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Milrinone Modulates Endotoxemia, Systemic Inflammation, and Subsequent Acute Phase Response after Cardiopulmonary Bypass (CPB)

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Background: **Compromised splanchnic perfusion and the resulting intestinal mucosal injury leads to a decreased mucosal barrier function, which allows translocation of intestinal flora and endotoxemia. The authors evaluated the effects of milrinone on splanchnic oxygenation, systemic inflammation, and the subsequent acute-phase response in patients undergoing coronary artery bypass grafting.**

Methods: **This open, placebo-controlled randomized clinical study enrolled 22 adult patients in two groups. Before induction of anesthesia, baseline values were obtained and patients were randomized to receive milrinone (30 μg/kg bolus administered progressively in 10 min, followed by a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or saline. The following parameters were determined: hemodynamics; systemic oxygen delivery and uptake; arterial, mixed venous and hepatic venous oxygen saturation; intramucosal *p*H (*p*Hi); and mixed and hepatic venous plasma concentrations of endotoxin, interleukin 6, serum amyloid A, and C-reactive protein.**

Results: **Milrinone did not prevent gastrointestinal acidosis as measured by *p*Hi, but its perioperative administration resulted in significantly higher *p*Hi levels compared with control. Venous and hepatic venous endotoxin and the interleukin 6 concentration were reduced significantly in the milrinone group. Serum amyloid A values were attenuated in the milrinone group 24 h after surgery. No significant differences could be seen in routinely measured oxygen transport–derived variables.**

Conclusions: **Perioperative administration of low-dose milrinone may have antiinflammatory properties and may improve splanchnic perfusion in otherwise healthy patients undergoing routine coronary artery bypass grafting. (Key words: Acute phase response; cardiac surgery; endotoxemia; milrinone; splanchnic perfusion.)**

GASTROINTESTINAL complications in patients undergoing cardiopulmonary bypass (CPB) occur in about 2.3%. However, the mortality rate in these patients is high (16.4%), but specific preoperative risk factors can be identified before surgery.[1] Apart from patients having procedures such as cardiac transplantation, which has a reported incidence of abdominal complications of 17% to 34%,[2] severely ill patients with poor left ventricular function or those requiring high doses of catecholamines, mechanical support by intraaortic balloon pumping during and after the procedure, or both are at risk.[1] Impairment of systemic and splanchnic perfusion with subsequent endotoxemia, reperfusion injury after myocardial ischemia, and activation of the complement and coagulation system may contribute to the incidence of systemic inflammation after cardiac surgery. Most of the complications seen after CPB result from hypoperfusion, but other factors, such as microemboli and the release of the vasoconstrictors angiotensin II, vasopressin, and thromboxane A2, may have a role in impairing gut blood flow. Compromised splanchnic perfusion and the resulting intestinal mucosal injury leads to a decreased mucosal barrier function, allowing translocation of intestinal flora and endotoxemia.[3] The addition of pulsatile flow during CPB might reduce the incidence of gastrointestinal complications, but adequate splanchnic blood flow should be maintained in the postoperative period.[4] Many investigations have studied the effects of catecholamines and vasodilators to maintain gut perfusion. Most of them were performed in the intensive care unit in critically ill patients or in patients undergoing CPB using gastric mucosal *p*H (*p*Hi) as an index for gastrointestinal perfusion.[5–12] Few of them use monoethylglycinexylidide

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(MEGX) formation from lidocaine or indocyanine green clearance to prove an increase in splanchnic blood flow.[13,14] However, increasing blood flow does not necessarily improve gastrointestinal microcirculation and villus blood flow. We recently showed that the phosphodiesterase inhibitor enoximone could not prevent gastric mucosal acidosis in patients having cardiac surgery, but we did find a marked but insignificant reduction in endotoxin levels in hepatic venous blood samples.[10] In another study, we showed that continuous infusion of dopexamine did not blunt endotoxemia during and after CPB, but it did reduce systemic inflammation without affecting splanchnic oxygenation.[11]

We performed this study to evaluate the effects of milrinone, a phosphodiesterase III inhibitor, on splanchnic oxygenation, systemic inflammation, and the subsequent acute-phase response in patients undergoing routine coronary artery bypass grafting. Therefore, we examined the effects of perioperatively administered milrinone on gastric *p*Hi; hepatic venous oxygen saturation; and mixed and hepatic venous plasma concentrations of endotoxin, interleukin-6 (IL-6), serum amyloid A (SAA), and C-reactive protein (CRP).

Materials and Methods

The protocol was approved by the institutional review board of the University of Münster. This open, placebo-controlled, randomized clinical study enrolled 22 adult patients scheduled for elective coronary artery bypass grafting after they gave written informed consent. Patients with impaired left ventricular function (ejection fraction less than 0.5), gastrointestinal disorders, and diabetes were excluded from the trial.

Study Protocol

All patients were premedicated with 1 or 2 mg flunitrazepam (Rohypnol; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) and 150 mg ranitidine (Zantic; Glaxo Wellcome. Hamburg, Germany) orally to prevent erroneously low *p*Hi values 90 min before induction of anesthesia.[15] Before induction of anesthesia, baseline values were obtained and patients were randomized to receive milrinone (Corotrop; Sanofi Winthrop, München, Germany; in a 30-μg/kg bolus dose administered progressively in 10 min, followed by a continuous infusion of 0.5 $\mu g/kg^{-1}/min^{-1}$) or saline. General anesthesia was induced with intravenous midazolam (Dormicum; Hoffmann-La Roche; in a 0.1 mg/kg dose), fentanyl (Fentanyl; Janssen, Beerse, Belgium; in a 5–10 μg/kg dose), and pancuronium bromide (Pancuronium; Organon, Oberschleißheim, Germany; in a 0.1 mg/kg dose) while the patients inspired 100% oxygen. After endotracheal intubation, the patients were mechanically ventilated with oxygen and air ($F_{I_{O_2}}$ 0.5). The ventilation was adjusted to maintain an arterial carbon dioxide tension (P_{CO_2}) of 35 to 40 mmHg or an end-tidal carbon dioxide level of 4.5 to 5 mmHg. Anesthesia was maintained by body weight–related doses of fentanyl, midazolam, and pancuronium bromide. The infusion of the study drug or placebo was started after induction of anesthesia, 20 min after the start of infusion, 20 min after extracorporeal circulation, 20 min after weaning from CPB, after admission to the perioperative anesthesia care unit, and 6, 12, and 24 h thereafter the following parameters were determined: hemodynamics; systemic oxygen delivery and uptake; arterial, mixed venous, and hepatic venous oxygen saturation; *p*Hi; and mixed and hepatic venous plasma concentrations of glucose, lactate, endotoxin, IL-6, SAA, and CRP. Creatine clearance was determined after 12 and 24 h in the perioperative anesthesia care unit. In addition, endotoxin concentrations in the prime solutions used for CPB were measured before surgery. As a standard procedure, all patients received 2 million U aprotinin (Trasylol; Bayer, Leverkusen, Germany) before CPB, 2 million U aprotinin in the pump priming, plus a continuous infusion of 500,000 units aprotinin during CPB. Anticoagulation was achieved through an intravenous dose of heparin (Heparin-Natrium; Braun Melsungen AG, Melsungen, Germany; initial bolus dose of 400 IE/kg, targeting an activated clotting time of $\geq$ 440 s) and monitored using the activated clotting time. Management of extracorporeal circulation was standardized with pump flows of 2.3 to 2.8 $l \cdot min^{-1} \cdot m^2$, normothermia (36.5°C), and an α-stat regulation of arterial blood gases. Cold cardioplegic arrest was induced using Bretschneider-HTK solution (Custodiol; Köhler, Alsbach, Germany) and topical cooling. Mechanical ventilation was stopped and the lungs were kept uninflated during cold cardioplegic arrest. To maintain perfusion pressures of 60 mmHg norepinephrine was added if the perfusion pressure kept low despite increasing pump flow and/or filling of the patient. After aortic declamping, the lungs were ventilated with 100% oxygen. Subsequently, the $F_{I_{O_2}}$ in air was adjusted to maintain an arterial oxyhemoglobin saturation at more than 95%. A positive end-expiratory pressure of 5 cm H_2O was applied after CPB. Heparin was neutralized in a standardized manner by administration of protamine. Patients were weaned from CPB using nitroglycerin (Perlinganit; Schwarz Pharma,

Monheim, Germany; in a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), epinephrine (Suprarenin; Hoechst, Bad Soden, Germany), norepinephrine (Arterenol; Hoechst), or all of these when needed. In the intensive care unit, mechanical ventilation was maintained as just described. Adequate analgesia and sedation were achieved with repetitive doses of piritramide and midazolam according to standard procedures at our institution. Patients' tracheas were extubated 6–10 h after surgery.

Cardiopulmonary Monitoring

Routine monitoring before induction of anesthesia was performed using an electrocardigraph (including lead V_5), two large peripheral venous cannulas, and an intraarterial line placed in the left radial artery. After induction of anesthesia, a flow-directed balloon-tipped 7-French gauge Edwards thermodilution catheter was passed from the left internal jugular vein to the pulmonary artery and positioned to obtain a reliable pulmonary capillary wedge pressure tracing during balloon inflation. Cardiac output was measured by thermodilution. The mean of three measurements was calculated and used for statistical evaluation.

Additional Monitoring

In addition to the routine monitoring just described, all study participants received an oximetric balloon catheter (Opticath; Abbott Critical Care, Mountain View, CA) placed in the right hepatic vein under fluoroscopic guidance *via* the right jugular vein. This catheter allowed the continuous determination of liver venous oxygen saturation. Instead of a normally used nasogastric tube, all patients received a gastric tonometer (TRIP NGS-catheter; Tonometrics, Worcester, MA) to identify changes of *p*Hi. The proper position of this catheter in the stomach was verified by fluoroscopy. Both catheters were maintained after operation in the intensive care unit by radiographic monitoring.

Measurement of Gastric Intramucosal pH (pHi)

Determination of intramucosal P_{CO_2} values (P_{iCO_2}) by nasogastric tonometry[16] is a minimally invasive procedure to assess impaired gastrointestinal perfusion[17] and to estimate the prognosis of critically ill patients.[18] According to Bergofsky[19] and Dawson *et al.*,[20] tonometry relies on the fact that hollow visceral tissues are highly permeable to carbon dioxide with an equilibrium between the intramucosal P_{CO_2} and the intraluminar P_{CO_2}. An increase in the intraluminar P_{CO_2} therefore can indicate impaired perfusion, metabolic changes of the mucosa, or both. Based on this theoretical background, Fiddian-Green developed gastric tonometry[16,21] where the intraluminal carbon dioxide content of the stomach is determined indirectly by a nasogastric tonometer. Normal saline (2.5 ml at room temperature) was injected in the anaerobic balloon, and after an equilibration time of more than 30 min, saline was sampled and analyzed using a blood gas analyzer (ABL2; Radiometer, Copenhagen, Denmark). At the same time, the arterial blood bicarbonate concentration was obtained from an arterial sample. Because this blood gas analyzer is not calibrated to saline, thus leading to an overestimation of the calculated *p*Hi, we used a correction factor to determine the true P_{CO_2} in the saline solution (the correction factor for ABL2 was 1.15).[22] The Henderson Hasselbalch equation was used to determine gastric *p*Hi:

$$p\text{Hi} = \frac{6.1 + \log 10[HCO_3^-]}{P_{CO_2}(SS) \times 0.03}$$

Analysis of Endotoxin, Interleukin-6, Serum Amyloid A, and C-Reactive Protein

We analyzed endotoxin, IL-6, SAA, and CRP as described in previous studies.[10,11,23] Endotoxin levels were determined using a chromogenic Limulus amoebocyte lysate test described by Schedel *et al.*[24] After blood collection under sterile conditions, 5 ml blood was collected in sterile, endotoxin-free sodium heparin tubes (Endo Tube ET, Chromogenix, Sweden). All reagents (Kabi Vitrium, Stockholm, Sweden) and materials were endotoxin free, and all preparation steps except for photometry were performed under sterile conditions. Blood samples were stored at −30°C until they were analyzed. The sensitivity of the test was 1.2 pg/ml, and the intra- and interassay coefficients of variations were less than 10%.

Blood samples of IL-6, SAA, and CRP were collected into chilled tubes containing ethylenediaminetetraacetic acid, centrifuged, and stored at −70°C, −20°C, or −25°C, respectively, according to the manufacturers' recommendations until they were analyzed. IL-6 (Immunotech, S.A., Marseilles, France), SAA (BioSource International, Camarillo, CA), and CRP (N Latex CRP Reagents; Behring Diagnostics, Marburg, Germany) were analyzed using commercially available immunoenzymometric assay kits. The sensitivity values of the assays were 5 pg/ml for IL-6, 5 μg/ml for SAA, and 2.5 mg/dl for CRP. Intraassay and interassay coefficients of variation were 6.8% and 13.8% for IL-6, 5.3% and 8.7% for SAA, and 2.4% and 9.8% for CRP. Measurements of all parameters were performed in duplicate, and mean values were used for analysis.

Table 1. Demographic Data of Patients

	Control	Milrinone
Age (yr)	61 ± 6	60 ± 8
BSA (m^2)	1.86 ± 0.11	1.86 ± 0.09
Time on CPB (min)	67 ± 16	71 ± 11
Cross-clamp time (min)	39 ± 9	45 ± 9
Number of venous grafts	3 ± 0.7	3 ± 0.7

BSA = body surface area; CPB = cardiopulmonary bypass.

Statistical Evaluation of the Data

Data are presented as mean values ± SD. All study parameters were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) by Friedman and subsequent Wilcoxon tests. The matched-pair rank test was used to compare values of different observation time points with initial values. Differences between the groups were subjected to the Mann–Whitney U test. To reduce the probability of a type 1 error (α error), the significance level α of single Wilcoxon and Mann–Whitney U tests was additionally corrected according to the numbers of tests. In figures 1–5 we compared the curves of control and milrinone patients using the overall means of the single curves. The calculated P values that indicated significance are given in the tables and in the figure legends.

Results

All patients were separated successfully from CPB and remained in the postanesthesia care unit for 24 h. All patients left the hospital for further rehabilitation according to the length of hospital stay usually recommended out at our institution. No major postoperative complications, such as perioperative myocardial infarction, or relevant cardiac arrhythmias occurred.

Table 1 summarizes patient demographic data. There were no significant differences between groups in the variables noted. All patients received one internal mammary artery bypass graft onto the left anterior descendent artery. The number of venous grafts was not significantly different between the groups. There were no significant differences in the administered vasoactive drugs (table 2). Milrinone-treated patients received a significantly higher amount of perioperative administered colloids ($P \leq 0.05$, table 3). Four hours after admission to the perioperative anesthesia care unit, control patients had significantly higher body core temperatures ($P \leq 0.05$, table 4). Creatinine clearance was not significant within groups (85 ± 24 after 12 h in the intensive care unit and 112 ± 25 after 24 h in the intensive care unit in the control group *vs.* 103 ± 32 after 12 h and 90 ± 23.5 after 24 h in the intensive care unit in the milrinone group).

Table 2. Vasoactive Drugs Used for Weaning from Cardiopulmonary Bypass (CPB) and on Post Anesthetic Care Unit (PACU)

	Control	Milrinone
Epinephrine	3/11	4/11
Weaning from CPB ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.023	0.111
Epinephrine	1/11	5/11
PACU ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.08	0.0572
Norepinephrine	3/11	0/11
Weaning from CPB ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.02	
Norepinephrine	1/11	2/11
PACU ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.02	0.035

Table 3. Volume Loading before Cardiopulmonary Bypass

	Control	Milrinone
Ringers lactate (ml)	827 ± 82	886 ± 64
Hydroxyethyl starch (ml)	209 ± 220	752 ± 141*

* $P \leq 0.05$ between groups.

Hemodynamics and Systemic Oxygenation

Twenty minutes after administration of milrinone, we noted a significant increase in cardiac output ($P \leq 0.025$), and a significant decrease in systemic vascular resistance ($P \leq 0.025$) and pulmonary vascular resistance ($P \leq 0.025$) (fig. 1). At this point, cardiac output and systemic vascular resistance were significantly different from control (fig. 1). The improvement in hemodynamics before CPB resulted in a significant increase in mixed venous oxygen saturation ($P \leq 0.025$) and systemic oxygen delivery ($P \leq 0.025$). The latter was significantly different from control (fig. 2). There were no further significant differences in hemodynamics and systemic oxygenation between groups during the rest of the study.

Splanchnic Oxygenation

Hepatic venous oxygen saturation did not change significantly. In both groups a marked decrease could be

Table 4. Body Core Temperature during Stay on PACU

	Control	Milrinone
Admission on PACU	36.4 ± 0.5	36.2 ± 0.6
4 h after admission	38.3 ± 0.6*	37.9 ± 0.4*†
8 h after admission	38.3 ± 0.4*	38.2 ± 0.3*
16 h after admission	37.9 ± 0.5*	37.7 ± 0.4*
24 h after admission	37.4 ± 0.8*	37.7 ± 0.4*

* $P \leq 0.013$ *versus* admission on PACU within groups.

† $P \leq 0.05$ between groups.

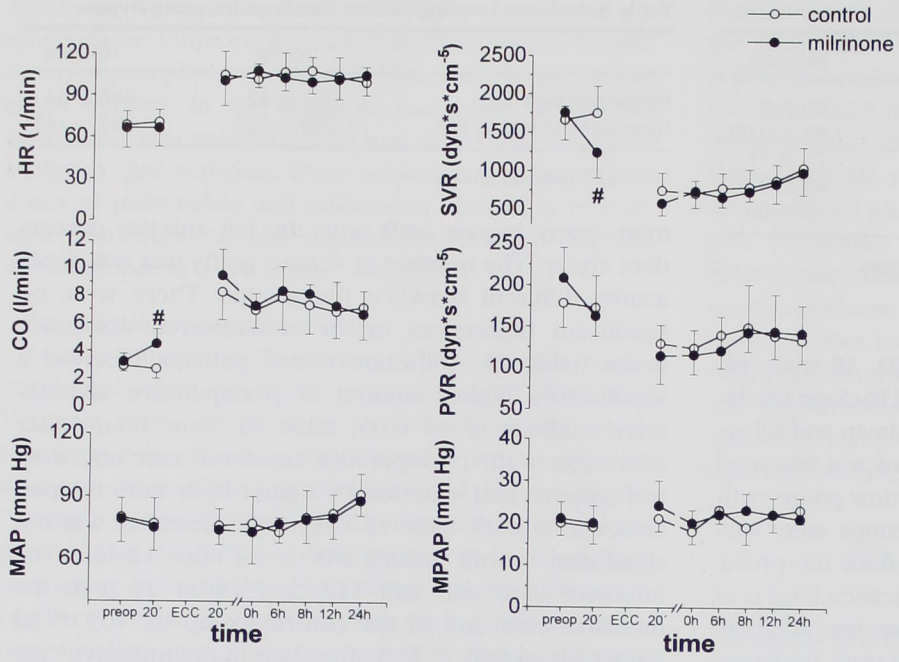

Fig. 1. Hemodynamic data of patients. HR = heart rate, CO = cardiac output, MAP = mean arterial pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, MPAP = mean pulmonary artery pressure, preop = preoperative, and ECC = extracorporeal circulation. #$P \leq 0.05$ milrinone *versus* control.

observed during CPB, which was restored after weaning from CPB. Mesenteric oxygen extraction increased significantly in both groups during CPB ($P \leq 0.017$) and *p*Hi decreased in both groups 8 h after admission to the perioperative anesthesia care unit ($P \leq 0.01$). Sixteen hours later, *p*Hi was significantly less in the controls ($P \leq 0.05$). Hepatic venous lactate levels increased significantly after CPB, with a maximum 8 h after admission to the perioperative anesthesia care unit ($P \leq 0.01$; fig. 3).

Endotoxemia, Systemic Inflammation, and the Acute-phase Response

In all patients the endotoxin concentration increased to its highest levels 20 min after the start of extracorporeal

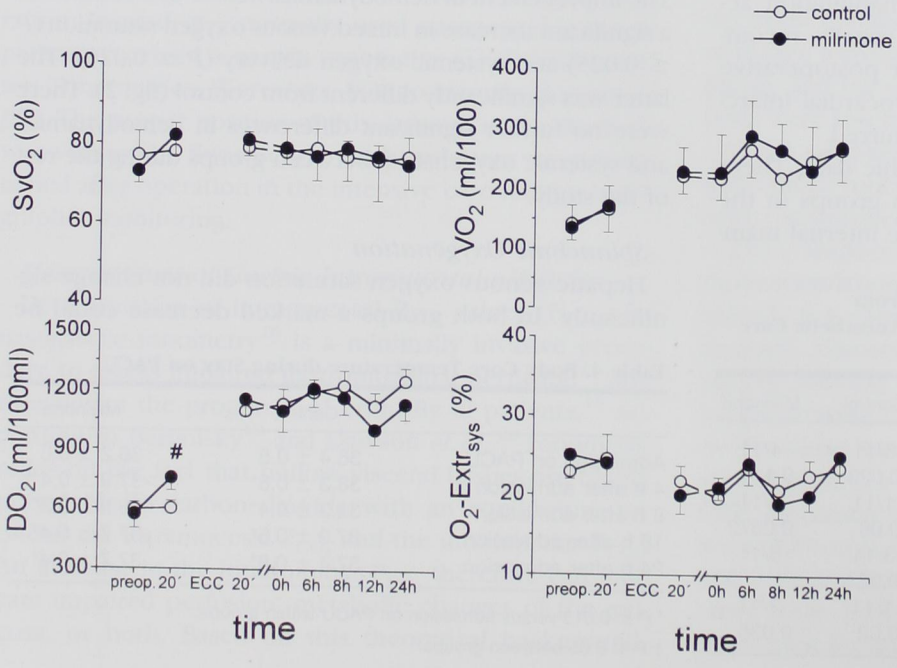

Fig. 2. Systemic oxygenation. SvO_2 = mixed venous oxygen saturation, DO_2 = oxygen delivery, VO_2 = oxygen uptake. #$P \leq 0.05$ milrinone *vs.* control.

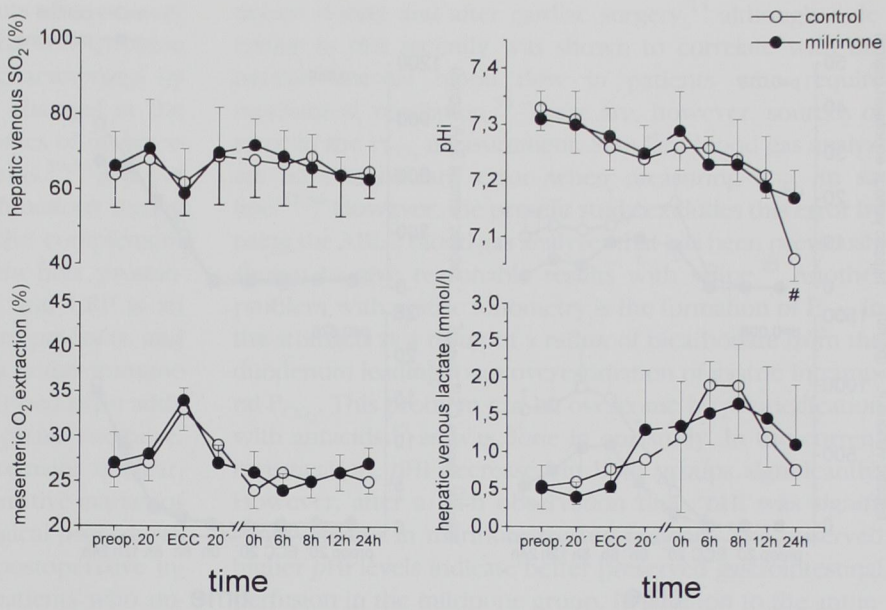

Fig. 3. Splanchnic oxygenation. *p*Hi = intramucosal *p*H. #$P \leq 0.05$ milrinone *versus* control.

circulation and decreased thereafter ($P \leq 0.007$; figs. 4 and 5). Interleukin-6 concentrations could be measured first during CPB and showed a comparable time course to that of endotoxin ($P \leq 0.007$). All patients treated with milrinone showed suppressed mixed and hepatic venous concentrations of endotoxin and IL-6 compared with controls (figs. 4 and 5). Serum amyloid A values increased 6 h after operation ($P \leq 0.013$) and were reduced in milrinone-treated patients 24 h after surgery in the mixed venous and liver venous blood ($P \leq 0.05$; figs. 4 and 5). The CRP level increased significantly in both groups ($P \leq 0.017$; figs. 4 and 5). There were no significant differences between mixed and hepatic venous concentrations for any of the inflammatory parameters.

Discussion

In the current study, milrinone did not prevent gastrointestinal acidosis as measured by *p*Hi, but its perioperative administration resulted in significantly higher *p*Hi levels compared with control patients 24 h after surgery. Venous and hepatic venous endotoxin and IL-6 levels were signifi-

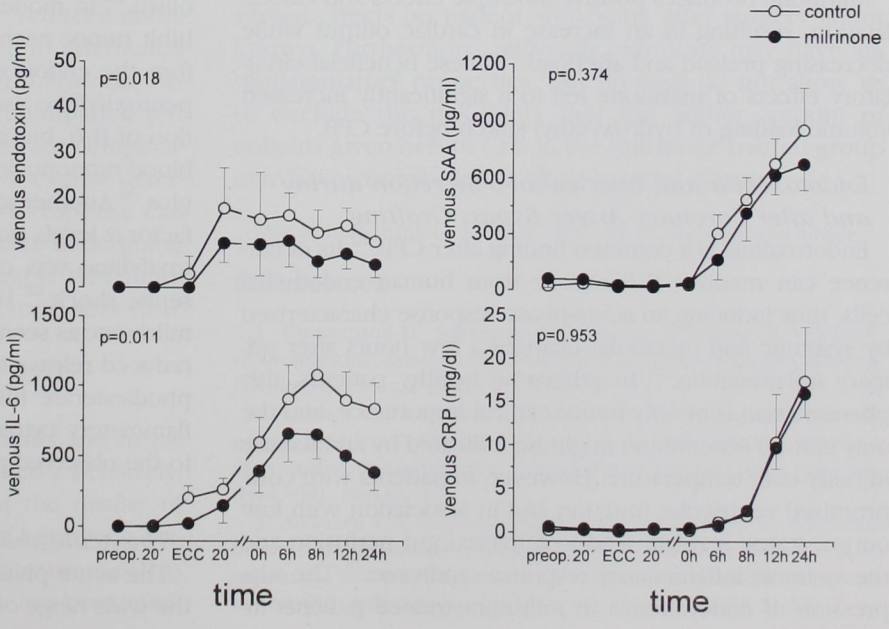

Fig. 4. Endotoxemia, systemic inflammation, and acute-phase response in mixed venous blood. IL-6 = interleukin 6, SAA = serum amyloid A, CRP = C-reactive protein. Endotoxin ($P = 0.018$) and IL-6 ($P = 0.011$) concentrations were suppressed for comparisons of overall means of curves, milrinone *versus* control.

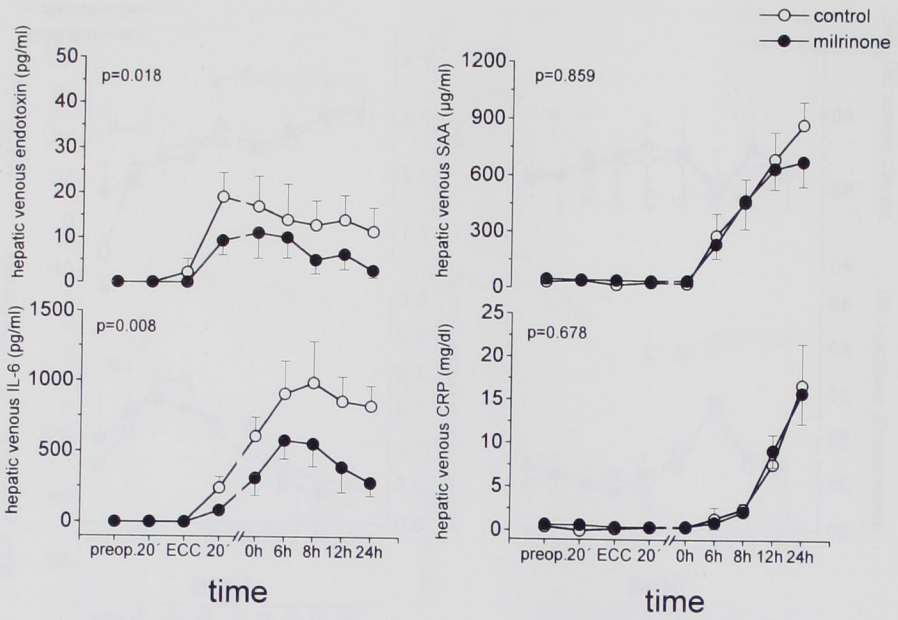

Fig. 5. Endotoxemia, systemic inflammation, and acute-phase response in hepatic venous blood. IL-6 = interleukin 6, SAA = serum amyloid A, CRP = C-reactive protein. Endotoxin (P = 0.018) and IL-6 (P = 0.008) concentrations were suppressed for comparisons of overall means of curves, milrinone *versus* control.

cantly reduced in milrinone-treated patients. Serum amyloid A values were attenuated in milrinone-treated patients 24 h after surgery in the mixed venous and liver venous blood. No significant differences could be detected in routinely measured oxygen transport–derived variables such as mixed venous oxygen saturation, systemic oxygen delivery, uptake, and extraction. No significant differences could be seen in hepatic venous oxygen saturation, mesenteric oxygen extraction, and hepatic venous lactate levels.

Hemodynamics and Oxygenation

Milrinone produces positive inotropic effects and vasodilatation, resulting in an increase in cardiac output while decreasing preload and afterload.[25] These beneficial circulatory effects of milrinone led to a significantly increased volume loading of hydroxyethyl starch before CPB.

Endotoxemia and Interleukin-6 Secretion during and after Coronary Artery Bypass Grafting

Endotoxemia is a common finding after CPB.[12] Its occurrence can mediate IL-6 release from human endothelial cells, thus inducing an acute-phase response characterized by systemic and metabolic changes a few hours after primary inflammation.[23] In otherwise healthy patients, this phenomenon is of only minor clinical importance, and the only clinical observation might be indicated by an increase in body core temperature. However, in patients with compromised ventricular function and in association with low output states, it might lead to impaired gut perfusion and the systemic inflammatory response syndrome.[23] The suppression of endotoxemia in milrinone-treated patients influences IL-6 production, and therefore antiinflammatory properties could be speculated.

As noted before, milrinone is a phosphodiesterase inhibitor and as such has the potential for immunomodulation by inhibiting intracellular cyclic nucleotide phosphodiesterase, thus increasing the intracellular concentration of cyclic adenosine monophosphate. The most studied phosphodiesterase inhibitor in this respect is pentoxifylline, which modulates the production of pro- and antiinflammatory cytokines by endotoxemia-stimulated monocytes through cyclic adenosine monophosphate metabolism.[26] In models of endotoxemia, pentoxifylline can inhibit tumor necrosis factor-α production when given before the endotoxin challenge.[27] However, high doses of pentoxifylline also have been shown to trigger the production of IL-6, but not tumor necrosis factor-α by peripheral blood mononuclear cells in the absence of any other stimulus.[26] Another study showed a decrease in tumor necrosis factor-α levels but no difference in IL-6 levels when pentoxifylline was compared with placebo in patients with septic shock.[28] However, attenuation of IL-6 secretion by milrinone as seen in this study probably was caused by the reduced release of endotoxin. Another effect of the phosphodiesterase inhibitors is the production of the anti-inflammatory cytokine IL-10.[29] This could have contributed to the observed phenomenon.

The Acute-phase Response after Cardiac Surgery

The acute phase of the inflammatory response refers to the wide range of physiologic changes after an infection or

physiologic trauma that occurs a few hours after primary inflammation in response to endotoxemia and cytokine secretion. The acute-phase response is characterized by fever; changes in vascular permeability; changes in the biosynthetic, metabolic, and catabolic profiles of many organs; and an increase in acute-phase proteins.[30,31] Most of these acute-phase proteins have unique functions during the acute-phase response. For example, the complement proteins enhance the immune reaction of the host, proteinase inhibitors regulate enzyme activities, and CRP is an opsonizing factor for cellular breakdown products and many bacterial antigens, and it regulates some immune functions. Serum amyloid A has been described as an additional and sensitive marker of the acute-phase response. However, its pathophysiologic function remains unclear. As we found before, SAA is an especially sensitive marker of the acute-phase response after cardiac surgical procedures with close positive correlation with the postoperative increased body core temperature seen in patients who underwent CPB, we chose SAA and CRP as markers of the acute phase response because we previously found SAA especially is a sensitive marker of the acute phase response after cardiac surgical procedures with close positive correlation to the postoperative increased body core temperature seen in patients who underwent CPB.[23] Furthermore, IL-6 is a potent stimulator for SAA and CRP synthesis in human hepatocytes and Kupffer cells.[32]

The acute-phase response that occurs after primary inflammation after CPB is normally temporary and of only minor clinical importance. However, in severe cases it may lead to low cardiac output syndrome multiple organ failure, or both. In our study, reduced endotoxemia and IL-6 concentrations resulted in attenuated SAA concentrations in patients receiving milrinone. Because we evaluated only patients with unimpaired left ventricular function, and no clinically relevant complications developed in any of our patients, we cannot determine whether the attenuated acute-phase response can influence the outcome of high-risk patients undergoing cardiac surgery. However, our data suggest that milrinone can attenuate the proinflammatory state after CPB.

Gastric Intramucosal pH *during and after Cardiopulmonary Bypass*

Measurement of *p*Hi in critically ill patients and in patients during and after CPB has been studied extensively, and many investigators use it to control the quality of splanchnic perfusion with the possibility of improving outcome.[16,18,33,34] However, the value of a decrease in *p*Hi as a result of impaired splanchnic blood flow has been questioned during and after cardiac surgery,[14] although a decrease in *p*Hi recently was shown to correlate with impaired mucosal blood flow in patients who require mechanical ventilation.[35] There are, however, sources of error in the P_{CO_2} measurement. Standard blood gas analyzers have significant error when measuring P_{CO_2} in saline.[22,36] However, the present study excludes this error by using the ABL-2 blood gas analyzer that has been previously shown to give reasonable results with saline.[22] Another problem with gastric tonometry is the formation of P_{CO_2} in the stomach as a result of a reflux of bicarbonate from the duodenum leading to an overestimation of gastric intramural P_{CO_2}. This problem can be overcome by premedication with antacids,[15] as was done in our study. In the current investigation, *p*Hi decreased in both groups significantly. However, after a 24-h observation time, *p*Hi was significantly greater in milrinone-treated patients. The observed higher *p*Hi levels indicate better preserved gastrointestinal perfusion in the milrinone group. In addition to the antiinflammatory properties of milrinone, significantly higher volume loading in the milrinone-treated group before CPB also could have contributed to higher *p*Hi levels. This indirect effect, because of the need for colloid volume loading, cannot be excluded.[37]

However, newer techniques such as continuous intraluminal P_{CO_2} monitoring might be the perfect alternative to measuring continuous P_{CO_2} when clinically available.[38]

In conclusion, administration of milrinone improves splanchnic perfusion after coronary artery bypass grafting and diminishes endotoxemia and the subsequent acute-phase response. However, the impact of the observed effects on patient well-being after surgery is not known. Furthermore, although milrinone may have antiinflammatory properties, our findings do not allow us to exclude the possibility that the higher amount of colloids given before CPB in the milrinone-treated group may have contributed to the observed effects.

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