The role of methylmethacrylate monomer in the formation and haemodynamic outcome of pulmonary fat emboli


From St Michael’s Hospital and the University of Toronto, Canada

We examined the roles of methylmethacrylate (MMA) monomer and cementing technique in the formation, and haemodynamic outcome, of pulmonary fat emboli. The preparation of the femoral canal and the cementing technique were studied in four groups of adult dogs as follows: control (no preparation); lavage; cement pressurisation; and cement pressurisation after lavage. We measured the intramedullary pressure, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure and bilateral femoral vein levels of triglyceride, cholesterol and MMA monomer at rest and after reaming, lavage, and cementing.

Femoral vein triglyceride and cholesterol levels did not vary significantly from resting levels despite significant elevations in intramedullary pressure with reaming, lavage and cementing (p = 0.001). PAP was seen to rise significantly with reaming (p = 0.0038), lavage (p = 0.0031), cementing (p = 0.0024) and cementing after lavage (p = 0.0028) while the pulmonary capillary wedge pressure remained unchanged.

MMA monomer was detected in femoral vein samples when cement pressurisation was used. Intramedullary lavage before cementing had no significant effect on the MMA level. Haemodynamic evidence of pulmonary embolism was noted with reaming and intramedullary canal preparation, irrespective of the presence of MMA monomer. We found no relationship between MMA monomer level and intramedullary pressure, PAP or pulmonary capillary wedge pressure.

Our findings suggest that the presence of MMA monomer in femoral venous blood has no effect on the formation of fat emboli or their pulmonary haemodynamic outcome during cemented hip arthroplasty.

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Patient demand and good clinical results have resulted in a large increase in the number of total hip arthroplasties (THAs) performed.\textsuperscript{1-5} The technique for THA necessitates reaming of the proximal femoral intramedullary canal to give optimal fit and stability.\textsuperscript{2,3,6} The use of polymethylmethacrylate cement provides increased prosthetic fixation because PMMA conforms to the macroscopic irregularities of the femoral canal.\textsuperscript{3,4} Preparation of the canal by intramedullary lavage has been reported to give deeper penetration of cement thereby enhancing the shear strength of the cement-bone interface.\textsuperscript{5}

Acute hypotension is common during cement introduction and the insertion of prostheses with long intramedullary stems, and has been associated with elevated pulmonary artery pressure (PAP).\textsuperscript{7-9} Pulmonary fat embolism has been implicated in the pathophysiology of these circulatory disturbances,\textsuperscript{9-13} but the role of methylmethacrylate (MMA) monomer in the aetiology of fat emboli is still controversial. One theory is that marrow fat enters the venous system as a result of the high intramedullary pressures generated by reaming, cementing and insertion of the prosthesis.\textsuperscript{9,11,13} By contrast, Lehman and Moore have suggested that agglutinated plasma chylomicrons are a possible source of fat emboli and have proposed the existence of a substance which reduces the stability of the plasma fat emulsion.\textsuperscript{14-17} Some have speculated that the release of MMA monomer into the bloodstream during cemented THA facilitates agglutination and subsequent embolisation of fat.\textsuperscript{7,16}

Our aim was to investigate the effect of reaming, lavage
and cement pressurisation on triglyceride and cholesterol levels in the femoral vein and to determine the role of MMA monomer in the formation and haemodynamic outcome of pulmonary fat emboli.

Materials and Methods

We used 20 skeletally mature cross-bred dogs (12 female, 8 male) with a mean weight of 29.4 kg (22 to 33). All procedures were approved by the local animal care committee and were performed in an operating room using aseptic techniques. After premedication and preparation of the left leg, anaesthesia was induced by sodium pentothal 25 mg/kg and maintained after endotracheal intubation with a ventilation mixture of 33% NO2, 1.5% halothane and 65.5% O2. Oxyromphine (DuPont Pharma, Dorval, Canada) 1.5 mg was used at induction as a narcotic analgesic and repeated at three hours during the procedure.

Before surgery we introduced a 3 mm silastic left femoral vein catheter and an 8 Fr left external jugular catheter. A 7.5 Fr Swan Ganz catheter was passed through the heart into the pulmonary artery (PA) and its position confirmed by image intensification. A craniolateral approach to the femur and trochanteric fossa using minimal soft-tissue dissection gave access to the proximal 10 cm of the bone. A pressure transducer was inserted into the intramedullary canal 9 cm distal to the tip of the greater trochanter.

We made baseline measurements of the pulmonary artery pressure, intramedullary canal pressure, and levels of triglycerides, cholesterol and MMA monomer levels in the femoral vein. In all dogs we then performed antegrade reaming of the femoral intramedullary canal using Precision (Howmedica, Rutherford, New Jersey) cannulated flexible reamers sequentially from 6.0 to 9.0 mm. After reaming, the same outcome parameters were reassessed.

A 9.0 mm De Puy (Warsaw, Indiana) cement restrictor was inserted distal to the position of the intramedullary pressure transducer. The animals were then randomly assigned to one of four groups of five: group 1, control (reaming only); group 2, reaming and lavage with normal saline; group 3, reaming followed by cement pressurisation; and group 4, reaming, lavage and cement pressurisation. We performed lavage of the intramedullary canal by hand using sterile saline solution in two full 50 ml syringes. While still semiliquid, Simplex P (Howmedica, Rutherford, New Jersey) MMA cement was introduced into the medullary canal using a 20 ml syringe, ensuring that there was a press fit into the reamed hole. Pressurisation of the cement was accomplished by inserting a 5 × 150 mm Steinmann pin (Synthes, Mississauga, Canada) into the intramedullary canal approximately two minutes after mixing. Immediately after each intervention, all parameters were recorded. Before reaming and at each intervention three serial samples were taken from the ipsilateral femoral vein.

After centrifugation the serum was removed and the levels of triglyceride, cholesterol and MMA monomer were analysed. Serum triglycerides were measured by an enzymatic assay using an Ektachem clinical chemistry slide (Kodak, Rochester, New York) by a method similar to that described by Spayd et al.18 A 10 μl sample was deposited on the slide and the level of triglycerides determined by colorimetric reaction. The density of the dye formed is proportional to the triglyceride concentration present in the sample and is measured by reflectance spectrophotometry.

The serum cholesterol was also determined by an enzymatic assay using an Ektachem chemistry slide (Kodak, Rochester, New York) by a method similar to that described by Allain et al.19 A 10 μl sample was deposited on the slide and the level of cholesterol determined by colorimetric reaction. The density of the dye formed is proportional to the cholesterol concentration present in the sample and is measured by reflectance spectrophotometry.

Part of each collected serum sample (2 ml) was immediately placed in heparinised glass vials with 0.6 g of sodium chloride and hydroquinone crystals as a stabiliser. The samples were frozen at −20°C and stored for later batch analysis of MMA monomer levels using liquid chromatography. The method involves standardisation by mixing 10 μl of MMA (9.36 mg) in 50 ml of acetonitrile to obtain a concentration of 18.7 mg/100 ml. Samples were prepared after thawing by pipetting 1 ml into a glass test tube and adding 1 ml of acetonitrile. After vortex, the supernatant was removed into an injection vial and capped. A Walters 712 WISP autosampler was used to inject 5 μl of the samples into a Lambda-Max Model 481 liquid chromatography spectrophotometer (Walters-Millipore, Massachusetts). Using a phosphate buffer of 5 mmol/l at pH5, acetonitrile and methanol (6:2:2) as a mobile phase, the flow rate was 1.4 ml/min. A C18 column was used as a stationary phase and the retention time was three minutes. The threshold for detection of MMA using this technique was 0.02 μg/ml.20,21

All data are reported as means and standard errors of the means. Differences within each experimental group over time were evaluated by a paired t-test. One-factor analysis of variance was performed to determine whether there were differences between three or more means. If differences existed, those between two groups were tested using an unpaired t-test. Statistical analysis of the data obtained was performed using Instat2 (GraphPad, London, Canada).

Results

All the animals tolerated the procedure well and there were no complications which required killing or exclusion from the study.

Femoral vein lipids. The mean resting level for triglycerides was 0.37 ± 0.02 mmol/l. The mean resting level for cholesterol was 3.55 ± 0.10 mmol/l. Neither changed significantly after reaming alone, lavage after reaming, cement pressurisation alone or cementing after lavage (Table I, Figs 1 and 2). When the levels for cementing after lavage...
were compared with those with cementing alone, there was no statistical difference in either the triglyceride or the cholesterol level.

**Intramedullary pressures.** The mean resting intramedullary pressure of the canine femoral canal was $6.0 \pm 1.0$ mmHg. The mean peak intramedullary pressure rose sharply with each stage of canal preparation (Table I) and there was a significant increase with reaming alone ($p = 0.001$), lavage ($p = 0.001$), cement pressurisation ($p = 0.001$), and cementing after lavage ($p = 0.001$) (Fig. 3).

**Pulmonary haemodynamics.** The mean resting PAP was $12.0 \pm 1.5$ mmHg; with cementing it increased to a peak

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**Table I.** Mean (±SEM) changes in femoral vein serum lipid, intramedullary pressure, pulmonary haemodynamic indices and MMA monomer levels at each stage of preparation of the femoral canal

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Ream</th>
<th>Lavage</th>
<th>Cement</th>
<th>Lavage + Cement</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.37 ± 0.02</td>
<td>0.41 ± 0.03</td>
<td>0.36 ± 0.03</td>
<td>0.36 ± 0.04</td>
<td>0.36 ± 0.03</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>3.55 ± 0.10</td>
<td>3.69 ± 0.18</td>
<td>3.76 ± 0.34</td>
<td>3.33 ± 0.21</td>
<td>3.64 ± 0.30</td>
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<tr>
<td>Intramedullary pressure (mmHg)</td>
<td>6 ± 1</td>
<td>325 ± 40*</td>
<td>109 ± 2*</td>
<td>449 ± 51*</td>
<td>432 ± 15*</td>
</tr>
<tr>
<td>PAP† (mmHg)</td>
<td>12.0 ± 1.5</td>
<td>16.0 ± 1.3*</td>
<td>17.0 ± 1.5*</td>
<td>21.0 ± 1.8*</td>
<td>20.0 ± 1.6*</td>
</tr>
<tr>
<td>PCWP† (mmHg)</td>
<td>10.0 ± 1.2</td>
<td>11.0 ± 1.2</td>
<td>10.0 ± 1.3</td>
<td>12.0 ± 2.4</td>
<td>13.0 ± 2.3</td>
</tr>
<tr>
<td>MMA monomer (µg/ml)</td>
<td>ND†</td>
<td>ND</td>
<td>ND</td>
<td>1.61 ± 0.11</td>
<td>1.68 ± 0.21</td>
</tr>
</tbody>
</table>

* denotes statistical significance from rest value ($p < 0.05$)
† PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; ND, not detected

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**Fig. 1**
Ipsilateral femoral vein serum triglyceride levels (mmol/l) at rest and with reaming, lavage, cement pressurisation and cementing after lavage (Lav) of the femoral intramedullary canal.

**Fig. 2**
Ipsilateral femoral vein serum cholesterol levels (mmol/l) at rest and with reaming, lavage, cement pressurisation and cementing after lavage (Lav) of the femoral intramedullary canal.

**Fig. 3**
Femoral intramedullary pressures (mmHg) at rest and with reaming, lavage, cement pressurisation and cementing after lavage (Lav) of the intramedullary canal(*=statistical significance from rest value, $p < 0.05$).
mean of 21.0 ± 1.8 mmHg. There was a significant rise compared with resting levels with reaming (p = 0.0038), lavage (p = 0.0031), cement pressurisation (p = 0.0024) and cementing after lavage (p = 0.0028). There was no significant difference between the rise in the PAP after cementing compared with cementing after lavage (Fig. 4).

The mean resting pulmonary capillary wedge pressure was 10.0 ± 1.2 mmHg. It did not change significantly after reaming, lavage, cementing or cementing after lavage (Fig. 4).

**Femoral vein MMA monomer levels.** The levels of MMA monomer were not detectable at rest, after reaming or lavage. Immediately after cement introduction they were detectable with a mean of 1.61 ± 0.11 µg/ml. When lavage was performed before cementing the mean level was 1.68 ± 0.21 µg/ml. There was no significant difference between these values.

**Discussion**

In cemented THA adverse circulatory reactions may occur during the insertion of the cement and implant which may range from brief episodes of acute hypotension to bradycardia, cardiac arrest, and even intraoperative death. The pathophysiology of these reactions has not been completely elucidated, but they are associated with an elevated PAP and pulmonary fat embolism has been strongly implicated as a main cause. Echocardiography studies during THA have consistently demonstrated embolic particles which have been shown to include fat.

There are two main theories for the genesis of pulmonary fat embolism. The first proposes that fat emboli are formed from traumatised depots of adipose tissue, especially the bone marrow. In a canine post-fracture model Kerstel et al. showed that the fatty acid composition of triglycerides from pulmonary emboli matched the profile of the triglycerides in the bone marrow, but differed from that of subcutaneous and plasma triglycerides. It has been shown that with elevated intramedullary pressures the medullary contents of the long bones, including fat, marrow elements and bone debris, embolise to the pulmonary circulation. Supporters of the mechanical intravasation theory have proposed methods for decreasing the embolic load of fat such as removal of intramedullary fat by lavage or suction drain before the insertion of cement or an implant, and venting techniques such as the use of a 4.5 mm drill hole in the cortex.

The second theory suggests that fat emboli are formed by changes in the physical state of the blood lipids. Under normal conditions, all lipids present in blood appear to be bound to one or more protein moieties, termed lipoproteins, and are classified according to their density. We have measured triglycerides, which include chylomicrons and the lower-density lipoproteins, and cholesterol which is the main component of the higher-density lipoproteins. Evidence of pulmonary fat embolism in non-traumatic inflammatory conditions such as pancreatitis, osteomyelitis, and fatty liver supports Lehman and Moore’s hypothesis that some unknown substance causes the agglutination of the existing plasma lipoprotein emulsion. These two theories of the origin of pulmonary fat emboli are not necessarily mutually exclusive, and each may simultaneously contribute to the final clinical picture.

Previous studies have shown significant levels of MMA monomer in the systemic blood during THA, but none has evaluated its possible role in causing the plasma agglutination of lipids and thereby contributing to the haemodynamic effect of pulmonary fat embolism.

In our study, MMA cement pressurisation after reaming of the femoral intramedullary canal produced detectable levels of MMA monomer in the ipsilateral femoral vein. Reduction of medullary fat and particulate debris by lavage before cement pressurisation resulted in a slight trend towards higher levels of MMA monomer in the femoral vein possibly due to deeper penetration of MMA into the surrounding bone, but this was not statistically significant. The MMA monomer levels which we found were low compared with the mean maximum levels detected in the pulmonary artery (7.8 µg/ml) in previous studies on THA. One possible explanation is that in a canine model less MMA cement is needed to fill the proximal femoral canal and therefore less MMA monomer enters the surrounding veins. Also, MMA is rapidly degraded by hydrolytic activity in the blood and the liver, and the timing of our samples may have coincided with post-peak levels in the pharmacokinetic pro-
file of the MMA plasma concentration. 20,32

In previous studies using an identical method of reaming and intramedullary canal preparation we have shown historically that fat emboli along with small bony spicules were embolised to the lungs, and subsequently to the kidneys and brain. 12 Although in the present study there is no pathological confirmation of this, the pulmonary haemodynamic values strongly suggest that similar embolic phenomena did occur during the reaming and preparation of the intramedullary canal. Given that the pulmonary capillary wedge pressure did not change significantly, an increased circulating volume could not account for the significantly elevated PAP during reaming and cement pressurisation. As expected, reaming and cement pressurisation gave the greatest increase in intramedullary canal pressure. This intramedullary hypertension is consistent with the conditions associated with the detection of pulmonary fat emboli previously shown in studies on insertion of a prosthesis and intramedullary nailing. 7,22

In our study, elevated intramedullary pressures and pulmonary haemodynamics consistent with pulmonary fat embolism were noted without cement pressurisation or detectable MMA levels. This suggests that the presence of MMA monomer is not required for the production of pulmonary fat emboli and implicates mechanical factors in their pathogenesis. Additional studies support our findings; no decrease in fat emboli was noted when inert bone wax was used as ‘cement’ instead of MMA in a rabbit model of THA, 7 and in a dog model pulmonary emboli were found after both cemented and non-cemented THA. 33

When MMA cementing was performed and MMA monomer was detected, there was no change in the lipid profile in the femoral vein. The levels of triglycerides and cholesterol did not vary significantly with reaming, lavage or cement pressurisation. If MMA monomer caused the agglutination of blood lipids and the formation of emboli, we would have expected to see a decrease in plasma lipoproteins with their consumption. 29

Also, the pulmonary haemodynamic outcome parameters did not change irrespective of whether MMA monomer was present or not. This suggests that its presence has no effect on the haemodynamic outcome of pulmonary fat emboli. Our findings are compatible with a previous study which observed that during THA the peak MMA monomer levels did not correlate with the maximum decrease in blood pressure or the maximum increase in PAP. 32

Our results show that reaming, lavage and MMA cement pressurisation of the proximal femur have no effect on ipsilateral femoral vein triglycerides or cholesterol. In addition, we conclude that the presence of MMA monomer has no effect on the incidence or haemodynamic outcome of pulmonary fat emboli produced by femoral reaming and the preparation of the intramedullary canal. Our results do not support the theory that MMA cement causes the agglutination of plasma chylomicrons leading to pulmonary fat embolism during THA. We recognise that our conclusions are based on results in an animal model and must be applied with caution to man. Further in vitro and human clinical studies to determine the effect of MMA monomer on plasma lipoproteins would have expected to see a decrease in plasma lipoproteins.

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


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