

Myocardial Ischemia in Untreated Hypertensive Patients: Effect of a Single Small Oral Dose of a Beta-Adrenergic Blocking Agent

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In a non-double-blind, prospective, randomized study, the intraoperative electrocardiograms of 128 mildly hypertensive surgical patients were examined in order to determine the incidence of myocardial ischemia during anesthesia. No patient had been receiving chronic antihypertensive therapy prior to the study, but a single small oral dose of a beta-adrenergic blocking agent (labetalol, atenolol, or oxprenolol) was given to 89 of them along with premedication. Forty-four per cent of the untreated control patients and 61% of the patients pretreated with a beta-adrenergic blocking agent had normal preoperative electrocardiograms and no risk factors for coronary artery disease other than hypertension (this difference between groups was not statistically significant). During tracheal intubation and/or emergence from anesthesia, a brief, self-limited episode of myocardial ischemia was detected in 11 of 39 untreated control patients, and in two of 89 patients pretreated with a beta-adrenergic blocking agent ($P < 0.001$). Tachycardia always accompanied the ischemic events, but a conspicuous increase in blood pressure did not. The authors conclude that mild hypertension, when untreated prior to the induction of anesthesia, is associated with a high incidence of myocardial ischemia; and that a single small oral dose of a beta-adrenergic blocking agent, given with premedication, can significantly reduce that risk. (Key words: Anesthesia; cardiovascular disease. Heart; myocardial ischemia. Patient; hypertension, untreated or pretreated. Sympathetic nervous system, beta-adrenergic blockade; hemodynamic effect; prophylaxis.

MYOCARDIAL ISCHEMIA has been found to occur more frequently during anesthesia in hypertensive patients who are untreated than in those receiving chronic antihypertensive therapy.¹⁻³ Nevertheless, many untreated hypertensive patients are scheduled for surgery. Some have never before been aware of their hypertension,

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and others have been told that their blood pressure was not high enough to warrant therapy. The anesthesiologist then faces a dilemma. When hypertension is severe, postponement of elective surgery is appropriate and justified. However, when hypertension is mild, logistical considerations often predominate, for this large and important subgroup has not been previously investigated. This study was, therefore, undertaken first to determine the incidence of myocardial ischemia during anesthesia in untreated, mildly hypertensive patients and, second, to evaluate one type of acute prophylaxis for these patients. Beta-adrenergic blocking agents were chosen for their antihypertensive, antianginal, and antiarrhythmic properties. We tested a single small oral dose of three different drugs, each belonging to a separate class, to determine which was most effective or best tolerated during anesthesia.

Materials and Methods

One hundred and twenty-eight patients were studied with their informed consent and the approval of the Central Oxford Research Ethics Committee. To qualify, a patient was required to have had a minimum of three blood pressure measurements of between 160/90 and 200/100 mmHg taken at least 1 h apart in the hospital on the day before surgery, and not to have received any antihypertensive medication for at least a year. Patients with angina pectoris, ECG changes indicative of active coronary artery disease, left bundle branch block, or left ventricular hypertrophy and strain were excluded from the study. Those with cardiac failure, bradycardia, second- or third-degree heart block, and bronchial asthma were also excluded. Study subjects, all of whom underwent major operations necessitating general endotracheal anesthesia, were randomly allocated among four groups. Those in the control group ($n = 39$) received no pretreatment with beta-adrenergic blocking agents. The others were given a single oral tablet of labetalol 100 mg ($n = 29$), atenolol 50 mg ($n = 30$), or oxprenolol 20 mg ($n = 30$) 2 h before the induction of anesthesia. Other premedication, and the choice and conduct of anesthesia, were left to the discretion of independent anesthesiologists who were not blinded to their patients' preoperative medication, and who were instructed to provide their smoothest and least traumatic form of anesthesia.

TABLE 1. Demographic Data

	Control (n = 39)	Labetalol (n = 29)	Atenolol (n = 30)	Oxprenolol (n = 30)
Age (years)*	68 ± 2	63 ± 3	65 ± 2	65 ± 3
Males (n)	28	21	19	22
Normal ECG & no hx of CAD (n)	17	16	19	19
Nonspecific ST-T wave abnormalities (n)	17	10	8	10
Old myocardial infarct (n)	5	3	3	1
Premedication				
Narcotic (n)	29	22	24	17
Sedative (n)	18	14	10	10
Vagolytic (n)	20	18	23	19
Induction agents				
Fentanyl (n)	33	19	19	21
Thiopental (n)	31	24	26	27
Etomidate (n)	8	5	4	3
Primary anesthesia				
Halothane (n)	27	21	19	14
Enflurane (n)	6	4	3	7
N ₂ O-narcotic (n)	6	4	8	9
Type of surgery				
Abdominal (n)	15	16	14	15
Peripheral (n)	16	8	12	13
Vascular (n)	8	5	4	2
Duration of anesthesia (min)*	109 ± 16	98 ± 13	101 ± 14	84 ± 9

* Mean ± SEM.

Demographic details are compiled in table 1. Narcotics were frequently administered as premedication, and many patients received a vagolytic drug and/or a benzodiazepine. Those who did not receive narcotic premedication were given fentanyl 1–3 µg/kg as part of the induction of anesthesia. Sleep was induced with either thiopental 3–5 mg/kg or etomidate 0.2–0.3 mg/kg. A muscle relaxant, either succinylcholine 1 mg/kg or atracurium 0.25 mg/kg, was always administered to facilitate tracheal intubation. Halothane was the most commonly used primary anesthetic, and those patients who received a volatile agent for more than 2 h frequently were given additional narcotic medication before emergence. About half of the patients in each group received atropine 1 mg and neostigmine 2.5 mg to reverse residual muscle relaxation. Patients underwent abdominal operations, such as herniorrhaphies, cholecystectomies, and bowel resections. Others had orthopedic surgery or vascular procedures of the aorta or its major branches. The length of surgery varied between one and several hours.

In the operating room and the recovery area, heart rate and blood pressure were measured and recorded every minute by a non-invasive Datascope Accutorr® system. A calibrated electrocardiographic V5 lead was continuously displayed, and paper strip recordings were obtained intermittently: 1) at a quiet control period

prior to the start of anesthesia, 2) throughout induction of anesthesia and the early phase of surgery, 3) during subsequent intraoperative periods when the level of stimulation increased, 4) from the beginning of emergence from anesthesia until transport, 5) from admission to the recovery area until the patient was made quiet and comfortable, and 6) at any time the vital signs changed significantly or an ischemic pattern appeared on the monitor. These electrocardiographic recordings were subsequently interpreted by a cardiologist who was blinded to the patients' treatment. The diagnosis of myocardial ischemia was based upon the appearance of new ST-segment depression of 1 millivolt or more, having a horizontal or downsloping configuration, for at least a minute.

Venous blood samples (5 ml) were drawn just prior to induction, and again upon entry to the recovery room. After centrifugation, the supernatant was frozen and saved for future quantitative analysis. The plasma concentrations of labetalol were determined by high-pressure liquid chromatography using a method with a sensitivity of 4 ng/ml and a coefficient of variability of 3%.⁴ The plasma concentrations of atenolol were determined by gas-liquid chromatography using a method with a sensitivity of 5 ng/ml and a coefficient of variability of 6%.⁵ The plasma concentrations of oxprenolol were determined by gas-liquid chromatography using a

method with a sensitivity of 10 ng/ml and a coefficient of variability of 3%.⁶

Data were compared statistically by analysis of variance and two-sample *t* tests. *P* values were adjusted using a Bonferroni type inequality. Standard chi-square analysis and the Fisher exact test were done to evaluate categorical data. *P* < 0.05 was considered significant.

Results

Myocardial ischemia, based on electrocardiographic recordings, was diagnosed in 13 of the 128 study subjects. When there was no apparent ischemia seen on the monitor, the length of the strips used for diagnosis averaged about 17 feet in each of the four groups. When an ischemic pattern was detected, the recording length increased to 23 feet. Nine patients were found to have a single ischemic episode, and four others had two of them. Every episode took place during stressful stimulation; seven during tracheal intubation, eight during emergence from anesthesia, one during surgical stimulation of the aorta, and one during manipulation of a femoral fracture. All patients who developed ischemia had an episode during either tracheal intubation or emergence from anesthesia. These episodes were brief, never lasting longer than a few minutes, and always resolving spontaneously before therapy could be instituted. No patient suffered a clinically obvious perioperative myocardial infarction.

Myocardial ischemia occurred in 11 of 39 untreated patients (28%), and in two of 89 patients pretreated with a beta-adrenergic blocking agent (2%) (*P* < 0.001). Those patients who developed ischemic events were of a mean age of 70 ± 3 yr, and significantly older than the rest who averaged 65 ± 1 yr (*P* < 0.05). Patients in the untreated control group tended to be older and tended to have a higher incidence of latent coronary artery disease (56% vs. 39%) (table 1), but these differences did not reach statistical significance. Five of the untreated patients who developed ischemia had a normal preoperative electrocardiogram, and were without risk factors for coronary artery disease other than hypertension. The remaining six untreated and the two pretreated patients, who developed myocardial ischemia during the study, had either an abnormal preoperative electrocardiogram or a medical history indicative of ischemic heart disease. The two pretreated patients who developed ischemia had both received labetalol; however, statistical analysis did not indicate that this drug provided less protection against ischemia than the other two beta-adrenergic blocking agents, and therapeutic plasma levels were achieved with all three (table 2).

On the day before surgery, the patients in the four groups were noted to have similar heart rates (table 3). Following premedication, but prior to the induction of

TABLE 2. Plasma Concentrations of Beta-adrenergic Blocking Agents (ng/ml)

	Preop	Postop
Labetalol	95 ± 27	43 ± 9*
Atenolol	324 ± 54	321 ± 40
Oxprenolol	237 ± 34	135 ± 23*

Mean ± SEM.

* Significant difference from the preoperative measurement.

anesthesia, heart rate decreased in the three pretreated groups (*P* < 0.01), but did not change in the untreated control group. At that time, patients pretreated with atenolol had the slowest mean heart rate (60 ± 2 beats/min, *P* < 0.01). Coincident with tracheal intubation and emergence from anesthesia, heart rate increased in every group (*P* < 0.05). During these periods of stressful stimulation, the most rapid peak mean heart rate was found in the untreated patients, 100 ± 2 beats/min (*P* < 0.01). A significantly slower peak mean heart rate of 79 ± 2 beats/min occurred in patients pretreated with beta-adrenergic blocking agents. The slowest (72 ± 2 beats/min) was noted in the atenolol pretreated group (*P* < 0.05). The eleven untreated patients who exhibited brief ischemic ECG changes during tracheal intubation and/or emergence from anesthesia had a concurrent peak mean heart rate of 120 ± 5 beats/min, which was significantly higher than that found in their untreated counterparts who withstood intubation and emergence without ischemia (92 ± 3 beats/min, *P* < 0.01). The two pretreated patients who developed ischemia had accompanying peak heart rates of 89 and 106 beats/min. During tracheal intubation and emergence from anesthesia, ventricular ectopic beats were recorded more frequently in the control (18%) than in the pretreated groups (3%, *P* < 0.05). The episodes of tachycardia and/or arrhythmias were always brief and self-limited, subsiding shortly after the stimulus was withdrawn.

Bradycardia, defined as a persistent heart rate of less than 45 beats/min, did not occur in untreated patients. Although 11 patients pretreated with atenolol (37%),

TABLE 3. Heart Rate (Beats/min)

	Day Before Surgery	Pre-induction	Intubation (Peak)	Emergence (Peak)
Untreated	79 ± 2	78 ± 3	99 ± 3†	100 ± 2†
Labetalol	82 ± 2	71 ± 2*	80 ± 2†	81 ± 2†
Atenolol	78 ± 2	60 ± 2*	72 ± 2†	71 ± 2†
Oxprenolol	80 ± 2	68 ± 2*	83 ± 2†	84 ± 3†

Mean ± SEM.

* Significant difference from day before surgery.

† Significant difference from pre-induction.

TABLE 4. Mean Arterial Pressure (mmHg)

	Day Before Surgery	Pre-induction	Intubation (Peak)	Emergence (Peak)
Untreated	116 ± 1	112 ± 2*	125 ± 3†	127 ± 2†
Labetalol	115 ± 2	98 ± 2*	92 ± 3	101 ± 4
Atenolol	117 ± 2	100 ± 3*	106 ± 5	107 ± 3
Oxprenolol	119 ± 2	108 ± 2*	118 ± 4†	119 ± 3†

Mean ± SEM.

* Significant difference from day before surgery.

† Significant difference from preinduction.

six with labetalol (21%), and four with oxprenolol (13%) developed bradycardia, no significant difference emerged between the three pretreated groups. About half of the patients who became bradycardic were given atropine, 1 mg iv, by their anesthesiologists. This therapy resulted in an increase in the heart rate of 5–10 beats/min.

The patients in the four groups had similar mean arterial pressures on the day before surgery (table 4). In the operating room, after premedication but prior to the induction of anesthesia, mean arterial pressure decreased in every group ($P < 0.05$). This change was least pronounced in the untreated patients, and more pronounced in the patients pretreated with labetalol and atenolol, than in those who received oxprenolol ($P < 0.05$). Coincident with tracheal intubation and emergence from anesthesia, the untreated patients demonstrated the highest peak mean arterial pressure ($P < 0.01$). The pressor response during these periods was blunted more effectively by labetalol and atenolol than by oxprenolol ($P < 0.05$). When untreated patients exhibited ischemic ECG changes, peak mean arterial pressure was 130 ± 9 mmHg. This pressure was not significantly higher than that found in untreated patients who did not develop ischemia during intubation and/or emergence (125 ± 6 mmHg). The two pretreated patients who experienced ischemic episodes had concurrent peak arterial pressures of 122 and 130 mmHg. In all instances, hypertensive responses, whether associated with ischemia or not, were of such a short duration that specific therapeutic measures were not undertaken.

During induction of anesthesia, the systolic blood pressure fell to below 70 mmHg for several minutes, despite a rapid crystalloid infusion in seven patients pretreated with labetalol (24%), in three with atenolol (10%), in two with oxprenolol (7%), and in two in the control group (5%). There was no statistically significant difference between the four groups, or between the control group and all the pretreated patients combined. Hypotensive episodes were always associated with a slow or normal heart rate, and never accompanied by ischemic ECG changes.

Discussion

Hypertension afflicts sixty million Americans: one-quarter of the adult population, and one-half of the elderly.⁷ Two-thirds receive no treatment, and only one-half are aware of their condition. Epidemiological studies have established that, with each incremental rise in either systolic or diastolic blood pressure, the hypertensive patient sustains a progressive increase in mortality and morbidity from coronary artery disease.⁸ Even mildly hypertensive, untreated, and asymptomatic individuals are twice as likely to develop cardiovascular problems as their normotensive counterparts.⁹ Men aged 40–59 yr with diastolic pressures between 80 and 87 mmHg have a 50% greater chance of suffering coronary events than matched subjects with diastolic pressures below 80.¹⁰ Isolated systolic hypertension, which affects one-third of the population over 65,⁹ is a risk factor at least as ominous, and probably more so, than one due to an elevation of the diastolic blood pressure.¹¹

Nevertheless, in a much-quoted paper, Goldman and Caldera did not find that untreated patients with mild or moderate hypertension had a greater incidence of myocardial infarction in the perioperative period, and they questioned the clinical practice of postponing elective surgery to begin antihypertensive therapy when the diastolic blood pressure did not exceed 110 mmHg.¹² No attempt was made to determine the prevalence of intraoperative myocardial ischemia, and they based their recommendations solely upon postoperative data. Although only a very small fraction of patients (and sometimes none) who demonstrate transient intraoperative myocardial ischemia go on to develop a frank postoperative infarct,^{13–18} there is a documented relationship between intraoperative myocardial ischemia and postoperative infarction.^{15,16} Moreover, it has been shown that, compared to historical controls, careful monitoring and prompt aggressive therapy greatly reduce the incidence of reinfarction in the perioperative period.¹⁹

Tracheal intubation and emergence from anesthesia are often associated with augmented catecholamine secretion and a transient increase in heart rate and arterial pressure.²⁰ In the hypertensive patient, this hyperdynamic stress response is exaggerated,^{21–23} and undoubtedly causes a large increase in myocardial oxygen demand. In fact, these anesthetic stresses can be of a sufficient magnitude to induce myocardial ischemia, and might well be considered an obligatory, or at least an unavoidable, stress test. Patients with fixed obstructive coronary lesions tolerate stress under anesthesia poorly, and myocardial ischemia is detected electrocardiographically in 35–40% of them,^{13–16} and more frequently using techniques of greater sensitivity.^{17,18}

Short-acting intravenous anesthetics,²⁴ potent inhalational agents,²⁵ narcotics,²⁶ vasodilators,²⁷ and lidocaine, both intravenous and topical,²⁸ all have been used in an attempt to blunt these spikes of sympathetic overactivity. None have been entirely successful,^{20,22} and breakthroughs occur especially on emergence, when anesthetics and other drugs have been largely eliminated. Beta-adrenergic blockade also diminishes the stress response during anesthesia, and provides the added therapeutic advantage of lessening the incidence of evoked ventricular arrhythmias during laryngoscopy and tracheal intubation.²⁹ Good results have been achieved with chronic beta-blocker therapy prior to surgery,³⁰ with several days of acute preoperative treatment,³¹ and with an infusion begun in the operating room.³² The beneficial effects are thought to be largely, although not exclusively, the result of decreased myocardial oxygen demand.³³

It has been reported that beta-adrenergic blockade may become incomplete during surgery.³⁴ However, in our study, therapeutic plasma levels were achieved at the start of anesthesia and maintained into the recovery room with a single tablet of the smallest commercially available dose of each of the three drugs tested (table 2). The plasma concentrations of labetalol and oxprenolol decreased by approximately 50% during the operation, whereas the atenolol level did not change. The former are relatively short-acting drugs, usually prescribed four times a day, and the latter is a long-acting preparation taken daily. It would be wise to choose a beta-adrenergic blocking agent with a duration of action long enough to cover both the operative and the early postoperative period in which pain or other stresses are expected. Supplemental intravenous doses can also be considered when surgery and recovery are prolonged.

Beta-adrenergic blockade has little effect on the normal heart with the subject at complete rest; however, when sympathetic activation of the heart is elevated, beta-adrenergic blocking agents decrease both heart rate and myocardial contractility. When ambulatory patients receive beta-adrenergic blocking agents for the first time, bradycardia and postural hypotension may be encountered.³⁵ Anesthesia imposes additional myocardial depression upon the beta-blocked patient.³⁶ However, the combination is usually well tolerated,³⁷ probably because anesthesia is commonly accompanied by vasodilatation, which unloads the ventricle and facilitates forward flow. In this study, patients pretreated with beta-adrenergic blocking agents frequently developed bradycardia in the recovery room and during periods when noxious stimulation was not intense. This bradycardia always responded to 1 mg of intravenous atropine, which is a required dose in the face of beta-adrenergic blockade.³⁸ Hypotension also occurred in a substantial number of patients, and one must not forget

that myocardial blood flow to regions supplied by narrowed coronary vessels is pressure dependent. Parenthetically, blood pressure appeared to decrease during induction to a lesser extent in patients pretreated with oxprenolol, a beta-adrenergic blocking agent with intrinsic sympathomimetic activity, than among those who received labetalol or atenolol. Perhaps this partial beta-agonistic property allows subjects with impaired ventricular function to better withstand the combination of beta-adrenergic blockade and anesthesia.^{39,40} Nevertheless, it must also be pointed out that, even though no ischemic events were detected in patients pretreated with oxprenolol, the hemodynamic consequences of the stress response appear to be better ablated by the other two beta-adrenergic blockers.

We tried to randomize our patients into groups with an equal chance of developing myocardial ischemia, but we may have failed, and a type II statistical error may have occurred. A double-blind experimental protocol would have been ideal, for it would have insured that physician bias could not influence anesthetic management. However, double-blind studies are difficult to achieve with drugs that have a demonstrable effect on heart rate. Moreover, we chose not to standardize the anesthetic management in a predetermined manner, for we believe clinicians provide their best care when allowed to respond to each patients' individual needs.⁴¹

In summary, this study demonstrates that even mildly hypertensive patients, if untreated, are likely to develop a brief hyperdynamic stress response and myocardial ischemia during the stimulation which accompanies tracheal intubation and emergence from anesthesia. More importantly, the data indicate that the risk of myocardial ischemia can be diminished 12-fold by the preoperative administration of a single small oral dose of a beta-adrenergic blocking agent. Tachycardia and arrhythmias are also inhibited during noxious stimulation, but, when stimulation is not intense, bradycardia occurs more frequently, and there is an apparent increase in the incidence of hypotension. The prophylaxis is just as effective at the end of anesthesia as during induction. It is probably premature to advocate beta-blocker prophylaxis for everyone who undergoes anesthesia, but patients with hypertension and/or ischemic heart disease may well benefit from such pretreatment.

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