

In summary, EPWA or transmission of the epidural pulsatile pressure waveform is improved by the use of 3-hole catheters, higher volume of injectate, and older patients. We do agree that the technique is simple, sensitive, and inexpensive and uses equipment readily available in any operating room.

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doi:10.1053/j.jvca.2006.11.020

## Fish Baffles Doctors: Scombroid Fish Poisoning or Fish Allergy?

To the Editor:

Patients allergic to fish are known to have cross-reactivity with protamine,<sup>1</sup> and the administration of protamine to susceptible individuals can lead to clinically important adverse events.<sup>2</sup> We present a patient who gave a history of previous fish allergy and was extensively investigated.

A 58-year-old, 54-kg man with New York Heart Association class III angina was diagnosed with triple-vessel coronary artery disease. He had a history of skin flushing, nausea, vomiting, and diarrhea within 20 minutes after consumption of kingfish (*Scomberomorus commerson*, narrow-barred Spanish mackerel). He had this reaction on several but not every occasion he was exposed to the fish. The duration of symptoms ranged from a few hours to 24 hours and subsided without any intervention. There was never any evidence of facial swelling or airway obstruction.

The patient was screened for a fish allergy. The total immunoglobulin (Ig) E levels were elevated (623 kU/L [normal = <100 kU/L]). In an attempt to determine cross-reactivity with protamine, a skin test was performed with intradermal protamine sulfate (0.1 mL diluted to 0.1 mg/mL). There was no wheal observed nor was there a palpable induration. In vitro serum enzyme-linked immunosorbent assay (ELISA; Pharmacia CAP System Allergens, Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) revealed no serum antiprotamine IgE and antiprotamine IgG antibodies. The patient's complete blood cell count was normal.

The patient underwent coronary artery bypass graft surgery performed using cardiopulmonary bypass (CPB). Tranexamic acid was used for antifibrinolysis. In addition to monitoring according to the American Society of Anesthesiologists recommendations, a pulmonary artery catheter was used to monitor pulmonary artery pressures and cardiac output variables. The airway pressures were monitored continuously because an increase in plateau airway pressure after protamine administration would have suggested a probable protamine reaction. Unfractionated heparin, 20,000 U, was administered based on a Hemochron heparin response test (International Technidyne Corporation, Edison, NJ) targeting an activated coagulation time of 480 seconds during CPB.

The circuit was comprised of a hollow-fiber oxygenator with a heparin-coated biosurface (Trillium Affinity NT; Medtronic Inc, Minneapolis, MN), a poly-2-methoxyethylacrylate-coated extracorporeal circulation tubing set (Terumo Europe NV, Leuven, Belgium), and a centrifugal pump. The CPB circuit was primed with 1.6 L of heparinized lactated Ringer's solution using 2,500 U of heparin. The patient was cooled to 32°C, and myocardial protection was achieved with antegrade blood cardioplegia. The surgery was performed by using the left internal mammary artery to the anterior descending artery and saphenous vein grafts to the first obtuse marginal branch of the circumflex artery and the posterior descending artery. The aortic cross-clamp time was 40 minutes, and the CPB time was 65 minutes. The patient was successfully weaned from CPB without difficulty.

After a test dose of protamine sulfate (5 mg through a peripheral vein), a total dose of 160 mg was administered to reverse residual heparin activity. No more than 50 mg of protamine sulfate was administered intravenously in any 10-minute period. The total dose of protamine was based on a Hemochron protamine response test (International Technidyne Corporation).

Hemodynamic variables were measured (Table 1) and showed no sign of a protamine reaction. The blood loss was 300 mL intraoperatively and 440 mL in the first 24 hours. No transfusions were given. After an uneventful recovery, he was discharged home on the fifth day with the advice to attend the allergy clinic to identify the cause for the elevated IgE levels.

This patient with a history of allergic skin rash on fish consumption had elevated IgE antibody levels. We were concerned about

Table 1. Hemodynamic Parameters of the Patient

| Parameter                                                                                        | Baseline | Before Heparinization | After Heparinization | Before Protamine (10 minutes post-CPB) | 5 Minutes After Protamine Test Dose | 10 Minutes After Complete Protamine Reversal |
|--------------------------------------------------------------------------------------------------|----------|-----------------------|----------------------|----------------------------------------|-------------------------------------|----------------------------------------------|
| Heart rate (beats/min)                                                                           | 76       | 72                    | 68                   | 76                                     | 81                                  | 71                                           |
| Pulmonary artery wedge pressure (mmHg)                                                           | 14       | 14                    | 11                   | 15                                     | 15                                  | 16                                           |
| Mean central venous pressure (mmHg)                                                              | 11       | 11                    | 11                   | 10                                     | 11                                  | 10                                           |
| Cardiac Index (2.8-4.2 L/min/m <sup>2</sup> )                                                    | 3.98     | 3.79                  | 2.74                 | 4.52                                   | 4.44                                | 4.34                                         |
| Stroke index (30-65 mL/beats/m <sup>2</sup> )                                                    | 52.4     | 54.2                  | 40.2                 | 59.5                                   | 60.3                                | 47                                           |
| Systemic vascular resistance index (1,500-2,400 dynes · sec · cm <sup>-5</sup> /m <sup>2</sup> ) | 1225     | 1096                  | 1812                 | 831                                    | 777                                 | 1510                                         |
| Pulmonary vascular resistance index (250-400 dynes · sec · cm <sup>-5</sup> /m <sup>2</sup> )    | 140      | 242                   | 205                  | 141                                    | 165                                 | 264                                          |
| Left ventricular stroke work index (45-60 g/m <sup>2</sup> )                                     | 39.2     | 35.4                  | 33.9                 | 32.4                                   | 34.4                                | 37.7                                         |
| Right ventricular stroke work index (45-60 g/m <sup>2</sup> )                                    | 5.7      | 4.42                  | 3.83                 | 12.14                                  | 8.20                                | 9.58                                         |

the possibility of an anaphylactic reaction during heparin reversal with protamine on conclusion of CPB. Protamine administration can produce IgE- and IgG-mediated hypersensitivity,<sup>3</sup> and the incidence of adverse reactions after its administration to neutralize heparin has been reported to be between 0.06% and 27%.<sup>1</sup> In addition, patients allergic to fish when exposed to protamine are at risk of developing a type 2 immunoglobulin-mediated anaphylactic/anaphylactoid reaction.<sup>1</sup> A fish allergy was found to be an independent risk factor (odds ratio = 24.5; 95% confidence interval, 1.24-482.3;  $p = 0.035$ ) for clinically important adverse events after protamine administration after CPB.<sup>2</sup> Individuals allergic to fish may have serum antibodies directed against protamine. Commercial protamine preparations may be contaminated with fish proteins to which patients allergic to fish may react,<sup>1</sup> and some case reports link allergy to true vertebrate fish with the development of anaphylaxis after protamine exposure.<sup>4,5</sup>

Therefore, in the development of a management strategy, it was important that this patient with suspected fish allergy was thoroughly investigated. IgE-mediated sensitivity to protamine can be identified by cutaneous testing, whereas ELISA can measure protamine-specific IgE and IgG antibodies as well as specific antibodies against food allergens.<sup>3</sup> It has to be kept in mind that a positive skin test might predict an adverse reaction, but a negative reaction does not rule out the possibility.<sup>1</sup> Serum-based laboratory tests like ELISA also have intrinsic limitations in terms of false-positive and false-negative results.<sup>1</sup>

Since there was a concern of protamine allergy due to the possibility of all the tests being false-negative, we did consider revascularization off CPB (off-pump coronary artery bypass surgery) with low-dose heparin and no protamine reversal in this patient. The intramyocardial course of the coronary arteries and poor distal target vessels of the patient ruled out this possibility.

In case of an adverse response to protamine, immediate reinstitution of CPB (with reheparinization) and prolonged organ support was planned. After stabilization of the hemodynamics and separation of the patient from the CPB, we would have allowed spontaneous reversal of heparin over a period of time along with meticulous surgical hemostasis.

Protamine was administered after a test dose while simultaneously monitoring the hemodynamics for any adverse reaction. Because no untoward reaction was encountered, heparin neutralization was completed based on the protamine response time results. As acute protamine-induced pulmonary vasoconstriction with catastrophic acute pulmonary hypertension has been described,<sup>7</sup> the pulmonary vasculature was monitored with a pulmonary artery catheter.

On review of the literature, we found that scombroid fish poisoning is often misdiagnosed as fish allergy, and histamine is the toxin responsible for scombroid fish poisoning.<sup>8</sup> Scombroid fish poisoning is a chemical intoxication that occurs after eating bacterially contaminated fish of the dark meat varieties, such as the families of Scombridae or Scomberesocidae including tuna, kahawai, mackerel, bonito, and butterfly kingfish. Certain bacteria produce the enzyme histidine decarboxylase, which breaks down free histidine, a naturally occurring chemical that is present in larger quantities in Scombridae, resulting in the formation of histamine and other amines. Once histamine is formed, it cannot be removed by heat or freezing.

This illness should be suspected in anyone who develops allergic manifestations like flushing, sweating, burning-peppery taste sensations about the mouth and throat, dizziness, nausea, and headache within minutes to 2 hours of eating a scombroid fish. Confirmation of scombroid poisoning is a simple histamine analysis of the suspect fish by fluorometry. Histamine is normally present at levels less than 0.1 mg per 100 g of fish. Samples of fish that produce poisoning contain histamine levels of at least 20 mg per 100 g of fish.<sup>9</sup>

In view of the negative skin and ELISA tests for allergens and the absence of a response to protamine administration after CPB, the patient in this report probably suffered from recurrent scombroid fish poisoning. However, we had to rule out a fish allergy before arriving at this suggestion of scombroid fish poisoning. The cause for the patient's IgE levels being elevated is unknown and might reflect an atopic state.

In conclusion, it should be stressed that all fish allergies have to be thoroughly investigated. If true allergies to fish and/or protamine are identified, alternative strategies for the conduct of CPB have to be considered. Scombroid (histamine fish) poisoning

is a diagnosis by exclusion after testing for a true fish allergy. Conditions like scombroid fish poisoning that might mimic fish allergies and complicate the preoperative workup should also be borne in mind by the cardiac team.

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doi:10.1053/j.jvca.2007.04.005

## Caution When Positioning Central Venous Catheter and Its Relationship to the Pericardial Reflection

*To the Editor:*

Pericardial tamponade secondary to the perforation of the superior vena cava, right atrium, or right ventricle with a central venous catheter (CVC) remains an important everyday concern because millions of CVCs are inserted annually. We appreciate Bayer et al's<sup>1</sup> recent article in which they observed the variable measurements and relationships of the pericardial reflection in relation to the superior vena cava (SVC). Although their study certainly should be acknowledged with respect to their in vitro findings, caution should be taken regarding the authors' recommending that all catheters be placed below the pericardial reflection.

We have concerns regarding these conclusions. First, it seems imprudent to increase the risk of life-threatening pericardial tamponade for patients by placing catheters below the pericardial reflection. Caruso et al<sup>2</sup> showed that the pericardial reflection covers the distal half of the SVC. Furthermore, it has been shown that perforation resulting in tamponade can transpire in areas (eg, distal SVC and heart) included in the pericardial reflection.<sup>3</sup> Although Bayer et al<sup>1</sup> stated that catheters in the distal third of the SVC are likely to be parallel to the long axis of the vein, there is a higher likelihood of perforation secondary to catheter movement with each respiratory cycle, heart contraction, and patient movement. In addition, CVCs placed via the left jugular or subclavian veins may still not reliably be in an orientation in which the catheter tip is parallel to the SVC. Guidelines of the Food and Drug Administration note that catheters should not migrate into or be placed in the heart.<sup>4</sup>

Second, although we agree that the correct placement of CVCs is a complicated and debatable issue, placement of the CVC above the pericardial reflection is safer. The risks and benefits of using the Bayer et al<sup>1</sup> method must be weighed. CVC placement above the pericardial reflection could potentially result in hemo- or hydrothorax but not catastrophic pericardial tamponade. Erosions of the catheter against vessel walls, angles of the catheter with the vessels, and type of catheter materials and design all are important factors leading to vessel-wall perforation. From in vitro modeling, data exist to help us choose more favorable catheters, such as pigtail catheters, or single- or double-lumen catheters versus triple lumen to decrease the risk of perforation.<sup>5</sup>

When clinicians place CVCs, prudence dictates that they preferably should be placed above the pericardial reflection to minimize the risk of a vascular perforation resulting in often-fatal pericardial tamponade.

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