

Commentary

Metabolic effects of phosphodiesterase III inhibitors: another reason to promote their use?

Vladislava Simkova^{1,2}, Peter Radermacher¹ and Eberhard Barth¹

¹Sektion Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Universitätsklinikum, Parkstrasse 11, D-89073 Ulm, Germany

²Anesteziologicko-resuscitacni klinika, Fakultni nemocnice u sv Anny, Brno, Czech Republic

Corresponding author: Peter Radermacher, peter.radermacher@uni-ulm.de

Published: 11 June 2007

This article is online at <http://ccforum.com/content/11/3/139>

© 2007 BioMed Central Ltd

Critical Care 2007, **11**:139 (doi:10.1186/cc5924)

See related research by Heringlake *et al.*, <http://ccforum.com/content/11/2/R51>

Abstract

Phosphodiesterase III inhibitors combine positive inotropic and vasodilator properties. These inhibitors are therefore frequently used to treat low cardiac output and/or severe left heart failure associated with cardiac surgery. Their effects on energy metabolism and visceral organ function are not well studied, however, particularly in comparison with their 'competitors' in daily practice (that is, catecholamines).

In the previous issue of *Critical Care*, Heringlake and colleagues compared the metabolic and renal effects of adrenaline and the phosphodiesterase III inhibitor milrinone in patients with low cardiac output after coronary artery bypass surgery [1]. Demographic data of the study population, the cardiopulmonary bypass time and baseline hemodynamics were well matched. Adrenaline or milrinone were randomly administered to achieve a cardiac index >3 l/min/m² and were maintained thereafter for the 14-hour study period. Patients without the need for inotropic support served as controls. Despite comparable hemodynamics, blood lactate, pyruvate, and glucose concentrations were higher in the adrenaline-treated patients, the latter being affiliated with higher exogenous insulin requirements. This metabolic pattern was accompanied with transitory higher lactate/pyruvate ratios, indicative of a less balanced cytosolic redox status [2].

In the context of the landmark studies on intensive insulin use by the group of Van den Berghe and colleagues, particularly in patients undergoing cardiac surgery [3], the metabolic effects of catecholamines and alternative drugs may assume particular importance. It is well established that, similar to other shock states, cardiogenic shock is characterised by a hypermetabolic condition with insulin resistance, hyperlactatemia and increased oxygen demand that coincide with both compromised tissue microcirculatory perfusion and mitochondrial dysfunction [4,5].

In contrast to catecholamines, the metabolic effects of phosphodiesterase III inhibitors have been poorly studied. Phosphodiesterase III inhibitors (that is, enoximone, milrinone and olprinone) have both vasodilatory and inotropic properties, and have been shown to effectively increase the cardiac index in patients with cardiogenic shock of various etiologies [6,7]. In patients with hyperdynamic septic shock, enoximone was associated with enhanced energy expenditure and oxygen consumption but significantly reduced the rate of hepatic gluconeogenesis, while plasma lactate and glucose concentrations and the lactate turnover rate did not change [8]. This finding is of particular interest since gluconeogenesis is a highly oxygen-demanding pathway accounting for 50% of hepatic oxygen consumption [9] and is inversely related to the protein synthesising capacity of the liver [10].

In line with these observations, plasma lactate and glucose levels did not change in the milrinone-treated patients in the present study, possibly suggesting a more balanced hepatosplanchnic oxygen demand and supply. In fact, perioperative milrinone had antiinflammatory properties and improved splanchnic perfusion in patients undergoing coronary artery bypass grafting [11], and in patients with septic shock enoximone but not dobutamine increased hepatosplanchnic oxygen uptake concomitant with improved metabolic capacity and a decreased hepatic tumor necrosis factor alpha release [12]. Data for whole body oxygen consumption, carbon dioxide production and cytokine release are lacking in the present study, so the mechanism of the milrinone-related improvement of the patients' metabolic status remains unresolved. It should be noted in this context that the glucose control was handled fairly liberally at least in the adrenaline group, since glycemia levels up to 240 mg/dl were tolerated. A tighter glucose control in this group would consequently probably have requested even higher insulin doses, which in

turn might have also influenced the patients' hemodynamic status: in patients with chronic left heart failure undergoing a euglycemic hyperinsulinemic clamp, insulin increased the cardiac output as a result of moderate peripheral vasodilation, while superior mesenteric flow remained unaffected [13].

In their present study, Heringlake and colleagues did not find any significant effect of milrinone on standard parameters of renal function (that is, creatinine clearance and fractional sodium excretion). In contrast, blood cystatin-c levels and the urinary α_1 -microglobulin concentrations – parameters that are referred to closely mirror impaired glomerular filtration and tubular injury, respectively [14] – showed more pronounced impairment in the adrenaline-treated patients than in the milrinone and control groups. The mechanism of this putative renal protective property of milrinone remains unsettled in the present study. One might speculate that phosphodiesterase III inhibition increased juxtaglomerular cAMP concentrations, thus causing increased renin secretion and a consecutively higher renal perfusion pressure [15]. In addition, the less strict glucose control in the adrenaline group might also be responsible for the authors' observation: even transient hyperglycemia enhances formation of reactive oxygen species [16], which in turn was shown to damage human proximal tubular epithelial cells [17].

In summary, a number of studies are now available showing that, during shock states, phosphodiesterase III inhibitors may exert less 'metabolic stress' than the more potent catecholamines adrenaline and noradrenaline. It is well established that catecholamines may cause hyperlactatemia and hyperglycemia, the degree of which is directly related to their specific β -receptor activity [18]. Given the hyperglycemia-related aggravation of oxidative stress, phosphodiesterase III inhibitors might prove an attractive alternative and/or adjunct to the use of catecholamines in patients with low cardiac output.

Competing interests

The authors declare that they have no competing interests.

References

- Heringlake M, Werner M, Gruenfeld J, Klaus S, Heinze H, Bechtel M, Bahlmann L, Poeling J, Schoen J: **The metabolic and renal effects of adrenaline and milrinone in patients with myocardial dysfunction after coronary artery bypass grafting.** *Crit Care* 2007, **11**:R51.
- Leverve XM: **From tissue perfusion to metabolic marker: assessing organ competition and co-operation in critically ill patients?** *Intensive Care Med* 1999, **25**:890-892.
- Vanhorebeek I, Ingels C, Van den Berghe G: **Intensive insulin therapy in high-risk cardiac surgery patients: evidence from the Leuven randomized study.** *Semin Thorac Cardiovasc Surg* 2006, **18**:309-316.
- Revelly JP, Tappy L, Martinez A, Bollmann M, Cayeux MC, Berger MM, Chioloro RL: **Lactate and glucose metabolism in severe sepsis and cardiogenic shock.** *Crit Care Med* 2005, **33**:2235-2240.
- Okuda M: **A multidisciplinary overview of cardiogenic shock.** *Shock* 2006, **25**:557-570.
- Orime Y, Shiono M, Hata H, Yagi S, Tsukamoto S, Kimura S, Ohmiya S, Sezai A, Yamada H, Obana M, Sezai Y: **Post-operative effects of olprinone after coronary artery bypass grafting.** *Ann Thorac Cardiovasc Surg* 1998, **4**:340-346.
- Siostrzonek P, Koreny M, Delle-Karth G, Haumer M, Koller-Strametz J, Heinz G: **Milrinone therapy in catecholamine-dependent critically ill patients with heart failure.** *Acta Anaesthesiol Scand* 2000, **44**:403-409.
- Schricker T, Radermacher P, Träger K, Kugler B, Georgieff M: **Metabolic and hemodynamic response to the phosphodiesterase-III-inhibitor enoximone in septic patients.** *Clin Intensive Care* 1996, **7**:116-120.
- Jungas RL, Halperin ML, Brosnan JT: **Quantitative analysis of amino acid oxidation and related gluconeogenesis in humans.** *Physiol Rev* 1992, **72**:419-448.
- Ayuso MS, Vega P, Manchon CG, Parrilla R: **Interrelation between gluconeogenesis and hepatic protein synthesis.** *Biochim Biophys Acta* 1986, **883**:33-40.
- Möllhoff T, Loick HM, Van Aken H, Schmidt C, Rolf N, Tjan TD, Asfour B, Berendes E: **Milrinone modulates endotoxemia, systemic inflammation, and subsequent acute phase response after cardiopulmonary bypass (CPB).** *Anesthesiology* 1999, **90**:72-80.
- Kern H, Schröder T, Kaulfuss M, Martin M, Kox WJ, Spies CD: **Enoximone in contrast to dobutamine improves hepatosplanchnic function in fluid-optimized septic shock.** *Crit Care Med* 2001, **29**:1519-1525.
- Parsonage WA, Hetmanski D, Cowley AJ: **Beneficial haemodynamic effects of insulin in chronic heart failure.** *Heart* 2001, **85**:508-513.
- Trof RJ, Di Maggio F, Leemreis J, Groeneveld AB: **Biomarkers of acute renal injury and renal failure.** *Shock* 2006, **26**:245-253.
- Chiu YJ, Hu SH, Reid IA: **Inhibition of phosphodiesterase III with milrinone increases renin secretion in human subjects.** *J Pharmacol Exp Ther* 1999, **290**:16-19.
- Samikkannu T, Thomas JJ, Bhat GJ, Wittman V, Thekkumkara TJ: **Acute effect of high glucose on long-term cell growth: a role for transient glucose increase in proximal tubule cell injury.** *Am J Physiol Renal Physiol* 2006, **291**:F162-F175.
- Leverve X: **Hyperglycemia and oxidative stress: complex relationships with attractive prospects.** *Intensive Care Med* 2003, **29**:511-514.
- Barth E, Albuszies G, Baumgart K, Matejovic M, Wachter U, Vogt J, Radermacher P, Calzia E: **Glucose metabolism and catecholamines.** *Crit Care Med* 2007, **35**(Suppl):in press.