Review article

Cardiorespiratory and vascular dysfunction related to major reconstructive orthopedic surgery

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Major orthopedic reconstructive surgery is highly traumatic and may be associated with serious perioperative cardiorespiratory and vascular complications which occasionally may be fatal. These complications are commonest in patients receiving cemented hip prostheses following femoral neck fractures. The etiology is multifactorial. Bone traumatization induces activation of the hemostatic system, i.e., thrombin generation, in venous blood draining the operation area. When this activated blood passes the lung, more thrombin is generated and the blood becomes hypercoagulable and causes fibrin-formation in the lung vessels, with trapping of cellular debris. Thrombin has many hormone-like effects beyond its function in the coagulation cascade system. It may increase vein wall permeability and cause constriction of vessels, which increases blood pressure in the lung. In addition, impaction of bone cement to fill bone cavities or to fix prostheses causes additional mechanical trauma and further release of procoagulant substances into venous blood. Further, release of the cytotoxic chemical methylmethacrylate monomer into venous blood is superimposed on the thrombin-primed hemostatic disturbances in the lung microvasculature. All these effects may finally induce hemodynamic insufficiency, which occasionally may be fatal. To prevent these adverse reactions, thrombin activity should be reduced and impaction of bone cement minimized.

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Since 1970, many case reports have described intraoperative cardiorespiratory dysfunction and deaths in patients undergoing cemented major reconstructive orthopedic surgery (Powell et al. 1970, Cohen and Smith 1971, Thomas et al. 1971, Kepes et al. 1972, Kirwan 1973, Nicholson 1973, Modig et al. 1974, Brown and Parmley 1982, Dahl 1984, Dahl et al. 1988a, Learned and Hantler 1992, Lennox and McLauchlan 1993, Enneking and Malawer 1995, Kim et al. 1995). Even after prosthetic reconstruction of the knee or marrow nailing with cement-fixation of femoral shaft fractures, intraoperative deaths have been reported (Ferris and Kinsella 1984, Byrick et al. 1986, Persson and Bauer 1994, Enneking and Malawer 1995). Recently, a fatal hemodynamic collapse was reported in a patient undergoing revision arthroplasty of the hip. This occurred during removal of the bone cement with an ultrasonic device, which probably caused microfragmentation of the bone and cement which embolized to the lungs (Woo et al. 1995).

The highest mortality (about 11%) has been reported following cemented hip arthroplasty in patients with fracture of the femoral neck (Duncan 1989). However, after elective hip prosthesis in patients with arthrosis, the mortality rate declines to about 0.6% (Dahl et al. 1988a, Ereth et al. 1992, Lennox and McLauchlan 1993), but remains unacceptably high. The hemodynamic collapse occurs mostly in close relation to impaction of cement and prosthesis (Schulitz et al. 1971, Schlag 1988, Dahl et al. 1988a, Duncan 1989, Ereth et al. 1992), but may even occur some hours after the operation (Lennox and MacLauchlan 1993).

Etiology

Autopsy findings

Autopsy studies of the lungs in patients suffering from intraoperative death during cemented reconstructive major surgery have shown a spectrum of pathological findings ranging from normal tissue architecture, accumulation of fat droplets and air bubbles in the lungs to major pulmonary thromboembo-

lism and cardiac infarction (Hyland and Robins 1970, Zichner 1972, Herndon et al. 1974, Dahl 1984, Zichner 1987). Consequently, embolization of bone marrow content has been thought to contribute to these reactions (Modig et al. 1974, Heinrich et al. 1985). However, the clinical relevance of fat in the lung microvasculature (Zichner 1972, Woo et al. 1995) is still debated and some authors believe it is an epiphenomenon (Bone 1993, Gitin et al. 1993).

Bone traumatization and venous embolization of bone marrow contents

It has been claimed that the high pressure applied to the femoral bone cavity during implantation of cement and prosthesis may cause intravasation of medullary contents (Schlag et al. 1976, Rinecker 1980, Rinecker and Höllenriegel 1987, Zichner 1987) and embolization to the lungs, the primary target organ for such blood-borne material (Modig et al. 1974, 1975b, Heinrich et al. 1985, Zichner 1987, Svartling 1988). Transesophageal doppler registration during intraoperative bone preparation has shown showers of venous blood-borne material which may be consistent with released embolized material from the bone marrow, reaching the right side of the heart (Heinrich et al. 1985, Svartling 1988, Christie et al. 1994). Substantially more embolized material has been found with impaction of cement than with the noncemented procedure (Ereth et al. 1992, Johnson et al. 1995). These emboli may be trapped in the lung capillaries and contribute to mechanical obstruction, which subsequently may induce right cardiac failure (Modig 1974, 1975b, Schlag 1988).

Hemostatic activation

Disseminated activation of coagulation in the lung blood due to contact with sequestered procoagulant material may contribute to intraoperative cardiorespiratory and vascular dysfunction, since a correlation beween activation of coagulation and intraoperative decrease in blood pressure has been demonstrated (Modig et al. 1975a). Earlier experimental findings support this hypothesis. Saldeen (1969) induced transient intravascular coagulation in the lungs of rats by intravenous injection of adipose tissue. This effect was thought to be caused by the tissue factor content of the fat cells, since pretreatment of the animals with heparin, reduced the coagulation-promoting effect. Later, it was definitely shown that adipose tissue contained high levels of procoagulant factors, mainly tissue factor (thromboplastin) (Giercksky 1977), the most potent activator of the coagulation system known (Camerer et al. 1996). Intravenous injection of purified human tissue factor into rats caused respiratory distress with accumulation of fibrin and platelets in the lung capillaries, and even death within a few minutes (Giercksky et al. 1976, Giercksky 1977). Later, the same group demonstrated that increased levels of apoprotein III, the protein component of tissue factor, were found in venous blood during traumatization of the bone marrow in patients undergoing hip replacement surgery (Giercksky et al. 1979). These studies indicate that activation of coagulation may play a pathophysiological role in development of serious cardiorespiratory complications.

Thrombin generation. It has been demonstrated that bone traumatization induces a substantial local venous activation of coagulation—i.e., thrombin generation—in patients undergoing hip replacement surgery (Dahl et al. 1995). At the same time, systemic thrombin is formed in huge amounts in the lung microvasculature, a process which is triggered by venous blood-borne procoagulant cellular debris from traumatized bone tissue (Dahl et al. 1988b, 1992, 1993, 1995)

Thrombin is an enzyme with various potent effects. It is a pivotal enzyme in the coagulation process and has many hormone-like effects (Fenton 1995). It interacts with endothelium and induces cell-shape changes (Galdal and Evensen 1981), increases the permeability for albumin, especially in the lung vasculature (Belloni et al. 1992, DeMichele and Minnear 1992), induces aggregation and chemotaxis of leukocytes (Bizios et al. 1986) and causes postcapillary pulmonary vasoconstriction and increases pulmonary arterial pressure (Horgan et al. 1987). Thus, thrombin plays a key role in processes related to trauma and repair.

Taking into account the findings of Giercksky and associates (1977, 1979), one sees clearly that bone marrow cells are a rich source of tissue factor. These cells or cell fragments with exposed tissue factor are released into blood during hip replacement surgery and trigger substantial thrombin generation (Dahl et al. 1988b, 1992, 1993, 1995). Thus, it is tempting to speculate that thrombin may play a major role in the hemodynamic alterations that may occur centrally and peripherally during this kind of surgery.

Complement activation

When thrombin is bound to the transmembranous thrombomodulin on the endothelial cell surface (Esmon 1989), the protein C pathway is initiated. Its cofactor protein S complexes with the C4b-binding protein, which is one of the regulatory proteins in the complement system and thus forms a link between the coagulation and complement systems (Dahlbäck 1984). It has also been shown that complement split

products like C3b stimulate tissue factor synthesis in monocytes, representing a further link between complement activation and coagulation (Prydz et al. 1977). Activation of the complement cascade ends in formation of the terminal complement complex which can destroy cell membranes by lytic attack (Mollnes 1985). An uncontrolled systemic activation of complement may thus be deleterious.

Evidence of complement activation during total hip replacement, leading to cardiorespiratory impairment, is conflicting. Kepes and coworkers (1972) claimed that the complement system was activated during hip replacement surgery and could initiate anaphylactic reactions. On the other hand, Monteny et al. (1978) found no difference in plasma whole complement activity during and shortly after hip replacement in patients receiving cement-fixed or noncement-anchored hip prostheses. This is supported by our own findings, showing only a slight reduction in plasma levels of factor C4 and fragment C3c (Dahl et al. 1988b). In addition, bone cement has not been found to release histamine to plasma (Mitsuhata et al. 1994). This supports the view that allergic reactions do not seem to be involved in the hip replacement-associated immediate intraoperative adverse reactions. However, reduced plasma whole complement activity (CH50), reduced levels of C3, C4 and C5 and increased levels of anaphylatoxins (C3a and C5a) have been found from half an hour to 24 hours after impaction of cement and prosthesis (Bengtson et al. 1987). This may indicate a delayed activation of complement following hip replacement surgery which may affect the postoperative outcome of the patients and is reflected in a higher perioperative mortality in patients who have received cemented prostheses than in those with noncemented fixed implants (Lennox and McLauchlan 1993). Further, complement activation in relation to hip replacement surgery was shown to increase lung vascular permeability lasting more than 24 hours and to induce spasms of smooth muscles and impairment of atrioventricular function (reviewed in Bengtson et al. 1987). The same authors also exposed plasma to increasing concentrations of methylmethacrylate monomer (1–100 µg/mL) in vitro and demonstrated a dose-related formation of anaphylatoxins (Bengtson et al. 1987). These findings strongly suggest that complement is activated by methylmethacrylate monomer, but does not seem to play any major role in the immediate cardiorespiratory and vascular instability occurring during hip replacement surgery. However, this process of complement activation may enhance the postoperative activation of inflammation and increase cytokine production and release (Dahl et al. 1993) which, in turn, may enhance lung vascular permeability (Worthen et al. 1987) and may also contribute to prolonged postoperative activation of coagulation (Stouthard et al. 1996).

Bone cement hyperthermia

The hyperthermia induced by curing bone cement has by some investigators been thought to affect the coagulation system (Stamatakis et al. 1977, Rinecker 1980, Bergentz 1988, Planes et al. 1990). Animal experiments have shown that a rise in the temperature at the interface between cement and cortical bone scarcely exceeded 40 °C when a femoral prosthesis was introduced during hardening of the cement and had no influence on local activation of coagulation in femoral vein blood (Dahl et al. 1995). These findings are also confirmed by human studies, which showed no additional systemic activation of coagulation during the phase of hyperthermic hardening of the femoral shaft cement (Dahl et al. 1988b, 1992, 1993). Thus, these studies showed that the contribution of hyperthermia to plasma proteolytic activation probably is of little, if any, importance.

Methylmethacrylate monomer toxicity

Methylmethacrylate monomer, a main component of bone cement, was early recognized as a possible inducer of fatal reactions during hip replacement. It was shown that the monomer was highly toxic when injected into animals (Deichmann 1941, Spealman et al. 1945). However, many investigators claimed that this chemical could not induce these reactions in humans (Charnley 1970, Homsy et al. 1972, Holland et al. 1973, Schlag et al. 1976, Rinecker 1980, Ries et al. 1993), since much higher blood concentrations than those found in animal experiments were necessary to induce cardiorespiratory dysfunction (Homsy et al. 1972, Eggert et al. 1974, Modig et al. 1975a, b, Svartling et al. 1985, 1986, Wenda et al. 1988). On the contrary, no fatal cardiorespiratory dysfunction has ever been reported during uncemented prosthesis implantation and a higher perioperative mortality has been reported in patients with cemented prostheses than in those with noncemented implants (vide supra) (Lennox and McLauchlan 1993). Consequently, impaction of bone cement and release of methylmethacrylate monomer may in one way or another contribute to these reactions.

Organ toxicity and hemodynamic alterations. Animal experiments have shown soft tissue damage, i.e., congestion, edema and necrosis after injection of monomer (Homsy et al. 1972, Holland et al. 1973). Intravascular thrombosis in microcapillaries has been induced by exposure of the cheek pouch of hamsters to the monomer (Linder 1976). It has also been noted

that respiratory arrest seems to be the primary cause of death, since the heart has continued to beat following complete apnea (Deichmann 1941, Spealman et al. 1945, Homsy et al. 1972, Dahl 1984). It thus seems that the nervous regulation of the respiratory system is more sensitive to exposure to methylmethacrylate monomer than the myocardium, although the functions of both organs are depressed in a dose-related manner (Ohnsorge and Kutzner 1974, Wong et al. 1977). Animal experiments (Homsy et al. 1972, Holland et al. 1973, McMaster et al. 1974, Orsini et al. 1987, Dahl et al. 1997b) and observations on humans have also demonstrated increased central arterial blood pressure, combined with decreased peripheral arterial blood pressure (Holland et al. 1973, Schlag et al. 1976) and a drop in pulmonary arterial oxygen tension (Modig et al. 1975a, Rinecker 1980, Mebius and Hedenstierna 1982, Svartling et al. 1985) when monomer was injected intravenously (Homsy et al. 1972, Ellis and Mulvein 1974, McMaster et al. 1974) or bone cement and prosthesis were implanted into the femoral shaft (Kallos 1975, Alexander and Barron 1979, Ereth et al. 1992). Recently, Ries and colleagues (1993) found marked alterations in the proportions of circulating blood passing the lungs, without participating in gas exchange, consistent with increased intraoperative and postoperative (< 48 h) shunting in patients undergoing hip replacement. Although some of these studies have indicated that methylmethacrylate monomer from bone cement may be involved in hemodynamic alterations, it has repeatedly been stated by a number of authors that the amount of monomer in blood of humans in relation to hip replacement hardly could trigger these reactions (Charnley 1970, Homsy et al. 1972, Holland et al. 1973, Rinecker 1980, Schlag 1988, Ries et al. 1993).

However, it is often forgotten that laboratory experiments with monomethyl- and polymethacrylates have been performed in young healthy animals, without preinduced hemostatic alterations. This situation differs fundamentally from that in old patients with limited cardiorespiratory reservoirs, who undergo a major operation with massive bone traumatization and an excessive triggering of plasma proteolytic enzyme cascades prior to exposure to bone cement. These assumptions are highlighted by the findings of a sequential appearance of thrombin and methylmethacrylate monomer in blood during hip substitute surgery (Dahl et al. 1992). Cellular and animal experiments have also made it possible to study separately the effects of bone cement, i.e., methylmethacrylate monomer and hyperthermia, and bone traumatization, on initiation of the coagulation process (Dahl et al. 1994a, b, 1995).

Methylmethacrylate monomer blood levels and influence on different cells. Blood methylmethacrylate monomer levels reported in patients undergoing joint replacement cover a wide spectrum of concentrations (Svartling et al. 1985, 1986, Wenda et al. 1988, Dahl et al. 1992). The highest concentration has been reported by Pahuja and coworkers (1971), who found 2000 μg/mL in mixed venous blood. The reason for the diverging results may be that methylmethacrylate monomer rapidly penetrates lipid membranes, e.g., blood cells, vessel wall cells and nerve sheaths and is quickly removed from plasma (Mohr 1958, Rijke and Johnson 1977). Recent studies support this view (Dahl et al. 1997b). In addition, the sampling sites differ in the various studies (Svartling et al. 1985, 1986, Wenda et al. 1988, Dahl et al. 1992), i.e., from central, mixed venous and arterial blood. Thus, this may help to explain the wide range of methylmethacrylate monomer concentrations in blood and why usually small concentrations have been found in patients undergoing joint replacement. Doughy cement contains pure unpolymerized monomer, which is quickly absorbed into blood vessels lining cement-impacted areas. High concentrations of monomer may thus destroy blood cells, e.g., granulocytes and monocytes, which may release potentially harmful substances like proteolytic enzymes with autodigestive effects (Henson et al. 1992, Bereznowski 1994, Dahl et al. 1994a). In addition, destruction of cell membranes may expose tissue factor on subendothelium (Weiss et al. 1989) or induce flip-flop movements of the cell membrane phospholipids. This can, under various conditions, bring procoagulant phospholipids (phosphatidyl serine) normally located on the inside of the membrane, to the outside where they may trigger binding of coagulation factors and activation of coagulation (Bevers et al. 1989, Schroit and Zwaal 1991). Damaged cells and cell debris may be brought with venous blood (Ereth et al. 1992) and caught in the lung filter (Modig et al. 1975a) and contribute to pulmonary microvascular disturbances (Worthen et al. 1987, Fairman et al. 1984, Dahl et al. 1992, Ereth et al. 1992).

The highest concentrations of monomer in mixed venous blood entering the lungs were found to be delayed because of maximal activation of coagulation in the blood passing the lung microcirculation (Dahl et al. 1992). The load of monomer is thus superimposed on the preexisting hemostatic imbalance and even small concentrations of monomer may add to chemical alterations in the lung vasculature (Fairman et al. 1984). This may contribute to subsequent hemodynamic instability, which occasionally may cause cardiovascular collapse.

These assumptions are based on in vitro studies with leukocytes and endothelial cells, which showed that thrombin alone or in combination with methylmethacrylate monomer (10–500 μg/mL) increased tissue factor expression on monocytes and endothelial cells in a dose-response relationship (Dahl et al. 1994b). Flow cytometric studies have shown that platelets are activated between 10–1000 μg/mL monomer concentrations (unpublished data). Monomer above 500 μg/mL caused depression of endothelial cell functions and above 5000 μg/mL, which most probably is found in blood near cement-implanted areas, caused endothelial cell detachment, exposure of subendothelial procoagulant constituents and triggering of local thrombogenic processes in endothelial cell cultures (Dahl et al. 1994a, b). Finally, animal studies have shown that intravenously injected methylmethacrylate monomer which produces blood levels of 100 μg/mL may cause cardiodepression and reduce blood pressure and that the lethal level has been thought to be above 1000 μg/mL (Bright et al. 1972, Homsy et al. 1972).

Prophylaxis

To avoid perioperative cardiorespiratory dysfunction several preventive suggestions should be considered. Hypercoagulation, i.e., thrombin generation and activity should be reduced to restrict hemostatic activation and subsequent proteolytic reactions. Low molecular weight heparin, which has a better antithrombotic effect than unfractionated heparin (Leizorovicz et al. 1992), should be injected prior to surgery, according to the manufacturer's recommendations. To reduce entrapment of cellular debris in the lung circulation and prevent respiratory distress, dextran-70 should be infused during induction of regional analgesia and during the operation (Bergentz 1978, Davidson et al. 1980, Rutherford et al. 1984, Modig 1986, Menger et al. 1989, Dahl et al. 1997c). The combination of low molecular weight heparin and dextran-70 does not seem to increase operative bleeding (Holst et al. 1992, Matthiasson et al. 1994a, b, Hjertberg et al. 1995, Dahl et al. 1997a).

Whether the surgical technique modifies development of cardiorespiratory and vascular disorders is unknown, since reaming and broaching of bone cause release of tissue factor containing cellular debris into venous blood and initiate local and systemic thrombin generation prior to implantation of cement and prosthesis into the femoral shaft (Dahl et al. 1988b, 1992, 1993, 1995). To reduce the high intramedullary pressure caused by insertion of cement and stem into the femoral canal, a venting-hole distal in the femoral bone or a catheter introduced into the femoral shaft during the implantation procedure has been used (Alexander and Barron 1979, Engesæter et al. 1984). However, the clinical consequences of these minor procedures remain to be demonstrated. Administration of high-dose corticosteroids has also been investigated and no obvious clinical or pathophysiological beneficial effects were found (Høgevold 1996). If possible, bone cement should be avoided or used in only small amounts to reduce synergistic stimulation of the coagulation system and avoid toxic cell effects. Finally, anesthetic techniques that influence the afferent vegetative nerve pathways should be preferred and sympatheticomimetics may be administered prior to the critical femur implantation to reduce cardiorespiratory depression (Rudigier and Ritter 1983).

Summary

Evidence exists that substantial amounts of thrombin are generated as a consequence of bone traumatization, i.e., reaming and broaching and impaction of bone cement. In addition, thrombin and methylmethacrylate monomer from the bone cement seem to contribute to local and systemic activation of coagulation, cell destruction, release of proteolytic enzymes, resulting in a complex pathophysiological process which may alter hemodynamic stability during major reconstructive orthopedic surgery. This may trigger cardiorespiratory and vascular impairment, which occasionally may be fatal. Installation of cementless prosthesis instead of cemented prosthesis causes less bone marrow displacement, releases less bone marrow-derived embolic materials into the venous blood, induces less local activation of coagulation, causes a smaller decline in blood pressure and lower perioperative mortality (Orsini et al. 1987, Ereth et al. 1992, Lennox and McLauchlan 1993, Christie et al. 1994, Dahl et al. 1995).

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