did not administer thrombolytic agent intraoperatively; this may have prevented the devastating consequences of an epidural hematoma.

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Cardiopulmonary Bypass in Hereditary Angioedema

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AN absence of functional inhibitor of the activated form of the first complement component (C1INH) causes uninhibited activation of the complement cascade and

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the clinical picture of angioedema. Complement activation is seen in cardiac surgery, and is caused by a number of factors, including exposure of blood to the bypass circuit and administration of protamine.[1-3]

Twenty-five patients with hereditary angioedema undergoing 41 noncardiac operations were recently reported by Wall et al.[4] This constitutes the largest series of such patients to date. To our knowledge, only two previous case reports of patients with C1INH deficiency undergoing cardiac surgery with cardiopulmonary bypass exist in the literature. One patient died with evidence of unregulated complement activation after separation from bypass.[5] The other, a child with biochemical, but no clinical, symptoms of hereditary angioedema, underwent ASD closure uneventfully.† We report the case of a patient with hereditary angioedema

CASE REPORTS

Table 1. Perioperative Serum Complement Concentrations

Date	Time	Comment	Complement Concentration (mg/dl)				
			C3 70–190	C4 10–40	B 20–50	C1Q 35–56	C1INH 16–34
10/25	08:46	Baseline					11
10/28	08:00	Preinduction	105	20	36	60	12
10/28	09:45	Postintubation	94	18	32	46	9
10/28	11:37	Bypass + 30 min	59	12	21	19	9
10/28	12:45	Protamine administration	50	8	15	25	6
10/28	14:30	Postbypass	54	11	20	45	9
10/28		Lowest concentration (% of prebypass baseline)	0.48	0.4	0.42	0.32	0.54
10/28		Lowest concentration (% of norm)	0.71	0.8	0.73	0.54	0.38

Concentrations were measured at the intervals listed. Normal ranges are given. Also listed are the lowest complement concentrations achieved during the perioperative period, expressed as a percentage of preinduction values and as a percentage of the lower normal limit.

who underwent successful myocardial revascularization after long-term androgen therapy and a perioperative increase in the patient's usual androgen dosing.

Case Report

A 71-yr-old man with a history of stable angina and hereditary angioedema was admitted with 6 h of unrelenting anginal pain. An EKG showed new right bundle branch block and left posterior hemiblock. CPK-MB fractions were increased, consistent with a small myocardial infarction. Prior serial exercise thallium studies had shown evidence of worsening ischemia. Cardiac catheterization revealed three vessel disease with a left ventricular ejection fraction of 60%, and was accomplished uneventfully. A decision was made that the patient's coronary artery disease would be best treated surgically.

The patient had a long history of angioedema. His father, sister, and grandmother all had documented hereditary angioedema. The patient's symptoms included edema of the hands, airway, GI tract, and genitals brought on by trauma and cold. He had received hormonal therapy for 25 yr, initially with methyltestosterone, and more recently with stanozolol. The patient's only prior surgery was a tonsillectomy performed in childhood without sequelae. Since receiving treatment, he had suffered no attacks. He reported no adverse effects from hormonal therapy, and had never received antifibrinolytic agents. His baseline C1INH level drawn 4 days before surgery was 11 mg/dl (normal: 16–34 mg/dl). C4 levels were normal. His stanozolol dose was increased from 2 mg twice daily to 2 mg four times daily for 5 days before surgery. He was given no perioperative fresh frozen plasma (FFP).

The patient underwent uneventful coronary artery bypass grafting with a membrane oxygenator. Cross clamp time was 54 min, and total bypass time was 95 min. Complement levels, components of the coagulation cascade, and coagulation studies were drawn at five intervals in the perioperative period: before entering the operating room, after tracheal intubation, 30 min after initiating bypass, immediately after protamine administration, and 120 min after sepa-

ration from cardiopulmonary bypass (table 1). All measured complement levels decreased in the prebypass period. All but C1INH levels decreased dramatically with the onset of bypass, and reached a nadir with the administration of protamine. Some recovery of complement levels was seen by the time the patient reached the intensive care unit. The patient's trachea was extubated on the evening of surgery without evidence of glottic edema. The patient was transferred out of the intensive care unit on postoperative day 1, and was discharged from the hospital on postoperative day 5.

Discussion

First described by Sir William Osler, hereditary angioedema is a genetic disease transmitted as an autosomal dominant and manifested by episodes of painless swelling brought on by minor trauma, cold, or emotional upset.‡ Typically, the swelling involves the extremities, gastrointestinal tract, or face. Swelling of the tissues of the upper airway can lead to airway compromise and death. In 30% of these patients, death is caused by airway swelling, typically brought on by minor trauma, such as that which occurs during routine dental procedures.[6,7]

A deficiency of functional inhibitor of the activated form of the first complement component is responsible for the clinical manifestations of the disease. A deficiency of C1INH results in the unimpeded action of activated C1 on its substrate, C4. As a result, C4 levels are reduced in patients with hereditary angioedema. Activated C4 cleaves its substrate C2, generating the fragment, C2 kinin. C2 kinin increases vascular permeability and may cause the clinical manifestations of the disease.[8,9] There are two forms of the disease. Eighty-five percent of patients have a deficiency of C1INH, and 15% of patients have normal serum levels

‡ Osler W: Hereditary angioneurotic oedema. Am J Med Sci 95: 362–367, 1888.

of functionally inactive C1INH.[10] There is also an acquired C1INH deficiency seen in patients with various lymphoproliferative disorders, autoimmune hemolytic anemia, adenocarcinoma of the rectum, and myelofibrosis.[11]

Therapy for angioedema can be categorized into long-term therapy, short-term preventative therapy, and the treatment of acute attacks. Fortunately, most patients do not require long-term therapy unless their attacks are frequent or life threatening. If indicated, long-term prophylaxis is undertaken with either hormonal therapy or antifibrinolytic agents. Hormonal therapy consists, most commonly, of treatment with androgens, such as stanozolol. These drugs are often referred to as "attenuated androgens" because of their limited androgenic potential. Side effects are fewer than with methyltestosterone, the first hormonal agent introduced for therapy in 1960.[6] Nevertheless, adverse side effects, such as hepatic dysfunction, suppression of clotting factors with an increase in prothrombin time, bladder irritation, fluid retention, and hypertension, can occur. Hormonal therapy is thought to increase plasma C1INH levels by increasing hepatic synthesis of this protein.

Antifibrinolytics are thought to improve the clinical course of hereditary angioedema by inhibiting plasmin activation. Side effects, such as muscle pain and weakness, fatigue, sedation, and postural hypotension, may limit their use in up to 25% of patients.[6]

Authors have suggested that, if a patient not receiving long-term therapy presents for surgery and 2–3 days are available before surgery must be performed, FFP infusion, a short course of antifibrinolytics, or androgens may prevent acute attacks.[4] Whether this approach would be effective as prophylaxis in a patient undergoing cardiac surgery with cardiopulmonary bypass is a matter of speculation.

For an acute attack, no effective therapy has been readily available. The use of epinephrine, steroids, and antihistamines has met with little success. Fresh frozen plasma, antifibrinolytics, and androgens have no role in the acute setting.

This patient's baseline complement levels were what one would expect in a patient treated for this disease.[7,11] His C1INH was 68% of normal, and his C4 level was normal. Untreated patients generally have reduced C4 levels because of accelerated cleavage by an abundance of activated C1. An adequately treated patient will have nearly normal C4 levels, indicating closely controlled C1 activation by sufficient levels of C1INH.[7–9]

It is interesting that, despite 5 days of increased androgen dosing, C1INH levels increased minimally. The time course of drug effects appears to vary among patients. Most authors report increased C1INH levels after 5–12 days of therapy, with a plateau reached from 9–17 days.[7,12] However, these are responses to initiating therapy, rather than augmenting therapy in a chronically treated patient.

During CPB, levels of C3, C4, factor B, C1INH, and C1Q all declined to 35–50% of control, and all but C1Q levels reached their nadir with protamine administration (table 1). This is not surprising, because the heparin-protamine complex is a known activator of complement. The decrease in serum complement levels is consistent with that reported by others looking at complement levels, as well as other plasma proteins.[3,13] Much of this decline in complement levels is secondary to hemodilution. However, evidence exists to indicate that complement activation with consumption plays a role, as well.[1,2,14–19]

We believe that the difference in outcome between our case report and that of Bonser et al. may be caused by preoperative levels of C1INH. In the previous case report, a patient with acquired angioedema and a preoperative C1INH level 30% of normal underwent CPB. He experienced exaggerated activation of complement, and died in the operating room. It is most likely that the hemodilution associated with this procedure reduced existing C1INH to levels inadequate for prevention of unchecked complement activation. The patient in our case report had C1INH levels 75% of normal preoperatively, which were reduced to 38% of normal at the time of CPB. The difference in starting and diluted factor levels could have been responsible for the difference in outcome reported.

Whether a safe, lower-limit C1INH level exists is unknown. Some have advocated maintaining C1INH levels greater than 50% of normal.[8] Others have reported that low-dose attenuated androgen therapy may prevent attacks of angioedema, even when levels of C1INH and C4 (which may be corrected initially) return to baseline levels.[9,20] These authors suggest that, because androgens, such as stanozolol, increase protein synthesis by the liver, they will increase the synthesis of other inhibitor proteins that may compensate for the lack of C1INH.

This may not be adequate for patients undergoing CPB. These patients not only have their C1INH diluted, but CPB itself activates complement. Furthermore, after termination of CPB, protamine administration provides

CASE REPORTS

yet another stimulus for complement activation. All of the above may prove disastrous for the patient with angioedema. To best prepare the patient with angioedema for CPB, the necessary time should be taken, and an adequate dose of androgen should be given to increase the C1INH to a level as close to normal as is practically possible. In patients just beginning therapy with androgens, 9–17 days may be required for C1INH levels to reach a plateau. Documentation of plasma levels also appears advisable.

For acute episodes of angioedema, there has been no readily available, effective method for terminating the attack. In 1980, Gadek *et al.* reported successful treatment of acute angioedema with partially purified C1INH in five patients.[21] Only recently, however, has purified C1INH become available for life-saving emergencies using an open-label protocol that has FDA approval (C$_1$ Inhibitor [human] Vapor-Heated, IMMUNO; Immuno Clinical Research, New York, NY).

Anecdotal reports have lead to the recommendation that FFP be used in acute attacks of hereditary angioedema.[22] This practice is of unproved value. Not only does use of FFP carry with it the risk of infectious complications, but it has been observed to actually worsen the attack.[4] In addition to C1INH, FFP contains C2 and C4, substrate for the complement cascade.[11]

We hypothesize that the patient described in this report did well because he started the operation with C1INH levels 75% of normal. Whether the increased dose of stanozolol contributed to the effectiveness of the treatment is unknown. Even so, his C1INH level declined to 38% of normal by the end of CPB. Pretreatment for 9–17 days may be inconvenient, but can be done with relatively little risk to the elective patient. Until there are data establishing a safe limit for C1INH levels in patients with angioedema undergoing CPB, prudence dictates increasing the patient's C1INH level before the procedure. The time should be taken to establish C1INH levels as near normal as is practical. Furthermore, for those patients who develop acute angioedema despite prophylaxis, the availability of commercial purified C1INH may prove life saving.

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Anesthesiologists' Management of Isolated Limb Perfusion with "High-dose" Tumor Necrosis Factor α

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TUMOR necrosis factor α (TNFα) is a polypeptide cytokine produced mainly by activated monocytes. It possesses a broad spectrum of biologic properties, and is one of the most important mediators of multiple-organ system response in endotoxic and septic shock.[1] Human recombinant TNFα has been shown to have antitumor activity against advanced malignant tumors in humans.[2] However, because of severe systemic side effects of clinically effective doses in patients with cancer, the results of phase I clinical trials have been disappointing. The maximum tolerated single dose in humans, administered systemically, is only 250–350 µg/m², which is less than that needed to reach a significant antitumor effect.[2] Side effects of recombinant TNFα de-

scribed during systemic treatment of cancer in humans include: fever up to 41° C (63% of cases), hypotension (48%), dyspnea (23%), chest tightness (10%), and peripheral cyanosis (40%).[3] In addition, abnormalities of liver function, thrombocytopenia, malignant hyperthermia, cardiovascular collapse with unrecordable blood pressure, peripheral capillary leak syndrome, acute renal failure, and bleeding into a brain metastasis with fatal outcome have also been reported as side effects of recombinant TNFα treatment in humans.[2-6]

Isolated perfusion of limbs with high doses of cytotoxic drugs is an established treatment modality in severe forms of melanoma and sarcoma. It allows the use of 10 to 20 times higher doses of antitumor drugs than would be tolerated systemically. This method was used by Lienard et al. to administer high-dose recombinant TNFα together with interferon τ (IFNτ) and the alkylating agent, melphalan, both of which have been shown to increase the antitumor activity of TNFα.[2,7] The clinical results of this study and other phase II clinical trials are quite promising for patients with advanced malignant melanoma or sarcoma on the extremities.[7] Approximately 85% complete remission and 15% partial recurrence have been reported in patients with metastatic melanoma, and the rate of limb sparing has been as high as 92%.[7] Thus, it is more than likely that anesthesiologists will be increasingly involved in this kind of therapy, as well as dealing with the severe side effects of this treatment. We discuss below the anesthetic management of this procedure, together with a case of a severe "septic-shock-like" reaction causing multiple-organ system dysfunction in a patient treated

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