COMPLEMENT AND ANAPHYLATOXIN RESPONSES TO CROSS-CLAMPING OF THE AORTA

Studies During General Anaesthesia With or Without Extradural Blockade

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Clamping of the aorta during reconstructive vascular surgery may produce alterations in haemodynamic and respiratory variables (Perry, 1968). Hypoperfusion, as indicated by altered acid–base status, and increases in lactate concentration and the plasma concentrations of purine metabolites, may occur (Schoenberg, Fredholm and Hohlbach, 1985). In addition, hypoperfusion and cross-clamping of the aorta are associated frequently with activation of the complement cascade and the formation of the anaphylatoxins C3a and C5a (Heideman and Bengtson, 1985). As the anaphylatoxins are potent mediators of smooth muscle contraction of arteries, trachea and airway preparations, and influence vascular permeability, significant circulatory and respiratory disturbances may occur as a result of the increase in anaphylatoxin activity (Hugli, 1979; Mahler et al., 1975; Pavek, Piper and Smedegård, 1979; Regal, Eastman and Pickering, 1980).

The neuroendocrine response to surgical stress and trauma includes increases in the plasma concentrations of the catecholamines, cortisol and free fatty acids (Carlsson and Liljedahl, 1963; Kehlet, 1982; Pflug, Halter and Tolas, 1982). Extradural analgesia provides a partial afferent neurogenic blockade that partially inhibits the endocrine-metabolic response to major surgery or trauma (Bromage, Shibata and Willougby, 1971; Engquist et al., 1977; Kehlet, 1982). It has been documented that extradural anaesthesia can modulate suppression of monocyte and lymphocyte functions during and after surgery (Walton, 1978; Hole and Unsgaard, 1983).

This investigation was designed to evaluate whether complement is activated during elective surgery for aortic occlusive disease and whether perioperative extradural blockade might influence anaphylatoxin formation during the period of aortic clamping.

PATIENTS AND METHODS

Patients

Twenty-eight patients were studied prospectively in association with elective surgery for aortic occlusive disease.

Premedication with pethidine and hyoscine i.m. was given 30 min before the scheduled time of surgery. All patients received a general anaesthetic technique which utilized 70% nitrous oxide in oxygen, fentanyl 0.002 mg/kg body weight, barbiturate (thiopentone 4 mg/kg body weight)
and neuromuscular blockade (pancuronium 0.1 mg/kg body weight).

In 12 of the patients lumbar extradural blockade was provided in addition. A 22-gauge epidural catheter was placed in the L1-2 space with the aid of a Tuohy needle. Mepivacaine solution 2% was injected through the catheter until the block reached the T4 level. Additional mepivacaine (10 ml of 2% solution) was administered every 2 h throughout the operative procedure.

**Methods**

Arterial blood was obtained 5 min before aortic clamping, 5 min before the initial release of the cross-clamp restored the circulation to the first extremity, 5 min after the release of this clamp, and 5 min after the release of the second clamp.

Blood samples were immediately placed in tubes with EDTA (ethylene diamine tetra acetic acid 7.2 mg in 5 ml of blood) for plasma or without EDTA for serum. The tubes were centrifuged to remove the cells and the plasma or serum samples were kept at −80 °C until the complement activity, plasma concentrations of components Cl esterase inhibitor (Cl INH), C3, C4, C5, C3a and C5a were determined.

Whole complement (CH$_{50}$) was determined according to Mayer (1971). The complement components C1 INH, C3, C4, C5 and C5a were determined with a rocket immunoelectrophoresis technique (Laurell, 1966). The plasma concentrations of C3a and C5a antigens were determined with a RIA-method (Wagner and Hugli, 1984). The concentrations of these components in our standard plasma did not differ from corresponding concentrations in a known reference plasma. All assays were carried out in duplicate with good correlation between the duplicate measurements.

**Statistics**

Mean values and standard errors of the mean are presented. Fisher's test was used for comparison of groups and correlation studies (Bradley, 1968). Differences were described as significant when $P < 0.05$. The least squares linear regression test was used for correlation studies (Colton, 1974).

**RESULTS**

Age, duration of operation, duration of aortic clamping and blood loss were similar in both groups (table I).

Whole complement values (CH$_{50}$) in all patients are given in table II. Whole complement activity decreased during the period of aortic clamping in the patients studied ($P < 0.05$). This reduction was, however, less pronounced in the extradural group ($P < 0.05$).

Plasma C1 INH, C4, C3 and C5 decreased in both groups during surgery ($P < 0.05$). However, these variables remained within their normal ranges even after cross-clamping of the aorta. The decreases in these components did not differ significantly in the two groups studied.

Simultaneously, the plasma concentrations of C3a increased (fig. 1) in both groups (extradural group $P < 0.05$; non-extradural group...
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**Fig. 1.** The increase in plasma C3a concentration during cross-clamping in patients with (△) and without (●) extradural blockade. \((P < 0.001)\)

**Fig. 2.** The increase in plasma C5a concentrations in patients with (△) and without (●) extradural blockade. \((P < 0.05)\)

\(P < 0.001\). However, the plasma C3a concentration increased more in patients who did not receive the extradural block compared with those who did \((P < 0.001)\). Similar changes in plasma concentrations of C5a were also seen during aortic clamping. Plasma C5a concentration increased during the period of aortic clamping (fig. 2) in patients with and without extradural blockade \((P < 0.05 \text{ and } P < 0.01, \text{ respectively})\). C5a concentrations increased more in the group without extradural block \((P < 0.05)\).

Duration of clamping correlated with the increase in plasma C3a concentration \((r = 0.64, n = 16, P < 0.05)\) in patients without extradural block. This positive correlation was not observed \((r = 0.16, n = 12)\) in the extradural group (fig. 3).

Frequency of postoperative complications such as infection, bacteraemia and ARDS did not differ between the two groups. One patient in each group developed multisystem organ failure with pulmonary, renal and hepatic insufficiency in the postoperative period.

**DISCUSSION**

This study indicates that the complement cascade is activated during reconstructive surgery for aortic occlusive disease. The complement variables measured were similar in both groups before the clamping of the aorta. The activation occurs primarily during aortic clamping and is detected by a decrease in whole complement activity and an increase in plasma anaphylatoxin concentrations. \(CH_{50}\) titres indicate the absolute activity and C3a concentrations indicate the plasma range of active and non-active C3a. This might be one reason why \(CH_{50}\) titres decreased by about 20% while C3a increased by around 270%. Increases in pulmonary artery pressure and pulmonary vascular resistance are often found in patients undergoing surgery for aortic aneurysm or aortic occlusive disease (Lunn, Dannemiller and Stanley, 1979). These haemodynamic changes might be partly explained by the increases in anaphylatoxin activity, as C3a and C5a increase vascular tone (Marceau and Hugli, 1984). During extradural blockade, the degree of complement activation during operation was less pronounced when compared with general anaesthesia alone.
Similarly, the formation of the anaphylatoxins increased only slightly in the extradural group.

Perioperative extradural blockade might be beneficial in regard to the incidence of peri- and postoperative complications although, in this study, we were unable to find any correlation with the incidence of postoperative infection, wound healing and multi-system organ failure. However, the groups studied were too small, and the trauma possibly insufficiently extensive, to reveal clinically observed changes in a multifactorial disease with a relative low incidence.

The mechanisms behind the effects of extradural blockade on complement activation and anaphylatoxin release are not fully understood. The influence of local anaesthetics on biological structures and living cells have been documented (Papahadjopoulos et al., 1975; Feinstein et al., 1977). In addition, inhibition of human leucocyte metabolism and random mobility by lignocaine has been reported (Hammer, Dahlgren and Stendahl, 1985). These responses are mediated by several factors, including the complement cascade. Membrane stabilization by local anaesthetics is one possible mechanism by which the complement cascade, and the formation of biologically active split products, might be influenced. Afferent inhibition by extradural blockade might be another mechanism influencing the activation of complement.

Recent evidence indicates that anaphylatoxins stimulate biosynthesis of the arachidonic acid products, leucotrienes and prostaglandins (Stimler et al., 1982). Prostaglandin production has been reported in association with altered pulmonary function and central haemodynamics (Cooper et al., 1980).

As anaphylatoxins are potent mediators of histamine, leucotrienes, prostaglandins, thromboxane and the platelet-activating factor, they might account for clinical effects observed when increased concentrations of C3a and C5a appear in plasma (Goldstein et al., 1973; Habal, Movat and Burrowes, 1974; Kaplan, 1978; Bokisch and Muller-Eberhard, 1979; Ghebrehiwet, Silverberg and Kaplan, 1981). C5a is inactivated by circulating carboxypeptidase, which cleaves one arginine residue off the N-terminal end, producing C5a desArg (Bokisch and Muller-Eberhard, 1979). C5a and C5a desArg are bound avidly to neutrophils, where they are internalized and degraded (Chenoweth and Hugli, 1978, 1980). A rapid elimination pattern could, in fact, mask the increased formation of C5a. The leucocyte count was, however, never extremely low in either of the groups studied.

The correlation between duration of clamping and the increase in anaphylatoxin concentration fits well with the clinical impression that a long-standing occlusion of a major artery is associated with increased risk of haemodynamic complications. Other investigators have also found increases in anaphylatoxin concentrations in association with aortic surgery. They have suggested that an anaphylactic reaction against the aortic prosthesis could cause the release of the anaphylatoxin (Shepard et al., 1984; Roizen et al., 1985). Although different synthetic vascular prosthesis materials are able to induce anaphylatoxin release, the aortic cross-clamping itself is one reason for complement activation as the anaphylatoxins increase during clamping before the graft has been inserted.

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