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Sildenafil Prevents Cardiovascular Changes after Bone Marrow Fat Embolization in Sheep

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Background: **Sudden, intraoperative cardiovascular deterioration as a result of pulmonary embolization of bone marrow fat is a potentially fatal complication during total hip and knee arthroplasty, intramedullary nailing, and spine surgery. Anesthetic management is challenging in the presence of increased right ventricular afterload due to pulmonary hypertension. Selective pulmonary vasodilation may be an appropriate prophylactic or therapeutic measure. The effect of sildenafil (phosphodiesterase inhibitor) on cardiovascular deterioration after bone marrow fat embolization was therefore investigated.**

Methods: **Bone cement (polymethylmethacrylate) was injected into three lumbar vertebrae in 12 sheep. Invasive blood pressures and heart rate were recorded continuously until 60 min after the last injection. Cardiac output and arterial and mixed venous blood gas variables were measured at selected time points. Before the first cement injection, 6 animals received a bolus injection (0.7 mg/kg) of sildenafil, with continuous infusion (0.2 mg · kg^{-1} · h^{-1}) thereafter. Postmortem lung and kidney biopsies were taken for semiquantitative analysis of intravascular fat.**

Results: **Fat embolism was associated with a transient increase (21 ± 7mmHg) in pulmonary arterial pressure. A transient decrease in arterial blood pressure and temporary increases in central venous pressure and dead space were also observed. No significant changes in any cardiovascular variable were observed after fat embolism in the sildenafil group. There was significantly ($P < 0.05$) less intravascular fat in the lungs of the sildenafil (median count of 5 emboli per microscopic view) compared with the control group (median count of 1).**

Conclusions: **Administration of sildenafil prevented the acute cardiovascular complications after bone marrow fat embolism in sheep.**

EMBOLIZATION of bone marrow fat during orthopedic surgery can lead to intraoperative cardiovascular deterioration. Incidences have been observed during total hip[1] and knee[2] arthroplasty and intramedullary nailing for stabilization of fractured long bones.[3] More recently, fat embolism has also been reported during instrumented spine surgery[4] and augmentation of fractured osteoporotic vertebrae with bone cement (vertebroplasty).[5,6] Fat embolization occurs in almost all patients undergoing major orthopedic surgery; however, not every patient shows clinical signs. Cardiovascular changes after pulmonary fat embolization are characterized by an increase in pulmonary arterial pressure, systemic arterial hypotension, and a decrease in cardiac output, hypoxemia, and arrhythmia.[7,8] Cardiovascular deterioration is often transient but may be fulminant, resulting in cardiac arrest and even death.[5,6,9] The number of orthopedic interventions provoking fat embolization is increasing, and therefore, the risk of intraoperative cardiovascular emergencies is also increasing.

Prevention and correction of cardiovascular deterioration after fat embolization during orthopedic surgery are therefore gaining importance. Modifications of surgical techniques, such as drilling vent holes,[1,10] lavage of the bone marrow cavity,[11] or using different orthopedic tools,[12] have aimed at reducing the embolic load and thus the risk of severe cardiovascular deterioration. Anesthetic management consists of maintaining arterial blood pressure and cardiac output.[13,14] However, this may be challenging in the presence of increased right ventricular afterload and decreased left ventricular preload. Different authors have reported that the characteristic increase in pulmonary arterial pressure during fat embolism is a result of pulmonary vasoconstriction, rather than mechanical blockage.[7,8] Pharmacologic vasodilation of the pulmonary vasculature may therefore be an appropriate measure for preventing or alleviating cardiovascular deterioration after fat embolization. Administration of sildenafil, a type 5 phosphodiesterase inhibitor, caused selective pulmonary vasodilation[15] and alleviated pulmonary arterial hypertension after experimental embolism induced by injecting microspheres.[16] However, embolization of microspheres does not adequately reproduce the pathophysiologic complexity of bone marrow fat embolization after an orthopedic intervention.

Therefore, the use of sildenafil for preventing or alleviating pulmonary hypertension after bone marrow fat embolization was investigated using a clinically relevant animal model (vertebroplasty in sheep).

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Materials and Methods

Animal Model

Cardiovascular measurements were performed in 12 skeletally mature, mixed-bred ewes (4–6 yr old; mean body weight, 69.7 ± 9.7 kg). Animals were subjected to unilateral augmentation of three vertebral bodies (L2–L4) with bone cement to force bone marrow fat into the circulation. The study was approved by the animal ethics committee (Kantonales Veterinäramt, Zürich, Switzerland) and was conducted according to federal and state guidelines.

Instrumentation of Animals

Anesthesia was induced with propofol (6 mg/kg) and maintained with isoflurane (2–3%; minimum alveolar concentration in sheep is 1.5%) in oxygen (50%). Analgesia and muscle relaxation were achieved by administrating buprenorphine (0.005 mg/kg) and pancuronium (0.06 mg/kg). Lungs were ventilated mechanically for maintaining normal end-tidal and arterial carbon dioxide tension before cement injection. End-tidal carbon dioxide tension was measured with an infrared capnometer. Ventilation settings were not altered after cement injection. A drip infusion of lactated Ringer's solution was maintained *via* the left cephalic vein at $4\ ml \cdot kg^{-1} \cdot h^{-1}$. Electrodes were placed on the skin for electrocardiographic conduction.

Animals were positioned in dorsal recumbence for cardiovascular instrumentation. The left carotid artery was cannulated (angiography catheter, 7.1 FG, length 80 cm; William Cook Europe, Bjaeverskov, Denmark) for measuring left ventricular pressure. The correct position of the ventricular catheter was confirmed by recording typical pressure waves. The right carotid artery was cannulated (multiple lumen catheter, Quinto; B. Braun Medical AG, Sempach, Switzerland) for measuring arterial blood pressure and taking blood samples. An introducer (8 FG, Intro-Flex; Edwards Critical-Care Division, Irvine, CA) for a Swan-Ganz catheter was inserted into the right jugular vein. Subsequently, a Swan-Ganz standard thermodilution pulmonary artery catheter (7.5 FG, length 110 cm, CCO/VIP; Edwards Critical-Care Division) was floated into the pulmonary artery for measuring central venous pressure, pulmonary arterial pressure, and cardiac output and for taking mixed venous blood samples. The correct position of the catheter was confirmed by recording typical pressure waves. Catheters were connected to pressure transducers (Uniflow; Baxter, Volketswil, Switzerland) *via* pressure tubing filled with lactated Ringer's solution. Heart rate was derived from the electrocardiogram. Cardiovascular pressures and electrocardiogram were digitized at 1 Hz using an analog–digital converter (Hellige Messturm; Marquette-Hellige GmbH Medizintechnik, Freiburg, Germany) and stored on a computer for off-line analysis. Bolus thermodilution method was used for measuring cardiac output at certain time points. Cooled lactated Ringer's solution (< 10°C; 5 ml) was injected through the Swan-Ganz catheter, and values were calculated by a cardiac output machine (COM-2; Baxter).

Surgical Procedure and Cement Injection

Animals were turned to right lateral recumbence. A retroperitoneal approach was used for exposing the lateral aspects of three lumbar vertebral bodies (L2–L4). A cement injection hole (diameter 3.5 mm) was drilled into the proximal aspect of each vertebra to a depth of 10.0 mm. The proximal half of the injection hole was carefully widened so that a syringe tip (3 ml) would fit tightly into it.

Polymethylmethacrylate bone cement formulated for vertebroplasty (Mendec; Tecres Medical, Verona, Italy) was used for injection. Powder and chilled liquid (5°C) were mixed for 30 s and then drawn into 3-ml syringes (polycarbonate; Medicor AG, Cham, Switzerland). Cement was left to polymerize at room temperature until an appropriate viscosity for injection was reached. A volume of 6.0 ml cement was injected over 30 s, unless injection pressure was too high, meaning that filling of the vertebral body had been achieved.

Experimental Protocol

Pressure transducers were zeroed at the level of the heart. Invasive cardiovascular pressures and electrocardiogram were recorded continuously. Baseline cardiovascular evaluation was performed at least 20 min after termination of the surgical approach (fig. 1). Cardiac output measurements were taken in triplicate and averaged. Arterial and mixed venous blood samples were drawn for blood gas analysis (pH, carbon dioxide tension, oxygen tension), which was performed immediately (ABL 700; Radiometer GmbH, Copenhagen, Denmark). Thereafter, six animals (sildenafil group) received a bolus injection (0.7 mg/kg intravenous) of sildenafil (Pfizer AG, Zürich, Switzerland) over 15 min *via* an infusion pump. Subsequently, continuous sildenafil infusion ($0.2\ mg \cdot kg^{-1} \cdot h^{-1}$ intravenous) was established.

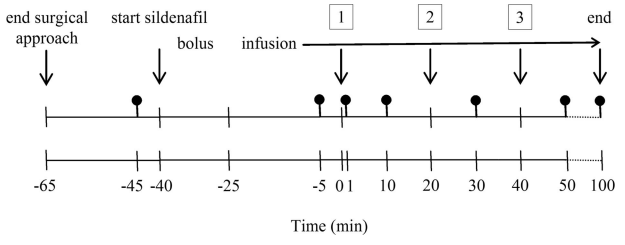

Fig. 1. Flow chart of experimental protocol. Blood sampling and measurement of cardiac output 30 min after the third cement injection are not shown. ● = Blood sampling and cardiac output measurements; 1, 2, 3 = cement injections; end surgical approach = end of open surgical approach to lumbar vertebrae and drilling of injection holes; end = end of experiment.

Control animals (n = 6) only received lactated Ringer's solution. At least 20 min after termination of the bolus injection of sildenafil, respectively, 20 min before the first cement injection in the control group, preinjection cardiovascular evaluation was performed (including cardiac output and arterial and mixed venous blood gas analysis) (fig. 1). Cement was then injected into three lumbar vertebral bodies (L2–L4) with time intervals of 20 min between subsequent injections. The duration of the intervals was sufficient for stabilization of cardiovascular variables on a new steady state.[7,17] Postinjection cardiovascular evaluation of cardiac output and blood gas variables was performed 1 and 10 min after having started the first injection; 10 min after having started the second injection; and 10, 30, and 60 min after having started the third injection. Invasive cardiovascular pressures and electrocardiogram were recorded until 60 min after having started the last (*i.e.*, third) cement injection. At the end of the protocol, animals were killed by intravenous injection of potassium chloride (2 mmol/kg) after administration of pentobarbital (1 g/sheep).

Histopathology

Postmortem two-lung tissue samples were taken from selected areas of each lobe (n = 5: right cranial, middle, and caudal lobes and left cranial and caudal lobes) and fixed in 10% neutral buffered formalin. In the sildenafil group, tissue samples were also collected from both kidneys. Specimens were stained with hematoxylin and eosin, as well as oil red O (fat stain). Two microscopic views (magnification ×5) were analyzed from each sample. The observer (K.N.) was blinded to the treatment. Semiquantitative analysis of the number of intravascular fat was performed counting the number of emboli in each view.

Analysis of Cardiovascular Data

To obtain baseline (presildenafil) (fig. 1) and preinjection values of continuously recorded cardiovascular variables, data were analyzed for 5-min periods and averaged. For postinjection values, data were analyzed for periods of 20 s at each time point and averaged. An increase or decrease in a cardiovascular variable of more than 15% present for more than 20 s was considered a cardiovascular response. Cardiac index, pulmonary vascular resistance index, systemic vascular resistance index, physiologic dead space, and intrapulmonary shunt were calculated using standard formulas.

Statistical Analysis

Data were calculated and presented as mean ± SD of the mean. Two-way analysis of variance for repeated measures was used to test for intergroup and intragroup differences. *Post hoc* analyses were performed using the Newman–Keuls test. Nonparametric data were calculated and presented as median and 95% confidence interval. Differences between groups were tested with the Mann–Whitney U test. Two and multiple variables were compared using the Sign test and Friedman two-way analysis of variance, respectively. Spearman rank order analysis was used for investigating correlations between variables. A P value (two-tailed) of 0.05 or less was considered significant for all statistical analyses. Statistical analyses were performed using Statistica 7 software (StatSoft GmbH, Hamburg, Germany).

Results

Cement Injection

In each group, one injection was unsuccessful, because cement volumes insufficient for eliciting cardiovascular responses had been injected (*i.e.*, less than 3 ml). Cement viscosity had been too high for injecting more volume. Data from these two injections were excluded from analysis. The quantity of cement injected (95% confidence interval, 4.5–5.5 *vs.* 4.0–4.8 ml) and the duration of cement injections (95% confidence interval, 26–38 *vs.* 23–33 s) were not significantly different between the control and the sildenafil group. Postmortem, cement leakage into epidural and paravertebral veins was discovered in one sildenafil animal and two control animals.

Cardiovascular Changes

There were no significant differences in the cardiovascular variables between the two groups at baseline (before sildenafil) (table 1 and figs. 2–4). Sildenafil administration resulted in pulmonary and systemic vasodilation before the first cement injection and throughout the experiment (fig. 4). Systemic vascular resistance index had decreased by 50 ± 15%. However, there were no significant changes in mean arterial blood pressure (MABP), pulmonary arterial pressure (MPAP), intrapulmonary shunt, or arterial oxygen tension after sildenafil administration (table 1 and figs. 2 and 3).

In the control group, cement injections resulted in an increase in MPAP that lasted for 5 min (fig. 2). Furthermore, a transient decrease in MABP and temporary increases in mean central venous pressure and dead space were observed (table 1, fig. 2). In the sildenafil group, no significant changes in any cardiovascular variable were observed after the cement injections (table 1 and figs. 2–4). Seven cement injections events resulted in a maximal increase in MPAP of 42 ± 23% and a maximal decrease in MABP of 0.1 ± 19% (table 2). In the control group, 17 and 15 injections resulted in a maximal increase in MPAP of 108 ± 32% and a maximal decrease in MABP of 36 ± 16% respectively (intergroup difference: $P < 0.05$).

Table 1. Inhalation Settings and Blood Gas Variables before and after Fat Embolization

	Baseline (n = 6)	Preinjection (n = 6)	1 min post 1 (n = 6)	10 min post 1 (n = 6)	10 min post 2 (n = 5)	10 min post 3 (n = 6)	30 min post 3 (n = 6)	60 min post 3 (n = 6)
Isoflurane, %								
Control	2.7 ± 0.2	2.7 ± 0.2	2.7 ± 0.2	2.8 ± 0.2	2.8 ± 0.3	2.7 ± 0.2	2.7 ± 0.2	2.7 ± 0.2
Sildenafil	2.9 ± 0.3	2.9 ± 0.3	2.9 ± 0.2	2.8 ± 0.2	2.9 ± 0.2	2.9 ± 0.3	2.9 ± 0.3	2.7 ± 0.4
pH								
Control	7.48 ± 0.03	7.48 ± 0.03*	7.46 ± 0.03	7.47 ± 0.03	7.47 ± 0.02	7.46 ± 0.02	7.47 ± 0.02	7.47 ± 0.02
Sildenafil	7.47 ± 0.04	7.45 ± 0.03	7.45 ± 0.04	7.44 ± 0.04	7.42 ± 0.06†	7.42 ± 0.05†	7.42 ± 0.05†	7.41 ± 0.05†
$Paco_2$, mmHg								
Control	39 ± 3	39 ± 3*	42 ± 2	40 ± 3	40 ± 3	41 ± 4	40 ± 2	41 ± 4
Sildenafil	38 ± 5	38 ± 5	41 ± 1	39 ± 5	4.9 ± 3	41 ± 0.9	40 ± 7	42 ± 5
Pao_2, mmHg								
Control	270 ± 105	270 ± 105*	270 ± 98	270 ± 98	263 ± 113	270 ± 120	263 ± 120	278 ± 135
Sildenafil	263 ± 113	27 ± 113	225 ± 143	225 ± 128	240 ± 143	203 ± 75	218 ± 120	210 ± 120
V_D/V_T								
Control	0.12 ± 0.07	0.12 ± 0.07*	0.20 ± 0.04†	0.12 ± 0.07	0.13 ± 0.09	0.16 ± 0.08	0.16 ± 0.05	0.16 ± 0.06
Sildenafil	0.08 ± 0.06	0.10 ± 0.06	0.10 ± 0.06	0.10 ± 0.04	0.05 ± 0.04	0.15 ± 0.05	0.12 ± 0.07	0.11 ± 0.09
Q_S/Q_T								
Control	0.015 ± 0.006	0.015 ± 0.006*	0.015 ± 0.003	0.015 ± 0.003	0.017 ± 0.004	0.016 ± 0.004	0.018 ± 0.005	0.015 ± 0.005
Sildenafil	0.020 ± 0.007	0.028 ± 0.012	0.026 ± 0.011	0.029 ± 0.011	0.029 ± 0.008	0.029 ± 0.004	0.031 ± 0.006	0.029 ± 0.007

* Baseline and preinjection values are identical because only one measurement has been taken before injection. † $P < 0.05$ from preinjection value.

1 min post 1 = value 1 min after first cement injection; 10 min post 1 = value 10 min after first cement injection; 10 min post 2 = value 10 min after second cement injection; 10 min post 3 = value 10 min after third cement injection; 30 min post 3 = value 30 min after third cement injection; 60 min post 3 = value 60 min after third cement injection; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; Preinjection = value before first cement injection; Q_S/Q_T = intrapulmonary shunt; V_D/V_T = dead space.

Histopathology

Intravascular fat and bone marrow cells were present in all lung lobes of both groups (fig. 5). Intravascular bone cement was detected in three lung lobes (control group, n = 2; sildenafil group, n = 1). There were no significant differences in the cardiovascular responses recorded in these animals compared with animals without pulmonary cement embolism. No significant differences in the count of fat emboli were observed between the different lung lobes and the right and the left side (table 3). The count of fat emboli in all five lobes was significantly lower in the sildenafil group compared with the control group. No intravascular fat was present in any kidney tissue sample.

In the control group, there was a positive correlation ($R = 0.84$, $P = 0.04$) between the injected cement volume and the fat emboli count. There was no correlation ($R = 0.03$, $P = 0.9$) between these two variables in the sildenafil group. Injected cement volumes or the fat emboli count were not correlated with the severity of cardiovascular changes in any of the groups (control group: $R = 0.28$, $P = 0.6$ and $R = -0.2$, $P = 0.7$; sildenafil group: $R = 0.3$, $P = 0.6$ and $R = -0.5$, $P = 0.4$).

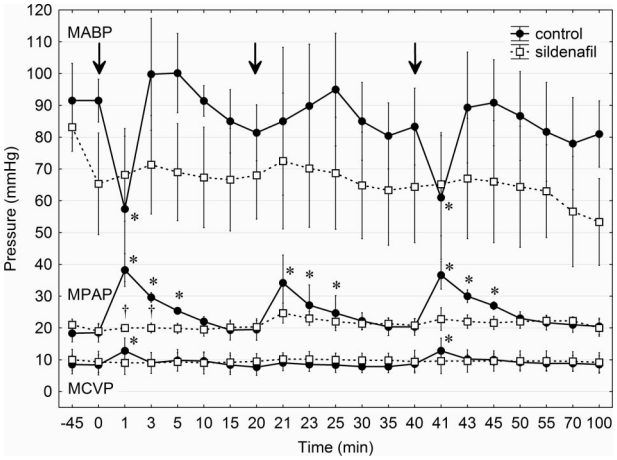

Fig. 2. Mean arterial blood pressure (MABP), mean pulmonary arterial pressure (MPAP) and mean central venous pressure (MCVP) before and after cement injections. The *arrows* indicate the three cement injections. The number of measurements was five at 1, 3, 5 min and 41, 43, 45 min for the control and sildenafil groups, respectively, and six for all the other time points. * $P < 0.05$ from value before injection. † $P < 0.05$ from control group.

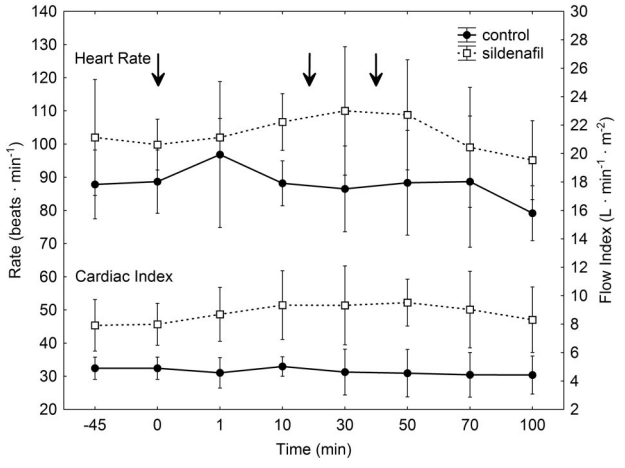

Fig. 3. Heart rate and cardiac output before and after cement injections. In the control group, baseline and preinjection values of cardiac index are identical because only one measurement has been taken before injection. The *arrows* indicate the three cement injections. The number of measurements was six for all time points.

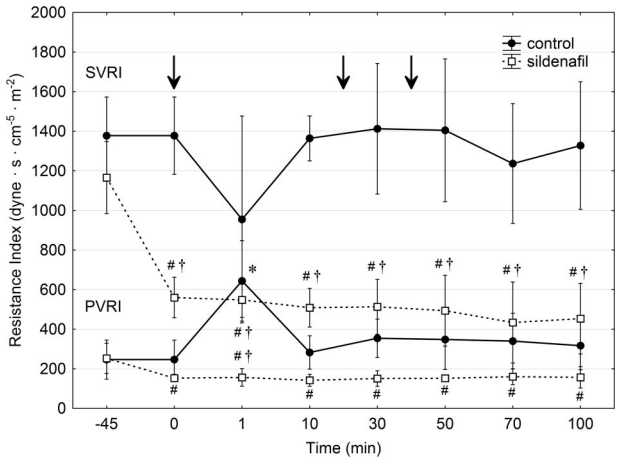

Fig. 4. Pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) before and after cement injections. In the control group, baseline and preinjection values are identical because only one cardiac output measurement has been taken before injection. The *arrows* indicate the three cement injections. The number of measurements was six for all time points. # $P < 0.05$ from baseline value. * $P < 0.05$ from preinjection value. † $P < 0.05$ from control group ($P < 0.05$).

Discussion

Injection of polymethylmethacrylate into vertebral bodies was associated with pulmonary embolism of bone marrow fat and cardiovascular changes, such as an increase in pulmonary vascular resistance and consequently pulmonary hypertension, a decrease in arterial blood pressure, and increases in central venous pressure and dead space. Administration of sildenafil prevented these cardiovascular changes. Furthermore, there was significantly less intravascular fat in the lung tissue samples of the sildenafil group.

In the sildenafil group, there were no significant changes in any cardiovascular variable after embolization. In the control group, all embolization events elicited an increase (62%) in pulmonary vascular resistance, which resulted in a 100% increase in MPAP. Pulmonary hypertension lasted for 5 min and resulted in a decrease (36%) in MABP and an increase (50%) in mean central venous pressure. The current results are in accordance with a previous study[16] demonstrating that sildenafil administration induced pulmonary vasodilation and thus alleviated pulmonary hypertension after embolization of microspheres. Similarly, administration of nitric oxide has been reported to be beneficial for alleviating pulmonary hypertension after embolization of air[18] and microspheres.[19] However, nitric oxide did not alter cardiovascular deterioration as a result of fat embolization during cemented arthroplasty in dogs.[20]

Increased right ventricular afterload after pulmonary embolization of bone marrow fat during orthopedic surgery, such as arthroplasty, intramedullary nailing, or spine interventions, may lead to heart failure and death. Reducing right ventricular afterload is therefore crucial for correcting cardiovascular deterioration after fat embolization and preventing fatalities. This requires administration of selective pulmonary vasodilators because systemic vasodilation would aggravate cardiovascular changes, *i.e.*, hypotension. The current results suggest that sildenafil may be suitable for alleviating or even preventing cardiovascular deterioration, namely pulmonary hypertension, after fat embolization. Intravenous preparation of sildenafil represents a major advantage for widespread clinical use during anesthesia and in critical care.

Sildenafil administration (0.7-mg/kg bolus followed by 0.2 mg · kg^{-1} · h^{-1}) elicited systemic vasodilation before fat embolization in the current study. This may have been dose related or inherent to the chosen animal species. Doses higher than 1 mg/kg body weight per hour have been reported to cause systemic vasodilation in piglets.[21] Optimal pulmonary selectivity occurred at 0.2 mg · kg^{-1} · h^{-1}. In dogs, administration of a bolus of 1 mg/kg sildenafil followed by continuous infusion of 0.3 mg · kg^{-1} · h^{-1} did not cause any changes in MABP.[16] Single doses of 2 mg/kg or higher caused a decrease in MABP in lambs.[15] No systemic vasodilatory effects were observed after administrating a single dose of up to 1.5 mg/kg. Optimal dosage for clinical applications needs to be determined, which cannot be achieved using animal models. Another undesired effect of sildenafil administration is redistribution of pulmonary blood flow ensuing from vasodilation and resulting in pulmonary shunt flow and decreased arterial oxygen tension.[21,22] However, in the current study, changes in intrapulmonary shunt and arterial oxygen tension were not significant. Reports regarding the effect of sildenafil on cardiac output are controversial. Cardiac output was increased after administrating different doses of sildenafil (0.5 to 2.5 mg/kg) in piglets,[22] which may have been the result of increased pulmonary blood flow[23] or a positive inotropic effect of sildenafil.[22] However, cardiac output did not increase

Table 2. Cardiovascular Peak Response to Fat Embolization

	Number of Injections with Response	Max Change, mmHg	$T_{to\ max\ change}$, s
MABP			
Control	15/17	−31 ± 14	42 ± 17
Sildenafil	7/17*	−1 ± 12†	48 ± 22
MPAP			
Control	17/17	21 ± 7	46 ± 19
Sildenafil	7/17*	8 ± 5†	36 ± 8
MCVP			
Control	12/17	5 ± 3	56 ± 19
Sildenafil	0/17*	0	0

* $P < 0.05$ from control group (Fisher exact test). † $P < 0.05$ from control group (unpaired Student *t* test).

MABP = mean arterial blood pressure; Max change = maximal change (*i.e.*, peak change) from preinjection value (pooled data); MCVP = mean central venous pressure; MPAP = mean pulmonary arterial pressure; $T_{to\ max\ change}$ = time from preinjection value to maximal (*i.e.*, peak) value (pooled data).

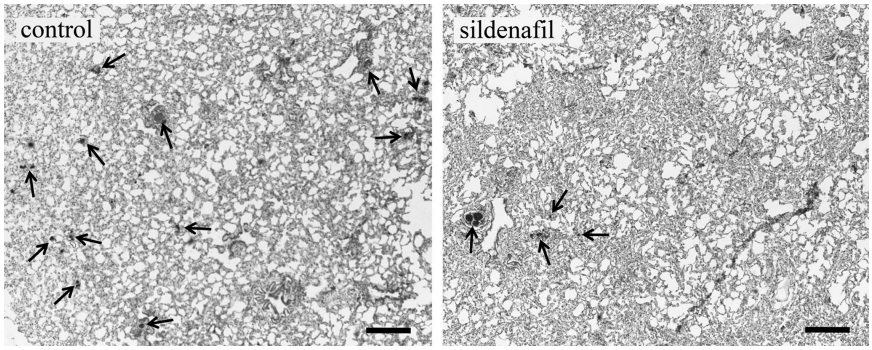

Fig. 5. Histology sections (oil red O) showing intravascular fat (*arrows*) in the lungs of a control (*left*) and sildenafil (*right*) animal. *Bar* represents 300 μm.

significantly in the current study, which is in accordance with the majority of previous reports.[15,16,21]

There was significantly less intravascular fat in the lung tissue samples of the sildenafil group, even though similar volumes of cement were injected and thus similar volumes of bone marrow fat were forced into the circulation in both groups. Differences may have been the result of blood flow redistribution in the sildenafil group[21,22] transporting emboli to different lung regions compared with the control group. Tissue samples were taken from the same locations in all animals. However, selected regions may not have represented emboli sites for the sildenafil group. Alternatively, blood flow redistribution and pulmonary vasodilation in the sildenafil group may have facilitated the passage of emboli through the lungs, resulting in systemic embolization. Spontaneous passage of fat emboli through the lungs, in the absence of a foramen ovale, has been reported to occur within 3–4 h after initial embolization.[9,24] However, it is unlikely that systemic embolization occurred in the current study, because no emboli were detected in any kidney tissue sample. Nevertheless, the fate of bone marrow fat emboli after sildenafil administration must be investigated further.

The current results support the hypothesis that pulmonary vasoconstriction rather than mechanical blockage is the reason for cardiovascular deterioration after bone marrow fat embolization. No correlation was observed between the quantity of intravascular fat in the lungs and the severity of cardiovascular changes (*i.e.*, increase in MPAP). Beneficial effects of administrating sildenafil, a pulmonary vasodilator, furthermore suggest that fat embolization induces pulmonary vasoconstriction. Methylmethacrylate has been reported to cause myocardial depression[25] and pulmonary vasoconstriction.[26] However, concentrations of methylmethacrylate required to elicit cardiovascular changes *in vivo* are severalfold higher than concentrations measured clinically.[27,28]

Bias as a result of unblinded administration of the treatment may have influenced the interpretation of the results and pertains to the limitations of the current investigation. However, analyses of collected data were performed according to predetermined protocols used in a previous study.[7] Embolism induced in the current model was not severe enough to result in significant changes in blood gas variables. This is in accordance with clinical observations during vertebroplasty.[29] Previously, fat embolism had resulted in a decrease in arterial oxygen tension and respiratory acidosis after cement injections into vertebral bodies in sheep.[10] Pulmonary cement embolism, which occurred in one sildenafil and two control animals, may have aggravated cardiovascular responses and masked the effects of fat embolization. However, cardiovascular changes in these animals were not more severe compared with the other animals in the respective groups. Recently published results suggest that pulmonary embolization of polymethylmethacrylate bone cement (2 ml) only causes minor cardiovascular changes (*i.e.*, $<$ 10% increase in MPAP).[30] Occurrence and severity of embolization were not investigated using cardiac ultrasound. However, the nature of the emboli cannot be determined by ultrasound, and histopathology of the lungs confirmed bone marrow fat embolism. In a previous study using the same animal model,[17] embolization of the pulmonary artery was visualized using transesophageal echocardiography. Anesthetics and analgesics used in the current study may have interfered with the cardiovascular response to bone marrow fat embolism. Propofol has been reported to inhibit the contraction of pulmonary artery smooth muscle cells.[31]

Table 3. Count of Intravascular Fat Emboli in the Lung Tissue Samples

	Control		Sildenafil	
	Median	95% CI	Median	95% CI
LCR (n = 12)	4	2–6	1	0–2
LCD (n = 12)	4	0–7	1	0–2
RCR (n = 12)	6	2–8	1	0–3
RMID (n = 12)	5	0–13	2	0–5
RCD (n = 12)	6	1–12	2	0–5
All lobes (n = 60)	5	4–7	1*	1–2

Counts of intravascular fat emboli in the analyzed microscopic views of the lung tissue samples.

* $P < 0.05$ from control group.

CI = confidence interval; LCD = left caudal lobe; LCR = left cranial lobe; n = number of analyzed microscopic views; RCD = right caudal lobe; RCR = right cranial lobe; RMID = right middle lobe.

However, cardiovascular evaluation was started at least 2 h after induction with propofol that has a reported half-life of 30 min after injection in sheep (6 mg/kg).[32] Opioids may inhibit pulmonary artery contraction,[33] but bone marrow fat embolism elicited pulmonary hypertension of similar magnitude that was observed in the same experimental model without the administration of opioids.[7] Isoflurane inhalation may have attenuated the pulmonary vasorelaxant effect of cyclic guanosine monophosphate.[34] Nevertheless, sildenafil administration significantly alleviated cardiovascular deterioration after bone marrow fat embolization in the current study. Vertebral filling achieved in the present study (20–30%) was higher compared with the clinical situation (6–15%). However, studying cardiovascular changes after fat embolization, it was crucial to force a similar volume of bone marrow fat into the circulation, thus injecting a similar volume (3–6 ml) of cement compared with the clinical situation. Results obtained from this animal study can only be extrapolated to clinical practice with caution. However, the range of baseline cardiovascular variables and the responses to sildenafil administration and bone marrow fat embolism are comparable with those recorded in humans.

In conclusion, administration of sildenafil prevented cardiovascular complications after bone marrow fat embolism in sheep.

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