extrasystoles at baseline and postoperatively, making heart rate variability data impossible to analyze; thus data from 9 patients receiving clonidine and 10 receiving placebo are presented. Patient demographics were similar between groups (table 1). In addition, there was no difference between groups in type of procedure, preoperative antihypertensive therapy, or coexisting coronary and respiratory disease. Concentrations of clonidine were stable throughout the perioperative period (fig. 1A). Postoperative concentrations of alfentanil in plasma were similar between the two groups (fig. 1B). Respiratory rate and arterial carbon dioxide tension were also similar between groups during the recovery period (table 1).

**Concentrations of Catecholamine and Circulatory Variables**

Within the placebo group, concentrations of norepinephrine and epinephrine increased significantly at time R1 (1 h postanesthesia, figs. 1C and 1D). These differences did not persist at time R3 (3 h postanesthesia). Conversely, no significant increase occurred at either time postoperatively in the clonidine group. On the day before surgery (baseline), blood pressure and mean RR interval were similar between groups. Clonidine resulted in significantly lower SBP and higher mean RR interval than placebo at all time periods (fig. 2). Clonidine also reduced the number or
mean duration of episodes of hypertension and tachycardia intraoperatively and postoperatively (table 2). The clonidine group required significantly less nicardipine postoperatively to manage hypertensive episodes (table 1). There was no difference in the incidence of hypotension intraoperatively or postoperatively, and there were no episodes of significant bradycardia requiring atropine in either group.

Control of Heart Rate and Blood Pressure

Figures 3 and 4 represent individual examples of raw hemodynamic and spectral data to contrast a patient given placebo with one given clonidine. The results of the analysis of the primary end points for all patients are illustrated in figure 5. Spontaneous baroreflex slope decreased postoperatively in patients given placebo (fig. 5A) but was preserved in the patients given clonidine. Similarly, a reduction in RR interval power occurred postoperatively in the patients given placebo, whereas power was preserved in the patients given clonidine (figs. 5B–D). The SD of RR interval was significantly greater in the clonidine group after surgery. Conversely, the SD of SBP was lower postoperatively at time R3 in the clonidine group (fig. 2).
Discussion

This study demonstrated a decrease in cardiac baroreflex slope and RR interval power during the early postoperative period in a group of patients with preexisting hypertension. Preoperative/intraoperative administration of clonidine resulted in a preservation of the slope of the cardiac baroreflex postoperatively. Moreover, compared with placebo, administration of clonidine led to (1) decreased SBP and heart rate postoperatively with decreased requirements for vasodilators; (2) increased SD of heart rate and reduced SD of blood pressure; and (3) decreased concentrations of catecholamine in plasma.

Methodology

Measurements. Baseline blood pressure measurements used in the calculation of baroreflex sensitivity were performed on the day before surgery. The noninvasive Finapres apparatus was used for these measures rather than intraarterial monitoring for practical and ethical reasons. However, Finapres has been shown to track trends in blood pressure reliably compared with intraarterial measurements during autonomic testing. Further, measurements were performed identically in both groups, suggesting a valid intergroup comparison.

Patients were monitored for number and duration of episodes of circulatory events, as secondary end points,
## Table 2. Adverse Hemodynamic Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Clonidine (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Total Number of Episodes</td>
</tr>
<tr>
<td>Intraoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data for duration reported as mean ± SD.

* Significant difference for number of episodes.
† Significant difference for duration.

using a dedicated observer rather than automated analysis of continuous recordings of heart rate and blood pressure. Although it is possible that not all episodes were identified, the double-blind randomized design and a higher requirement for postoperative antihypertensive treatment in the placebo group would support the validity of the differences noted between the groups. The clinical significance or relationship of these hemodynamic events to perioperative morbidity is beyond the scope of this study.

### Data Analysis

The spontaneous baroreflex method was used to calculate the sensitivity of the cardiac baroreflex by measuring the chronotropic responses to spontaneous blood pressure fluctuations. This method has been shown to yield a reliable index of parasympathetic responsiveness of the baroreflex within its resting operating range. As such, the spontaneous baroreflex method does not provide a "full range" analysis and thus does not track conditions of extreme parasympathetic recruitment during very large excursions in pressure as is seen using the vasoactive drug method.

Heart rate and blood pressure variability were determined using SD, which gives a measure of overall variability, as well as using power spectral analysis to study the variability of RR interval within defined frequency ranges. High-frequency power (0.15–0.50 Hz) is dominated by the influence of respiration and parasympathetic activity. More than the parasympathetic activity per se, high-frequency power reflects the reactivity of parasympathetic control of heart rate. Low-frequency power is influenced by multiple variables, including parasympathetic, sympathetic, and hormonal input on the heart. Thus, the postoperative reduction of high-frequency power and spontaneous baroreflex slope found in the patients receiving placebo indicate primarily a reduction in parasympathetic heart rate control.

Respiratory parameters are known to exert an influence on measures derived from power spectral analysis. As respiratory rate and arterial carbon dioxide tension were similar between groups during recovery, tidal volume could reasonably be assumed to be similar as well. Thus, the differences observed between groups postoperatively in spectral power (fig. 5) were likely not influenced by differences in respiratory pattern. In addition, postoperative respiratory rate was not significantly changed from baseline in either group, and arterial carbon dioxide tension was only slightly increased from normal values postoperatively, suggesting a minimal effect of postoperative changes in respiration on spectral measures. Finally, one patient from each group remained intubated during the R1 measurement period. It is possible that the presence of the endotracheal tube could have affected the hemodynamic responses in these two patients, although both patients appeared comfortable and were breathing spontaneously during the first postoperative hour.

The sample size of this study (n = 20) was chosen to detect a significant change in baroreflex sensitivity between groups. Several secondary end points were analyzed from the data collected such as episodes of tachycardia and hypertension (table 2). The small sample size may not yield sufficient power to interpret negative data relating to the secondary end points, and conclusions regarding these end points must be interpreted with caution.
Anesthesia. An anesthetic technique comprising mainly of short-acting agents was chosen to minimize the effects of residual drugs after surgery. Concentrations of alfentanil in plasma were similar between groups. Thus, residual effects of alfentanil do not likely explain the intergroup differences in heart rate control. Outside the anesthetic setting, an inverse relationship exists between the level of arousal and the sensitivity of the cardiac baroreflex, with mental relaxation resulting in increased sensitivity of the cardiac baroreflex. Within the current anesthetic setting, noncardiovascular inputs such as pain, environmental stimuli, or anxiety may lead to sympathetic activation, tachycardia, hypertension, and reduction of the cardiac baroreflex. By contrast, the current use of analgesic/sedative drugs for control of pain and tachycardia may reduce sympathetic activation and its effect on circulatory control. However, these agents could not be ethically omitted. In addition, clonidine possesses sedative/analgesic properties that act synergistically with opiates, and it reduces the tonic activity of the locus coeruleus on emergence from anesthesia. Thus, the peculiar sedative effect of clonidine or its opiate-sparing effect may lead to a more efficient filtering of noncardiovascular inputs on the baroreflex arc. Conversely, its effect on the vasomotor center on emergence from anesthesia may induce an effect intrinsic to the baroreflex arc (see improved circulatory stability with clonidine).
SURGERY, CARDIAC BAROREFLEX, AND CLONIDINE

A  Baseline

B  Recovery

PLACEBO

CLONIDINE

Fig. 4. Power spectral analysis of RR interval of the data shown in figure 3 at baseline (Bl; left) and 3 h postoperatively (R3; right). The patient given placebo (A and B) showed a profound postoperative reduction of power across low-frequency (0.00–0.15 Hz) and high-frequency (0.15–0.50 Hz) ranges, consistent with the reduced variability of RR interval observed in figure 3B. The patient given clonidine (C and D) showed a preservation of power across the high- and low-frequency ranges in the postoperative period, consistent with the large amplitude of RR interval variation observed in figure 3D.

Hypertension in the Perioperative Period

Heart rate is normally closely regulated on a beat-by-beat basis via the baroreflex response to oscillations in blood pressure. Thus, healthy individuals respond to alterations in blood pressure with steep alterations in heart rate, a phenomenon quantified by a high cardiac baroreflex sensitivity. In general, beat-by-beat circulatory control in healthy volunteers is improved during conditions of low sympathetic activity and high parasympathetic activity. Several studies have examined preoperative and intraoperative autonomic control in normotensive patients. By contrast, few investigators have focused on the recovery period. A decrease in baroreflex slope using the phenylephrine method in healthy individuals undergoing surgery was observed intraoperatively, which returned to normal 30–60 min after anesthesia. Conversely, hypertensive patients have repeatedly demonstrated lower than normal baroreflex sensitivity and measures of parasympathetic nervous system control of the heart at baseline. The current study confirmed relatively low baseline cardiac baroreflex sensitivity and high frequency RR interval power, two measures of parasympathetic control of heart rate, in hypertensive patients compared with data from previous

Anesthesiology, V 90, No 3, Mar 1999
Fig. 5. (A) Spontaneous cardiac baroreflex slope. (B–D) RR interval spectral power (B, total power, 0.0–0.5 Hz; C, low frequency power, 0.00–0.15 Hz; D, high frequency power, 0.15–0.50 Hz), shown as mean ± SEM. Patients given placebo demonstrated reductions in cardiac baroreflex slope and RR interval power compared with preinduction values, whereas patients given clonidine demonstrated a preservation of spontaneous cardiac baroreflex slope and RR interval power in the postoperative period (Treatment × Study period interaction of ANOVA; baroreflex slope $P = 0.04$; total power $P = 0.001$; low frequency power $P = 0.005$; high frequency power $P = 0.001$). *Significant difference between groups; †significant difference from respective baseline value by post hoc Tukey's tests.

studies using healthy subjects. This study is the first to document a further reduction in these parameters in the early postoperative period in hypertensive patients. This reduction observed after relatively major surgery in hypertensive patients is in keeping with the profound and prolonged reduction in slope of the cardiac baroreflex observed after moderate injury in young patients. Using identical methods of data analysis as in the current study, we previously monitored perioperative changes in spontaneous baroreflex slope and RR interval variability in normotensive patients. These patients demonstrated markedly higher baroreflex sensitivity at baseline than the hypertensive patients in the current study ($13.2 ± 1.5$ vs. $4.5 ± 0.6$ ms/mmHg, respectively) and greater high-frequency RR interval power ($575 ± 139$ vs. $150 ± 50$ ms$^2$/Hz). Two hours into the recovery period, the normotensive patients studied previously showed a return of these parameters to baseline. This was not observed in the hypertensive patients given placebo in the current study after $3$ h of recovery (baroreflex slope, $12.7 ± 1.4$ vs. $2.2 ± 0.6$ ms/mmHg; high-frequency power, $569 ± 115$ vs. $33 ± 12$ ms$^2$/Hz for normotensive and hypertensive groups, respectively). Although suggestive of different recovery profiles for hypertensive and normotensive individuals, the differences in age and anesthetic protocol between these two studies prevents a firm conclusion that the postoperative changes found in the current study are specific to patients with preexisting essential hypertension.

Three further observations are apparent. First, al-
though postoperative blood pressure was unchanged from preinduction values in the patients given placebo, high doses of nicardipine were necessary for postoperative management of blood pressure in this group. A possible explanation for this observation may be a resetting toward higher pressure of the activity of the vasomotor center. Such a resetting has been observed previously during emergence from anesthesia in animals.\textsuperscript{32,38,39} Second, the reduced slope of the cardiac baroreflex indicates that the normally tight beat-by-beat control of heart rate observed in healthy individuals is virtually nonexistent in hypertensive patients after surgery. Thus, the cardiac vagal motoneurons\textsuperscript{40} which normally generate a brisk reduction in heart rate on spontaneous increases in pressure may have lost their rapid responsiveness. Nociceptive or suprabulbar stimuli have been shown to suppress vagally induced bradycardia at the site of these cardiac vagal motoneurons.\textsuperscript{41} Finally, the reduced high-frequency and total RR interval power confirm that the physiologic periodic fluctuations mediated by the autonomic nervous system\textsuperscript{26} are dramatically decreased postoperatively in these patients. The mechanism for the increased perioperative circulatory liability in hypertensive patients recovering from surgery may relate to sympathetic hyperactivity, reduced parasympathetic responsiveness, or both.

\textbf{Improved Circulatory Stability with Clonidine}

The \(\alpha\)-adrenergic agonist clonidine reduces sympathetic output from the vasomotor center, resulting in reduced blood pressure, heart rate, and circulating catecholamines.\textsuperscript{7–9} A resetting of the activity of the adrenergic component of the vasomotor center toward a lower pressure has been observed in rats after administration of clonidine.\textsuperscript{10,11} Further, sympathetic nerve activity is reduced despite lowered blood pressure after administration of clonidine in humans.\textsuperscript{42} In the current study, during the postoperative period, clonidine led to decreased blood pressure associated with an unchanged mean RR interval, indicating a leftward shift of the set point of the cardiac baroreflex. There was no change in baroreflex slope or RR interval power, suggesting that parasympathetic and sympathetic activity were preserved at preoperative levels. Thus, clonidine may preserve the reactivity of cardiac vagal motoneurons to spontaneous increases in pressure, leading to the maintained ability to buffer spontaneous changes in pressure. This buffering, or antioscillatory, effect is further illustrated by the reduced SD of SBP (significant at time R3), combined with the increased SD of RR interval (fig. 2), and the reduction in episodes of perioperative hypertension and tachycardia, observed in the clonidine group. These features have made \(\alpha\)-agonists attractive for use in attenuating perioperative circulatory responses in a variety of operative situations, particularly those involving patients with underlying essential hypertension.\textsuperscript{7–9}

The measures of autonomic control used in the current study were determined only in the early postoperative period. It is not known what the duration of the effects of the dose of clonidine used (total 9 \(\mu\)g/kg over 7–10 h) would be, or whether continued administration of the drug would confer more prolonged protective effects. There is evidence that sympatholysis throughout the perioperative period using \(\beta\)-adrenergic blocking drugs reduces cardiac complications for many months postoperatively.\textsuperscript{43} Whether perioperative use of clonidine would result in similar protection remains to be explored.

A decrease in control of heart rate was documented after surgery in patients with preexisting hypertension, which was prevented by administration of clonidine. This may represent an explanation for the improvement in circulatory stability seen with perioperative administration of clonidine in hypertensive patients.

The authors thank Drs. Tissot, Fischer, Barthes, and Beji for referral of patients; Dr. Nageotte for monitoring the study; the nurse anesthetists of Pavillon D and T, Hôpital E Herriot, for their assistance; and Bioscientia, Mainz, Germany for assaying clonidine.

\textbf{References}

27. Conway J, Boon N, Vann Jones J, Sleight P: Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypertension* 1983; 5:746–8