Reversible Cardiac Sympathectomy by High Thoracic Epidural Anesthesia Improves Regional Left Ventricular Function in Patients Undergoing Coronary Artery Bypass Grafting

A Randomized Trial

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Hypothesis: To evaluate the effects of high thoracic epidural anesthesia (TEA) on global and regional myocardial function and on perioperative coronary risk in patients undergoing coronary artery bypass grafting.

Design, Setting, and Patients: Prospective and randomized clinical trial blinded for the primary outcome measure of 73 patients scheduled for coronary artery bypass grafting who had a left ventricular ejection fraction of 50% or more conducted from February 1, 2000, through August 31, 2000, at University Hospital, Münster, Germany.

Interventions: Of 73 randomized patients, 37 were control subjects (who received general anesthesia only) and 36 were in the group who received general anesthesia and high TEA.

Main Outcome Measures: The primary outcome measure was regional left ventricular function after myocardial revascularization, assessed by transesophageal echocardiography. We further determined the plasma concentrations of cardiac troponin I and atrial and brain natriuretic peptides. Secondary outcome measures were postoperative complications recorded to 14 days and mortality recorded to 720 days.

Results: High TEA was effective in all patients of this group, the somatosensory block extended from T1 through T7 vertebrae. Regional left ventricular function was significantly improved (mean [SD] global wall motion index, 0.74 [0.18] vs 0.38 [0.16]; \(P<.05\)), and cardiac troponin I concentrations were reduced by 72% (mean [SD], 5.7 [1.5] vs 1.6 [0.7] ng/mL, \(P<.05\)) in patients with high TEA. Natriuretic peptide concentrations peaked during reperfusion (atrial natriuretic peptide) and 24 hours after reperfusion (brain natriuretic peptide). High TEA reduced the mean (SD) peak concentrations of atrial natriuretic peptide by 54% (211 [63] vs 98 [33] ng/mL, \(P=.03\)) and brain natriuretic peptide by 43% (189 [39] vs 108 [21] ng/mL, \(P=.01\)). One of 36 patients who received high TEA and 3 of 37 controls died.

Conclusions: Reversible cardiac sympathectomy by high TEA improves regional left ventricular function and reduces postoperative ischemia after coronary artery bypass grafting. These effects of high TEA may improve the long-term outcome after myocardial revascularization.

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Prevention of perioperative myocardial ischemia in patients undergoing coronary artery bypass grafting (CABG) is essential to avoid potentially fatal metabolic, electrophysiological, and mechanical dysfunction of the heart. Drugs, equipment, and anesthetic techniques have dramatically changed in recent years, and tools such as heparin prophylaxis for venous thrombosis and pulmonary embolism have significantly reduced postoperative mortality and morbidity. Moreover, some modern volatile anesthetics have been demonstrated to have cardioprotective effects in animal models. On the other hand, no specific volatile or opioid-based anesthetic technique has been shown to be superior to another in preventing ischemic events. An activation of myocardial sympathetic nerves in cardiac surgery can result in myocardial ischemia especially in patients with coronary artery disease. Consequently, a reversible cardiac sympathectomy by high thoracic epidural an-
esthesia (TEA) may have anti-ischemic effects owing to the blockade of efferent sympathetic fibers.\textsuperscript{5, 6} We hypothesized that a combination of general anesthesia and reversible cardiac sympathectomy by high TEA may reduce perioperative ischemia and improve regional left ventricular function in patients undergoing CABG.

Transesophageal echocardiography is used to examine global and segmental left ventricular function. This method seems to be the ideal modality for early detection of intraoperative ischemia and has been well established for cardiac surgical procedures during the last decade. Moreover, we measured the plasma concentrations of cardiac troponin I and atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Troponin I is a specific and highly sensitive marker for the detection of minor myocardial injury and one of the most sensitive markers of postoperative ischemia.\textsuperscript{7} The natriuretic peptides ANP and BNP are hormones secreted from the heart that act through guanylyl cyclase receptors.\textsuperscript{8-10} An ANP is primarily produced by atrial myocytes, whereas BNP is of atrial and ventricular origins. The physiological effects of these peptides include natriuresis and diuresis, aldosterone antagonism, relaxation of vascular smooth muscle cells, and direct antiproliferative effects on cardiac myocytes counteracting hypertrophy and destruction of sarcomere structure.\textsuperscript{10} Increased plasma concentrations of ANP and BNP have been found to be associated with hypotension, congestive heart failure, myocardial ischemia, renal insufficiency, and cerebral salt wasting.\textsuperscript{11-16} Both peptides are powerful prognostic risk indicators in coronary ischemia and heart failure.\textsuperscript{17-19}

The study was approved by the institutional review board of University Hospital, Münster, Germany, and conducted in accord with the principles of the Declaration of Helsinki. All participants gave written informed consent.

**METHODS**

The study was conducted from February 1, 2000, through August 31, 2000, at University Hospital, Münster. Eligible patients had coronary artery disease with a left ventricular ejection fraction of 50% or more and were scheduled for elective CABG. Exclusionary criteria were any preexisting endocrinological diseases, renal insufficiency, coagulation disorders, or right and/ or left ventricular dysfunction; concomitant disorders of heart valves; having undergone cardiac surgical procedures; acute myocardial infarction; and heart failure. Randomization was carried out by a computer-generated sequence without any restriction. Assignments were concealed in opaque, sealed envelopes that were numbered consecutively by a study nurse. After enrollment of patients by the study coordinator, the envelopes were opened to allow placement of the epidural catheter 1 day prior to surgery for those who were assigned to this group.

**INTERVENTIONS**

Before any intervention, all patients received 130 kDa of 500-mL hydroxyethyl starch via a peripheral venous line to prevent a decrease in mean arterial pressure caused by a reduction of left ventricular afterload during the induction of general anesthesia and/or initiation of high TEA. Radial and flow-directed balloon-tipped 7F Edwards (Baxter Healthcare Corp, Irvine, Calif) thermodilution pulmonary artery catheters (one each) were inserted for routine monitoring of hemodynamic parameters.

In patients randomized for additional high TEA, the epidural catheter was inserted at level C7-T1 vertebra by the median approach and hanging drop technique the day before surgery. Correct position was tested by the injection of 2 mL of 0.5% bupivacaine hydrochloride with epinephrine hydrochloride. Prior to surgery and before the induction of general anesthesia, high TEA was initiated by 6 to 12 mL of 0.5% bupivacaine hydrochloride and 15 to 25 µg of sufentanil citrate into the epidural space to block the somatosensory level T1-T3 vertebrae for reversible cardiac sympathectomy. The somatosensory blockade was evaluated by touching the skin with ice and performing the pinprick test. The extent of the epidural blockade was recorded. Twenty minutes after completion of the epidural block, we determined hemodynamic factors in the awake patients before general anesthesia was started. During the surgical procedure a continuous epidural infusion of 2 mL of 0.75% bupivacaine hydrochloride per hour was initiated for intraoperative analgesia and further postoperative patient-controlled analgesia.

General anesthesia was induced in all patients using intravenous midazolam maleate (0.1 mg/kg per dose), sufentanil citrate (2-5 µg/kg per dose), and pancuronium bromide (0.1 mg/kg per dose) while patients inspired 100% oxygen. After endotracheal intubation, the patients received mechanically ventilated oxygen and air (fraction of inspired oxygen 0.3). The mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide tension of 35 to 40 mm Hg. Patients who only received general anesthesia also received body weight–related doses of sufentanil citrate (1-2 µg/kg per hour) and propofol (1.5-3 µg/kg per hour). In patients with high TEA, general anesthesia was maintained by propofol infusion (1.5-3 mg/kg per hour) supported by repetitive injections of sufentanil citrate (0.2-1 µg/kg).

As a standard procedure all patients received 2 million U of aprotinin (Trasylo; Bayer, Leverkusen, Germany) in the pump priming before and a continuous infusion of 500,000 U of aprotinin during cardiopulmonary bypass. Anticoagulation was achieved giving an intravenous dose of heparin sodium (Heparin-Natrium; Braun, Melsungen, Germany) (initial bolus dose of 400 IU/kg, targeting an activated clotting time of 440 seconds) and monitored using the activated clotting time. Management of extracorporeal circulation was standardized with pump flows of 2.3 to 2.8 L/min·m², normothermia (36.5°C), and the arterial blood gas analyses during cardiopulmonary bypass were not corrected for body core temperature. Cold cardioplegic arrest was induced using Bretschneider-HTK solution (Custodiol; Köhler, Alsbach, Germany) and topical cooling. After aortic declamping, the lungs were mechanically ventilated with 100% oxygen. Subsequently, the fraction of inspired oxygen was adjusted to maintain an arterial oxygen saturation of more than 95%. A positive end-expiratory pressure of 5 cm H₂O was applied after cardiopulmonary bypass. Hypothermia (32°C) and brain cooling (24°C) were achieved giving an intravenous dose of heparin sodium (Heparin-Natrium; Braun, Melsungen, Germany) and 0.02 to 0.1 µg/kg per minute of epinephrine (Suprarenin; Hoechst, Bad Soden, Germany) as requested. In the intensive care unit (ICU), mechanical ventilation was maintained as just described. Weaning the patient from the respirator and extubation were performed according to standard procedures.

**MAIN OUTCOME MEASURES**

The primary outcome was regional left ventricular function after myocardial revascularization. Thirty minutes after induc-
tion of general anesthesia and on admission to the ICU left ventricular systolic function and afterload were assessed by transesophageal echocardiography: global left ventricular wall motion score (expressed as points) as a summary measure of regional wall motion abnormalities for regional left ventricular function, fractional area change (expressed as a percentage) for global left ventricular function, and left ventricular end-systolic meridional wall stress (expressed as dynes per square centimeter) for afterload.

Global left ventricular wall motion was assessed by the 16-segment model from the midesophageal 4-chamber view (3 septal and 3 lateral segments), midesophageal 2-chamber view (3 anterior and 3 inferior segments), midesophageal long axis (2 anteroseptal and 2 posterior segments), and transgastric short axis (6 segments at the mid level). Estimation of wall motion was performed and scored as follows: 0 indicates normal wall motion; 1, hypokinesia; 2, akinesia; or 3, dyskinesia.20 Echocardiographic examinations were recorded on videotape in all patients by the same observer (C.S.), consecutively numbered, blinded for groups, and post hoc analyzed by a cardiologist (H.R.).

Fractional area change was determined by outlining the end-systolic and end-diastolic left ventricular area (leading-edge technique) in the midpapillary cross-sectional view and calculated using the following formula:

\[
FAC = \frac{EDA - EDA}{EDA \times 100},
\]

where \( FAC \) indicates fractional area change; \( EDA \), end-diastolic area; and \( ESA \), end-systolic area.

M-mode meridional end-systolic wall stress (\( \sigma \)) was calculated using the following formula:21,22

\[
\sigma = \frac{[(1.35 \times BP_{sys} \times LVID)] \times (4 \times h \times (1 + h/LVID))}{LVID},
\]

where \( BP_{sys} \) indicates systolic blood pressure; \( LVID \), left ventricular internal diameter; \( h \), end-systolic posterior wall thickness, 1.35 conversion factor from millimeters of mercury to dynes per square centimeter.

Additionally, we analyzed the plasma of all patients for ANP and BNP (both expressed as picograms per milliliter) 10 minutes prior to the induction of anesthesia; 20 minutes after the onset of cardiopulmonary bypass; 10 minutes after the onset of myocardial reperfusion; 20 minutes after cardiopulmonary bypass; on admission to the ICU; and at 6, 12, 24, and 48 hours after admission to the ICU. To calculate normal ranges of ANP and BNP, blood samples were collected from 40 healthy volunteers. We further determined heart rate (beats per minute), mean arterial pressure (millimeters of mercury), cardiac output (liters per minute), systemic vascular resistance (dynes per second per centimeter\(^2\)), central venous and pulmonary artery occlusion pressures (millimeters of mercury), preoperative and postoperative cardiac troponin I concentrations (nanograms per milliliter), and the activity of the brain and cardiac muscle isoenzyme of creatine kinase (units per liter).

The secondary outcome was patients’ 14-day morbidity and 2-year mortality. Preoperative morbidity of patients was determined by the Cleveland score.23 Postoperatively, complications (relevant bleeding, severe myocardial ischemia, malignant tachyarrhythmias, low cardiac output syndrome, myocardial infarction, and intra-aortic balloon counterpulsation) were recorded to 14 days. A 12-lead electrocardiogram (ECG) was taken on admission to the ICU and at 12 and 24 hours later. Severe myocardial ischemia was defined as new ST-segment changes of more than 2 mV detected in the ECG. Moreover, the occurrence of new supraventricular or ventricular arrhythmias was indicative for myocardial ischemia. In addition, transesophageal examination was performed in cases with ECG changes, arrhythmias, or hemodynamic instability (characterized by increased preload pressure, decreased afterload, low cardiac output, mixed venous oxygen saturation, or elevated lactate concentrations). Acute low cardiac output syndrome was defined as follows: cardiac index lower than 2.2 L/min per square meter, systemic vascular resistance higher than 1000 dyne-s\(^{-1}\)·cm\(^{-5}\), tachycardia (heart rate, >120 beats/min), oliguria (<2 mL/h), and metabolic acidosis. Diagnosis of myocardial infarction was based on ECG changes (new persistent Q waves and ST-segment deviations: 1-mV ST-segment elevation in 2 or more limb leads and/or 2-mV ST-segment elevation in 2 or more precordial leads), a typical rise and fall in levels of serum creatine kinase and creatine kinase brain isoenzyme MB on the activity curves. We assumed a relevant bleeding when the blood loss was higher than 150 mL/h during the first 3 hours after admission to the ICU, and when this blood loss did not decrease during the first 6 hours after admission or after normalization of serum coagulation parameters. The patient’s mortality was recorded to 720 days and assessed by telephone interviews with patients or their relatives and, in cases of death, with the practitioner.

**BIOCHEMICAL ANALYSES**

The plasma concentrations of ANP and BNP were measured by radioimmunoassays (Peninsula Laboratories, Belmont, Calif), as previously described, using polyclonal rabbit IgG-antiserum samples to the following peptides: \( \alpha \)-ANP 1-28 (human) and referred BNP-32 (human).18 For measurements, 10 mL of venous blood was drawn into a chilled syringe, transferred into polypropylene tubes containing EDTA (3 mmol/L) and aprotinin (500 kIU/mL) at 4°C, and centrifuged at 1600 rpm for 15 minutes at 4°C. Plasma was stored at −70°C until analysis. Peptides were extracted from 5 mL of plasma (Sep-Pak C\(\text{18} \)), Waters Associates, Milford, Mass) and eluted with 3 mL of a mixture of 60% acetonitrile, 0.1% trifluoroacetic acid, and 39% distilled water (by volume). All samples were assayed in triplicate and analyzed as a batch to minimize assay variations. Standard curves were constructed with standard human ANP and BNP in radioimmunoassay buffer. The mean recovery of added natriuretic peptides from plasma was 60% to 80%, and the lower detection limits as defined by 95% of the upper plateau of the standard curve were 0.1 nmol per tube for ANP and 0.5 nmol per tube for BNP. Cross-reactivity between natriuretic peptides was less than 0.1%. The intra-assay and interassay coefficients of variations were 3.8% and 9.6% for ANP and 6.1% and 7.9% for BNP, respectively.

Plasma concentrations of cardiac troponin I were measured using a commercially available 1-step colorimetric immunoassay based on the “sandwich” principle (Dimension RxL; Dade Behring, Marburg, Germany). After sampling, the plasma was stored at −70°C until analysis. For analysis, samples were incubated with chromium oxide particles coated with a monoclonal antibody specific for the cardiac troponin I molecule, and a conjugate reagent (alkaline phosphate–labeled monoclonal antibody specific for cardiac troponin I, to form the particle/cardiac troponin I/conjugate sandwich. Unbound conjugates were removed by magnetic separation and washing. The particle/cardiac troponin I/conjugate sandwiches were then transferred to the cuvette where the sandwich bond triggered an amplification cascade finally converting 3,5-dichloro-2-hydroxybenzenesulfonic acid and 4-aminonitropryzine to a colored product that absorbs at 510 nm. The color change was directly measured proportional to the concentration of cardiac troponin I present in the patient sample. The intra-assay and interassay coefficients of variations were 3.2% and 4.7%, respectively. The cross-reactivity of the assay with human skeletal muscle troponin I, cardiac troponin T, and cardiac troponin C.
was 0.04%, 0.34%, and 0.00%, respectively. The sensitivity was 0.04 ng/mL.

STATISTICAL ANALYSIS

The sample size of 36 patients per group was estimated on the basis of the assumption that the study would have 80% power (2-sided, \( \alpha = 0.05 \), \( df = 0.6 \)) to detect differences of global left ventricular wall motion values between the 2 groups. Nominal scale variables were described by using relative and absolute frequencies, and the \( \chi^2 \) test was used to assess differences among groups. The Fisher exact test was used if matched cells were rare (expected frequencies <5). Interval or rational-scaled variables were described as mean (SD). Unpaired \( t \) test or repeated-measures analysis of variance was used to compare groups (Statistical Package for the Social Science System, version 10.0; SPSS Inc, Chicago, Ill). In the analysis of variance we calculated between and within group differences. Between-subjects factors were analyzed by simple contrasts; polynomial contrasts were used to analyze within-subjects factors. Covariation between variables was assessed with Pearson product moment correlation analyses. \( P < 0.05 \) was considered statistically significant.

RESULTS

STUDY POPULATION

Of the 91 screened patients, 73 patients underwent randomization—37 patients to the general anesthesia only group and 36 patients to the general anesthesia and high TEA group—between February 3, 2000, and August 29, 2000. The remaining 18 patients were not enrolled because they refused to participate (3 patients), they developed unstable angina prior to surgery (3 patients), or because of the detection of hyperglycemia (4 patients), elevated serum creatinine concentrations (6 patients), or having received systemic anticoagulant therapy that did not allow the placement of an epidural catheter (2 patients). In both groups all patients received the allocated intervention, completed the 14-day follow-up, and all videotapes could be analyzed for primary outcome measures without intention-to-treat (Figure 1).

Both groups were comparable for preoperative medication of \( \beta \)-receptor blockers and other specific drugs. All patients had 2- to 3-vessel coronary artery disease and received 1 internal mammary artery bypass on the left anterior descendent artery and additional venous grafts.

High TEA was successfully performed in all patients of this group without any observed complication. The mean level of the upper vertebral blockade was T1 and the mean lower vertebral blockade T7. The mean (SD) duration of postoperative patient-controlled analgesia via the epidural catheter was 4 (1.4) days. All patients of both groups were weaned from therapy for the cardiopulmonary bypass and remained in the ICU for the next 24 hours. The duration of postoperative mechanical ventilation was significantly shorter in patients with additional high TEA. None of the patients had any relevant complication that was detectable such as postoperative bleeding or severe myocardial ischemia. The patients' demographic data, highest postoperative creatine kinase (brain and cardiac muscle isoenzyme MB) concentrations, comorbidity, and left ventricular ejection fraction, duration of cardiopulmonary bypass and cross clamping, administration of epinephrine during the weaning period from cardiopulmonary bypass and ICU therapy, and number of venous grafts are summarized in Table 1. Heart rate, cardiac output, mean arterial pressure, central venous and pulmonary artery occlusion pressures, and systemic vascular resistance did not significantly differ between groups during the entire study period. Only heart rate and systemic vascular resistance tend to decrease in patients with high TEA without reaching statistical significance in the awake patients 20 minutes after completion of the somatosensory blockade (Table 2).

GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION

Global left ventricular function as assessed by fractional area change was comparable in all patients independent of the existence of reversible cardiac sympathectomy by high TEA during the study period. Preoperatively, regional left ventricular function as assessed by the global left ventricular wall motion score was comparable in all patients. Postoperatively, however, global left ventricular wall motion was significantly improved in patients with additional reversible cardiac sympathectomy. Left ventricular afterload as assessed by left ventricular end-systolic meridional wall stress was slightly decreased in all patients and did not differ between groups. Postoperatively, peak cardiac troponin I concentrations were significantly lower in patients who received additional high TEA compared with those who received general anesthesia only (Figure 2).
The mean plasma concentration of ANP in healthy volunteers was 26.8 (9.7) pg/mL. In all patients baseline values of ANP were slightly elevated compared with controls (P < .05). In patients who received general anesthesia only, ANP concentrations increased to their highest levels during the reperfusion period after cross clamping and decreased thereafter. The increase in ANP concentrations was significantly lower in patients with additional high TEA (P < .05). The mean control value of BNP was 15.9 (9.6) pg/mL. The BNP concentrations were also moderately elevated in all patients at baseline (P < .05). The secretion pattern of BNP was different from that of ANP. The BNP concentrations increased 6 hours after admission to the ICU reaching their highest levels 24 hours postoperatively (P < .05). This secretion pattern of BNP was significantly attenuated in patients with additional high TEA compared with those who received general anesthesia only (P < .05). The ANP and BNP concentrations in patients with and without reversible cardiac sympathectomy by high TEA are shown in Figure 3. Overall the patients’ postoperative peak concentrations of BNP (r = 0.49, r² = 0.24, P < .001, N = 73) and troponin I (r = 0.38, r² = 0.14, P = .04, N = 73) correlated with the postoperative values of the global left ventricular wall motion score. No correlation could be calculated between ANP concentrations and the global left ventricular wall motion score as well as the troponin I concentrations.

**MORBIDITY AND MORTALITY**

Two of 37 patients who received general anesthesia only but none of the 36 patients who received general anesthesia and high TEA needed ICU therapy for more than 24 hours because of intermittent respiratory insufficiency (Table 1). Three patients who received general anesthesia only and 1 patient who received general anesthesia and high TEA died during the first 720 days after CABG. The 3 patients of the general anesthesia only group died 95, 153, and 441 days and the 1 patient of the general anesthesia and high TEA group died 579 days after CABG for cardiac reasons.

### Comment

Epidural analgesia is well proven as an efficacious method of pain relief and a well-established anesthesia technique for patients who undergo noncardiac surgical procedures. A recently published meta-analysis of 141 trials revealed a small but significant reduction in mortality and morbidity in patients allocated to neuroaxial blockade compared with patients who receive general anesthesia for noncardiac surgical procedures. However, there is still considerable debate over the advantages and disadvantages of regional vs general anesthesia, and large randomized studies are lacking. It was recently shown that high TEA not only controls pain but also has anti-ischemic effects in patients with unstable angina pectoris, most likely owing to the blockade of efferent sympathetic fibers. We hypothesized that a reversible cardiac sympathectomy performed using high TEA (added to a routine general anesthesia) may reduce perioperative ischemia and coronary risk in patients undergoing CABG surgery.

Data described in this study show that a combination of general anesthesia and high TEA has a positive effect on heart function and cardiac risk in patients undergoing CABG. Heart function was assessed by intraoperative transthoracic echocardiography, a useful and standardized technique to monitor global ventricular function and to detect intermittent wall motion abnormalities during the perioperative period. Global left ventricular function, for example, the overall contractility of the left ventricle, and the ejection fraction were not different between patients who received high TEA with general anesthesia and patients who only received general anesthesia. This finding was not unexpected insofar as our patients had no signs of preexisting left ventricular dysfunction evaluated by preoperative angiography and echocardiography. However, the average postoperative regional wall motion score in patients who received high TEA and general anesthesia was about 50% lower compared with the controls, indicating a substantially reduced incidence of regional wall motion abnormalities. Regional wall motion abnormalities are the earliest signs of intraoperative ischemia detectable.

### Table 1. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Who Received GA Only</th>
<th>Patients Who Received GA and High TEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 36)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59 (12)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174 (9)</td>
<td>176 (8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.2 (10.3)</td>
<td>75.4 (11.2)</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>11/26</td>
<td>9/27</td>
</tr>
<tr>
<td>Body surface area, cm²</td>
<td>1.7 (0.3)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Cleveland score†</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>66 (12)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>Cross-clamping time, min</td>
<td>43 (10)</td>
<td>41 (12)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>65 (15)</td>
<td>62 (16)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, h</td>
<td>9.2 (4.3)</td>
<td>3.4 (1.9)</td>
</tr>
<tr>
<td>Intensive care unit therapy &gt;24 h, No. (%) of patients/total No. of patients</td>
<td>2/37 (5.4)</td>
<td>0/36‡</td>
</tr>
<tr>
<td>CK-MB, highest postoperative value, U/L</td>
<td>17 (11)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Nonsurvivors, %§</td>
<td>3/37 (8.1)</td>
<td>1/36 (2.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CK-MB, creatinine kinase–isoenzyme MB; GA, general anesthesia; TEA, thoracic epidural anesthesia.

*Data are given as the mean (SD) unless otherwise indicated.
†The Cleveland score estimates the patient’s preoperative morbidity; the highest value is 32 points indicating very severe risk.
‡P < .05 when comparing patients who received general anesthesia vs patients who received general anesthesia and high TEA.
§Mortality was recorded to 720 days postoperatively.
fore ECG changes indicate ischemia. Thus, these data suggested that high TEA can significantly reduce myocardial ischemia during surgery.

Postoperative troponin I concentrations were 3.5-fold higher in anesthetized patients who only received general anesthesia compared with patients who received general anesthesia and high TEA. The concentration of troponin I is a specific and highly sensitive marker for minor myocardial injury. Slightly elevated troponin I concentrations are not unusual in heart surgery because of ischemia-induced damage during aortic cross clamping and/or decreased regional myocardial perfusion after the surgical procedure. However, a more than 3-fold-higher value in the patients without high TEA is

Figure 2. Patients’ global and regional left ventricular function and afterload. Preoperative and postoperative values of global left ventricular wall motion index (A), left ventricular fractional area change (FAC) (C), and left ventricular end-systolic meridional wall stress(es) (D) as well as postoperative concentrations of cardiac troponin I in patients who received general anesthesia (GA) only or GA and high thoracic epidural anesthesia (TEA) (B). Values are given as mean (SD). Asterisks indicate P < .05.

Table 2. Hemodynamic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group</th>
<th>Baseline</th>
<th>20 Minutes after High TEA</th>
<th>20 Minutes after CPB</th>
<th>Duration in ICU, h</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Heart rate, beats/min GA</td>
<td>65 (15)</td>
<td>ND</td>
<td>82 (18)</td>
<td>90 (12)</td>
<td>85 (13)</td>
</tr>
<tr>
<td>Cardiac output, &lt;l/min GA</td>
<td>42 (1.0)</td>
<td>ND</td>
<td>5.0 (10.8)</td>
<td>7.1 (2.5)</td>
<td>6.5 (2.3)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg GA</td>
<td>77 (11)</td>
<td>ND</td>
<td>59 (12)</td>
<td>75 (12)</td>
<td>77 (14)</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>74 (12)</td>
<td>69 (17)</td>
<td>56 (14)</td>
<td>73 (9)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>Pulmonary artery occlusion</td>
<td>10 (5)</td>
<td>ND</td>
<td>8 (4)</td>
<td>11 (6)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Systemic vascular resistance,</td>
<td>1276 (476)</td>
<td>ND</td>
<td>754 (289)</td>
<td>812 (331)</td>
<td>802 (244)</td>
</tr>
<tr>
<td>Table 2. Hemodynamic Data*</td>
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*Data are given as mean (SD).

Abbreviations: CPB, cardiopulmonary bypass; GA, general anesthesia; ICU, intensive care unit; ND, not detected; TEA, thoracic epidural anesthesia.
remarkable and indicates a significantly increased risk for ischemia and myocardial damage in these patients.27

The ANP and BNP concentrations were used as additional markers of myocardial function. Both ANP and BNP act through the guanylyl cyclase A receptor, and the secretion of both natriuretic peptides is induced by similar mechanisms such as stretch and catecholamines.18 Based on transgenic mice models, it was hypothesized that ANP and BNP may play slightly different and complementary roles in the regulation of cardiovascular homeostasis. The ANP is thought to be primarily involved in blood pressure regulation and water-electrolyte balance, whereas BNP may also function as a ventricular local regulator to protect the heart from damage and fibrosis. In accord with this concept, ANP plasma concentrations in our patients peaked during reperfusion after aortic cross clamping. In this period the heart is reloaded with volume after cardiac arrest. Thus, the main trigger of ANP secretion in our patients is most likely volume reloading, and the 2-fold higher levels in patients who only received general anesthesia may reflect increased cardiac stress during this critical phase.

The BNP concentrations peaked 24 hours after surgery in both patient groups and were approximately 2-fold higher in patients who only received general anesthesia. The BNP is a more powerful predictor of left ventricular damage than the ANP.18,19 This observation may be explained by the fact that BNP has not only a natriuretic but also an autocrine-paracrine role to modulate left ventricular and coronary vascular function to abbreviate contractile function and to accelerate isovolumic relaxation mediated by its second messenger guanosine 3’,5’-cyclic monophosphate.10 In accord with this concept, the patients who died during the 2-year observation period had the highest BNP plasma concentrations 24 hours after surgery. Moreover, we found positive correlations between BNP and the wall motion score, and between BNP and troponin I concentrations—2 independent risk predictors. However, we found no such correlation to ANP.

The percentage of patients who died during the first 2 years after CABG was higher in patients without high TEA. Although the sample size of our study was too low to detect significant differences in long-term outcome, we examined 2 homogeneous patient groups who underwent and received exactly the same surgery, treatment, and general anesthesia. Thus, this difference in mortality may point to an improvement of patients’ long-term outcome after CABG, probably caused by the described anti-ischemic properties of high TEA. However, a relevant limitation of our study is that it was not powered to detect a mortality rate difference between both groups.

CONCLUSIONS

This study shows that effective perioperative cardiac sympathetic and pain therapy by high TEA in addition to general anesthesia significantly improves regional left ventricular function and reduces ischemia and coronary risk in patients with coronary artery disease. Further studies are necessary to evaluate the long-term outcome and to examine whether the combination of high TEA and general anesthesia may also provide benefits in patients with coronary artery disease undergoing non-cardiac surgical procedures.

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Figure 3. Natriuretic peptide concentrations. Time course of atrial natriuretic peptide (ANP) (A) and brain natriuretic peptide (BNP) (B) concentrations during and after coronary artery bypass grafting in patients who received general anesthesia (GA) only or GA and high thoracic epidural anesthesia (TEA). Mean (SD) control values of healthy volunteers are indicated by the dotted lines. CPB indicates cardiopulmonary bypass; ICU, intensive care unit.
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