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Pharmacokinetics of Methylmethacrylate Monomer During Total Hip Replacement in Man

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Summary. The concentration of methylmethacrylate monomer (MMA) in the blood stream after implantation of the components of 15 total hip prostheses using bone cement was determined in the pulmonary artery, the radial artery, and the superior vena cava after cement application, and correlated with the observed drop in blood pressure and the increase in the pulmonary arterial pressure. In all samples MMA was found. The values ranged from 0.02 µg/ml to 59 µg/ml. The mean maximum value after implantation of the stem was measured to be 7.8 µg/ml in the pulmonary artery, 4.6 µg/ml in the radial artery, and 1.75 µg/ml in the superior vena cava. After implantation of the cup the values were clearly lower. The simultaneously recorded blood pressure decreased slightly during the first 3 min and then returned to previous values. The pulmonary arterial mean pressure increased from 18 to 20 mm Hg during the first 10 min. Although in some patients a drop in blood pressure started at the same time as MMA reached maximum values, high concentrations did not result in a greater effect on the circulatory parameters. Statistical analysis by the Spearman test revealed no correlation between MMA concentrations and the decrease in blood pressure or the increase in the pulmonary arterial pressure.

Zusammenfassung. Während der Implantation von fünfzehn Totalendoprothesen mit Knochenzement wurden die Konzentrationen von Methylmethacrylatmonomer (MMA) in der Arteria pulmonalis, der Arteria radialis und der Vena cava superior bestimmt und mit dem beobachteten Blutdruckabfall und dem Anstieg des pulmonalarteriellen Druckes korreliert. In den Proben konnten MMA-Konzentrationen zwischen 0,02 µg/ml und 59 µg/ml nachgewiesen werden. Die mittlere Maximalkonzentration betrug nach Implantation des Schaftes 7,8 µg/ml in der Pulmonal-, 4,6 µg/ml in der Radialarterie und 1,75 µg/ml in der Vena cava superior. Die Konzentrationen nach Implantation der Pfanne waren deutlich geringer. Der gleichzeitig aufgezeichnete Blutdruck fiel geringgradig während der ersten drei Minuten und kehrte dann auf Ausgangswerte zurück. Der pulmonalarterielle Mitteldruck stieg von 18 auf 20 mm Hg während der ersten zehn Minuten. Obwohl bei einigen Patienten der Blutdruckabfall mit dem Auftreten maximaler MMA-Konzentrationen zusammenfiel, hatten höhere MMA-Konzentrationen keinen größeren Effekt auf die zirkulatorischen Parameter. Bei der statistischen Analyse mit dem Spearman Test bestand keine statistische Korrelation zwischen den MMA-Konzentrationen und dem Abfall des Blutdruckes bzw. dem Anstieg des pulmonalarteriellen Druckes.

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Circulatory reactions in total hip replacements after implantation of cup and stem with acrylic bone cement are well known [3, 5, 12, 14, 18, 19, 21]. There are four main theories about the etiology: (a) pulmonary embolism caused by tissue debris from the bone marrow cavity [1, 23], (b) a neurogenic reflex mechanism [24, 25], (c) an air embolism [10], and (d) a pharmacological effect of circulating methylmethacrylate monomer (MMA) [12, 20].

All but the pharmacological effect are considered to be results of high intramedullary pressure during the impaction of the prosthesis. A 4.5 mm venting hole, drilled about 2 cm below the tip of the stem, has

been used in addition to the Charnley procedure to avoid high intramedullary pressure. Such a venting hole reduces the intramedullary pressure more effectively than a temporary suction drainage in the femoral cavity during the cementation [29].

In order to elucidate the pathogenesis of intraoperative arterial hypotension, pulmonary arterial pressure and blood pressure were registered in 15 patients undergoing total hip replacement procedures with bone cement and were correlated with the concentrations of circulating MMA in the blood stream.

Materials and Methods

Patients

The investigations were performed during 15 total hip arthroplasties. The patients (12 women and three men) were operated upon because of fracture of the femoral neck [11] or coxarthrosis [4]. Their ages ranged from 59 to 89 years.

Surgical Procedure

A Müller-type Protasol-10 stem prosthesis with a polyethylene cup was implanted using bone cement (Refobacin-Palacos R, E. Merck, Darmstadt, manufactured by Kulzer & Co. GmbH, Wehrheim/Ts., West Germany). In addition to the Charnley procedure, a 4.5 mm venting hole was drilled about 2 cm distal to the tip of the stem in the lateral femur to minimize the intramedullary pressure. The bone cement, which consists mainly of 33.8 g polymethylmethacrylate, 0.5 g gentamicin, and 18.4 g MMA, was applied exactly 2 min after the components were mixed; the cups were inserted 15 s after the cement was applied, while the stems were implanted 1 min after the femoral cavity was filled with cement by the digital packing method.

All patients were operated on while under spinal anesthesia and were sufficiently infused with regard to clinical parameters; blood loss was substituted.

Monitoring

For monitoring and blood sampling purposes, a Swan-Ganz catheter (Edwards Laboratories, St. Anna, California, USA) was introduced through the cubital vein and placed in the pulmonary artery. Samples to determine the presence of MMA could be drawn from the pulmonary artery and the superior vena cava. The pulmonary arterial pressure was monitored and graphed by a video printer (Hellige, Freiburg, West Germany). In addition, a cannula was placed in the radial artery for monitoring the blood pressure and drawing the blood samples. MMA was measured by headspace gas chromatography. The samples were drawn (before application of the cement and 1, 2, 3, 5, and 10 min thereafter) at the same time in five patients, from the pulmonary artery, the radial artery, and the superior vena cava.

During five operations, the intramedullary pressure in the femoral cavity was measured by a sonde (3 mm in diameter) which was placed about 3 cm below the venting hole. The pressure was transmitted by a transducer (Bell and Howell, Pasadena, California, USA) and graphed by a printer (Rikadenki, Freiburg, West Germany).

Statistics

The significance of the changes in the circulatory parameters (blood and pulmonary arterial pressure) was analyzed by the Wilcoxon test. The blood concentrations of MMA varied greatly and were not distributed normally. Therefore, the correlation between the MMA levels and the circulatory parameters was analyzed by the Spearman test, which does not depend on a normal distribution of the values.

Results

The MMA concentrations in blood varied a great deal among the patients. Maximum values were found between 1 and 2 min after application of the cement (Fig. 1). MMA was found in all samples, at values ranging from 0.02 µg/ml to 59.4 µg/ml. The mean maximum values after implantation of the stem amounted to 7.8 µg/ml in the pulmonary artery, 4.6 µg/ml in the radial artery, and 1.75 µg/ml in the superior vena cava. The MMA concentrations in the respective vessels were clearly lower after implantation of the cup than after implantation of the stem (Fig. 1).

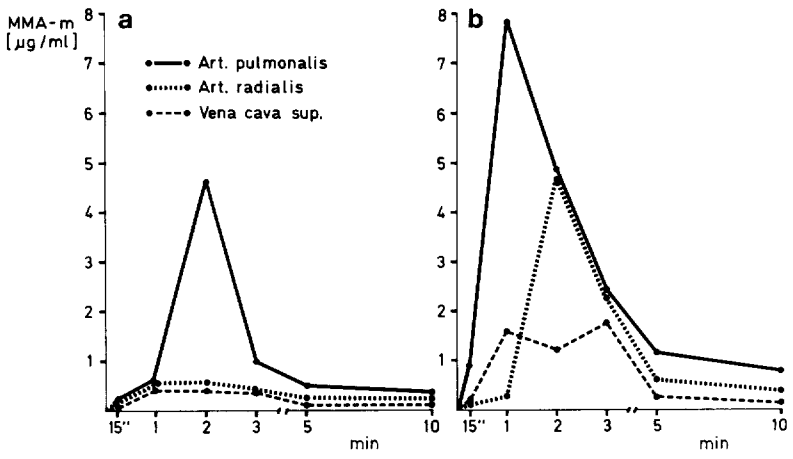

Fig. 1a, b. Concentrations of methylmethacrylate monomer after application of bone cement during total hip replacement in human subjects. Mean values ($n = 5$) in pulmonary artery, radial artery, and superior vena cava after insertion of bone cement in the acetabulum (**a**) and the femoral cavity (**b**)

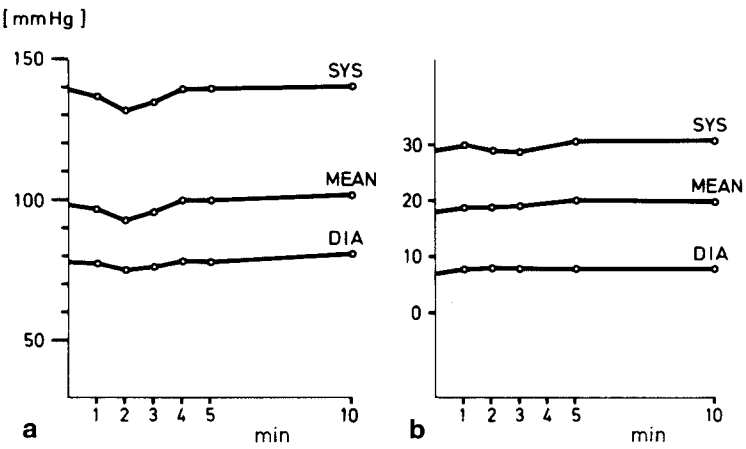

Fig. 2a Blood pressure ($n = 30$) and **b** pulmonary arterial pressure ($n = 20$) after application of bone cement. The cup was inserted 15 s and the stem 1 min thereafter

Table 1. Statistical analysis of correlation between MMA concentrations and decrease in blood pressure or increase in pulmonary arterial pressure

Spearman test ($n = 25$)		Coefficient	Correlation
$-\Delta RR_{mean}/MMA_{rad}$	ac	0.29	no
$-\Delta RR_{mean}/MMA_{rad}$	fe	0.23	no
$-\Delta RR_{sys}/MMA_{rad}$	ac	0.42	no
$-\Delta RR_{sys}/MMA_{rad}$	fe	0.28	no
$-\Delta RR_{mean}/MMA_{pulm}$	ac	0.42	no
$-\Delta RR_{mean}/MMA_{pulm}$	fe	0.28	no
$-\Delta RR_{sys}/MMA_{pulm}$	ac	0.46	no
$-\Delta RR_{sys}/MMA_{pulm}$	fe	0.20	no
$\Delta PAP_{mean}/MMA_{pulm}$	ac	−0.08	no
$\Delta PAP_{mean}/MMA_{pulm}$	fe	0.19	no
$\Delta PAP_{sys}/MMA_{pulm}$	ac	−0.22	no
$\Delta PAP_{sys}/MMA_{pulm}$	fe	0.29	no

MMA_{rad}, MMA concentration in the radial artery; MMA_{pulm}, MMA concentration in the pulmonary artery; ac, acetabulum; fe, femur; RR, blood pressure; PAP, pulmonary arterial pressure

The simultaneously recorded blood pressure decreased slightly during the first 3 min and then returned to previous values (Fig. 2). Thirty courses of the blood pressure after application of bone cement could be observed in the 15 operations (in each case after implantation of cup and stem). In 18 instances drops of systolic, mean, and diastolic blood pressure were observed. Sixteen of them did not exceed more than 10% of the starting value, while two courses revealed a decrease of between 10% and 20%.

Statistical analysis of all values together showed a significant decrease 1–2 min after cement application. The decrease was less after implantation of the cup than after implantation of the stem (Wilcoxon test).

Correct placement of the Swan-Ganz catheter was possible during ten operations, so that 20 courses of the pulmonary arterial pressure could be registered. Fourteen times there was a slight, constant increase during the first few minutes. Analysis of all values showed that this increase was statistically significant. However, it was significant only after implantation of the stem, not after implantation of the cup (Wilcoxon test).

To calculate correlation between the concentration of MMA and the decrease in blood pressure and the increase in pulmonary arterial pressure from each investigated vessel (pulmonary artery, radial artery, and superior vena cava) 25 pairs of values could be analyzed (Table 1).

There was no concentration-related correlation between the decrease in systolic and arterial mean pressure or the increase in the systolic and mean pulmonary arterial pressure and the concentrations of MMA with the Spearman test at each interval (1, 2, 3, 5, and 10 min). There was also no correlation between the peak concentration of MMA and the maximum decrease in blood pressure or the increase in pulmonary arterial pressure.

Monitoring of the intramedullary pressure in the femoral cavity showed a typical pattern (Fig. 3): a first peak (440 ± 141 mm Hg) after insertion of the cement by the digital packing method and a second peak (690 ± 162 mm Hg) after insertion of the stem of the prosthesis. After each phase of raised intramedullary pressure the values returned to starting levels within about 25 s.

Discussion

Total hip arthroplasty with bone cement is a common operation worldwide. In 1983, 159000 operations were performed in the United States [26], while 55000 were carried out in West Germany [17]. Circulatory reactions during the operation are well known and can be

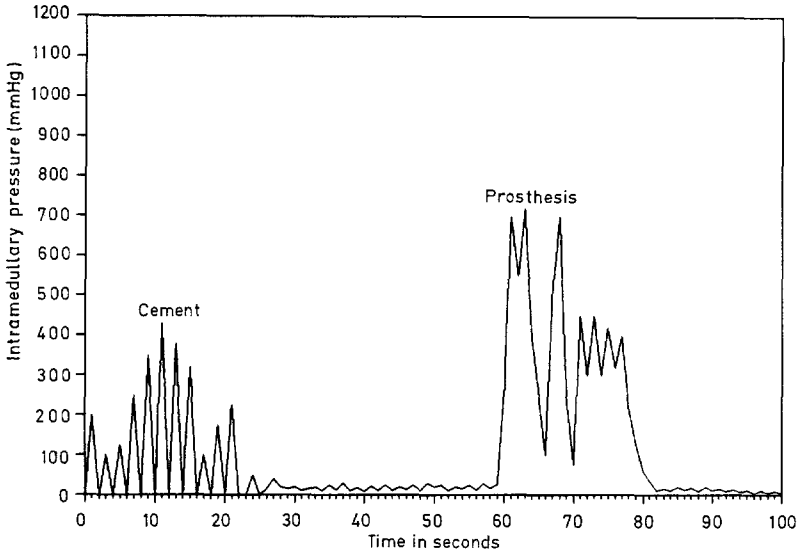

Fig. 3. Intramedullary pressure in the femoral cavity after application of bone cement by the digital packing method and after insertion of the stem. The pressure was registered 5 cm below the tip of the stem. A 4.5-mm venting hole was drilled about 2 cm below the expected location of the stem's tip and 3 cm above the registering sonde in the lateral femur

observed with a frequency ranging from 0.02% [3] to 95% [7].

In the early 1970s there were case reports in the literature of intraoperative cardiac arrest [4, 16, 22] and even death [33]. The etiology of these complications has been discussed widely. Besides the intravasation of particles of the bone marrow cavity due to the increased intramedullary pressure during the implantation, leading to a pulmonary embolism [10, 19, 23], air embolism [10], neurogenic reflex [24, 25], and a pharmacological effect of circulating MMA have been considered. The last of these assumptions is based on animal studies in which intravenous application of liquid MMA caused a severe drop in blood pressure [11, 20] and impairment of pulmonary function [9].

In the cases presented, concentrations of MMA observed during hip replacement in human subjects were correlated with the changes in blood pressure and pulmonary arterial pressure. The blood levels ranged from 0.02 μg/ml to 59 μg/ml, with a peak in the first 2 min after application of bone cement. These results are in good agreement with those of other authors. Svartling et al. [27] found levels of 0.05 μg/ml–31.89 μg/ml with a peak at 30 s, Homsy et al. [11] about 13 μg/ml with the peak between 1 and 3 min, and Crout et al. [6] 0.24 μg/ml–15.1 μg/ml. Peak concentrations were quickly reduced. In accordance with McLaughlin et al. [15], the clearly lower levels in the radial artery compared with those in the pulmonary artery can be explained as rapid elimination by the lungs through the first passages. Metabolization, as described by Crout et al. [6], may cause the differences between the radial artery and the superior vena cava.

The transient drop in blood pressure during the first 5 min after application of the cement in the study presented was observed by other authors as well [3, 12, 19].

From our point of view, the different interpretations of the cause depend on the simultaneity of MMA levels in the blood stream and high intramedullary pressure. Blood pressure decrease is observed during a phase of the operation in which MMA levels and high intramedullary pressure are present. An exact comparison of various studies is difficult, as different surgical techniques are used. Some operators use a suction drainage for venting, some a venting hole, and others no venting of the femoral cavity. The results of Eggert et al. [7], who found a considerable blood pressure decrease in 95% of patients after 69 implantations of bone cement simultaneous with MMA concentrations in the blood, may be related to the fact that no venting hole was used.

Statistical analysis is impaired by the great variation in the MMA concentrations. Therefore, a non-distribution-dependent test was applied. The Spearman test in the study presented showed no correlation between the MMA concentration in the pulmonary artery and the increase in the pulmonary arterial pressure or between those in the radial artery and the decrease in blood pressure. Corresponding results are described by Svartling et al. [27], who found no correlation between MMA concentrations in the inferior vena cava and blood pressure decrease. The results are further supported by the investigations of Burke et al. [2], in which centrifuged and control specimens of bone cement in dogs had no effect on blood pressure in spite of demonstrable MMA levels. Obviously, MMA concentrations in the blood stream

after application of bone cement are not comparable to those after intravenous application, which undoubtedly leads to impairment of the circulation [11, 20] and pulmonary function [9]. In our study, recording of the intramedullary pressure in the femur revealed considerable values, in spite of venting of the femoral cavity during the insertion of the cement ($x = 440$ mm Hg) and the stem ($x = 690$ mm Hg). Whitenack and Hausberger [32] demonstrated in rabbits that even lower pressures cause pulmonary embolism. Neurogenic reflexes are possible as well.

Other authors [8, 13, 28] confirm pulmonary embolism and impairment of lung function by high intramedullary pressure. The intramedullary pressure peaks registered by Tronzo et al. [28] during hip replacement in human subjects were lower than those in our study, especially when a venting hole was used, but the position of the measuring cannula was different. In the study of Tronzo et al. the cannula was placed above the condyle, while in our study it was about 5 cm below the tip of the stem of the prosthesis. In addition, Tronzo et al. [28] used a cannula 1.5 mm in diameter; in our study a 3-mm needle was employed. The different positions and diameters may contribute to the different pressures. It was recently shown that with different techniques for applying the cement, the peaks of the intramedullary pressure occur at different times [30]. Using the digital packing method, the maximum pressure occurs during application of the cement. After application of the cement by a syringe, the maximum pressure occurs after insertion of the stem. The onset of the drop in blood pressure was correlated with the intramedullary pressure peaks. Further studies showed [31] that after the bone marrow cavity is filled with a cancellous bone plug and a venting hole distal to the plug is drilled, no significant decrease in blood pressure is observed.

In conclusion, no pharmacological effect of MMA concentrations in the blood stream occurring during total hip replacement in human subjects could be demonstrated, so that circulatory reactions can be referred to effects of intramedullary pressure.

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