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Assessment of the cardiopulmonary functions during total hip arthroplasty in the dog

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Assessment of the cardiopulmonary functions during total hip arthroplasty in the dog

by

Ayaad Wassef Assaad

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LIST OF ABBREVIATIONS

A/D	Analog to Digital
AF	Air Flow (l/min)
ALM	Alveolar Lining Material
AoP	Aortic Blood Pressure (mm Hg)
AWR	Airway Resistance (cm H_2O/l/sec)
BE	Base Excess (mEq/l)
°C	Degree Celsius
C	Control
CI	Cardiac Index (ml/min/m^2 body surface area)
cm	centimeter
cm H_2O	centimeter of water pressure
CO	Cardiac Output (ml/min)
DPT	Dimethylparatoluidine
DP/DT	Myocardial Contractility (mm Hg/sec)
ECG	Electrocardiogram
EM	Electron Microscopy
EP	Esophageal Pressure (cm H_2O)
GLM	General Linear Model
H & E	Hematoxylin and Eosin
HCO_3-	Bicarbonate (mEq/l)
Hg	Mercury
HPLC	High Pressure Liquid Chromatography
HR	Heart Rate (beats/min)

IP	Intrapleural Pressure (cm H_2O)
iu	international unit
iv	intravenous
Kg	Kilogram
LSM	Least Square Mean
l	liter
LC	Lung Compliance (ml/cm H_2O)
LVP	Left Ventricular Pressure (mm Hg)
M	Mean
m	meter
mEq	milliequivalent
mg	milligram
min	minute
ml	milliliter
mm	millimeter
MV	Minute Ventilation (l/min)
n	number of animals per group
$PaCO_2$	Partial Pressures of Arterial Blood Carbon Dioxide (Torr)
PaO_2	Partial Pressures of Arterial Blood Oxygen (Torr)
PAP	Pulmonary Arterial Pressure (mm Hg)
PC	Phosphatidylcholine
PCO_2	Partial Pressures of Carbon Dioxide (Torr)
PD	Play Dough
PE	Phosphatidylethanolamine
PG	Phosphatidylglycerol

PI	Phosphatidylinositol
PS	Phosphatidylserine
PMM	Polymethylmethacrylate Bone Cement
PO_2	Partial Pressures of Oxygen (Torr)
PVR	Pulmonary Vascular Resistance (mm Hg/ml/sec)
RR	Respiratory Rate (breath/min)
rpm	revolution per minute
SAP	Systemic Arterial Pressure (mm Hg)
sec	second
SELSM	Standard Error of Least Square Mean
SEM	Standard Error of the Mean
SS	Sham Surgery
SV	Stroke Volume (ml/beat)
SVR	Systemic Vascular Resistance (mm Hg/ml/sec)
T	Time (period of recording)
TCO_2	Total Carbon Dioxide (Torr)
THA	Total Hip Arthroplasty
TV	Tidal Volume (ml/breath)
$\dot{V}CO_2$	Carbon Dioxide Production (ml/min)
$\dot{V}O_2$	Oxygen Consumption (ml/min)
V/Q	Ventilation/Perfusion Ration
v/v	volume by volume
WB	Work of Breathing (l·cm H_2O)

DEDICATION

DEDICATED TO

MY PARENTS

FOR THE UNCOMPROMISED PRINCIPLES THAT THEY INSTILLED IN THEIR CHILDREN

MY CHILDREN

ANDREW AND CHRISTIAN

FOR MAKING LIFE MEANINGFUL

I. INTRODUCTION

Disease processes or abnormalities of the dog's coxofemoral (hip) joint are frequently encountered. These conditions interfere with the normal physiological function of the joint, cause disabling pain (Hoefle, 1974; Olmstead et al., 1983; Olmstead et al., 1981), and may partially or totally limit joint function.

Since 1962, many disabling conditions of the hip joint have been successfully treated in man with prosthetic total hip arthroplasty (THA) pioneered by Sir John Charnley. The success of Charnley's prosthesis in man has led to the production of a similar prosthesis for the dog (Leighton, 1980).

Clinical THA in the dog has evolved from the use of the dog as a model for a device that could be applied to humans, into a form of treatment for the animal with debilitating joint disease (Nunmaker, 1985).

THA has proven to be extremely effective in alleviating pain and restoring function for the diseased or deformed coxofemoral joint in both man and dog. However, this procedure in man is well known to be associated with intraoperative systemic complications. These systemic complications may include systemic hypotension, pulmonary hypertension, pulmonary fat embolism, respiratory failure, and cardiac arrest. Most of these systemic complications have been attributed to the possible cardiopulmonary toxicity of the cementing material, polymethylmethacrylate bone cement (PMM).

The few concerns that have been published in the veterinary orthopedic literature regarding THA in the dog were the local complications, such as infection, and the mechanical failure of the procedure (Olmstead et al., 1983; Olmstead et al., 1981; Leighton, 1980; Nunmaker, 1985; Haupton, 1985), without any mention of possible systemic and cardiopulmonary complications that may be encountered during the surgical procedure.

Whether THA procedure in a clinical setting, and/or PMM can cause similar systemic and cardiopulmonary complications in the dog is not known. Except for a few experimental studies on the dog which have been published in human orthopedic literature, to our knowledge, no comprehensive study has been reported in the veterinary orthopedic literature, addressing the possible systemic complications of THA in the dog.

This project was designed to investigate the cardiopulmonary functional changes that may develop during THA in the dog by addressing three questions:

1. What is the nature of the cardiopulmonary changes that may develop during THA in the dog?
2. Does PMM have any toxic effects on the cardiopulmonary functions of the dog?
3. What is the role of the lungs in mediating any cardiopulmonary changes that may be observed during THA in the dog?

II. LITERATURE REVIEW

Lesions of the coxofemoral joint are fairly common in both man and dog. The coxofemoral joint of the dog is the most susceptible joint to injury (Hoefle, 1974). In man, the coxofemoral joint accounts for eight percent of disabling arthritis (Liang and Cullen, 1984). Because most of these conditions in both man and dog are usually neither curable nor fatal, reduction in disability by preservation and restoration of the functional capacity of the damaged joint is considered major goals of management and treatment, whether by medical, rehabilitative, or surgical intervention. The major contribution of surgery in these conditions is to improve the function of damaged joints (Wood, 1976).

At present, the most significant breakthrough for treatment of arthritic diseases of the hip joint, as well as other congenital deformities of the hip, is the development of the total hip arthroplasty surgery (Stinchfield, 1982). Total hip arthroplasty is a highly successful and established treatment for end-stage hip diseases (Nevitt et al., 1984; Kay et al., 1983; Chandler et al., 1981). THA is regarded as one of the major recent advances in surgery (Nevitt et al., 1984; Gordon, 1982).

Joint replacement techniques can alieviate pain, handicap, and offer restoration of normal activity against which other forms of medical intervention (e.g., corticosteroids) are of very limited value (Nevitt et al., 1984; Crowninshield, 1982; Taylor, 1976).

A. Total Hip Arthroplasty (THA)

Arthroplasty means plastic surgery of a joint or joints. Total hip arthroplasty means total reconstruction of the hip joint utilizing surgical techniques. Total hip replacement, pioneered by Sir John Charnley and introduced in 1962 with the material currently in use, began the modern era of major joint reconstruction (Crowninshield, 1982). The severely

damaged hip is replaced with an artificial joint composed of a plastic acetabular component made of an ultra-high molecular weight polyethylene (Taylor, 1976), and a femoral component made of one of the following materials: stainless steel, cobalt-chromium-molybdenum alloy, cobalt-chromium-tungsten alloy, tantalum, or titanium (Eftekhar, 1978). The metal component is inserted into the medullary cavity of the proximal portion of the femur, and both components are held in the bone with methylmethacrylate bone cement. Attempts to surgically reconstruct the hip joint were not new, they started even before the era of anesthetics and antiseptics.

Gluck in 1891, in Germany, attempting to reconstruct the hip joint, fashioned an ivory ball-and-socket joint and fixed it to bone with nickle-plated steel screws and a cement composed of resin, pumic powder, and plaster of Paris (Wilcock, 1979). In 1938, Wiles inserted a stainless steel femoral head and an acetabulum that fit into one another precisely in a human patient. The acetabular component was anchored to a buttressed plate by screws, and the femoral component was secured to the neck of the femur by a bolt (Eftekhar, 1978; Wilcock, 1979).

In 1946, the Judet brothers in France, introduced their perspex or plexiglas femoral head prosthesis that was made of polymethylmethacrylate (Feith, 1975). The Judet's contribution is significant because it proved that mechanical replacement of the hip joint utilizing plastic material can be tolerated in the human body with minimum tissue reaction (Eftekhar, 1978).

In man, osteoarthritis of the hip joint is considered the major indication for total hip replacement (Wood, 1976; Kelsey, 1982). Other indications include fracture-dislocation of the femoral head and neck, rheumatoid arthritis, aseptic necrosis of the femoral head and neck, and revision of previous hip arthroplasties (Kelsey, 1982).

Total hip arthroplasty was introduced into veterinary surgery in 1957, when a prosthetic hip joint was evaluated for a probable applications in humans. Since that time, there have been a number of attempts to develop a prosthesis that could be successfully used in the dog (Haupton, 1985). These prosthesis have been made of stainless steel in combination with stainless steel, teflon, vinylidine fluoride resin. Unfortunately, these combinations of materials usually wore excessively and were not satisfactory (Hoefle, 1974). In the 1970s, a prosthesis was developed for the dog which has been successfully used for total hip replacement (Haupton, 1985).

Disabling hip dysplasia in the dog is the primary indication for implantation of a total hip prosthesis. Other, less frequently encountered indications, in order of frequency, include: primary osteoarthritis unrelated to hip dysplasia, chronic non-reducible coxofemoral luxations, failed excision arthroplasties, severe fractures, non-unions or malunions of the femoral head, neck, or acetabulum, and avascular necrosis of the femoral head (Olmstead et al., 1983; Nunmaker, 1985; Haupton, 1985).

The high level of success of this procedure in the short term in man is well documented; the long term prognosis (ten years and beyond) is less well known (Wilcock, 1979). The amount of pain is reduced after the surgery. The improvement in quality of life for most of the patients is remarkable. Young and middle-aged adults can frequently return to work, while older adults may live a relatively active and pain-free life (Taylor, 1976; Kelsey, 1982). In veterinary surgery, the long term reliability of the commercially*

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*Richards Canine II Total Hip System, Richards Manufacturing Co, Memphis, TN.

available canine hip prosthesis has been established, and the benefits of treating disabling diseases of the dog's coxofemoral joint with THA have been clearly demonstrated (Olmstead et al., 1983). Elimination of pain, and marked increase in activity and endurance were consistently reported by owners (Olmstead et al., 1981).

The three outstanding features of THA are:

1. The unusually high quality of the functional activity obtained.
2. The regularity with which a major human or animal affliction can be successfully treated.
3. The stimulus that this hip operation represents to develop similar replacement of other joints (Harris, 1977). THA is a unique surgical procedure because of what it can do to the quality of life, however, it is not a life-saving operation (Wood, 1976).

Though the operation is well established, the technical elements, such as biomaterials and design of the prosthesis, are changing rapidly as knowledge increases (Gordon, 1982).

B. Polymethylmethacrylate Bone Cement (PMM)

The range of application of PMM as an acrylic bone cement in orthopedic surgery is steadily increasing. In particular the use of acrylic cement has facilitated the solution of numerous problems in the fixation of artificial joints. This has made it possible to expand the use of artificial joints and to give many patients with an invalidating arthroplasty a better life (Feith, 1975). PMM was first used on a large scale in orthopedic surgery when Robert and Jean Judet introduced their perspex or plexiglas femoral head prosthesis in 1946. The interest in PMM as a bone cement was revived when Charnley stabilized his first hemiarthroplasty of the hip with cold-curing PMM. Shortly after, Charnley (1961) and

McKee and Farrar (1966), both developed a total hip prosthesis that they anchored with the acrylic cement.

Since the early seventies, this bone cement has become an indispensable aid in orthopedic surgery. The method of fixation which fills the space between the prosthesis and previously prepared bone defects with malleable plastic setting in situ was revolutionary. It was therefore not until several years later that the concept of relying on the strength of the cement to support the prosthesis rather than having it rest on the bone, was generally accepted. Acrylic cement greatly supported the era of total joint replacements (Feith, 1975).

Other uses of PMM include its use in plastic surgery of the nose and orbital region; in thoracic surgery as plombage (therapeutic deflation of the lung); in cranial surgery to fill defects in the skull; and in orthopedic surgery to stabilize pathological fractures (Klein, 1974). PMM has been used successfully to fill large defects in long bones after massive tumor resection, eliminating the problems associated with bone grafting (Baddeley and Cullen, 1979). In ophthalmology, PMM is utilized to manufacture contact lenses, intraoccular lenses, and repair of lacrimal ducts; in otology to replace ossicles; and in urogenital surgery for plastic cosmetic replacement of testicles.

1. Chemical and physical characteristics of PMM

PMM is a plastic material composed of macromolecules. The material is prepared for implantation by mixing a polymer powder with a liquid monomer that consists mainly of methylmethacrylate. The powder contains polymethylmethacrylate in granular form; the polymerization activator, benzoylperoxide, and the chemical agent, dimethylparatoluidine (DPT). The liquid portion is the methylmethacrylate monomer whose chemical configuration is similar to chloroform. It is a highly volatile, potent lipid solvent, and toxic

fluid with a characteristic penetrating odor, to which the polymerization inhibitor, hydroquinone, has been added.

Each chemical ingredient plays an important role in transforming the powder and liquid into a usable state. Hydroquinone prevents slow and spontaneous polymerization of methylmethacrylate monomer into a solid resin state, and rapid polymerization is induced by the activator, benzoylperoxide. In the presence of this activator, physical factors such as heat and ultraviolet light can initiate polymerization.

In the case of self-curing acrylic cement, which is the type of methylmethacrylate used in surgical procedures, the polymerization reaction is initiated chemically by the agent DPT. The chemical reaction is exothermic. This sudden response is associated with "hardening" of the cement, and it produces temperatures varying from 80°C to 100°C (Klein, 1974). This heat is released during the change of the high-energy unstable monomer molecule to the low-energy stable polymer, to the extent that 100 grams of methylmethacrylate monomer produce 13 kilocalories on polymerization (Jefferiss et al., 1975). Studies in dogs showed that PMM plug temperatures ranged between 95°C and 107°C and that temperatures at the cement-bone interface ranged from 50°C to 95°C. Curing temperatures therefore are high enough to cause bone necrosis (Schatzker et al., 1975).

2. Mechanical fixation and load transmission by PMM

Acrylic cement has no adhesive property to steel or wet bone. When used as a stiff paste or dough, it has space-filling properties. Acrylic cement can fill spaces between the stem of the prosthesis and the endosteal surface of the bone. The cement is forced down the track of the medullary canal as a stiff dough and the insertion of the point of the tapered stem of the prosthesis expands the stiff dough and forces the cement into the cancellus

lining of the marrow space. In this way the cement makes an accurate cast of the lining of the canal with strong bone trabeculae indenting it, and with soft cancellus spaces being invaded by it. When the cement has hardened, the prosthetic stem and the sheath of cement function as one unit (Charnley, 1970). By interdigitation of the cement into the bone during cyclic loading and unloading of the transmission of body weight, the whole surface of the interior of the bone is subjected to the load, thus preventing stress concentration at any given area of contact. Therefore shearing forces between prosthesis and bone are reduced by the absence of friction between the two surfaces (Eftekhar,1978).

3. Side effects of methylmethacrylate monomer

It is known that PMM bone cement itself and the method of its intramedullary implantation have a distinct influence on the surrounding tissues and on various physiological functions of the body. As a result, several clinical and experimental studies have been carried out regarding the unfavorable side effects of the acrylic cement.

Most of these studies have focused on the causes of systemic physiological disorders such as systemic hypotension and pulmonary fat embolism during introduction of the acrylic cement into the femoral medullary canal.

Generally, there is an agreement that all these side effects are due to the chemical composition of the monomer component of PMM, its metabolites, to the exothermic reaction during polymerization, and to the method of implantation in the medullary cavity (DeWijn et al., 1975).

a. Pulmonary system Methylmethacrylate is known to be a powerful irritant. Inhalation of its vapor produces cellular responses and irritation of the respiratory membranes of experimental animals (Dichman, 1941; Tansy and Kendall, 1979), and sometimes death due to respiratory failure (Kessler et al., 1977; Spealman et al., 1945).

An intravenous injection of the monomer in sheep causes a dose-dependent increase in pulmonary microvascular permeability, and transient pulmonary hypertension after high doses (Fairman et al., 1984). Also in dogs, intravenous injection of the monomer causes pulmonary hypertension of transient nature (d'Hollander et al., 1979).

McLaughlin et al. (1973) found that a dose of intravenously injected monomer of at least seventy-five milligrams per kilogram body weight was required to depress arterial PaO_2 and elevate $PaCO_2$. This dose is about thirty to forty times larger than that which probably reaches the blood during clinical THA in man.

Similar findings were reported by Modig et al. (1975a). They concluded that the monomer in concentrations similar to those reported in man during THA, has no effects on the cardiopulmonary functions. Furthermore, they attributed the cardiopulmonary changes observed during THA to efflux of thromboplastic products from crushed marrow tissue into the blood stream during impaction of the femoral prosthesis.

b. Cardiovascular system Impairment of cardiovascular and pulmonary function during the insertion of orthopedic prosthesis fixed with acrylic cement is adequately described in the literature. To explain the cardiovascular dysfunction, the majority of authors pointed out the role of pulmonary embolism, frequently encountered following THA. They also suggested the hypothetic systemic toxicity of resorbed methylmethacrylate monomer in clinical situation (d'Hollander et al., 1979).

Ellis and Mulvein (1974) compared the cardiovascular effects of intravenous injection of pure monomeric methylmethacrylate with those of the whole liquid compound in the dog. By injecting enough material of both compounds to reach blood level of 40-45 mg/100 ml of blood, both compounds produced a fall in mean arterial blood pressure, a rise in the heart rate, and an increase in cardiac output without significant changes in the

central venous pressure. They concluded that the cardiovascular disturbance is caused by the monomeric methylmethacrylate alone rather than by any of the other constituents.

In a similar study, Peebles et al. (1972) compared the cardiovascular effects of the monomeric methylmethacrylate liquid with the polymeric methylmethacrylate powder in the dog. Intravenous injection of a suspension of the powder failed to produce any cardiovascular changes, while injection of 0.25 ml (11.2 mg/100 ml blood) and 0.5 ml (22.4 mg/100 ml blood) of the monomeric liquid produced a significant fall in the mean arterial pressure, an increase in the pulse rate and cardiac output, with no changes in the central venous pressure. They concluded that the main underlying mechanism seemed to be peripheral vasodilation produced by the monomer.

Homsy et al. (1967) reported that intravenous administration of low doses of methylmethacrylate monomer (5-10 mg/100 ml blood) produced an immediate but minor blood pressure decrease. Doses as high as 50-125 mg/100 ml blood were necessary to induce a significant and acute cardiovascular depressant effects. They concluded that the compound did not seem to have any overt acute toxicity with its clinical use as seating compound for orthopedic implants. Similar findings were reported by Modig et al. (1975a).

Since THA is usually associated with significant blood loss, McMaster et al. (1974) studied the significance of blood volume deficit as a potentiator of the systemic blood pressure lowering effect of methylmethacrylate monomer. They found that graded blood volume depletion potentiated the systemic blood pressure lowering effect of intravenously injected monomer in the dog. Their data supported the previously reported mechanism of action of the compound, which is peripheral vasodilation without myocardial depression.

Berman et al. (1974) found that peripheral resistance and blood pressure were decreased in both normovolemic and hypovolemic dogs after an intravenous injection of methylmethacrylate monomer. However, cardiac output increased in normovolemic dogs and decreased in the hypovolemic ones.

d'Hollander et al. (1979, 1976) found that the cardiovascular depressant effect of intravenously injected methylmethacrylate monomer in the dog is dose-dependent. Furthermore, the blood levels of the compound associated with cardiovascular depression in dogs were about 10 to 100 times higher than that reported in man after total hip arthroplasty. They concluded that the dose-dependent toxic effect of the product could not be responsible for the cardiovascular changes seen during total hip arthroplasty.

Yasuda and Iwatsuki (1975) studied the direct effect of methylmethacrylate monomer on the isolated dog heart muscle, they found that the compound exerted a direct negative inotropic effect on the myocardium. Wong et al. (1977) conducted a similar study on the rabbit's heart and found that the compound produced a dose-dependent depression of the left ventricular contractility, and a depression of the spontaneous heart rate.

Ramanathan et al. (1983) found that application of the monomer to the rabbit's aorta in vitro directly inhibited the vascular smooth muscle, they proposed that the action of the compound may be related to its effect on the intracellular calcium and/or contractile proteins.

c. Cellular immune response Deep infection after total hip arthroplasty remains a serious problem in both human and veterinary orthopedic surgery, mainly because its disastrous consequences. This problem has stimulated several investigators to examine the possibility that methylmethacrylate may disturb host immune function and render tissues more susceptible to infection. Panush and Petty (1978a) found an

immunosuppressive effects of methylmethacrylate upon human lymphocytes in vitro. Petty (1978a) found that methylmethacrylate significantly decreased the ability of human polymorphonuclear leukocytes to phagocytose and kill bacteria in vitro. The result indicated that the compound impaired the killing property more than the phagocytic activity of the leukocytes.

Welch (1978) found that the liquid monomer reduced the phagocytic activity of mice peritoneal macrophages. Also, the monomer demonstrated cytotoxic effect to blood cells in vitro, with more damage sustained by phagocytic polymorphonuclear neutrophils than lymphocytes.

Heggers et al. (1978), using experimentally sensitized guinea pigs, proposed that methylmethacrylate was capable of evoking an immune response in previously exposed animals. Nicastro et al. (1975) found that methylmethacrylate at various curing stages, caused decreased phagocytosis and hexosmonophosphate shunt activity in rabbit alveolar macrophages.

Petty (1978b) demonstrated that methylmethacrylate depressed the formation of the chemotactic factors in normal human serum when it was added to the serum prior to its activation. However, the compound did not affect the chemotactic activity of either the bacteria or the serum if the serum had been activated prior to its exposure to the compound.

d. Occupational hazards in orthopedic surgery The liquid part of PMM bone cement contains methylmethacrylate monomer, a polymerization accelerator, dimethylparatoluidine, and the self-polymerization inhibitor hydroquinone. The monomer and its additives are potential sensitizers. The powder part contains methylmethacrylate polymer, and the polymerization inhibitor benzoylperoxide. The polymer itself has no allergenic potential, while benzoylperoxide is a sensitizer. However, when exposure to

methylmethacrylate products induces sensitization, this is rarely due to the additives but mainly blamed on the liquid monomer (Eftekhar, 1978; Fregert, 1983). When the two components are mixed together (the liquid and the powder) during THA, the low molecular weight liquid monomer polymerizes to the high molecular weight polymer. The polymerization, however, is not complete, allowing spontaneous release of the monomer from the hardened cement for some time.

Methylmethacrylate monomer penetrates intact surgical rubber gloves in a few minutes, and the penetration of acrylates through the gloves continues even after the direct contact has ceased (Fregert, 1983; Fries et al., 1975). Fries et al. (1975) reported several cases of allergic contact dermatitis in orthopedic surgeons handling acrylic cement. Also, inhaled methylmethacrylate vapor may cause headache and irritation of the eyes and the respiratory tract in the operating room personnel (Fregert, 1983).

e. Local tissue effects Acrylic bone cement may cause local tissue injury in at least two ways: thermally, through the amount of heat produced by the polymerization process, which depends on the amount of cement used, and chemically, through the amount of residual monomer leached out from the cement to the surrounding tissues during the polymerization process. The magnitude of monomer leak depends on the stage of polymerization of the cement and the surface area of the cement.

Clinically, the thermal damage may be minimized by using thin layers of the cement to anchor the prosthesis, and diverting the heat of polymerization by the cold metal femoral stem. The chemical damage may be partially reduced by allowing most of the polymerization process to take place outside the body, before incorporating the cement with the raw surface of the bone.

1) Effects on soft tissues Linder and Romanus (1976) demonstrated that polymerizing acrylic bone cement in contact with living tissue caused severe and irreversible microcirculatory changes in the hamster's cheek pouch, even in the absence of thermal factors and pressure on the tissue. Linder (1976) studied the effect of the monomer on the microvascular system of the rabbit's ear, and demonstrated that severe tissue reaction and necrosis always followed its application.

2) Effects on bone The reactions of bone to implanted methylmethacrylate determine to a large extent the success or failure of the prosthesis and its function (Willert et al.,1974).

Bone necrosis adjacent to self curing polymethylmethacrylate is a matter of accepted fact. Among the possible causes are mechanical and vascular damage from the preparation of the bone cavity, chemical damage from the monomer and free radicals in the cement dough, and thermal damage from the heat of polymerization, occurring in this order (Jefferiss et al., 1975).

Willert et al. (1974) were able to distinguish three different phases of bone reactions to implanted acrylic cement:

1. The initial phase or the postoperative tissue damage lasts up to three weeks postoperatively, and is characterized by a layer of necrotic tissue and fibrin up to three millimeters thick and located at the inner surface of the implant bed, immediately adjacent to the cement.
2. The second phase or repair of tissue damage lasts from three weeks to two years postoperatively, and is characterized by remodeling, reinforcement, or replacement of the necrotic bone, either by apposition of newly formed lamellar bone or by

osteoplastic metaplasia. The replacement of the necrotic bone is usually completed after two years.

3. The final phase or formation of the permanent implant bed. It lasts one to two years postoperatively, and is characterized by the formation of a thin connective tissue membrane (0.1 to 1.5 millimeter thick) surrounding the cement. Minimum bone remodeling continues during this phase.

Pedersen et al. (1983) demonstrated a dose-dependent depression of methylmethacrylate monomer on bone turnover in vitro. This effect may initially be augmented by the thermal damage induced by polymerization of the cement. These two factors, separate or combined, may play a role in the pathogenesis of the postoperative loosening of the surgical implants.

4. Metabolism of methylmethacrylate in the body

It is known that methylmethacrylate monomer is slowly leached out of the polymerized acrylic cement into the surrounding tissues for some time following implantation. Petty (1980) found low concentrations of methylmethacrylate monomer in cancellous bone adjacent to the cement, and that they were sustained only for a brief period of time. Homsy et al. (1972) in simulating canine total hip arthroplasty, were able to detect methylmethacrylate monomer in central venous and aortic arch blood within one minute after implantation. The peak level of the monomer of about 1 mg/100 ml blood was reached within three minutes on the venous side of the lungs, and about one third of this level on the arterial side. In a similar work, McLaughlin et al. (1973) were able to detect a venous blood monomer level of 3.5 mg/100 ml blood, which corresponds to only 0.5 per cent of the total amount of implanted monomer. However, they could not detect any monomer in the arterial blood. This may indicate the active role of the pulmonary system

as a possible major metabolic or excretory system for the monomer and/or its metabolites (Rijke and Johonson 1977; Bart and Hathway, 1977; McLaughlin et al., 1973).

Bright et al. (1972) reported a concentration of 1 mg/100 ml blood or less of monomer in human patients undergoing THA, without any significant ECG or blood pressure changes.

Corkill et al. (1976) found that methylmethacrylate was rapidly hydrolyzed into methacrylic acid and methanol in human blood in vitro. They also demonstrated a half life of 20-40 minutes of methylmethacrylate in the blood. McLaughlin et al. (1973) could not detect any monomer in venous blood nineteen minutes after injection.

Crout et al. (1979) found that methylmethacrylate was also hydrolyzed into methacrylic acid and methanol in patients undergoing THA. They could not find any correlation between changes in the concentrations of methylmethacrylate and methacrylic acid, and the hemodynamic changes observed during the procedure. They suggested that methacrylic acid is converted to coenzyme A ester through the action of a non-specific enzyme. The conversion of methacrylic acid into the coenzyme A ester, would permit methacrylic acid to enter a normal catabolic pathway which leads, via the tricarboxylic acid cycle, to carbon dioxide. Their view was supported by the finding of Bart and Hathway (1977), that over 80% of an administered dose of C^{14} labeled methylmethacrylate in the rat, was respired as carbon dioxide within 5–6 hours.

Although there have been some problems and complications with the use of acrylic cement in orthopedic surgery, acrylic cement has been the foundation on which the success of total hip arthroplasty has rested. In general, acrylic cement has demonstrated excellent physical characteristics, adequate tissue compatibility, and minimal toxicity when applied

properly. Its relative inertness, mechanical properties, and ease of applicability have guaranteed its popularity and wide acceptance (Feith, 1975).

C. Systemic Effects of THA in Man

1. Cardiopulmonary complications

The use of methylmethacrylate bone cement in the fixation of orthopedic implants has been one of the great advances in orthopedic surgery in the last two decades. However, several problems exist with its use, particularly after impaction of the femoral component of the prosthesis (Alexander and Barron, 1979).

Elective orthopedic procedures such as THA performed on patients of advanced age pose a particular problem in management. There is a greater incidence of deep venous thrombosis and pulmonary embolism in this than any other group of surgical patients (Barber et al., 1977). Venous thromboembolic disease is the most frequent and serious complication in the postoperative period after THA (Harris et al., 1975; Eftekhar et al., 1976; Hampson et al., 1974; Johnson et al., 1977). The incidence of deep vein thrombosis after THA ranges from 30 to 70 per cent, with 10 per cent incidence of pulmonary embolism, and overall mortality rate of 2 per cent due to massive pulmonary emboli (Barber et al., 1977; Pini et al., 1985; Jennings et al., 1976; Belch et al., 1982; McManus, 1976; Coventry et al., 1974; Sautter et al., 1983; Hirsh, 1984). Higher mortality rate due to massive pulmonary emboli after THA, ranging from 5 to 8 per cent have also been reported (Pini et al., 1985; Stulberg et al., 1982). There is substantial evidence that the thrombi that form in the veins of the thigh or iliac region are the principal sources of major pulmonary emboli (Harris et al., 1976; Kettunen et al., 1973).

Pulmonary fat, bone marrow, and air emboli (pulmonary embolism) have been confirmed in autopsy specimens from patients dying during or shortly after THA

(Alexander and Barron, 1978; Modig et al., 1975b; Dandy, 1973; Kepes et al., 1972; Cohen and Smith, 1971). However, Dandy (1973) reported two deaths with confirmed pulmonary fat embolism, associated with Thompson arthroplasty without PMM.

The possibility of sudden death in the immediate postoperative period from pulmonary embolism is a continued source of anxiety to all surgeons engaged in hip surgery. In spite of the intensive effort that has been directed toward this problem, no clear way of avoiding this complication has emerged (Kay, 1973).

Arterial hypoxemia particularly after insertion of the femoral prosthesis has been reported by several investigators (Kallos, 1975; Park et al., 1973; Koide et al., 1974; Turnbull et al., 1974; Alexander and Barron, 1978; Modig et al., 1975b; Modig and Molmberg, 1975; Modig, 1976).

Other pulmonary complications that have also been reported are pulmonary capillary leaks (Safwat and Dror, 1982), an increased venous admixture (Turnbull et al., 1974; Modig and Molmberg, 1975; Modig, 1976), pulmonary hypertension, and elevated pulmonary vascular resistance (Modig and Molmberg, 1975; Rinecker, 1980).

Contrary to previously reported pulmonary complications, Hughes et al. (1972) reported no evidence of pulmonary dysfunction after THA with PMM in man. Gooding et al. (1981) found no significant changes in pulmonary hemodynamics or gas exchange after THA with PMM.

The cardiovascular complications associated with THA are numerous. Brown and Pormley (1982) reported second-degree atrioventricular block after application of PMM during THA. Cardiac arrest has been reported by several authors, particularly after inserting the femoral prosthesis and PMM into the reamed femur (Dandy, 1973; Kepes et al., 1972; Cohen and Smith, 1971; Kirman, 1973; Powell et al., 1970; DeAngelis and

Jaques, 1973; Nice, 1973). In most of the cardiac arrest cases, pulmonary embolism was confirmed at autopsy (Dandy, 1973; Kepes et al., 1972; Cohen and Smith, 1971).

The most common cardiovascular complication that was reported during THA was systemic arterial hypotension (Wong et al., 1977; Eftekhar et al., 1976; Koide et al., 1974; Alexander and Barron, 1978; Modig and Molmberg, 1975; Dandy, 1973; Newens and Volz, 1972; Philips et al., 1971; Thomas et al., 1971; Schuh et al., 1973; Kim and Ritter, 1972). Myocardial infarction, congestive heart failure, and cardiac arrhythmias have also been reported as complications of THA (Eftekhar et al., 1976; Coventry et al., 1974).

The cardiopulmonary complications associated with THA in man have been attributed to one or more of the following factors:

1. Toxicity of the monomer absorbed into the systemic circulation (Kirman, 1973; Powell et al., 1970; Nice, 1973; Philips et al., 1971; Kim and Ritter, 1972).
2. Fat embolism and release of thromboplastic products into the systemic circulation (Alexander and Barron, 1978; Modig et al., 1975b; Rinecker, 1980; Cohen and Smith, 1971; DeAngelis and Jaques, 1973; Nice, 1973; Newens and Volz, 1972; Philips et al., 1971).
3. Old age and pre-existing cardiopulmonary disease (Koide et al., 1974; Alexander and Barron, 1978; Powell et al., 1970; DeAngelis and Jaques, 1973; Nice, 1973; Schuh et al., 1973).
4. The massive surgical intervention and severe musculoskeletal trauma associated with THA (Modig and Molmberg, 1975; DeAngelis and Jaques, 1973; Convery et al., 1975).
5. Severe blood loss, aggressive blood transfusion, and replacement fluids (DeAngelis and Jaques, 1973; Kim and Ritter, 1972).

6. The possible synergistic effect of the monomer and the volatile halogenated anesthetics (Nice, 1973; Newens and Volz, 1972).
7. The anesthetic used in the procedure, the anesthetic technique, and the duration of anesthesia (Modig, 1976; Zawadski et al., 1976).

2. The impact of surgical trauma induced during THA

The operative procedure of THA involves a considerable amount of trauma to both soft tissues and bony structures. Hemorrhage, soft tissue damage, laceration of bone marrow tissue under high pressure, and introduction of a foreign material such as PMM and prosthesis into living tissue, are all encountered (Modig et al., 1974).

The major traumatic event in THA is the reaming of the acetabulum and the femoral medullary canal to prepare a bed for the prosthetic implants. Reaming of the medullary cavity has been an accepted technique in orthopedic surgery for many years, however certain risks are involved with this procedure.

The medullary cavity is essentially a low pressure system with thin walled arteries, veins, and sinuses (Barron, 1979). After reaming, most of the medullary blood vessels are completely destroyed, with the resultant increase in the intramedullary pressure (Danckwordt-Lilliestrom and Lorenzi, 1970). Insertion of PMM and the femoral prosthesis in the reamed medullary cavity further increase the intramedullary pressure and values of 290 to 900 torr and higher of intramedullary pressure have been recorded (Kallos et al., 1974; Tranzo et al., 1974; Hallin et al., 1974).

Such high intramedullary pressure forces the marrow contents of crushed tissue, air, fat, and thromboplastic products, into the opened vessels in the Haversian and Volkmans canals, and via the venous drainage system of the femur into the systemic veins, the right heart (Barron, 1979; Danckwordt-Lilliestrom and Lorenzi, 1970; Kallos et al.,

1974; Hallin et al., 1974), and finally, they are trapped in the pulmonary capillaries, causing pulmonary microembolism (Modig et al., 1974; Barron, 1979).

The medullary contents have been reported to appear in the lung field within 10 to 120 seconds after insertion of PMM and the femoral prosthesis (Kallos et al., 1974). The presence of medullary contents, rich in thromboplastic products (Modig et al., 1973), in the pulmonary circulation could cause platelet aggregation and fibrin deposition in the pulmonary capillaries. The release of thromboplastic products into the systemic circulation may be involved in producing the cardiopulmonary complications observed after insertion of PMM and prosthesis into the medullary cavity (Modig et al., 1975b; Modig et al., 1974; Hallin et al., 1974).

3. Effects of THA on blood coagulation

Several investigators have reported significant changes in several blood clotting factors following THA in man. The correlation between such changes and the development of postoperative deep vein thrombosis and subsequent pulmonary embolism was high.

Houghton et al. (1978) reported significant increase in factors II, V, and VIII in blood obtained from the operated limb compared to blood obtained from the systemic circulation. These changes were attributed to damage to vessel wall after forceful manipulation, sustained retraction, and prolonged recumbency while supine. Venostasis, a major contributing factor to hemostasis disturbance, occurs during dislocation of the hip and is probably magnified by retraction to expose the acetabulum. Venous injury following THA has been confirmed experimentally in the canine model of THA (Stewart et al., 1983).

Gitel et al. (1979) found that antithrombin III decreased significantly following THA, which indicates thrombin activation and subsequent activation of the coagulation

cascade. They attributed such activation to vessel wall injury and venostasis as well as liberation of tissue thromboplastin from traumatized tissue and fat cells during the intensive surgical manipulation.

Walsh et al. (1976, 1974) reported significant increase in platelet coagulant activities following THA. These activities are capable of initiating the intrinsic coagulation pathway through two alternative mechanisms: a) by protecting active clotting factors from inactivation by their natural inhibitors and b) by catalyzing subsequent coagulation reactions.

Aaron et al. (1978) found a progressive rise in the levels of fibrin degradation products following THA, and this rise was highly predictive of subsequent development of deep vein thrombosis. At the same time, antithrombin III levels declined while levels of soluble fibrin complexes were elevated.

D. The Mechanism of Pulmonary Damage Following Physical Trauma

Physical trauma, particularly that of the musculoskeletal system, can induce pulmonary damage and deleterious effects to pulmonary functions through several mechanisms:

1. Spontaneous formation of blood-borne microaggregate

It has been recently shown that trauma is associated with spontaneous formation of blood-borne microaggregates and the amount of microaggregate was correlated well with the severity of the trauma. These microaggregates consist of fibrin, injured platelets, cellular debris, and bacteria. These microaggregates would represent a phagocytic load to the reticuloendothelial system, resulting in opsonic deficiency or consumption

They exert their deleterious effect on the lung and other end organs via microembolization (Rosoff et al., 1971).

2. Pulmonary fat embolism

Pulmonary fat embolism is one of the most serious pulmonary complications of trauma (Meek et al., 1972; Emson, 1958; Peltier, 1969). It is a pathological condition in which the smaller blood vessels of the lungs are occluded by intravascular fat globules (Ross, 1970; Meek et al., 1972). It is estimated that 90-100 per cent of patients dying shortly after sustaining fractures, have fat emboli in their lungs (Ross, 1970), and a good correlation was established between the extent of the bone injury and the appearance of the fat in the lungs (Peltier, 1965; Jacobs and McLain, 1979). These fat emboli produce significant damage to the alveolar-capillary membrane (Peltier, 1969).

In orthopedic surgery, pulmonary fat embolism is a well recognized complication, and is considered as a major cause of mortality (Miller et al., 1983; Lachiewitz and Ranawat, 1981). Thus, it appears that histological fat embolism occurs after almost every bone fracture, deliberate or accidental.

Several types of bone injuries can lead to pulmonary fat embolism: i) gross fractures of bones, particularly long bones; ii) concussion or jarring without obvious fractures; and iii) orthopedic surgery and manipulations (Scully, 1956).

a. Genesis of Post-Traumatic Pulmonary Fat Genesis of post-traumatic pulmonary fat embolism can be explained by two theories:

1) The Mechanical Theory It states that macroglobules of fat, originating in the bone marrow injured by fracture, are released directly into the venous blood stream and lodged in the pulmonary capillaries. For the mechanical theory to operate, three conditions should be available: i) ruptures of envelopes of fat, ii) tearing of

veins, and iii) local increase in the pressure that forces the fat into the venous system (Meek et al., 1972; Talucci et al., 1983; Serota, 1984; Scully, 1956; Emson, 1958). In bones, anatomical fixations of the veins to the walls of the Haversian canals are believed to prevent their collapse and to favor admission of fat into the systemic venous circulation (Serota, 1984; Scully, 1956), and pulmonary fat emboli could be detected within seconds after injury (Peltier, 1965; Emson, 1958).

2) The Biochemical Theory It proposes that the stress of trauma causes the release of catecholamines (Serota, 1984; Peltier, 1969), which mediate mobilization of free fatty acids from adipose tissue and induce coalescence of chylomicrons and other serum lipids. Fat microglobules are then formed and, as in the mechanical theory must reach the lung via the venous circulation (Meek et al., 1972; Talucci et al., 1983; Serota, 1984; Scully, 1956).

Once the fat reaches the lung it is not irreversibly trapped in the pulmonary capillaries, but rather it circulates between the pulmonary and systemic circulation, however, most of the fat is located in the pulmonary vessels. Fat emboli may reach the systemic arterial circulation, embolizing more visceral organs, via three different pathways: i) pulmonary arteriovenous shunts resulting from postembolic pulmonary hypertension (Serota, 1984), ii) the postembolization communications that develop between the pulmonary and bronchial circulations, and iii) a patent or non-functional foramen ovale that starts to function due to development of postembolic right heart hypertension.

b. Mechanism of pulmonary injury following fat embolism The consequences of pulmonary fat embolism are dependent on the extent of pulmonary vascular obstruction, reflex humoral factors, and the pre-embolic condition of the vessels. Degranulation of platelets coating the embolus will result in the release of vasoactive

substances causing local bronchial and pulmonary vasoconstriction, loss of surfactant and the development of atelectasis, increased pulmonary vascular resistance with subsequent right heart failure and cor pulmonale, and finally ischemic infarction of the lung tissue (Peterson and Goldman, 1985). Disruption of the alveolar-capillary membrane as well as extensive cytotoxic effects of Type I and II alveolar pneumocytes have been reported following pulmonary embolism (Peltier, 1969). Fat emboli can induce pulmonary injury by different mechanisms:

1) Mechanical obstruction of pulmonary vessels Simple mechanical obstruction of the pulmonary capillaries with fat globules following embolism (Peltier, 1969) will result in reduction in the cross sectional area of the pulmonary vasculature. The immediate results of such an obstruction are reduced cardiac output and tissue perfusion, increased pulmonary arterial pressure and pulmonary vascular resistance, hypocapnic bronchial constriction, ventilation/perfusion inequality, and finally hypoxemia due to opening of pulmonary arteriovenous shunts. Furthermore, neutral fat microglobules might accumulate fibrin and platelets causing microthrombi to form in the lungs, which would mediate the activation of the fibrinolytic system, with subsequent release of vasoactive amines and prostaglandins, resulting in local vasoconstriction and further obstruction to the pulmonary blood flow (Serota, 1984). Mechanical blockage of the pulmonary capillaries will lead to local hypoperfusion and alveolar cell injury due to lack of nutritional blood supply (Blaisdell et al., 1970; Peltier, 1969). Production of surfactant by these damaged cells will be compromised and atelectasis is a probability. Moreover, extravasation of protein into the alveoli from the damaged capillary wall may also inhibit surfactant activity. Mechanical obstruction and subsequent release of vasoactive mediators into the pulmonary circulation will result in pulmonary hemodynamic disturbances characterized by a widely

varying microcirculatory flow. Following pulmonary embolism, a widely dilated metarteriole-capillary networks interspersed with vasoconstricted networks are created. Local and generalized vasoconstriction is mediated by different neurohumoral mechanisms, and is opposed by vasodilation mediated by metabolic factors. The balance between the dominating vasoconstriction and the pronounced vasodilation at the level of metarteriole, creates uneven vasomotor patterns and uneven blood flow. These flow maldistributions are made worse by red cell and platelet aggregates (Shoemaker et al., 1980).

Stasis in the microcirculation secondary to the initial emboli may set the stage for further thrombosis because of endothelial cell damage distal to the emboli, or thromboplastines flushed from peripheral circulatory beds (Blaisdell et al., 1970).

2) Hydrolysis of neutral fats in the lung and release of free fatty acids

Blood lipids exist in the form of triglycerides, cholesterol, phospholipids, and free fatty acids (Gurd, 1970). The effect of trauma on fat metabolism is complex and not fully understood (Bergentz, 1968). Following severe trauma, there is a significant increase in the amount of circulating neutral fat. This fat is then hydrolized and elevated levels of circulating free fatty acids can be detected (Parker et al., 1974). Two extra sources of free fatty acids exist following trauma. First, the hydrolysis of embolic neutral fat in the pulmonary vascular bed through the action of pulmonary lipase. Pulmonary lipase is formed and released by the metabolically active alveolar pneumocytes (Peltier, 1969). Pulmonary lipases will act on those lipid layers of the embolic fat which are immobilized within the capillaries, with subsequent increase in free fatty acids concentrations at the interface between those emboli and the capillary wall. The resulting injury to the capillary wall will lead to extravasation of fat globules into the alveolar spaces (Fonte and Hausberger, 1971). The second source of circulating free fatty acids following trauma is

the free fatty acids mobilized from the systemic depots as a reaction to the stress of injury and the release of catecholamines (Frayn et al., 1985; Fonte and Hausberger, 1971; Serota, 1984; Mason et al., 1971; Bergentz, 1968; Parker et al., 1974; Peltier, 1969). Catecholamines activate the adenyl cyclase system which catalyzes the inactive lipase to active lipase. The active lipase then hydrolyzes depots triglycerides to free fatty acids and glycerol. These free fatty acids are originally mobilized from the body fat depots to meet the energy demands following trauma (Baker et al., 1971).

Several reports (Alexander and Barron, 1979; Armstrong et al., 1979; Barron, 1980) have indicated that THA in man is associated with elevated levels of free fatty acids and lipase, particularly in those patients developing postoperative deep vein thrombosis and pulmonary embolism.

The mechanism by which free fatty acids induce tissue injury is not well understood. However, it was postulated that the toxic effect of free fatty acids may be caused by displacement of lipoproteins from the cell walls and their subsequent destruction, or by removal of calcium from cell walls (Fonte and Hausberger, 1971).

Elevated levels of serum free fatty acids have been shown to cause pulmonary capillary congestion and pulmonary edema, an abnormal thickening of the alveolar-capillary membrane, and infiltration of the alveolar septa by polymorphonuclear leukocytes (Serota, 1984; Mason et al., 1971).

High levels of free fatty acids have long been known to accelerate blood clotting mechanism by activating platelet aggregation and Hageman factor (factor XII) (Mason et al., 1971; Baker et al., 1971). This effect of free fatty acids on coagulation may be amplified by catecholamines released in increased amounts under the stress of trauma. Catecholamines are known to trigger the clotting mechanism by stimulation of alpha

receptors on the blood vessel wall (Whitaker et al., 1969). Epinephrine may also activate factor V (Forwell and Ingram, 1957). Recently, the concept of pulmonary damage induced by elevated levels of plasma free fatty acids have been challenged. Many studies showed that pulmonary microvascular damage following fat embolism may be attributed to intravascular coagulation and the resultant fibrin entrapment in the pulmonary capillaries and leuckocytosis, rather than the result of increased circulating fatty acids levels (Serota, 1984; Barie et al., 1981; Barie and Malik, 1982).

Whether fat embolization represents only a superimposition without direct pathogenetic importance or whether it is a central factor in the pulmonary damage, is not yet known (Serota, 1984; Alho, 1982).

3) The surfactant system of the lung The alveoli of the mammalian lung are coated with an alveolar lining layer, and the pulmonary surfactant is one component of this layer (Kuroki et al., 1986). The physiologic function of this layer is to decrease the surface tension at end-expiration, preventing atelectasis, and to increase surface tension at the end of inspiration, facilitating elastic recoil (Avery et al., 1986). By doing so, the surfactant system reduces the work of breathing by reducing the surface tension at the air-alveolar interface, and it also tends to keep the alveoli dry by reducing the tendency of fluid movement across the alveolar-capillary membrane into the alveolar spaces (Hills, 1981). The pulmonary surfactant is synthesized in alveolar Type II pneumocytes and secreted into the alveolar spaces (Kuroki et al., 1986), and its deficiency results in alveolar collapse at end-expiration and progressive ventilatory failure (Strayer et al., 1986). A pathological condition called respiratory distress syndrome (RDS) develops in premature infants with immature lungs deficient in pulmonary surfactant. The pulmonary surfactant system is rich in phospholipids, particularly dipalmitoyl phosphatidylcholine (Kuroki et al.;

1986; Avery et al., 1986; Smith, 1983). Some pathological as well as non-pathologic conditions are known to change the activity of the pulmonary surfactant system. Interstitial lung disease may change pulmonary surfactant because of direct damage to Type II pneumocytes, or their proliferation (Baker et al., 1986). In patients undergoing cardiopulmonary bypass, pulmonary surfactant activity may be inhibited because of leaking of plasma components into the air spaces, through the leaking lung membranes, causing lung collapse and edema (Phang and Keough, 1986). In pulmonary embolism, blood supply to different lung segments are interrupted. Interference with blood supply causes a decrease in metabolic activity of Type II alveolar pneumocytes, with subsequent depletion of surfactant. Surfactant deficiency may be responsible for the abnormal respiratory function tests and chest radiographs associated with pulmonary embolism (Smith, 1983; Sutnick et al., 1969). Direct contact between neutral fats or their hydrolized products, free fatty acids, and the phospholipid layer within the alveolar spaces, inhibits surfactant activity with the resultant changes in lung mechanics (Peltier, 1969). Surfactant abnormalities has been reported as a major contributing factor to the pathophysiology of trauma and shock. Impared lung mechanics associated with traumatic shock have been attributed to the loss of elasticity of the alveolar surfactant film (Petty et al., 1977). Abnormal chest radiographs, characterized by discoid atelectasis (Coventry et al., 1974, Daniel et al., 1972), as well as significant changes in pulmonary function have been reported in man following THA. The possibility of toxic damage to the surfactant system have been explored as an explanation of some of these changes (Rinecker, 1980).

c. Elimination of fat emboli from the pulmonary circulation Several mechanisms exist to eliminate fat emboli out of the pulmonary circulation (Emson, 1958; Gurd, 1970; Serota, 1984): i) hydrolysis of the emboli by pulmonary lipases into free fatty

acids and glycerol; ii) lysis of the fibrin elements, trapped in the fat particles, by the fibrinolytic system into fibrin degradation products; iii) elimination by phagocytosis by macrophages; iv) expectoration of fat particles extravasated into the alveolar spaces; and v) crossing of fat particles, through the pulmonary vascular bed, into the systemic circulation, which may be removed with urine, or embolize other systemic organs (brain, kidney, etc.).

3. Activation of the cascade system

The cascade system is a system which is activated sequentially. The coagulation, fibrinolytic, kallikrein-kinin, and the complement system are all cascade systems, closely related, and activation of one system will lead to sequential activation of the other systems. Trauma can activate the cascade system through four different pathways (Risberg and Heidman, 1980):

1. Thromboplastic products will be released from traumatized tissue and fat cells (Modig et al., 1976; Saldeen, 1969), with subsequent activation of the coagulation system through the external pathway. Several studies (Blaisdell et al., 1970; Bergentz, 1968) reported a significant decrease in several coagulation factors following trauma, particularly factors II, V, VII, VIII, X, and platelet counts. This decrease is followed by a significant increase in fibrinolysis and plasminogen activation. These results suggest consumption coagulopathy, intravascular coagulation, and the resultant activation of the fibrinolytic system.

   Intravascular coagulation can produce several pathological changes in the lung. These changes consist of pulmonary congestion and edema, hemorrhage, atelectasis, microthrombi formation and entrapment in pulmonary capillaries, and finally, hyaline membrane formation (Serota, 1984; Mason et al., 1971).

Furthermore, procoagulants released from traumatized tissue into systemic circulation, can induce clotting in the pulmonary circulation itself, or adding thrombus to previously deposited emboli (Blaisdell et al., 1970).

The end result of the embolic process in the pulmonary circulation (thromboemboli and fat emboli) is the loss of microcirculatory integrity due to ischemic damage to the endothelial cells and basement membrane (Blaisdell et al., 1970). This damage was found to be more pronounced in the area of the pulmonary capillary bed (Sturm et al., 1986; Parker et al., 1974). Recent studies showed that the magnitude of tissue thromboplastin release and pulmonary microembolism were significantly correlated to the degree of pulmonary dysfunction and damage following trauma (Modig et al., 1976).

2. The fibrinolytic system will be triggered by thromboemboli trapped in pulmonary capillaries. Plasmin, a proteolytic enzyme that digests fibrin, will be formed in increased amounts from its precursor plasminogen following activation of the fibrinolytic system. Local fibrinolysis in the lung causes rapid breakdown of fibrin in the pulmonary vessels (Saldeen, 1969), with subsequent formation of toxic fibrin degradation products. Levels of fibrin degradation products are always elevated following trauma (Blaisdell et al., 1970).
3. The complement system is activated by plasmin generated during activation of the fibrinolytic system. Generation of plasmin will result in cleavage of complement proteins and formation of complement-derived chemotactic and leukocyte-aggregating peptides, C3a and C5a, and activation of the complement system (Stormorken, 1979). The complement system is activated in the early post-

traumatic phase, with the resultant formation of protein fractions which have different biological effects, resulting in cell lysis and destruction.

4. The kallikrein-kinin system is activated through several pathways. The most important pathway is through activation of Hageman factor and plasmin, resulting from post-traumatic activation of the coagulation and fibrinolytic systems. They will act on prekallikerin converting it to kallikerin. Plasma kallikerin will act on high molecular weight kininogen, converting it to bradykinin. Bradykinin causes pulmonary edema by increasing pulmonary capillary permeability. Bradykinin is inactivated in the pulmonary circulation by the action of angiotensin converting enzyme located on the surface of the pulmonary vascular endothelium. The edematogenic effect of bradykinin on the lung may be amplified by the lack of its inactivation in the pulmonary circulation following postembolic pulmonary endothelial damage.

The different cascade systems are all activated post-traumatically and are not only involved in the systemic response to trauma, but also in the specific pathological changes taking place in the lungs (Risberg and Heidman, 1980). Recent studies showed that postembolic pulmonary damage is due to activation of different cascade systems (Barie et al., 1981; Barie and Malik, 1982), however, the specific role of these systems in inducing pulmonary injury remains to be evaluated (Risberg and Heidman, 1980).

4. Release of vasoactive and bronchiactive compounds

The deleterious effects of trauma on the lungs is probably mediated by the release of several potent smooth muscle active substances from different sources:

1. Histamine is released from pulmonary tissue damaged by vascular obstruction or by peptides released during activation of the coagulation system (Modig et al., 1976; Blaisdell et al., 1970).
2. Serotonin released by thrombin from platelet coating of the emboli (Blaisdell et al., 1970; Rosoff et al., 1971; Peltier, 1969). Beside its effects on vascular and bronchial smooth muscles, serotonin can cause aggregation of blood elements as early as 15 minutes after trauma, promoting further microthrombi formation and occluding more pulmonary capillaries (Swank et al., 1964). The deleterious effects of serotonin on the lung may be aggravated by depression of its uptake and metabolism (Flink et al., 1982) by the damaged pulmonary endothelium. Depression of serotonin uptake and metabolism following post-traumatic microembolization may be due to: i) changes in pulmonary blood flow and its regional distribution; ii) decreased available surface area for exchange due to mechanical obstruction; iii) endothelial injury following microembolization; and iv) saturation of serotonin uptake mechanism due to its postembolic overproduction in the pulmonary circulation. It was suggested that serotonin might be the agent responsible for the reflex and direct cardiopulmonary changes associated with pulmonary embolism (Rosoff et al., 1971).
3. Fibrin degradation products are released during activation of the fibrinolytic system. They induce pulmonary vascular injury via neutrophil sequestration and activation in the pulmonary vessels, with the resultant release of toxic oxygen radical (Malik, 1985).

Vasoactive and bronchiactive compounds can induce acute lung damage by several mechanisms:

1. Alveolar constriction with the resultant increase in airway resistance and work of breathing, and decrease in lung compliance.
2. Pulmonary vasoconstriction and subsequent increase in both pulmonary arterial pressure and pulmonary vascular resistance.
3. Increase in pulmonary vascular permeability and development of pulmonary edema.

5. Mechanism of pulmonary repair following acute damage

The lungs have remarkable ability to recover from serious damage. This is possible due to the rapid regeneration and differentiation of Type II alveolar pnuemocytes into Type I cells, repairing the alveolar lining with its coat of phospholipids in a few days (Bachofen and Weibel, 1974; Peltier, 1969). The lung parenchyma is also protected against postembolic infarction by having three sources of oxygen supply. These are: the pulmonary arteries, the bronchial circulation, and direct diffusion of oxygen from the alveolar spaces (Peterson and Goldman, 1985).

III. MATERIALS AND METHODS

A. Experimental Design

Thirty-one mature mongrel dogs weighing 15-22 Kg, heartworm free, were obtained from Laboratory Animal Resources at Iowa State University. Heartworm evaluations were confirmed again during post mortem examination. All animals were fasted for 12-18 hours before the experiment.

A simple split plot design was used in which the thirty-one experimental animals were randomly divided into four unequal groups. Group I consisted of nine dogs on which THA was performed utilizing PMM bone cement.* Group II consisted of eight dogs on which THA was performed utilizing Play Dough† (PD) as a control for PMM. PD is a soft, non-toxic polysaccharide dough. It was chosen as a control for PMM because of its similar thickening consistency, malleability, and handling properties to PMM. Group III, representing massive surgical trauma induced during THA procedure, consisted of eight dogs on which Sham THA Surgery (SS) was performed. The Sham procedure included all muscle and bone exposures, manipulation, and preparation except no cementing material was used. Group IV consisted of six dogs on which no THA surgical procedure was done; however, blood vessels were surgically exposed and cannulated for the purpose of physiological monitoring of the cardiopulmonary functions during the experiment. This group served as a control (C) to study the effects of anesthesia alone on

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*Surgical Simplex P, Howmedica, Inc., Rutherford, N.J.

†Play-Doh, Kenner Products, Cincinnati, OH.

the cardiopulmonary functions during the lengthy procedure of THA. Surgical approach to the first three groups (PMM, PD, and SS) was unilateral, with either the right or the left hip operated on.

A pilot study was performed prior to the actual study in which eight dogs were utilized. The objectives of the pilot study follow:

1. To gain the necessary surgical skills and knowledge required to perform the complicated orthopedic procedure of THA.
2. To time different stages of the procedure (muscle exposure, reaming the acetabulum and femur, as well as recording of different physiological parameters).
3. To coordinate the process of sample collection at different stages of the surgical procedure.
4. To test the efficiency of different monitoring equipment and computers during the experiment.
5. To estimate the total blood loss during surgery for subsequent fluid replacement in the actual study.
6. To obtain experience with the general response of the cardiopulmonary system to different stages of the procedure.

In two of the pilot study dogs, bilateral THA was performed for the sake of practice. In all of the pilot study animals, THA was performed utilizing PMM bone cement. No data from any pilot study animals were included in the present study.

B. Experimental Procedures

All animals were anesthetized with sodium pentobarbital (25 mg/Kg, iv) initially. Subsequent administration of small bolus doses was continued throughout the experiment to maintain the animals under a light surgical plane of anesthesia. The depth of anesthesia

was determined by monitoring different cardiopulmonary parameters as well as peripheral reflexes (pain reflex and jaw tone). Intravenous anesthesia was favored over inhalation anesthesia to avoid any interference in the proposed study of lung mechanics and gas exchange.

1. Lung mechanics and gas exchange

After induction of anesthesia, the dogs were intubated with cuffed endotracheal tube, and strapped in lateral recumbency on a thermal pad. The endotracheal tube was connected to a pneumotachograph and a differential pressure transducer as well as an oxygen analyzer and carbon dioxide analyzer. The differential pressure transducer as well as O_2 and CO_2 analyzers were subsequently connected to a Beckman recorder. This setup was utilized to measure oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and air flow (AF). Air flow was then electrically integrated to give tidal volume (TV). Detailed description of the system, formulas, and calibrations procedures have been reported elsewhere (Baker, 1986).

An esophageal catheter, connected to a Statham transducer and a Beckman recorder, was inserted into the esophagus to measure the esophageal pressure (EP) as representative of the intrapleural pressure (IP). The tip of this catheter was located at the level of the thoracic inlet and verified by the characteristic waveform.

2. Systemic and pulmonary hemodynamics

A two-inch incision was made in the femoral triangle of the opposite limb to the operated one. The femoral artery and vein were identified, isolated, and cannulated with a double lumen Swan-Ganz thermodilution catheters. The tip of the arterial catheter was located in the left ventricle to measure the left ventricular pressure (LVP), while the proximal port was located in the aortic arch to measure aortic pressure (AoP) as

representative of the systemic arterial pressure (SAP). The location of each port was verified by the characteristic waveforms of both the left ventricle and the aortic arch. The arterial catheter was also used to obtain anaerobic arterial blood samples for blood gas analyses.

The tip of the venous catheter (thermodilution catheter) was located in the pulmonary artery to measure the pulmonary arterial pressure (PAP). The location of the tip of this catheter was verified by the characteristic waveform of the pulmonary artery. The venous catheter was also utilized to measure cardiac output (CO) by thermodilution technique and to obtain mixed venous blood for blood gases analysis and hemoglobin determination by cyanmethemoglobin method (Davidsohn and Nelson, 1969). When difficulties were encountered cannulating the pulmonary artery through the femoral vein, the external jugular vein was then exposed and cannulated as an alternative route to the pulmonary artery.

All pressure catheters were connected to Statham pressure transducers and a Beckman recorder. All vascular catheters were kept patent by frequent flushing by heparinized saline solution (10 iu of heparin/ml), particularly before each recording period.

Cardiac output was measured by a thermodilution cardiac output unit connected to the Swan-Ganz pulmonary arterial catheter, and the proximal port of that catheter was utilized to inject the cold saline solution. Figure 1 shows a block diagram of the experimental setup and different recording systems.

3. Recording procedures

Lung mechanics and gas exchange parameters as well as systemic and pulmonary hemodynamic parameters were recorded on the Beckman recorder, and were processed by a microcomputer through an A/D convertor (analog to digital). Figure 2 shows a typical

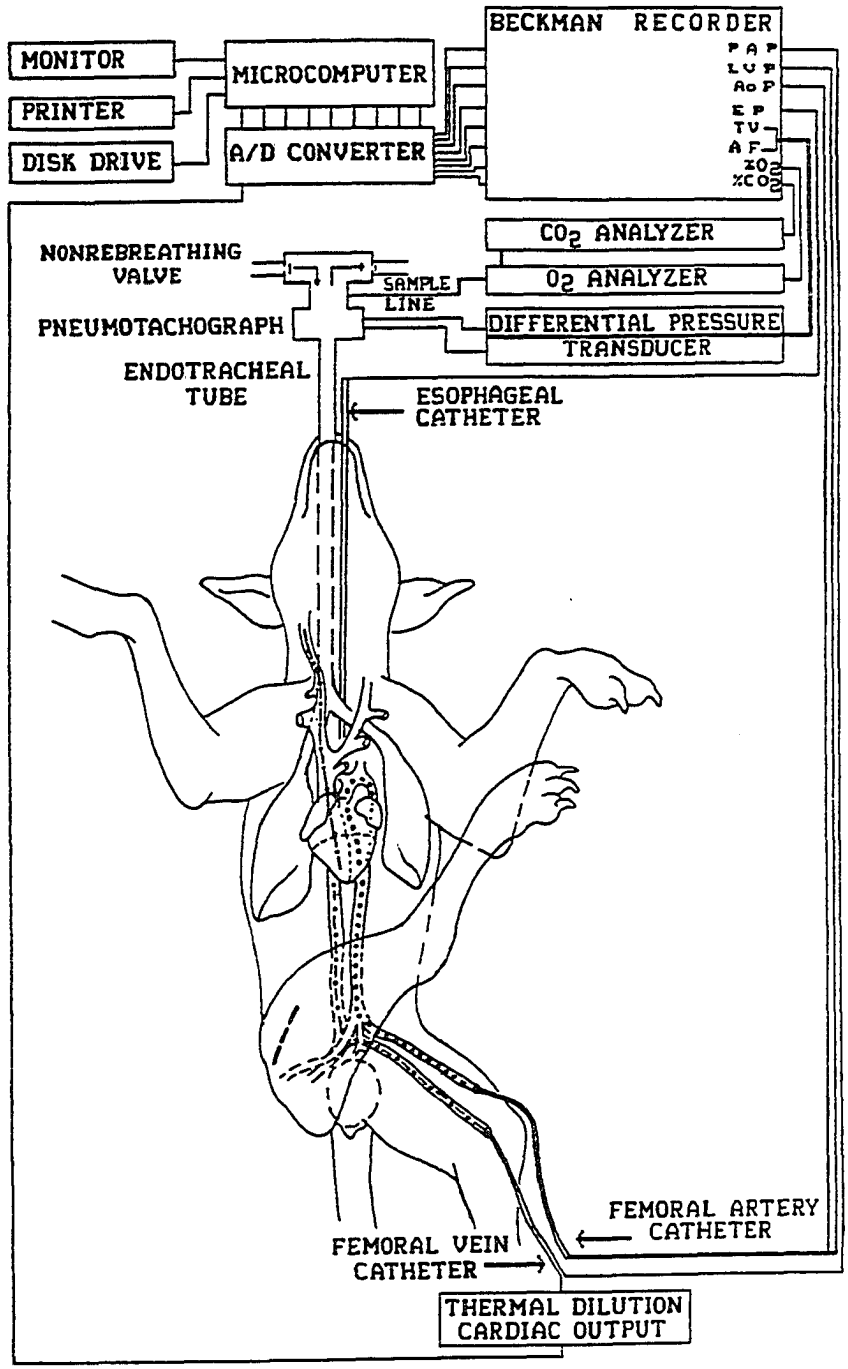


Figure 1. Block diagram of the experimental setup and different recording systems

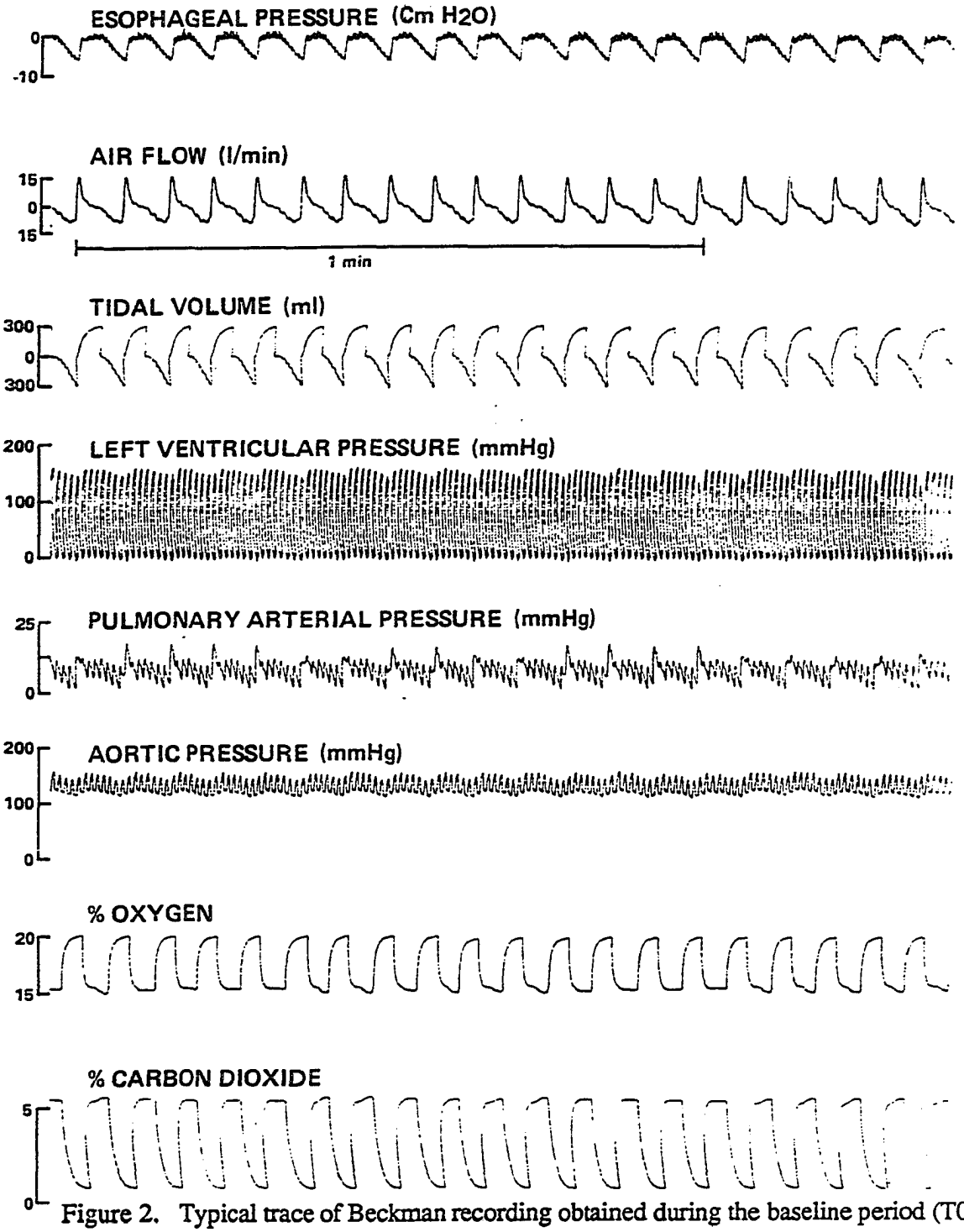


Figure 2. Typical trace of Beckman recording obtained during the baseline period (T0)

Beckman recording obtained during the base line period (T0). Data from the thermodilution cardiac output unit were processed directly by the microcomputer through the A/D converter. This system allowed us to obtain an online numerical data of all the parameters recorded. Utilizing standard formulas, the microcomputer was programmed to derive several other physiological parameters from the originally recorded parameters: cardiac index (CI), stroke volume (SV), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), heart rate (HR), myocardial contractility (DP/DT), minute ventilation (MV), lung compliance (LC), airway resistance (AWR), and work of breathing (WB).

Standard formulas, operation and calibration of different monitoring equipment and electronics, as well as programming of the computer, have been discussed in detail (Engwall, 1986; Engwall, 1980).

4. THA procedure

THA was performed according to a technique described by Olmstead et al. (1981). The amount of blood loss during the procedure was minimized by using surgical electrocautery unit and careful manipulation of the tissues. To avoid hypovolemia resulting from blood loss during the procedure, fluid replacement was initiated with normal saline solution. An amount of 180 ± 60 ml of normal saline solution was infused throughout the procedure through a vena catheter inserted in the cephalic vein. Only PMM, PD, and SS groups received iv saline infusion, group C (control, no THA) did not receive any since blood loss was not anticipated. The amount of replacement fluid used in this study was approximately the same amount of blood lost measured in the pilot study. While using the surgical electrocautery, all the recording equipments and other electronic devices were shutdown momentarily to avoid electrical interferences with the recording signals.

5. Recording periods

Each experiment was divided into 7 different stages, T0-T6. Figure 3 shows a block diagram of the different stages of the experiment and the different recording periods. For group SS, since no cementing was done, a period of 20 minutes was elapsed between T2 and T3. For group C, since no surgery was done, recording periods T0 to T6 were recorded according to the time intervals shown in Figure 3. These time intervals were approximated from those measured in the pilot study. At each recording period, a full set of the following parameters were recorded:

1. lung mechanics and gas exchange,
2. systemic and pulmonary hemodynamics, and
3. arterial and mixed venous blood gases.

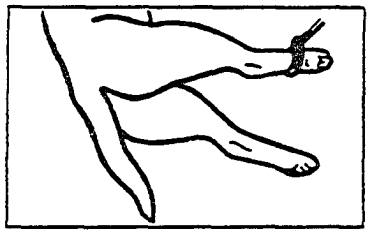
Also, a full set of other physiological parameters calculated from the originally recorded parameters was obtained.

6. Blood gas analyses

Anaerobic arterial and mixed venous blood samples were collected in heparinized syringes, placed immediately in an ice bath, and analyzed later on a 513 Blood Gas Analyzer (Instrumentation Laboratories). The following blood gases parameters were measured in each blood sample: pH, partial pressures of oxygen (PO_2), and partial pressure of carbon dioxide (PCO_2). The following parameters were calculated by the blood gas machine utilizing the measured parameters: base excess (BE), bicarbonate (HCO_3-), and total carbon dioxide (TCO_2).

7. Histopathological study

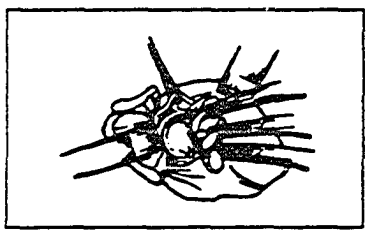
At the end of each experiment, the animal was killed with an iv injection of a saturated solution of magnesium sulfate (20-30 ml). Death was verified by termination of



T_0

BEFORE THE BEGINNING
OF THE EXPERIMENT

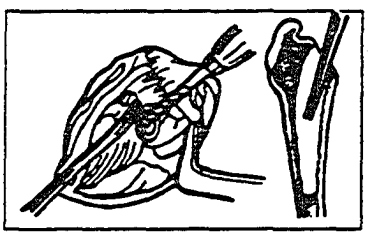
0 MINUTES



T_1

AT THE END OF SOFT
TISSUE TRAUMA :
a) SKIN INCISION
b) MUSCLES SEPARATION
c) EXPOSURE OF THE JOINT
d) OPENING OF JOINT CAPSULE

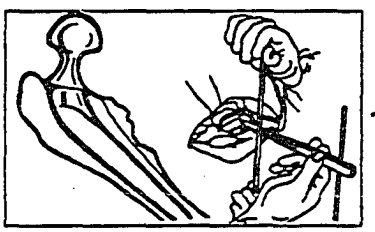
45 MINUTES



T_2

AT THE END OF BONE TRAUMA:
a) SEVERING OF THE ROUND
LIGAMENT
b) FEMORAL HEAD AND NECK
OSTEOTOMY
c) REAMING FEMORAL SHAFT
d) PREPARING ACETABULAR BED

85 MINUTES



T_3

AT THE END OF IMPLANTATION:
a) SEATING OF ACETABULAR CUP
(PMM OR PD)
b) INSERTION OF FEMORAL
ENDOPROSTHESIS (PMM OR PD)

105 MINUTES

T_4

15 MINUTES POSTOPERATIVELY

120 MINUTES

T_5

30 MINUTES POSTOPERATIVELY

135 MINUTES

T_6

45 MINUTES POSTOPERATIVELY

150 MINUTES

Figure 3. Block diagram of different stages of the experiment and recording periods

the cardiopulmonary functions. The lungs and heart were then removed from the thoracic cavity through a ventral midline sternotomy incision, and examined grossly. A lung lobe was randomly selected, excised, and immersed in a jar containing 10% buffered formaldehyde solution. At the same time, the stem bronchus of that lobe was cannulated and perfused with the same solution under physiological pressure (25-30 cm H_2O) until nearly full inflation was achieved.

Following 24 hours of refrigeration, eight blocks of lung tissue from each animal were randomly cut and processed for light microscopic examination according to standard histopathological techniques. Four sections were stained with Hematoxylin and Eosin (H & E) for routine histopathological examination. The other four sections were stained with a lipid specific stain, oil-red-O. These four sections were utilized for quantitative estimation of fat emboli in the lung.

8. Quantitative analysis of pulmonary fat

The large variability in the shapes and sizes of the fat globules observed within each lung section, made it very difficult to use conventional quantitative histopathological techniques for fat (number of fat globules per microscopic field). These techniques have been utilized before to study pulmonary fat embolism following THA in man (Sevitt, 1972). The statistical errors that may be created if lung fat was quantitated by conventional techniques, had forced us to find a different, more reliable, quantitative technique with less errors. Accordingly, a Zeiss image analysis system was utilized in order to avoid the errors that may be created by counting fat globules of different shapes and sizes.

In each of the four lung sections (from each animal) stained with oil-red-O, five microscopic fields were randomly selected by an anatomist (Dr. C. Jacobson, Department of Veterinary Anatomy, Iowa State University), who was not familiar of the nature of the

project, for quantitative estimation of fat particles. A total of 20 microscopic fields of lung tissue from each animal were then subjected to image analysis by Zeiss Image Analysis System. The system was programmed to discriminate between the bright red color of fat particles, and the surrounding parenchymal tissue (stained blue). In each field, two different images were measured in square millimeters: a) the fat particles stained red and b) the total area of the field, excluding air spaces, occupied by both fat and parenchymal tissue. The ratio between the dimension of fat and total area was computed, and expressed as percent fat per low power microscopic field. Image analysis techniques have been described elsewhere (Schwarz, 1986).

9. Ultrastructural study

Lung tissue from a total of eight randomly selected dogs, two animals from each experimental group, were processed for the electron microscopic (EM) study according to techniques previously described (Hayat, 1970). At the end of the experiment, animals selected for EM study were given additional sodium pentobarbital to depress the cardiopulmonary functions significantly. The depth of anesthesia was verified by monitoring different cardiopulmonary parameters. The thorax was opened through a ventral midline sternotomy incision, and a lung lobe was randomly selected. The blood vessels and the stem bronchus to that lobe were identified, occluded by a Satinsky cardiovascular clamp then severed with a scalpel blade and immediately immersed in a 4% glutaraldehyde solution. The principal bronchus was cannulated and perfused with 4% glutaraldehyde solution as previously discussed. The animal was then killed with an iv injection of magnesium sulfate. This procedure was followed to avoid most of the ultrastructural changes subsequent to post mortem damages.

10. Collection and processing of the Alveolar Lining Material (ALM)

Collection of ALM began as soon as the lungs were removed from the thoracic cavity, and before collecting tissue for histopathological study. In animals selected for ultrastructural study, lung tissue was collected first then the rest of the lung was lavaged. Utilization of Satinsky cardiovascular clamp prevented contamination of ALM with red blood cells.

The lung was lavaged by 500 ml of normal saline solution. A cuffed endotracheal tube was introduced into the trachea and advanced into the right or left principal bronchus. The cuff was then inflated, and the tube was then connected to a saline reservoir 30 cm above the level of the lung. The saline was then introduced into the lung in small increments, about 50-75% of the tidal volume, and collected in small increments to avoid alveolar rupture and subsequent contamination of the ALM with blood cells. However, accidental contamination with red blood cells occurred in several samples and they were automatically excluded from the study. The lavage fluid was then centrifuged for 15 minutes at 2000 rpm to eliminate cellular debris and mucus. The supernatant fluid was recentrifuged at 20,000 rpm for another 60 minutes, and the supernatant fluid was discarded. The ALM was then gently collected from the bottom of the centrifuge tube, lyophilized and stored in a dark cold place until analyzed. Phospholipids were extracted from the lyophilized ALM in chloroform/methanol solution (2:1, v/v). The extract was washed with 0.74% aqueous potassium chloride solution to remove traces of nonlipid contaminants. The isolated chloroform fraction was then evaporated at 47°C under a stream of nitrogen. The moist residue was redissolved in 2 ml chloroform/methanol (1:1, v/v) and stored under nitrogen at -20°C for further analysis. Quantitative identification of the major fractions of phospholipids components of ALM was done utilizing High Pressure

Liquid Chromatography (HPLC) system according to the modified technique of Kaduce et al. (1983) which is described in Engwall (1986). These fractions included phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), and phosphatidylserine (PS). Values of different phospholipid fractions of ALM were expressed as a percentage of the total phospholipid contents of the ALM.

C. Statistical Analysis

In order to correct for (and to reduce) the variability between the animals at the beginning of the experiment, T0 of all physiologically recorded parameters was utilized as a covariate in the statistical analysis. In PMM, PD, and SS groups, since all animals went through the same steps between T0 and T2 of THA procedure, values of T0 to T2 of all the animals in these three groups were treated as one group. This procedure was not followed with group C (control group) since no surgical trauma was done on this group. Statistical analysis was done on all recorded physiological parameters of the four experimental groups in two steps. In the first step, values of recording periods T0 to T2 were statistically analyzed. In the second step, values of recording periods T3 to T6 were analyzed.

This procedure of analysis was performed to separate the effect of surgical trauma on different physiological parameters from the effect of post implantation period on the same parameters, and to allow us to study separately the effect of surgical trauma alone.

A General Linear Model (GLM) analysis procedure was run on the values of each recording period to test for a treatment difference. Values of different recorded physiological parameters were expressed as Least Square Mean ± Standard Error of Least Square Mean (LSM ± SELSM).

Student's t test was run on the values of the two studies described below to test for treatment difference:

1. The image analysis study of pulmonary fat emboli to test for differences in per cent fat between the experimental groups;
2. The ALM study, to test for differences in the phospholipid components of the ALM between the experimental groups.

Values for the latter two studies were expressed as Mean ± Standard Error of the Mean (M ± SEM).

For all studies, (P) value of less than 0.05 was considered as a statistically significant difference between the experimental groups. A (P) value of more than 0.05 but less than 0.1 was considered as approaching significance for a difference between the experimental groups.

All graphs presented in this study were plotted by the TELL.A.GRAPH computer system at Iowa State University Computation Center. All data presented in figure form are also presented in tables in the Appendix.

The figures showing trends were presented without imposing statistical significant points. Therefore, all important statistical comparisons are presented in the text and listed in the tables in the Appendix.

IV. RESULTS

A. Post Mortem Examination of Experimental Animals

Post mortem examination of the lungs of the thirty one dogs did not reveal any significant pathological changes. Occasionally, patchy areas of atelectasis were observed in the dependent lung lobes. These atelectatic areas were observed in several animals in all four groups and were consistently located in the dependent lung lobes, consequently they were considered as having no pathological significance.

B. Histopathological Study of Pulmonary Tissue

Microscopic examination of lung tissue stained with H & E revealed no significant histopathological changes in any of the four experimental groups.

Microscopic examination of lung sections stained with oil-red-O revealed varying numbers of bright, red stained fat globules of different sizes and shapes. These fat globules were detected in every lung section examined in both PMM and PD groups, and in most lung sections of SS group. No fat globules were detected in C group (control group). These fat globules were randomly distributed throughout the microscopic field and they were located in the intravascular spaces of the pulmonary arterioles and capillaries. Plate 1 consists of photomicrographs of lung sections representing the four experimental groups, stained with oil-red-O where fat globules stained bright red. Plate 2 contains photomicrographs of lung sections representing the same four groups, stained with osmic acid where fat globules stained black (obtained during processing of lung tissue for the EM study). In these sections, pulmonary arterioles and capillaries were plugged and distended

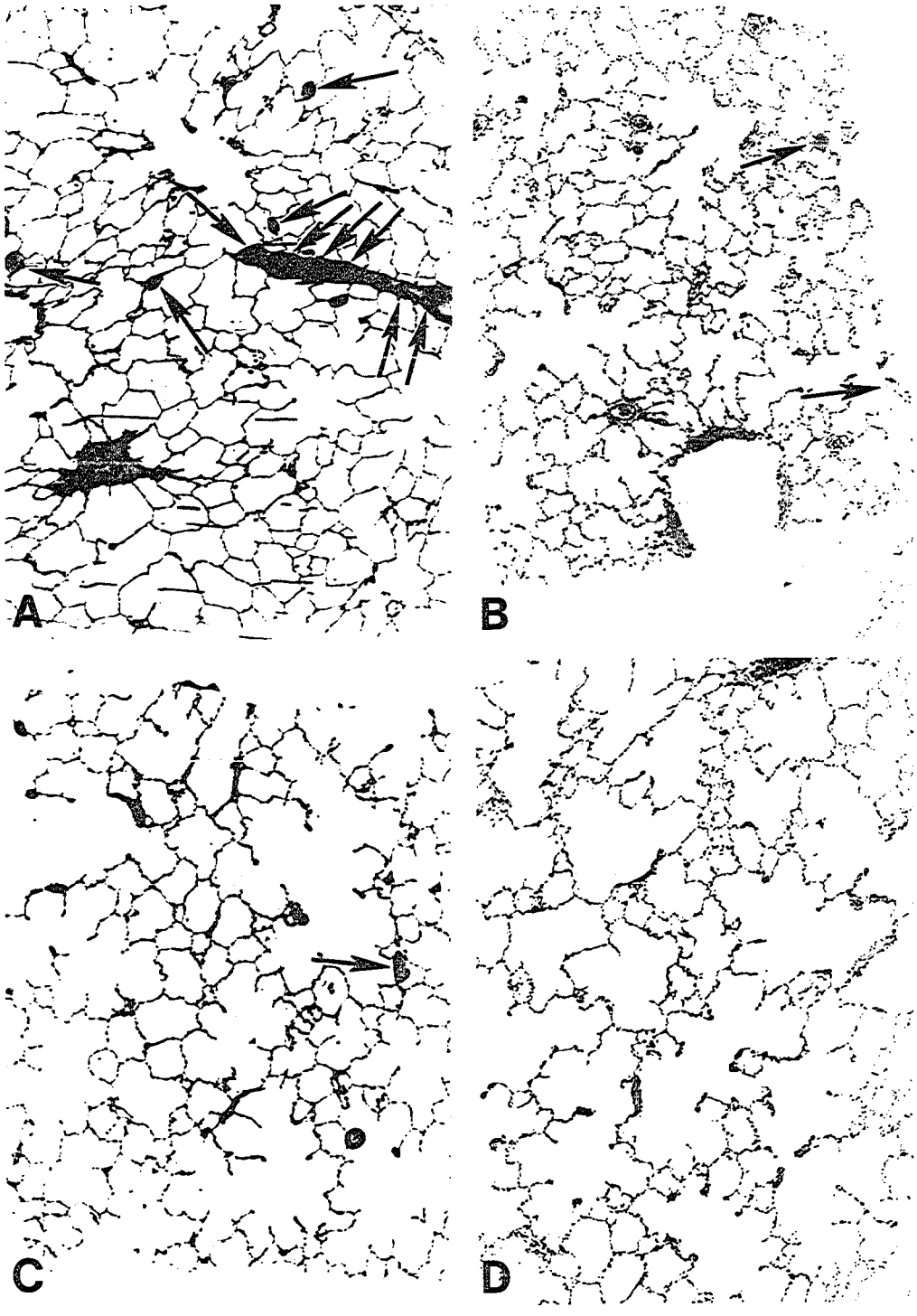
Plate 1. Photomicrographs of lung sections from the four experimental groups at the end of the experiment illustrating pulmonary fat emboli (arrows) (oil-red-O X 60)

A. PMM group
B. PD group
C. SS group
D. C group


A
B

Plate 2. Photomicrographs of lung sections from the four experimental groups at the end of the experiment illustrating pulmonary fat emboli (arrows) (osmic acid. X 60)

A. PMM group
B. PD group
C. SS group
D. C group


A
B
C
D

with round or oval fat globules. At the periphery, the vessel walls and their endothelial linings were tightly compressed, suggesting great tension.

C. Quantitative Analysis of Pulmonary Fat Emboli

Image analysis study of pulmonary fat showed that lung tissue from PMM group contained significantly more fat particles, on the bases of per cent fat per low power microscopic field, than the other three groups ($p<0.05$). There was not any significant difference between PD and SS groups in pulmonary fat contents. However, PD group was significantly higher than the control ($p<0.05$), and SS group was approaching significant difference from control ($p<0.1$) (Figure 4 and Table A1).

D. Ultrastructural Study

EM study of lung tissue revealed the following:

1. Platelet adhesions to the capillary wall and platelet degranulation in PMM group (Figure 5 and 6).
2. PMM group also showed endothelial blebs (ballooning), and endothelial cell rupture (Figure 7).
3. PMM group (Figure 8) and PD group (Figure 9) both showed an engorgement of the pulmonary capillaries with electron-dense material (fat microemboli), as well as ruptures and mechanical tears in the capillary wall and endothelium, exposing the thrombogenic subendothelial layer.
4. SS group (Figure 10) and C group (Figure 11) both showed no significant ultrastructural changes with normal alveolar-capillary membrane, and granulated, non-adhering platelets freely moving in the capillary lumen.

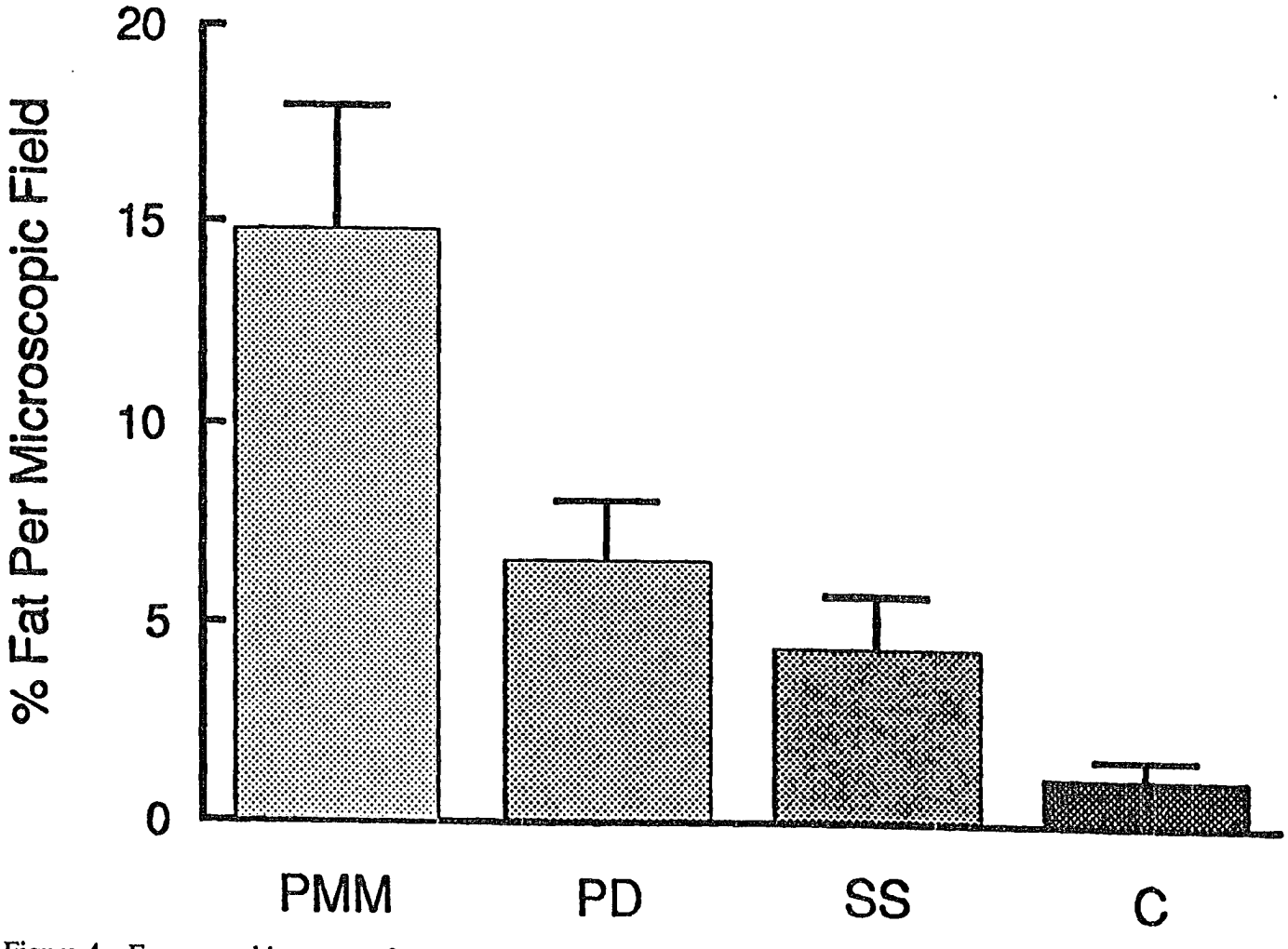


Figure 4. Frequency histogram of per cent fat per low power microscopic field of lung tissue in the four experimental groups at the end of the experiment

Figure 5. Electron micrograph of a canine lung (PMM group) illustrating a platelet (P) adhering to a capillary wall (arrows) (X 15,700)

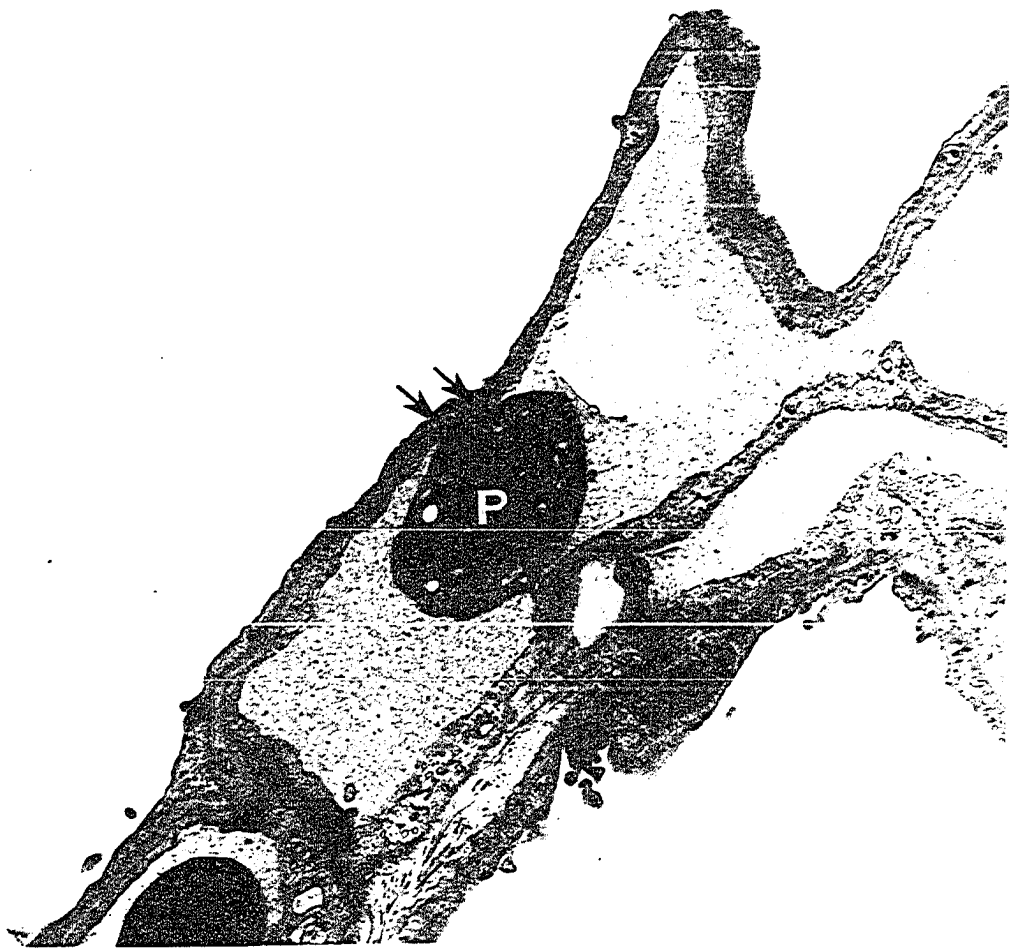

P

Figure 6. Electron micrograph of a canine lung (PMM group) illustrating a degranulated platelet (P) with empty vacules (V) as well as adhesions between the platelet and the capillary wall (arrows) (X 71,600)

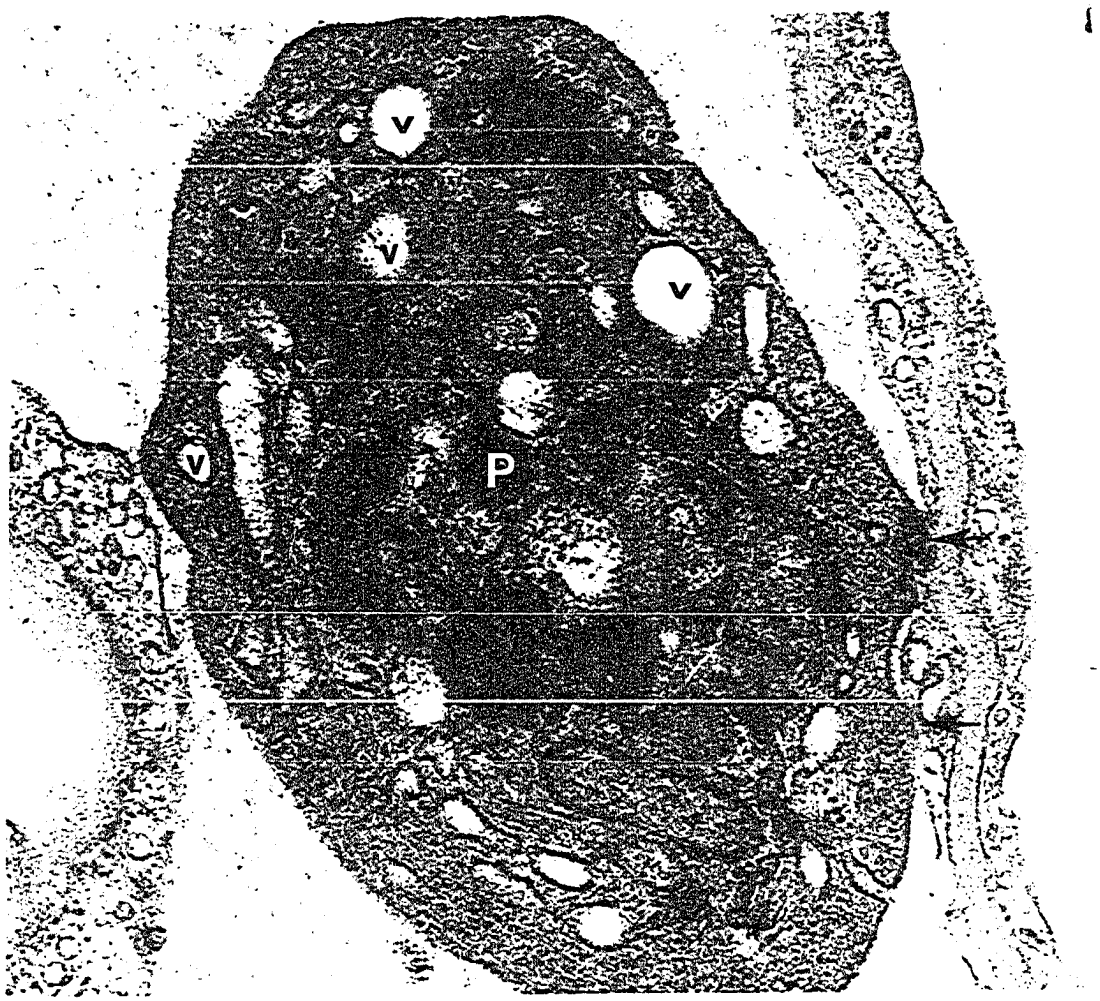

V
V
V
V
P

Figure 7. Electron micrograph of a canine lung (PMM group) illustrating endothelial blebs (ballooning) (B) and endothelial cell rupture (arrow) (X 71,600)

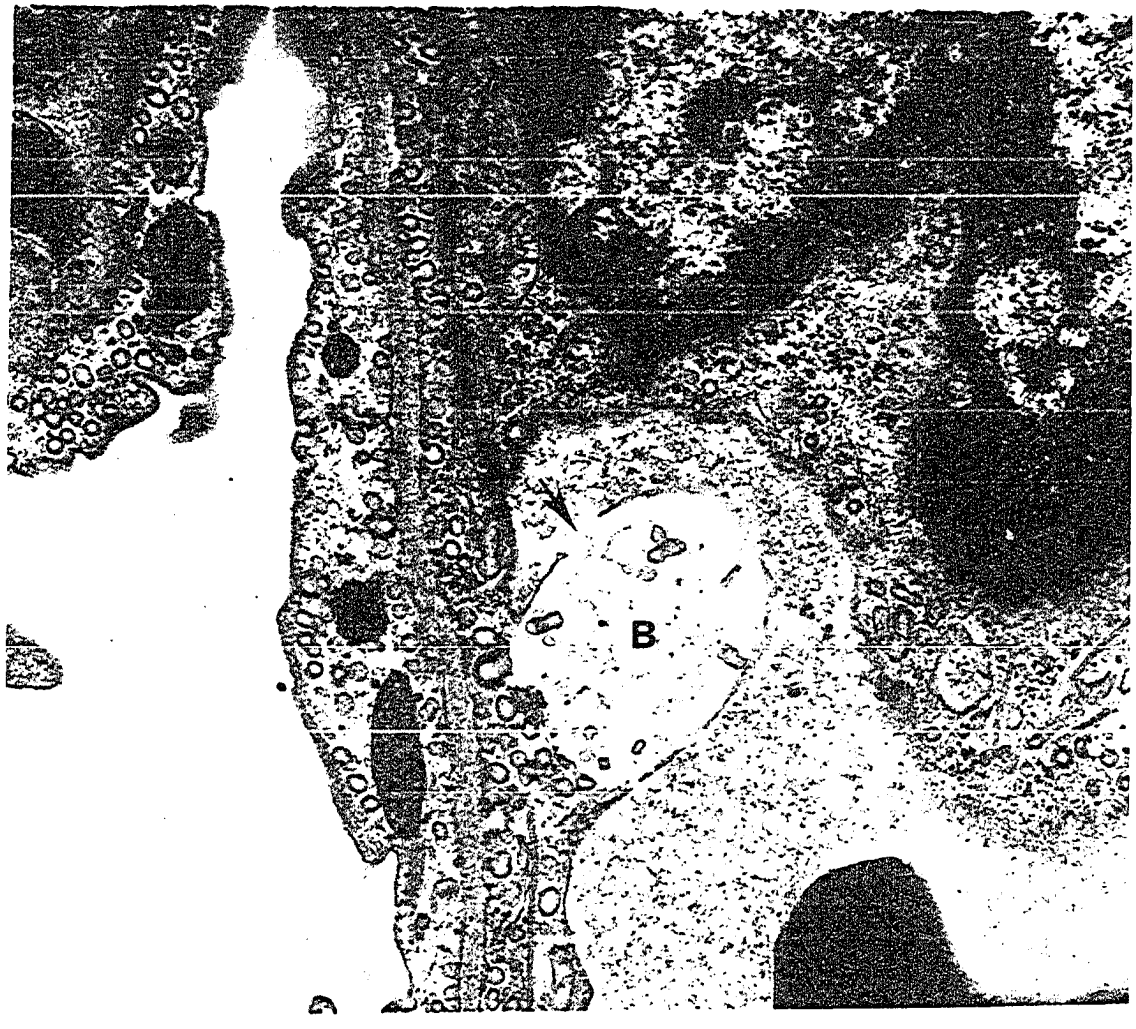

B

Figure 8. Electron micrograph of a canine lung (PMM group) illustrating pulmonary capillary engorgement with electron-dense material (fat microembolus) (F) and ruptures and mechanical tears in the capillary wall and endothelium (arrows) (X 7980)

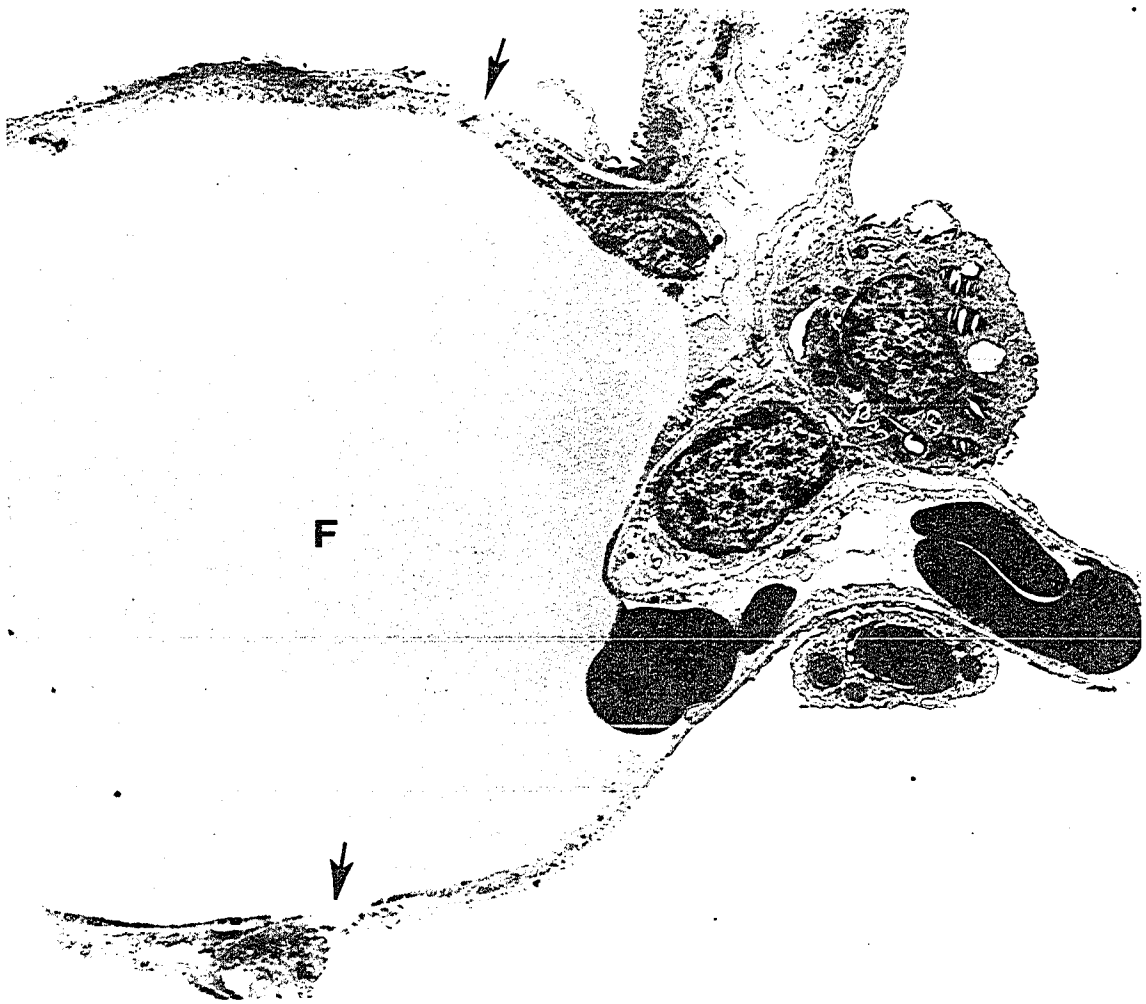

F

Figure 9. Electron micrograph of a canine lung (PD group) illustrating pulmonary capillary engorgement with electron-dense material (fat microembolus) (F) and mechanical tears in the capillary wall and endothelium (arrow) (X 11,700)

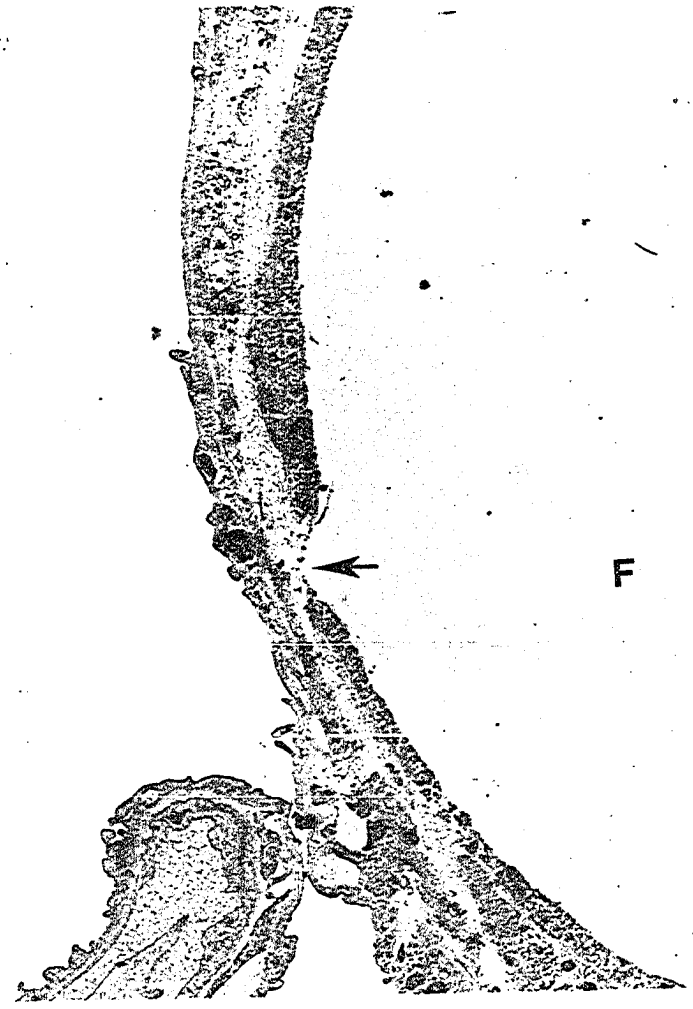

F

Figure 10. Electron micrograph of a canine lung (SS group) illustrating granulated, non-adhering platelet (P) and a normal alveolar-capillary wall (arrows) (X 71,600)

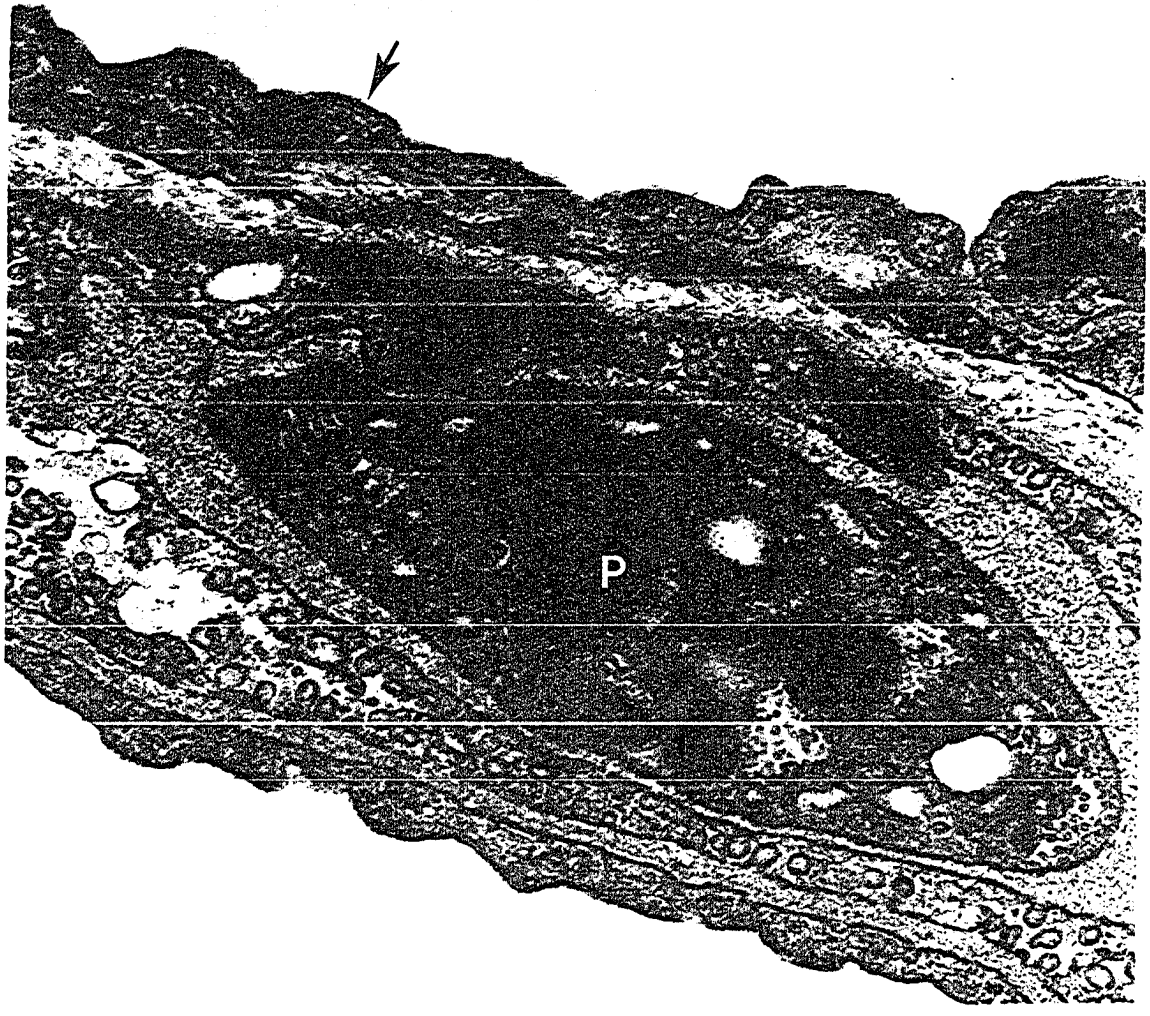
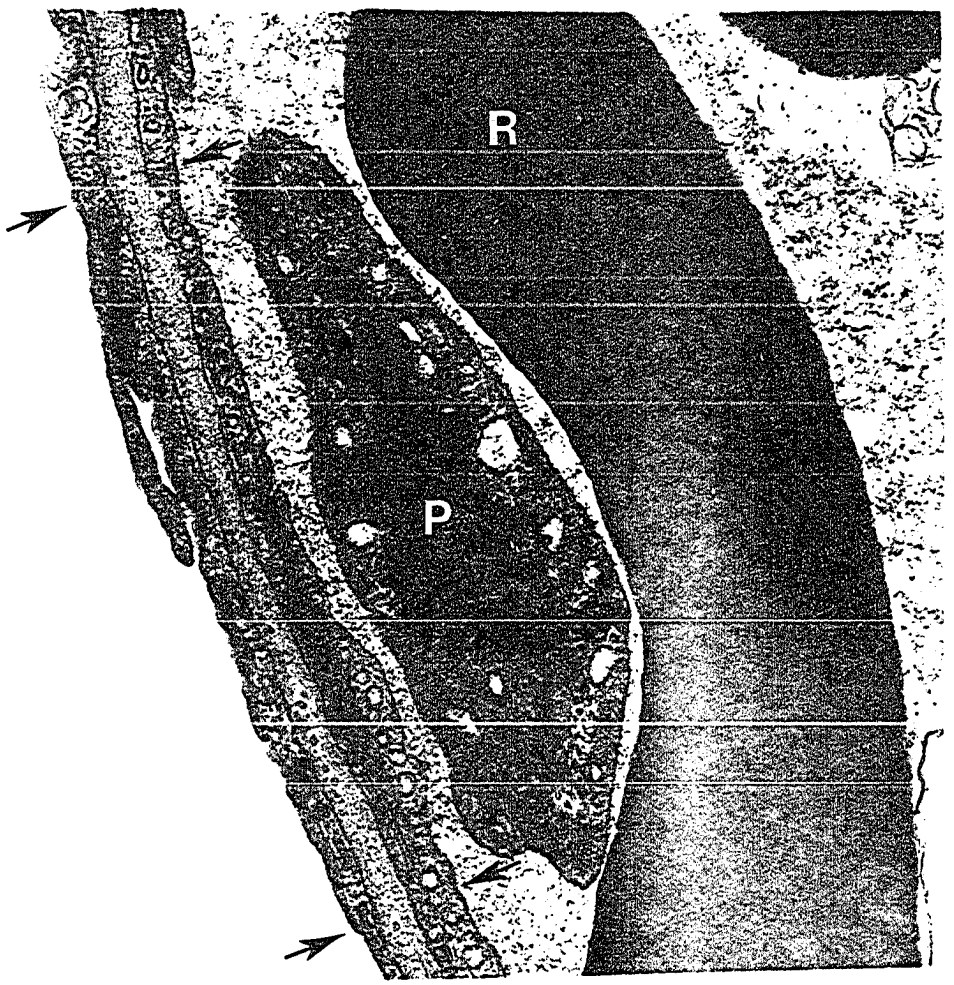

P

Figure 11. Electron micrograph of a canine lung (C group) illustrating granulated, non-adhering platelet (P) and a normal alveolar-capillary wall (arrows), and a red blood cell (R) (X 51,300)

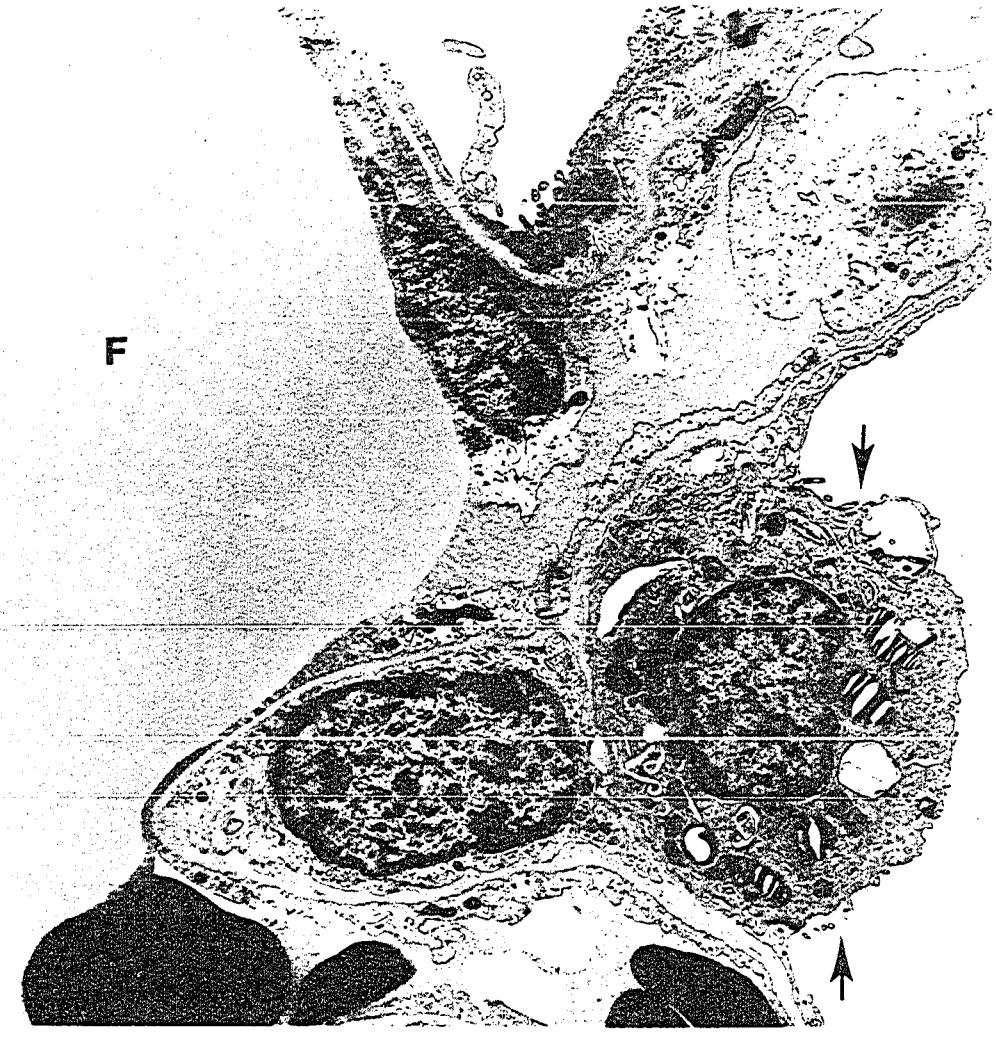

R
P

5. All groups showed normal Type II alveolar pneumocytes loaded with dense lamellar bodies. Figure 12 is an electron micrograph of Type II alveolar pneumocyte in PMM group.

E. Systemic and Pulmonary Hemodynamics Study

1. Average hemoglobin concentration (HB) did not show any significant differences between the four groups at the different stages of the experiment (Figure 13 and Table A2).
2. Average mean systemic arterial blood pressure (AoP) did not show any significant differences between the four groups at the different stages of the experiment (Figure 14 and Table A3).
3. Average systemic vascular resistance (SVR) for the first three groups (PMM, PD, and SS) at T2 was significantly higher than its baseline value at T1 ($p<0.05$). At T5 and T6, PMM group showed significant elevation over the control value (C group) ($p<0.05$) (Figure 15 and Table A4).
4. Average mean left ventricular pressure (LVP) did not show any significant differences between the four groups at the different stages of the experiment (Figure 16 and Table A5).
5. Average myocardial contractility (DP/DT) did not show any significant differences between the four groups at the different stages of the experiment (Figure 17 and Table A6).
6. Average heart rate (HR) did not show any significant changes between the four groups at the different stages of the experiment (Figure 18 and Table A7).

Figure 12. Electron micrograph of a canine lung (PMM group) illustrating normal Type II alveolar pneumocyte (arrows) loaded with dense lamellar bodies (L) and a pulmonary capillary engorged with electron-dense material (fat microembolus) (F) (X 11,700)


F

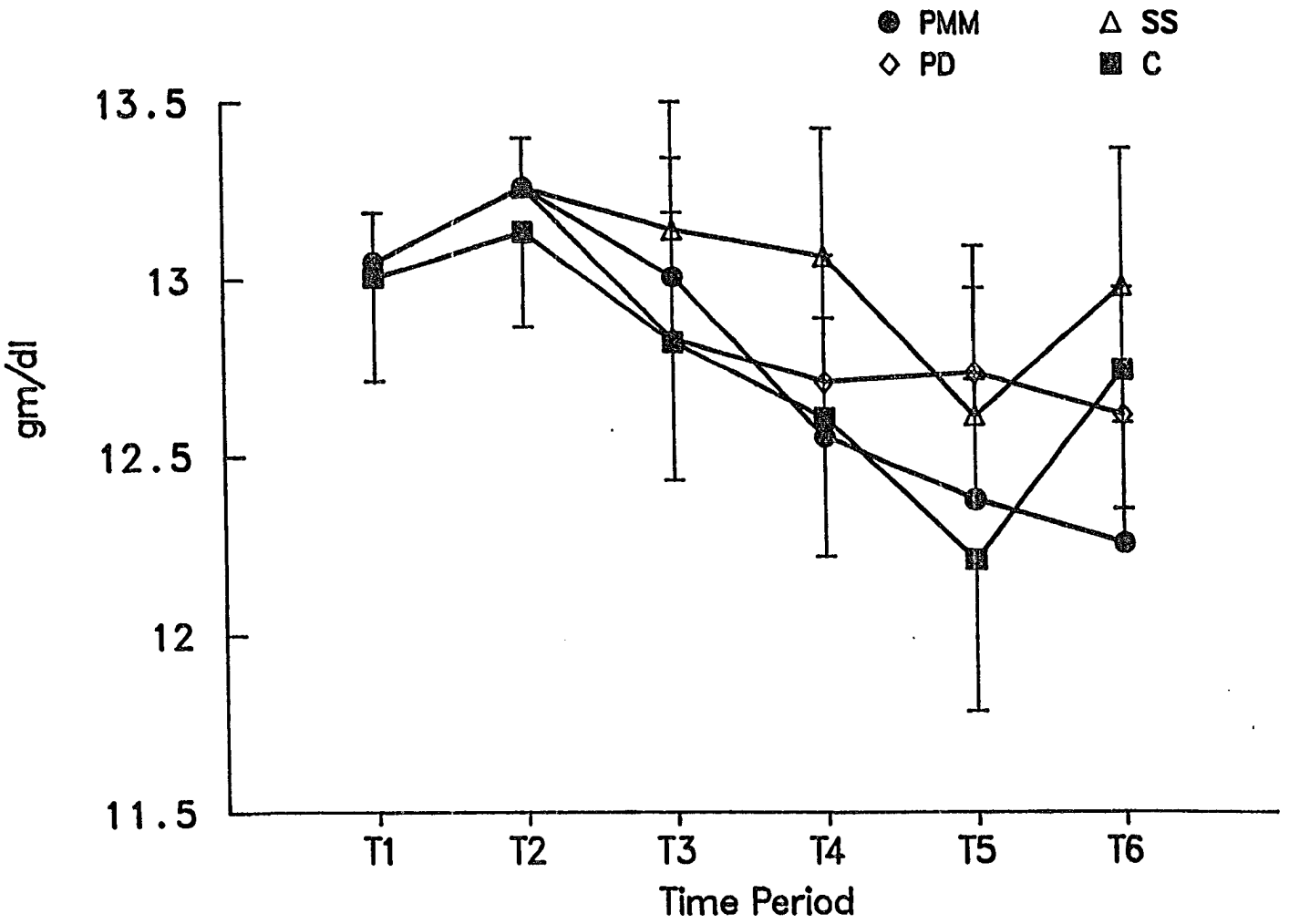


Figure 13. Time course changes in average hemoglobin concentration in the four experimental groups during the experiment

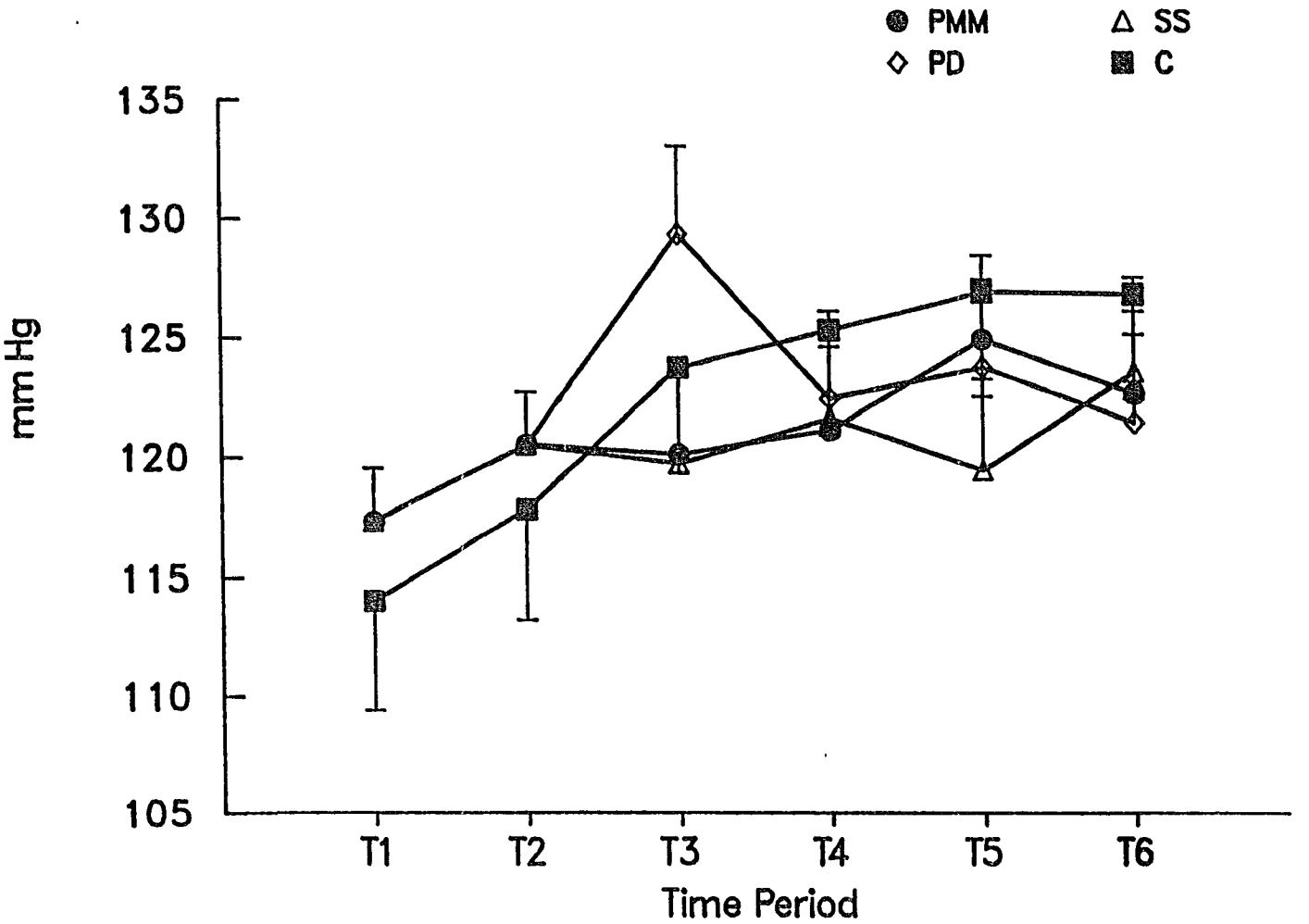


Figure 14. Time course changes in average mean systemic arterial pressure in the four experimental groups during the experiment

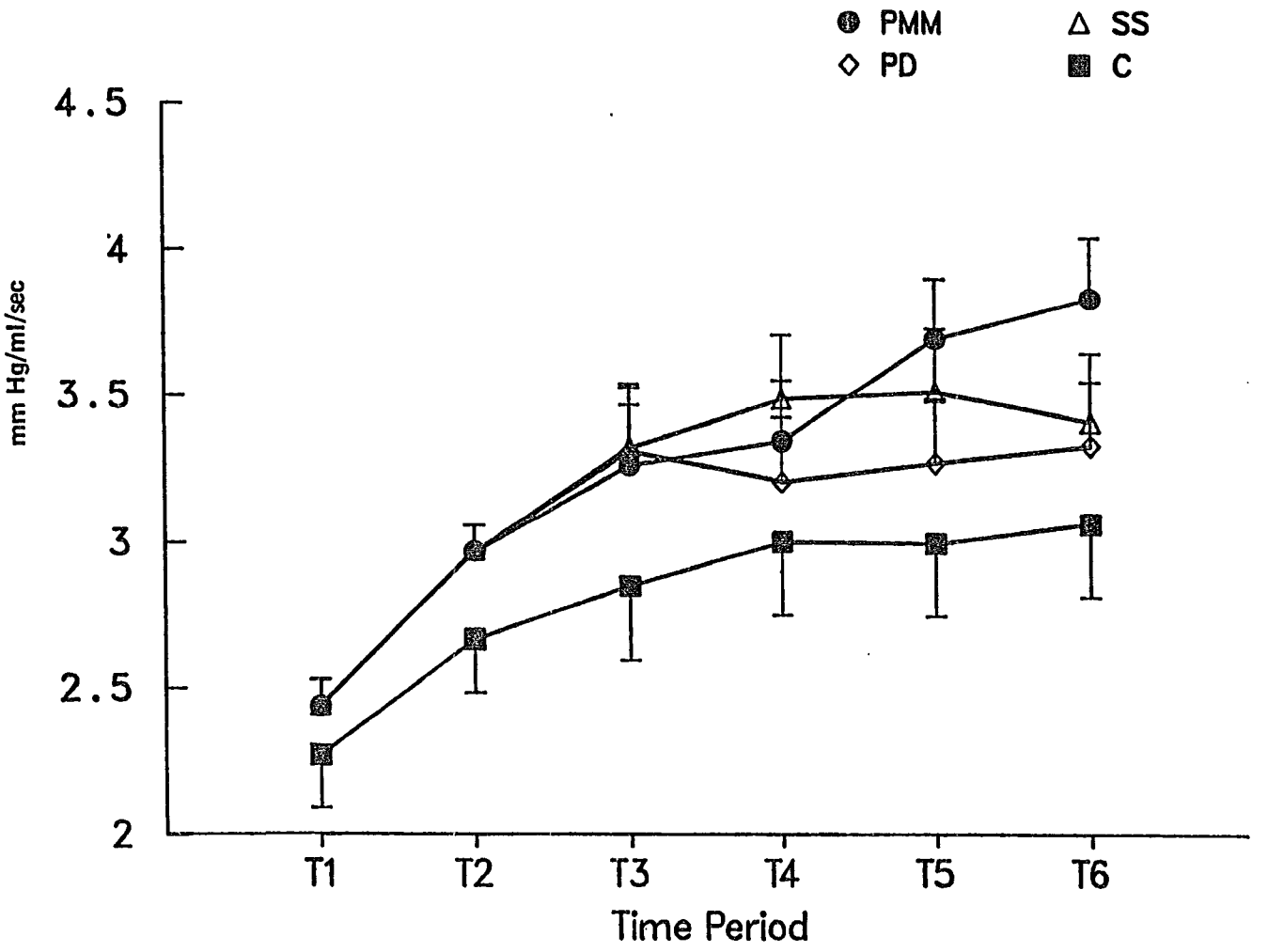


Figure 15. Time course changes in average systemic vascular resistance in the four experimental groups during the experiment

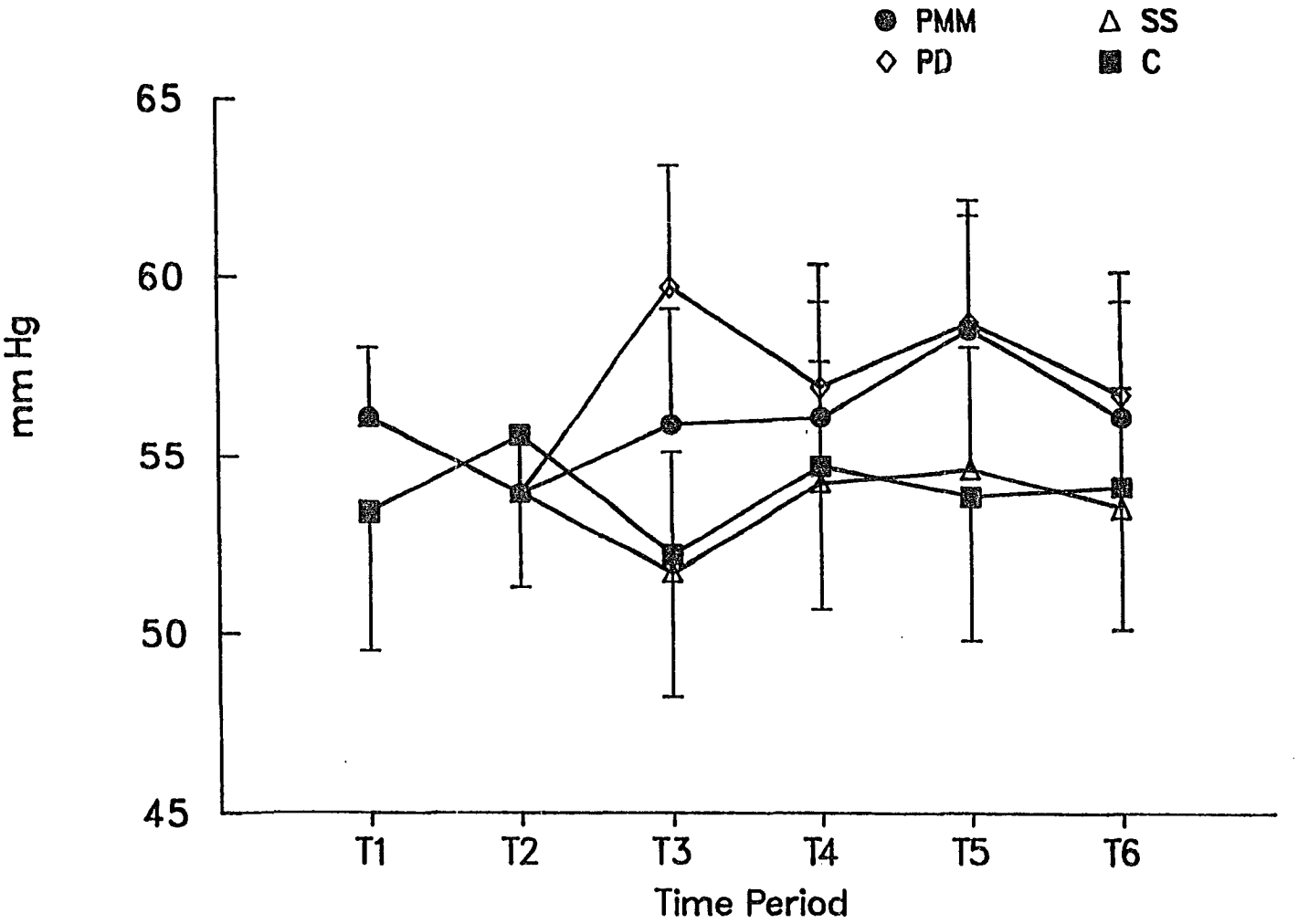


Figure 16. Time course changes in average mean left ventricular pressure in the four experimental groups during the experiment

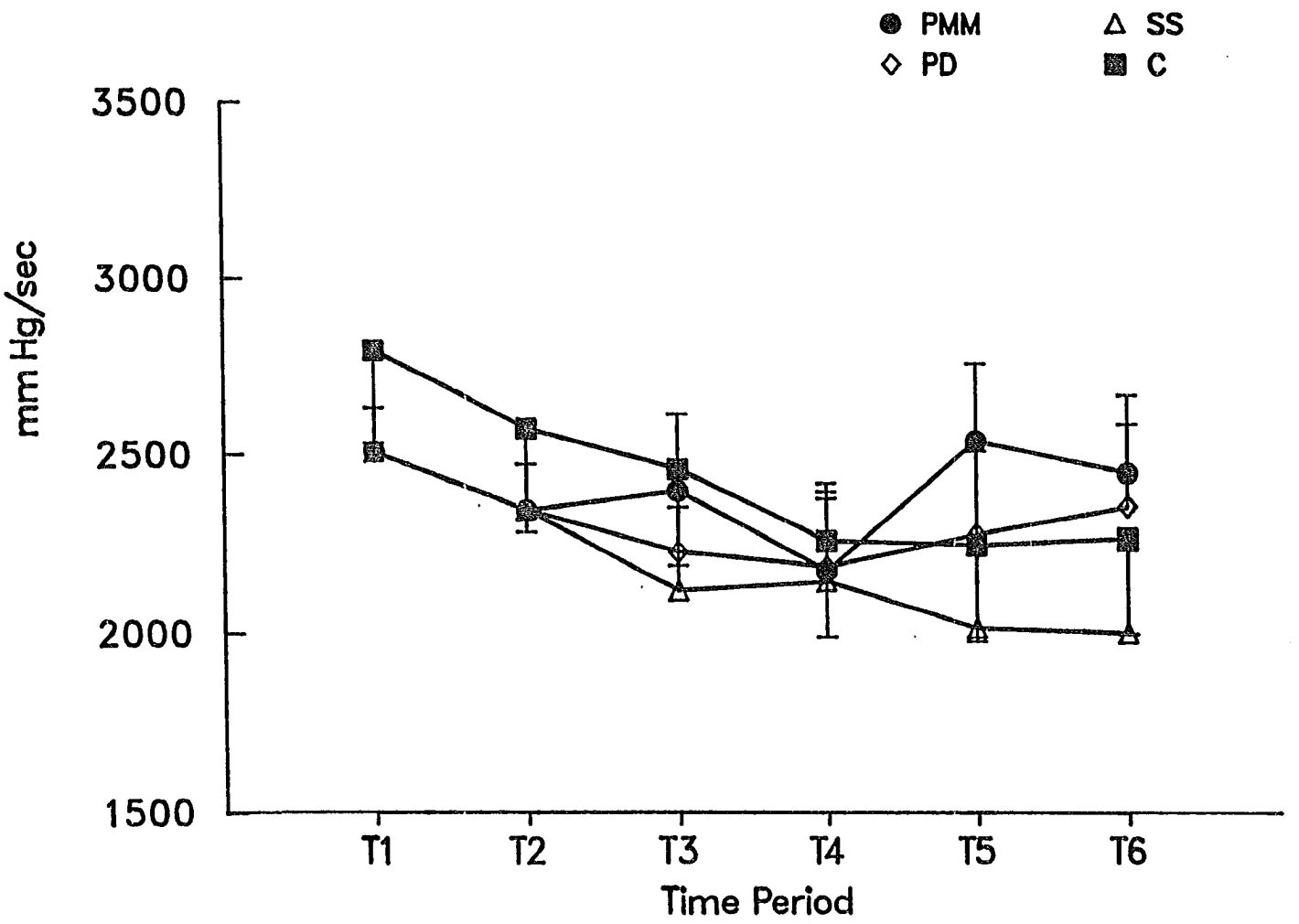


Figure 17. Time course changes in average myocardial contractility in the four experimental groups during the experiment

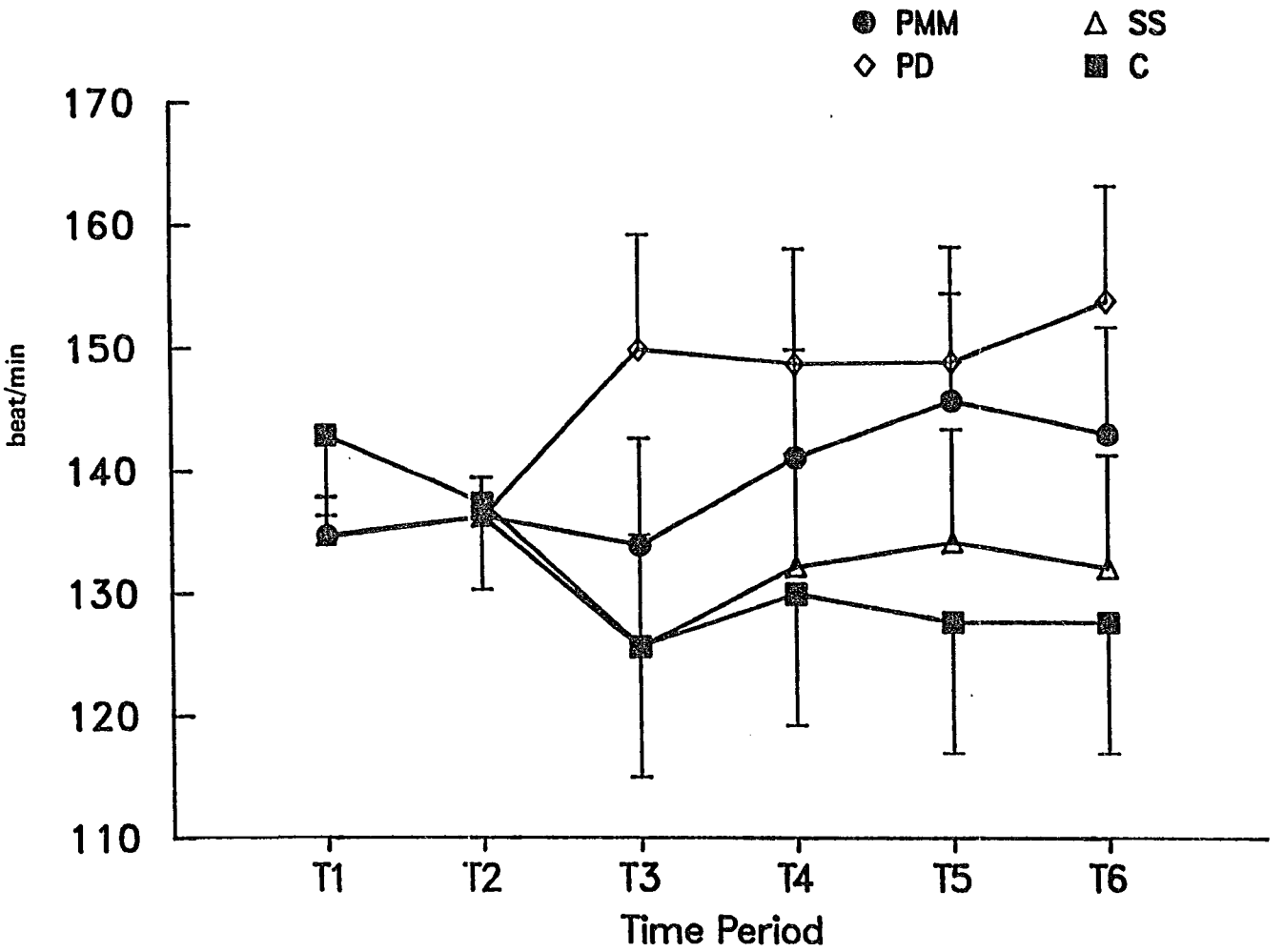


Figure 18. Time course changes in average heart rate in the four experimental groups during the experiment

7. The average value of stroke volume (SV) for the first three groups (PMM, PD, and SS) at T2 was significantly lower than its baseline value at T1 ($p<0.05$). At T3 the first three groups again were significantly lower than the control ($p<0.05$). At T5 and T6, only groups PMM and PD were significantly different from control ($p<0.05$) (Figure 19 and Table A8).
8. Average cardiac output (CO) followed a pattern similar to that of SV. Average CO for the first three groups (PMM, PD, and SS) at T2 was significantly lower than its baseline value at T1 ($p<0.05$). At T3 and T5 SS group was significantly lower than the control ($p<0.05$), while PMM group was approaching significant difference from control ($p<0.1$) at T3 and T4. At T5 and T6 PMM group was significantly lower than the control ($p<0.05$), while SS group was approaching significant lower values than the control at T6 ($p<0.1$) (Figure 20 and Table A9).
9. The changes in average cardiac index (CI) showed a similar pattern to those observed with CO. The average value of the first three groups (PMM, PD, and SS) at T2 was significantly lower than the baseline value at T1 ($p<0.05$). At both T5 and T6 PMM group was significantly lower than the control ($p<0.05$), while SS group was approaching significant drop from the control group ($p<0.1$) (Figure 21 and Table A10).
10. Average mean pulmonary arterial pressure (PAP) did not show any significant differences between the four groups at the different stages of the experiment (Figure 22 and Table A11).
11. Average pulmonary vascular resistance (PVR) followed a pattern similar to that observed with SVR. The average value for the first three groups (PMM, PD, and SS) at T2 was significantly higher than the baseline value at T1 ($p<0.05$). The

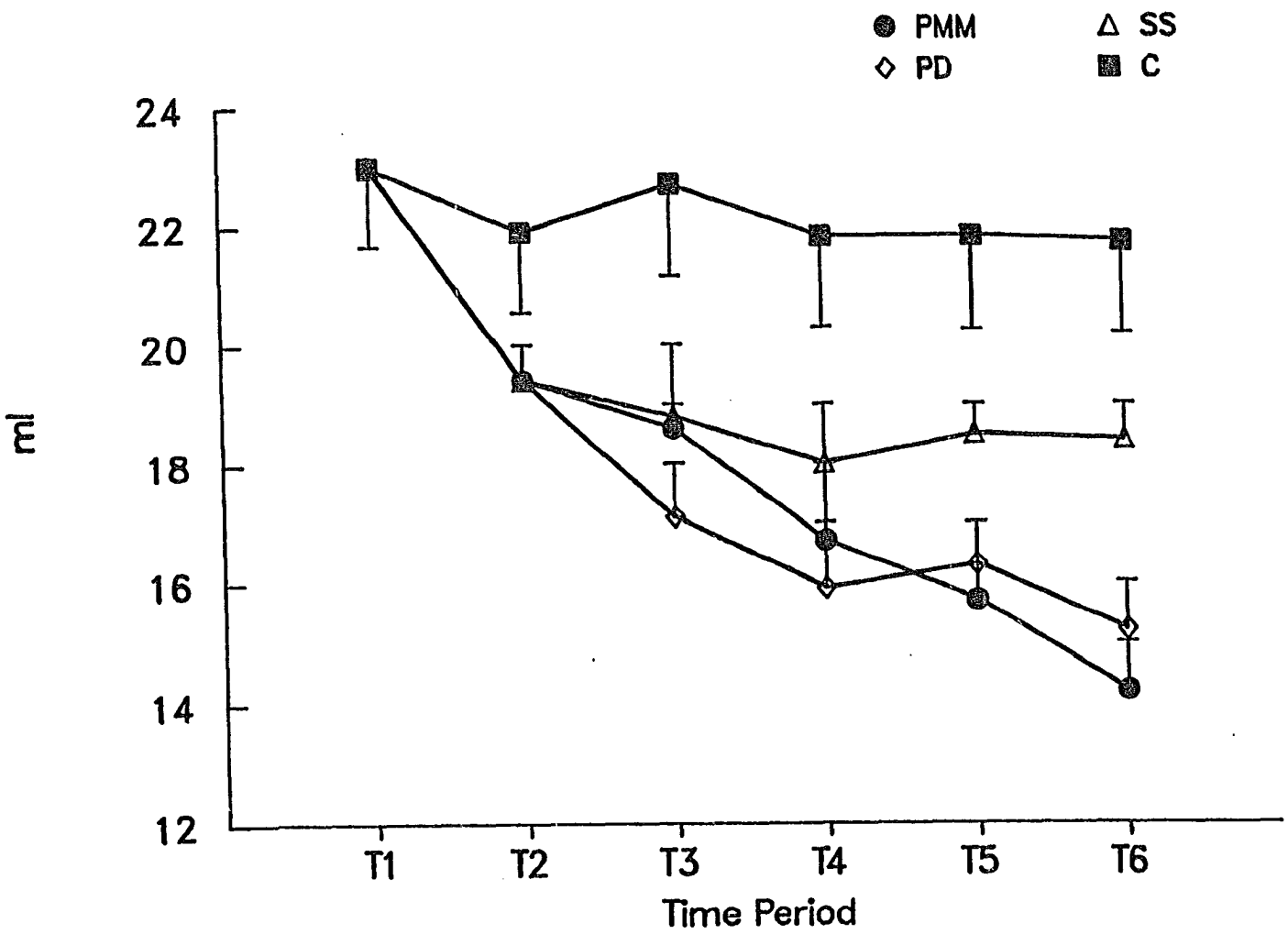


Figure 19. Time course changes in average stroke volume in the four experimental groups during the experiment

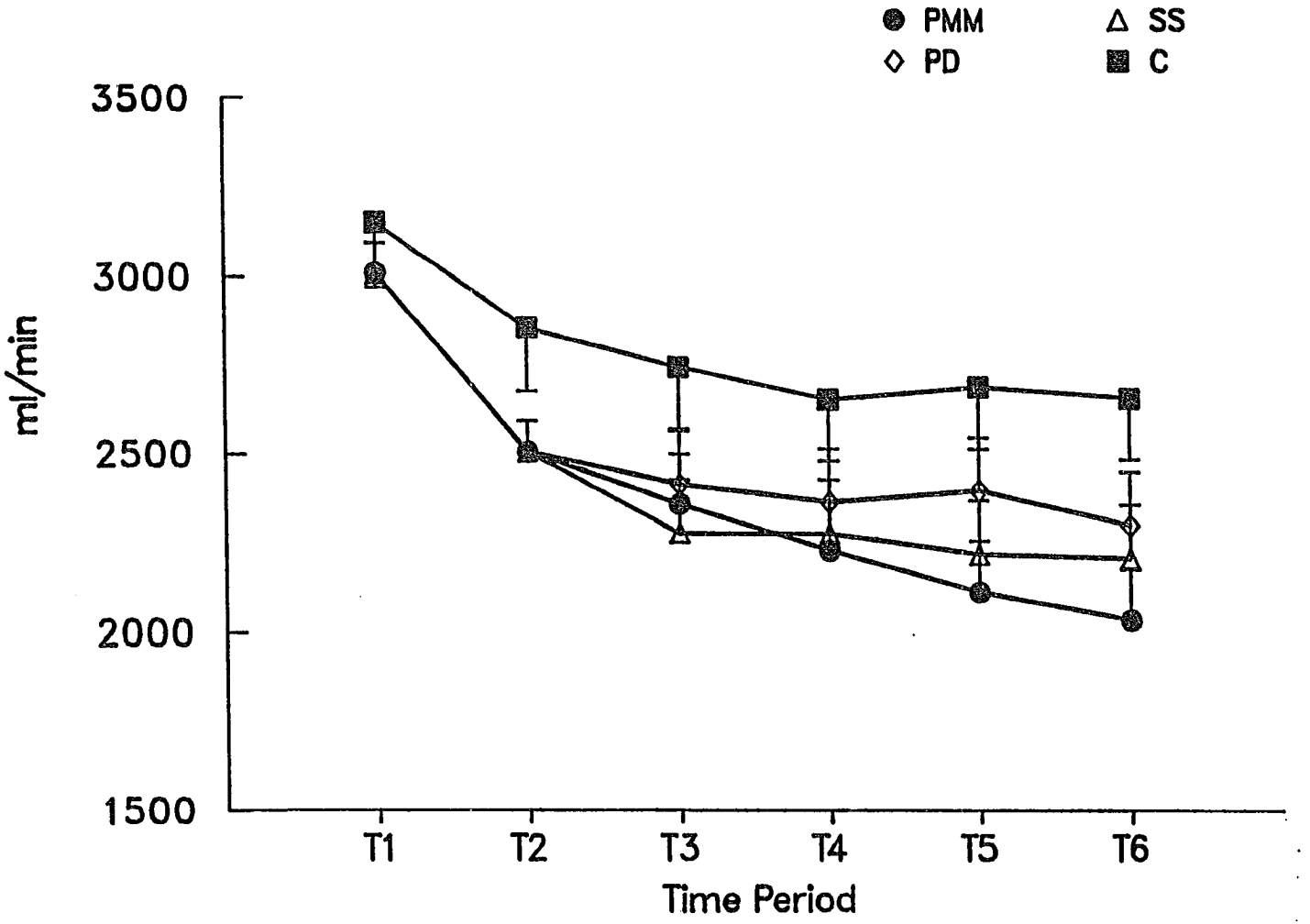


Figure 20. Time course changes in average cardiac output in the four experimental groups during the experiment

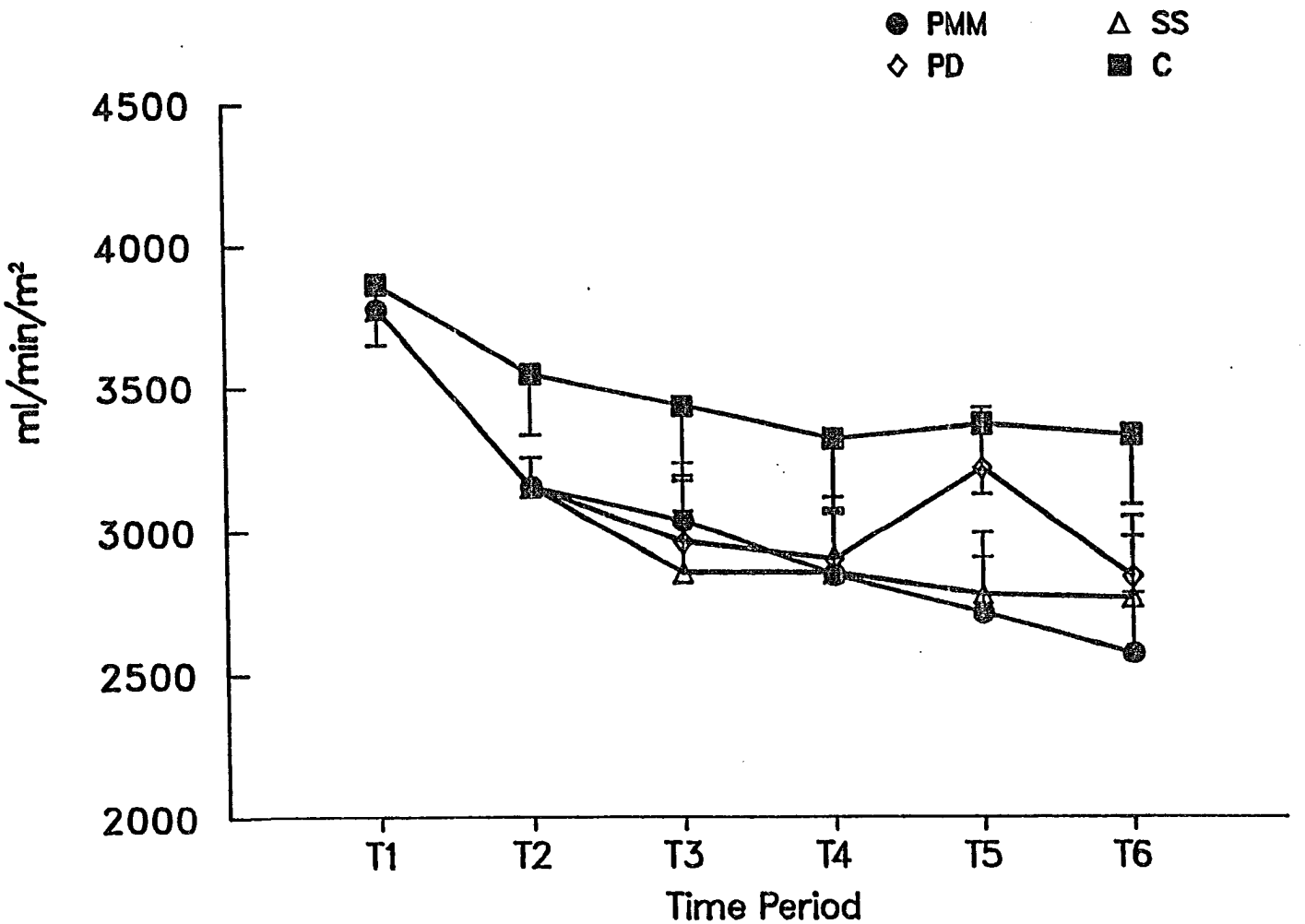


Figure 21. Time course changes in average cardiac index in the four experimental groups during the experiment

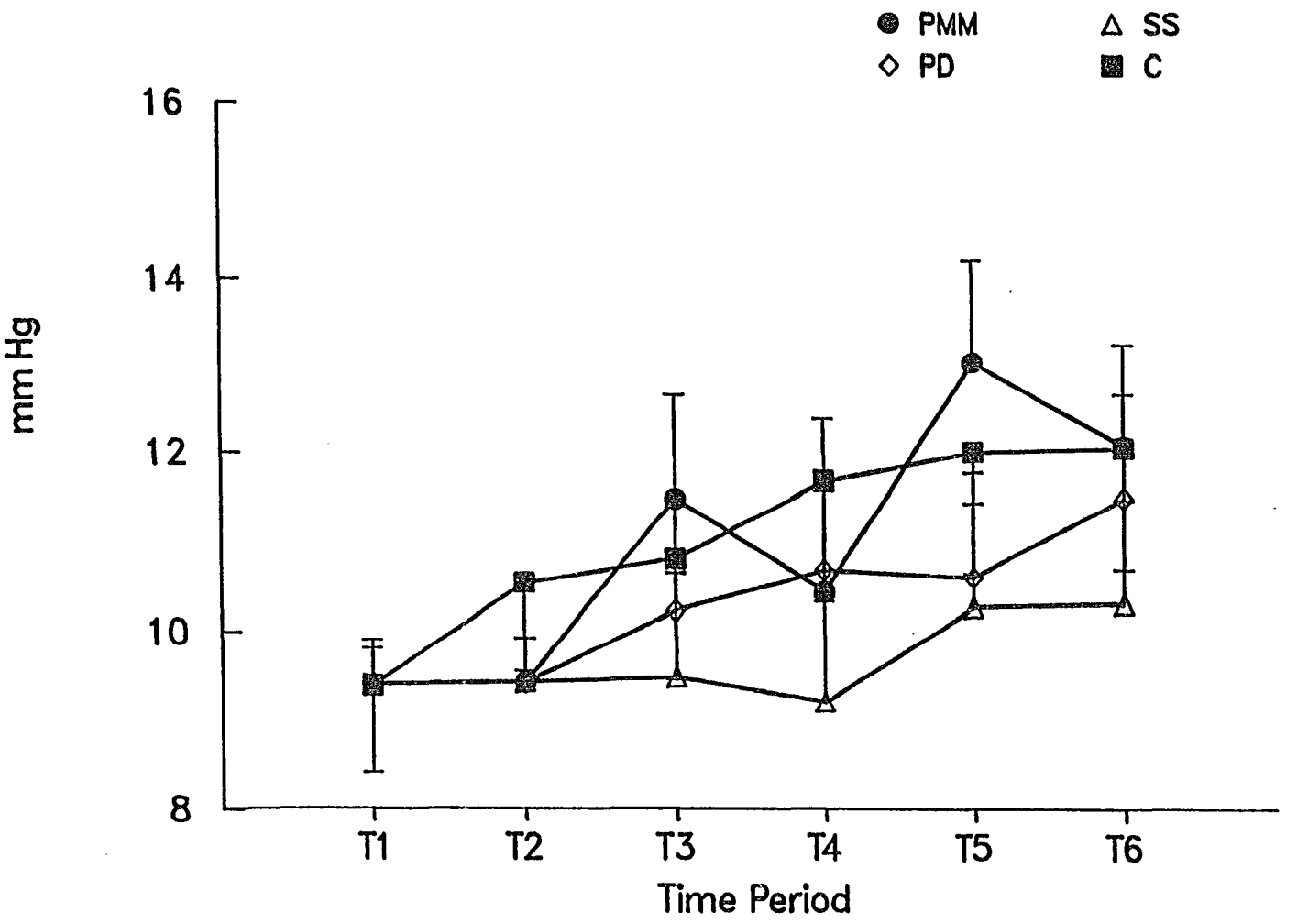


Figure 22. Time course changes in average mean pulmonary arterial pressure in the four experimental groups during the experiment

average values for PMM group showed a tendency toward elevation throughout the experiment, and at T5 it was significantly higher than PD group ($p<0.05$) and approaching significant elevation from both control and SS groups ($p<0.1$), while at T6 it approached significant elevation from SS group ($p<0.1$) (Figure 23 and Table A12).

During injection of PMM in the femoral medullary canal of group I and PD in group II and insertion of the femoral prosthesis, a sudden and an unexpected elevation was observed in all systemic and pulmonary hemodynamic parameters that were recorded on the Beckman recorder (AoP, PAP, LVP, HR) (Figures 24 and 25). That sudden elevation in pressures was transient in nature, lasted for few seconds, and all pressures returned back to its pre-insertion values. That higher elevation was not high enough to cause an overall significant changes in these parameters at T3 (when either PMM or PD and the femoral prosthesis were inserted into the femoral medullary canal). The magnitude of such an elevation in PMM group was higher than its magnitude in PD group. These changes were not observed in SS group (Figure 26).

F. Lung Mechanics and Gas Exchange

1. Respiratory rate (RR) for PMM group showed a tendency to increase from T2 to T6. At T5 it was significantly higher than PD group ($p<0.05$), and at T6 it was significantly higher than the other three groups ($p<0.05$) (Figure 27 and Table A13).
2. Oxygen consumption ($\dot{V}O_2$) for PMM group showed a similar pattern to RR of the same group. It started to increase at T3 to approach significant difference from SS group ($p<0.1$), and at T5 it was significantly different from SS group ($p<0.05$) and approaching significant difference from control ($p<0.1$). At T6 PMM group was

significantly higher than the control and SS group ($p<0.05$) (Figure 28 and Table A14).

3. Carbon dioxide production ($\dot{V}CO_2$) tended to increase throughout the experiment for PMM group, following a similar pattern to $\dot{V}O_2$. At T6, $\dot{V}CO_2$ for PMM group was significantly higher than SS group ($p<0.05$), and approaching significant elevation from control ($p<0.1$) (Figure 29 and Table A15).
4. Ventilation perfusion ratio (V/Q) for PMM group showed a tendency to increase throughout the experiment. The average value for the first three groups (PMM, PD, and SS) at T2 was significantly higher than its baseline value at T1. At T5 and T6, PMM group was significantly higher than the control ($p<0.05$) (Figure 30 and Table A16).
5. Airway resistance (AWR) did not change significantly until T6 when PMM and PD groups showed significant elevation from control ($p<0.05$) (Figure 31 and Table A17).
6. Work of breathing (WB) tended to increase gradually for PMM group throughout the experiment and at T6, WB for that group was significantly higher than the control ($p<0.05$). At T4 PD group was significantly higher than the control ($p<0.05$) (Figure 32 and Table A18).
7. Dynamic lung compliance (LC) did not show any specific significant changes except at T3 where PD group was significantly higher than the control ($p<0.05$) (Figure 33 and Table A19).

Again, during injection of PMM in the femoral medullary canal of group I and PD in group II and insertion of the femoral prosthesis, a sudden and an unexpected elevation was observed in all respiratory parameters that were recorded on the Beckman recorder

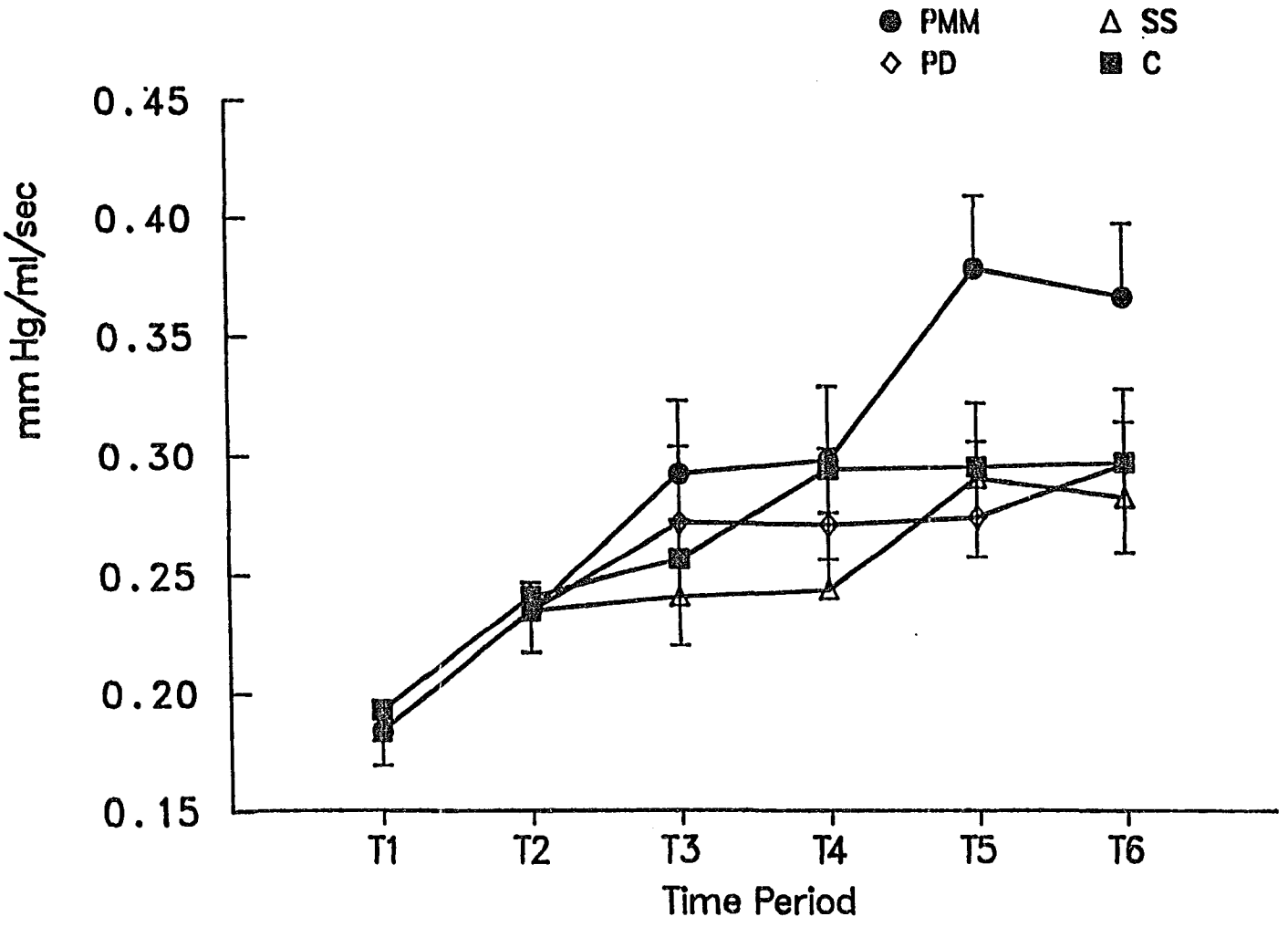


Figure 23. Time course changes in average pulmonary vascular resistance in the four experimental groups during the experiment

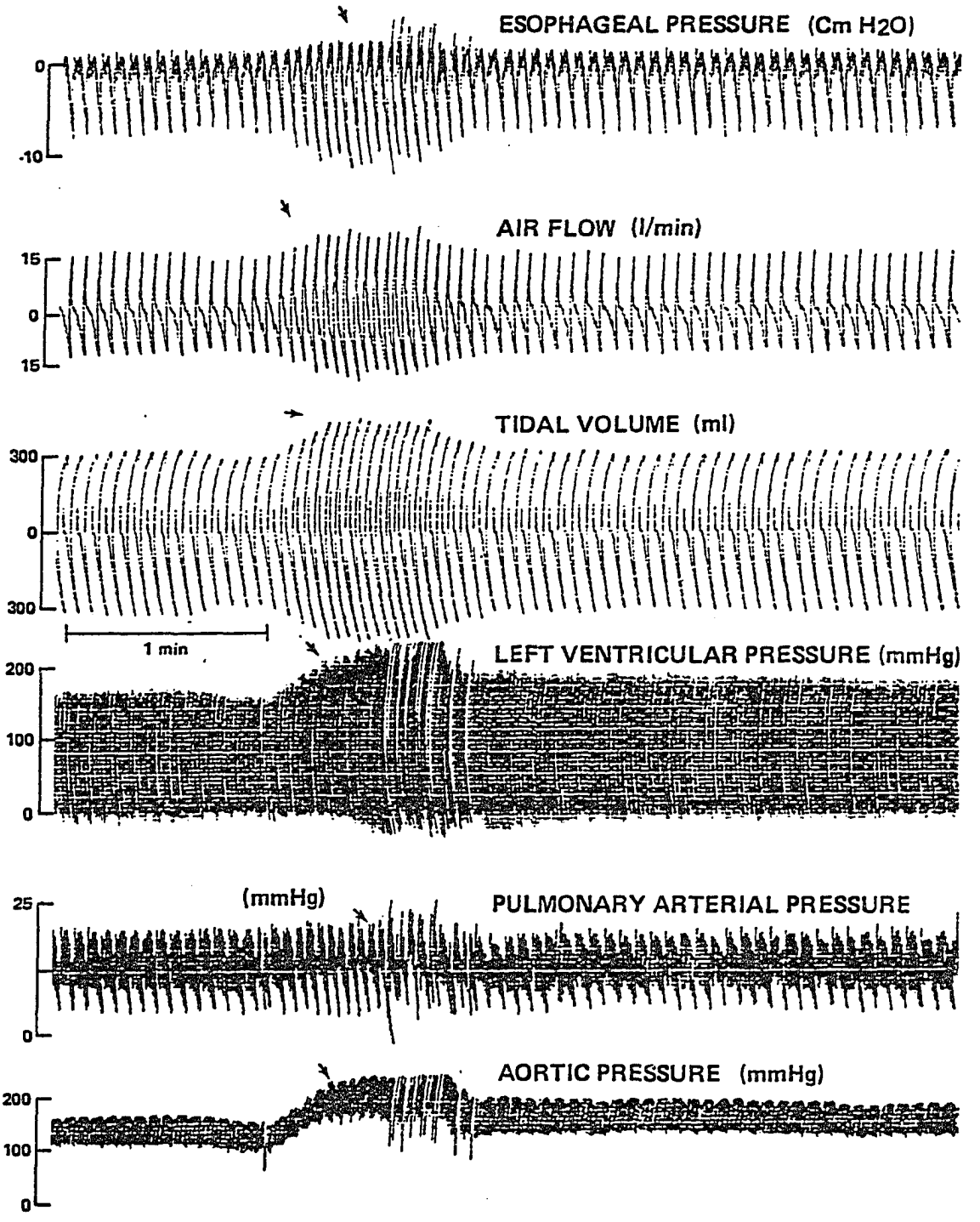


Figure 24. Typical trace of Beckman recording obtained during injection of PMM into the femoral canal and insertion of the femoral endoprosthesis (arrows)

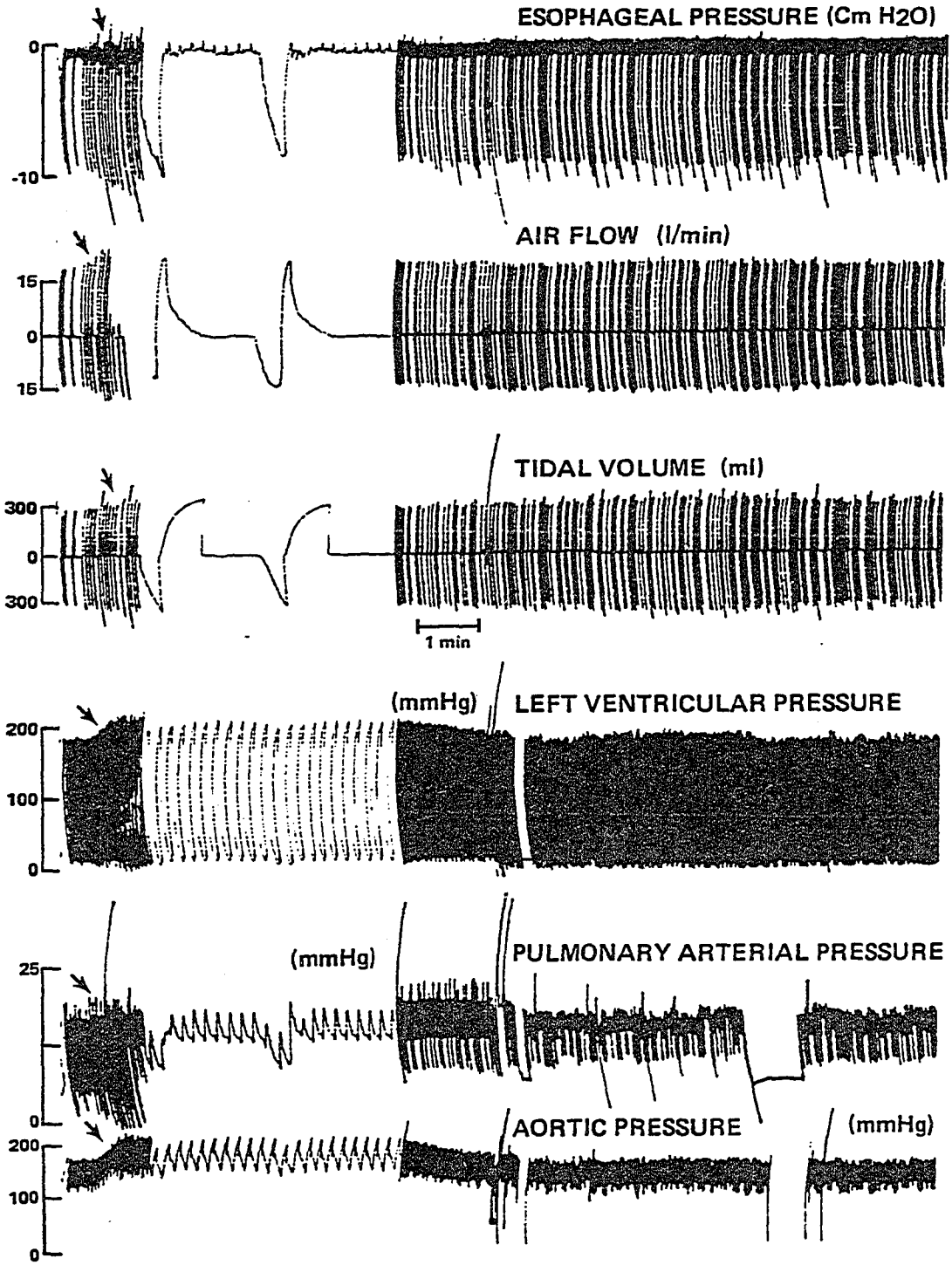


Figure 25. Typical trace of Beckman recording obtained during injection of PD into the femoral canal and insertion of the femoral endoprosthesis (arrows)

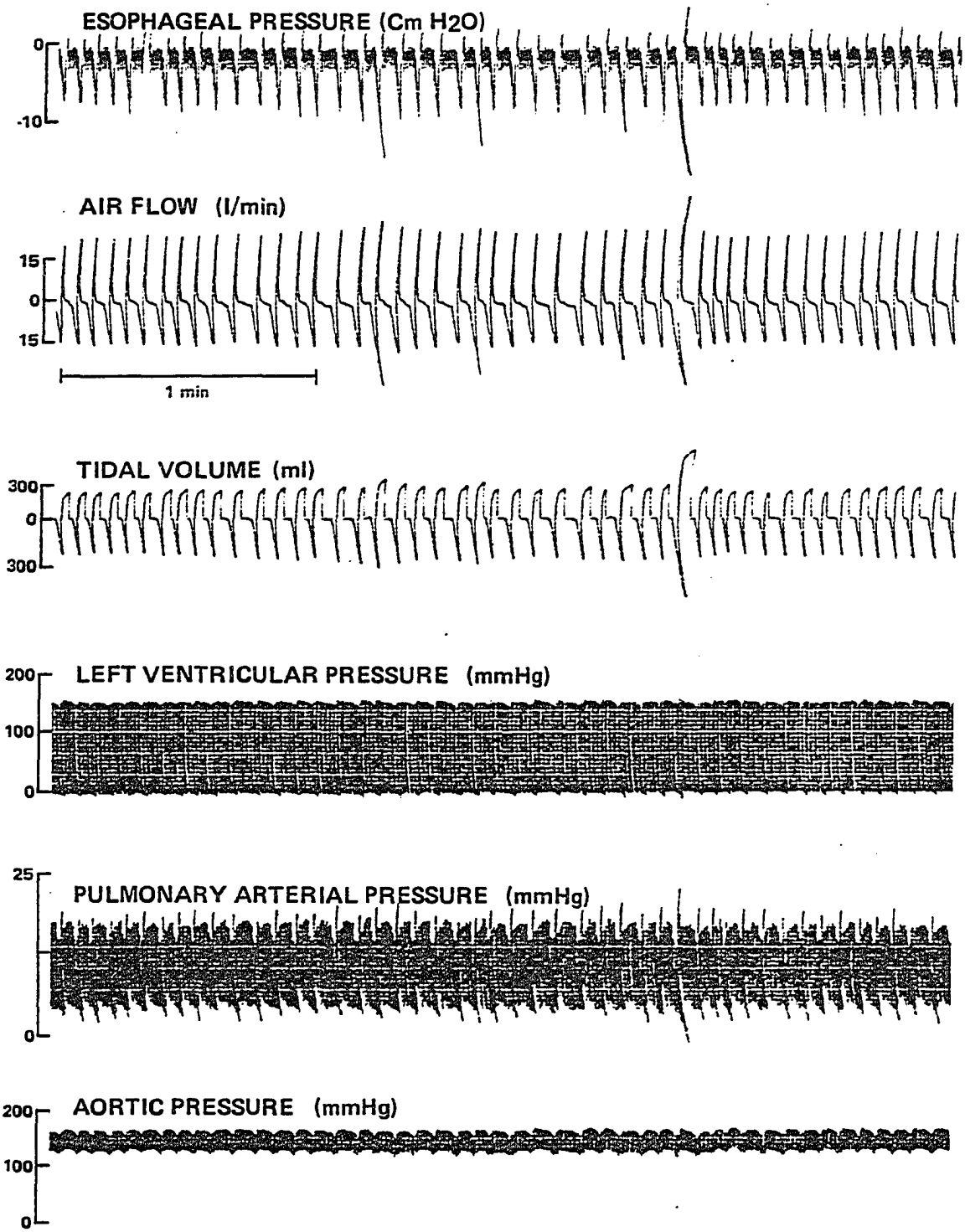


Figure 26. Typical trace of Beckman recording obtained at the end of reaming the femoral canal (SS group)

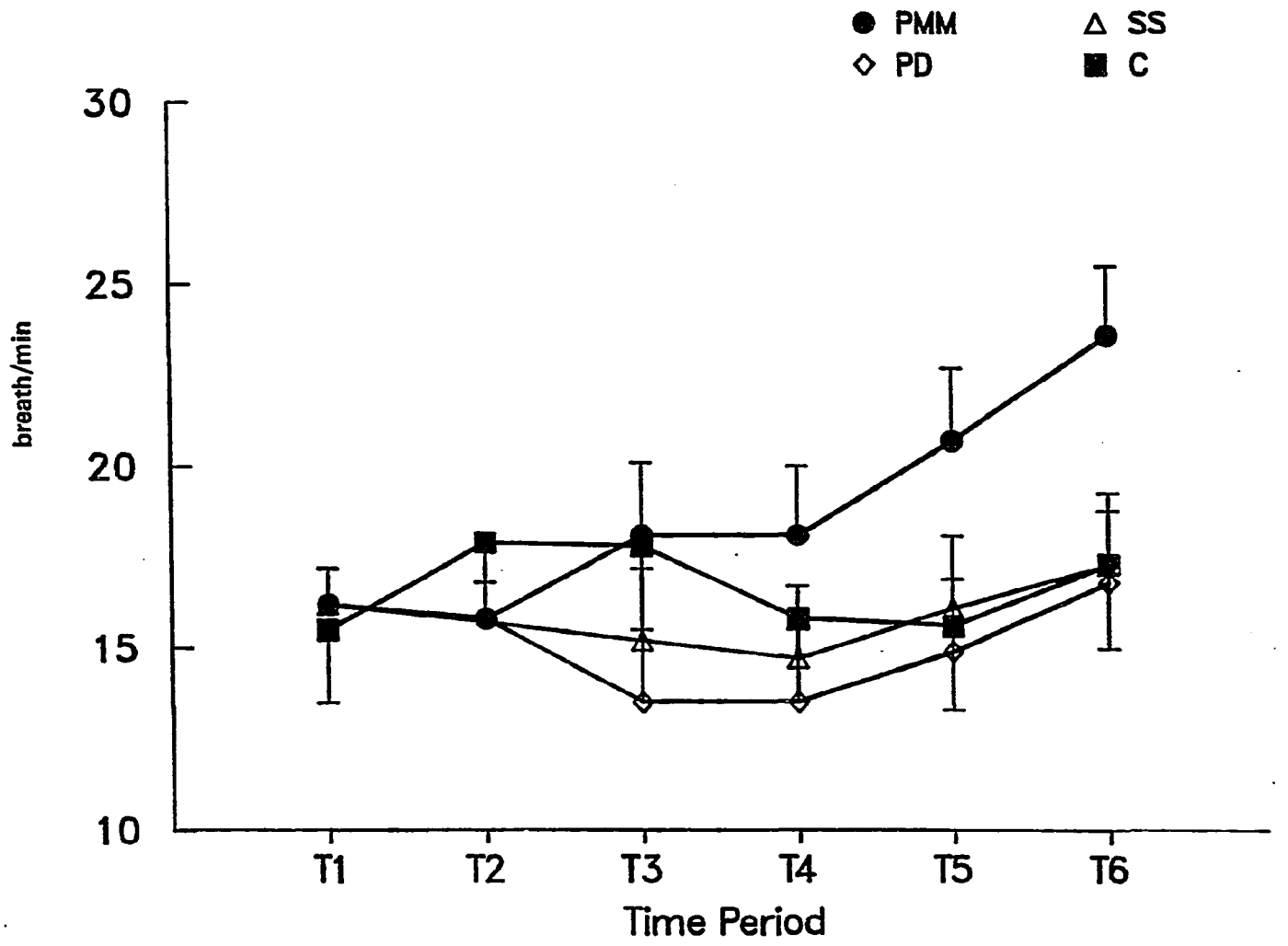


Figure 27. Time course changes in average respiratory rate in the four experimental groups during the experiment

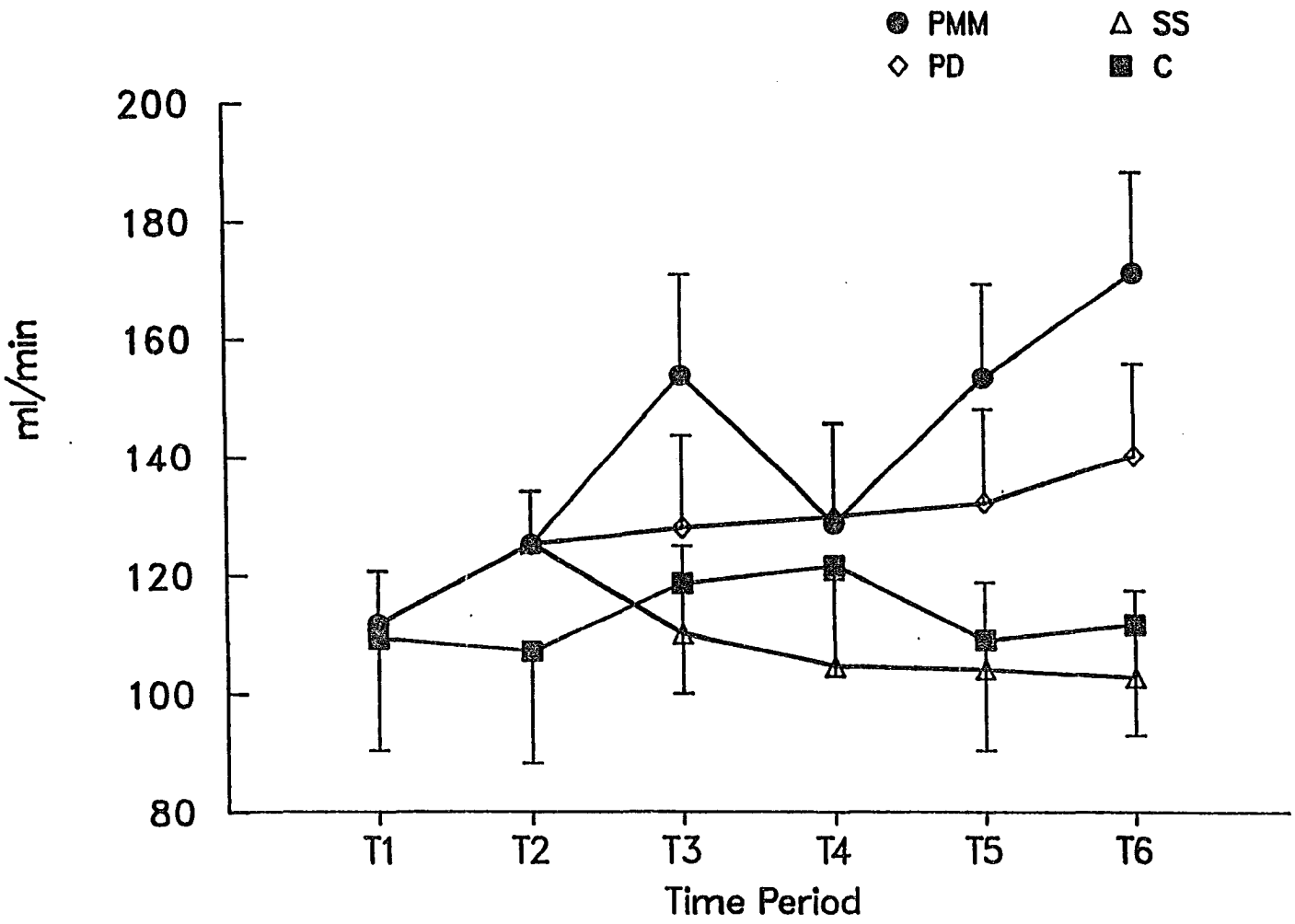


Figure 28. Time course changes in average oxygen consumption in the four experimental groups during the experiment

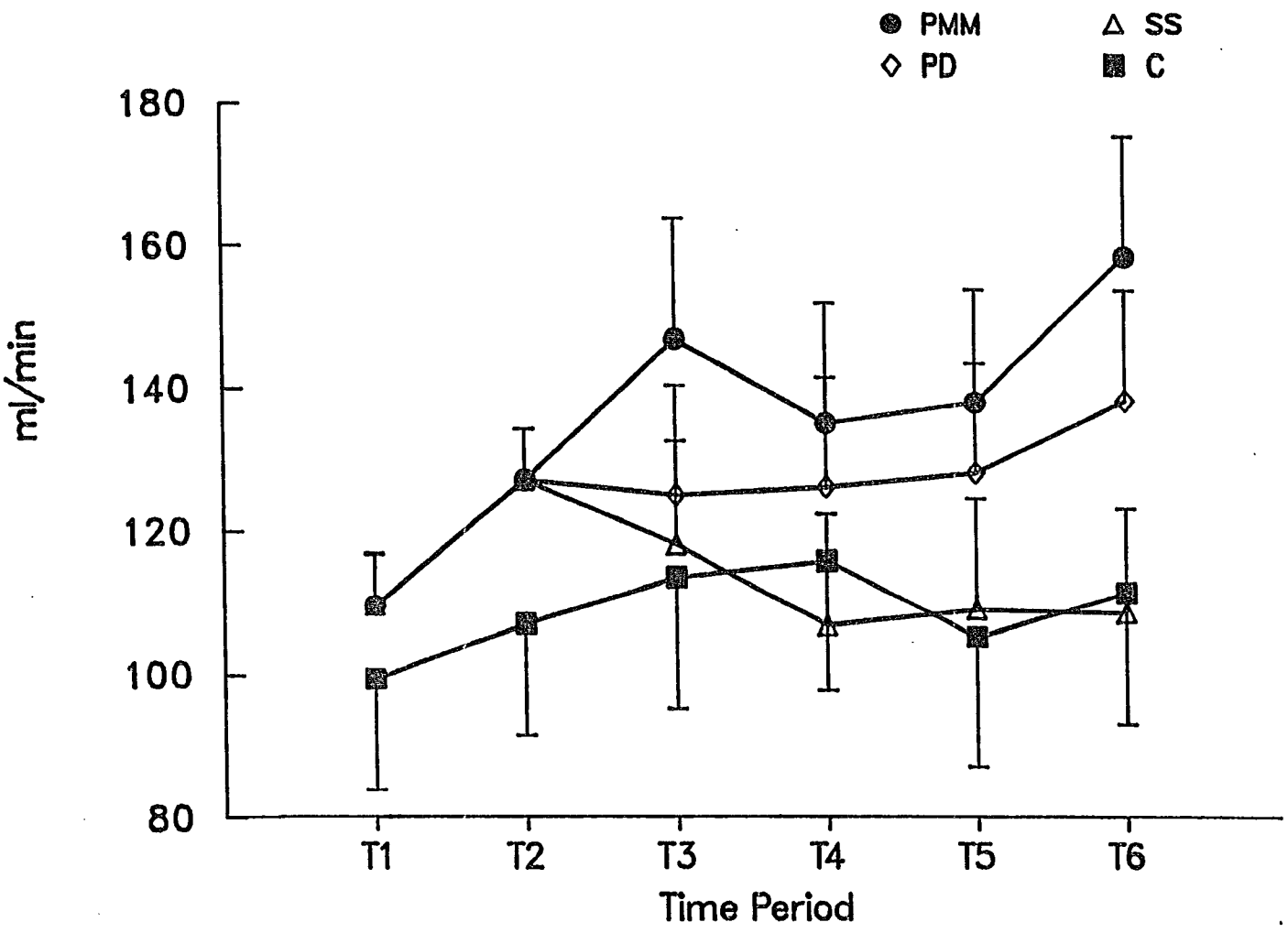


Figure 29. Time course changes in average carbon dioxide production in the four experimental groups during the experiment

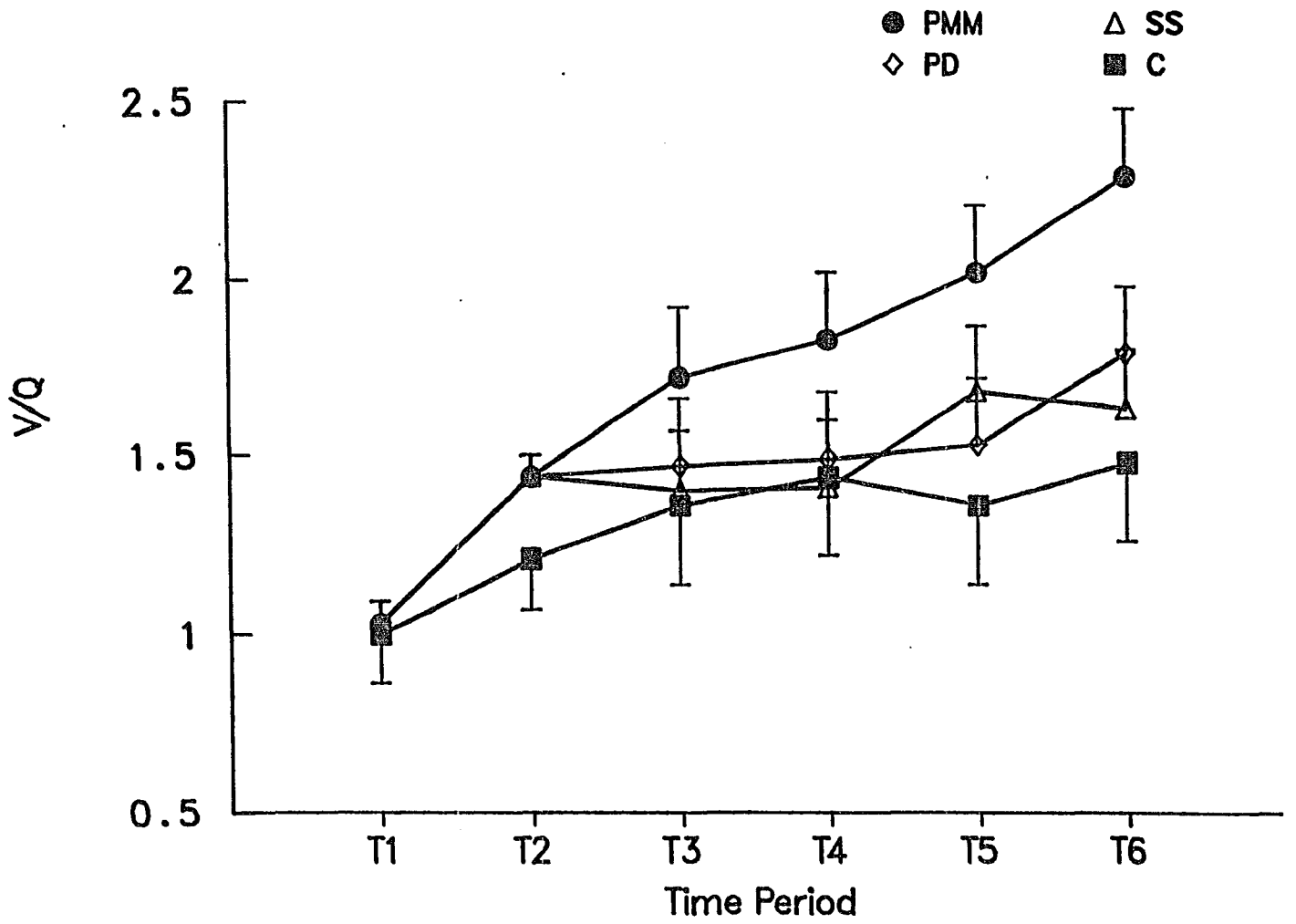


Figure 30. Time course changes in average ventilation/perfusion ratio in the four experimental groups during the experiment

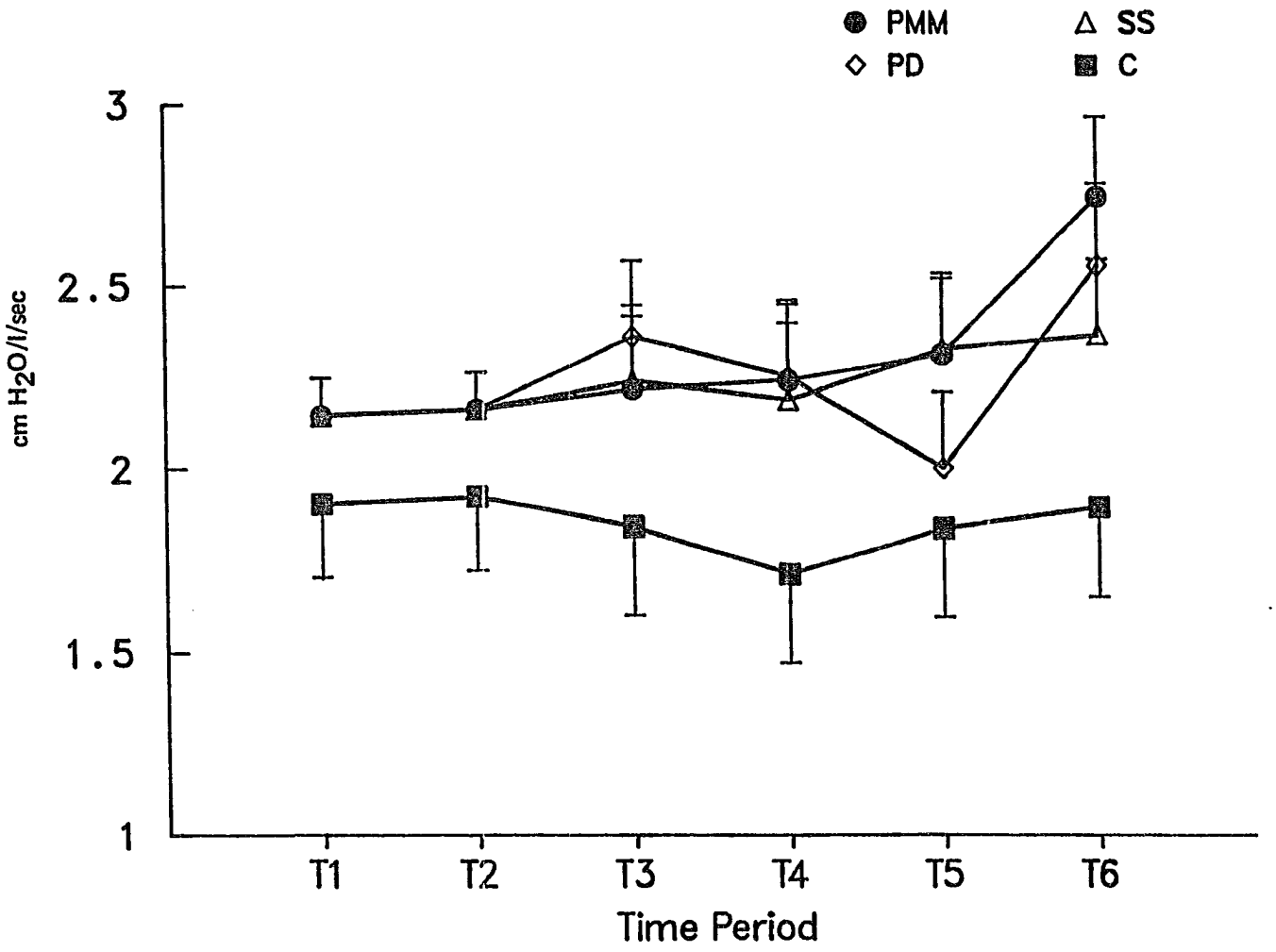


Figure 31. Time course changes in average airway resistance in the four experimental groups during the experiment

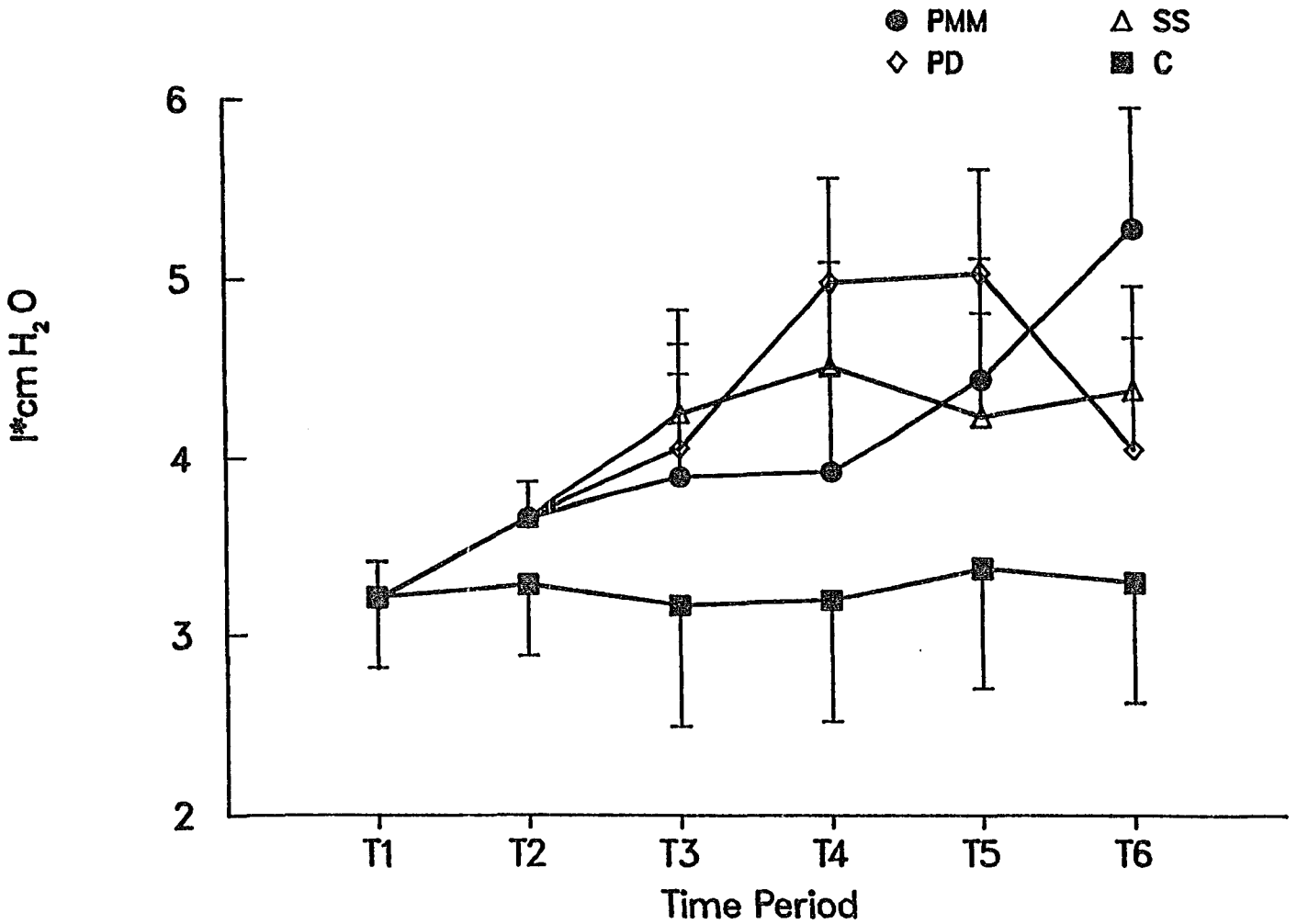


Figure 32. Time course changes in average values for work of breathing in the four experimental groups during the experiment

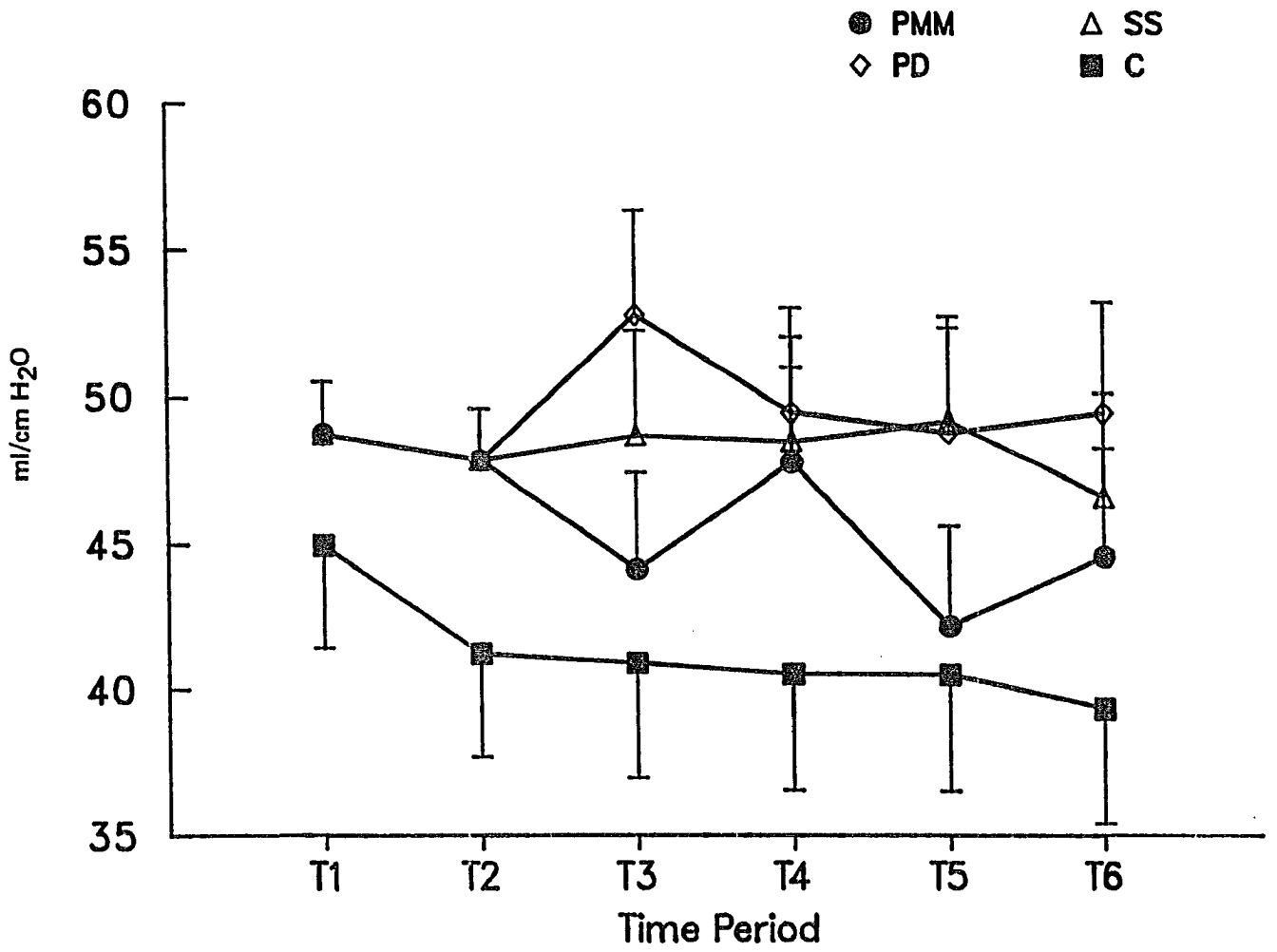


Figure 33. Time course changes in average dynamic lung compliance in the four experimental groups during the experiment

(EP, AF, TV, RR) (Figures 24 and 25). That sudden elevation in respiratory parameters was transient in nature, lasted for few seconds, and all parameters returned back to its pre-insertion values. That increase was not high enough to cause an overall significant changes in these parameters at T3 (when PMM or PD and the femoral prosthesis were inserted into the femoral medullary canal). The magnitude of such an elevation in PMM group was higher than its magnitude in PD group. Again, these changes were not observed in SS group (Figure 26).

G. Blood Gas Analyses

1. Partial pressures of arterial blood oxygen (PaO_2) did not show any significant differences between the four groups at different stages of the experiment (Figure 34 and Table A20).
2. Partial pressures of arterial blood carbon dioxide ($PaCO_2$) did not show any significant differences between the four groups at different stages of the experiment (Figure 35 and Table A21). However, PMM group showed a tendency for lower $PaCO_2$ values from T2 to T4.
3. Arterial blood pH showed only one significant difference at T4 where PMM group was significantly higher than SS group ($p<0.05$). However, PMM group tended to show gradual increase in pH starting at T2 to T4 matching the gradual decrease in $PaCO_2$ observed for the same group (Figure 36 and Table A22).

H. Analysis of Alveolar Lining Material (ALM)

Biochemical analysis of ALM for its major components did not reveal any significant differences between the four groups for any component (Figure 37 and Table A23).

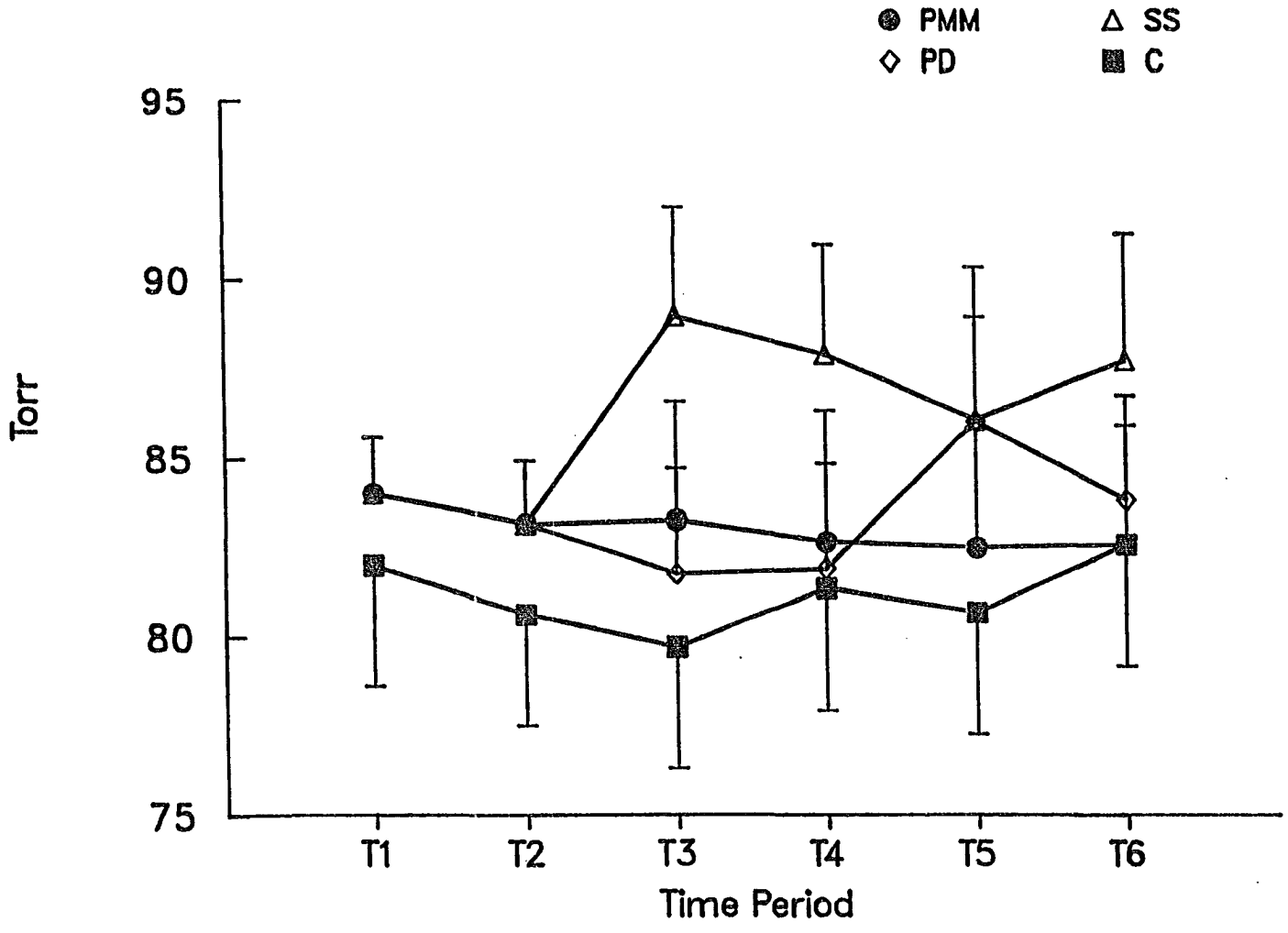


Figure 34. Time course changes in average partial pressures of oxygen in the arterial blood of the four experimental groups during the experiment

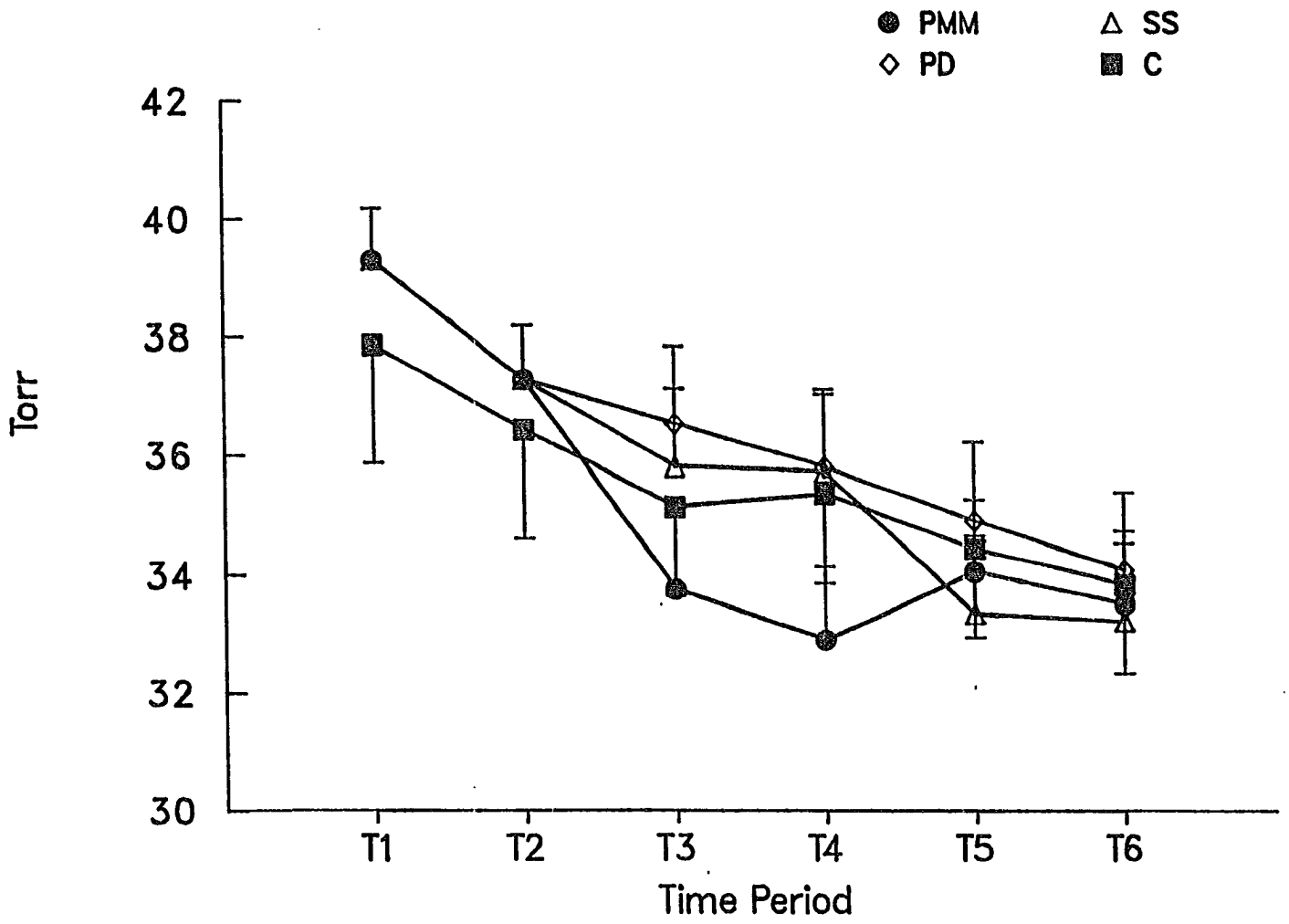


Figure 35. Time course changes in average partial pressures of carbon dioxide in the arterial blood of the four experimental groups during the experiment

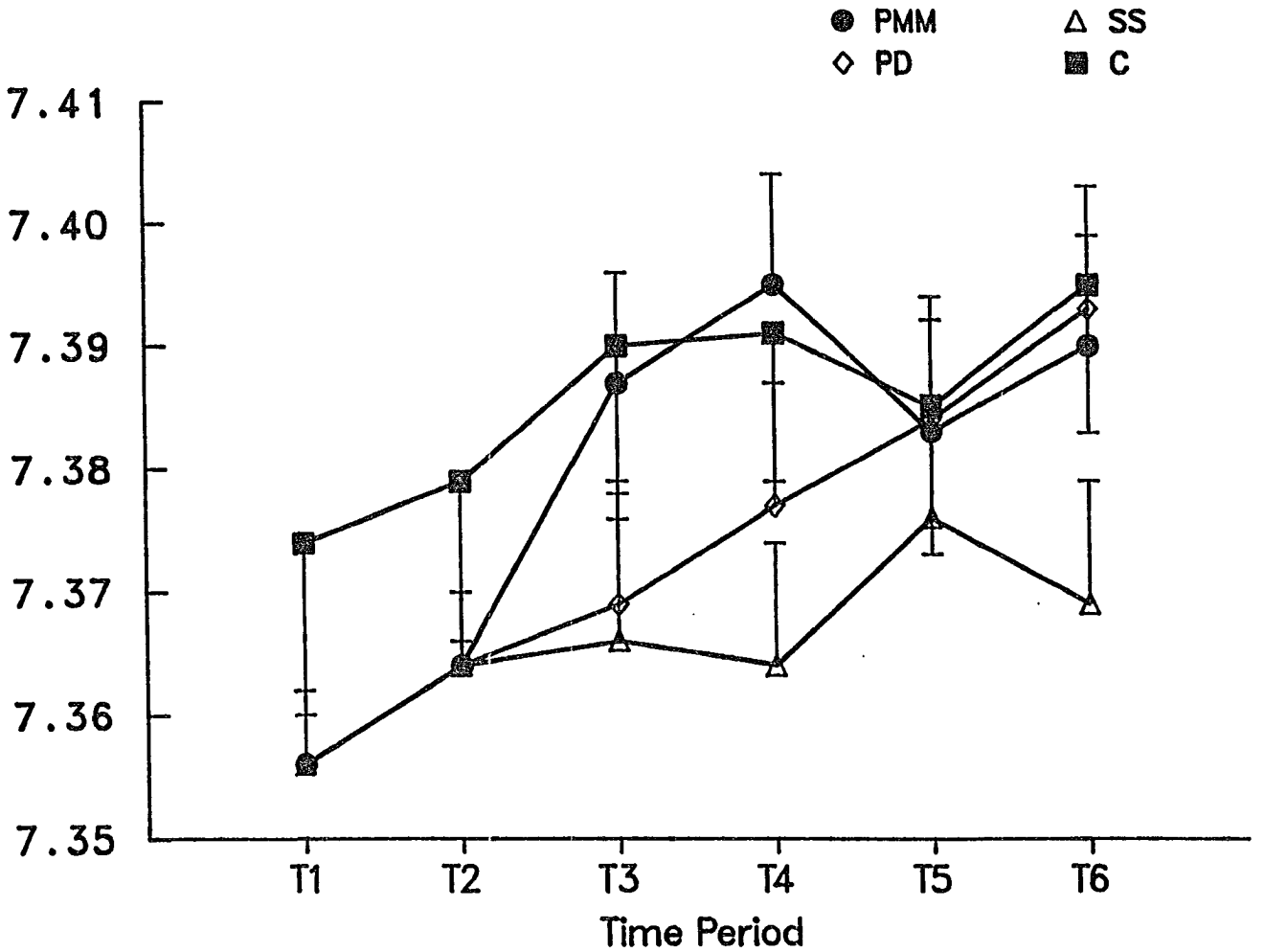


Figure 36. Time course changes in average arterial blood pH in the four experimental groups during the experiment

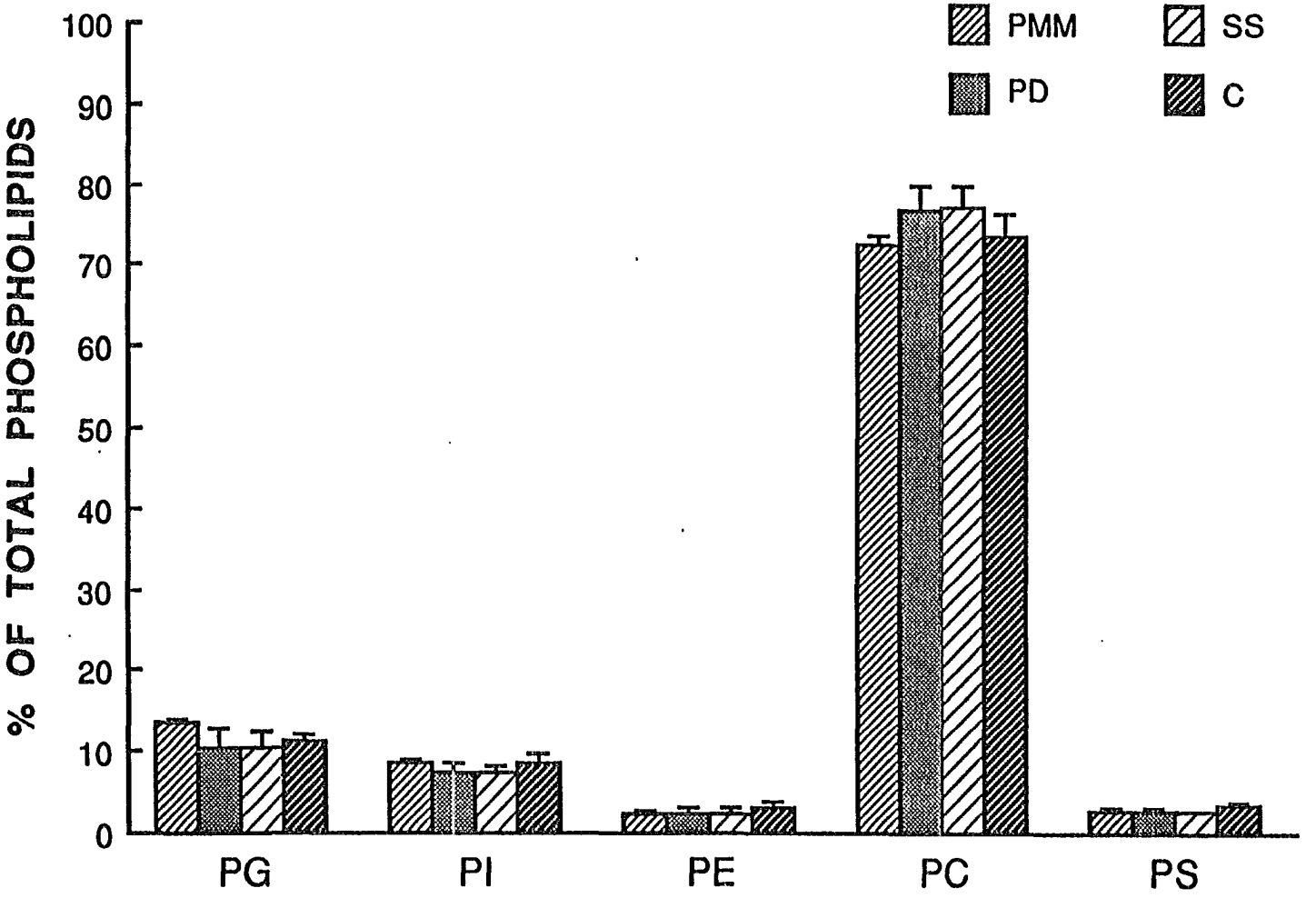


Figure 37. Frequency histogram of the composition of the alveolar lining material (ALM) of the four experimental groups at the end of the experiment

V. DISCUSSION

A. Histopathological Study and Quantitative Analysis of Pulmonary Fat

The absence of significant gross and microscopic lung lesions (except for pulmonary fat emboli) in our study is in agreement with Scully's study (1956). He was unable to find any characteristic gross or microscopic pathologic changes in lungs showing fat embolism in Korean battle casualties. Also, he was not able to detect any edema, focal hemorrhage, patchy emphysema, or atelectasis described consistently in the lungs with the more severe grades of pulmonary fat embolism. The absence of histologic lung lesions in our study could also be explained by the acute nature of the study and the short duration of the experiment.

In our study, pulmonary fat emboli were detected microscopically in all animals in the first three groups (PMM, PD, SS). The presence of pulmonary fat emboli in SS group could be explained by the fact that reaming of the medullary canal alone, even without forced insertion of cement and prosthesis, may give rise to pulmonary fat emboli (Dandy, 1971). This may be due to elevation of the intramedullary pressure (Danckwordt-Lilliestrom and Lorenzi, 1970), forcing bone marrow elements into the destroyed medullary vessels, and into the systemic venous circulation to the lungs. Forced insertion of PMM or PD and femoral prosthesis into the reamed medullary cavity further increase the intramedullary pressure, forcing more fat and bone marrow elements into the venous circulation. Values of intramedullary pressure, as high as 900 torr, have been recorded during forced insertion of PMM and the femoral prosthesis into the femoral medullary canal (Kallos et al., 1974; Tranzo et al., 1974; Hallin et al., 1974). Similar values have also

been reported when bone wax and femoral prosthesis were inserted into the femoral medullary canal of experimental animals (Breed, 1974).

Bone, because of its high content of fat, extensive vascularity, and the rigidity of its structure, provides an ideal condition for the intravasation of fat globules after trauma (Peltier, 1957). Several investigators were able to demonstrate the release of fat globules, detected in the blood aspirated from the pulmonary arterial catheter, into the systemic circulation of every patient they have studied during THA (Alexander and Barron, 1978; Busch et al., 1975; Herndon et al., 1974). Presence of bone fragments have been described in lung sections from patients dying following THA (Bras and Veraart, 1980). In our study, we were unable to detect any bone fragments in any lung section.

The presence of significantly large amount of fat in the PMM group may be explained by the fact that PMM is a potent lipid solvent, and the exothermic reaction associated with its polymerization generates a very high temperature. These two properties of PMM may help in disrupting the fat distribution of the medullary cavity. High intramedullary pressure could be created during THA by three different mechanisms: a) reaming the femoral medullary canal, b) insertion of PMM and the femoral prosthesis, and c) air expansion due to the exothermic reaction. These three factors could facilitate the introduction of the already melted and relatively smaller fat globules into the systemic venous circulation through the destroyed vessels of the femoral medullary canal.

PD lacks the lipid solvent property of PMM and it does not polymerize or generate any temperature when implanted into the medullary cavity. However, forced insertion of PD and femoral prosthesis into the femoral medullary canal of PD group resulted in significantly less amount of pulmonary fat in that group, compared to PMM group. These data indicate that fat solvency and the exothermic reaction associated with PMM are major

contributors to the development of pulmonary fat emboli during THA. The amount of pulmonary fat in the PD group was not statistically different from the SS group. This further emphasizes the role of some specific physical and chemical characteristics of PMM which render its use to be associated with higher amount of pulmonary fat emboli.

The presence of small amount of fat in the SS group may indicate the possible contributing role of surgical trauma alone in the pathophysiological changes associated with THA. The fat emboli observed in the SS group are the result of increased intramedullary pressure associated with femoral shaft reaming and destruction of the medullary circulation, facilitating the entrance of fat and other bone marrow elements into the venous circulation.

Microscopically, we were not able to detect a single fat embolus in the C group, however, our image analysis study of pulmonary fat revealed a $1.19 \pm 0.48\%$ fat in that group. This very low value is probably not a true fat, but it is the faint red background color of some lung fields that was picked up by the highly sensitive Zeiss image analysis system.

The data from the histopathological study and quantitative analysis of pulmonary fat suggest:

1. Pulmonary fat embolism is a common and reproducible phenomenon associated with THA in the dog.
2. Factors other than intramedullary reaming and forced insertion of PMM and the femoral prosthesis are responsible for the significantly higher amount of fat detected in the PMM group. These factors include the lipolytic property of PMM and the high temperature generated during its polymerization.
3. Surgical trauma alone could partially contribute to the development of pulmonary fat emboli following THA.

B. Ultrastructural Study

EM study of lung tissue from the four experimental groups showed pulmonary microvascular injury, characterized by mechanical tears in the capillary wall in both PMM and PD groups as well as endothelial blebs and platelet adhesions and degranulation in the PMM group only. The greater pulmonary microvascular damage observed in the PMM group, may be well correlated to the significantly larger amount of fat emboli detected in the pulmonary capillaries and arterioles of that group. However, the PD group showed only minor pulmonary capillary injury while the SS group did not show any ultrastructural changes. In the PD group, we were able to locate and study a damaged pulmonary capillary distended with a fat embolus. In SS group, we were not able to locate and study an embolized pulmonary capillary. This observation may further indicate the role of pulmonary intravascular fat in initiating pulmonary microvascular damage associated with pulmonary fat embolism.

Bone marrow elements released into the venous circulation, and trapped in the lungs, following fractures and bone trauma may injure pulmonary vascular endothelium by several mechanisms:

1. Activation of the coagulation cascade with subsequent formation of toxic fibrin degradation products (FDP). The fibrinolytic system in the dog lung is very potent, consequently this potent fibrinolytic mechanism may generate a great increase in plasmin activity and in FDP in response to a given embolic process (Malik, 1983).
2. Platelet aggregation and leukostasis (Barie et al., 1981).
3. Generation of toxic free fatty acids from fat emboli by the action of pulmonary lipases (Fonte and Hausberger, 1971; Mason et al., 1971; Baker et al., 1971; Peltier, 1969; Armstrong et al., 1979). Free fatty acids have been shown to injure

the endothelium directly by depleting calcium ions which is essential for endothelial stability (Peltier, 1957).

4. Mechanical obstruction of the pulmonary capillaries and arterioles producing a high distending pressure, and a higher linear velocity of blood flow through the partially obstructed pulmonary circulation might be sufficient to injure the pulmonary endothelium (Barie et al., 1981; Ohkuda et al., 1978). Damage of vascular endothelium has been reported in the systemic veins of the dog following THA (Stewart et al., 1983).

The presence of endothelial blebs indicates an accumulation of edema fluid between the endothelial cells and subjacent basement membrane, thereby lifting away the endothelial cells from the underlying basement membrane into the capillary lumen, forming a bleb. These blebs may finally rupture or become completely detached from the capillary wall, exposing the thrombogenic subendothelial basement membrane (Teplitz, 1968). Although blebs were present, we were unable to detect any edema fluid in lung sections by the light microscope.

Our study showed platelet adhesions to the pulmonary capillary wall as well as platelet degranulation, which may indicate platelet activation. Platelet coagulant activities have been reported to increase significantly following THA in man, and the development of deep vein thrombosis following THA was attributed to such increased platelet activity (Walsh et al., 1976; Walsh et al., 1974). Thrombocytopenia and increased pulmonary platelet trapping have been reported following musculoskeletal trauma (Blaisdell et al., 1970; Jansson et al., 1985; Thorne et al., 1986), bone fractures (Scully, 1956; Gruner, 1971; Olsson et al., 1972; Bergentz and Nilsson, 1961; Bradford et al., 1970), and THA (Modig et al., 1974; Engesaeter et al., 1984).

Vascular damage results in an immediate response (Mackie and Pittilo, 1985) whereby platelets adhere at the site of the damage attempting to bridge the vascular endothelial defect (Morris and Mitchell, 1977) to assist hemostasis (Radegran, 1971; Yardumian et al., 1986) and protect the organism from foreign materials and chemicals introduced into its vascular system. Platelets aggregate when exposed to the subendothelial components of the vessel wall, mainly collagen, basement membrane, and the subendothelial microfibrils (Morris and Mitchell, 1977). After the initial attachment of platelets to the damaged vessel wall, they spread along the vessel surface in order to cover the site of damage. The initial platelet contact and adhesion to the vessel wall appears to involve specific structural components of the subendothelium, platelet membrane receptors, and factor VIII von Willebrand factor (Mackie and Pittilo, 1985; Yardumian et al., 1986).

The process of platelets adhesion and aggregation is mainly related to their degranulation (Peterson and Goldman, 1985) and the subsequent release of several active endogenous compounds. These active endogenous compounds may include ADP, ATP, 5-HT, an antiheparin factor, enzymes, and proteins (Radegran, 1971; Morris and Mitchell, 1977). ADP appears to be responsible for attracting other platelets to stick to each other and to the original platelet mass already adhered to the vessel wall (Morris and Mitchell, 1977).

The evidence of the correlation between deep vein thrombosis and subsequent development of fatal pulmonary thromboembolism following THA is substantial (Pini et al., 1985; Belch et al., 1982; Harris et al., 1976; Kettunen et al., 1973; Hull and Raskob, 1986; Schondorf and Hey, 1976; Dechavanne et al., 1976; Sagar et al., 1976; Mannucci et al., 1976). Many of these reports consider pulmonary thromboembolism to be a sequel to deep vein thrombosis, and it is the thrombi that form in the veins of the thigh or illiac

region which are the principal sources of major pulmonary emboli. However, our ultrastructural findings of acute pulmonary microvascular damage, following THA, demonstrate that the pulmonary vessels, after being damaged by fat emboli, could serve a role as a potential initiator to the thromboembolic process within the pulmonary vessels. Intravascular coagulation within the pulmonary vessels has been reported in experimental fat embolism (Saldeen, 1969).

The data from the ultrastructural study suggest:

1. THA in the dog may be associated with pulmonary microvascular injury.
2. The magnitude of such an injury may be dependent upon the amount of fat emboli trapped in the pulmonary capillaries and arterioles.
3. The pulmonary vessels, after being damaged with fat microemboli, could serve a role as potential initiators of the thromboembolic process within the pulmonary vessels.

C. Systemic and Pulmonary Hemodynamics Study

Average hemoglobin concentration (HB) did not show any significant differences between the groups during the experiment. This indicates the relative stability of the red blood cell mass. Hemoconcentration with significant elevation of HB levels may be observed following massive trauma, such an elevation could be explained by two mechanisms:

1. Massive sympathetic stimulation to the spleen and the liver with subsequent release of red cells into the systemic circulation;
2. Development of pulmonary edema, due to increased pulmonary capillary permeability, and leakage of blood fluids into the lung interstitium. Pulmonary

capillary leaks have been reported during THA in man (Safwat and Dror, 1982). In our study, the absence of pulmonary edema was confirmed histopathologically.

Hemoconcentration may also develop initially during massive surgical intervention because of blood loss, resulting in an increase in sympathetic outflow to the spleen and the liver.

The systemic parameters, mean systemic arterial pressure (AoP), mean left ventricular pressure (LVP), myocardial contractility (DP/DT), and heart rate (HR) remained stable during the experiment. However, a significant drop occurred in cardiac output (CO) in PMM group without significant blood loss. Pooling of blood in the venous side of the circulatory system and decreased vascular impedance in the PMM group could contribute to decreased CO. This observation may be supported by the following evidence:

1. THA in the canine model induced significant ultrastructural changes to the remote veins, but no changes were observed in the arteries (Stewart et al., 1983). These ultrastructural changes may also reflect functional changes, with subsequent loss of the venous tone and blood pooling in the venous side.
2. Several investigators (Kepes et al., 1972; Schuh et al., 1973; Anderson and Stasior, 1976; Byrick et al., 1986a) have suggested a peripheral vasodilatory action of methylmethacrylate monomer without myocardial depression.
3. Other investigators (Modig and Molmberg, 1975; Modig et al., 1973) have proposed that the peripheral vasodilation observed during THA may be due to the release of thromboplastic products into the systemic circulation during THA procedure.
4. The most significant amount of intravascular pulmonary fat was observed in PMM group. This amount of fat may mechanically obstruct a portion of the pulmonary

vascular bed, reducing the venous return and cardiac output. However, the pulmonary arterial pressure did not rise significantly in PMM group to indicate a significant role of pulmonary vascular obstruction as the only cause for the falling CO, which may further indicate that the drop in CO was more likely the result of peripheral venodilation and venous pooling.

In our study, CO dropped significantly in the PMM group. Byrick et al. (1986b) reported similar results in their dog model of bilateral THA. However, the increased amount of pulmonary fat emboli, resulting from the bilateral procedure, may have influenced their results. A significant drop in CO during THA has also been reported in man (Wong et al., 1977; Convery et al., 1975). Other investigators have reported no significant changes in CO associated with THA in man (Modig and Molmberg, 1975; Gooding et al., 1981; Modig et al., 1974) and in dog (Sherman et al., 1983).

There is a general agreement in the literature (Charnley, 1970, Philips et al., 1971; Thomas et al., 1971) that hemodynamic instability observed during THA in man is more significant following the insertion of PMM and prosthesis into the femoral medullary canal than that observed following insertion of PMM and prosthesis into the acetabulum. This observation is difficult to explain on the basis of PMM absorption and toxicity, which would be expected to occur from both these sites (Pelling and Butterworth, 1973). In our study, no hypotensive episodes were encountered during the procedure with PMM or PD. Moreover, CO started to drop during the procedure and before insertion of PMM or PD and prosthesis into the femoral medullary canal. Accordingly, significant systemic monomer toxicity could be excluded as the sole cause for diminished venous return observed in our study. The more pronounced drop in CO observed in PMM group may be due to the release of increased amounts of tissue thromboplastic products from thermally damaged

tissue or to the release of increased amounts of endogenous compounds from embolized lungs. This observation may support those of Cadle et al. (1972), Pelling and Butterworth (1973), Gooding et al. (1981), Dandy (1973), and Modig et al. (1973), that PMM does not appear to have any significant direct toxicity on the cardiopulmonary functions. It is either the tissue thromboplastic products released during the procedure (Modig et al., 1975b), or the pulmonary fat embolism (Feith, 1975), or a synergistic interaction between these two factors that could be responsible for the hemodynamic instability observed in our study.

The significant increase in systemic vascular resistance (SVR) in PMM group may be explained by the significant decrease in CO in that group, since SVR is the interaction of AoP and CO. Also, possible release of vasoactive endogenous compounds from the embolized lung, may further increase SVR in that group. The significant decrease in CO and increase in SVR in T2 compared to T1 for the first three groups (PMM, PD, and SS groups), may indicate the contribution of the surgical trauma alone in inducing such hemodynamic changes.

The changes that were observed in both stroke volume (SV) and cardiac index (CI), are direct reflection to the changes in CO. Hypotensive episodes following insertion of PMM and the femoral prosthesis into the reamed femoral medullary canal have been reported in the literature by several investigators in man (Modig et al., 1975b; Modig and Molmberg, 1975; Kepes et al., 1972; Schuh et al., 1973; Modig et al., 1973) as well as different animal species (Breed, 1974; Pelling and Butterworth, 1973; Byrick et al., 1986). In our study, not one single episode of hypotension was recorded during insertion of either PMM or PD and the femoral prosthesis into the medullary cavity. Other investigators have reported similar observations to ours regarding systemic blood pressure at that stage of THA procedure. Sherman et al. (1983) reported no consistent or significant changes in

mean arterial blood pressure following insertion of PMM and the femoral prosthesis into the reamed femoral medullary canal of the dog. Cadle et al. (1972) reported a biphasic response in blood pressure following insertion of PMM and the femoral prosthesis in man. They observed a fall with subsequent rise in the systemic arterial blood pressure. Engesaeter et al. (1984) and Gooding et al. (1981) did not observe any significant changes in systemic arterial blood pressure in man during THA. James (1984) observed marked hypotension only in patients with pre-existing cardiovascular disease, and none of his disease-free patients showed any marked fall in systemic arterial pressure.

Mean pulmonary arterial pressure (PAP) did not show any significant changes in our study. However, in PMM group, PAP showed a slight, but not significant elevation immediately after insertion of PMM and the femoral prosthesis into the femoral shaft, and again after 30 minutes. To produce a significant elevation in PAP, at least 50% of the pulmonary vascular bed should be obstructed (Malik, 1983). In our study, the lack of increase in PAP may be attributed to two mechanisms:

1. The pulmonary arterioles and veins are highly compliant;
2. The recruitment of additional pulmonary vessels, following embolization, minimizes the pressure changes.

Histopathologically, our study did not show that high magnitude (>50%) of pulmonary vascular obstruction, which may further indicate that mechanism(s) other than pulmonary vascular obstruction alone, may be responsible for the elevated PAP consistently reported in the literature during THA. Increased PAP following embolization is caused by active pulmonary vasoconstriction as well as passive mechanical obstruction . Several investigators have reported significant elevation in PAP following insertion of

PMM and femoral prosthesis in both man (Modig and Molmberg, 1975; Rinecker, 1980; Modig et al., 1973) and dog (Sherman et al., 1983; Byrick et al., 1986b).

Pulmonary vascular resistance (PVR) showed a steady and gradual increase in the PMM group. This increase in PVR may be explained by several mechanisms:

1. The significant decrease in CO observed in that group during the experiment;
2. The small mechanical obstruction caused by fat emboli;
3. Possible release of vasoactive endogenous compounds from the embolized lung, particularly serotonin;
4. The slight, but not significant, increase in PAP observed in that group.

Gooding et al. (1981) reported a steady, but not significant, increase in PVR during THA in man. Other investigators have reported a significant elevation in PVR during THA in man (Modig and Molmberg, 1975; Rinecker, 1980; Modig et al., 1973) and in dog (Sherman et al., 1983).

Reflex hyperdynamic state was observed during THA. The transient elevation in several hemodynamic parameters that we observed during insertion of PMM or PD and the femoral prosthesis appears to be contradictory to the hypodynamic state consistently reported in the literature during THA. Pelling and Butterworth (1973) reported a sudden fall in systemic arterial pressure in both rabbit and cat when either PMM or plasticine (a control material for PMM) was inserted in the femoral medullary canal. However, they indicated that the pattern and timing of the acute cardiovascular changes in the cat differed from those in the rabbit. Breed (1974) reported similar observations in the rabbit. In both studies, the fall in systemic arterial pressure coincided with the elevation in the intramedullary pressure observed during the insertion of PMM (or the test material) and the

prosthesis into the femoral medullary canal. This observation was interpreted as a neural reflex mechanism triggered by the elevation in the intramedullary pressure.

Sherman et al. (1983) reported that in dog, the mean arterial pressure response to introduction of PMM and the femoral prosthesis was varied, and no consistent or significant changes in blood pressure were recorded during that stage of the procedure.

Chiray et al. (1940) reported reflex hypertension in the dog following elevation of the intramedullary pressure. The hypertensive response was associated with an increase in respiratory rate and changes in the pattern of breathing. They also suggested that the magnitude of hypertension may be dependent upon the level of anesthesia, the nature of the test substance injected in the medullary cavity, and the pressure under which it was injected. Animals deeply anesthetized with sodium pentobarbital did not exhibit the hypertensive response to increased intramedullary pressure. Also, they reported that injection of irritant substances under pressure into the medullary cavity resulted in significant hypertension. The bone marrow is supplied with sympathetic nerve fibers that produce vasomotor reflex effects when stimulated (Grant and Root, 1952).

In our study, the hypertensive response which we observed following insertion of PMM or PD may be in agreement with Chiray et al. (1940) for the following reasons:

1. Significant elevation in the intramedullary pressure may have resulted following pressurizing PMM or PD and the femoral prosthesis into the medullary cavity.
2. The magnitude of hemodynamic changes was higher in response to PMM than to PD, this may be due to the irritant nature of PMM as compared to PD.
3. Our animals were maintained under light surgical anesthesia with sodium pentobarbital.

Reflex hypertension following long bone trauma may be a compensatory mechanism to correct for the shock and hypotension associated with bone trauma (Chiray et al., 1940). Hypertension following bone fractures has been reported before (Morton and Kendall, 1965).

We are aware of two reports in the literature (Gooding et al., 1981; James, 1984) in which an elevation of blood pressure, rather than a fall was reported following insertion of PMM and femoral prosthesis into the femoral medullary canal. In one of these reports (James, 1984) the elevation of the systemic arterial pressure was significant, particularly in patients with the least analgesia and lightest levels of anesthesia.

Hypertension following insertion of PMM and femoral prosthesis may have not been frequently reported in the literature because of the domination of hypotensive anesthetic techniques in THA. Deliberate induction of hypotensive anesthesia for THA has been highly recommended (James, 1984; Davis et al., 1974; Thompson et al., 1978). Hypotensive anesthesia in THA minimizes blood loss, allows a clear surgical field, and minimizes lamination of blood in the cement. Hypotensive anesthesia may significantly depress cardiovascular reflexes, enough to inhibit any hypertensive reflexes associated with increased intramedullary pressure during THA procedure. Depression of hypertensive reflexes, in already hypotensive patients, may render these patients more susceptible to hypotensive episodes. Also, most of THA patients are of advanced age group and with pre-existing cardiopulmonary disease. Hemodynamic instability existed in our study, however, our experimental animals were young and healthy, and they were maintained under light surgical anesthesia, consequently, their cardiovascular system and reflexes were able to maintain cardiovascular hemodynamic parameters unchanged.

The difference between our results and those reported in the literature (Breed, 1974; Pelling and Butterworth, 1973) regarding the response of the systemic arterial pressure to increased intramedullary pressure may be due to a) the species, age, and the status of the cardiopulmonary system of the experimental animal involved and/or b) the level of anesthesia achieved during the experiment.

The data summarized from the systemic and pulmonary hemodynamics study suggest the following:

1. Pulmonary edema did not develop during any of our experiments.
2. The blood loss associated with our surgical intervention was not significant enough to influence any subsequent changes in the hemodynamic parameters that were recorded during the experiment.
3. Several changes in hemodynamic parameters were encountered during THA in the dog with PMM.
4. Most of these hemodynamic changes could be attributed to diminished venous return.
5. PMM does not appear to have any direct significant toxicity on the cardiopulmonary functions of healthy and young dogs.
6. The surgical trauma itself can contribute partially to some of these hemodynamic changes.
7. These hemodynamic changes are well tolerated by young and healthy dogs.
8. The hypertensive reflex observed during the procedure may have masked any hypotensive response to insertion of PMM and the femoral prosthesis.

D. Lung Mechanics and Gas Exchange Study

The steady increase in respiratory rate (RR) for PMM group may be explained by the following mechanisms:

1. It may be the result of direct afferent stimulation of vagal nerve endings in the lung by fat emboli (Ross, 1970), particularly J and C fibers (Malik, 1983).
2. Increased intramedullary pressure with subsequent development of reflex tachypnea. Hyperventilation has been reported in man during THA (Rinecker, 1980).

The steady increase in oxygen consumption ($\dot{V}O_2$) in PMM group may be explained by an increase in metabolic activity following trauma as well as an increase in oxygen utilization by the respiratory muscles to meet the demand for increased RR.

The increase in carbon dioxide production ($\dot{V}CO_2$) observed in PMM group may be explained by the increased metabolic activity following trauma, increased oxygen consumption, and the fact that methylmethacrylate monomer is metabolized to carbon dioxide, through the tricarboxylic acid cycle, and removed by the lungs (Corkill et al., 1976). These data are in agreement with a similar study in the dog (Byrick et al., 1986b).

The steady increase in ventilation perfusion ratio (V/Q) in PMM group may be explained by the steady increase in RR coupled with a steady decrease in CO, resulting in hyperventilation of poorly perfused lung units, and the development of new lung units with high V/Q (Dantzker and Bower, 1982).

Airway resistance (AWR) did not change significantly until the end of the experiment for both PMM and PD groups. This increase in AWR may be a direct reflection of airway smooth muscle constriction, and could be explained by two different mechanisms:

1. Secondary constriction through mechanical obstruction of pulmonary vessels (hypocapnic bronchoconstriction) (Malik, 1983; Saldeen, 1976).
2. Release of vasoactive endogenous compounds from the embolized lung, particularly serotonin (Malik, 1983; Thomas et al., 1964). Increased AWR due to bronchial and airway constriction has been reported in man during THA (Modig and Molmberg, 1975; Rinecker, 1980; Modig et al., 1973; Mebius and Hedenstiema, 1982).

The steady and gradual increase in the work of breathing (WB) observed in PMM group may be explained by the increased resistive work associated with the tachypnea observed in that group (Comroe, 1974). Marked increase in WB has been reported in patients with post-traumatic pulmonary embolism (Blaisdell et al., 1970)

Dynamic lung compliance (LC) did not change significantly during the experiment. However, a biphasic response of LC was observed in PMM group. This biphasic response consisted of a sudden decrease following implantation of PMM and femoral prosthesis, followed by a return to the pre-implantation value after 15 minutes, then another sudden drop at 30 minutes post-implantation. This biphasic decrease in LC response matches exactly the biphasic increase in PAP response observed following implantation of PMM and prosthesis into the femoral medullary canal. This matching in response for LC and PAP may indicate a similar origin for both responses. The original stimulus for both responses could be the neural reflex observed following implantation, or the active compounds possibly released from the embolized lung, particularly serotonin. The significant increase in RR observed in PMM group could explain the decrease in LC observed in that group. However, the increase in RR in PMM group was linear, while the decrease in LC was biphasic. A biphasic decrease in LC has been reported in man during

THA (Rinecker, 1980, Mebius and Hedenstierna, 1982). However, in one report (Rinecker, 1980), the decrease in LC was statistically significant. The significance in the previous report could be due to the technique of statistical analysis utilized. LC in the previous study was calculated as a per cent change from the control value, which means that any small drop in a low value of LC may turn to be statistically significant. In our study, values for LC was expressed as the LSM of the absolute values. Changes in LC have been reported following severe trauma and pulmonary embolism, and most investigators have attributed such changes to the release of serotonin from damaged lung, and subsequent development of bronchial constriction (Sturm et al., 1986, Halmagyi et al., 1964, Austin and Sagel, 1972, Puckett et al., 1973). Also, the possible toxic effects of free fatty acids, released following pulmonary fat embolism, on the surfactant system, have been indicated (Peltier, 1969).

E. Blood Gases Study

Partial pressures of oxygen (PaO_2) did not show any significant changes. However, the significant drop in CO observed in PMM group did not depress PaO_2. This could be explained by the tachypnea and the hyperventilatory response (Philbin et al., 1970) observed in that group. Depressed levels of PaO_2 have been reported during THA in man (Modig and Molmberg, 1975; Mebius and Hedenstierna, 1982) and in dog (Sherman et al., 1983; Byrick et al., 1986b). Contradictory results, indicating no significant changes in PaO_2 during THA, have been reported in man (Gooding et al., 1981; Philips et al., 1971). Modig et al. (1974) reported an insignificant increase, rather than a decrease, in PaO_2 during THA in patients receiving lumbar epidural analgesia. Elevated levels of arterial PaO_2 have been reported following massive trauma, and they were explained by the hyperventilatory response associated with trauma (Modig et al., 1976).

The relative stability of partial pressures of carbon dioxide ($PaCO_2$) is in agreement with a previous study in man (Philips et al., 1971). The insignificant decrease in $PaCO_2$ observed in PMM group is explained by the tachypnea observed in that group.

The hyperventilatory response observed in PMM group was reflected again in the increase in arterial blood pH.

The data from the lung mechanics study and blood gases suggest:

1. The changes that were observed in several respiratory parameters during THA in the dog were minimal.
2. These changes were well tolerated by the young and healthy dogs.
3. Most of these respiratory changes could be attributed to pulmonary vascular obstruction with fat emboli and subsequent release of bronchioactive compounds, particularly serotonin.

F. Alveolar Lining Material (ALM) Study

Analysis of ALM was performed for the following reasons:

1. PMM is a potent lipid solvent, and its main route of excretion in the postoperative period is the pulmonary system. This means that PMM could damage the surfactant system during its passage through the alveolar-capillary membrane.
2. Free fatty acids, released from pulmonary fat emboli during THA, could injure the pulmonary surfactant system. However, our analysis of ALM did not reveal any significant differences between the groups in any of the phospholipid components of ALM. The data of our ALM analysis may be explained by:

   a. The acute nature of our study, and the fact that enough existing surfactant is capable of maintaining alveolar stability for at least three hours post-embolization (Sutnick et al., 1969);

b. The possible role of the bronchial circulation which maintains a sufficient blood flow to different lung units following embolization and thus preventing hypoxic damage to the surfactant system (Sutnick et al., 1969);

c. The very potent fibrinolytic system of the dog (Malik, 1983) may be capable of clearing the obstructed pulmonary vessels, with resumption of adequate pulmonary circulation shortly after embolization.

The data from ALM study suggest that the surfactant system is not involved in the acute respiratory mechanical changes associated with THA in the dog. This observation is in agreement with the ultrastructural study, where Type II alveolar pneumocytes were found to be free from any significant ultrastructural damage and loaded with dense lamellar bodies.

VI. SUMMARY AND CONCLUSIONS

This project was designed to examine the possible development of cardiopulmonary complications that may develop during THA in the dog. The three major questions that we have tried to address were the nature of the cardiopulmonary changes that may develop during THA, the possible cardiopulmonary toxicity of PMM in the dog, and the possible role of the lung in the development of these cardiopulmonary changes. The most significant hemodynamic change that was observed in the PMM group was a drop in CO without significant changes in blood volume, myocardial contractility, or systemic blood pressure, indicating diminished venous return and venous blood pooling. The diminished venous return could be explained by venodilation induced possibly by the release of tissue thromboplastic products as well as endogenous compounds from embolized lungs. Moreover, pulmonary vascular obstruction with fat may have partially contributed to the depressed CO observed in that group. The specific role of each factor is unknown. A possible direct significant role of PMM in inducing such hemodynamic changes was excluded. However, some chemical and physical characters of PMM, such as the exothermic reaction produced during polymerization and its lipolytic property, may render its use to be associated with the release of increased amount of marrow fat contents into the systemic circulation.

The presence of pulmonary fat emboli in PMM, PD, and SS groups indicates that pulmonary fat embolism is a consistent finding following THA in the dog and the orthopedic trauma alone is capable of generating pulmonary fat emboli.

Pulmonary microvascular damage, characterized by mechanical tears, endothelial blebs, and platelet adhesions and degranulation, was observed in the PMM group, while

only mechanical tears were observed in the PD group. The magnitude of such damage could be attributed to the degree of pulmonary vascular embolization with fat.

The presence of pulmonary fat emboli in SS group as well as the significant changes that were observed in some hemodynamic parameters at the end of the surgical preparation of the femur and acetabulum, indicates that surgical trauma alone may partially contribute to the hemodynamic changes observed during THA in the dog.

The observed changes in lung mechanics parameters and gas exchange in PMM group were within the physiological tolerance of the animal, and could be attributed to pulmonary vascular obstruction and subsequent release of endogenous compounds. Furthermore, the pulmonary surfactant system was found to play no significant role in the development of such acute changes in lung mechanics. However, the lung may play a role in the development of hemodynamic changes observed during THA, directly by mechanical obstruction of the pulmonary vascular bed with fat, and indirectly by the release of vasoactive endogenous compounds from embolized lungs.

Healthy, young dogs were able to tolerate the hemodynamic instability that was observed during THA by responding with the appropriate reflexes. The depth of anesthesia during THA in the dog, the age of the animal, and the preoperative condition of the cardiopulmonary system, may all have a significant influence on the response of the animal with the appropriate reflexes to counteract any hemodynamic instability that may develop during THA.

VII. RECOMMENDATIONS

Based upon our data, we recommend the following:

1. The risks should be evaluated before recommending THA to dogs with pre-existing cardiopulmonary disease and older dogs.
2. Anesthesiologists should be aware of the fact that cardiopulmonary complications may develop during THA and be prepared to deal with them.
3. Preoperative evaluations of the cardiopulmonary functions are necessary and may include heartworm test, chest radiogram, electrocardiogram, and arterial blood gases.
4. Adequate preoperative hydration and intraoperative fluid loading are highly recommended to avoid the possibility of significant drop in cardiac output during the procedure.
5. Intraoperative evaluations of cardiovascular hemodynamics (cardiac output, systemic arterial pressure) particularly when hemodynamic problems may be anticipated.
6. Any postoperative signs of cardiopulmonary disease, if they develop, should be approached vigorously as a possible sign of pulmonary embolism.

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IX. BIBLIOGRAPHY

Aaron, R. K., A. Carvalho, L. Ellman, and W. H. Harris. 1978. The relationship of intravascular coagulation and fibrinolysis to venous thrombosis following total hip replacement. Clin. Orthop. 135:148-153.

Alexander, J. P. and D. W. Barron. 1978. Clinical considerations in anaesthesia for hip arthroplasty. Anaesthesia 33:784-751.

Alexander, J. P. and D. W. Barron. 1979. Biochemical disturbances associated with total hip arthroplasty. J. Bone Joint Surg. (Br.) 61(1):101-106.

Alho, A. 1982. Fat embolism syndrome—A variant of post-traumatic pulmonary insufficiency. Ann. Chir. Gynaecol. 71 (Suppl. 196):31-36.

Anderson, R. L. and O. G. Stasior. 1976. Self-curing methyl methacrylate: Is it safe? Ophthalmic Surg. 7(4):28-30.

Armstrong, P., A. A. Scott, A. Angel, and M. F. X. Glynn. 1979. Thrombosis and free fatty acids in patients subjected to total hip arthroplasty. Can. J. Surg. 22(4):366-368.

Austin, J. H. and S. S. Sagel. 1972. Alterations of airway caliber after pulmonary embolization in the dog. Invest. Radiol. 7:135-139.

Avery, M. E., H. W. Taeusch, and J. Floros. 1986. Surfactant replacement. N. Eng. J. Med. 315(13):825-826.

Bachofen, M. and E. R. Weibel. 1974. Basic pattern of tissue repair in human lungs following unspecific injury. Chest. (Supplement) 65(4):14S-19S.

Baddeley, S. and J. C. Cullen. 1979. The use of methylmethacrylate in the treatment of giant cell tumors. Aust. N.Z. J. Surg. 49(1):120-122.

Baker, G., C. Duck-Chong, K. Cleland, and N. Berend. 1986. The surfactant system as an intrinsic monitor of acute interstitial lung disease. Chest 89(3):126s-127s.

Baker, P. L., J. A. Pazell, and L. F. Peltier. 1971. Free fatty acids, catecholamines, and arterial hypoxemia in patients with fat embolism. J. Trauma 11(12):1026-1030.

Baker, Philip Donald. 1986. On-line measurement of canine respiratory function and gas exchange using a microcomputer-based system. M.S. Thesis. Iowa State University. 76 pp.

Barber, H. M., E. J. Feil, C. S. B. Galasko, D. H. Edwards, R. A. Sutton, D. W. Haynes, and G. Bentley. 1977. A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. Postgrad. Med. J. 53:130-133.

Barie, P. H. and A. B. Malik. 1982. Role of intravascular coagulation and granulocytes in lung vascular injury after bone marrow embolism. Circ. Res. 50:830-838.

Barie, P. S., F. L. Minear, and A. B. Malik. 1981. Increased pulmonary vascular permeability after bone marrow injection in sheep. Am. Rev. Respir. Dis. 123:648-653.

Barron, D. W. 1979. Intramedullary pressure patterns. Clin. Orthop. 145:183-186.

Barron, D. W. 1980. Pulmonary embolic syndrome caused by cementing of hip endoprosthesis. Acta Orthop. Scand. 51:921-923.

Bart, H. and D. E. Hathway. 1977. Fate of methylmethacrylate in rats. Br. J. Cancer 36:114-119.

Belch, J. F., D. R. Meek, G. D. Lowe, A. F. Campbell, A. B. Young, C. D. Forbes, and C. R. Prentice. 1982. Subcutaneous ancord in prevention of deep vein thrombosis after hip replacement surgery. Thromb. Res. 25:23-31.

Bergentz, S. E. 1968. Fat embolism. Prog. Surg. 6:85-120.

Bergentz, S. E. and I. M. Nilsson. 1961. Effect of trauma on coagulation and fibrinolysis in dogs. Acta Chir. Scand. 122:21-29.

Berman, A. T., H. L. Price, and J. F. Hahn. 1974. The cardiovascular effects of methylmethacrylate in dogs. Clin. Orthop. 100:265-269.

Blaisdell, F. W., R. C. Lim, and R. J. Stallone. 1970. The mechanism of pulmonary damage following traumatic shock. Surg. Gynecol. Obstet. 130:15-22.

Bradford, D. S., R. R. Foster, and H. L. Nossel. 1970. Coagulation alterations, hypoxemia, and fat embolism in fracture patients. J. Trauma 10(4):307-321.

Bras, J. M. and B. E. Veraart. 1980. Pulmonary bone embolism after total hip replacement. J. Bone Joint Surg. (Br.) 62(1):22-24.

Breed, A. L. 1974. Experimental production of vascular hypotension, and bone marrow and fat embolism with methylmethacrylate cement. Clin. Orthop. 102:227-244.

Bright, D. S., H. G. Clarck, and D. E. McMollum. 1972. Serum analysis and toxic effects of methylmethacrylate. Surg. Forum 23:455-457.

Brown, D. L. and C. L. Pormley. 1982. Second-degree atrioventricular block after methylmethacrylate. Anesthesiology 56(5):391-392.

Busch, C., J. Modig, S. Olerud, and T. Saldeen. 1975. Pulmonary microembolism during total hip replacement surgery. Bibl. Anat. 13:275-276.

Byrick, R. J., D. Forbes, and J. P. Waddell. 1986a. A monitored cardiovascular collapse during cemented total knee replacement. Anesthesiology 65:213-216.

Byrick, R. J., G. Howie, J. C. Kay, J. P. Waddell, and B. Mullen. 1986b. Monitoring for marrow embolism during cemented arthroplasty procedures (Abstract). Can. Anaesth. Soc. J. 33(3):S120-S121.

Cadle, D., M. L. James, R. S. Ling, R. F. Piper, D. L. Pryer, and C. C. Wilmshurst. 1972. Cardiovascular responses after methylmethacrylic cement. Br. Med. J. 4:107-108.

Chandler, H. P., F. T. Reineck, R. L. Wixson, and J. C. McCarthy. 1981. Total hip replacement in patients younger than thirty years old: A five year follow up study. J. Bone Joint Surg. (Am.) 63(9):1426-1434.

Charnely, J. 1970. Acrylic cement in orthopaedic surgery. Williams and Wilkins Company, Baltimore. 131 pp.

Charnley, J. 1961. Arthroplasty of the Hip: A new operation. Lancet 1:1129-1132.

Charnley, J. 1979. Low friction arthroplasty of the hip: Theory and practice. Springer-Verlag Company, New York, N.Y. 376 pp.

Chiray, M., L. Justin-Besancon, R. Benda, C. Debray, and M. Lacour. 1940. Influence des injections intra-medullaires osseuses sur la pression arterielle du chien (in French). Ann. Med. 46(4):267-275.

Cohen, C. A. and T. Smith. 1971. The intraoperative hazard of acrylic bone cement: Report of a case. Anesthesiology 35(5):547-549.

Comroe, J. H. 1974. Physiology of respiration. 2nd ed. Year Book Medical Publishers, Chicago, Illinois. 316 pp.

Convery, F. R., D. R. Gunn, J. D. Hughes, and W. E. Mortin. 1975. The relative safety of polymethyl-methacrylate. J. Bone Joint Surg. (Am.) 57(1):57-64.

Corkill, J. A., E. J. Lloyd, D. H. G. Crout, R. S. Ling, M. L. James, and R. J. Piper. 1976. Toxicology of methyl-methacrylate: The rate of disappearance of methyl methacrylate in human blood in vitro. Clin. Chim. Acta 68:141-146.

Coventry, M. B., R. D. Beckenbaugh, D. R. Nolan, and D. M. Ilstrup. 1974. 2,012 Total hip arthroplasties: A study of prospective course and early complications. J. Bone Joint Surg. (Am.) 56(2):273-284.

Crout, D. H. G., J. A. Corkill, M. L. James, and R. S. Ling. 1979. Methylmethacrylate metabolism in man. Clin. Orthop. 141:90-95.

Busch, C., J. Modig, S. Olerud, and T. Saldeen. 1975. Pulmonary microembolism during total hip replacement surgery. Bibl. Anat. 13:275-276.

Byrick, R. J., D. Forbes, and J. P. Waddell. 1986a. A monitored cardiovascular collapse during cemented total knee replacement. Anesthesiology 65:213-216.

Byrick, R. J., G. Howie, J. C. Kay, J. P. Waddell, and B. Mullen. 1986b. Monitoring for marrow embolism during cemented arthroplasty procedures (Abstract). Can. Anaesth. Soc. J. 33(3):S120-S121.

Cadle, D., M. L. James, R. S. Ling, R. F. Piper, D. L. Pryer, and C. C. Wilmshurst. 1972. Cardiovascular responses after methylmethacrylic cement. Br. Med. J. 4:107-108.

Chandler, H. P., F. T. Reineck, R. L. Wixson, and J. C. McCarthy. 1981. Total hip replacement in patients younger than thirty years old: A five year follow up study. J. Bone Joint Surg. (Am.) 63(9):1426-1434.

Charnely, J. 1970. Acrylic cement in orthopaedic surgery. Williams and Wilkins Company, Baltimore. 131 pp.

Charnley, J. 1961. Arthroplasty of the Hip: A new operation. Lancet 1:1129-1132.

Charnley, J. 1979. Low friction arthroplasty of the hip: Theory and practice. Springer-Verlag Company, New York, N.Y. 376 pp.

Chiray, M., L. Justin-Besancon, R. Benda, C. Debray, and M. Lacour. 1940. Influence des injections intra-medullaires osseuses sur la pression arterielle du chien (in French). Ann. Med. 46(4):267-275.

Cohen, C. A. and T. Smith. 1971. The intraoperative hazard of acrylic bone cement: Report of a case. Anesthesiology 35(5):547-549.

Comroe, J. H. 1974. Physiology of respiration. 2nd ed. Year Book Medical Publishers, Chicago, Illinois. 316 pp.

Convery, F. R., D. R. Gunn, J. D. Hughes, and W. E. Mortin. 1975. The relative safety of polymethyl-methacrylate. J. Bone Joint Surg. (Am.) 57(1):57-64.

Corkill, J. A., E. J. Lloyd, D. H. G. Crout, R. S. Ling, M. L. James, and R. J. Piper. 1976. Toxicology of methyl-methacrylate: The rate of disappearance of methyl methacrylate in human blood in vitro. Clin. Chim. Acta 68:141-146.

Coventry, M. B., R. D. Beckenbaugh, D. R. Nolan, and D. M. Ilstrup. 1974. 2,012 Total hip arthroplasties: A study of prospective course and early complications. J. Bone Joint Surg. (Am.) 56(2):273-284.

Crout, D. H. G., J. A. Corkill, M. L. James, and R. S. Ling. 1979. Methylmethacrylate metabolism in man. Clin. Orthop. 141:90-95.

Eftekhar, N. 1978. Principles of total hip arthroplasty. Mosby Company, St. Louis. 656 pp.

Eftekhar, N. S., H. A. Kiernar, and F. E. Stinchfield. 1976. Systemic and local complications following low-friction arthroplasty of the hip joint. Arch. Surg. 111:150-155.

Ellis, R. H. and J. Mulvein. 1974. The cardiovascular effects of methylmethacrylate. J. Bone Joint Surg. (Br.) 56(1):59-61.

Emson, H. E. 1958. Fat embolism studied in 100 patients dying after injury. J. Clin. Pathol. 11:28-35.

Engesaeter, L. B., T. Strand, T. S. Raugstad, S. Huseb, and N. Langeland. 1984. Effects of a distal venting hold in the femur during total hip replacement. Arch. Orthop. Trauma. Surg. 103(5):328-331.

Engwall, Michael James. 1980. Changes in pulmonary hemodynamics and lung function associated with an acute intravenous dose of ethanol. M.S. Thesis. Iowa State University. 91 pp.

Engwall, Michael James. 1986. Cardio-pulmonary effects of inhaled solvents: Computer assisted measurements and analysis. Ph.D. Dissertation. Iowa State University. 121 pp.

Fairman, R. P., C. Morrow, and F. L. Glauser. 1984. Methylmethacrylate induces pulmonary hypertension and increases lung vascular permeability in sheep. Am. Rev. Resp. Dis. 130:92-95.

Feith, R. 1975. Side-effects of acrylic cement implanted into bone. Acta Orthop. Scand. (Suppl. 161):13-25.

Flink, J. R., B. R. Pitt, G. L. Hammond, and C. N. Gillis. 1982. Selective effect of microembolization on pulmonary removal of biogenic amines. J. Appl. Physiol. 52(2):421-427.

Fonte, D. A. and F. X. Hausberger. 1971. Pulmonary free fatty acids in experimental fat embolism. J. Trauma 11(8):668-672.

Forwell, G. D. and G. I. C. Ingram. 1957. The effect of adrenaline infusion on human blood. J. Physiol. (Lond.) 135:371-383.

Frayn, K. N., R. A. Little, P. F. Maycock, and H. B. Stoner. 1985. The relationship of plasma catecholamines to acute metabolic and hormonal responses to injury in man. Circ. Shock 16:229-240.

Fregert, S. 1983. Occupational hazards of acrylate bone cement in orthopedic surgery. Acta Orthop. Scand. 54:787-789.

Fries, I. B., A. A. Fisher, and E. A. Salvati. 1975. Contact dermatitis in surgeons from methylmethacrylate bone cement. J. Bone Joint Surg. (Am.) 57(4):547-549.

Gitel, S. N., E. A. Salvati, S. Wessler, H. J. Robinson, and M. H. Worth. 1979. The effect of total hip replacement and general surgery on antithrombine III in relation to venous thrombosis. J. Bone Joint Surg. (Am.) 61(5):653-656.

Gooding, J. M., J. T. Weng, R. R. Kirly, and R. A. Smith. 1981. Methylmethacrylate seeks an appeal. South. Med. J. 74(10):1209-1210.

Gordon, S. L. 1982. Introduction. Page I in NIH Consensus Development Conference: Total Hip Joint Replacement, Program Abstracts. National Institutes of Health, Washington, D.C.

Grant, W. C. and W. S. Root. 1952. Fundamental stimulus for erythropoiesis. Physiol. Rev. 32:449-498.

Gruner, O. P. 1971. Platelets, fibrinogen, and fat embolism after femoral fracture in rabbits. Acta Chir. Scand. 137:407-414.

Gurd, A. R. 1970. Fat embolism: An aid to diagnosis. J. Bone Joint Surg. (Br.) 52(4):732-737.

Hallin, G., J. Modig, L. Nordgren, and S. Olerud. 1974. The intramedullary pressure during the bone marrow trauma of total hip replacement surgery. Upsala J. Med. Sci. 79:51-54.

Halmagyi, D. F., B. Starzecki, and G. J. Horner. 1964. Humoral transmission of cardiorespiratory changes in experimental lung embolism. Circ. Res. 14:546-554.

Hampson, W. G., F. C. Harris, H. K. Lucas, P. H. Roberts, I. W. McCall, P. C. Jackson, N. L. Powell, and G. E. Staddon. 1974. Failure of low-dose heparin to prevent deep-vein thrombosis after hip replacement arthroplasty. Lancet 2:795-797.

Harris, W. H. 1977. Total hip replacement. N. Eng. J. Med. 297(12):650-651.

Harris, W. H., C. Athanasoulis, A. C. Waltman, and E. W. Salzman. 1976. Cuff-impedence phlebography and ^{125}I fibrinogen scanning versus roentgenographic phlebography for diagnosis of thrombophlebitis following hip surgery. J. Bone Joint Surg. (Am.) 58(7):939-944.

Harris, W. H., E. W. Salzman, C. Athanasoulis, A. Waltman, S. Baum, R. W. DeSanctis, M. S. Potsaid, and H. Sise. 1975. Comparison of ^{125}I fibrinogen count scanning with phlebography for detection of venous thrombi after elective hip surgery. N. Eng. J. Med. 292(13):665-667.

Haupton, J. 1985. Total hip replacement. Pages 2174-2177 in D. H. Slater, ed. Text book of small animal surgery. W. B. Saunders, Philadelphia, Pa.

Hayat, M. A. 1970. Principles and techniques of electron microscopy (Vol. 1). Van Nostrand Reinhold Company, New York, New York. 412 pp.

Heggers, J. P., J. B. Talmage, and S. T. Barnes. 1978. Cellular immune response to methylmethacrylate in experimentally sensitized guinea pig. Milit. Med. 143(3):192-195.

Herndon, J. H., C. O Bechtol, and D. P. Crickenberger. 1974. Fat embolism during total hip replacement. J. Bone Joint Surg. (Am.) 56(7):1350-1362.

Hills, B. A. 1981. What is the true role of surfactant in the lung? Thorax 36:1-4.

Hirsh, J. 1984. Prophylaxis of venous thromboembolism. Mod. Concepts Cardiovasc. Dis. 53(5):25-29.

Hoefle, W. D. 1974. A surgical procedure for prosthetic total hip replacement in the dog. J. Am. Anim. Hosp. Assoc. 10:269-276.

Homsy, C. A., H. S. Tullos, and J. W. King. 1967. Evaluation of rapid-cure acrylic compound for prosthesis stabilization. Clin. Orthop. 67:169-171.

Homsy, C. A., H. S. Tullos, M. S. Anderson, N. M. Differrante, and J. W. King. 1972. Some physiological aspects of prosthesis stabilization with acrylic polymer. Clin. Orthop. 83:317-328.

Houghton, G. R., E. G. Papadakis, and C. R. Rizza. 1978. Changes in blood coagulation during total hip replacement. Lancet 1:1336-1338.

Hughes, J. D., F. R. Convery, and J. P. Drucker. 1972. Total hip replacement with polymethylmethacrylate: Lack of early effect on lung function in man. Am. Rev. Resp. Dis. 105:974-977.

Hull, R. D. and G. E. Raskob. 1986. Prophylaxis of venous thromboembolic disease following hip and knee surgery. J. Bone Joint Surg. 68(1):146-150.

Jacobs, R. R. and O. McLain. 1979. The role of embolic fat in post-traumatic pulmonary insufficiency. Int. Orthop. 3:71-75.

James, M. L. 1984. Anaesthetic and metabolic complications. Pages 1-17 in R. S. Ling, ed. Complications of total hip replacement. Churchill Livingstone, Edinbrough.

Jansson, I., L. Loven, L. Rammer, and S. Lennquist. 1985. Pulmonary trapping of platelets and fibrin after musculoskeletal trauma: An experimental model. J. Trauma 25(4):288-298.

Jefferiss, C. D., J. C. Lee, and R. S. Ling. 1975. Thermal aspect of self-curing polymethylmethacrylate. J. Bone Joint Surg. (Br.) 57(4):511-518.

Jennings, J. J., W. H. Harris, and A. Sarmiento. 1976. A clinical evaluation of aspirin prophylaxis of thromboembolic disease after total hip arthroplasty. J. Bone Joint Surg. (Am.) 58(7):926-928.

Johnson, R., J. R. Green, and J. Charnley. 1977. Pulmonary embolism and its prophylaxis following the Charnley total hip replacement. Clin. Orthop. 127:123-132.

Kaduce, T. L., K. C. Norton, and A. A. Spector. 1983. A rapid, isocratic method for phospholipid separation by high-performance liquid chromatography. J. Lipid Res. 24:1398-1403.

Kallos, T. 1975. Impaired arterial oxygenation associated with use of bone cement in the femoral shaft. Anesthesiology 42(2):210-216.

Kallos, T., J. E. Enis, F. Gollan, and J. H. Davis. 1974. Intramedullary pressure and pulmonary embolism of femoral medullary contents in dogs during insertion of bone cement and a prosthesis. J. Bone Joint Surg. (Am.) 56(7):1363-1367.

Kay, A., B. Davidson, E. Badley, and S. Wagstaff. 1983. Hip arthroplasty: Patient satisfaction. Br. J. Rheumatology 22:243-249.

Kay, N. R. 1973. Some complications of total hip replacement. Clin. Orthop. 95:73-79.

Kelsey, J. 1982. Total hip replacement: Epidemiology and impact. Pages 23-30 in NIH Consensus Development Conference: Total Hip Joint Replacement, Program Abstracts. National Institutes of Health, Washington, D.C.

Kepes, E. R., P. S. Underwood, and L. Becsey. 1972. Intraoperative death associated with acrylic bone cement. J. Am. Med. Assoc. 222(5):576-577.

Kessler, M. J., J. L. Kupper, and R. J. Brown. 1977. Accidental methylmethacrylate inhalation toxicity in a rhesus monkey (Macaca mulatta). Lab. Anim. Sci. 27(3):388-390.

Kettunen, K., P. Karjalainen, E. Poikolainen, and M. A. Mattila. 1973. Dextran 70 for the prevention of deep-vein thrombosis following elective hip surgery. Ann. Chir. Gynaecol. 62:350-353.

Kim, K. C. and M. A. Ritter. 1972. Hypotension associated with methymethacrylate in total hip arthroplasties. Clin. Orthop. 88:154-160.

Kirman, W. O. 1973. Systemic phenomena and bone cement. Ir. J. Med. Sci. 142:342-345.

Klein, S. L. 1974. Molecular structure of bone cement. Anesthesiology 40(2):206-207.

Koide, M., R. N. Pilon, L. D. Vandam, and J. D. Lowell. 1974. Anesthetic experience with total hip replacement. Clin. Orthop. 99:78-85.

Kuroki, Y., K. Dempo, and T. Akino. 1986. Immunohistochemical study of human pulmonary surfactant apoproteins with monoclonal antibodies. Am. J. Pathol. 124(1):25-33.

Lachiewicz, P. F. and C. S. Ranawat. 1981. Fat embolism syndrome following bilateral total knee replacement with two condylar prosthesis: Report of two cases. Clin. Orthop. 160:106-108.

Leighton, R. L. 1980. Placement of a total canine hip prosthesis. Mod. Vet. Pract. 61(4):329-331.

Leyvras, P. F., J. Richard, F. Bachmann, G. V. Melle, J. M. Treyvaud, J. J. Livio, and G. Candardjis. 1983. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. N. Eng. J. Med. 309(16):954-958.

Liang, M. H. and K. E. Cullen. 1984. Evaluation of outcomes in total joint arthroplasty for rheumatoid arthritis. Clin. Orthop. 182:41-55.

Linder, L. 1976. Tissue reaction to methylmethacrylate monomer. Acta Orthop. Scand. 47:3-10.

Linder, L. and M. Romanus. 1976. Acute local tissue effects of polymerizing acrylic bone cement. Clin. Orthop. 115:303-312.

Mackie, I. J. and R. M. Pittilo. 1985. Vascular integrity and platelet function. Int. Anesthesiol. Clin. 23(2):3-21.

Malik, A. B. 1983. Pulmonary microembolism. Physiol. Rev. 63(3):1115-1207.

Malik, A. B. 1985. Mediators of pulmonary vascular injury and edema after thrombin. Pages 429-454 in S. I. Said, ed. The pulmonary circulation and acute lung injury. Futura Publishing Company, Mount Kisco, New York.

Mannucci, P. M., L. E. Citterio, and N. Panajotopoulos. 1976. Low-dose heparin and deep-vein thrombosis after total hip replacement. Thromb. Haemost. 36:157-164.

Mason, E. E., D. D. Gordy, F. A. Chemigoy, and K. J. Printen. 1971. Fatty acid toxicity. Surg. Gynecol. Obstet. 133:992:998.

McKee, G. K. and W. J. Farrar. 1966. Replacement of arthritic hip by McKee-Farrar prosthesis. J. Bone Joint Surg. (Br.) 48:245-259.

McLaughlin, R. E., C. A. DiFozio, M. Hakala, B. Abboot, J. A. McPhail, W. P. Mack, and D. E. Sweet. 1973. Blood clearance and acute pulmonary toxicity of methylmethacrylate in dogs after simulated arthroplasty and intravenous injection. J. Bone Joint Surg. (Am.) 55(8):1621-1628.

McManus, F. 1976. The incidence of deep venous thrombosis after total hip replacement using dextran 70 prophylaxis—A venographic study. Ir. J. Med. Sci. 145(6):201-206.

McMaster, W. C., G. Bradley, and T. R. Waugh. 1974. Blood pressure lowering effect of methylmethacrylate monomer. Clin. Orthop. 98:254-257.

Mebius, C. and G. Hedenstiema. 1982. Gas exchange and respiratory mechanics during hip arthroplasty. Acta Anaesthesiol. Scand. 26:15-21.

Meek, R. N., B. Woodruff, and D. B. Allardyce. 1972. Source of fat macroglobules in fracture of the lower extremity. J. Trauma 12(6):432-434.

Miller, F., D. C. Young, and G. J. Wang. 1983. The incidence of thromboembolic disease. Clin. Orthop. 176:210-216.

Modig, J. 1976. Respiration and circulation after total hip replacement surgery. Acta Anaesthesiol. Scand. 20:225-236.

Modig, J. and P. Molmberg. 1975. Pulmonary and circulatory reactions during total hip replacement surgery. Acta Anaesthesiol. Scand. 19:219-237.

Modig, J. S. Olerud, and P. Molmberg. 1973. Sudden pulmonary dysfunction in prosthetic hip replacement surgery. Acta Anaesth. Scand. 17:276-282.

Modig, J., C. Busch, and G. Waernbaum. 1975a. Effects of graded infusions of monomethylmethacrylate on coagulation, blood lipids, respiration, and circulation. Clin. Orthop. 113:187-197.

Modig, J., C. Busch, S. Olerud, and T. Saldeen. 1974. Pulmonary microembolism during intramedullary orthopedic trauma. Acta Anaesthesiol. Scand. 18:133-143.

Modig, J., C. Busch, S. Olerud, T. Saldeen, and G. Waernbaum. 1975b. Arterial hypotension and hypoxaemia during total hip replacement: The importance of thromboplastic products, fat embolism and acrylic monomers. Acta Anaesthesiol. Scand. 19:28-43.

Modig, J., S. Olerud, P. Molmberg, and C. Busch. 1973. Medullary fat embolization during total hip replacement: A preliminary report. Injury 5:161-164.

Modig, J., U. Hedstrand, J. Fischer, and J. Lundstrom. 1976. Early recognition and treatment of post-traumatic pulmonary microembolism. Crit. Care Med. 4(4):180-185.

Morris, G. K. and J. R. A. Mitchell. 1977. The aetiology of acute pulmonary embolism and the identification of high risk groups. Br. J. Hosp. Med. 18(1):6-12.

Morton, K. S. and M. J. Kendall. 1965. Fat embolism: Its production and source of fat. Can. J. Surg. 8:214-220.

Nevitt, M. C., W. V. Epstein, M. Masen, and W. R. Murray. 1984. Work disability before and after total hip arthroplasty. Arthritis and Rheumatism 27(4):410-421.

Newens, A. F. and R. G. Volz. 1972. Severe hypotension during prosthetic hip surgery with acrylic bone cement. Anesthesiology 36(3):298-300.

Nicastro, J. F., H. Shaji, G. D. Rovere, and A. G. Gristina. 1975. Effects of methylmethacrylate on S. aureus growth and rabbit alveolar macrophage phagocytosis and glucose metabolism. Surg. Forum 26:501-503.

Nice, E. J. 1973. Case report: Cardiac arrest following use of acrylic bone cement. Anaesth. Intensive Care 1(3):244-245.

Nunmaker, D. M. 1985. Total joint replacement. Pages 555-560 in C. D. Newton and D. M. Nunmaker, eds. Text book of small animal orthopedics. J. P. Lippincott Company, Philadelphia, Pa.

Ohkuda, K., K. Nakahara, W. J. Weidner, A. Binder, and N. C. Staub. 1978. Lung fluid exchange after uneven pulmonary artery obstruction in sheep. Circ. Res. 43(2):152-161.

Olmstead, M. L., R. B. Hohn, and T. M. Turner. 1981. Technique for canine total hip replacement. Vet. Surg. 10:44-50.

Olmstead, M. L., R. B. Hohn, and T. M. Turner. 1983. A five-year study of 221 total hip arthroplasty in the dog. J. Am. Vet. Med. Assoc. 183(2):191-194.

Olsson, P., K. Radegran, and J. Swedenborg. 1972. Effects of disseminated intravascular coagulation on pulmonary circulation and respiration. Int. Anesthesiol. Clin. 10:173-179.

Panush, R. S. and R. W. Petty. 1978. Inhibition of human lymphocyte responses by methylmethacrylate. Clin. Orthop. 134:356-363.

Park, W. Y., P. Balingit, P. I. Kenmore, and T. E. Macnamara. 1973. Changes in arterial oxygen tension during total hip replacement. Anesthesiology 39(6):642-644.

Parker, F. B., S. D. Wax, K. Kusajima, and W. R. Webb. 1974. Hemodynamic and pathological findings in experimental fat embolism. Arch. Surg. 108:70-74.

Pedersen, J. G., B. Lund, and I. Reimonn. 1983. Depressive effects of acrylic cement components on bone metabolism. Acta Orthop. Scand. 54:796-801.

Peebles, D. J., R. H. Ellis, and S. D. K. Stride. 1972. Cardiovascular effects of methylmethacrylate cement. Br. Med. J. (1):349-351.

Pelling, D. and K. R. Butterworth. 1973. Cardiovascular effects of acrylic bone cement in rabbits and cats. Br. Med. J. 2:638-641.

Peltier, L. F. 1957. An appraisal of the problem of fat embolism. Intl. Abstr. Surg. 104(4):313-324.

Peltier, L. F. 1965. The diagnosis of fat embolism. Surg. Gynecol. Obstet. 121:371-379.

Peltier, L. F. 1969. Fat embolism. Clin. Orthop. 66:241-253.

Peterson, R. T. and A. L. Goldman. 1985. Pulmonary embolism. Primary Care 12(2):383-396.

Petty, T. L., O. K. Reiss, G. W. Paul, G. W. Silvers, and N. D. Elkins. 1977. Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with trauma and shock. Am. Rev. Resp. Dis. 115:531-536.

Petty, W. 1978a. The effect of methylmethacrylate on bacterial phagocytosis and killing by human polymorphnuclear leukocytes. J. Bone Joint Surg. (Am.) 60(6):752-757.

Petty, W. 1978b. The effect of methylmethacrylate on chemotaxis of polymorphnuclear leukocytes. J. Bone Joint Surg. (Am.) 60(4):492-498.

Petty, W. 1980. Methylmethacrylate concentrations in tissues adjacent to bone cement. J. Biomed. Mater. Res. 14:427-438.

Phang, P. T. and K. M. Keough. 1986. Inhibition of pulmonary surfactant by plasma from normal adults and from patients having cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg. 91:248-252.

Philbin, D. M., S. F. Sullivan, F. O. Bowman, J. R. Malm, and E. M. Papper. 1970. Postoperative hypoxemia: Contributions of the cardiac output. Anesthesiology 32(2):136-142.

Philips, H., P. V. Cole, and A. W. Lettin. 1971. Cardiovascular effects of implanted acrylic bone cement. Br. Med. J. 3:460-461.

Pini, M., E. Espadini, L. Carluccio, C. Giovanordi, E. Magnani, U. Ugolotti, and E. Uggeri. 1985. Dextran/ aspirin versus heparin/dihydroergotamine in preventing thrombosis after hip fractures. J. Bone Joint Surg. (Am.) 67(2):305-309.

Powell, J. N., P. J. McGrath, S. K. Lahiri, and P. Hill. 1970. Cardiac arrest associated with bone cement. Br. Med. J. 3:362.

Puckett, C. L., A. S. Gervin, G. R. Rhodes, and D. Silver. 1973. Role of platelets and serotonin in acute massive pulmonary embolism. Surg. Gynecol. Obstet. 137:618-622.

Radegran, K. 1971. Circulatory and respiratory effects of induced platelet aggregation. An experimental study in dogs. Acta Chir. Scand. (Supplement 420):1-24.

Ramanathan, S., A. K. Mosik, J. Arismendy, J. Cholon, and H. Turndrof. 1983. Direct inhibitory effect of methylmethacrylate monomer on vascular smooth muscle (Abstract). Anesthesiology 59(3):A56.

Rijke, A. M. and R. A. Johonson. 1977. On the fate of methylmethacrylate in the blood. J. Biomed. Mater. Res. 11:211-221.

Rinecker, H. 1980. New clinico-pathophysiological studies on the bone cement implantation syndrome. Arch. Orthop. Trauma. Surg. 97:263-274.

Risberg, B. and M. Heidman. 1980. The cascade system in posttraumatic pulmonary insufficiency. Acta Chir. Scand. (Suppl. 499):107-112.

Rogers, F. B., C. M. Sheaff, P. J. Nolan, A. P. Robin, G. Merlotti, and J. A. Barrett. 1986. Fibronectin depletion and microaggrate clearance following trauma. J. Trauma 26(4):339-342.

Rosoff, C. B., E. W. Salzman, V. Gurewich, and H. K. Schroeder. 1971. Reduction of platelet serotonin and the response to pulmonary emboli. Surgery 70(1):12-19.

Ross, A. P. J. 1970. The fat embolism syndrome: With special reference to the importance of hypoxemia in the syndrome. Ann. R. Coll. Surg. Engl. 46:159-171.

Safwat, A. M. and A. Dror. 1982. Pulmonary capillary leak associated with methylmethacrylate during general anesthesia. Clin. Orthop. 168:59-63.

Sagar. S., D. Nairn, J. D. Stamatakis, F. H. Maffei, A. F. Higgins, D. P. Thomas, and V. V. Kakkar. 1976. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. Lancet 1:1151-1154.

Saldeen, T. 1969. Intravascular coagulation in the lungs in experimental fat embolism. Acta Chir. Scand. 135:653-662.

Saldeen, T. 1976. The microembolism syndrome. Microvasc. Res. 11:227-259.

Sautter, R. D. et al. 1983. Aspirin-sulfinpyrazone in prophylaxis of deep venous thrombosis in total hip replacement. J. Am. Med. Assoc. 250(19):2649-2654.

Schatzker, J., J. G. Horne, G. Sumner-Smith, R. Sanderson, and J. P. Murnaghan. 1975. Methylmethacrylate cement: Its curing temperature and effect on articular cartilage. Can. J. Surg. 18:172-178.

Schondorf, T. H. and D. Hey. 1976. Combined administration of low dose heparin and aspirin as prophylaxis of deep vein thrombosis after hip joint surgery. Haemostasis 5:250-257.

Schuh, F. T., S. M. Schuh, M. G. Viguera, and R. N. Terry. 1973. Circulatory changes following implantation of methylmethacrylate bone cement. Anesthesiology 39(4):455-457.

Schwarz, H. 1986. Morphometric requirements for image analysis and the IBAS interactive automatic image analysis system. Anal. Quant. Cytol. Histol. 8:267-271.

Scully, R. E. 1956. Fat embolism in Korean battle casualties. Am. J. Pathol. 32(3):379-397.

Serota, M. L. 1984. Fat embolism syndrome. West. J. Med. 141:501-505.

Sevitt, S. 1972. Fat embolism in patients with fractured hips. Br. Med. J. 2:257-262.

Sherman, R. M., R. J. Byrick, J. C. Kay, T. R. Sullivan, and J. P. Waddell. 1983. The role of lavage in preventing hemodynamic and blood-gas changes during cemented arthroplasty. J. Bone Joint Surg. (Am.) 65(4):500-506.

Shoemaker, W. C., P. Appel, L. S. Czer, R. Bland, S. Schwartz, and J. A. Hopkins. 1980. Pathogenesis of respiratory failure (ARDS) after hemorrhage and trauma: I. Cardiorespiratory patterns preceding the development of ARDS. Crit. Care Med. 8(9):504-512.

Smith, F. B. 1983. Role of the pulmonary surfactant system in lung disease in adults. NY State J. Med. 83(6):851-856.

Spealman, C. R., R. J. Main, and H. B. Hoog. 1945. Monomeric methylmethacrylate Studies on toxicity. Ind. Med. 14:292-298.

Stewart, G. J., P. D. Alburger, E. A. Stone, and T. W. Soszka. 1983. Total hip replacement induces injury to remote veins in a canine model. J. Bone Joint Surg. (Am.) 56(1):97-102.

Stinchfield, F. 1982. Institutional considerations: facilities, staffing, training. NIH Consensus Development Conference: Pages 64-65 in Total Hip Joint Replacement, Program Abstracts. National Institutes of Health, Washington, D.C.

Stormorken, H. 1979. Interrelations between the coagulation, the fibrinolytic and the kallikrein-kinin system. Scand. J. Haematol. (Suppl. 34):24-27.

Strayer, D. S., T. A. Merritt, J. Lwebuga-Mukasa, and M. Hallman. 1986. Surfactant-anti-surfactant immune complexes in infants with respiratory distress syndrome. Am. J. Pathol. 122(2):353-362.

Stulberg, B. N., L. D. Dorr, C. S. Ranawat, and R. Schveider. 1982. Aspirin prophylaxis for pulmonary embolism following total hip arthroplasty. Clin. Orthop. 168:119-123.

Sturm, J. A., D. H. Wisner, H. J. Oestern, C. J. Kant, H. Tscherne, and H. Creutzig. 1986. Increased lung capillary permeability after trauma: A prospective clinical study. J. Trauma 26(5):409-418.

Sutnick, A. I., L. D. Miller, M. M. Cronlund, and A. J. Donnelly. 1969. Lung lipid metabolism and surface tension phenomena following pulmonary embolism. Ann. Surg. 175(5):839-847.

Swank, R. L., W. Hissen, and S. E. Bergentz. 1964. 5-Hydroxytryptamine and aggregation of blood elements after trauma. Surg. Gynecol. Obstet. 119:779-784.

Talucci, R. C., J. Manning, S. Lampard, A. Bach, and C. J. Carrico. 1983. Early intramedullary nailing of femoral shaft fractures: A cause of fat embolism syndrome. Am. J. Surg. 146:107-111.

Tansy, M. F. and F. M. Kendall. 1979. Update on the toxicity of inhaled methyl methacrylate vapor. Drug Chem. Toxicol. 2(4):315-330.

Taylor, D. G. 1976. The costs of arthritis and the benefits of joint replacement surgery. Proc. R. Soc. Lond. B. 192:145-155.

Teplitz, C. 1968. The ultrastructural basis for pulmonary pathophysiology following trauma. J. Trauma 8(5):700-703.

Thomas, D., M. Stein, G. Tanabe, V. Rege, and S. Wessler. 1964. Mechanism of bronchoconstriction produced by thromboemboli in dogs. Am. J. Physiol. 206(6):1207-1212.

Thomas, T. A., I. C. Sutherland, and T. D. Waterhouse. 1971. Cold curing acrylic bone cement. Anaesthesia 26(3):298-303.

Thompson, G. E., R. D. Miller, W. C. Stevens, and W. R. Murray. 1978. Hypotensive anesthesia for total hip arthroplasty: A study of blood loss and organ function (brain, heart, liver, and kidney). Anesthesiology 48:91-96.

Thorne, J., S. Blomquist, O. Elmer, B. A. Jonsson, S. Lindahl, and S. E. Strand. 1986. Early posttraumatic pulmonary platelet trapping and potentiation by oral pretreatment with alcohol. Am. J. Surg. 151:216-220.

Tranzo, R. G., T. Kallos, and M. Q. Wyche. 1974. Elevation of intramedullary pressure when methylmethacrylate is inserted in total hip arthroplasty. J. Bone Joint Surg. (Am.) 56(4):714-718.

Turnbull, K. W., J. L. Berezowskyj, J. B. Poulsen, and L. S. Root. 1974. General anaesthesia and total hip replacement. Can. Anaesth. Soc. J. 21(6):546-556.

Walsh, P. N., P. H. Rogers, V. J. Marder, G. Gangnatelli, E. S. Escovitz, and S. Sherry. 1974. Platelet coagulant activities and venous thrombosis after hip surgery. Trans. Assoc. Am. Physicians 87:140-152.

Walsh, P. N., V. J. Marder, G. Gangnatelli, E. S. Escovitz, and S. Sherry. 1976. The relationship of platelet coagulant activity to venous thrombosis following hip surgery. Br. J. Haematol. 32:421-437.

Welch, A. B. 1978. Effects of simplex liquid methylmethacrylate monomer on cells. J. Biomed. Mater. Res. 12:775-790.

Whitaker, A. N., D. G. McKay, and I. Csavossy. 1969. Studies of catecholamine shock. I. Disseminated intravascular coagulation. Am. J. Pathol. 56(2):153-176.

Wilcock, G. K. 1979. Economic aspects of the demand for total hip replacement in the elderly. Age and Ageing 8:32-35.

Willert, H. G., J. Ludwig, and M. Semlitsch. 1974. Reaction of bone to methacrylate after hip arthroplasty. J. Bone Joint Surg. (Am.) 56(7):1368-1382.

Wong, K. C., W. E. Martin, W. F. Kennedy, T. J. Akamatsu, R. F. Convery, and C. L. Show. 1977. Cardiovascular effects of total hip replacement in man with observations on the effects of methylmethacrylate on the isolated rabbit heart. Clin. Pharmacol. Ther. 21(6):709-714.

Wood, P. H. 1976. Aetiology, epidemiology, and social impact: Arthritis calling for surgical treatment. Proc. R. Soc. Lond. B. 192:131-134.

Yardumian, D. A., I. J. Mackie, and S. J. Machin. 1986. Laboratory investigation of platelet function: A review of methodology. J. Clin. Pathol. 39:701-712.

Yasuda, I. and K. Iwatsuki. 1975. Direct effect of acrylic bone cement monomer on isolated heart muscle. Tohoku J. Exp. Med. 117:93-97.

Zawadski, A., W. J. Ciaston, A. Mazurek, and B. Jakubczyk. 1976. Assessment of methods of anaesthesia used for total alloplasty of hip joint with application of bone cement. Anaesthesiol. Resusc. Intensive Therap. 4(3):181-158.

X. APPENDIX

Table A1. Percent fat per low power microscopic field in the lungs of the four experimental groups at the end of the experiment

	Group			
	PMM	PD	SS	C
n	7	6	6	4
% Fat	14.76[ab] ± 3.26	6.44[c] ± 1.62	4.31[d] ± 1.4	1.19 ± 0.48

[a]Values represent M ± SEM.

[b]Significantly different from the other three experimental groups ($p<0.05$).

[c]Significantly different from the control group ($p<0.05$).

[d]Approaching significant difference from the control group ($p<0.1$).

Table A2. Average hemoglobin concentration (gm/dl) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	13.05[a] ± 0.14	13.26± 0.14	13.01 ± 0.34	12.55 ± 0.34	12.37 ± 0.34	12.26 ± 0.34
PD	8	13.05 ± 0.14	13.26 ± 0.14	12.83 ± 0.36	12.71 ± 0.36	12.73 ± 0.36	12.62 ± 0.36
SS	8	13.05 ± 0.14	13.26 ± 0.14	13.14 ± 0.36	13.06 ± 0.36	12.61 ± 0.36	12.98 ± 0.39
C	6	13.01 ± 0.3	13.14 ± 0.27	12.82 ± 0.39	12.61 ± 0.39	12.21 ± 0.39	12.74 ± 0.39

[a]Values represent LSM ± SELSM.

Table A3. Average mean systemic arterial pressure (mm Hg) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	117.3[a] ± 2.2	120.5 ± 2.2	120.1 ± 3.5	121.1 ± 3.5	124.9 ± 3.5	122.6 ± 3.5
PD	8	117.3 ± 2.2	120.5 ± 2.2	129.3[b] ± 3.7	122.4 ± 3.7	123.7 ± 3.7	121.4 ± 3.7
SS	8	117.3 ± 2.2	120.5 ± 2.2	119.7 ± 3.8	121.6 ± 3.8	119.4 ± 3.8	123.5 ± 4
C	6	114 ± 4.6	117.8 ± 4.6	123.7 ± 4.4	125.3 ± 4.4	126.9 ± 4.4	126.8 ± 4.4

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from PMM and SS groups at the same sampling period ($p<0.1$).

Table A4. Average systemic vascular resistance (mm Hg/ml/sec) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	2.440[a] ± .088	2.969[b] ± .088	3.259 ± 0.207	3.343 ± 0.207	3.692[c] ± 0.207	3.832[cd] ± 0.207
PD	8	2.440 ± .088	2.969 ± .088	3.306 ± 0.219	3.202 ± 0.219	3.267 ± 0.219	3.328 ± 0.219
SS	8	2.440 ± .088	2.969 ± .088	3.319 ± 0.219	3.486 ± 0.219	3.510 ± 0.219	3.407 ± 0.234
C	6	2.271 ± 0.180	2.665 ± 0.180	2.849 ± 0.253	3.002 ± 0.253	2.996 ± 0.253	3.066 ± 0.253

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Significantly different from the control group at the same sampling period ($p<0.05$).

[d]Approaching significant difference from SS group at the same sampling period ($p<0.1$).

Table A5. Average mean left ventricular pressure (mm Hg) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	56.1[a] ± 1.9	53.9 ± 1.9	55.9 ± 3.2	56.1 ± 3.2	58.5 ± 3.2	56.1 ± 3.2
PD	8	56.1 ± 1.9	53.9 ± 1.9	59.7[b] ± 3.4	56.9 ± 3.4	58.7 ± 3.4	56.7 ± 3.4
SS	8	56.1 ± 1.9	53.9 ± 1.9	51.7 ± 3.4	54.2 ± 3.4	54.6 ± 3.4	53.5 ± 3.4
C	6	53.4 ± 3.9	55.6 ± 4.3	52.2 ± 4	54.7 ± 4	53.8 ± 4	54.1 ± 4

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from SS group at the same sampling period ($p<0.1$).

Table A6. Average myocardial contractility (mm Hg/sec) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	2508[a] ± 128	2343 ± 128	2397 ± 219	2174 ± 219	2537 ± 219	2446 ± 219
PD	8	2508 ± 128	2343 ± 128	2227 ± 232	2185 ± 232	2276 ± 232	2353 ± 232
SS	8	2508 ± 128	2343 ± 128	2118 ± 233	2143 ± 233	2013 ± 233	1998 ± 233
C	6	2795 ± 262	2573 ± 291	2457 ± 268	2257 ± 268	2244 ± 268	2264 ± 268

[a]Values represent LSM ± SELSM.

Table A7. Average heart rate (beats/min) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	135[a] ± 3	136 ± 3	134 ± 9	141 ± 9	146 ± 9	143 ± 9
PD	8	135 ± 3	136 ± 3	150[b] ± 9	149 ± 9	149 ± 9	154[b] ± 9
SS	8	135 ± 3	136 ± 3	126 ± 9	132 ± 9	134 ± 9	132 ± 9
C	6	143 ± 7	137 ± 7	126 ± 11	130 ± 11	128 ± 11	128 ± 11

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from both the control group and SS group at the same sampling period ($p<0.1$).

Table A8. Average stroke volume (ml/beat) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	23[a] ± 0.7	19.4[b] ± 0.7	18.6[cd] ± 1.3	16.8[c] ± 1.4	15.7[c] ± 1.3	14.3[ce] ± 1.4
PD	8	23 ± 0.7	19.4 ± 0.7	17.1[c] ± 1.4	16[c] ± 1.4	16.4[c] ± 1.4	15.3[c] ± 1.4
SS	8	23 ± 0.7	19.4 ± 0.7	18.8[c] ± 1.4	18.1[f] ± 1.4	18.6 ± 1.4	18.4 ± 1.4
C	6	23 ± 1.4	21.9 ± 1.4	22.7 ± 1.6	21.9 ± 1.6	21.8 ± 1.6	21.7 ± 1.6

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Significantly different from the control group at the same sampling period ($p<0.05$).

[d]Significantly different from the value of the same group at T6 ($p<0.05$).

[e]Significantly different from SS group at the same sampling period ($p<0.05$).

[f]Approaching significant difference from control at the same sampling period ($p<0.1$).

Table A9. Average cardiac output (ml/min) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	3009[a] ± 87	2505[bc] ± 87	2357[c] ± 141	2227[c] ± 141	2112[d] ± 141	2033[d] ± 141
PD	8	3009 ± 87	2505 ± 87	2412 ± 149	2363 ± 149	2396 ± 149	2298 ± 149
SS	8	3009 ± 87	2505 ± 87	2274[d] ± 150	2273 ± 151	2216[d] ± 151	2205[c] ± 151
C	6	3150 ± 179	2854 ± 179	2741 ± 173	2651 ± 173	2686 ± 173	2655 ± 173

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Approaching significant difference from the control group at the same sampling period ($p<0.1$).

[d]Significantly different from the control group at the same sampling period ($p<0.05$).

Table A10. Average cardiac index (ml/min/m^2) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	3774[a] ± 104	3149[bc] ± 104	3032 ± 198	2846 ± 211	2711[d] ± 198	2572[d] ± 211
PD	8	3774 ± 104	3149 ± 104	2959 ± 210	2902 ± 210	3214 ± 210	2840 ± 210
SS	8	3774 ± 104	3149 ± 104	2853[d] ± 212	2854 ± 212	2778[c] ± 212	2765[c] ± 212
C	6	3864 ± 213	3547 ± 213	3429 ± 243	3318 ± 243	3368 ± 243	3330 ± 243

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Approaching significant difference from the control group at the same sampling period ($p<0.1$).

[d]Significantly different from the control group at the same sampling period ($p<0.05$).

Table A11. Average mean pulmonary arterial pressure (mm Hg) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	9.4[a] ± 0.5	9.4 ± 0.5	11.5 ± 1.2	10.4 ± 1.2	13[b] ± 1.2	12.1 ± 1.2
PD	8	9.4 ± 0.5	9.4 ± 0.5	10.2 ± 1.2	10.7 ± 1.2	10.6 ± 1.2	11.5 ± 1.2
SS	8	9.4 ± 0.5	9.4 ± 0.5	9.5 ± 1.2	9.2 ± 1.2	10.3 ± 1.2	10.3 ± 1.2
C	6	9.4 ± 1	10.5 ± 1	10.8 ± 1.3	11.7 ± 1.3	12 ± 1.3	12 ± 1.3

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from SS group at the same sampling period ($p<0.1$).

Table A12. Average pulmonary vascular resistance (mm Hg/ml/sec) in the four experimental groups during the experiment

Group	n	Sampling Period					
		T1	T2	T3	T4	T5	T6
PMM	9	0.184[a] ± 0.012	0.235[b] ± 0.012	0.292[c] ± 0.031	0.298 ± 0.031	0.378[de] ± 0.031	0.366[f] ± 0.031
PD	8	0.184 ± 0.011	0.235 ± 0.011	0.272 ± 0.032	0.271 ± 0.032	0.274 ± 0.032	0.296 ± 0.032
SS	8	0.184 ± 0.011	0.235 ± 0.011	0.241 ± 0.032	0.244 ± 0.032	0.290 ± 0.032	0.282 ± 0.032
C	6	0.193 ± 0.024	0.241 ± 0.024	0.257 ± 0.037	0.294 ± 0.037	0.295 ± 0.037	0.297 ± 0.037

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Significantly different from the value of the same group at T5 ($p<0.05$).

[d]Significantly different from PD group at the same sampling period ($p<0.05$).

[e]Approaching significant difference from control and SS group at the same sampling period ($p<0.1$).

[f]Approaching significant difference from SS group at the same sampling period ($p<0.1$).

Table A13. Average respiratory rate (breath/min) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	16[a] ± 1	16 ± 1	18 ± 2	18[b] ± 2	21[cd] ± 2	24[e] ± 2
PD	8	16 ± 1	16 ± 1	14 ± 2	14 ± 2	15 ± 2	17 ± 2
SS	8	16 ± 1	16 ± 1	15 ± 2	15 ± 2	16 ± 2	17 ± 2
C	6	16 ± 2	18 ± 2	18 ± 2	16 ± 2	16 ± 2	17 ± 2

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same group at T6 ($p<0.05$).

[c]Significantly different from PD group at the same sampling period ($p<0.05$).

[d]Approaching significant difference from the control group at the same sampling period ($p<0.1$).

[e]Significantly different from the other three groups at the same sampling period ($p<0.05$).

Table A14. Average oxygen consumption (ml/min) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	112[a] ± 9	125 ± 9	154[b] ± 17	129 ± 17	153[c] ± 16	171[d] ± 17
PD	8	112 ± 9	125 ± 9	128 ± 16	130 ± 16	132 ± 16	140 ± 16
SS	8	112 ± 9	125 ± 9	110 ± 15	105 ± 15	104 ± 15	103 ± 15
C	6	109 ± 19	107 ± 19	119 ± 19	122 ± 19	109 ± 19	112 ± 19

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from SS group at the same sampling period ($p<0.1$).

[c]Significantly different from SS group ($p<0.05$) and approaching significant difference from control group ($p<0.1$) at the same sampling period.

[d]Significantly different from both control and SS group at the same sampling period ($p<0.05$).

Table A15. Average carbon dioxide production (ml/min) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	110[a] ± 7	127 ± 7	147 ± 17	135 ± 17	138 ± 16	158[b] ± 17
PD	8	110 ± 7	127 ± 7	125 ± 15	126 ± 15	128 ± 15	138 ± 15
SS	8	110 ± 7	127 ± 7	118 ± 14	107 ± 15	109 ± 15	109 ± 14
C	6	99 ± 16	107 ± 16	114 ± 18	116 ± 18	105 ± 18	112 ± 18

[a]Values represent LSM ± SELSM.

[b]Significantly different from SS group ($p<0.05$) and approaching significant difference from the control group at the same sampling period ($p<0.1$).

Table A16. Average ventilation/perfusion ratio in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	1.03[a] ± 0.06	1.44[b] ± 0.06	1.72[c] ± 0.2	1.83 ± 0.19	2.02[de] ± 0.19	2.29[ef] ± 0.19
PD	8	1.03 ± 0.06	1.44 ± 0.06	1.47 ± 0.19	1.49 ± 0.19	1.53 ± 0.19	1.79 ± 0.19
SS	8	1.03 ± 0.06	1.44 ± 0.06	1.4 ± 0.18	1.41 ± 0.19	1.68 ± 0.19	1.63 ± 0.17
C	6	1 ± 0.14	1.21 ± 0.14	1.36 ± 0.22	1.44 ± 0.22	1.36 ± 0.22	1.48 ± 0.22

[a]Values represent LSM ± SELSM.

[b]Significantly different from the value of the same three groups at T1 ($p<0.05$).

[c]Significantly different from the value of the same group at T6 ($p<0.05$).

[d]Significantly different from the control group at the same sampling period ($p<0.05$).

[e]Approaching significant difference from PD group at the same sampling period ($p<0.1$).

[f]Significantly different from the control group and SS group at the same sampling period ($p<0.05$).

Table A17. Average airway resistance (cm H_2O/l/sec) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	2.15[a] ± 0.1	2.16 ± 0.1	2.22 ± 0.2	2.24 ± 0.21	2.31 ± 0.21	2.74[b] ± 0.22
PD	8	2.15 ± 0.1	2.16 ± 0.1	2.36 ± 0.21	2.25[c] ± 0.21	2.00 ± 0.21	2.56[b] ± 0.22
SS	8	2.15 ± 0.1	2.16 ± 0.1	2.24 ± 0.21	2.19 ± 0.21	2.33 ± 0.21	2.36 ± 0.21
C	6	1.91 ± 0.2	1.92 ± 0.2	1.84 ± 0.24	1.71 ± 0.24	1.84 ± 0.24	1.90 ± 0.24

[a]Values represent LSM ± SELSM.

[b]Significantly different from control at the same sampling period ($p<0.05$).

[c]Approaching significant difference from control at the same sampling period ($p<0.1$).

Table A18. Average values for work of breathing (l × cm H_2O) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	3.21[a] ± 0.2	3.66 ± 0.2	3.89 ± 0.58	3.92 ± 0.55	4.44 ± 0.67	5.28[b] ± 0.67
PD	8	3.21 ± 0.2	3.66 ± 0.2	4.06 ± 0.58	4.98[b] ± 0.58	5.03 ± 0.58	4.05 ± 0.62
SS	8	3.21 ± 0.2	3.66 ± 0.2	4.25 ± 0.58	4.51 ± 0.58	4.23 ± 0.58	4.38 ± 0.58
C	6	3.22 ± 0.4	3.29 ± 0.4	3.17 ± 0.67	3.2 ± 0.67	3.38 ± 0.67	3.3 ± 0.67

[a]Values represent LSM ± SELSM.

[b]Significantly different from control at the same sampling period ($p<0.05$).

Table A19. Average dynamic lung compliance (ml/cm H_2O) in the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	48.7[a] ± 1.8	47.8 ± 1.8	44.2 ± 3.2	47.8 ± 3.2	42.2 ± 3.4	44.6 ± 3.7
PD	8	48.7 ± 1.8	47.8 ± 1.8	52.8[b] ± 3.5	49.5[c] ± 3.5	48.8 ± 3.5	49.4[c] ± 3.8
SS	8	48.7 ± 1.8	47.8 ± 1.8	48.7 ± 3.5	48.5 ± 3.5	49.2 ± 3.5	46.6 ± 3.5
C	6	45 ± 3.6	41.2 ± 3.6	40.9 ± 4	40.5 ± 4	40.5 ± 4	39.3 ± 4

[a]Values represent LSM ± SELSM.

[b]Significantly different from the control group ($p<0.05$) and approaching significant difference from PMM group ($p<0.1$) at the same sampling period.

[c]Approaching significant difference from control at the same sampling period ($p<0.1$).

Table A20. Average partial pressures of oxygen (Torr) in the arterial blood of the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	84[a] ± 1.6	83.2 ± 1.8	83.3 ± 3.4	82.6 ± 3.7	82.5 ± 3.4	82.6 ± 3.4
PD	8	84 ± 1.6	83.2 ± 1.8	81.8 ± 2.9	81.9 ± 2.9	86 ± 2.9	83.8 ± 2.9
SS	8	84 ± 1.6	83.2 ± 1.8	89[b] ± 3.1	87.9 ± 3.1	86 ± 4.3	87.7 ± 3.5
C	6	82 ± 3.4	80.6 ± 3.1	79.7 ± 3.4	81.4 ± 3.4	80.6 ± 3.4	82.6 ± 3.4

[a]Values represent LSM ± SELSM.

[b]Approaching significant difference from control at the same sampling period ($p<0.1$).

Table A21. Average partial pressures of carbon dioxide (Torr) in the arterial blood of the four experimental groups during the experiment

		Sampling Period					
Group	n	T1	T2	T3	T4	T5	T6
PMM	9	39.3[a] ± 0.9	37.3 ± 0.9	33.8 ± 1.2	32.9 ± 1.2	34.1 ± 1.2	33.5 ± 1.2
PD	8	39.3 ± 0.9	37.3 ± 0.9	36.5 ± 1.3	35.8 ± 1.3	34.9 ± 1.3	34.1 ± 1.3
SS	8	39.3 ± 0.9	37.3 ± 0.9	35.8 ± 1.3	35.7 ± 1.3	33.4 ± 1.3	33.2 ± 1.3
C	6	37.9 ± 2.0	36.4 ± 1.8	35.2 ± 1.5	35.4 ± 1.5	34.4 ± 1.5	33.8 ± 1.5

[a]Values represent LSM ± SELSM.

Table A22. Average arterial blood pH in the four experimental groups during the experiment

		Sampling Period					
	Group n	T1	T2	T3	T4	T5	T6
PMM	9	7.356[a] ± 0.006	7.364 ± 0.006	7.387 ± 0.009	7.395 ± 0.009	7.383 ± 0.009	7.390 ± 0.009
PD	8	7.356 ± 0.006	7.364 ± 0.006	7.369 ± 0.010	7.377 ± 0.010	7.384 ± 0.010	7.393 ± 0.010
SS	8	7.356 ± 0.006	7.364 ± 0.006	7.366 ± 0.010	7.364[b] ± 0.010	7.376 ± 0.010	7.369[c] ± 0.010
C	6	7.374 ± 0.014	7.379 ± 0.013	7.390 ± 0.012	7.391 ± 0.012	7.385 ± 0.012	7.395 ± 0.012

[a]Values represent LSM ± SELSM.

[b]Significantly different from PMM group ($p<0.05$) and approaching significant difference from the control group ($p<0.1$) at the same sampling period.

[c]Approaching significant difference from both control and PD group at the same sampling period ($p<0.1$).

Table A23. Composition of the alveolar lining material (ALM) (% of total phospholipids) in the four experimental groups at the end of the experiment

		ALM components[a]				
Group	n	PC	PE	PI	PG	PS
PMM	7	72.6[b] ± 1.0	2.4 ± 0.4	8.5 ± 0.6	13.4[c] ± 0.5	2.9 ± 0.3
PD	6	76.6 ± 3.4	2.4 ± 0.6	7.4 ± 1.3	10.6 ± 2.3	2.9 ± 0.3
SS	6	77.1 ± 2.7	2.5 ± 0.5	7.5 ± 0.9	10.3 ± 2.0	2.6 ± 0.2
C	5	73.8 ± 2.4	3.2 ± 0.5	8.5 ± 1.2	11.1 ± 0.9	3.4 ± 0.4

[a]Following is the legend of the ALM components:
PC = Phosphatidylcholine
PE = Phosphatidylethanolamine
PI = Phosphatidylinositol
PG = Phosphatidylglycerol
PS = Phosphatidylserine

[b]Values represent M ± SEM.

[c]Approaching significant difference from control ($p<0.1$).