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Inhaled and intravenous application of a stimulator of the soluble guanylate cyclase (BAY 41-8543) reduces pulmonary vascular resistance in a model of septic shock

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Background

Cardiac failure in septic shock usually originates from hypovolaemia, impaired global contractility or right ventricular failure (RVF). Acute RVF due to endotoxin-mediated pulmonary hypertension results in global hypoperfusion. However, the treatment of pulmonary vascular resistance (PVR) in septic patients remains a black box.

Methods

After ethical approval, septic shock was induced in 32 pigs (25 ± 3 kg) by continuous infusion of endotoxin (Escherichia coli serotype 0111:B4). The animals received a protocol-based treatment with fluids and vasopressors according to the surviving sepsis campaign guidelines. Then, they were randomized to either inhaled (i.h.) (240μg kg^{-1}) or intravenous (i.v.) (24μg kg^{-1}) treatment with BAY 41-8543 or controls. Heart rate (HR (bpm)), mean arterial pressure (MAP (mmHg)), mean pulmonary artery pressure (MPAP (mmHg)), cardiac output (CO (l min^{-1})) and PVR (dyn sec cm^{-5}) were assessed every 15 minutes for 1 h after starting the treatment. Following a wash out period of 1 h, the animals were once more randomized to double dose (D2) i. h. or i.v. respectively or to simultaneous administration of Bay 41-8543 at a single dose together with NO (i.h.) at 20 ppm. Hemodynamic measurements were taken for another hour. Data are expressed as mean ± SD at

Table 1

	shock *(n=32)*	i.h. *(n=12)*	i.v. *(n=14)*	con (n=6)	i.h. D2 (n=6)	i.h. no *(n=5)*	i.v. D2 (n=5)	i.v. no (n=5)	con no (n=5)
HR	127 (34)	150 (21)	163** (28)	123 (34)	140 (35)	146 (19)	171 (29)	148 (29)	113 (34)
MAP	58 (7)	71 (7)	68 (6)	73 (8)	75 (6)	69 (9)	68 (14)	73 (10)	73 (8)
MPAP	38 (7)	40 (7)	37 (8)	44 (6)	42 (10)	42 (9)	40 (16)	37** (9)	39** (9)
PVR	1246 (401)	491** (106)	469** (198)	972 (325)	691** (322)	573** (245)	849* (815)	460** (103)	887** (296)
CO	2.02 (0.51)	4.65** (0.76)	5.04** (1.43)	2.93 (0.89)	3.73 (1.71)	4.16* (1.44)	4.3** (2.85)	4.06** (0.78)	2.46 (0.67)

* p<0.05 **p<0.01 vs. control group (con)

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shock and 30 minutes after treatment. Differences between groups were analyzed using a linear mixed-effects model.

Results

Both during i.h. and i.v. application of BAY 41-8543, a significant decrease in PVR and an increase in CO was observed. Additive inhaled NO decreased PVR more than doubling the dose of BAY 41-8543 (Table 1).

Conclusion

The stimulator of the soluble guanylate cyclase BAY 41-8543 offers a treatment option for pulmonary hypertension in septic shock. Both inhalative and intravenous administration of BAY 41-8543 reduces PVR and increase CO. Further, there seems to be an additive effect of inhaled NO.

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