

Fat Embolism and Acute Hypotension During Vertebroplasty

An Experimental Study in Sheep

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Study Design. An experimental study of cardiovascular complications that arise during vertebroplasty was conducted.

Objective. To investigate the sequential occurrence of fat embolism and hypotension during vertebroplasty.

Summary of Background Data. Vertebroplasty, the augmentation of vertebrae with polymethylmethacrylate, is a technique for treating osteoporotic compression fractures and achieving prophylactic stabilization of osteoporotic vertebral bodies at risk of fracture. However, there is concern that fat embolism and acute hypotension could occur as in a variety of other orthopedic procedures.

Methods. In six sheep, 6 mL of polymethylmethacrylate was injected unilaterally into L1. Transesophageal echocardiography monitored the pulmonary artery for echodense particles. Heart rate, arterial and venous pressures, and blood gas values were recorded before and for 25 minutes after injection. The lungs were subjected to postmortem histologic evaluation and compared with lung specimens from two sheep that had not undergone vertebroplasty.

Results. Injection of cement elicited a very rapid decrease in heart rate (within 2 ± 1 seconds) and a rapid increase in venous pressure (within 3 ± 1 seconds), which was followed by a fall in arterial pressure (within 5 ± 2 seconds) (phase 1). Thereafter, showers of echogenic material appeared (within 6 ± 1 seconds) and lasted for 138 ± 36 seconds. A second more severe fall in arterial pressure was observed beginning at 18 ± 2 seconds (phase 2). The injection resulted in an increase in partial pressure of carbon dioxide and a decrease in pH. The histology showed intravascular fat globules and bone marrow cells in lung tissue.

Conclusions. The results suggest that immediately after cement injection, there was a reflex fall in heart rate and arterial pressure. The second fall in arterial pressure was a consequence of fat emboli passing through the heart and getting trapped in the lungs. [Key words: bone cement, fat embolism, hypotension, polymethylmethacrylate, sheep spine, transesophageal echocardiography, vertebroplasty] **Spine 2002;27:460-466**

Percutaneous vertebroplasty fat embolism is a technique which involves augmenting vertebral bodies with polymethylmethacrylate. Originally, percutaneous vertebroplasty was introduced to treat vertebral hemangiomas.¹⁷ Subsequently, this technique was used to provide pain relief for patients with malignant vertebral tumors²⁰ or osteoporotic compression fractures.²³ Percutaneous vertebroplasty now is suggested for the prophylactic stabilization of osteoporotic vertebral bodies at risk of fracture.^{3,6}

Clinically, percutaneous vertebroplasty has been shown to provide long-lasting partial or complete pain relief in 80% to 90% of treated patients within the first 72 hours after surgery.^{4,13,19,25} The reported complication rate is low, and mainly associated with polymethylmethacrylate leakage into adjacent structures.^{10,11,13} This can cause spinal cord or nerve root compression and pulmonary embolism.^{8,19,40} Some authors have mentioned fat embolism and hypotension as potential complications during percutaneous vertebroplasty.^{3,18} Fat embolism is a common complication observed during cemented or noncemented hip and knee arthroplasty,^{9,16,28,30} after the fracture of long bones^{33,37} and during intramedullary nailing.^{32,38} This complication occurs when bone marrow particles are released into the circulation, resulting in the occlusion of blood vessels downstream, most notably in the lungs. The acute consequences of fat embolism are hypotension, cardiac arrest, and, in some cases, sudden death.^{16,27}

The mechanisms responsible for the hypotension after fat embolism are not fully understood. Released bone marrow particles cause a microembolization of the arterioles and capillaries of the lungs.^{21,39} This has led to the suggestion that the emboli cause an increase in pulmonary arterial pressure, a systemic arterial hypotension, and a drop in heart rate.³⁹ Others have suggested that the hypotension is a result of the cement monomers and vasoactive mediators gaining access to the circulation from the bone.^{26,31} Another possibility is a reflex autonomic response initiated by increased intramedullary pressure resulting from injection of cement into the bone marrow.³⁵

Although there have been several clinical studies on percutaneous vertebroplasty, some important questions remain unanswered,¹⁵ such as the possible complications and risks of this procedure, especially since the augmentation of several vertebral bodies has been proposed. Because fat embolism is a well-recognized complication in orthopedic surgery, this study aimed to create an animal

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model to investigate whether fat embolism is a complication during vertebroplasty, and to study any initial cardiovascular responses subsequent to fat embolism using this model.

■ Methods

Animal Model. Six adult mixed-bred ewes between 2 and 3 years old, weighing an average of 53.7 kg, underwent a unilateral cement augmentation of L1 or L2. Two control animals were anesthetized, using halothane/oxygen mixture and positive pressure ventilation, but did not undergo surgical procedure. The study was approved by the local animal ethics committee.

Surgical Procedure. Anesthesia was induced with a thiopental bolus of 1 g per sheep and maintained with a halothane (2–3%) and oxygen (2 L/min) mixture throughout the experiment. The animals underwent positive-pressure ventilation. The rate and end-tidal pressure were adjusted to maintain a normal arterial partial pressure of carbon dioxide ($p\text{CO}_2$) before the cement injection. A saphenous vein was cannulated and a saline drip infusion established.

With the sheep in a sternal position, a 15-cm median cutaneous incision was made over the vertebral spinal processes of TH13–L3. The paravertebral muscles then were detached dorsoventrally, exposing the intervertebral joint line. In light of the anatomic differences between ovine and human vertebral bodies, the open procedure was chosen to simplify the technique and to allow clear visualization and confirmation of the right position of the drill hole,¹² thus reducing the risk of injecting cement into the spinal canal. A 3-mm hole was drilled into L1 from a cranial direction. The hole then was widened to 3.2 mm to a depth of 1 cm so a syringe would fit tightly into it.

Protocol. A Hewlett Packard Sonos 2000 ultrasound machine and a Hewlett Packard (Andover, Massachusetts) 5-MHz biplane transesophageal ultrasound probe were used to image the right heart. The transesophageal probe was passed to the distal esophagus, and optimal images of the main pulmonary artery were obtained. These images were monitored continuously for echogenic particles during the study and recorded on Super VHS videotape for subsequent offline analysis.

A catheter was placed in a jugular vein (14-gauge catheter) and a carotid artery (16-gauge catheter). Each was attached to pressure transducers to permit venous and arterial pressure measurement. The arterial and venous pressures were digitized at 100 Hz using a MacLab A/D converter and displayed on a Macintosh LCIII computer (ADI Instruments, Castle Hill, NSW, Australia). The heart rate was derived from the arterial pulse. A second carotid artery catheter was used for arterial blood sampling. At least four arterial blood gas samples were taken before cement injection to measure partial pressure of oxygen ($p\text{O}_2$), $p\text{CO}_2$, pH, and bicarbonate (HCO_3^-).

Baseline arterial and venous pressure and heart rate were recorded for at least 10 minutes before injection of the cement. The cement was a medium-viscosity bone cement CMW3 (DePuy, Auckland, New Zealand). To standardize the composition of the cement, the same procedure was followed in each animal. The base and monomer were mixed for 1 minute, then drawn into two 3-mL syringes with reinforced plungers. To get a pasty consistency, the cement was allowed to cure at room temperature for 5 minutes.²⁹ Then 6 mL of cement was injected unilaterally into L1. At the start of injection, an event marker

was inserted onto the MacLab trace and onto the echocardiogram video. Venous and arterial pressure and signals from the echocardiogram were monitored continuously for 25 minutes. Arterial blood samples were drawn at 1, 3, 5, 7, 15, and 25 minutes after the cement injection was started for blood gas analysis. At the end of the protocol, the animal was killed by an overdose of barbiturates, and postmortem tissue samples were collected for histology.

Histology. The lungs were harvested immediately after euthanasia. The major vessels of the lung were ligated before removal. Three specimens each were taken from the right cranial, middle, and caudal lobes, and from the left cranial and caudal lobes. The specimens were immersed in 10% neutral buffered formalin.

The specimens were stained with osmium tetroxide, then processed, cut into microsections, and stained with hematoxylin and eosin. Three sections from each lobe were randomly selected and partitioned into 1-mm square areas using a microscopic grid overlay (original magnification grid $\times 10$; lung tissue $\times 100$). The squares containing fat were counted and expressed as percentages of the total examined areas. The lung specimens of the two control sheep were prepared and examined the same way.

Statistical Analysis. The mean and standard deviations of the baseline data were calculated to determine the variability of the blood pressure and heart rate. It was considered that a change in blood pressure and heart rate after injection had occurred when change greater than 1 standard deviation from the mean baseline value was observed. Similarly, it was considered that recovery had occurred when the variable had returned to within 1 standard deviation of the baseline value.

In addition, the time to reach the minimum value (or maximum in the case of venous pressure) was determined, and the value at that time was recorded. Finally, the blood pressure and heart rate 25 minutes after injection was calculated. The effect of injecting bone cement was statistically examined using a paired Student's *t* test for the cardiovascular data, comparing the minimum value against the baseline value.

The four blood gas samples taken before the injection of cement were averaged to represent the baseline $p\text{O}_2$, $p\text{CO}_2$, pH and HCO_3^- . The percentage of change from baseline was calculated and the response analyzed using an analysis of variance (ANOVA) with repeated measures and Dunnett's *post hoc* test.

■ Results

Cement Augmentation

A mean of 5.3 mL (range, 3.5–6 mL) of cement was injected into the vertebral bodies. The variation in quantity was a result of variations in the individual size of the vertebral bodies, and in one case the cement (3.5 mL) hardened too quickly. Injection of the cement required 30 to 45 seconds.

Echocardiography

Technically satisfactory echocardiograms were recorded in five sheep. In the sixth sheep, the right heart could not be visualized adequately.

No echogenic particles were imaged during the surgical approach, nor while the hole was being drilled into the vertebral body (Figure 1A). Echogenic particles (Figure 1B) after cement injection were observed in all five

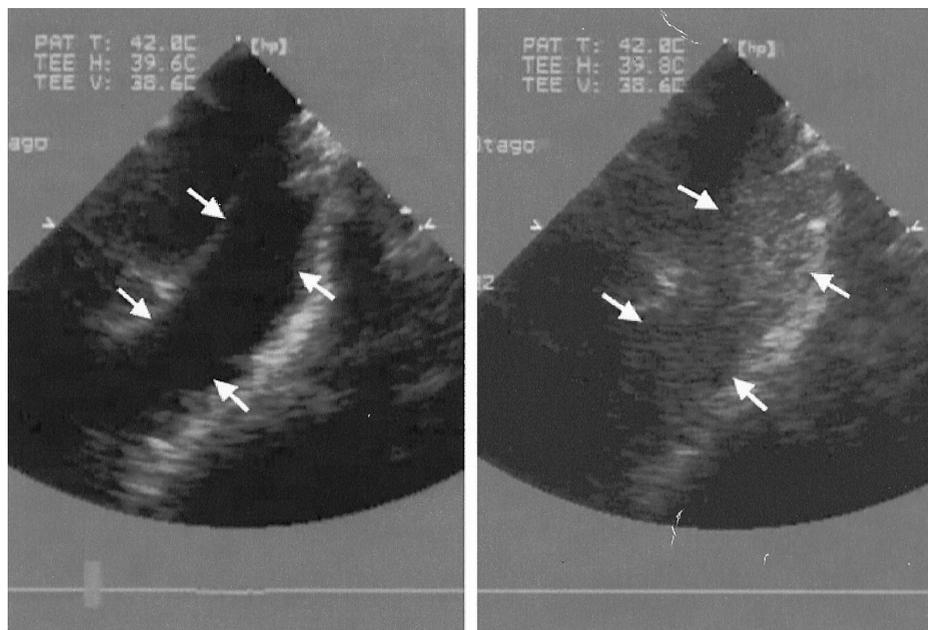


Figure 1. **A**, Transesophageal echocardiogram showing the main pulmonary artery (arrows) before injection of cement. **B**, Transesophageal echocardiogram showing the main pulmonary artery (arrows) filled with echogenic material ("snow storm") after injection of cement.

adequately imaged sheep. The first showers of echogenic material ("snow storm") were visible 6 ± 1 seconds after the cement injection began and lasted for 138 ± 36 seconds. Almost immediately after the appearance of echogenic material in the pulmonary artery, a marked decrease in the velocity of the echogenic particles was seen. At this time, there was transient swirling of material in the pulmonary artery consistent with a marked decrease in pulmonary blood flow. This appearance had resolved after 20 ± 3 seconds.

In one sheep, an ovoid-shaped echodense particle ("snake") was observed to pass slowly across the pulmonary valve and through the pulmonary artery over a period of approximately 1 minute, which coincided with the passage of small echodense particles.

Hemodynamic Changes

Table 1 shows the heart rate and blood pressure response to bone cement injection in six animals. Figure 2 shows the typical cardiovascular response in a single sheep. Injection of bone cement elicited a very rapid decrease in heart rate (within 2 ± 1 seconds) followed by a fall in

mean arterial pressure (within 5 ± 2 seconds) (phase 1) and an increase in venous pressure (within 3 ± 1 seconds). A second phase in the hypotensive response was observed beginning at 18 ± 2 seconds.

Injection of bone cement caused a maximum fall in heart rate of $19\% \pm 10\%$ ($P = 0.005$) at 14 ± 13 seconds. This was accompanied by a delayed maximum fall in mean arterial pressure of $42\% \pm 18\%$ ($P = 0.002$) at 33 ± 8 seconds. Venous pressure reached a maximum of $133\% \pm 61\%$ ($P = 0.02$) at 32 ± 8 seconds.

Heart rate had returned to baseline value by 107 ± 88 seconds. Mean arterial and venous pressure had recovered by 164 ± 91 and 163 ± 151 seconds, respectively. Neither the heart rate nor the two pressures were different from the baseline value at 25 minutes.

Blood Gas Analysis

Table 2 and Figure 3A to 3D show the pO_2 , pCO_2 , pH, and HCO_3 responses to the cement injection. The injection caused a $25\% \pm 9\%$ increase in pCO_2 and a $1.3\% \pm 2\%$ decrease in pH 3 minutes after the injection was started. These changes were sustained throughout the

Table 1. Hemodynamic Changes After Cement Injection

	Baseline	Min/Max	25 min	Phase 1 (sec)	Phase 2 (sec)	$T_{\min/\max}$ (sec)	T_{rec} (sec)
HR (beats/min) (n = 6)	106 ± 17	$85 \pm 13^*$	110 ± 14	2 ± 1		14 ± 13	107 ± 88
MAP (mmHg) (n = 6)	85 ± 15	$49 \pm 17^*$	76 ± 18	5 ± 2	18 ± 2	33 ± 8	164 ± 91
MVP (mmHg) (n = 4)	4 ± 2	$9 \pm 2^\dagger$	3 ± 3	3 ± 1		32 ± 8	151 ± 163

HR = heart rate; MAP = mean arterial pressure; MVP = mean venous pressure; Baseline = resting values for each variable; Phase 1 = time to change 1 standard deviation from basal; Phase 2 = time of onset of the second phase; Min/Max = minimum (HR and MAP) or maximum (MVP) values achieved; $T_{\min/\max}$ = time to reach the minimum (HR and MAP) or maximum (MVP); T_{rec} = time to recover to basal values; 25 min = value recorded 25 minutes after starting cement injection; n = number of animals (venous pressure was recorded in four animals).

* $P < 0.01$.

† $P < 0.05$.

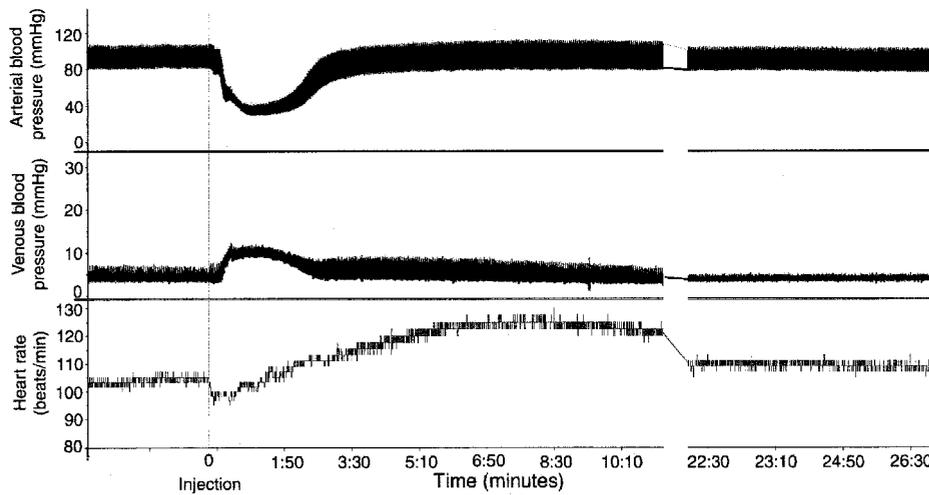


Figure 2. Arterial and venous pressure and heart rate changes in response to cement injection in a single sheep. The two-stage fall in blood pressure can be seen, as well as the very rapid fall. Venous pressure increases as a result of venous pooling.

monitoring period. The mean pO_2 at 1 minute was $20\% \pm 30\%$ below baseline value ($P = 0.17$), and subsequent values were unchanged. There were no statistically significant changes in HCO_3 values.

Histopathology

A string of cement wrapped into an ovoid shape approximately 3 cm long was found in a main pulmonary artery of one sheep that corresponded with the snake-shaped signal observed during the echocardiographic recordings. No leakage of cement into the spinal canal was detected in any of the sheep.

The histology of the lung specimens showed intravascular fat globules and bone marrow cells (Figure 4). The percentage of areas occupied by intravascular fat was $4.1\% \pm 3.4\%$. No intravascular fat or bone marrow cells were present in the control specimens.

Discussion

The study results clearly show that in the sheep model, vertebroplasty provoked fat embolism and resulted in a two-phase decrease in arterial blood pressure. The authors believe the first phase resulted from an autonomic reflex. The second phase was coincident with the passage of fat emboli through the right heart.

The unilateral augmentation of only one vertebral body provoked an embolic shower observed on the echocardiogram. No echogenic material was visible during the surgical approach or the drilling. Echodense material

was imaged in the pulmonary artery after the cement injection in all cases. Similar echocardiographic recordings have been made in other clinical and experimental studies during arthroplasty and intramedullary nailing.^{9,14,28,32,34,41,42} Histology of the lungs showed intravascular fat globules and bone marrow cells. This has been reported by other studies after arthroplasty or intramedullary nailing.^{14,22,36,41}

The vertebroplasty in the current study differed from clinical vertebroplasty in several ways. In this study, vertebroplasty was performed in sheep with healthy, nonfractured bones, whereas most patients receiving percutaneous vertebroplasty have compression fractures resulting from osteoporosis. However, because bone is replaced by fat in osteoporotic vertebral bodies, it is to be expected that the augmentation of an osteoporotic vertebral body with cement could release an even higher quantity of fat emboli,²⁶ especially during the prophylactic augmentation of more than one osteoporotic vertebral body. The presence of a fracture may decrease the release of bone marrow particles during vertebroplasty as a result of decompression if the procedure is performed during the first days after injury, as documented during the intramedullary nailing of fractured femurs.²⁴ However, most patients with vertebral compression fractures receive percutaneous vertebroplasty when healing is already advanced. Therefore, decompression may not occur during injection, and the same amount of bone

Table 2. Changes of pO_2 , pCO_2 , pH, and HCO_3 After Cement Injection

	Baseline (n = 6)	1 min (n = 6)	3 min (n = 5)	5 min (n = 6)	7 min (n = 4)	15 min (n = 5)	25 min (n = 5)
pO_2 (mmHg)	385 ± 72	311 ± 134	393 ± 72	386 ± 74	384 ± 48	363 ± 107	444 ± 34
pCO_2 (mmHg)	37.3 ± 9.1	34.3 ± 8.4	50.6 ± 14.3	$47.8 \pm 13.3^*$	49.3 ± 13.3	46.0 ± 11.8	$47.8 \pm 13.2^*$
pH	7.402 ± 0.107	7.365 ± 0.108	$7.279 \pm 0.090^*$	$7.312 \pm 0.106^\dagger$	7.296 ± 0.076	$7.327 \pm 0.094^*$	$7.314 \pm 0.108^*$
HCO_3 (mmol/L)	22.9 ± 2.3	20.2 ± 2.6	20.7 ± 0.9	20.0 ± 4.7	21.5 ± 0.3	21.0 ± 3.2	21.8 ± 2.2

Baseline = mean resting values and standard deviations for each variable; 1 min, 3 min, 5 min, 7 min, 15 min, 25 min = mean values and standard deviations for each variable recorded 1, 3, 7, 15, and 25 minute after starting cement injection; n = number of samples.

* $P < 0.05$.

† $P < 0.01$.

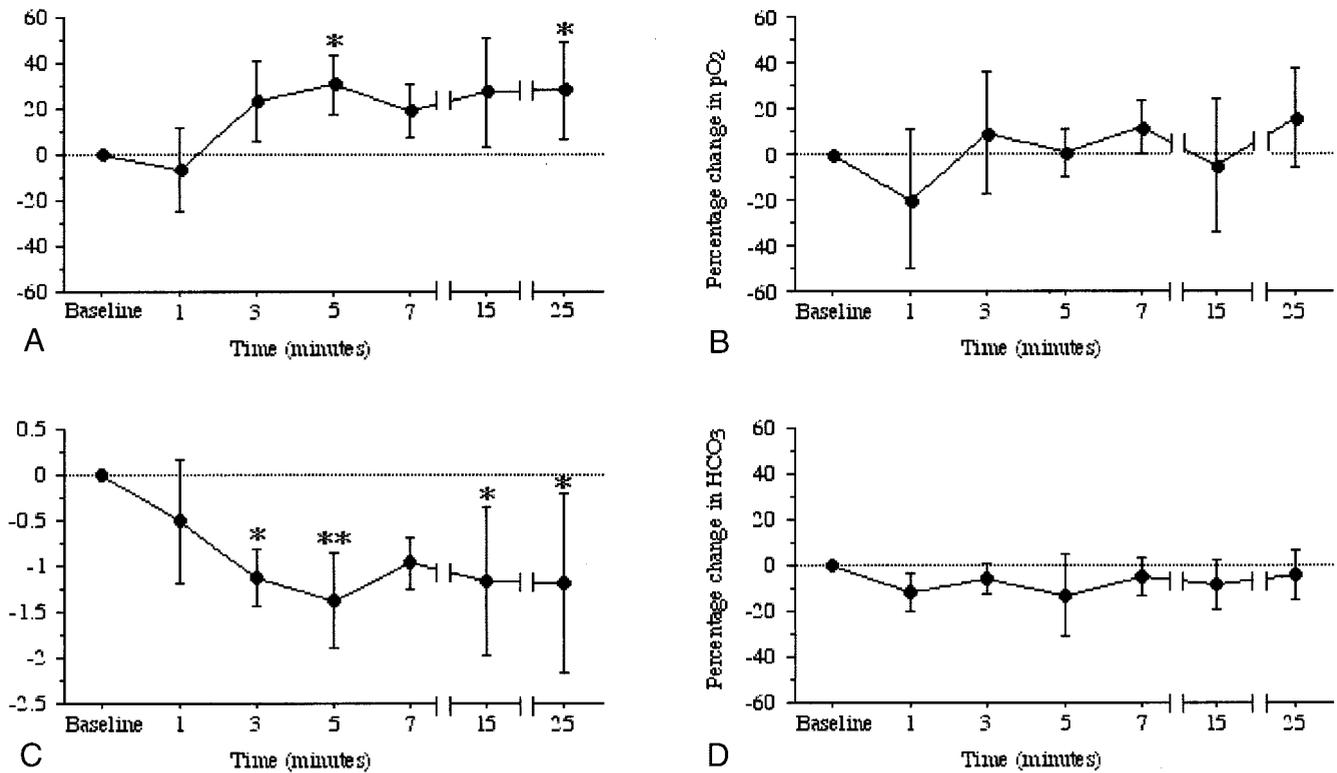


Figure 3. **A**, Percentage of change in pCO₂ (*P < 0.05). **B**, Percentage of change in pH (*P < 0.05; **P < 0.01). **C**, Percentage of change in pO₂. **D**, Percentage of change in HCO₃⁻.

marrow particles may be released as from an intact vertebral body.

Some authors suggest the use of alternative augmentation materials, such as calcium phosphate, for percutaneous vertebroplasty, to avoid the potential complications attributed to the toxic and exothermic properties of polymethylmethacrylate.^{3,5,6,12} However, the injection of these alternative materials will still force bone marrow

and fat particles out of the vertebral body into the circulation, causing fat embolism.

Cement leakage occurs during clinical percutaneous vertebroplasty despite fluoroscopy or computed tomography control and venography.^{10,11,13,40} Leakage into the vascular system and subsequent embolization are acknowledged potential complications of percutaneous vertebroplasty, with one reported clinical case so far.²⁹ In the current study, some cement escaped through the venous system in one sheep, appearing as a "snake" signal on the echocardiogram. The authors believe that the pressure from injecting the cement into the vertebral body caused the extrusion of some, as yet not polymerized, cement out of the bone channels containing nutrient vessels. On occasion, the string of extruding cement within the channel can enter a vein. Previous authors have described the occurrence of large "serpentine" emboli on echocardiography during arthroplasty similar in appearance to that observed in one animal in the current study.^{9,32,34,42} The composition of these "serpentine" emboli has been unclear in the absence of histologic examination. It has been suggested that they are composed of accumulated fat, bone marrow, fibrin, and thrombocytes,^{9,34,42} although the shape of these "serpentine" emboli is not typical of a thrombus.³² In the current study, an ovoid string of cement, whose dimensions corresponded well with the dimensions of the snake-shaped echo, was found in the distal pulmonary artery of one animal. Cement extruded into the venous circulation

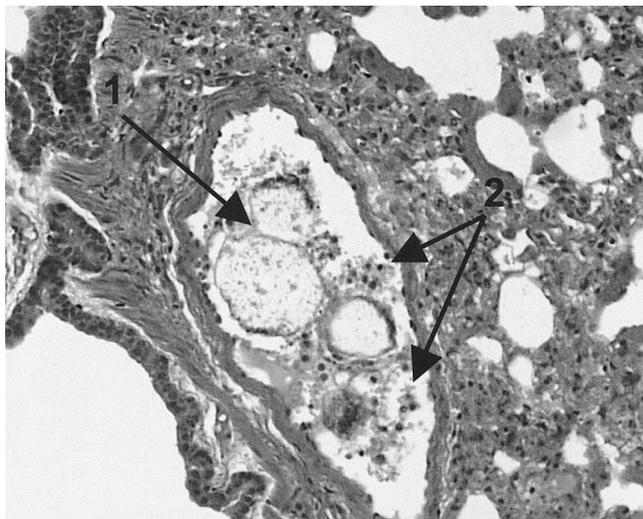


Figure 4. Histologic specimen of lung tissue, after staining with osmium tetroxide and hematoxylin and eosin, demonstrating intravascular fat globules and bone marrow cells (original magnification $\times 100$). 1 = fat globules, 2 = bone marrow cells

may therefore explain the appearance of the “serpentine” emboli reported in previous studies.

The very rapid decrease in heart rate and the first part of the fall in arterial blood pressure are likely to be mediated by a reflex inhibition of the heart. This assumption is based on the very rapid nature of the response (≈ 2 seconds) and the fact that it occurred before the observation of emboli passing through the pulmonary artery 6 seconds after the injection. It therefore is not likely to be the result of obstruction in the lungs. The idea that the initial bradycardia and hypotension are a reflex response is supported by the work of Rudigier and Ritter.³⁵ These investigators pressurized the medullary space of the tibia in rabbits, with the femoral vein and muscles of the ipsilateral leg ligated, thus preventing emboli from reaching the general circulation. They observed a decrease in arterial blood pressure within 2 seconds after the pressure was applied. Rudigier and Ritter³⁵ concluded that the hypotension was caused by a nerve reflex response. The reflex hypotension possibly results from stimulation of the sensory nerve endings by the solvent, the monomers, of the bone cement. However, Breed⁷ ruled this out in his study when he injected wax into the medullary space instead of bone cement and observed a fall in blood pressure with a time course similar to that resulting from bone cement injection.

The conclusion of current authors that the initial cardiovascular changes are the result of a nerve reflex response also is supported by Ahmed et al¹ and Antonacci et al,² who postulate that vertebral bodies are equipped with sensory nerve endings. These nerves are thought to have a vasoregulatory function.¹

In the current study, the second phase of hypotension began as fat and bone marrow material were observed on the echocardiogram to be passing through the right heart. Arterial blood pressure reached a minimum pressure approximately 33 seconds after cement injection began, and returned to baseline after approximately 164 seconds.

The current findings are consistent with those of Breed,⁷ who also observed a decrease in arterial blood pressure when pressurizing the bone marrow during the insertion of cemented hip prosthesis in dogs. The decrease in arterial pressure began 2 to 4 seconds after pressurization and lasted up to 90 seconds. However, Breed⁷ did not observe a two-phased drop in arterial pressure.

During the arterial hypotension, the venous pressure was observed to increase. The time course was consistent with the decrease in cardiac output, as suggested by the decrease in heart rate and the weak contraction of the ventricles. A decrease in cardiac output would result in an accumulation of blood on the venous side, and thus an increase in venous pressure.

There are several possible reasons for the sustained increase in $p\text{CO}_2$ and the respiratory acidosis observed after injection of cement. Fat emboli accumulating in the lungs would reduce perfusion of blood to the exchange surface, resulting in increased physiologic dead space and an accumulation of CO_2 . All the sheep were me-

chanically ventilated at a rate that maintained arterial $p\text{CO}_2$ at normal values during baseline measurements. The tidal volume was determined by end-tidal airway pressure. The ventilation settings were not changed after the cement injection. An increase in $p\text{CO}_2$ also can occur if there is bronchoconstriction or pulmonary edema. Both would reduce the compliance of the lungs, thus decreasing the tidal volume achieved for a given airway pressure and resulting in hypoventilation and accumulation of CO_2 . The drop in $p\text{O}_2$ at 1 minute was not statistically significant, and thus there can be no certainty about any real change. Subsequent values also were unchanged. A reduction in $p\text{O}_2$ would not be completely unexpected. It could be caused by ventilation-to-perfusion inequality.

Currently, fat embolism during percutaneous vertebroplasty is considered only as a potential complication.³ The current authors are unaware of any reports of fat embolism in clinical studies. However, the current study, unlike published clinical studies, had continuous monitoring of the pulmonary artery together with arterial and venous pressure and heart rate. Weill et al⁴⁰ reported the death of one patient through pulmonary embolism. These authors did not attribute the death to the vertebroplasty because no cement was found on the chest radiographs. They did not consider fat embolism as a potential cause.

The current authors conclude that they have devised a reproducible animal model for fat embolism during vertebroplasty. An initial reflexive decrease in heart rate and arterial blood pressure is followed by the appearance of fat and bone marrow emboli passing through the right side of the heart, which is accompanied by a more sustained fall in arterial blood pressure. This indicates that fat embolism may occur during vertebroplasty in human patients. Although patients may cope well with vertebroplasty of just one vertebral body, serious complications may occur during the augmentation of several vertebral bodies.

■ Key Points

- Echocardiography has shown echogenic showers during experimental vertebroplasty, and lung histology has shown intravascular fat emboli.
- The first fall in arterial pressure after cement injection may be caused by a nerve reflex response.
- The second fall in arterial pressure occurred after the appearance of echogenic particles on the echocardiogram.
- Fat embolism and acute hypotension have to be considered as complications, especially during the augmentation of several vertebral bodies.

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