Laboratory Investigations

Milrinone improves intestinal villus blood flow during endotoxemia

Werner Schmidt MD, Marco Tinelli CAND MED, Andreas Secchi MD, Martha-Maria Gebhard MD,* Eike Martin MD FANZCA, Heinfried Schmidt MD DEAA

Purpose: To determine whether the compromised intestinal villus blood flow in a rat model of endotoxemia could be improved by continuous infusion of the phosphodiesterase (PDE) inhibitor milrinone.

Methods: Twenty-four anesthetized and ventilated rats were laparotomized and an ileal portion was exteriorized and opened by an antimesenteric incision. The ileal segment was fixed with the mucosal surface upward. Microcirculatory parameters were assessed by intravital videomicroscopy. The animals were randomly assigned to receive one of three treatments: infusion of *Escherichia coli* lipopolysaccharides without phosphodiesterase inhibitor pretreatment (=LPS group); or infusion of LPS with milrinone pretreatment (= milrinone group), or without infusion of LPS or milrinone (=control group). Macrohemodynamic parameters (MAP, HR) and microhemodynamic parameters of ileal mucosa (mean diameter of central arterioles = D_A and mean erythrocyte velocity within the arterioles= V_E) were measured 30 min before and at 0, 60, and 120 min after induction of endotoxemia. Mucosal villus blood flow was calculated from D_A and V_E.

Results: In the milrinone group MAP decreased 60 min after induction of endotoxemia whereas it remained stable in the control and the LPS group. In both groups given endotoxin V_E decreased after start of LPS infusion. In contrast, D_A decreased in the LPS group, but increased in the milrinone group after 120 min of endotoxemia. Thus, the endotoxin-induced decrease of intestinal villus blood flow was diminished but not fully restored by milrinone infusion.

Conclusion: Our results indicate that milrinone has some beneficial microcirculatory effects during endotoxemia. Although it contributed to systemic hypotension, it attenuated intestinal mucosal hypoperfusion.

Objectif : Déterminer si le flot sanguin intestinal dont les grandes fonctions sont altérées dans un modèle d'endotoxémie chez le rat peut être amélioré par une perfusion continue d'un inhibiteur de la phosphodiestérase (PDE), la milrinone.

Méthode : Vingt-quatre rats sous anesthésie et ventilation ont été laparotomisés et une portion iléale a été extériorisée et ouverte par une incision antimésentérique. Le segment iléal a été fixé par la surface muqueuse extériorisée. Les paramètres microcirculatoires ont été évalués par vidéomicroscopie vitale. Les animaux ont été assignés à l'un des trois groupes de traitements : une perfusion de lipopolysaccharides d'*Escherichia coli* sans prétraitement avec l'inhibiteur de la phosphodiestérase (groupe LPS), ou une perfusion de LPS avec un prétraitement à la milrinone (groupe milrinone), ou sans perfusion de LPS ou de milrinone (groupe témoin). Les paramètres macrohémodynamiques (TAM, FC) et microhémodynamiques de la muqueuse iléale (diamètre moyen des artérioles centrales D_A et vélocité moyenne des érythrocytes dans les artérioles V_E) ont été mesurés 30 min avant l'induction de l'endotoxémie et à 0, 60 et 120 min après. Le flot sanguin des villosités muqueuses a été calculé à partir de D_A et de V_E.

Résultats : Dans le groupe milrinone, la TAM a baissé 60 min après l'induction de l'endotoxémie alors qu'elle est demeurée stable chez les témoins et dans le groupe LPS. Dans les deux groupes qui ont reçu l'endotoxine, V_E a diminué après le début de la perfusion de LPS. Par ailleurs, D_A était plus faible dans le groupe LPS, mais plus grand dans le groupe milrinone après 120 min d'endotoxémie. Donc, la baisse du flot sanguin intestinal induite par l'endotoxine a été réduite mais non complètement éliminée par la perfusion de milrinone.

Conclusion : Nos résultats indiquent que la milrinone présente certains effets microcirculatoires positifs pendant l'endotoxémie. Même si elle contribue à l'hypotension générale, elle limite l'hypoperfusion de la muqueuse intestinale.

From the Departments of Anesthesiology and Experimental Surgery,* University of Heidelberg, D-69120 Heidelberg, Germany.

Address correspondence to: Werner Schmidt MD, Department of Anesthesiology, University of Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany. Phone: +49-6221-56-6404; Fax: +49-6221-56-4208; E-Mail: werner.schmidt@urz.uni-heidelberg.de

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ENDOTOXEMIA and sepsis contribute to multiple organ failure which is still the most important cause of death in critically ill patients.[1,2] Intestinal mucosal hypoperfusion and hypoxia and the concomitent disturbances of gut barrier failure have been shown to play a pivotal role in the development and maintenance of sepsis and multiple organ failure.[3,4] The unique microvascular architecture of the intestinal villus with the countercurrent exchange network makes the gut mucosa particularly susceptible to ischemia. Blood is supplied to the intestinal villus by a central arteriole and is drained by venules surrounding the inflow vessel. Thus, the tip of the villus easily becomes hypoxic because tissue oxygen tension decreases from the base of the villus to the apex as a result of consumption and of arteriovenous oxygen shunting. The intact gut mucosal barrier prevents the translocation of intraluminal bacteria and toxins to extra-intestinal sites and into the systemic circulation.[5] During endotoxemia or sepsis, bacterial translocation may aggravate the clinical course of sepsis.[6,7]

Milrinone, a selective phosphodiesterase (PDE) III inhibitor, is an agent that possesses a combination of positive inotropic and vasodilating properties as a result of preventing the degradation of cAMP. Milrinone is a bipyridine derivative of amrinone, with approximately 20 to 50 times greater positive inotropic potency, and a reduced side effect profile.[8] It is used clinically in the management of heart failure as it decreases systemic vascular resistance (afterload), decreases the determinants of left ventricular filling pressure (preload) and improves cardiac contractility. There are only a few clinical studies investigating the use of milrinone during SIRS or sepsis.[9,10] Although milrinone has been shown to improve cardiac performance in these patients, it is not recommended as an agent of first choice in the treatment of sepsis, mainly because of its vasodilatory effect. However, milrinone has been shown to possess additional anti-inflammatory properties besides its cardiovascular effects.[11–14] Immune cells contain type IV and type III PDE, thus PDE inhibitors are potent regulators of various immune processes. Sepsis and endotoxemia lead to the activation and accumulation of leukocytes and circulatory disorders in several tissues. This is especially true for the gut, which has been demonstrated to exert a decrease of intestinal mucosal blood flow[15,16] and the sticking of leukocytes in postcapillary venules [17] during endotoxemia. Another cardiovascular drug, the synthetic catecholamine dopexamine, has been shown to maintain the endotoxin-induced decrease of intestinal villus blood flow[18] and to possess additional anti-inflammatory properties during sepsis.[19,20] Whether the PDE inhibitor milrinone is beneficial in improving compromised tissue perfusion of the intestinal mucosa during endotoxemia has not been investigated. In order to elucidate this possible beneficial effect of milrinone on gut perfusion we studied the hypothesis that pretreatment with milrinone may be effective in maintaining mucosal villus blood flow during septic conditions.

Materials and Methods

Animal preparation

All experimental procedures and protocols used in this investigaton were approved by the Governmental Animal Protection Committee. Male Wistar rats (250-300g) were kept on a diet of standard rat chow and water ad libitum. Food was withheld from the animals 12 hr before the experiment. Free access to water was permitted. Anesthesia was initially induced with an intraperitoneal injection of 60 $mg \cdot kg^{-1}$ sodium pentobarbital and was later maintained by a continuous intravenous infusion of 3 $mg \cdot kg^{-1} \cdot hr^{-1}$ midazolam, 5 $mg \cdot kg^{-1} \cdot hr^{-1}$ ketamine, and 0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ pancuronium. The animals were instrumented with an arterial catheter in the left carotid artery and two venous catheters in the right jugular vein, and the left femoral vein, respectively. A tracheostomy was performed for airway control. Initially, all rats breathed spontaneously during surgical preparation. The rectal temperature was measured with a thermistor probe and maintained at 37°C using a heating lamp. The preparation of the intestinal mucosa for intravital microscopy was performed using a modified procedure according to Bohlen[21] and Gore.[22] The rats were placed on a plexiglass stage lying on their left side. A small segment of the terminal ileum was exteriorized through an abdominal midline incision and was opened along its antimesenteric border over a length of about 20 mm by using electrocautery. The edges of the opened intestinal segment were fixed with the mucosal surface upward to a frame with four sutures (0.7 metric Ethilon II, Ethicon, Norderstedt, Germany) on each side. This procedure was performed with care to avoid trauma to the exposed tissue. The animals were then transferred beneath the microscope. The continuous midazolam/ketamine/pancuronium infusion via the jugular vein catheter was started and the tracheostoma cannula was connected to a small animal ventilator (RUS-1301, Föhr Medical Instruments, Seeheim, Germany). Mechanical ventilation was performed with room air and $PaCO_2$ was maintained between 4.8 to 5.6 kPa. Mean arterial pressure was measured via the carotid artery catheter connected to a pressure transducer (Uniflow; Baxter, Unterschleissheim, Germany) switched to a small animal haemodynamic monitoring

device (Monitor 2.5, Koch-Medizintechnik, Munster, Germany). The exposed mucosal surface was continuously superfused with a thermostat-controlled (36°C), bicarbonate-buffered salt solution (132 mM sodium chloride, 4.7 mM potassium chloride, 2 mM calcium chloride, 1.2 mM magnesium chloride, and 18 mM sodium bicarbonate) equilibrated with CO_2 5% in nitrogen to adjust the pH to 7.35, the PO_2 to 3.7-4.0 kPa, and the PCO_2 to 4.8-5.6 kPa. To determine intestinal villus blood flow, all animals received an intravenous injection of 0.5 $mL \cdot kg^{-1}$ labeled erythrocytes 30 min before microscopy. The erythrocytes were taken from donor rats and were labeled with fluorescein isothiocyanate (FITC, F-7250, Isomer I, Sigma Chemicals, Deisenhofen, Germany), using a modified procedure according to Butcher and Weissman[23] and Sarelius and Duling.[24]

Experimental protocol.
Rats were randomly assigned to three groups of eight animals. After a 30-min stabilization period following the end of the preparation, baseline measurements were performed (time point 30 min). Immediately after this, animals of the milrinone group received a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ milrinone (Corotrop®, Sanofi Winthrop, Munich, Germany) via the jugular vein catheter. Animals of the LPS and the control group received an equivalent volume of a continuous NaCl 0.9% infusion. The investigator was blinded to the drug preparation and the administration of the drugs. The second measurements were performed 30 min later (time point 0 min). Subsequently, endotoxemia was induced in the LPS, and the milrinone group by continuous intravenous infusion of 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ endotoxin (lipopolysaccharides from *Escherichia coli* 026:B6; Sigma Chemicals) diluted in NaCl 0.9% via the femoral vein catheter. The LPS infusion was maintained over the remaining observation period of 120 min. In the control group, an equivalent volume of saline was administered. Total volume resuscitation in all animals was calculated to be 10 $mL \cdot kg^{-1} \cdot hr^{-1}$.

Macrohemodynamic parameters (MAP, HR) and microhemodynamic parameters of ileal mucosa (mean diameter of central arterioles = D_A, and mean erythrocyte velocity within the arterioles = V_E) were measured 30 min before and at 0, 60, and 120 min after induction of endotoxemia. At the end of the experiment, the animals were killed with an overdose of sodium-pentobarbitone.

Intravital microscopy
Gut mucosal microcirculation was observed using a specially designed microscope (Orthoplan; Leica, Wetzlar, Germany) equipped with 40-fold water immersion lens (Achroplan 40/0.75W; Zeiss, Jena, Germany). The labeled erythrocytes running through the central arteriole of a single intestinal villus were visualized by epi-illumination using an epifluorescence illuminator (Ploemopak; Leica), consisting of a 100 W short arc mercury lamp (Osram, Munich, Germany) and a filter system for the fluorescence excitation (blue light excitation: I 3; Leica). To protect the preparation from heat, a heat protection filter (KG1; Leica) was located in the body of the microscope. Microscopic images were transferred to a monitor (PVM 1444QM; Sony, Tokyo, Japan) by a low light camera (Kappa CF 8/1; Kappa Messtechnik, Gleichen, Germany) and recorded using a videotape-recorder (S-VHS AG-7350-E; Panasonic, Matsushita, Japan).

Measurement of blood flow in the villus central arterioles
At each time point, at least ten ileal mucosal villi were microscoped and videotaped. The tapes were analyzed offline with an computer-assisted video-analysis system (Cap Image, Zeintl, Heidelberg, Germany) by an observer who was unaware of the treatment of the animals. Video images were recorded with a recording speed of 50 frames per second. Each villus receives its arterial supply from a single arteriole which runs through the center of the villus. Erythrocyte velocity was determined from the distance a labeled erythrocyte passed within the arteriole between two video frames, and the time interval of 20 msec. For each villus, the velocities of at least 20 erythrocytes were determined and the mean value of these 20 measurements was used as mean erythrocyte velocity (V_E). The mean arteriolar diameter of the villus (D_A) was calculated from eight single measurements of the diameter between the base and the tip of each villus. Thus, the villus blood flow for each single villus was calculated from V_E and D_A according to the equation:

$$\text{villus blood flow} = \pi \cdot (D_A/2)^2 \cdot V_E \cdot 60 \cdot 10^{-3} \ (nl \cdot min^{-1})$$

In each experiment, and at each time point, the villus blood flow of at least ten mucosal villi was determined. The mean value of these ten single values represented the mucosal villus blood flow at each time point.

Statistical analysis
Data are expressed as mean ± SD. For statistical analysis, a two-way analysis of variance (ANOVA) for repeated measurements was performed. To compare mean values within and between the groups, a post hoc test (*Scheffé* test) was used. Differences resulting in P values < 0.05 were considered statistically significant.

Results

The groups showed no differences concerning age and weight of the animals. None of the animals showed any signs of infection or sepsis before the experimental procedure. All the animals survived the actual observation period and were sacrificed at the end of the experiment.

Macrohemodynamic changes

At baseline (t = -30 min), MAP and HR showed no differences among the groups (Table). The MAP did not change in the control and LPS groups throughout the observation period. In the group given milrinone, MAP did not change 30 min after onset of milrinone infusion (time point 0 min). After start of LPS infusion, however, MAP decreased and at the end of the observation period, MAP in the milrinone group was significantly lower than in the control group. The HR remained stable in the control group. In the LPS group, HR increased after the start of LPS infusion and was higher than in the control group at 120 min. In the milrinone group, HR did not change during the first 30 min of milrinone infusion. After the start of endotoxemia, HR increased and was higher than in the control group at 60 min and 120 min, respectively. There were no differences in the HR of the milrinone group compared to the LPS group at 120 min.

Microhemodynamic changes

Mean erythrocyte velocity (V_E) of central arterioles of ileal mucosa were similar in all three groups at baseline measurements (t=-30 min, Table). The V_E remained unchanged in the control group. In the LPS group, V_E decreased just after 60 min of endotoxemia and further decreased after 120 min. In the milrinone group, the initial PDE inhibitor infusion led to no change of V_E. During endotoxemia, V_E decreased in a similar way as in the LPS group. Mean diameters (D_A) of central arterioles of ileal mucosa were similar in all three groups at baseline (t=-30 min) and remained unchanged in the control group throughout the observation period (Table). In the LPS group, endotoxemia led to a decrease of D_A. The initial milrinone infusion caused an increase in D_A. During endotoxemia D_A slightly decreased again, but was still higher than its baseline value after 120 min of endotoxemia.

The mean values of central arteriolar blood flow of intestinal villi are demonstrated in the Figure. According to the values of D_A and V_E, the baseline values were similar in all three groups. In the control group arteriolar blood flow remained stable throughout the study period. In the LPS group, blood flow decreased after 60 and 120 min of endotoxemia, respectively. In the milrinone group, villus blood flow remained stable after 30 min of milrinone infusion (time point 0 min). During the following LPS infusion, it decreased and was lower than in the control group at the end of the observation period, but was still higher than in the LPS group after 120 min of endotoxemia.

Discussion

We investigated the influence of the phosphodiesterase-inhibitor milrinone on intestinal villus blood flow in a normotensive model of endotoxemia and

TABLE Macrohemodynamic and microhemodynamic changes in the three groups

		Time from Start of Endotoxin or Saline			
		-30 min	*0 min*	*60 min*	*120 min*
MAP (mmHg)	Control	117 ± 10	116 ± 12	112 ± 14	109 ± 12
	LPS	121 ± 10	114 ± 15	111 ± 16	106 ± 16
	Milrinone	119 ± 9	108 ± 14	100 ± 16*	89 ± 18*†
HR (min^{-1})	Control	394 ± 17	393 ± 20	406 ± 22	413 ± 24
	LPS	392 ± 19	383 ± 21	428 ± 26*	451 ± 28*†
	Milrinone	382 ± 19	398 ± 22	435 ± 28*†	466 ± 31*†
V_E ($mm \cdot sec^{-1}$)	Control	1.9 ± 0.3	2.1 ± 0.3	1.9 ± 0.3	1.9 ± 0.3
	LPS	2.0 ± 0.3	2.1 ± 0.3	1.7 ± 0.3*	1.4 ± 0.5*†
	Milrinone	2.0 ± 0.3	1.8 ± 0.4	1.5 ± 0.4*†	1.4 ± 0.4*†
D_A (μm)	Control	8.3 ± 0.5	8.2 ± 0.4	8.2 ± 0.5	8.3 ± 0.7
	LPS	8.2 ± 0.6	8.1 ± 0.5	7.7 ± 0.6‡	7.1 ± 0.6*‡
	Milrinone	8.0 ± 0.5	8.8 ± 0.6*‡	8.4 ± 0.5	8.6 ± 0.6*

Values: mean ± SD

MAP = mean arterial pressure, HR = heart rate, V_E = mean erythrocyte velocity, D_A = arteriolar diameter

* $P < 0.05$ *vs* -30 min

† $P < 0.05$ *vs* control group

‡ $P < 0.05$ *vs* other groups

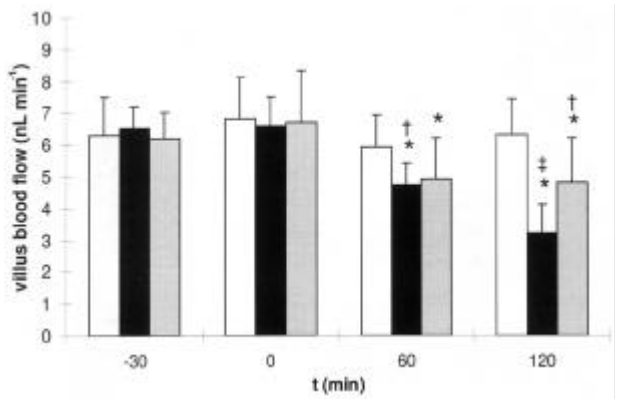

FIGURE Effects of milrinone before and during LPS infusion on central arteriolar blood flow of intestinal villi of rat ileum (t = –30 min: start of milrinone infusion; t = 0 min: start of LPS infusion). Data are mean ± SD. White bars, control group (n=8); black bars, LPS group (n=8); gray bars, milrinone group (n=8).
* $P < 0.05$ *vs* -30 min
† $P < 0.05$ *vs* control group
‡ $P < 0.05$ *vs* other groups

found that milrinone attenuated the endotoxin-induced decrease in mucosal villus blood flow. We used a normotensive model of endotoxemia in order to exclude secondary effects of hypotension on mucosal perfusion. Mucosal villus blood flow is very susceptible to hypotensive phases and is accompanied by a vasoconstriction of central arterioles of mucosal villi. This vasoconstriction often prolongs the duration of the systemic hypotensive phase. Our model meets the criteria of a chronic resuscitated sepsis state[25,26] and the criteria for laboratory models of sepsis proposed by Fink and Heard.[27]

A continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of milrinone was chosen in order to prevent possible hypotension by bolus administration. Our results showed that milrinone in this dosage did not change the measured macrohemodynamic parameters MAP and HR. This indicates that the animals were sufficiently resuscitated. Although MAP in the LPS group was still in a normal range after 120 min of endotoxemia, systemic vascular resistance was supposed to be decreased, and MAP was obviously maintained by the increase in heart rate. After the start of endotoxemia in the milrinone group, MAP decreased indicating that there was an additive effect of milrinone and LPS leading to a lower MAP in the milrinone group compared to the LPS group. However, it has to be emphasized, that the animals in the LPS group in this study were still normotensive.

Most investigators studying milrinone in sepsis have found a decrease in systemic arterial pressure but also an improvement in cardiac performance.[9,10] Lindgren *et al.*[28] concluded that, in the settings of their porcine septic shock model, milrinone treatment had no beneficial effect. In the milrinone-treated animals cardiac index was maintained for a longer period of time but blood pressure was significantly reduced compared with the control pigs. Pulmonary vasoconstriction was little affected by pretreatment with milrinone. Unexpectedly, four out of seven milrinone-treated pigs, but only one out of seven septic control pigs died during the observation period.

There are only a few clinical studies investigating the effects of milrinone during SIRS or sepsis. In a clinical study investigating pediatric patients with nonhyperdynamic septic shock, Barton *et al.*[9] found that cardiac index, and oxygen delivery significantly increased while systemic vascular resistance significantly decreased when compared to placebo after *iv* administration of milrinone. No adverse effects were observed. The authors concluded that milrinone may improve cardiovascular function in a volume-resuscitated pediatric patient with septic shock, when administered in addition to catecholamines. Heinz *et al.*[10] investigated the effects of milrinone in adult patients with nonhyperdynamic SIRS/sepsis compared with that in patients with congestive heart failure (CHF). They hypothesized that there might be an outstanding beneficial effect of milrinone in the setting of SIRS/sepsis because of the potency of PDE inhibitors to inhibit cytokine production and expression. The authors showed that milrinone led to an improvement in cardiac function but this effect was not superior to the effect observed in CHF patients. Preexisting catecholamines had to be increased in both groups. Milrinone was discontinued in one of nine patients due to profound hypotension. Although the authors concluded that milrinone does not appear to offer any additional benefit because of a cytokine inhibitory action in terms of cardiac performance when compared to CHF patients, this study showed that milrinone was effective in patients with a hypodynamic course of SIRS/sepsis and significantly improved cardiac function.

Vincent *et al.*[29] investigated the hemodynamic effects of the PDE-III inhibitor amrinone in a canine septic shock model and concluded that if there is already excessive endotoxin-induced hypotension, the PDE inhibitor appears to add little or nothing to worsen the circulatory collapse. Additionally, the results of Vincent *et al.*[29] showed an increase in oxygen delivery and in oxygen consumption during infusion of amrinone, indicating an improved tissue perfusion. If this

would also be true for the PDE inhibitor milrinone then, according to our results, it appears that the intestinal mucosa is one of the tissues that profits from improved tissue perfusion. The continuous infusion of endotoxin in the LPS group led to a decrease of mucosal blood flow caused by both a vasoconstriction of central arterioles and a decrease of blood flow velocity. This confirms the results of our own previous studies[16,30] and the observations of other investigators.[31,32] The pathophysiologic mechanisms responsible for vasoconstriction and hypoperfusion of intestinal mucosa during endotoxemia are not fully clear. An imbalance between vasodilative and vasoconstrictive mechanisms and especially an increased release of vasoconstrictors, such as endothelin or noradrenaline, are discussed.[33,34] Lindgren *et al.*[35] reported that milrinone is a potent agent to dilate vessels precontracted by noradrenaline. They studied the relaxant effects of milrinone on isolated human mesenteric arteries and veins *in vitro*. In preparations contracted by noradrenaline, milrinone produced about 60% maximum relaxation. Arteries, compared with veins, were more sensitive to this inhibition of noradrenaline contraction. In the present study, milrinone did not fully prevent the decrease in intestinal villus blood flow but prevented the vasoconstriction of central arterioles. Erythrocyte velocity decreased in the milrinone group similar to that in the LPS group. However, prevention of vasoconstriction of central arterioles was sufficient to attenuate the endotoxin-induced decrease in mucosal villus blood flow. Whether the prevention of endotoxin-induced vasoconstriction is mainly a direct vasodilative effect of milrinone or whether any anti-inflammatory properties of milrinone, combined with a suppressed release of vasoactive mediators might play a role, can not be concluded from the results of this study. Several investigators reported that milrinone and other PDE inhibitors have the potential to inhibit inflammatory cell activation,[11] e.g. milrinone suppressed the endotoxin-stimulated production of TNF-alpha and IL-1 beta in human monocytes[12,13] and inhibited the respiratory burst of polymorphonuclear neutrophils to a certain degree.[14]

Recently, Möllhoff *et al.*[36] investigated the effects of milrinone on splanchnic oxygenation, systemic inflammation, and the subsequent acute-phase response in patients undergoing coronary artery bypass grafting. Compromised splanchnic perfusion and the resulting intestinal mucosal injury during and after cardiopulmonary bypass lead to a decreased mucosal barrier function, which enables translocation of intestinal bacteria and endotoxemia. One result of this study was that the perioperative administration of milrinone did not prevent gastrointestinal acidosis as measured by pHi, but it resulted in higher pHi levels than in the control group. The authors concluded that perioperative administration of low-dose milrinone may have anti-inflammatory properties and may improve splanchnic perfusion in patients undergoing routine coronary artery bypass grafting. To date no clinical study investigated comparable parameters in septic patients, but the results of our study indicate that at least mucosal hypoperfusion might be attenuated by milrinone infusion in septic patients.

In summary, we showed that milrinone improved compromised tissue perfusion of intestinal mucosa during endotoxemia, mainly by preventing villus arteriolar vasoconstriction. Its detrimental effect on systemic arterial hypotension may limit its use as a single cardiovascular drug in sepsis. However, in combination with vasoconstrictive agents it might be beneficial in the treatment of SIRS or sepsis, especially if it proves to attenuate systemic inflammation. Further studies are necessary to evaluate these potential beneficial effects of milrinone during sepsis.

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