Catastrophic Cardiovascular Adverse Reactions to Protamine

To the Editor:

The article by Viaro et al1 (September 2002) provides important and interesting data on the side effect profile of protamine. However, their article raises a number of important points that need addressing.

First, clinically, when protamine is administered slowly, the vast majority of patients experience a minimal cardiovascular effect. A few individuals show elevated pulmonary artery pressures and develop acute right ventricular dilatation, which is obvious on inspection to a cardiac surgeon. This would seem to indicate an idiosyncratic mechanism, and not a fixed pathway. In the setting of pulmonary hypertension, administering nitric oxide (NO) in the form of nitroprusside is not uncommon, although the use of inhaled NO is more usual. Administering methylene blue would reduce the pulmonary NO level, precipitating a pulmonary hypertensive crisis, necessitating the readministration of heparin and the recommencement of cardiopulmonary bypass, an obvious retrograde step.

Second, Viaro et al1 seem to confuse low systemic vascular resistance (SVR), or vasoplagia, postoperatively with a reaction to protamine, utilizing the reaction as an argument for the use of methylene blue. Numerous other factors have been described as a cause of vasoplagia postoperatively.2 The rarity of vasoplagia on-pump cardiac surgery would seem to eliminate protamine as the main pathophysiologic effect of protamine administration. We would have to disagree, since patients with vasoplagia who are unresponsive to catecholamine therapy would reduce the pulmonary NO level, precipitating a pulmonary hypertensive crisis, necessitating the readministration of heparin and the recommencement of cardiopulmonary bypass, an obvious retrograde step.

Third, Viaro et al1 maintain that a low SVR is the main problem with protamine administration. We would have to disagree, since it is well known that the administration of protamine directly into the left side of the heart, usually via a dedicated left atrial line, dramatically reduces the cardiovascular effects of protamine administration. The reasons that this technique has not found widespread adoption are twofold: infrequent use of direct left atrial lines, and fear of cerebral embolic episodes. This would seem to refute the claim of Viaro et al1 that a low SVR is the main pathophysiologic effect of protamine administration.

Fourth, Viaro et al1 quite rightly present conflicting evidence with regard to the possible mechanism of action of protamine and the role of NO. However, two additional important points need to be made. A number of the studies that they quote utilized different organs and even different species, and we already know that the lungs behave differently from species to species and from the systemic circulation. In addition postcardiopulmonary bypass endothelial function is impaired, which means that agents that directly produce/inhibit NO may be effective (eg, nitroprusside); however, agents that rely on endothelial function (eg, glycyl trinitrate/L-NG-nomonomethyl-L-arginine) will be ineffective.

Finally, the claim that isolated pulmonary vasodilatation may cause systemic hypotension is difficult to understand. As far as we are aware, isolated pulmonary vasodilatation may actually increase cardiac output and BP by increasing left ventricular filling.

Of course, in vasoplagia, which Viaro et al1 seem to confuse with “a reaction to protamine,” a low pulmonary vascular resistance does occur, but shunting, as is seen in the systemic circulation in patients with vasoplagia, also occurs.

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REFERENCES
1 Viaro F, Dalio M, Evora PRB. Catastrophic cardiovascular adverse reactions to protamine are nitric oxide/cyclic guanosine monophosphate dependent and endothelium mediated. Chest 2002; 122:1061–1066

To the Editor:

The first comment of the letter by Poullis and Shackcloth focuses on the following two points: (1) protamine as a fixed pathway, and (2) methylene blue infusion as cause of pulmonary nitric oxide (NO) reduction. Multiple immunologic and nonimmunologic mechanisms have been reported for the pathophysiology of protamine reactions in human, animal, and in vitro models. The life-threatening cardiopulmonary collapse following protamine administration in humans appears to represent true anaphylaxis or allergy, mediated by immunospecific antibodies. Immunospecific antibodies against protamine (ie, allergic mechanisms) are the only logical explanation by Poullis and Shackcloth for the unpredictable protamine cardiovascular effects. Although protamine reactions have been classified according to pulmonary or systemic vascular effects, this does not elucidate the underlying pathophysiologic mechanisms.1 We focused on the nitric NO pathway in our article, and this approach may have led to the idea of a “fixed pathway.” This was not our intention. We trust in different trigger mechanisms, but we have to consider the direct action of protamine in stimulating endothelial NO release, and the protamine anaphylactic or anaphylactoid properties that also have NO as the final mediator. We do not agree that administering methylene blue would reduce pulmonary NO levels, precipitating a pulmonary hypertensive crisis. Methylene blue does not interfere with NO release, but it blocks guanylyl cyclase, avoiding NO-mediated vasodilatation.2,3 Our clinical and ongoing experimental protocols have proved that methylene blue infusion increases mean arterial pressure without affecting pulmonary artery pressure and cardiac output. This is not the case when we use NO synthesis blockers such as NG-nitro-L-arginine methyl ester or NG-nomonomethyl-L-arginine.

Their second comment focuses on the impression that our article emphasizes the confused concept that protamine infusion
is the crucial mechanism of low vascular resistance or vasoplegia. Again, our emphatic statements about the NO pathway and endothelium function may have led to this interpretation. We agree that cardiac surgery vasoplegia has multiple mechanisms, including drug interactions, as Poullis discussed in his excellent letter, which was motivated by the article of Argenziano et al on vasodilatory shock after cardiac surgery.

Their third comment rejects the notion that low systemic vascular resistance is “the main problem with protamine administration.” In our opinion, this is really the main hemodynamic protamine effect. These effects are closely related to infusion rate. Pulmonary hypertension and systemic hypotension routinely occur in most animal models when protamine or any other polycation is given by rapid injection. Many reports have suggested that there may be advantages to the intra-aortic (IA) administration vs the IV administration of protamine due to the reversal of heparin at the end of cardiopulmonary bypass. The cardiac surgical practice is consistent in presenting similar good results if protamine is infused by the IV or IA route. However, there is significant hypotension when protamine is infused by the IA route. NO release is mainly responsible for this effect, because the arterial endothelium is more adapted to this function than is the venous endothelium.

Their fourth comment focuses on the unpredictability of the endothelium function of different organs and animal species, and the unpredictability of NO donors and blockers effects. We completely agree with this comment. We did not emphasize these points, but they are relevant. When low systemic vascular resistance occurs during or after protamine infusion, NO release is a transitory consequence of the constitutive NO-synthetic expression. However, if protamine evokes an anaphylactic/anaphylactoid or inflammatory reaction, it causes massive overproduction of NO as consequence of inducible NO-synthetic isoform expression.

We agree that isolated pulmonary vasodilatation may increase cardiac output and BP by increasing left ventricular filling. This is true and happens when using inhaled NO to treat patients with pulmonary hypertension. However, even in the setting of pulmonary hypertension, and considering the possibility of hypovolemia, isolated pulmonary vasodilatation may cause systemic hypotension by volume redistribution. Finally, we would like to emphasize the three known vaso-dilatation mechanisms, as follows: guanosine monophosphate cyclic-dependent, adenosine monophosphate cyclic-dependent, and hyperpolarization-dependent. These three mechanisms are synergistic. Beside these three mechanisms, an arginine vasopres-sin deficiency also has been reported. From our point of view, a better understanding of this synergism is mandatory. If the vasoplegetic hypotension is unresponsive to catecholamines (adenosine monophosphate cyclic), methylene blue (guanosine monophosphate cyclic) infusion would be logical. In our opinion, this synergism is strongly suggested by the faster decrease of catecholamines after methylene blue infusion. Arginine vasopressin deficiency is a particular and individual possibility, because, in general, vasopressin levels remain increased until 48 to 72 h after cardiopulmonary bypass.

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Restoration of Antigen-Specific CD4 T-Cell Response Against Mycobacterium tuberculosis in HIV-Infected People

To the Editor:

In a recent issue of CHEST, Schluger et al reported on a very interesting study of the immune response against tuberculosis in HIV-infected patients who were receiving antiretroviral therapy. This finding is crucial in order to predict the relapse of tuberculosis infection and to develop new therapeutic approaches for HIV-infected people. However, there are some points in the study on which we would like to comment. (1) The proliferative response and amount of interferon-γ secretion when peripheral-blood mononuclear cells were stimulated with H37Ra were not different, based on previous tuberculin skin test results. In this respect, it is possible that live and heat-killed Mycobacterium tuberculosis H37Ra might not be specific. Thus, the results concerning immune reconstitution after antiretroviral therapy cannot be attributed to the restoration of the immune response against M tuberculosis. In order to clarify this question, it would also be interesting to know the results obtained when peripheral-blood mononuclear cells were stimulated with the other tested antigens (Mycobacterium bovis bacillus Calmette-Guérin-expressing strain and purified protein derivative). (2) The authors considered that all HIV-positive subjects were latently infected by M tuberculosis, because they were born outside the United States or they had risk factors for tuberculosis infection. However, the authors were not able to affirm the definitive diagnosis of latent M tuberculosis infection. Taking into consideration all these facts, we believe that the conclusions of Schluger et al should be considered cautiously since there is no evidence that the antigen used was a specific one. In the future, it would probably be useful to perform a new study using more specific antigens and to include patients with documented active and latent M tuberculosis infection.

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Communications to the Editor

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