Was a Magic Bullet Aimed in the Right Direction?

In a randomized, double-blind, placebo-controlled multicentered trial, Bone et al demonstrated that prostaglandin E₁ (PGE₁) failed to reduce mortality in postoperative and medical patients with ARDS. In the present issue, Silverman et al (see page 405) of this group describe the long-term effects of this agent on oxygen delivery (Do₂), oxygen consumption (Vo₂), and oxygen extraction (O₂ ext) in a subset of 37 of these patients who had received PGE₁ for six days or more. They concluded that this agent improved Do₂ and Vo₂, even though this did not lead to improved outcome. In the accompanying editorial to the first article, Jenkinson concluded that PGE₁ was not the magic bullet that improves survival in patients with ARDS. However, Silverman’s studies differed substantially from the earlier studies that treated first with fluid therapy the circulatory problems of postoperative shock, ie, low or maldistributed flow that was inadequate to supply the increased metabolic demands reflected by high Vo₂. Before accepting Jenkinson’s conclusion, it might be appropriate to ask if the bullet was pointed in the right direction. In the studies of Bone et al and Silverman et al the Vo₂ and Do₂ in the PGE₁ group averaged only 136 and about 500 ml/min/m², respectively, which is considerably below the 170 and 600 ml/min/m² values empirically observed in critically ill survivors. Even though they increased Do₂, the optimal goals were not achieved except in the nonsurvivor group after four days; under these conditions, increased metabolism is more likely due to late complications, principally sepsis. The authors failed to realize that the primary problem in postoperative shock and shock-related organ failure is tissue hypoxia and oxygen debt from inadequate or maldistributed flow and blood volume.

In earlier PGE₁ studies, volume therapy was first given to correct as much as possible the tissue hypoxia from postoperative or traumatic shock; then PGE₁ was added to further improve oxygen transport variables. If the action of PGE₁ is to inhibit platelet and neutrophil activation by the deleterious effects of thromboxane, it would seem appropriate first to correct as much as possible the tissue hypoxia to prevent the continued generation of more thromboxane by the cyclooxygenase mechanism. PGE₁ should be considered as ancillary therapy, not as a substitute for optimal fluid administration.

In the studies by Bone et al and Silverman et al, changes in Do₂ were closely associated with comparable changes in Vo₂ in most of their patients. An alternative conclusion might be that oxygen requirements had not been met and that further increases in Vo₂ would have resulted from additional increases in Do₂ as have been demonstrated with fluid therapy. Bone et al and Silverman et al have clearly shown that PGE₁ improves, but does not optimize oxygen transport variables in the inadequately fluid-loaded surgical patient. They may or may not have fired a magic bullet, but the real question is whether they expended it in the most effective fashion.

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Classification of Immediate-type, Life-threatening Allergic or Pseudoallergic Reactions

Human anaphylaxis is a medical emergency requiring immediate therapy. Although episodes of anaphylaxis may have spontaneous recovery, the risk of fatality is such that immediate therapy should be

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used, and if the patient is at risk for further episodes, immediate therapy for the patient is warranted. Further, if the risk of additional episodes is likely or even possible, appropriate care should include all reasonable attempts to prevent recurrences. In order to provide the greatest possible patient safety, it is important to identify the type of reaction, inciting agent where possible, or to use appropriate prophylactic pharmacotherapy for prevention or therapy. Although IgE-triggered anaphylaxis is the best understood and probably the most common type of problem, other immediate-type, life-threatening events may simulate anaphylaxis or provide a clinical problem of similar magnitude and urgency. Following is a review and classification of these types of reactions all of which have been seen by us. Examples of allergens are used rather than attempting to provide a complete listing of the numerous agents described.

**CLASSIFICATION AND SELECTED EXAMPLES**

I. **IgE antibody mediated systemic anaphylaxis.**
Definition: A systemic reaction due to bioactive mediator release from mast cells or basophils resulting in urticaria, angioedema, bronchospasm, hypotension, laryngeal edema, collapse, coma and death. All of these manifestations need not be present in each case.
A. Food. Examples: nuts, shellfish
B. Drugs. Examples: penicillin, foreign proteins
C. Venoms. Examples: hymenoptera, fire ant
D. Allergen immunotherapy
E. Blood products

II. **IgE mediated, local, life-threatening laryngeal obstruction.**
Example: inhalation of penicillin or peanut allergens.

III. **Immunologic but not IgE-mediated anaphylaxis.**
Definition: anaphylaxis due to activation of mast cells by components or products of the immune system.
A. Mediated by anaphylatoxins C3a and C5a (theoretical)
B. Monoclonal antibodies against lymphocyte receptors (mechanism unexplained)
C. Other new biologic products (theoretical) (examples IL-1, IL-2, α-interferon)

IV. **Munchausen’s anaphylaxis.**
Definition: real or simulated anaphylaxis produced by the patient.
A. IgE mediated: anaphylaxis due to purposeful self exposure to an allergen
B. Simulated: purposeful approximation of the vocal cords resulting in laryngeal stridor
C. Prevarication anaphylaxis (see below)

V. **Anaphylactoid:** synonyms—pseudoallergic, immediate-type, generalized reaction.
Definition: the various signs and symptoms of anaphylaxis produced by an agent through mast cell activation, but not by means of IgE antibody or immunologic stimuli.
A. Radiographic contrast medium: mechanism uncertain.
B. Pharmacologic: direct action of agents such as opiates and perhaps tachykinins on mast cells

VI. **Idiopathic anaphylaxis.**
Definition: immediate-type, life-threatening reactions unrelated to any external allergen or other stimulus. For clinical management, four categories are important.
A. Generalized, frequent
B. Generalized, infrequent
C. Angioedema (potentially life threatening), frequent
D. Angioedema (potentially life threatening), infrequent

The references listed describe further aspects of these types of reactions. Hereditary angioedema is an important, serious, life-threatening disease not included in the outline, but which must be considered in the differential diagnosis. An uncommon problem is listed above as prevarication anaphylaxis, a subcategory of Munchausen’s anaphylaxis. In prevarication anaphylaxis, the patient reports signs and symptoms of anaphylaxis on repeated occasions. The suspected clinical diagnosis, based on the history, is idiopathic anaphylaxis. With observation and repeated trials of therapy, no improvement or even worsening occurs, but there are never any clearly documented signs and symptoms of anaphylaxis by physicians. We have seen a series of four cases of prevarication anaphylaxis in which the characteristics shown in Table 1 were noted. In-hospital observation may be necessary in certain instances to help the physician differentiate patients with Munchausen’s anaphylaxis.

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**Table 1 - Prevarication Anaphylaxis: A Subclassification of Munchausen’s Anaphylaxis**

<table>
<thead>
<tr>
<th>Characteristics of Four Cases</th>
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<tr>
<td>History of multiple “life threatening” events, 4/4</td>
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<tr>
<td>Failure of documentation of physical findings of anaphylaxis at any time, 4/4</td>
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<tr>
<td>Health professionals, 3/4</td>
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<tr>
<td>No decrease in episodes with antihistamines and prednisone, 3/4; worsening with prednisone, 1/4</td>
</tr>
<tr>
<td>Involvement of multiple physicians, 4/4</td>
</tr>
<tr>
<td>Episodes occur persistently, waxing and waning in frequency but never result in documented findings, 4/4</td>
</tr>
<tr>
<td>Unusual personality traits, 4/4</td>
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</tbody>
</table>

*More than six episodes per year, or two or more episodes within a two-month period.
Mitril stenosis, by elevating pulmonary venous pressure, produces characteristic changes in lung structure and function. Which changes are reversible after surgical or transcatheter treatment of mitral stenosis?

Edema of the alveolar-capillary wall (interstitial edema) in mitral stenosis is reversible upon relief of left atrial hypertension. The radiologic sign of "Kerley B" lines, which are caused by edema of the connective tissue of septa and distention of lymphatics,1 appears or disappears when left atrial pressure exceeds or drops below about 24 mm Hg.2 Increased airways resistance, attributable to mucosal edema, is increased and lung compliance is reduced in patients with mitral stenosis.3 These abnormalities would be expected to be reversible upon relief of mitral stenosis to the extent that they are due to interstitial edema. However, irreversible changes in lung ultrastructure and in ventilatory function may arise if interstitial edema persists for many years. Chronic interstitial edema leads to proliferation of reticular and elastic fibrils that encase the alveolar capillaries.4 In severe cases, marked elevation of pulmonary venous pressure leads to diapedesis of red blood cells into the interstitium and alveolar space. The red blood cell fragments may be ingested by macrophages, which aggregate and form the roentgenographic appearance of pulmonary hemosiderosis or even ossification, the latter being comprised of osseous nodules of lamellar bone in a diameter of several millimeters.4

In mitral stenosis, pulmonary arterial hypertension is largely reversible if pulmonary venous pressure can be normalized. Active pulmonary hypertension, which occurs only in severe cases with chronic elevation of the left atrial pressure to more than 20 mm Hg,6 is due to medial hypertrophy and intimal fibrosis but not to plexiform lesions as in the case of central cardiac shunts. When mitral valve surgery or balloon valvuloplasty is performed, pulmonary vascular resistance and pulmonary artery pressure have been observed to fall.6 Since the effect of lowering left atrial pressure alone would be to increase pulmonary vascular resistance, it can be speculated that the muscular pulmonary arteries become more distensible after pulmonary venous pressure is lowered.4 In severe chronic...

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Stretching the Effect of the Balloon

Mitril Valvuloplasty and Pulmonary Function

This page contains a medical reference text discussing mitral valve stenosis and its effects on pulmonary function. The text references various studies and clinical observations to support the conclusions. The author, Roy Patterson, MD, F.C.C.P., and his co-authors present a comprehensive review of the topic, including the natural history of mitral valve disease, the incidence of complications, and the effectiveness of various treatment methods, such as transcatheter valvuloplasty. The text highlights the importance of early diagnosis and appropriate patient selection for these procedures. The references cited in the text provide a basis for further reading and research in this area of cardiology.