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Calcium Channel Blockade Does Not Offer Adequate Protection from Perioperative Myocardial Ischemia

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This study aimed to detect the difference in hemodynamic and electrocardiographic responses during the prebypass period in patients undergoing coronary bypass grafting who were receiving beta-adrenergic blocking drugs, calcium entry blocking drugs, or both beta-adrenergic and calcium entry blocking drugs. Electrocardiographic evidence of myocardial ischemia was noted significantly more frequently in patients receiving calcium entry blocking drugs alone at induction of anesthesia ($P < 0.03$), skin incision ($P < 0.05$), and sternotomy ($P < 0.002$). Heart rate at sternotomy was significantly higher in patients receiving calcium entry blocking drugs ($P < 0.02$) as compared to patients receiving beta-adrenergic blocking drugs or the combination of both drugs. In conclusion, patients treated with calcium entry blocking drugs alone had significantly higher incidence of perioperative ischemic ECG changes compared with patients receiving beta-adrenergic blocking drugs alone or in combination with calcium channel blocking drugs. (Key words: Anesthesia: cardiac. Heart: ischemia. Monitoring: electrocardiography. Pharmacology: calcium channel blocking drugs. Surgery: cardiac. Sympathetic nervous system: beta-adrenergic blocking drugs.)

PATIENTS with ischemic heart disease may be treated with nitrates, beta-adrenergic blocking drugs, and calcium entry blocking drugs. Increases in heart rate and myocardial contractility may occur during surgical stimulation in patients receiving calcium entry blocking drugs without concomitant beta-adrenergic blocking drugs. We therefore postulated that calcium entry blocking drugs alone did not offer adequate protection from perioperative myocardial ischemia. The present prospective study aimed to detect the difference in hemodynamic and electrocardiographic responses in patients receiving beta-adrenergic blocking drugs (BB), calcium entry blocking drugs (CEB), or both beta-adrenergic (BB) and calcium entry blocking drugs (CEB).

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Methods

Institution approval was obtained. Patients scheduled for routine coronary artery bypass grafting from January 1986 to March 1987 were included in the study. Exclusion criteria were patients with unstable angina, previous coronary artery bypass surgery, associated procedures, *e.g.*, ventricular aneurysm resection, poor ventricular function, and electrocardiogram, which prevented the diagnosis of ischemia, *e.g.*, LBBB, digoxin treatment, and when an investigator was not available for collection of data.

All preoperative antianginal medications (nitrates, BB, and CEB) were continued up to the time of surgery. For data analysis patients were divided into three groups based on their preoperative antianginal therapy: 1) patients receiving their usually prescribed BB only, 2) patients receiving a CEB only, and 3) patients receiving both BB and CEB. Patients were premedicated with diazepam 0.15 mg/kg per os 1.5 h preoperatively and morphine 0.15 mg/kg and perphenazine 0.75 mg/kg intramuscularly 1 h prior to induction of anesthesia. In the operating room iv, radial artery, and thermodilution pulmonary artery catheters were inserted under local anesthesia.

Anesthesia was induced with iv fentanyl 50 μg/kg, and the patients were paralyzed with pancuronium 0.1 mg/kg. After tracheal intubation the patients' lungs were ventilated to maintain normocapnia with 100% oxygen (O_2). Fentanyl 10 μg/kg was added prior to skin incision, with an additional 10 μg/kg given prior to sternotomy. Diazepam 1–5 mg iv was given as a supplement during induction and maintenance.

Intraoperative heart rate and blood pressure were maintained within 20% of the average ward value. For increased blood pressure infusion of nitroglycerin with or without the addition of an inhalational anesthetic, enflurane, or isoflurane, up to 0.5% inspired was used. For decreased blood pressure a volume bolus was given when pulmonary capillary wedge pressure was less than 15 mmHg and an infusion of phenylephrine was given simultaneously. For increased heart rate >90 beats/min, iv doses of propranolol were used. Propranolol was given at 1 mg/min up to a maximum of 3 mg. If heart rate persisted at >90 beats/min, an additional dose was given after 2 min.

TABLE 1. Preoperative and Intraoperative Variable

	BB (n = 22)	CEB (n = 23)	BB + CEB (n = 47)
Sex	20 M; 2F	22 M; 1F	36 M; 11F
Age (±SE) (yr)	59.9 ± 2.6	57.2 ± 3.2	56.7 ± 1.5
Weight (±SE) (kg)	81.8 ± 3.7	83.7 ± 4.6	80.8 ± 2.1
Ejection fraction (±SE) (%)	63.4 ± 3.4	66.1 ± 4.1	64.7 ± 1.9
LVEDP (mmHg)	14.6 ± 1.5	13.5 ± 1.8	14.3 ± 0.8
Xclamp (min)	48.0 ± 4.8	40.2 ± 5.9	49.8 ± 2.7

LVEDP = Left-ventricular end-diastolic pressure at heart catheterization; Xclamp = Ischemic cross-clamp time during cardiopulmonary bypass.

The groups did not differ significantly with respect to preoperative and intraoperative variables (ANOVA).

Calibrated electrocardiographic tracings of lead II and V_5 and complete hemodynamic profiles were recorded at the following time intervals: control (preinduction), 1 min after induction of anesthesia, tracheal intubation, skin incision, sternotomy, and cannulation of the atrium and aorta. Heart rate, arterial pressure, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were recorded. Thermodilution cardiac output determinations were averaged in triplicate using a Gould Laboratory Cardiac Output computer and injections of 10 ml of 5% dextrose in water. Derived hemodynamic variables included cardiac index (CI) and systemic vascular resistance index (SVRI). All data relating to preoperative characteristics and perioperative events were collected by three investigators who did not participate in the anesthetic care of the patients.

The electrocardiogram was examined for evidence of myocardial ischemia by two independent investigators without knowledge of the cardiac medication the patients were receiving. The ST-segment was evaluated with respect to the PQ junction at a point 80 ms following the S-wave nadir. Myocardial ischemia was defined as 1 mm or more of downsloping or horizontal ST-segment depression, greater than 2 mm of upsloping ST-segment depression, or ST-segment elevation greater than 1 mm. The incidence of myocardial ischemia, as evidenced by ECG changes, was analyzed according to the three groups of patients by ANOVA and multiple chi-square. Hemodynamic data was analyzed among the three groups at corresponding stages by analysis of covariance using control as covariate (ANCOVA). Noncontinuous data were examined by contingency table analysis using chi-square tests of significance. Null hypotheses were rejected when P values were less than or equal to 0.05.

TABLE 2. Preperative Antianginal Medication

	Daily Dose		
BB + CEB			
1	Atenolol	50 mg, Diltiazem	240 mg
1	Atenolol	50 mg, Diltiazem	120 mg
1	Atenolol	50 mg, Diltiazem	180 mg
2	Atenolol	100 mg, Diltiazem	180 mg
2	Atenolol	100 mg, Diltiazem	90 mg
3	Atenolol	100 mg, Diltiazem	240 mg
1	Atenolol	25 mg, Nifedipine	40 mg
2	Atenolol	100 mg, Nifedipine	30 mg
1	Metoprolol	100 mg, Diltiazem	90 mg
1	Metoprolol	100 mg, Diltiazem	120 mg
3	Metoprolol	100 mg, Diltiazem	180 mg
1	Metoprolol	100 mg, Diltiazem	270 mg
1	Metoprolol	100 mg, Diltiazem	360 mg
1	Metoprolol	150 mg, Diltiazem	180 mg
2	Metoprolol	200 mg, Diltiazem	90 mg
1	Metoprolol	200 mg, Diltiazem	270 mg
1	Metoprolol	200 mg, Diltiazem	360 mg
1	Metoprolol	50 mg, Nifedipine	30 mg
2	Metoprolol	50 mg, Nifedipine	40 mg
2	Metoprolol	50 mg, Nifedipine	60 mg
1	Metoprolol	100 mg, Nifedipine	20 mg
1	Metoprolol	100 mg, Nifedipine	60 mg
1	Metoprolol	150 mg, Nifedipine	80 mg
1	Metoprolol	200 mg, Nifedipine	120 mg
1	Nadolol	80 mg, Diltiazem	180 mg
1	Pindolol	15 mg, Diltiazem	360 mg
1	Pindolol	45 mg, Diltiazem	240 mg
1	Propranolol	120 mg, Diltiazem	270 mg
1	Propranolol	160 mg, Diltiazem	360 mg
1	Propranolol	320 mg, Diltiazem	90 mg
1	Propranolol	20 mg, Nifedipine	50 mg
1	Propranolol	60 mg, Nifedipine	60 mg
1	Timolol	10 mg, Diltiazem	270 mg
1	Timolol	10 mg, Diltiazem	360 mg
1	Timolol	20 mg, Diltiazem	240 mg
1	Timolol	20 mg, Nifedipine	40 mg
1	Timolol	40 mg, Nifedipine	90 mg
Total 47			
BB			
3	Atenolol	50 mg	
1	Metoprolol	50 mg	
7	Metoprolol	100 mg	
1	Metoprolol	150 mg	
1	Metoprolol	200 mg	
1	Nadolol	40 mg	
1	Oxprenolol	80 mg	
1	Pindolol	15 mg	
1	Propranolol	30 mg	
2	Propranolol	120 mg	
1	Sotalol	160 mg	
2	Timolol	20 mg	
Total 22			
CEB			
1	Diltiazem	90 mg	
3	Diltiazem	180 mg	
5	Diltiazem	240 mg	
3	Diltiazem	270 mg	
3	Diltiazem	360 mg	
4	Nifedipine	30 mg	
3	Nifedipine	40 mg	
1	Verapamil	240 mg	
Total 23			

Results

Ninety-two patients were studied; 22 received BB, 23 received CEB, and 47 received both BB and CEB. There was no significant difference in sex, age, weight, ejection fraction, and left-ventricular end-diastolic pressure at heart catheterization, and aorta cross-clamp time among the three groups (table 1). The groups did not differ significantly with respect to the number of grafts received. The antianginal medications the patients received preoperatively are listed in table 2.

ANOVA revealed no significant hemodynamic differences between groups at the control period. Heart rate at sternotomy was significantly higher in patients receiving CEB ($P < 0.02$) as compared with those receiving BB or both BB and CEB (fig. 1). There was no difference in mean arterial pressure (MAP), PCWP, or CI among the three groups of patients at various stages prebypass. When all six time intervals were considered, the three groups differed significantly with regard to HR ($P < 0.0001$) and MAP ($P < 0.0001$), (ANOVA for repeated measures). Heart rate and MAP were significantly higher in patients receiving CEB alone.

The baseline electrocardiogram showed that 4.4% of patients developed new ST changes compared to the preoperative electrocardiogram. The percentage of patients with electrocardiographically determined myocardial ischemia in the three groups of patients at different stages prebypass is shown in figure 2. Electrocardiographic changes of myocardial ischemia were noted significantly more frequently in patients receiving CEB at induction ($P < 0.03$), skin incision ($P < 0.05$), and sternotomy ($P < 0.002$). Two of 22 patients (9%) receiving BB developed prebypass ischemic changes, whereas six of 23 patients (26.1%) receiving CEB had prebypass myocardial ischemia. Of the 47 patients receiving both BB and CEB, eight developed prebypass ischemia (17%).

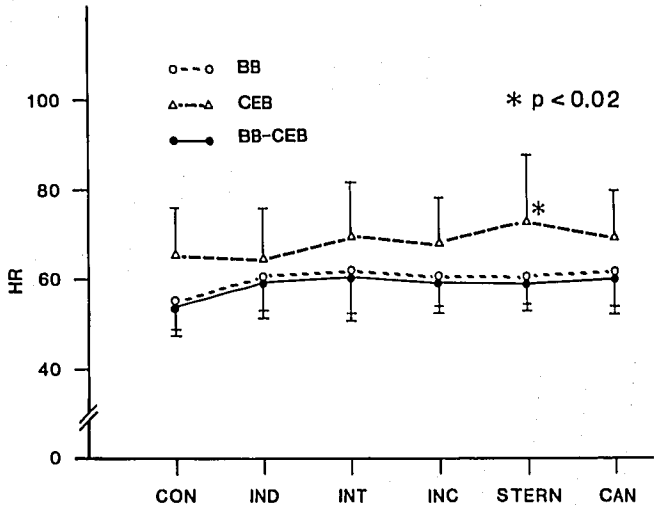

FIG. 1. Mean heart rate ± SEM (HR) at different stages prebypass, CON (control), IND (induction), INT (intubation), INC (incision), STERN (sternotomy), and CAN (cannulation of aorta), $P < 0.02$ (ANCOVA).

There was no significant difference in heart rate and MAP between the patients with and without myocardial ischemia. Significantly greater amounts of nitroglycerin were required to control blood pressure in patients receiving CEB *versus* those receiving BB or both BB and CEB ($P < 0.02$, table 3). There was a significantly higher number of patients receiving CEB who required intravenous propranolol to control their heart rate ($P < 0.0005$, Table 3), compared to the other two groups.

On discontinuing cardiopulmonary bypass, the three

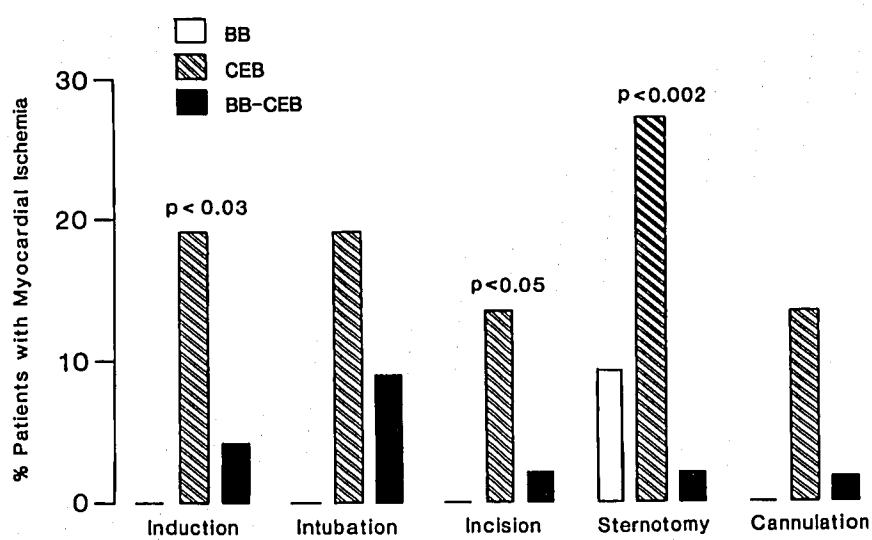

FIG. 2. Percent of patients with myocardial ischemia at different stages prebypass.

TABLE 3. Intraoperative Use of Adjunct Drugs

	BB	CEB	BB + CEB
Nitroglycerin (mg)	7.2 ± 2.3	14.1 ± 2.9*	3.2 ± 2.3
% of patients receiving iv propranolol	12	71†	18

* The groups differed significantly with respect to the amount of nitroglycerin required to control blood pressure prebypass ($P < 0.02$, ANOVA).

† The groups differed significantly with respect to the percentage of patients requiring iv propranolol ($P < 0.0005$, ANOVA).

groups did not differ significantly with respect to the need for inotropic support (table 4). The incidence of myocardial infarction as documented by Q waves in the postoperative electrocardiogram did not differ significantly among the three groups (table 4).

Discussion

Numerous reports have documented the beneficial effects of continuing BB until surgery for patients scheduled for CABG.[1-4] In the past few years a number of clinical trials have shown that CEB are equally effective in controlling stable angina pectoris as compared to BB.[5-8] Many patients are being treated with CEB as the sole medical therapy before their CABG. This study indicates that patients receiving CEB have a higher incidence of perioperative ischemia compared to patients receiving BB with or without CEB.

Patients receiving CEB and with no BB had almost a threefold increase in risk of developing prebypass ischemia; 26.1% of patients receiving CEB developed prebypass myocardial ischemia as compared to 9% of patients receiving BB. This difference in incidence of myocardial ischemia occurred despite blood pressure controlled within 20% of ward value and heart rate less than 90 beats/min intraoperatively. Significantly greater amounts of nitroglycerin were given to control the blood pressure and propranolol was required more frequently to control the heart rate in patients receiving CEB compared with patients in the other two groups. This may suggest that acute iv BB may not be as effective as chronic beta-blockade.

TABLE 4. Clinical Outcome of Patients

	BB	CEB	BB – CEB
Dopamine (%)	9	12.9	6.4
Calcium chloride (%)	18	23.0	25.0
Myocardial infarction (%)	0	0	4.2

The groups did not differ significantly with respect to the need for inotropic support postbypass and the incidence of myocardial infarction.

Contrary to our findings, Slogoff and Keats[9] found that BB prevented ischemia associated with tachycardia, and at lower heart rates, incidence of intraoperative ischemia did not differ between groups with and without BB or CEB. The documentation of ischemia in their study was divided into arrival and intraoperative ischemia only. No clarification of ischemia at induction, intubation, sternotomy, and cannulation was done. Because we documented that heart rate was significantly increased in CEB group at sternotomy only, the analysis of ischemia at that specific time might reveal significant results.

In the study by Slogoff and Keats[9] 44.4% of patients had new ischemia on arrival to the operating room compared with 4.4% in our group. This major discrepancy might be due that 50% of their patients had chronic therapy discontinued for at least 2 days before surgery, and these patients might have been suffering from acute withdrawal phenomenon.[2] In addition, no patients in their study received oral or topical nitrates as part of their preoperative regimen, which is contrary to our practice.

Our selection criteria required patients with a stable pattern of angina and good ventricular function. Mean preoperative ejection fraction was 0.65 for the patients in this study. In patients with lower ejection fraction and severe myocardial damage, the hemodynamic responsiveness to induction, incision, sternotomy, and aortic cannulation may be different. In patients receiving BB less hemodynamic lability occurred intraoperatively. A legitimate criticism of this study is that the degree of preoperative BB was not standardized. Some patients might have received inadequate doses of BB and serum levels of BB were not measured. Also, the choice of pancuronium as a muscle relaxant may have also contributed to the development of tachycardia and myocardial ischemia.[10]

The three major CEB are diltiazem, nifedipine, and verapamil. Nifedipine is the most potent systemic and coronary artery vasodilator. Verapamil has the most potent negative inotropic effect, and diltiazem is intermediate in potency between nifedipine and verapamil.[11] Reflex tachycardia is most prevalent in patients taking nifedipine and can cause an increased incidence of myocardial ischemia. In our study there is no statistically significant difference in the incidence of myocardial ischemia between the different CEB, but the number of patients may be too small to draw any valid conclusions.

Schulz *et al.*[12] studied four patient groups, categorized according to coronary anatomy, before and after nifedipine, and measured the ST-segment depression during exercise. They showed that after nifedipine, the mean ischemic ST-segment depression was reduced

21% in patients with a single stenotic coronary artery but was not significantly altered in patients with total occlusions with varying degree of collateralization. The antianginal effect of nifedipine appeared to depend on the degree of coronary artery harrowing and the presence of coronary collateral vessels.[12] Vasodilation of the resistance vessels by nifedipine increased supply to normally perfused areas, with no improvement or reduction in areas perfused by collateral circulation.[12] Thus, CEB which dilate small resistance vessels, have the potential to induce coronary artery steal, especially under certain circumstances of collateral vessels, tachycardia, and proximal stenosis of the conducting vessels supplying collaterals, and cause increased incidence of myocardial ischemia during anesthesia.

Casson *et al.* have shown that patients in whom nifedipine had been discontinued 24 hours before CABG, were significantly less likely to need inotropic support than those who continued receiving nifedipine.[13] In our study the three groups of patients did not differ significantly in their need for inotropic support (table 4). The difference in the results could be due to our small sample size and patient selection. Patients with poor ventricular function were excluded from our study, but in the study by Casson *et al.*[13] one-third of the patients had poor ventricular function.

Although the ejection fraction and left-ventricular end-diastolic pressure were not statistically different among our groups, it is possible that the severity of atherosclerotic heart disease was different. Patients receiving both BB and CEB might have more severe disease. This could account for the higher although not statistically significant difference of incidence of myocardial ischemia in the double therapy group (17%) *versus* those with BB (9%).

In summary, patients receiving CEB without BB preoperatively had a different hemodynamic and electrocardiographic response compared with patients receiving BB, or both BB and CEB. Prior to cardiopulmonary bypass, ischemic ECG changes were significantly more common in patients receiving CEB alone. Therefore, in patients with no contraindication to BB preoperative use of BB may be beneficial before coronary artery bypass surgery.

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