CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

COMPARISON OF PERIOPERATIVE MYOCARDIAL PROTECTION WITH NIFEDIPINE VERSUS NIFEDIPINE AND METOPROLOL IN PATIENTS UNDERGOING ELECTIVE CORONARY ARTERY BYPASS GRAFTING

A randomized study was performed on 70 patients undergoing elective coronary bypass grafting to examine whether the combined infusion of the calcium channel blocker nifedipine (10 $\mu\text{g/kg}$ per hour) and the β_1 -blocker metoprolol (12 $\mu\text{g/kg}$ per hour, $n = 34$) reduces the prevalence of perioperative myocardial ischemia and arrhythmias. The control group received nifedipine alone ($n = 36$). In both groups the infusion was started from the onset of extracorporeal circulation and maintained over a period of 24 hours. Repeated 12-lead electrocardiographic and 3-channel Holter monitor recordings for 48 hours were used to define perioperative myocardial ischemia (transient ischemic event, myocardial infarction) and arrhythmias (sinus tachycardia, supraventricular tachycardia, atrial flutter/fibrillation, ventricular tachycardia). Hemodynamic parameters were repeatedly assessed for 24 hours and serum enzyme levels (creatinine kinase, MB isoenzyme of creatine kinase) for up to 36 hours after the operation. The two groups did not differ significantly with respect to preoperative anamnestic and surgical data. No signs of perioperative myocardial infarction were detected in either group. However, a significantly lower incidence of transient ischemic episodes was observed in the nifedipine-metoprolol group than in the nifedipine group (3% vs 11%; $p < 0.05$). In addition, there was a tendency toward lower creatine kinase MB levels and peak values of creatine kinase and creatine kinase MB in the nifedipine-metoprolol group. With regard to perioperative arrhythmias, there was a significantly lower incidence of sinus tachycardia and atrial flutter/fibrillation in the nifedipine-metoprolol group (9% and 6%) than in the nifedipine group (33% and 27%, $p < 0.05$). In addition, postoperative heart rate was lower in the nifedipine-metoprolol group starting from the sixth hour after release of the aortic crossclamp ($p < 0.05$ and $p < 0.01$, respectively). No other hemodynamic parameters showed significant differences between the two groups and all returned to preoperative levels within 24 hours. In conclusion, perioperative application of nifedipine and metoprolol in patients undergoing elective coronary bypass grafting reduces the prevalence of

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Perioperative mortality and morbidity in patients undergoing elective coronary bypass procedures (CABG) have remained relatively stable at a remarkably low level during recent years.¹⁻³ Neverthe-

less, increasing numbers of patients with more severe coronary artery disease and impaired left ventricular function illustrate the need for further

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perioperative myocardial ischemia and arrhythmias without significant negative inotropic effects. The combined infusion of the two drugs appears superior to nifedipine alone in preventing perioperative myocardial ischemia and reducing reperfusion-induced arrhythmias. (J THORAC CARDIOVASC SURG 1995;110:1461-9)

improvements in perioperative patient management. Therefore, besides the technical quality of the surgical procedure, intraoperative and perioperative myocardial protection has become one of the most heavily discussed topics in cardiac surgery.⁴⁻⁷ Various forms of intraoperative myocardial protection, such as systemic and local hypothermia, antegrade and retrograde hypothermic crystalloid or blood cardioplegia, and warm blood cardioplegia, have been shown to be effective in experimental and clinical studies.^{6,7} The quality of intraoperative myocardial protection certainly contributes to the preservation of functional integrity of the myocardium during the ischemic period. However, its influence on the prevalence of myocardial ischemia and arrhythmias during the reperfusion period and the early postoperative period remains questionable. Consequently, adequate perioperative myocardial protection should include not only the intraoperative but also the early postoperative period.

In previous studies, we^{8,9} have shown that the continuous perioperative infusion of the calcium channel blocker nifedipine markedly reduces the prevalence of early postoperative myocardial infarction and transient ischemia. These beneficial effects were mainly triggered by the profound efficacy of nifedipine as a coronary vasodilator,^{10,11} because the dosages used had no measurable effect on perioperative hemodynamic parameters.^{12,13} In a different study, we¹⁴ showed that the calcium channel blocker diltiazem is able to reduce both prevalence and extent of postoperative myocardial ischemia, as well as supraventricular and intraventricular arrhythmias.

To further optimize the concept of perioperative antiischemic therapy, we conducted the current study to investigate whether a reduction of perioperative oxygen demand by an additive perioperative infusion of the selective β_1 -receptor antagonist metoprolol was able to potentiate the antiischemic efficacy of nifedipine. Metoprolol is known to reduce myocardial oxygen consumption by decreasing heart rate and myocardial contractility.^{15,16} In chronic coronary insufficiency (angina pectoris), as well as under circumstances of severe myocardial ischemia (myocardial infarction), the combination

of metoprolol and nifedipine has already been proved to be of potent antiischemic efficacy.^{15,17} Furthermore, it is a goal of this study to provide evidence whether metoprolol has perioperative antiarrhythmic effects similar to those of other β -blockers after coronary artery revascularization.^{18,19}

So that we could evaluate the perioperative antiischemic and antiarrhythmic potency of this drug combination, patients who received metoprolol and nifedipine from the onset of extracorporeal circulation were compared with those receiving nifedipine alone. In accordance with prior studies, perioperative myocardial ischemia was detected by means of a Holter monitor (Marquette Electronics (USA), Milwaukee, Wis.), serial assessment of changes in the electrocardiogram (ECG), and serum enzyme levels.^{8,9,14} The Holter monitor was used to evaluate the prevalence and characteristics of perioperative arrhythmias.

Patients and methods

The study was performed on 70 patients, randomly assigned to receive nifedipine ($n = 36$) or nifedipine and metoprolol ($n = 34$), all undergoing elective CABG. Patients with unstable angina, preoperative left or right bundle branch block, additional surgical or redo procedures, or a rethoracotomy necessitated by excessive postoperative bleeding were excluded. Two patients were excluded after the operation because of the need for reexploration to control bleeding (one in each group). None of the patients had a myocardial infarction less than 2 weeks before the operation. Catecholamine support was limited to low-dose intravenous dopamine in eight patients of the nifedipine group and 12 patients of the combined drug regimen group. Intraaortic balloon pump support was not necessary in any of the patients in the study. All patients signed an informed consent form in accordance with the guidelines of the ethical committee of the University of Vienna. The last medications (nitrates, β -blockers or calcium antagonists) were given to the patients on the evening before the operation.

Before the patient arrived in the operating room, premedication with 2 mg flunitrazepam was given orally. Anesthesia was then induced with etomidate, 0.2 to 0.3 mg/kg, fentanyl, 0.005 to 0.007 mg/kg, and diazepam, 0.1 to 0.3 mg/kg. Before intubation, a 0.1 mg/kg dose of pancuronium was administered. Anesthesia was maintained with oxygen/nitrous oxide, fentanyl, diazepam, and pancuronium. Artificial ventilation was used throughout

the operation and for at least 6 hours thereafter at a rate of 12 breaths/min and a tidal volume of 10 to 12 ml/kg. St. Thomas' Hospital cardioplegic solution (via the aortic root), systemic hypothermia (29° C rectal temperature), and topical cooling were used for intraoperative myocardial protection. The nifedipine group had a continuous intravenous nifedipine infusion (minimum dose 10 µg/kg per hour) from the onset of extracorporeal circulation until 24 hours after release of the aortic crossclamp, whereas patients assigned to the combination drug group had continuous intravenous infusion of metoprolol (continuous dose 12 µg/kg per hour) and nifedipine (minimum dose 10 µg/kg per hour). In case of hypertensive episodes, the nifedipine dosage was increased for patients in both groups to a maximum of 20 µg/kg per hour. This action was necessary in 15 patients of the nifedipine group and in 13 patients of the combined drug group. The metoprolol infusion was held constant throughout the study. No case of severe hypotension induced by either nifedipine or metoprolol was encountered.

Hemodynamic measurements. Arterial pressure was continuously recorded via a radial artery cannula, and pulmonary artery pressure was measured by a Swan-Ganz catheter (Baxter Healthcare Corp., Edwards Div., Santa Ana, Calif.) inserted percutaneously into the pulmonary artery via the jugular vein. Pulmonary artery wedge, central venous, and left atrial pressures (measured with a catheter inserted during the operation), as well as cardiac output (Edwards 9520A thermodilution computer), were assessed immediately before the operation (except left atrial pressure) and repeatedly thereafter up to 24 hours after release of the aortic crossclamp. From these data, pulmonary arterial resistance and cardiac index were calculated by means of standard formulas.

Holter monitor and ECG recordings. As previously described,^{8,9,14} perioperative ECG changes were analyzed in two ways^{8,9,14}:

Continuous recording with a 3-channel Holter monitor. Monitoring began 2 hours after release of the aortic crossclamp in the intensive care unit and lasted for 48 hours (Marquette Holter Recorder, Series 8500). Channels 1 to 3 corresponded to ECG leads V₂, V₅, and aV_F. All tapes were evaluated without knowledge of the patient's group assignment on a Marquette Laser Holter XP device by the same investigator.

Besides ST-segment analysis, the tapes were screened for perioperative arrhythmias defined as follows: *sinus tachycardia*: period of greater than 130 beats/min originating from the sinus node; *supraventricular tachycardia*: paroxysmal or sustained supraventricular tachycardia; *atrial flutter or atrial fibrillation*; *ventricular tachycardia*: more than three consecutive ventricular premature depolarizations.

Twelve-lead ECG recording. A 12-lead ECG recording was obtained immediately before the operation. After the operation, ECG recordings were made repeatedly during the first 36 postoperative hours (in parallel with biochemical analyses), as well as on every other day until the tenth postoperative day.

Two different forms of perioperative myocardial ischemia were defined by a combined analysis of ECG and Holter monitor recordings according to the following criteria: *transient ischemic event*: horizontal or downsloping

Table I. Preoperative clinical data

Variable	Nifedipine and metoprolol	Nifedipine
No. of patients	34	36
Male	31 (91%)	33 (92%)
Female	3 (9%)	3 (8%)
Age (yr)	61 ± 8	58 ± 8
Two-vessel disease	6 (18%)	6 (17%)
Three-vessel disease	28 (82%)	30 (83%)
Left main stenosis	5 (15%)	6 (17%)
Anterolateral MI	10 (29%)	7 (19%)
Posterior MI	14 (41%)	19 (53%)
NYHA functional class		
I or II	12 (35%)	14 (39%)
III or IV	22 (65%)	22 (61%)
Preoperative therapy		
Nifedipine	15 (44%)	18 (50%)
β-Blocker	9 (26%)	11 (31%)

MI, Myocardial infarction; NYHA, New York Heart Association.

ST-segment depression of 1 mm or more and lasting at least 1 minute, measured 60 to 80 msec from the J point in at least one Holter channel with no signs of evolving myocardial infarction; *myocardial infarction*: (1) persistent typical ST-segment elevation of 2 mm or more, measured 60 to 80 msec from the J point in at least one Holter channel, and development of a new Q wave (>0.04 second in duration and less than one fourth of the following R wave in amplitude) in the corresponding 12-lead ECG after 10 days or during the 36-hour observation period after the operation; (2) persistent negative coronary T wave of more than 3 mm in a 12-lead ECG during the 36-hour postoperative observation period or 10 days after the operation without the occurrence of a new Q wave.

Biochemical analysis. Creatine kinase (CK) and the MB isoenzyme of CK (CK-MB) were assessed by enzymatic fluorometric methods immediately before the operation and 1, 2, 4, 6, 8, 12, 16, 20, 24 and 36 hours after release of the aortic crossclamp.

Statistical analysis. Data in all tables are presented as mean ± standard deviation. The raw data for each point in time and the peak value of each parameter within a patient were used for the analysis. An unpaired *t* test was used to compare groups of data. Fisher's exact test was used for comparison of baseline categoric (anumeric) factors. An analysis of variance for repeated measures on hemodynamic and enzyme data was performed. The Bonferroni *t* test was used to compare values at different points in time with each other. For all results, the 95% and 99% levels for statistical significance were adopted.

Results

Table I shows preoperative data such as number of patients, age, sex, severity of coronary artery disease, history of infarction, New York Heart Association classification, and preoperative therapeutic drug regimen. A *t* test showed no statistical differences between the treatment group receiving

Table II. Surgical data

Variable	Nifedipine and metoprolol	Nifedipine
No. of patients	34	36
ACC time (min)	53 ± 14	57 ± 21
ECC time (min)	101 ± 23	106 ± 41
No. of grafts/patient	3.45	3.58
No. of ITA grafts	24	28
Endarterectomy	5	6
Mortality	0	0

ACC, Aortic crossclamp; ECC, extracorporeal circulation, ITA, internal thoracic artery.

nifedipine and metoprolol and the group receiving nifedipine alone. In addition, both groups were sufficiently matched with regard to preoperative nifedipine- or β -blocker treatment. Surgical data such as aortic crossclamp time, bypass time, number of vein grafts, and number of internal thoracic artery grafts are depicted in Table II. The analysis showed that the data were equally matched between the two groups without any statistically significant difference. No death occurred during hospitalization or within 30 days after the operation in the two groups.

Hemodynamics. Preoperative and postoperative hemodynamic parameters of both groups were analyzed by analysis of variance for repeated measures (Table III). No statistically significant difference in perioperative hemodynamic parameters was detected between the two treatment groups except for one: heart rate was significantly lower in the nifedipine-metoprolol group (Fig. 1) than in the nifedipine group, starting from the sixth hour after release of the aortic crossclamp. However, none of the patients required transient cardiac pacing to control substantial bradycardia (<55 beats/min) combined with unstable hemodynamic conditions while being weaned from cardiopulmonary bypass or during the postoperative course. All other hemodynamic parameters returned to preoperative levels within 24 hours.

ECG and Holter monitor recordings (Table IV). No patient in either group had a perioperative myocardial infarction. However, transient ischemic events were significantly less prevalent in the group receiving the combined drug regimen (3%) than in the nifedipine group (11%, $p < 0.05$). The perioperative infusion of nifedipine and metoprolol led to a substantial decrease in the prevalence of sinus tachycardia (9% vs 33%) and atrial fibrillation or flutter (6% vs 27%, $p < 0.05$) as compared with the prevalence in the nifedipine group. However, no

difference was detected between the two groups with regard to the occurrence of supraventricular and ventricular tachycardia.

Myocardial enzymes. Fig. 2 presents perioperative CK-MB levels. These levels tended to be lower in the combined drug group throughout the 36-hour observation period. At 4 hours after release of the aortic crossclamp, CK-MB values were significantly lower. However, at any other time the difference between the two groups did not reach statistical significance. Table V depicts peak values of CK and CK-MB enzymes. Peak values for both enzymes were slightly but insignificantly lower in the metoprolol-nifedipine group than in the nifedipine group.

Discussion

The combination of β -blockers and calcium channel blockers has already been shown to lessen the effects of ischemia under experimental conditions of myocardial ischemia.²⁰ The results of the present study demonstrate not only that the combined drug regimen of metoprolol and nifedipine is feasible in patients undergoing CABG, without inducing relevant hemodynamic problems, but also that it is even more effective in decreasing perioperative myocardial ischemia and reducing arrhythmias than the perioperative infusion of nifedipine alone.

Several possible pathophysiologic mechanisms may explain the potent antiischemic efficacy of nifedipine in combination with metoprolol in patients undergoing CABG procedures.

The potent coronary vasodilator nifedipine has been reported to increase myocardial blood flow, particularly in the subendocardium. This mechanism may be partly responsible for its antiischemic potency.^{10, 21, 22} On the other hand, experimental and clinical studies suggest that an additional mechanism may account for the antiischemic effects of nifedipine. Various factors like stress, exercise, or anesthesia activate the sympathetic nervous system, which among many other mechanisms also stimulates coronary α_2 -receptors via the physiologic neurotransmitter norepinephrine. Especially under conditions of myocardial ischemia, activated coronary α_2 -receptors induce additional, significant coronary vasoconstriction. Nifedipine is a functional antagonist of α_2 -receptor-mediated sympathetic coronary vasoconstriction and thereby reduces coronary vascular resistance, primarily under conditions of severe myocardial ischemia.^{10, 23}

In contrast to coronary α_2 -receptors, which have a direct influence on the regulation of myocardial

Fig. 1. Perioperative changes in heart rate. *pOP*, Preoperative; 1-24h mark the hours after opening of the aortic crossclamp. Data are given as mean $\pm$ standard deviation. Values differ significantly from that for nifedipine-metoprolol group (* $p < 0.05$, ** $p < 0.01$).

Table III. Hemodynamic data

Variable	Preoperative		One hour		Eight hours		Sixteen hours		Twenty-four hours	
	N+M	N	N+M	N	N+M	N	N+M	N	N+M	N
Mean arterial pressure (mm Hg)	73.8 $\pm$ 5.3	71.2 $\pm$ 6.7	66.3 $\pm$ 8.9	67.2 $\pm$ 7.3	74.8 $\pm$ 6.1	75.9 $\pm$ 5.9	73.4 $\pm$ 4.8	75.8 $\pm$ 4.4	83.2 $\pm$ 4.8	82.1 $\pm$ 5.1
Left atrial pressure (mm Hg)	—	—	7.4 $\pm$ 2.2	7.1 $\pm$ 1.9	8.6 $\pm$ 1.1	8.8 $\pm$ 0.8	9.1 $\pm$ 1.3	9.0 $\pm$ 0.7	9.2 $\pm$ 2.1	9.4 $\pm$ 0.9
Central venous pressure (mm Hg)	8.5 $\pm$ 3.6	9.2 $\pm$ 3.8	8.9 $\pm$ 3.5	9.3 $\pm$ 4.0	8.6 $\pm$ 3.2	8.6 $\pm$ 3.7	8.8 $\pm$ 4.8	8.1 $\pm$ 4.7	8.4 $\pm$ 4.7	8.3 $\pm$ 4.3
Mean pulmonary artery pressure (mm Hg)	17.4 $\pm$ 4.9	18.3 $\pm$ 5.9	16.4 $\pm$ 4.4	16.8 $\pm$ 4.5	18.3 $\pm$ 3.3	17.1 $\pm$ 4.2	18.3 $\pm$ 4.9	16.3 $\pm$ 4.9	17.9 $\pm$ 5.9	17.3 $\pm$ 4.9
Pulmonary arterial resistance (U)	4.5 $\pm$ 2.3	4.7 $\pm$ 1.6	3.7 $\pm$ 1.6	4.0 $\pm$ 1.5	4.5 $\pm$ 1.5	4.1 $\pm$ 1.4	3.8 $\pm$ 1.2	3.5 $\pm$ 1.6	3.6 $\pm$ 1.5	3.3 $\pm$ 0.8
Cardiac index (L/min/m ²)	2.2 $\pm$ 0.5	2.3 $\pm$ 0.6	2.4 $\pm$ 0.6	2.5 $\pm$ 0.7	2.2 $\pm$ 0.5	2.4 $\pm$ 0.7	2.6 $\pm$ 0.4	2.8 $\pm$ 0.7	2.6 $\pm$ 0.5	2.8 $\pm$ 0.5

Hemodynamic parameters before and for 24 hours after opening of the aortic crossclamp. N+M, Nifedipine plus metoprolol group ($n = 34$); N, nifedipine group ($n = 36$); U, arbitrary unit.

perfusion in poststenotic areas, an activation of myocardial β_1 -receptors produces no physiologically or pathophysiologically relevant coronary dilatation. Consequently, the rationale for using β_1 -receptor blockers such as metoprolol in the prevention of perioperative myocardial ischemia is its efficacy in decreasing myocardial oxygen consumption and the resulting improvement of the oxygen supply/demand ratio. Two basic mechanisms mediated by β_1 -recep-

tors should be mentioned that may account for their additional antiischemic potency when administered in combination with a calcium channel blocker such as nifedipine.

The *negative chronotropic effect* of β_1 -blockers causes an indirect antiischemic effect by reducing heart rate. Heart rate reduction leads to a prolongation of diastole, the phase during the cardiac cycle that is mainly responsible for beat-to-beat coronary

Table IV. Perioperative myocardial ischemia and arrhythmias

Variable	Nifedipine and metoprolol	Nifedipine	p Value
Transient ischemic event	1 (3%)	4 (11%)	<0.05
Myocardial infarction	0	0	NS
Sinus tachycardia	3 (9%)	12 (33%)	<0.05
Supraventricular tachycardia	1 (3%)	2 (6%)	NS
Atrial flutter and/or fibrillation	2 (6%)	10 (27%)	<0.05
Ventricular tachycardia	2 (6%)	0	NS

NS, Not significant.

perfusion.²⁴ Although we could not directly measure it, a reduction in heart rate during the perioperative period may also improve myocardial perfusion.²⁵

The *negative inotropic effect* of β_1 -blockers decreases the oxygen consumption of a normally perfused area located near a hypoperfused area and, consequently, prevents the development of a steal phenomenon, which leads to a supplementary damage to the hypoperfused area.²⁶ Furthermore, a reduction of oxygen demand in the hypoperfused area also optimizes the local oxygen distribution balance.²⁰

In this randomized study perioperative myocardial ischemia was detected by postoperative 48-hour Holter monitor recordings, serial assessment of 12-lead ECGs, analysis of myocardial enzymes, and continuous hemodynamic monitoring. The analysis of postoperative ST-segment changes, recorded by 3-channel Holter monitors, has become a widely used noninvasive method for the detection of myocardial ischemic events. The sensitivity of these recordings is comparable with that of exercise ECGs. By using the strict diagnostic criteria of combined analysis of Holter monitor recordings and 12-lead ECGs, we avoided misinterpreting ST-segment changes throughout the postoperative period—electrode imbalance, temperature changes, history of myocardial infarction, and postoperative pericarditis.

According to the diagnostic criteria used in the study, no patient in either group had a perioperative myocardial infarction. In contrast, the analysis provided evidence that nifedipine and metoprolol as a combined drug regimen significantly reduced the prevalence of postoperative transient ischemic events in comparison with nifedipine alone (3% vs 11%).

Although the clinical importance of perioperative supraventricular arrhythmias and their contribution to the occurrence of postoperative ischemia or other complications appear to be insignificant, such ar-

rhythmias are frequently not well tolerated by the patients and may induce various symptoms such as temporary hemodynamic instability, shortness of breath, or chest discomfort. Consequently, pharmacologic prevention of perioperative arrhythmias should be mandatory during postoperative treatment in the intensive care unit. In this study, the substantially lower incidence of supraventricular arrhythmias (sinus tachycardia and atrial fibrillation or flutter) in the nifedipine-metoprolol group as compared with the nifedipine group must be evaluated with respect to the documented antiarrhythmic efficacy of the β -blocker metoprolol.²⁷ Because an almost equal number of patients in both groups had preoperative treatment with β -blockers, it appears obvious that the perioperative infusion of metoprolol in the combined drug regimen group rather than use of preoperative β -blocker medication was responsible for the low incidence of arrhythmias in this group. There was no difference between the two groups with regard to the occurrence of ventricular tachycardia. Ventricular tachycardia is often triggered by significant myocardial ischemia or is the cause of ischemia. Thus the low incidence of ventricular tachycardia in both groups is in accord with the overall low incidence of manifestations of severe myocardial ischemia, such as myocardial infarction.

Analyses of serum enzymes sensitive for myocardial ischemia did not show any statistically significant differences between the two treatment groups. CK values were almost identical; both single and peak CK-MB values were only slightly lower in the metoprolol-nifedipine group than in the nifedipine group over the 36-hour observation period. The similar perioperative enzyme levels in the two groups may be explained by the fact that perioperative myocardial infarction is correlated with irreversible cell damage and high enzyme levels,²⁸ whereas transient ischemic events do not produce significant necrosis and higher enzyme levels. Because the two groups differed only with respect to the incidence of transient ischemic events, the enzyme analysis was unable to detect the lower incidence of perioperative myocardial ischemia in the metoprolol-nifedipine group. In addition, our earlier studies show that with nifedipine alone, perioperative enzyme plasma levels are already much lower than those of control groups treated with nitroglycerin, even in patients without any sign of myocardial ischemia on ECG or Holter monitor tracings.^{8,9} Consequently, the combined therapeutic regimen with metoprolol and nifedipine may have reached the pharmacologic and

Fig. 2. Perioperative serum creatine kinase-MB levels before the operation (*pOP*) and for 36 hours after opening of the aortic crossclamp. *MB*, MB isoenzyme of creatine kinase; Data are given as mean $\pm$ standard deviation. Value differs significantly from that for nifedipine-metoprolol group (* $p < 0.05$).

therapeutic limits in the prevention of perioperative myocardial ischemia.

The decrease in the prevalence of transient ischemic events in the metoprolol-nifedipine group in comparison with the nifedipine only group can be explained by the metoprolol-induced reduction of heart rate, starting 6 hours after release of the aortic crossclamp. All other perioperative hemodynamic, surgical (e.g., aortic crossclamp time, bypass time, number of distal anastomoses), or preoperative clinical data (e.g., age, sex, severity of coronary artery disease, history of myocardial infarction) predicting the occurrence of perioperative myocardial ischemia were sufficiently matched between the groups and did not influence the results of the study. The metoprolol-induced reduction in heart rate should account for a decrease in myocardial oxygen demand and a further increase in oxygen supply by increasing blood flow to the endocardium, especially in critically perfused areas. Consequently, it should lead to a further reduction in the prevalence of myocardial ischemia.^{24, 25}

Whereas the continuous infusion of low-dose metoprolol (12 μ g/kg per hour) was able to provide a substantial negative chronotropic effect, the hemodynamic data show no indication of profound negative inotropic activity of metoprolol: because hemodynamic parameters indirectly indicative of depressed myocardial contractility, such as cardiac index, mean

Table V. Enzyme data (IU/ml)

Variable	Nifedipine and metoprolol	Nifedipine
CK max	388 $\pm$ 41	418 $\pm$ 47
CK-MB max	15.7 $\pm$ 3.1	18.7 $\pm$ 3.9

aortic pressure, and left atrial pressure, were only slightly lower in the combined drug regimen group throughout the 24-hour observation period, the negative inotropic effect of metoprolol may have been negligible and, consequently, cannot account for the additional antiischemic efficacy of the combined regimen. However, metoprolol should not be infused in higher dosages that exert not only negative chronotropic effects but also substantial negative inotropic effects.²⁹ A marked depression of myocardial contractility may induce heart failure or the need for catecholamine or mechanical support, especially in patients with severely depressed myocardial function.

In conclusion, this randomized study with continuous perioperative infusion of nifedipine and metoprolol versus nifedipine alone provides evidence that the combined regimen is able to minimize the incidence of perioperative myocardial ischemia and arrhythmias. Whereas the immediate clinical value of the additional, metoprolol-induced reduction of perioperative transient ischemic events remains unclear, the reduction in reperfusion-induced arrhythm-

mias certainly improves the perioperative clinical situation of the patient and should be considered as an important goal for postoperative treatment.

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Discussion

Dr. Roland Fasol (*Bad Neustadt/Saale, Germany*). It is indeed an interesting approach to down-regulate the perioperative myocardial oxygen demand by decreasing the pulse/pressure rate and simultaneously increasing oxygen supply to the heart with this drug combination.

I congratulate you on your results of achieving significantly fewer perioperative arrhythmias and transient ischemic events in your study group by applying this perioperative regimen.

I think it may be assumed that a group of patients with fewer or no arrhythmias and ischemic events after CABG may consequently recover more quickly and require fewer

additional therapeutic interventions. This may thus contribute to efforts of improving cost efficiency in cardiac surgery.

Can you comment on the safety of applying β -blockers in patients with severely depressed myocardial function? Have you assessed the aspects of cost efficiency in regard to your clinical results of applying additional calcium antagonists and β -blockers in your group of patients?

Dr. Podesser. Thank you very much for your question, Dr. Fasol. It is always crucial to combine a low ejection fraction with a β -blocker. Fortunately, we had no patients with an ejection fraction less than 30% in this study. However, in such a case, close hemodynamic monitoring would be necessary while you use this regimen.

Concerning your second question, I would like to stress that we did not assess cost efficiency when we designed this study. I think you are right that this regimen might reduce the stay of the patient in the intensive care unit owing to arrhythmias and thereby produce more cost efficiency. On the other hand, the number of patients is too small to give real facts on this particular question.