Nicardipine for Preservation of Myocardial Metabolism and Function in Patients Undergoing Coronary Artery Surgery

Jacques J. Koolen, M.D.,* Harry B. van Wezel, M.D.,* Cees A. Visser, M.D.,† Adriaan C. Moulijn, M.D.,‡ Arnoud T. Rhelmecke Leyssius, M.D.,* John M. C. van Hal, M.D.,§ Louis Deen, M.D.,† Arend J. Dunning, M.D.†

The present study was designed to evaluate the myocardial protective effect of nicardipine (NIC) in patients with normal left ventricular (LV) function (control vs. NIC treatment group) and impaired LV function (control vs. NIC treatment group) during extracorporeal circulation for coronary artery surgery. NIC infusions were begun approximately 12 min before aortic cross clamping (AoX) at an infusion rate of 5 μg·kg⁻¹·min⁻¹ and maintained for 10 min. Prior to AoX an additional bolus of NIC 5 mg was given. Coronary hemodynamics, myocardial metabolic parameters (continuous thermodilution), and regional LV function (two-dimensional transesophageal echocardiography) were measured. At 15 min after discontinuation of AoX, lactate production was found in the two control groups but not in the two NIC treatment groups. In the control groups, lactate production returned to extraction at sternal closure. At that time regional area ejection fraction (RAEF) had significantly improved in both groups with impaired LV function compared with postintubation (baseline) values. In NIC-treated patients with impaired LV function, however, the percentage improvement in RAEF was significantly greater than that in the control groups. Between the groups, there were no differences in the number of patients requiring inotropic support, pacing, and/or diuretics after bypass or postoperatively. There were no significant differences in postoperative creatine kinase myocardial band release or in the incidence of dysrhythmias, myocardial infarction, or mortality. The results of the present study suggest that NIC iv may be used to provide additional myocardial protection during extracorporeal circulation. In addition, in NIC-treated patients with compromised LV function, this may be associated with a more apparent improvement in RAEF than that seen in nontreated patients. (Key words: Anesthetics, intravenous: fentanyl. Calcium entry blocking drugs: nicardipine. Measurement techniques: continuous thermodilution; two-dimensional transesophageal echocardiography. Heart, myocardial protection: St. Thomas cardioplegia. Surgery: coronary artery.)

In patients undergoing open heart surgery, preservation of myocardial cell function during extracorporeal circulation (ECC) should reduce postoperative morbidity and mortality. With the use of cardioplegic solutions and mild hypothermia during ECC, perioperative myocardial cell damage has been substantially reduced, although a certain degree of damage may still occur, as reflected by increased postoperative creatine kinase-MB (CK-MB) concentrations and impaired left ventricular (LV) function. Recently, it has been suggested that calcium entry blocking drugs (CEBD) may provide additional myocardial protection in patients undergoing coronary artery surgery (CAS). It is conceivable that CEBD, due to their inhibiting influence on breakdown of myocardial adenosine triphosphate (ATP), may have a beneficial effect on the preservation of cell structures during periods of ischemia, cardiac arrest, and reperfusion. This is mainly supported by animal experimental studies and some data obtained in patients. To test this hypothesis, nicardipine (NIC), a 1,4 dihydropyridine derivate with minimal negative inotropic activity, was used in the present study. This compound is a potent peripheral and coronary artery vasodilator. In addition, NIC is water-soluble, photoresistant, and has a relatively short elimination half-life. These properties suggest its potential usefulness in the anesthetic management of patients undergoing CAS. NIC was administered intravenously prior to ECC. The influence of calcium entry blockade on myocardial function and global myocardial metabolism was evaluated.

Methods

Fifty-six patients scheduled for elective CAS gave informed consent to participate in this study, which had the approval of the local ethics committee. Twenty-seven of these patients, with normal LV function at the preoperative catheterization (defined as ejection fraction [EF] > 50% and LV end-diastolic pressure [LVEDP] < 12 mmHg) were randomly allocated to one of two groups. These patients were all receiving beta-adrenergic blocking drugs (BABD) preoperatively. Both groups 1 (n = 14) and 2 (n = 13) received standard St. Thomas 1 cardioplegic solution (4°C). This cardioplegic solution contained: 147 mmol/l NaCl, 2 mmol/l KCl, 20 mmol/l CaCl₂, 16 mmol/l MgCl₂, and 1 mmol/l procaine HCl 1%. The osmolality was 350 mosm/l and the pH was 5. Cardioplegia was infused for a period of 3 min at a flow rate of 150 ml·m⁻²·min⁻¹. The patients were cooled to 27°C during ECC for myocardial protection. In addition, group 2 received NIC iv at an infusion rate of 5 μg·kg⁻¹·min⁻¹ for 10 min, followed by a bolus of 5 mg given over 2 min. NIC infusion was started after sternotomy at approximately 12 min before the start of aortic cross clamping (AoX). The remaining 29 patients had

* Senior Staff Member.
† Professor.
‡ Fellow.
Received from the Departments of Anesthesiology, Cardiology, and Cardiothoracic Surgery, Academisch Medisch Centrum, Amsterdam, The Netherlands. Accepted for publication May 16, 1989.

Address reprint requests to Dr. Koolen: Department of Cardiology, Academisch Medisch Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

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impaired LV function (defined as EF 25–50% and/or LVEDP > 12 mmHg) at the preoperative catheterization. Sixteen of these patients were receiving BABD preoperatively. These patients were randomly allocated to either group 3 (n = 15) or group 4 (n = 14). Both groups received St. Thomas 1 cardioplegic solution (4°C) and were cooled to 27°C during ECC. In addition, patients in group 4 received NIC iv at an infusion rate of 5 μg · kg⁻¹ · min⁻¹ for 10 min, starting 12 min before AoX, followed by a bolus dose of 5 mg given over 2 min. All NIC infusions in groups 2 and 4 were given via the proximal port of the pulmonary artery catheter and completed before the start of AoX. Excluded from the study were all patients who had a mean arterial blood pressure (MAP) lower than 70 mmHg between sternotomy and pericardietomy. The study had an open-label design.

PERFUSION TECHNIQUE

A colloid priming volume of 2,150 ml was used in combination with a Polystan roller pump (Polystan, Copenhagen) and a Cobe membrane oxygenator (Cobe, Lakewood, Colorado). A flow rate of 2.0–2.4 ml·m⁻²·min⁻¹ was used. The colloid priming contained: 1,500 ml Hae-macell, 500 ml Hartman, 100 ml mannitol 20%, and 50 ml Na-bicarbonate (8.4%).

ANESTHETIC TECHNIQUE

In all patients oral medication was continued until the morning of surgery. Lorazepam 4–5 mg orally was given 2 h before surgery. On arrival in the operating room standard electrocardiography leads were connected and leads II and V₅ continuously monitored. Two 14-G venous cannulae and an 18-G radial artery cannula were inserted after local analgesia. A triple-lumen thermodilution pulmonary artery catheter (Edwards Laboratories, Santa Anna, California) and a coronary sinus catheter (Wilton-Webster Laboratories, Alameda, California, type CCS-7U-90B) were introduced via the left subclavian vein. The coronary sinus catheter was advanced into the coronary sinus using image-intensification fluoroscopy and injection of contrast medium. The external thermistor was positioned 1–1.5 cm from the ostium. The absence of right atrial admixture in coronary sinus blood (coronary sinus reflex) was checked by injection of cold saline in the right atrium while coronary sinus thermodilution curves were recorded simultaneously. This was reconfirmed before each subsequent measurement. After preoxygenation, pancuronium 2 mg was given, followed by fentanyl 100 μg/kg injected over 5 min. When the patient became unresponsive to commands, an additional dose of pancuronium 6 mg was given, and ventilation was assisted and then controlled manually. After intubation of the trachea the lungs were ventilated with air/oxygen (FIO₂ = 0.5), and ventilation was adjusted to maintain the end-tidal CO₂ concentration between 4% and 4.5%. After tracheal intubation a transesophageal echotransducer (3.5 MHz phased array Diasonics), mounted on a flexible gastroscopy, was introduced and connected to a Diasonics 6400 ultrasonograph.

MEASUREMENT POINTS

Baseline measurements were obtained 15 min after intubation (A). Additional measurements were obtained after sternotomy when the pericardium was opened (B), 15 min after discontinuation of AoX (C) and after sternal

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**Fig. 1.** Diagram illustrating nine segments of the LV wall semiquantitatively evaluated in this study.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>1</td>
</tr>
<tr>
<td>Septum</td>
<td>2,3</td>
</tr>
<tr>
<td>Posterior lateral</td>
<td>4,5</td>
</tr>
<tr>
<td>Anterior lateral</td>
<td>6,7</td>
</tr>
<tr>
<td>Inferior</td>
<td>8,9</td>
</tr>
<tr>
<td>No. of patients</td>
<td>Group 1</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>Preoperative myocardial infarction</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Preoperative ejection fraction (%)</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Preoperative LVEDP (mmHg)</td>
<td>5 ± 2</td>
</tr>
</tbody>
</table>

Number of patients

| Single-vessel disease | 0 | 1 | 0 | 0 |
| Two-vessel disease    | 4 | 2 | 2 | 2 |
| Three-vessel disease  | 10 | 10 | 13 | 12 |

No. of patients using

| BABD | 14 | 13 | 9 | 7 |
| CBED | 10 | 9  | 8 | 7 |
| Diuretics | 1 | 0 | 6 | 7 |
| Long-acting nitrates | 10 | 11 | 14 | 14 |
| Digoxin | 0 | 0 | 8 | 6 |

closure (D). NIC infusions were started after measurement point B. At all measurement points simultaneous blood samples were taken from the radial artery and coronary sinus for determination of oxygen tension (Pₒ₂) and saturation (Sₒ₂), hemoglobin, and plasma lactate concentration. Coronary sinus blood flow was measured by continuous thermodilution.25 Sₒ₂ was determined by an OSM-11 hemoxymeter (Radiometer, Copenhagen); Pₒ₂ was determined by an ABL III (Radiometer, Copenhagen). Lactate concentration was measured using standard enzymatic techniques.26 Myocardial metabolic indices were calculated according to standard formulae.

\[ \text{CO}_2 (\text{ml/dl}) = \text{S}_2 \times \text{Hb} \times 2.23 + 0.003 \times \text{P}_2 \]

where Hb = hemoglobin (mM) and Pₒ₂ (mmHg)

\[ \text{MVO}_2 (\text{ml/min}) = \text{CSBF} \times (\text{Card}_2 - \text{Cso}_2) \]

where art = arterial, cs = coronary sinus, CSBF = coronary sinus blood flow.

\[ \text{MLE} (%) = \frac{\text{art lactate} - \text{cs lactate} \times 10}{\text{art lactate}} \]

\[ \text{CVR} (\text{mmHg/ml/min}) = \frac{\text{MAP} - \text{RAP}}{\text{CSBF}} \]

where RAP = mean right atrial pressure.

**Two-dimensional Echocardiography**

Transthoracic two-dimensional echocardiograms were obtained within 24 h before surgery, using a commercially available wide angle sector scanner (ATL mark 300 or Diasonics DRF 400). A standard approach was applied, i.e., multiple parasternal long-axis and short-axis views, as well as multiple apical and subcostal views. Echocardiograms were deemed adequate for analysis if all nine segments of the LV (fig. 1) could be studied in detail. All echocardiograms were videotaped and analyzed for presence and degree of regional wall motion abnormalities (RWMA). RWMA were defined as hypokinesis, akinesis and dyskinesis.

Transesophageal echocardiograms were obtained after introduction of the echotransducer into the esophagus (after intubation). Because depression of myocardial function may occur directly after intubation, echocardiographic data were obtained at least 15 min later. At that time prebypass evaluation of regional wall motion of the entire LV was performed in a semiquantitative way by obtaining multiple two-dimensional short-axis images at the level of the mitral valve leaflets, papillary muscles, and apex, as earlier described.5 In addition, a four-chamber view was obtained transthoracically 24 h before surgery to ensure that regional wall motion at measurement point A reflected the chronic state of LV function and not regional ischemia, induced by induction of anesthesia and intubation. Then the transducer was positioned and maintained at the level of the papillary muscles during the entire surgical procedure. Cross sections at this level were videotaped for quantitative analysis of regional wall motion postoperatively. Quantitative analysis of cross sections was performed with a commercially available computer-aided contouring system (Digisonics, Houston, Texas). The peak of the R-wave of the simultaneously displayed electrocardiogram was used to select end-diastolic stopframes. End-systolic stopframes were defined as

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the minimal cross-sectional area of the LV. In all instances, endocardial outlines were confirmed by playing through preceding and successive beats in real time, slow motion, and stopframe format. The outlines of the papillary muscles were excluded from the contour. The mean diastolic area of 3 consecutive beats was calculated and used as a loading parameter. Cross sections were then subdivided in eight equal areas, and the regional area shrinkage or ejection fraction (RAEF) was defined as follows:

\[
\text{diastolic area} - \text{systolic area} \times 100\%
\]

diastolic area

was calculated from the 3 consecutive beats and averaged, using a floating axis analysis system.\textsuperscript{50-92} Loading conditions to the LV, i.e., preload and afterload, were defined as end-diastolic area and systemic vascular resistance (SVR).

Postoperatively, in the intensive care unit CK-MB levels were measured six times at four hourly intervals, using radioenzymatic techniques.\textsuperscript{58} Electrocardiographic activity was continuously monitored (lead II). In addition, 12-

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>51 ± 13</td>
<td>55 ± 15</td>
<td>58 ± 17</td>
<td>2.8 ± 1.3</td>
</tr>
<tr>
<td>AoX (min)</td>
<td>2.6 ± 1.9</td>
<td>3.1 ± 1.1</td>
<td>2.9 ± 1.4</td>
</tr>
<tr>
<td>No. of grafts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Duration of Aortic Cross Clamping (AoX) and the Number of Saphenous Grafts Used

Data are given as mean ± SD.

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MAP = mean arterial pressure (mmHg); HR = heart rate (beats/min); PAP = pulmonary artery pressure (mmHg); PCWP = pulmonary capillary wedge pressure (mmHg); CI = cardiac index (1/min/m\(^2\)); SVR = systemic vascular resistance (dyne•s/cm\(^2\)); LVSWI = left ventricular stroke work index (g•m/m\(^2\)/beat).

\*P < 0.05 versus point A.

\+P < 0.01 versus point A.

\(\ddagger\)P < 0.05 versus group 3.
lead ECG was obtained after rewarming (36°C) and 6 h later. Perioperative myocardial infarction was defined as an increase in CK-MB levels > 70 IU/l with or without the occurrence of pathologic Q-waves. The number of patients requiring inotropic support, pacing, and/or diuretics after ECC or postoperatively was evaluated for each group. In addition, the incidence of ventricular dysrhythmias was evaluated.

**STATISTICAL ANALYSIS**

Data were analyzed using repeated measures two-way analyses of variance. When indicated, a modified t test was used to identify significant P values, calculated according to the method of Bonferroni. The distribution of the percentage change in RAIF was analyzed using the Kolmogorov-Smirnov test. A value of P < 0.05 was considered significant. Results are reported as mean ± SD. Unless indicated otherwise, patients in group 1 were compared with those in group 2 and patients in group 3 were compared with those in group 4.

**Results**

Preoperative patient characteristics are shown in table 1. The four groups were comparable with respect to age, weight, body surface area (BSA), and extent of coronary artery disease. The incidence of preoperative myocardial infarction in groups 3 and 4 (impaired LV function) was higher than that in groups 1 and 2 (normal LV function). Preoperative ejection fraction and LVEDP were not significantly different between groups 1 and 2 and between groups 3 and 4. The distribution of oral medication in groups 1 and 2 versus groups 3 and 4 was different. Between the groups the duration of AoX and the number of saphenous grafts were similar (table 2).

The mean duration of continuous NIC infusion was 10.8 ± 0.9 min in group 2 and 10.2 ± 1.2 min in group 4.

Hemodynamic results are shown in table 3. Compared with baseline measurements (point A), there were no significant differences between groups 1 and 2 (normal LV function preoperatively) at any time during the study. In group 4 cardiac index (CI) and left ventricular stroke work index (LVSWI) were significantly higher than in group 3 after cardiopulmonary bypass and at sternal closure.

CSBF, CVR, and MVO₂ are shown in figure 2. There were no significant differences between groups 1 versus 2 and groups 3 versus 4 with respect to CSBF, CVR, or MVO₂ at any measurement point during the study. Changes in myocardial lactate balance are shown in figure 3. At measurement points C and D, MLE was significantly lower than the values obtained at baseline in all groups. In the two control groups (1 and 3) MLE percentage changed from extraction to production at measurement point C (15 min after discontinuation of AoX). In contrast, MLE remained positive in groups 2 and 4 at that time. The difference between groups 1 and 2 and groups 3 and 4 at point C was significant (unpaired t test). At sternal closure MLE had returned to extraction in groups 1 and 3.

Transthoracic echocardiograms suitable for analysis were available in 49 patients. Adequate transesophageal
echocardiograms were available in all 56 patients. Table 4 shows the results of the comparison between preoperative transthoracic wall motion and intraoperative transesophageal wall motion. There was a significant correlation. A total number of 441 segments (9 × 49) was compared. Wall motion was unchanged in 387 of 441 (89%) segments, improved in 28 of 441 (6%) segments, and deteriorated in 24 of 441 (5%) segments.

Loading conditions at the four measurement points are shown in Table 5. Compared with point A, there was a significant reduction in end-diastolic area at point C in all groups. Compared with point B, there was also a significant reduction in end-diastolic area at point C in all groups. Compared with point A, SVR was not significantly reduced at any time during the study. This was due to a large interpatient variability. However, compared with group B, there was a significant decrease in SVR at point C in group II (but not in the other groups). Thus, loading conditions, i.e., preload and afterload, were only similar at measurement points A and D.

Wall motion analysis data obtained at measuring points A and D are shown in Figures 4 and 5. In the patients with normal LV function (Fig. 4), RAIF improved significantly following CAS and ECC. However, there was no significant difference in distribution of changes between treated and nontreated patients. Both groups of patients with impaired LV function preoperatively (groups 3 and 4) also showed a significant percentage increase in RAIF after grafting and ECC (Fig. 5). However, using the Kolmogorov-Smirnov test, it could be demonstrated that the distribution of the percentage improvement in RAIF in group 4 was significantly different from that in group 3. In other words, although the distribution of RAIF between groups 3 and 4 at measurement point A was similar before ECC and coronary revascularization, there were two different populations after these interventions (measurement point D).

**POSTOPERATIVE PERIOD**

Table 6 shows postoperative CK-MB release in groups 1–4, measured at 4-h intervals. In the first 24 h postoperatively, there were no significant differences in CK-MB concentrations between the groups. Following ECC and postoperatively, between groups 1 and 2 and groups 3 and 4 there were no significant differences in the number of patients requiring positive inotropic support, pacing, and/or diuretics. There was no significant difference in the incidence of dysrhythmias between the groups. One patient in each of groups 3 and 4 sustained a myocardial infarction (peak value of CK-MB > 70 IU/l). The postoperative period in all other patients was uneventful. There was no perioperative mortality in any of the groups. No symptomatic side effects that could be attributed to the study medication were found.

**Discussion**

Since the introduction of crystalloid cardioplegia in the late 1970s, used in combination with moderate hypothermia, myocardial protection during ECC has signifi-

| Table 4. Comparison of Semiquantitative Analyses of LV Segmental Wall Motion as Assessed by Transthoracic (TTE) and Transesophageal Echocardiography (TEE) in 49 Patients |
|---|---|---|---|---|
|          | TTE | TEE | Normal | Hypokinetic | Akinetic | Dyskinetic |
|          |     |     | Normal | Hypokinetic | Akinetic | Dyskinetic |
| Normal   | 325 | 307 | 18     | 0           | 0         | 0         |
| Hypokinetic | 62  | 18  | 40     | 4           | 0         | 0         |
| Akinetic  | 34  | 2   | 4      | 26          | 2         | 0         |
| Dyskinetic| 20  | 0   | 0      | 6           | 14        | 0         |

The number of segments showing normal, hypokinetic, akinetic or dyskinetic wall motion are shown.
TABLE 5. Loading Conditions of the LV at Baseline (A), after Pericardiotomy (B), 15 min after Discontinuation of Extracorporeal Circulation (C), and after Sternal Closure (D)

<table>
<thead>
<tr>
<th>Measurement Point</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>1,309 ± 305</td>
<td>1,305 ± 428</td>
<td>1,371 ± 240</td>
<td>1,292 ± 150</td>
</tr>
<tr>
<td>EDA</td>
<td>12.4 ± 2.0</td>
<td>11.5 ± 0.7</td>
<td>14.7 ± 1.3</td>
<td>15.4 ± 1.5</td>
</tr>
</tbody>
</table>

Data are mean ± SD. SVR = systemic vascular resistance (dyne·s/cm²); EDA = end-diastolic area (cm²).

* P < 0.05 versus point A.
† P < 0.01 versus point B.

Significantly improved.1–7 Myocardial cell damage, however, may still occur during ECC due to global ischemia and reperfusion and largely determines morbidity and mortality of cardiac surgery. Optimal myocardial protection during ECC is extremely important, especially in patients with compromised LV function. Animal studies have yielded evidence that myocardial protection can be further enhanced by the application of CEBD.10–16 By preventing excessive calcium influx and thus delaying myocardial ATP breakdown, these compounds may be of value during ECC, when inevitably periods of ischemia and reperfusion will occur.10,11

Limited data on the effect of calcium entry blockade during ECC in humans are available.15–21 These data are restricted to information on hemodynamic parameters and/or CK-MB release.58 In the present study, additional measurements, including myocardial metabolic parameters and regional myocardial contractile function, were obtained. Large doses of NIC iv were given prior to AoX, between pericardiotomy and the start of AoX. NIC, a 1,4 dihydropiridine derivate is chemically closely related to nifedipine but has been shown to exert a less negative inotropic effect when given intravenously or intracoronary.22–24,38–40 Long-lasting negative inotropy has been shown to be a disadvantage when patients have to be weaned off ECC.41 Furthermore, in contrast to nifedipine, NIC is water-soluble and not light-sensitive.26 After iv bolus administration, its hemodynamic effects will peak after 1–2 min. The elimination half-life of NIC is 40 ± 10 min.26

In the present study regional LV function as assessed by transesophageal echocardiography was related to simultaneously obtained hemodynamic and myocardial metabolic variables. Two-dimensional echocardiography has been shown to be highly sensitive for assessment of ischemia-induced wall motion abnormalities.42–44 The specificity of RWMA, however, especially during surgery and anesthesia, is subject to several controversies and uncertainties. Recently, these problems have been summarized by Thys.** There appears to be considerable heterogeneity of contraction at all levels of the ventricle in subjects without any evidence of heart disease.45 As a result, RWMA that could be attributed to ischemia can simply be the expression of normal physiologic variation in ventricular contraction.

An overestimation of regional dysfunction may occur in ventricles with RWMA because on the frame chosen for end-systole, nonischemic segments may be beyond their point of peak systolic shortening and, thus, may be labeled as ischemic.46 Conversely, ischemic segments that did not contract during the ejection phase might be able to shorten when the ventricle has nearly emptied. This post-systolic shortening of ischemic segments may lead to normal wall motion at minimum ventricular volume, although a significant abnormality of regional contraction is present.** In addition, it is not known to what extent mechanical ventilation, sternotomy, pericardiotomy, and cardiopulmonary bypass can influence the diagnosis of RWMA in patients with normal and abnormal LV function.47–49 When filling pressures and ventricular volume are normal or only slightly increased, the pericardium does not appear to affect LV systolic function or diastolic compliance in humans.47,48 Furthermore, loading conditions will affect RWMA because wall motion is dependent on preload, afterload, and contractility. In the present study end-diastolic area and SVR were used to assess loading conditions (table 5). Preload and afterload were only similar at measuring points A (baseline) and D (after sternal closure). Therefore, changes in RAEF from baseline could only be interpreted as changes in myocardial function at measuring points A and D.

Fig. 4. Percentage change in regional area ejection fraction in group 1 (112 segments) and group 2 (104 segments). Changes were measured between measurement points A (baseline) and D (sternal closure).

To ensure that our baseline measurements of wall motion reflected the chronic state of LV function and not regional ischemia induced by induction of anesthesia and intubation, we compared echocardiographic data obtained 24 h preoperatively with those obtained 15 min after intubation (table 4). There was an excellent correlation. This is in keeping with data from previous studies.\textsuperscript{49,6} Therefore, we consider the echocardiographic data presented in this study as valid. However, another problem, also recognized by Thys,\textsuperscript{22} arises when changes in RWMA are used to assess the effects of interventions, such as drug administration, as in the present study. If RWMA before the intervention are caused by reduced myocardial blood flow, it is conceivable that the low flow is adequate to preserve cellular viability but not to permit normal contractile function. Improvement of coronary flow by grafting or drug administration will most likely lead to improved contractile function. If, however, the etiology of RWMA is cellular damage, \ie, myocardial infarction, little improvement is to be expected from im-

Fig. 5. Percentage change in regional area ejection fraction in group 3 (120 segments) and group 4 (112 segments). Changes were measured between measurement point A (baseline) and D (sternal closure).
TABLE 6. Postoperative CK-MB Concentrations (IU/l) in the Intensive Care

<table>
<thead>
<tr>
<th>Group</th>
<th>Arrival</th>
<th>4 h</th>
<th>8 h</th>
<th>12 h</th>
<th>16 h</th>
<th>20 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 ± 11</td>
<td>28 ± 9</td>
<td>21 ± 10</td>
<td>16 ± 9</td>
<td>12 ± 6</td>
<td>5 ± 5</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>2</td>
<td>22 ± 9</td>
<td>29 ± 10</td>
<td>23 ± 14</td>
<td>19 ± 11</td>
<td>9 ± 7</td>
<td>6 ± 6</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>3</td>
<td>25 ± 18</td>
<td>32 ± 14</td>
<td>26 ± 15</td>
<td>22 ± 12</td>
<td>16 ± 10</td>
<td>8 ± 6</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>4</td>
<td>24 ± 19</td>
<td>34 ± 18</td>
<td>27 ± 16</td>
<td>20 ± 9</td>
<td>14 ± 8</td>
<td>6 ± 5</td>
<td>5 ± 6</td>
</tr>
</tbody>
</table>

proved coronary blood flow. Therefore, the reversibility of myocardial performance must be known to assess the influence of interventions.

Preoperative abnormal RAEF (<50%) may improve following CAS.49,44 This was demonstrated in both groups 3 and 4. Figure 5 shows the percentage change in RAEF in groups 3 and 4. The distribution of these changes between groups 3 and 4 was significantly different when compared by the Kolmogorov-Smirnov test.54-56 No such changes in distribution were found between groups 1 and 2 (fig. 4). In this context it is important to realize that reversibility of impaired myocardial performance plays an important role in the interpretation of the effect of CAS and/or nicardipine pretreatment on RAEF. The distribution of preoperative myocardial infarction in the groups with impaired LV function was not homogenous. In group 3, 53% (eight of 15) of patients had sustained a preoperative myocardial infarction, whereas this was 64% (eight of 14) in group 4 (table 1). Therefore, the potential reversibility of RWMA at baseline might have been higher in group 3 than in group 4. In these patients, however, the preoperative global LV function (LV ejection fraction and LVEDP, table 1) and the number of asynergic segments at baseline was similar. The additional improvement in myocardial performance in group 4 may be partly explained by our finding that in group 3 (as in group 1), MLE changed from extraction to production after ECC (at measuring point C). The absence of myocardial lactate production in both groups 2 and 4 suggests that NIC pretreatment may have mitigated the regional or global effects of ischemia on the myocardium and thus preserved myocardial function. However, the importance of NIC pretreatment on the myocardial lactate balance during ECC is difficult to interpret. Myocardial lactate production is a sensitive index of myocardial ischemia, but the myocardial lactate balance is dependent upon multiple metabolic parameters, and any absolute value short of production cannot be considered abnormal.50,51 Lactate production was only found in the two control groups. At the onset of ECC, ischemia frequently occurs, in particular, when satisfactory hypothermia cannot be obtained immediately. It is conceivable that at this stage of ECC, NIC pretreatment has exerted a cytoprotective effect due to reduction of calcium influx. This may have mitigated the extent of lactate production during periods of anerobic metabolism. A similar effect of NIC on the myocardial lactate balance during cardiac catheterization has been reported by Rousseau et al.24 They injected NIC directly intracoronary in awake, normothermic patients. In our patients NIC was given intravenously, approximately 12 min before start of AoX. At this stage of surgery, vasodilator therapy is frequently required to prevent and/or treat arterial hypertension. This may explain the absence of hypotension during NIC infusion in our patients. NIC was presumably sequestered in hypothermic, arrested myocardium, prior to long lasting periods of global ischemia. The "intramyocardial" pharmacology of this compound is totally unknown in this situation, but the influence of NIC on the myocardial lactate balance suggests that at least some pharmacologic properties of the drug must have remained intact.

Although myocardial lactate production is a sensitive index of myocardial ischemia, a more complete description of intracellular events might have been obtained if the measurement of other metabolic substrates (glucose, free fatty acids, ketone bodies, hypoxanthine, inosine, and/or inorganic phosphate) in both arterial and coronary sinus blood would have been included in our protocol.55-56 In our clinical study, however, there would have been an unacceptable prolongation of each measurement point if more blood samples were to be drawn from the coronary sinus and the radial artery.

Although we must recognize the limitations of the measurement techniques that were used in the present study, our findings suggest that patients with impaired LV function may benefit from the use of NIC. It therefore seems justified to perform more studies with this agent in larger groups of patients undergoing cardiac surgery. As with other CEBD, this compound holds the promise of a combined effect on both myocardial metabolism and the coronary and peripheral arterial systems. Recently, both NIC and nifedipine have been successfully used for blood pressure management in patients undergoing CAS.57,58-59 However, in those studies, as in the present

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one, no significant reduction in postoperative CK-MB release could be demonstrated.

In conclusion, the results of the present study suggest that iv NIC pretreatment may have a beneficial effect on the myocardial lactate balance during ECC. In addition, in NIC-treated patients with compromised LV function, this may be associated with a more apparent improvement in RAEF than in nontreated patients.

References