

## CORRESPONDENCE

Anesthesiology  
79:617, 1993  
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**In Reply:**—Lam and Mayberg express concern that our results<sup>1</sup> contradict some prior studies and offer an alternative mechanism by which our results may have been observed.

First, the studies cited by Lam and Mayberg are not reasonable benchmarks because both studies measured actual tissue blood flow with <sup>133</sup>Xe, which we believe cannot be used interchangeably with conduit vessel velocity. A more comparable paper would be that of Werner *et al.*<sup>2</sup> However, their use of a different species, significant other anesthetics including isoflurane and nitrous oxide, and the occurrence of large changes in blood pressure probably renders a comparison here meaningless as well.

Second, an intraarterial sampling catheter would have been useful for *post hoc* validation of ventilatory stability but would not have been useful for real-time control of normocapnia, and for the ethical and consent reasons outlined in our discussion, we chose to use the noninvasive technique, once validated. We know of no evidence that clinically inapparent chest wall rigidity can significantly alter the A-a gradient of carbon dioxide or that these opioids can cause pulmonary hypotension to a degree that can alter ventilatory dead space in the absence of significant changes in systemic blood pressure.

Finally, Lam and Mayberg's final comment is also on shaky ground, statistically speaking. Our data demonstrated variances that were somewhat larger than the differences between the means of end-tidal *versus* arterial carbon dioxide. The presence of variance about a mean implies that some subjects had a larger value than the mean, and an equal number had a lower number. This observation provides no evidence for a bias or offset of the mean of 7–8 mmHg as posited by Lam and Mayberg.

It is worth reemphasizing that transcranial Doppler ultrasonography provides useful information in its own right that does not always mirror blood flow. We believe that the transcranial Doppler technique, by providing information on velocity, will blossom into a useful noninvasive tool for pharmacologic research.

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(Accepted for publication June 4, 1993.)

Anesthesiology  
79:617–618, 1993  
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## Prior Vasectomy and Anaphylaxis Following Protamine: No Cause and Effect

**To the Editor:**—By choice of title and concluding sentence, the authors of a recent paper<sup>1</sup> imply that their patient suffered two anaphylactic reactions to protamine, that IgG antibodies to protamine were responsible for these reactions, and that IgG antibodies to protamine were a response to prior vasectomy. The case report, as presented, does not support these implications.

The first contention is that both reactions to protamine were anaphylactic. However, the first reaction, transient pulmonary hypertension and systemic hypotension responding “promptly” to boluses of inotropic agents and vasopressors, is more consistent with the pulmonary vasoconstriction syndrome described by others.<sup>2,3</sup> Heparin-protamine complexes, not immunoglobulins, are hypothesized to be responsible for this idiosyncratic reaction to protamine.<sup>4</sup>

The later reaction to protamine, systemic hypotension, and bradycardia responding “promptly” to fluids, antihistamines, and steroids, again suggests a nonanaphylactic origin. The transient nature of the reaction and return of stable hemodynamics without intense resuscitation is typical of histamine release, which occurs commonly with protamine administration.<sup>5</sup>

Intraoperative anaphylaxis usually presents as peripheral and pulmonary edema, bronchospasm with hypoxemia, and systemic hypotension without pulmonary hypertension, all potentially contributing to cardiovascular collapse.<sup>6</sup> Therapy usually requires high infusion rates of epinephrine, many liters of fluid, and prolonged mechanical ventilation.<sup>7</sup> This patient's reactions to protamine differed in quality and severity from the classic anaphylactic reaction.

Most anaphylactic reactions are mediated by IgE; reactions mediated by IgG and other immunoglobulins are termed "anaphylactoid" and do not require previous sensitization.<sup>6</sup> This patient possessed no IgE antibodies to protamine. Subclass 4 of IgG may be responsible for anaphylactic reactions as they can bind to mast cells and release histamine; this is not true of other IgG subclasses.<sup>7</sup> The authors do not state whether IgG detected in their patient was of this subclass.

The author's second contention is that IgG antibodies to protamine produce severe reactions to protamine. Most diabetic patients receiving protamine-containing insulin preparations develop IgG antibodies to protamine;<sup>8</sup> yet few diabetic patients with prior exposure to protamine suffer intraoperative anaphylactic reactions to protamine.<sup>9</sup>

Third, this patient had two opportunities to produce antiprotamine antibodies: his vasectomy and his exposure to intravenous protamine during catheterization. The authors do not state why his vasectomy should be the culprit. If the patient indeed had circulating antiprotamine antibodies prior to his catheterization, he apparently escaped anaphylaxis when given 45 mg protamine at catheterization but not when given 50 mg protamine 6 weeks later at operation.

In summary, the case report identifies a patient with a previous vasectomy, antiprotamine IgG antibodies, and two hypotensive episodes after receiving protamine. The association, if any, among these observations remains speculative. Two prospective studies of 8 and 20 vasectomized men did not detect any untoward responses to intraoperative protamine.<sup>9,10</sup> Current evidence, this case report included, remains inadequate to implicate prior vasectomy as a risk factor for severe reactions to protamine.

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Anesthesiology

79:618-619, 1993

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*In Reply:*—Metz is concerned with three issues that he believes we raised in our recent case report.<sup>1</sup>

First, he questions whether we should call the reactions to protamine "anaphylactic" because the patient responded to medical treatment, did not have pulmonary edema or bronchospasm, and had protamine-specific IgG (not IgE) antibodies in his serum. Anaphylaxis is a descriptive term delineating a severe, abrupt, life-threatening reaction manifested by cardiovascular, pulmonary, or cutaneous signs.<sup>2</sup> This patient experienced severe hypotension characterized by a decrease in systolic blood pressure from 95 to 40 mmHg in the operating room, within minutes after receiving protamine and again during cardiac catheterization in the radiology department 2 weeks later. Cardiovascular collapse or severe hypotension often is seen in the absence of skin signs and bronchospasm during anesthesia,<sup>3,4</sup> and many such patients respond promptly to treatment.<sup>5</sup> Furthermore, these reactions may be associated with complement activation

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(Accepted for publication June 4, 1993.)

through interaction of protamine and complement-fixing antiprotamine IgG antibody.<sup>6</sup> This type of reaction is defined as an "anaphylactic reaction" in the major textbook in this field.<sup>2</sup>

Second, Metz is apparently unaware that diabetic patients receiving protamine-containing insulin preparations are at risk for life-threatening reactions to protamine<sup>7,8</sup> and that antibody-mediated mechanisms are the likely cause for the increased risk.<sup>9</sup>

Third, vasectomy is thought to disrupt the blood testes barrier, after which 20-33% of such men develop hemagglutinating autoantibodies against protamine-like compounds.<sup>10</sup> It is possible that 45 mg protamine, given 6 weeks earlier at cardiac catheterization, may have contributed to the increased IgG level.

Our publication was a case report and did not address the issue of whether vasectomized males with high titers of antiprotamine IgG are at risk for developing life-threatening reactions to protamines. However, the demonstration of life-threatening cardiovascular re-