Influence of bone marrow fat embolism on coagulation activation in an ovine model of vertebroplasty

Krebs, J; Ferguson, S J; Hoerstrup, S P; Goss, B G; Haeberli, A; Aebli, N
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Abstract

BACKGROUND: Intraoperative cardiovascular deterioration as a result of pulmonary embolization of bone marrow fat is a potentially serious complication during vertebroplasty. The release of fatty material and thromboplastin from the bone marrow cavity during vertebroplasty may activate the coagulation cascade resulting in thrombogenesis, and pharmacological prophylaxis may therefore prevent cardiovascular complications. Thus, the effects of bone marrow fat embolism on coagulation activation during vertebroplasty were investigated with use of an animal model. METHODS: Polymethylmethacrylate was injected into three lumbar vertebrae of six sheep in order to force bone marrow fat into the circulation. Invasive blood pressures and heart rate were recorded continuously until sixty minutes after the last injection. Cardiac output, arterial and mixed venous blood gas parameters, and coagulation parameters were measured at selected time-points. Postmortem lung biopsy specimens were assessed for the presence of intravascular fat. RESULTS: Embolization of bone marrow fat resulted in a sudden and dramatic increase in mean pulmonary arterial pressure and a decrease in mean arterial blood pressure. There were no significant changes in any coagulation parameter from before the injection to after the injection. Intravascular fat and bone marrow cells were present in all lung lobes. CONCLUSIONS: Injection of polymethylmethacrylate into vertebral bodies caused embolization of bone marrow fat with subsequent transient cardiovascular deterioration, but no changes in coagulation parameters were observed. Thromboembolism did not contribute to the observed cardiovascular changes.
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Influence of Bone Marrow Fat Embolism on Coagulation Activation in an Ovine Model of Vertebroplasty

By Jörg Krebs, DVM, PhD, Stephen J. Ferguson, PhD, PD, Simon P. Hoerstrup, MD, Ben G. Goss, PhD, André Haeberli, PhD, and Nikolaus Aebli, MD, PhD

Investigation performed at the MEM Research Center, Institute for Surgical Technology and Biomechanics, Medical Faculty, University of Bern, Bern, Switzerland

Background: Intraoperative cardiovascular deterioration as a result of pulmonary embolization of bone marrow fat is a potentially serious complication during vertebroplasty. The release of fatty material and thromboplastin from the bone marrow cavity during vertebroplasty may activate the coagulation cascade resulting in thrombogenesis, and pharmacological prophylaxis may therefore prevent cardiovascular complications. Thus, the effects of bone marrow fat embolism on coagulation activation during vertebroplasty were investigated with use of an animal model.

Methods: Polymethylmethacrylate was injected into three lumbar vertebrae of six sheep in order to force bone marrow fat into the circulation. Invasive blood pressures and heart rate were recorded continuously until sixty minutes after the last injection. Cardiac output, arterial and mixed venous blood gas parameters, and coagulation parameters were measured at selected time-points. Postmortem lung biopsy specimens were assessed for the presence of intravascular fat.

Results: Embolization of bone marrow fat resulted in a sudden and dramatic increase in mean pulmonary arterial pressure and a decrease in mean arterial blood pressure. There were no significant changes in any coagulation parameter from before the injection to after the injection. Intravascular fat and bone marrow cells were present in all lung lobes.

Conclusions: Injection of polymethylmethacrylate into vertebral bodies caused embolization of bone marrow fat with subsequent transient cardiovascular deterioration, but no changes in coagulation parameters were observed. Thromboembolism did not contribute to the observed cardiovascular changes.

Clinical Relevance: Cardiovascular complications as a result of bone marrow fat embolism should be considered in patients undergoing vertebroplasty. Vertebroplasty with use of polymethylmethacrylate does not appear to activate the coagulation system or cause thromboembolism.

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I ntraoperative cardiovascular deterioration is a potentially serious complication during vertebroplasty. Pulmonary cement embolism is a reason for cardiovascular complications during vertebroplasty1-3. But cardiovascular changes, such as arterial hypotension, oxygen desaturation, and arrhythmia, have also been observed in the absence of cement embolism and have been attributed to bone marrow fat embolization4-6. Cardiovascular changes resulting from fat embolism are often transient, but may be fulminant, resulting in cardiac arrest and even death7-9. Aebli et al.10 demonstrated the embolization of bone marrow fat during vertebroplasty in an animal model, using transesophageal echocardiography and histopathology of the lungs. Associated cardiovascular deterioration was characterized by transient but severe pulmonary hypertension, arterial hypotension, decreased cardiac output, and respiratory acidosis in this animal model11.

Fat embolism is a well-known complication during total hip and knee arthroplasty12-15, intramedullary reaming16,17, and
instrumented spine surgery\textsuperscript{18,19}. Reducing the severity of fat embolism by 50% did not result in clinically relevant alleviation of cardiovascular deterioration during vertebroplasty in an animal model\textsuperscript{20}. Activation of the coagulation cascade may have resulted in an additional embolic burden rendering the reduction of fat emboli ineffective. It has been suggested that the release of fat emboli and thromboplastin from the bone marrow cavity during hip arthroplasty may result in thrombogenesis\textsuperscript{21-23}. Furthermore, polymethylmethacrylate may have inherent thrombogenic properties\textsuperscript{24,25}. Activation of the coagulation cascade may therefore play a role in the development of cardiovascular changes during vertebroplasty. Pharmacological prophylaxis of thrombogenesis in patients undergoing vertebroplasty may therefore be useful for preventing cardiovascular complications. Thus, the effects of bone marrow fat embolism and the injection of polymethylmethacrylate into vertebral bodies on coagulation activation were investigated with use of an animal model.

Materials and Methods

Animal Model

Investigations were carried out in six skeletally mature mixed-bred ewes (five to six years old with a mean body weight [and standard deviation] of 70 ± 10 kg), which were subjected to unilateral augmentation of three lumbar vertebral bodies (L2-L4) with polymethylmethacrylate. The study was approved by the State Animal Ethics Committee and was conducted according to federal and state guidelines.

Instrumentation of Animals

Anesthesia was induced with propofol (6 mg/kg) and was maintained with isoflurane (2% to 3%) in oxygen (50%). Analgesia and muscle relaxation were achieved by the administration of buprenorphine (0.005 mg/kg) and pancuronium (0.06 mg/kg), respectively. The lungs were ventilated mechanically to maintain physiologic end-tidal carbon dioxide tension prior to cement injection. End-tidal carbon dioxide tension was measured with an infrared capnometer. Ventilation parameters were not adjusted after cement injection. Lactated Ringer solution was infused through the left cephalic vein at 4 mL/kg/h. Electrocardiographic monitoring was obtained with skin electrodes.

For cardiovascular instrumentation, animals were placed in the supine recumbent position. An angiography catheter was inserted into the left carotid artery and was advanced into the left ventricle to measure blood pressure. The right carotid artery was cannulated to measure arterial blood pressure and to obtain blood samples. A Swan-Ganz thermodilution pulmonary artery catheter was inserted into the right jugular vein and was floated into the pulmonary artery to measure central venous pressure, pulmonary arterial pressure, and cardiac output and to obtain mixed venous blood samples. The correct position of the ventricular and pulmonary catheters was confirmed by recording typical pressure waves. Catheters were connected to pressure transducers (Uniflow; Baxter, Volketswil, Switzerland) by means of pressure tubing filled with liquid (Ringer lactate solution). Catheters were flushed with heparinized Ringer lactate solution (5000 IU/L) after insertion and after taking blood samples. Injected volumes were approximately 15 mL/h and deemed not to affect hemostasis\textsuperscript{26}. Heart rate was derived from the electrocardiogram. Cardiovascular pressures and the electrocardiographic recordings were digitized at 1 Hz with use of an analog-digital converter (Hellige Messturm; Marquette Hellige Medizintechnik, Freiburg, Germany) and stored on a computer for offline analysis.

Surgical Procedure and Cement Injections

Animals were placed in the right lateral recumbent position on the operating table. A retroperitoneal approach was used to expose the lateral aspect of three lumbar vertebral bodies (L2-L4). A cement injection hole (3.5 mm in diameter) was drilled into the cephalad aspect of each vertebral body to a depth of 10.0 mm. The proximal part of the injection hole was carefully widened to a diameter of approximately 4.0 mm, so that the tip of a 3-mL syringe would fit tightly into it.

Polymethylmethacrylate bone cement formulated for vertebroplasty (low viscosity, 30% barium) (Medecor, Cham, Switzerland) was used for injection. Powder and chilled liquid (5°C) were mixed in an open bowl for thirty seconds and then drawn into 3-mL polycarbonate syringes (Medecor, Cham, Switzerland). The cement was left to polymerize at room temperature (21°C to 23°C; 27% to 34% humidity) until an appropriate viscosity for injection was reached. A volume of 6.0 mL of cement was injected over thirty seconds until filling of the vertebral body was achieved.

Experimental Protocol

Pressure transducers were zeroed at the level of the heart. Blood pressures and electrocardiographic activity were continuously recorded until sixty minutes after beginning the last (i.e., third) cement injection. Cardiac output and blood gas parameters were measured before and at least twenty minutes after completion of the surgical approach. Cardiac output was measured three times and averaged. Arterial and mixed venous blood samples were drawn for blood gas analysis, which was carried out immediately. Cement was injected into three lumbar vertebrae (L2-L4) after a twenty-minute time-interval between injections. The duration of the time-intervals was sufficient for stabilization of cardiovascular parameters to a new steady state\textsuperscript{10,11}. Postinjection evaluation of cardiac output and blood gas parameters was carried out one minute and ten minutes after having started the first injection; ten minutes after having started the second injection; and ten minutes, thirty minutes, and sixty minutes after having started the third injection. At the end of the protocol, the animals were killed by intravenous injection of pentobarbital (1 g/sheep) and potassium chloride (2 mmol/kg).

Analysis of Cardiovascular Data

In order to obtain preinjection values of continuously recorded parameters (i.e., blood pressures and heart rate), data were averaged over five minutes. For postinjection values, data were
ate after sampling, and the plasma was stored at –70°C. Blood samples were centrifuged immediately after having started the second injection; and ten minutes after having started the first injection; ten minutes after starting the third injection. Blood samples were centrifuged immediately after sampling, and the plasma was stored at –70°C for averaged over twenty seconds. Cardiac index, pulmonary vascular resistance index, systemic vascular resistance index, physiologic dead space, and intrapulmonary shunt were calculated with use of standard formulas.

**Measurements of Coagulation Parameters**

Citrated blood samples were taken prior to induction of anesthesia (jugular vein) and prior to the first cement injection (i.e., after instrumentation and surgical approach) (carotid artery). Further samples (carotid artery) were taken one minute and ten minutes after having started the first injection; ten minutes after having started the second injection; and ten minutes, thirty minutes, and sixty minutes after having started the third injection. Blood samples were centrifuged immediately after sampling, and the plasma was stored at –70°C for batch analysis. The following parameters were measured: thrombocyte count, prothrombin time, partial thromboplastin time, fibrinogen, D-dimer, and thrombin-antithrombin complexes. Analyses were performed in two certified laboratories with use of standard protocols. A given parameter was always measured in the same laboratory.

**Histopathology**

After the animals were killed, two lung tissue samples were taken from two predetermined areas of each of the five lung lobes (right cranial, middle, and caudal lobes and left cranial and caudal lobes) and were fixed in 10% neutral buffered formalin. Specimens were stained with hematoxylin and eosin and oil red O (fat stain). Two microscopic views (at five times magnification) were analyzed from each sample for the

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**TABLE I Cardiovascular Parameters Measured Continuously**

<table>
<thead>
<tr>
<th></th>
<th>Before Injection (N = 17)</th>
<th>1 Min After Injection (N = 17)</th>
<th>3 Min After Injection (N = 17)</th>
<th>5 Min After Injection (N = 17)</th>
<th>10 Min After Injection (N = 17)</th>
<th>15 Min After Injection (N = 17)</th>
<th>30 Min After Injection (N = 6)</th>
<th>60 Min After Injection (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>86 ± 10</td>
<td>68 ± 24†</td>
<td>93 ± 18</td>
<td>95 ± 14</td>
<td>88 ± 11</td>
<td>82 ± 12</td>
<td>78 ± 15</td>
<td>81 ± 10</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>19 ± 3</td>
<td>36 ± 6†</td>
<td>29 ± 4†</td>
<td>26 ± 3†</td>
<td>22 ± 2</td>
<td>20 ± 3</td>
<td>21 ± 2</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Mean central venous pressure (mm Hg)</td>
<td>8 ± 3</td>
<td>11 ± 4†</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
<td>9 ± 2</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>89 ± 12</td>
<td>93 ± 17</td>
<td>91 ± 13</td>
<td>88 ± 13</td>
<td>88 ± 12</td>
<td>88 ± 12</td>
<td>89 ± 20</td>
<td>79 ± 8</td>
</tr>
</tbody>
</table>

*The values are given as the mean and the standard deviation. †Significantly different from preinjection value (p < 0.004). ‡Significantly different from preinjection value (p < 0.0000).

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**TABLE II Cardiovascular Parameters Measured Periodically**

<table>
<thead>
<tr>
<th></th>
<th>Before Injection (N = 6)</th>
<th>1 Min After First Cement Injection (N = 6)</th>
<th>10 Min After First Cement Injection (N = 6)</th>
<th>10 Min After Second Cement Injection (N = 5)</th>
<th>10 Min After Third Cement Injection (N = 6)</th>
<th>30 Min After Third Cement Injection (N = 6)</th>
<th>60 Min After Third Cement Injection (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>4.9 ± 0.8</td>
<td>4.6 ± 1.1</td>
<td>5.0 ± 0.7</td>
<td>4.6 ± 1.6</td>
<td>4.5 ± 1.7</td>
<td>4.4 ± 1.6</td>
<td>4.4 ± 1.3</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (dyne*s/cm⁵/m²)</td>
<td>246 ± 99</td>
<td>644 ± 203†</td>
<td>283 ± 84</td>
<td>354 ± 97</td>
<td>348 ± 152</td>
<td>340 ± 141</td>
<td>317 ± 122</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dyne*s/cm⁵/m²)</td>
<td>1208 ± 184</td>
<td>1124 ± 408</td>
<td>1198 ± 130</td>
<td>1412 ± 330</td>
<td>1405 ± 360</td>
<td>1237 ± 303</td>
<td>1327 ± 322</td>
</tr>
<tr>
<td>pH†</td>
<td>7.48 ± 0.03</td>
<td>7.46 ± 0.03</td>
<td>7.47 ± 0.03</td>
<td>7.47 ± 0.02</td>
<td>7.46 ± 0.02</td>
<td>7.47 ± 0.02</td>
<td>7.47 ± 0.02</td>
</tr>
<tr>
<td>Arterial carbon dioxide tension (kPa)</td>
<td>5.2 ± 0.4</td>
<td>5.6 ± 0.3</td>
<td>5.3 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>5.4 ± 0.5</td>
<td>5.3 ± 0.2</td>
<td>5.4 ± 0.5</td>
</tr>
<tr>
<td>Arterial oxygen tension (kPa)</td>
<td>36 ± 14</td>
<td>36 ± 13</td>
<td>36 ± 13</td>
<td>35 ± 15</td>
<td>36 ± 16</td>
<td>35 ± 16</td>
<td>37 ± 18</td>
</tr>
<tr>
<td>Dead space (Vd/Vt)†</td>
<td>0.12 ± 0.07</td>
<td>0.20 ± 0.04†</td>
<td>0.12 ± 0.07†</td>
<td>0.13 ± 0.09†</td>
<td>0.16 ± 0.08†</td>
<td>0.16 ± 0.05†</td>
<td>0.16 ± 0.06†</td>
</tr>
<tr>
<td>Intrapulmonary shunt (Qs/Qt)§</td>
<td>0.015 ± 0.006</td>
<td>0.015 ± 0.003†</td>
<td>0.015 ± 0.003§</td>
<td>0.017 ± 0.004§</td>
<td>0.016 ± 0.004§</td>
<td>0.018 ± 0.005§</td>
<td>0.015 ± 0.005§</td>
</tr>
</tbody>
</table>

*The values are given as the mean and the standard deviation. †Compared with the value before the first injection value, the difference was significant (p < 0.02). ‡Ratio of physiologic dead space to tidal volume. §Qs = shunt flow, and Qt = cardiac output.
presence of intravascular fat and bone marrow cells. Semi-quantitative analysis of intravascular fat was performed by counting the number of emboli in each photomicrograph. Counts were averaged and presented as a histopathologic score.

**Statistical Analysis**

According to data from previous studies\(^{10,20}\), the chosen sample size was sufficient to detect clinically relevant changes of blood pressure and blood gas variables from preinjection and post-injection values with the power ranging from 88% to 97%. Data were calculated and given as the mean and the standard deviation of the mean. One-way analysis of variance for repeated measures was used to test for significant differences. Post hoc analyses were performed with use of the Bonferroni test. The paired Student t test was used to test for differences in histopathologic scores between the different lung lobes. A p value of $\leq 0.05$ was considered significant for all statistical

![Fig. 1](image)

Mean pulmonary arterial pressure and mean arterial blood pressure after polymethylmethacrylate injection (pooled data). An asterisk indicates a significant difference from preinjection value ($p < 0.02$).

### TABLE III Coagulation Parameters Before and After Embolization*

<table>
<thead>
<tr>
<th></th>
<th>Before Induction of Anesthesia</th>
<th>Before First Cement Injection</th>
<th>1 Min After First Injection</th>
<th>10 Min After First Injection</th>
<th>10 Min After Second Injection</th>
<th>10 Min After Third Injection</th>
<th>10 Min After Third Injection</th>
<th>30 Min After Third Injection</th>
<th>60 Min After Third Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytes (10(^3)/(\mu)L)</td>
<td>315 ± 126 (6)</td>
<td>197 ± 54† (6)</td>
<td>223 ± 44† (6)</td>
<td>215 ± 48† (6)</td>
<td>204 ± 49† (6)</td>
<td>202 ± 42† (6)</td>
<td>198 ± 44† (6)</td>
<td>206 ± 46† (6)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>80 ± 5 (5)</td>
<td>74 ± 9 (6)</td>
<td>73 ± 8 (6)</td>
<td>74 ± 8 (6)</td>
<td>72 ± 10 (6)</td>
<td>73 ± 10 (6)</td>
<td>69 ± 9 (5)</td>
<td>68 ± 7 (5)</td>
<td></td>
</tr>
<tr>
<td>Partial thromboplastin time (sec)</td>
<td>31 ± 3 (5)</td>
<td>31 ± 4 (6)</td>
<td>30 ± 4 (6)</td>
<td>31 ± 3 (6)</td>
<td>29 ± 4 (5)</td>
<td>30 ± 5 (6)</td>
<td>32 ± 4 (5)</td>
<td>31 ± 4 (5)</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.1 ± 0.5 (5)</td>
<td>1.6 ± 0.4 (6)</td>
<td>1.6 ± 0.4 (6)</td>
<td>1.5 ± 0.4 (6)</td>
<td>1.6 ± 0.4 (5)</td>
<td>1.6 ± 0.3 (5)</td>
<td>1.5 ± 0.3 (4)</td>
<td>1.5 ± 0.3 (4)</td>
<td></td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>1.2 ± 1.3 (5)</td>
<td>0.9 ± 0.9 (6)</td>
<td>0.9 ± 0.9 (6)</td>
<td>0.9 ± 0.9 (6)</td>
<td>0.9 ± 0.9 (6)</td>
<td>1.0 ± 1.0 (5)</td>
<td>1.0 ± 1.0 (5)</td>
<td>1.0 ± 1.0 (5)</td>
<td></td>
</tr>
<tr>
<td>Thrombin-antithrombin complexes ((\mu)g/L)</td>
<td>1.16 ± 0.21 (5)</td>
<td>3.01 ± 0.75† (6)</td>
<td>4.26 ± 1.29† (6)</td>
<td>3.37 ± 0.82† (5)</td>
<td>4.03 ± 0.63† (4)</td>
<td>4.02 ± 0.75† (4)</td>
<td>4.28 ± 1.46† (4)</td>
<td>4.50 ± 1.28† (5)</td>
<td></td>
</tr>
</tbody>
</table>

*The values are given as the mean and the standard deviation, with the number of samples in parentheses. †Compared with value before induction of anesthesia, the difference is significant ($p < 0.003$). ‡Compared with value before induction of anesthesia, the difference is significant ($p < 0.05$).
analyses. Statistical analyses were performed with use of Statistica 7 software (StatSoft, Hamburg, Germany).

**Results**

**Cement Injections**

On the average, 4.7 ± 0.7 mL of polymethylmethacrylate was injected into each vertebral body over an average of 31 ± 11 sec. One injection was judged inadequate because insufficient cement volume had been injected (i.e., <3 mL). In that case, the cement viscosity had been too high to inject more volume. Cardiovascular data from this injection were excluded from analysis. At the postmortem examination, cement leakage into epidural and paravertebral veins was discovered in two animals.

**Cardiovascular Parameters**

There were no significant (p = 0.71) differences among the cardiovascular changes after the three cement injections and among the three preinjection values (p = 0.98). Injections of polymethylmethacrylate elicited a consistent cardiovascular response after each injection. Thus, the data of the continuously recorded parameters (i.e., invasive pressures and heart rate) from the three embolization events were pooled, and statistical analysis was performed.

Injection of polymethylmethacrylate elicited a significant (p < 0.0001) increase in the mean pulmonary vascular resistance index (150% ± 53%) and the mean pulmonary arterial pressure (108% ± 32%) (Tables I and II). Consequently, there was a significant (p < 0.004) decrease in the mean arterial blood pressure (36% ± 16%) and a significant (p < 0.004) increase in the mean central venous blood pressure (54% ± 29%). Values of mean arterial blood pressure and central venous blood pressure were no longer significantly (p > 0.9) different from preinjection values two minutes after inducing fat embolization. The mean pulmonary arterial pressure remained elevated until nine minutes after embolization (Fig. 1).

**Coagulation Parameters**

There was a significant (p < 0.05) decrease in thrombocyte count and a significant increase in the concentration of thrombin-antithrombin complexes from the preanesthetic to preinjection values (Table III). The mean plasma concentrations of thrombin-antithrombin complexes increased from the value before the injection (3.01 ± 0.75 μg/L) to one minute after the injection (4.26 ± 1.29 μg/L), and the mean prothrombin time decreased from the value before the injection (74% ± 9%) to sixty minutes after the injection (68% ± 7%). However, these changes were not significant (p > 0.3). There were no other changes in coagulation parameters from preinjection to postinjection values.

**Histopathology**

Intravascular fat and bone marrow cells were present in all lung lobes (Fig. 2). The mean histopathologic score for all five lobes (thirty specimens) was 4.9 ± 3.7. There were no significant (p = 0.16) differences in the histopathologic scores among the different lung lobes. Traces of intravascular bone cement (i.e.,
barium particles) were detected in two lung lobes. Cardiovascular responses recorded in these animals were not significantly (p = 0.9) different from responses in animals without pulmonary cement embolism.

Discussion

The cardiovascular response to bone marrow fat embolism after intravertebral injection of polymethylmethacrylate was characterized by a sudden (one minute postinjection) and dramatic (>100%) increase in mean pulmonary arterial pressure and a decrease in mean arterial blood pressure (36%). There were no significant changes in any coagulation parameter from preinjection to postinjection values.

In the present study, fat embolization during vertebroplasty in sheep with use of polymethylmethacrylate did not affect any of the measured coagulation parameters. In contrast, Barie and Malik\textsuperscript{27} observed a decrease in fibrinogen and an increase in fibrin degradation products after an intravenous injection of allogenic bone marrow suspension in sheep. Defibrinogenation completely prevented any cardiovascular changes. Fibrinogen depletion prevented thrombogenesis and therefore the blockage of the pulmonary vasculature. The process of harvesting bone marrow may have activated the coagulation cascade in their study. However, the present model mimics the clinical situation more closely.

Thrombogenesis has also been observed after arthroplasty and long-bone intramedullary reaming. These interventions cause more vascular and tissue damage compared with the injection of polymethylmethacrylate into vertebral bodies. An increase in thrombin-antithrombin complex concentration and changes in antithrombin and fibrinogen values were observed after reaming of the femoral medullary cavity for hip arthroplasty\textsuperscript{24} and intramedullary nailing\textsuperscript{28}, respectively. Modig et al.\textsuperscript{25} investigated the role of coagulation, fat embolism, and methylmethacrylate in the development of arterial hypotension and hypoxemia during total hip arthroplasty with cement. Activation of the coagulation cascade was observed immediately after the insertion of the femoral component. The recorded cardiovascular changes were correlated with the degree of coagulation activation, but not with the severity of fat embolization or the plasma concentrations of methylmethacrylate. More recently, coagulation activation during total hip arthroplasty with and without cement was demonstrated by an increase in thrombin-antithrombin complex and D-dimer values\textsuperscript{31}.

It has been suggested that coagulation may be activated by cell fragments released from the bone marrow cavity\textsuperscript{22,29} or thromboplastin (protease, which converts prothrombin to thrombin)\textsuperscript{22,29}. Thromboplastin may be released from adipose bone marrow tissue\textsuperscript{22} or as a result of subendothelial tissue damage in the bone marrow cavity\textsuperscript{28} or in the lungs\textsuperscript{27}. Furthermore, polymethylmethacrylate may have inherent thrombogenic properties\textsuperscript{24,25}. Serious concerns have been raised with regard to the use of calcium phosphate cement for vertebroplasty as it may aggravate cardiovascular complications by stimulating coagulation\textsuperscript{30}. Calcium phosphate cement may provide a scaffold for clot formation or may initiate the coagulation cascade by surface contact activation and providing calcium ions, an important cofactor for coagulation. However, more recent studies have found no coagulation activation after both polymethylmethacrylate and calcium phosphate cement came in contact with circulating blood in vitro\textsuperscript{32} and in vivo\textsuperscript{32,33}.

Quantification of thrombin-antithrombin complexes allows one to detect subtle degrees of coagulation activation. The key event of coagulation activation is the conversion of prothrombin to thrombin. However, only a small amount of circulating prothrombin (<1%) is activated to thrombin, and thrombin is rapidly neutralized by antithrombin, resulting in an increase in circulating thrombin-antithrombin complexes. In the present study, there was a significant increase in the concentration of thrombin-antithrombin complexes and a significant decrease in the thrombocyte count from the preanesthetic to preinjection values. This may have been the result of the instrumentation and the surgical approach to the lumbar spine. There was no significant change in thrombin-antithrombin complex or any other coagulation parameter from preinjection to postinjection values. Recording was terminated sixty minutes after the last embolization event, and coagulopathy may occur later on as a result of lung injury or blood flow disturbances\textsuperscript{34}. However, the focus of the present study was on the intraoperative cardiovascular changes after bone marrow fat embolism.

Activation of the coagulation cascade generating additional emboli did not contribute to the acute cardiovascular changes after fat embolism elicited by injections of polymethylmethacrylate into vertebral bodies. However, blockage of >50% of the pulmonary arterial vasculature would be required to elicit cardiovascular changes of the magnitude recorded in the present study\textsuperscript{35,36}. Blockage of this magnitude is improbable according to the histopathologic results and data reported in the literature\textsuperscript{10,29,37}, and thus mechanical blockage would not seem to be responsible for the recorded cardiovascular changes in the present study. The increase in pulmonary arterial pressure may have been caused by pulmonary vasoconstriction elicited by vasoactive mediators released from the bone marrow cavity or as a result of lung injury after embolization\textsuperscript{38,39}. Alternatively, a reflex response to embolization may have elicited pulmonary vasoconstriction\textsuperscript{40,41}. Methylmethacrylate has also been reported to cause pulmonary vasoconstriction\textsuperscript{42,43}. However, concentrations of methylmethacrylate required to elicit cardiovascular changes are more than twice as high as concentrations measured clinically\textsuperscript{44,45}.

It has been suggested that kyphoplasty may carry a lower risk of fat embolism compared with vertebroplasty. Kyphoplasty is only performed in vertebral bodies with acute (i.e., mobile) fractures, and fracture lines may offer a way of pressure release and escape for the fat emboli during inflation of the balloon. Potentially beneficial effects are therefore a result of the different indications (only acute compared with acute and old fractures) and are not inherent to the type of intervention (i.e., kyphoplasty compared with vertebroplasty). Vertebroplasty of unconsolidated or highly compressed ver-
tebral bodies also carries a low risk of fat embolism. On the other hand, augmentation of intact osteoporotic vertebral bodies at risk of fracture may carry a high risk of fat embolism.

Limitations of the present animal model have been discussed previously. Briefly, vertebral filling was higher compared with the clinical situation. However, it was crucial to inject similar volumes of cement compared with the clinical situation, displacing similar volumes of bone marrow fat. The aim of the present study was to investigate the pathophysiology of cardiovascular changes after bone marrow fat embolism, rather than replicating clinical vertebroplasty. Flushing catheters with heparinized Ringer solution may have affected measured coagulation parameters. The prothrombin time decreased by 8% from before anesthesia to before injection and again by 7% and 8% from before injection to thirty and sixty minutes after injection, respectively. There was a 15% decrease from before anesthesia to sixty minutes after injection. However, these changes were not significant, and, moreover, there were no changes in partial thromboplastin time. Therefore, injected volumes of heparin appeared to be insufficient to affect measured coagulation parameters.

In conclusion, injection of polymethylmethacrylate into vertebral bodies elicited embolization of bone marrow fat with subsequent transient cardiovascular deterioration. Thromboembolism did not contribute to the observed cardiovascular changes. Cardiovascular complications as a result of bone marrow fat embolism should be considered in patients undergoing vertebroplasty.

References


