EXPERIMENTAL

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Effect of increasing doses of magnesium in experimental pulmonary hypertension after acute pulmonary embolism

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Abstract *Objective:* To investigate the dose-related effects of magnesium on pulmonary vascular resistance and associated changes in cardiac output in porcine micro-embolic pulmonary hypertension. *Design:* Prospective, interventional animal study. *Setting:* University animal laboratory. *Subjects:* Forty anaesthetised and ventilated piglets. *Interventions:* Right heart catheterisation for the measurement of cardiac output, pulmonary artery pressure, central venous pressure and pulmonary capillary wedge pressure; arterial cannulation for measurement of arterial pressures and ionised magnesium levels; calculation of pulmonary and systemic vascular resistance before and after induction of acute pulmonary micro-embolism, and without or with the administration of magnesium (0.5, 1.0, 2.0 mmol/kg bolus and 1 mmol/kg bolus followed by 1 mmol/kg per h continuous infusion). *Measurements and main results:* The bolus administration of increasing doses of magnesium (0.5, 1.0, 2.0 mmol/kg) was associated with an increase in ionised serum magnesium levels and a dose-dependent decrease of mean pulmonary arterial pressure, an increase of cardiac output and a decrease of pulmonary vascular resistance. This effect was sustained after bolus administration (1 mmol/kg) followed by a continuous infusion of magnesium (1 mmol/kg per h). *Conclusions:* Magnesium has a directly dose-dependent beneficial effect on the circulation in acute embolic pulmonary hypertension and improves cardio-circulatory impairment in massive pulmonary embolism (PE).

Keywords Magnesium · Pulmonary embolism · Pulmonary hypertension · Animal experiment · Cardiac output · Pulmonary circulation

Introduction

Pulmonary embolism (PE) is a significant cause of morbidity and mortality in modern societies [1, 2] and rates of clinical outcomes, such as death and recurrence, vary widely among studies [3, 4, 5, 6, 7]. Massive PE leads to an acute increase of right ventricular afterload and possible right heart failure with consecutive impairment of the systemic cardiac output [8] and altered gas exchange. These pathophysiological findings explain the high incidence of acute death after fulminant PE [9, 10, 11, 12].

Therapeutic strategies include, after appropriate recognition of the underlying disease (i.e. thrombus, gas, fat or amniotic fluid embolism), the removal or dissolution of the embolic thrombi or interventional and surgical measures [9, 13, 14]. In severe forms, ventilation with high inspiratory oxygen concentration, selective pulmonary vasodilation and support of the cardiac output (CO) is beneficial for outcome [15, 16, 17, 18].

Magnesium plays a significant role in the tone of vascular smooth muscles and its effect can be characterised as calcium-antagonistic. Higher levels of ionised magnesium promote vascular relaxation. In several stud-

ies, magnesium sulphate was reported to have beneficial effects on primary pulmonary hypertension and secondary pulmonary hypertension after correction of congenital heart defects [19, 20, 21]. Additionally, its use in hypoxic pulmonary hypertension accentuates the effect of nitric oxide [22].

The objective of the present study was to investigate the dose-dependent effects of increasing doses of magnesium on the cardiovascular system in a porcine model of acute massive PE.

Material and methods

The study was approved by the local ethics committee (Senatsverwaltung fuer Gesundheit und Soziales des Landes Berlin, Ziffer G 0350/95). All investigations were performed at the animal research laboratories of the Humbold University of Berlin, Campus Charité, Rudolf Virchow Klinikum, Wedding, Berlin.

Animal preparation

We used German Landrace piglets with body weights from 12 to 18 kg. All animals were handled according to the guidelines published by the National Institutes of Health and the Council of the American Physiologic Society [23]. Following overnight fasting and premedication with azaperone (Stresnil; Janssen; Neuss, Germany; 4 mg/kg i.m.) and atropine 0.05 mg, the animals were anaesthetised using i.v. administered methohexital (Brevimythal, 1–4 mg/kg per h) and fentanyl (Janssen, 0.05–0.1 mg/kg) and paralysed with pancouronium bromide (Organon Teknika, Eppelheim, Germany; 0.1–0.3 mg/kg). Ringers' solution was administered during the entire study period at a rate of 3–5 ml/kg per h. After endotracheal intubation, the lungs were mechanically ventilated at a rate of 20 breaths/min (Servo 300 A Ventilator, Siemens Elema, Solna, Sweden). The tidal volume was adjusted to ensure a $PaCO_2$ between 35 and 40 mmHg with a maximal peak inspiratory pressure at 20 cmH_2O and a PEEP of 5 cmH_2O. The fraction of inspired oxygen (FIO_2) was set at 0.5. This ventilatory regimen was maintained throughout the initial study period. The rectal temperatures of all animals were maintained at a constant level of 35–37°C.

Using cutdown procedures, all animals underwent insertion of a right carotid arterial catheter, (Leader Cath 20G; Laboratoires Pharmaceutiques Vygon, Ecouen France), a right internal jugular vein 5.5 Fr thermistor-tipped flow-directed pulmonary artery catheter (93–631–5.5 Fr; Baxter Healthcare, Irvine, California) and a right external jugular central venous line (Arrow, CS-15854-E, 8.5 Fr, 20 cm).

The tip of the pulmonary artery catheter was placed in the pulmonary artery and the correct placement was verified by a recording of the typical pressure trace after the pulmonary artery was entered and measurement of the pulmonary capillary wedge pressure (PCWP). The position of the catheter tip was corrected during the study whenever necessary. Non-heparinised 0.9% normal saline solution (2 ml/h) was used to maintain the patency of all lines. Each catheter line was connected to a pressure transducer that was levelled to mid-heart. The transducer output was displayed and recorded continuously on a multi-channel recorder (Marquette). Measurements included systolic, diastolic and mean arterial pressure (SAP, DAP, MAP), heart rate (HR), central venous pressure (CVP), systolic, diastolic and mean pulmonary artery pressure (SPAP, DPAP, MPAP) and PCWP. All haemodynamic measurements were taken at end-expiration without expiratory hold.

At predetermined time points (T prae, T post, T-0, T-5, T-15, T-30 and T-60 min, see Fig. 1), the haemodynamic measurements were reported and CO was determined by the thermodilution method using a CO computer (Marquette). To achieve CO measurements, 5 ml boluses of ice-cold saline were injected at end-expiration via the injection port of the pulmonary artery catheter. The thermodilution curve was inspected for accurate measurement and the mean value from three consecutive measurements was recorded. The haemodynamic parameters were calculated using standard formulas: pulmonary vascular resistance (PVR)=(MPAP-PCWP) x CO^{-1}x79.9 and systemic vascular resistance (SVR)= (MAP-CVP) x CO^{-1}x79.9.

Fig. 1 Schematic presentation of the study protocol
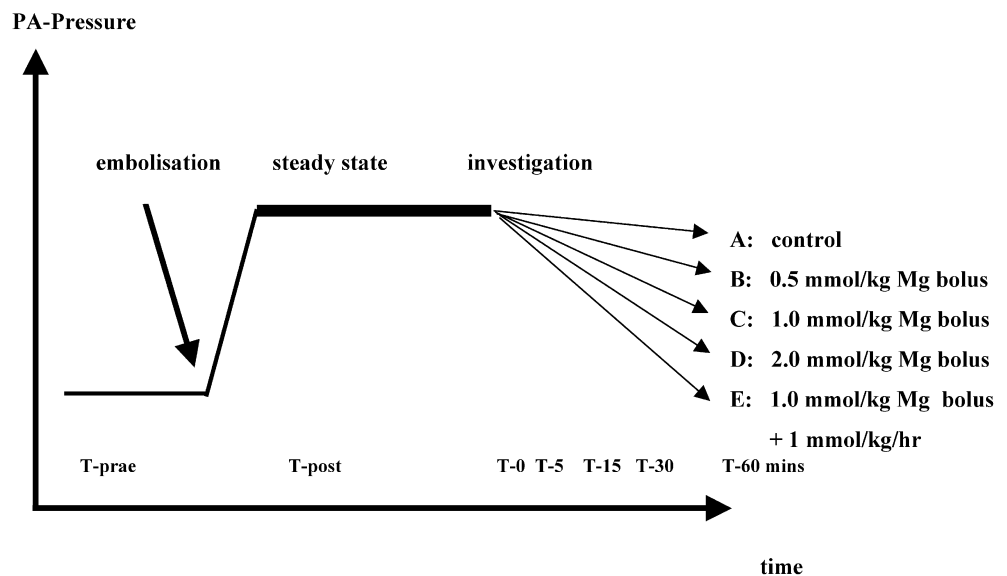
Table 1 Haemodynamic measurements before and after embolisation with microspheres

Parameter	Pre-embolisation	Post-embolisation			
		15 min	>60 min	120 min	*p* value
HR (beats/min)	125±38	152±31	143±25	139±32	<0.05
MAP (mmHg)	103±17	96±15	107±13	111±15	n.s.
LAP (mmHg)	6±3	5±2	6±3	6±3	n.s.
PAP (mmHg)	19±3	48±6	38±6	36±7	<0.001
CVP (mmHg)	5±3	11±4	10±3	8±3	<0.05
CO (l/min)	2.8±0.7	2±0.6	2.3±0.6	2.3±0.6	<0.05
PVR (dynes/s per cm^5)	375±158	1959±1007	1268±620	1114±539	<0.001
SVR (dynes/s per cm^5)	2953±1027	3797±1772	3780±1554	3831±1447	<0.01
i. Mg (mmol/l)	0.60±0.1			0.61±0.14	n.s.
Ca (mmol/l)	1.96±0.12			1.96±0.12	n.s.
PaO$_2$ (mmHg)	254±48			63±12	<0.001
PaCO$_2$ (mmHg)	38.4±4			49.1±7.1	<0.001
pH	7.43±0.04			7.36±0.05	<0.05

HR heart rate, *MAP* mean arterial blood pressure, *LAP* left atrial pressure, *PAP* pulmonary artery pressure, *CVP* central venous pressure, *CO* cardiac output, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance, *i. Mg* ionised magnesium, *Ca* calcium, PaO$_2$ arterial oxygen tension, PaCO$_2$ arterial CO$_2$ tension, *pH* blood hydrogen concentration

All values are indicated as means ± standard deviation.

N.B. The *p* value is calculated to compare the pre-embolisation value with the value at 120 min only.

Figures were rounded where appropriate.

Experimental protocol

After termination of the preparation period, all animals were allowed to stabilise for 60 min. All variables were then determined under steady-state conditions. Acute massive PE was induced by stepwise injection of 300 μm microspheres (Sephadex G25 superfine; Pharmacia Biotech, Freiburg, Germany) into the superior vena cava over 5 min [18, 22, 24, 25, 26].

Pilot experiments in our institution demonstrated a significant variability of the individual response of the animals to fixed doses of the microspheres injected [27] and the first two animals died due to acute right heart failure. We therefore used an individually titrated injection protocol to achieve an initial MPAP of 50 mmHg within a 5-min period. This was accompanied by an increase in HR and a decrease of the MAP, and can be interpreted as the acute circulatory response to massive PE. Usually a spontaneous decrease of the MPAP was observed after some minutes and a repeat injection was necessary thereafter. These findings are consistent with the findings of other animal models [18]. After induction of the massive PE, the animals were again allowed to stabilise for 60 min. Thereafter, all variables were determined again under the new steady-state conditions for another 60 min (see Table 1). Ventilation was adjusted to a FIO$_2$ of 100% and the respiratory rate was set to achieve a PaCO$_2$ of less than 50 mmHg and a pH of more than 7.3.

Following this period of stabilisation, the animals were randomly assorted to the different groups (A–E) of the study protocol. One group (A) did not receive any magnesium administration. In the subsequent groups B, C, and D magnesium was administered as a bolus of 0.5, 1.0 and 2.0 mmol/kg over 5 min, respectively. The last group (E) received a magnesium bolus of 1 mmol/kg over 5 min followed by a continuous infusion of 1 mmol/kg per h. Serial sets of measurements were taken at 0, and then 5, 15, 30 and 60 min after the start of the magnesium bolus. Serum levels of ionised magnesium were measured at the points T prae, T post, T-0, T-5, T-15, T-30 and T-60 min (see Fig. 1) after magnesium administration using atomic absorption spectroscopy (Perkin Elmer 1100, Ueberlingen, Germany; at 285.5 vm wavelength).

No attempts were made to correct any haemodynamic changes observed during the entire study period with additional fluid administration or inotropic agents. After completion of the protocol, all animals were killed by the injection of a lethal dose of potassium chloride and subsequent post mortem examinations were performed to exclude intracardiac shunts.

Statistical analysis

Statistical analysis was performed using the computer programme SPSS (Version 7.5). The data are presented as means and median values and standard deviation of the mean in each group. All measurements of the treatment groups B, C, D, and E were compared with the results of the control group (A) at the specific time points (T-0, T-5, T-15, T-30 and T-60). The analysis concentrated on the effects of this magnesium therapy on measurements of the variables: magnesium levels, MPAP, MSAP, CO, PVR and SVR. Due to the non-constant variance across the different groups and times involved, the following non-parametric analyses were conducted:

1. 'Friedman' and 'Kendall's W' tests for multiple related samples, to confirm that control group measurements remained steady over time.
2. At each time of observation (from "steady state" onwards), a Kruskal-Wallis test for comparison of multiple independent samples was conducted to determine whether differences existed between any of the groups at that time, followed by a series of Mann-Whitney U tests to confirm which of the groups differed significantly from the control group at that time.

The results of these tests are shown in the following graphs, one for each of the variables mentioned above. For each variable, the corresponding graph shows the observed mean measurement for each group at each time, together with a 95% confidence interval for the population mean. The annotations * and + on the graphs indicate that a significant result ($p < 0.05$ and $p < 0.01$, respectively) was obtained from the Mann-Whitney comparison test for that combination of group and time.
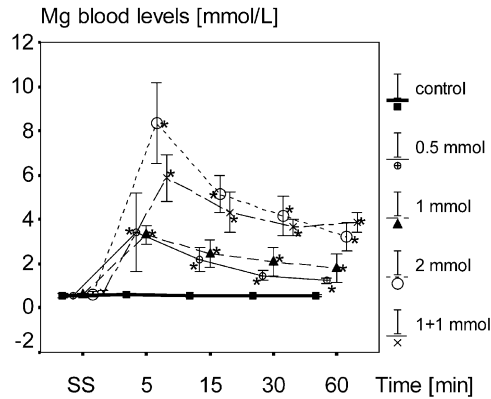
Fig. 2 Concentrations of ionised magnesium. *SS* steady state (T=0)
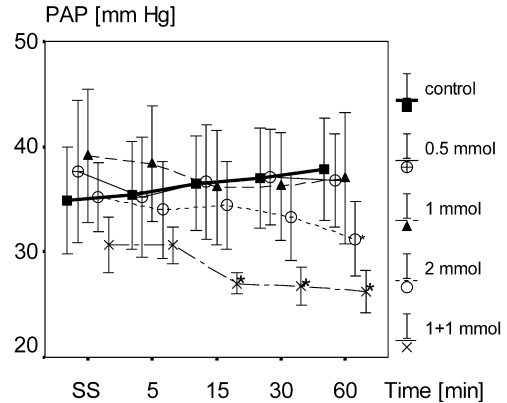
**Fig. 3** Mean pulmonary arterial blood pressure (*PAP*) after administration of magnesium. *SS* steady state (T=0)

Results

We administered consecutive doses of the micro-emboli to obtain an increase in pulmonary artery pressure (PAP) of about 50 mmHg. To achieve this, doses of 0.1–1.0 mg of microspheres had to be injected (median 0.35 mg). In the first two animals, acute PE led to an acute right heart failure and death. Subsequent administrations were changed and smaller doses were administered stepwise and no additional acute mortality was observed in the animals investigated.

The acute effects of the pulmonary embolisation are summarised in Table 1. The acute embolisation was followed by an increase in PAP, CVP and HR, and a massive increase (+400%) in PVR, as well as a decrease in MAP and CO. After the stabilisation period of 60 min the baseline measurements were used to compare the effects of the different doses of magnesium administered. The magnesium administration led to a dose-dependent increase of the concentration of ionised serum magnesium (see Fig.2). With bolus administration there was a rapid increase in serum magnesium and a subsequent decline. Bolus administration followed by a continuous infusion was able to stabilise the serum magnesium levels at about 4 mmol/l of ionised magnesium.

The increase of serum magnesium was followed by a dose-dependent decrease of PAP and CVP, and an increase in CO (see Figs. 3 and 4). There was no significant change in HR, but MAP and SVR decreased significantly at higher doses (see Figs. 5 and 6). The direct dose-dependent influence of the concentration of ionised serum magnesium on PVR is shown in Fig. 7. The control did not show significant changes compared to the baseline measurements. No significant changes in oxygenation or CO_2 exchange were seen.
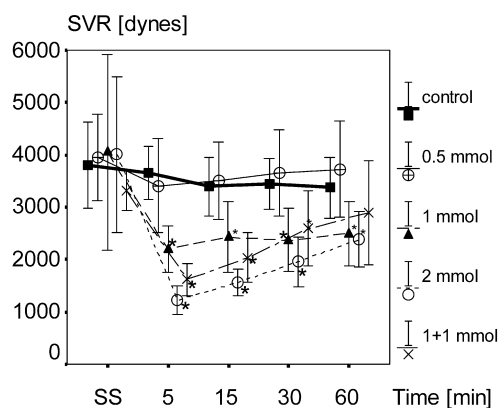
The post mortem examination performed in all animals excluded the presence of intracardiac shunts.
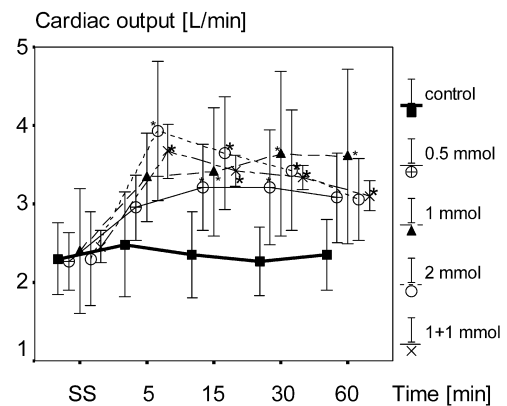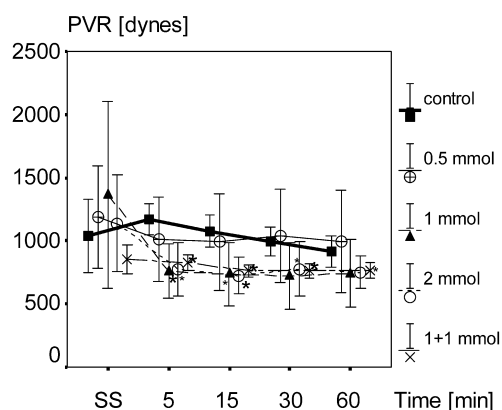

Fig. 4 Mean cardiac output measurements (*CO*) after administration of magnesium. *SS* steady state (T=0)
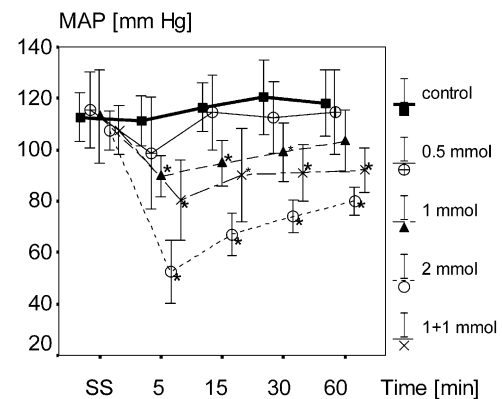
Fig. 5 Mean arterial blood pressure (*MAP*) after administration of magnesium. *SS* steady state (T=0)

Fig. 6 Mean systemic vascular resistance measurements (*SVR*) after administration of magnesium. *SS* steady state (T=0)

Fig. 7 Mean pulmonary vascular resistance measurements (*PVR*) after administration of magnesium. *SS* steady state (T=0)

Discussion

This investigational study is, to our knowledge, the first to report the beneficial dose-dependent effects of magnesium in severe experimental PE. Magnesium has been described as "nature's physiological calcium blocker" and is a muscle relaxant and a potent vasodilatory agent [28, 29, 30, 31]. Magnesium inhibits Ca^{2+}-induced muscle contraction by inhibition of the Ca^{2+} release from the sarcoplasmic reticulum and it competes with calcium at several binding sites on troponin and myosin [32, 33]. Magnesium ions are important for the regulation of Na+ and K+ transport across cell membranes, including cardiac and smooth muscle cells [34]. The effect of magnesium in hypoxic pulmonary vasoconstriction is related to the inhibition of Ca^{2+}-dependent K+ channels [22] and it is essential for cGMP- and cAMP-mediated mechanisms of pulmonary vascular relaxation [30]. The vasodilator effect of magnesium seems to be endothelium-independent but related to the serum concentrations [31].

Additionally, magnesium increases the local production of vasodilatory prostaglandins (i.e. prostacyclin) [35]. In vitro studies have shown that the magnesium ion (Mg^{2+}) modulates smooth muscle contractility and mediator release [33]. This effect is comparable to the inhibition of calcium-dependent muscle contraction of other divalent cations, such as zinc (Zn^{2+}) [36, 37], or specific calcium channel blockers, such as nifedipine, used to treat pulmonary hypertension [38, 39, 40, 41].

Several reports have suggested that magnesium may be a therapeutic agent with which to treat elevated PVR [20, 42]. Persistent pulmonary hypertension of the newborn (PPHN) is potentially fatal and various therapeutic strategies have been used including systemic and inhalant vasodilatory agents, ECMO and, more recently, inhaled nitric oxide [43, 44, 45, 46, 47]. Several clinical trials to treat PPHN with the use of magnesium have been published [19, 21, 48]. These results indicate that magnesium is very useful in improving oxygenation by pulmonary vasodilatation in these patients. The side effects observed were a slight decrease in heart rate [21] and various degrees of systemic hypotension [49, 50].

The normal plasma levels of magnesium range from 0.75 to 1.5 mmol/l and about 60% is ionised (0.4–0.7 mmol/l) [32]. Hypermagnesaemia (2.27±0.25 mmol total serum magnesium) lowered PAP and delayed the fall in SAP and stroke volume in lambs exposed to hypoxia-induced pulmonary hypertension [51]. This effect seems to be correlated to the level of oxygen in the pulmonary artery, and magnesium can prevent and reduce hypoxia-induced pulmonary hypertension [52, 53]. Increasing aliquots of 1 mmol/kg magnesium ions (as $MgSO_4$) resulted in a significant decrease in PVR. In septic lambs, however, a fall in SAP was observed. This effect could be increased by the additional administration of nitric oxide [22, 50].

The serum levels reported for treating pulmonary hypertension ranged between 2.5 mmol/l and 6.6 mmol/l [19, 21, 54]; no significant changes in HR, blood pressure, renal function or serum electrolytes were observed [48, 49, 54]. The magnesium doses administered in experimental and clinical studies to treat pulmonary hypertension varied from bolus administration of 0.5 mmol/kg up to continuous infusions of 4 mmol/kg per h [20, 48]. Significant effects were observed at serum concentrations of 2.5–4.0 mmol/l of total serum magnesium. In our animal model we tested the different doses described and could correlate increasing levels of ionised magnesium to decreasing PVR and increasing CO (see Figs. 4 and 7). Only at levels of ionised magnesium above 4 mmol/l did we find a significant decrease in the mean arterial blood pressure. This effect was not found in studies when smaller amounts of magnesium were administered and lower plasma levels were achieved [48, 49, 54]. Therefore the therapeutic usefulness of magnesium using high doses may be limited by its relative non-selectivity. However,

this side effect could be minimised by the administration of catecholamines for the circulatory support of severe PE [8, 55, 56].

The increase in PVR in micro-embolic lung injury occurs at the periphery of the pulmonary arterial tree [27, 57]. It rapidly (after 2 h) induces proinflammatory, mitogenic and vasoconstrictive gene expression (endothelins, arachidonate oxidases, thromboxane, serotonin) that increases with the severity and duration of vascular occlusion [58, 59]. A potential beneficial effect of magnesium on this secondary vasoconstriction has been discussed [22, 31, 35], but has not been proven yet. It is postulated that magnesium may act through an increase of the production of endogenous nitric oxide [60, 61] and this may contribute to its clinical effect.

Afterload reduction in acute cor pulmonale after massive PE is essential to improve the right ventricular dysfunction [8, 11]. This therapeutic principle was proven useful in other causes of right ventricular failure [62]. Selective pulmonary vasodilators, such as inhaled nitric oxide and aerolised prostacyclin, achieved pulmonary vasodilatation in patients with congenital cardiac defects and pulmonary hypertension [63]. In our animal model we could show a dose-dependent decrease in PVR and increase in CO (see Figs. 4 and 7). Right ventricular dysfunction has long been recognised as a marker for poor outcome in patients with PE, especially in those with haemodynamic instability. Cardiac arrest will occur within 1–2 h after the onset of clinical presentation in two thirds of fatal PE cases [10]. A significant reduction of PVR and PAP with an increase in CO within the first hour of treatment of massive PE could separate the survivors from the non-survivors [12].

In conclusion, this laboratory study provides evidence that the administration of magnesium may have therapeutic value as an adjunct to traditional therapy in acute PE or when other treatment strategies, such as NO or prostacyclins, are not available. It is also a simple treatment and of low cost. However, further experimental and clinical studies of magnesium and its potentially beneficial effect on the outcome of fulminant PE are needed.

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