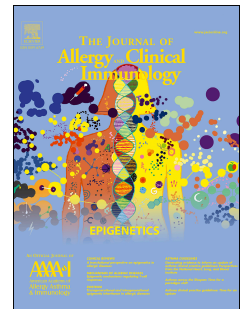


# Journal Pre-proof

Preventing Anaphylaxis Fatalities: Should We Target Bradykinin?

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## Preventing Anaphylaxis Fatalities: Should We Target Bradykinin?

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First line therapy of anaphylaxis requires administration of epinephrine as early as is possible, by intramuscular injection into the vastus lateralis muscle. However, the percentage of patients actually receiving epinephrine when indicated is unfortunately only 25-35 percent. Nevertheless the actual fatality rate is low and estimated to be about 1% of those hospitalized and 0.1% of those presenting to the emergency department<sup>1</sup>. Clinical experience, studies notwithstanding, support a positive contribution of epinephrine to the reduction of itch, urticaria, peripheral angioedema, and bronchospasm, at the very least. Fatalities are, however, due to profound hypotension (shock), laryngeal edema with asphyxia, severe bronchospasm, and cardiac arrhythmias. The cardiac effects can be primary or secondary to the other three.

I would like to focus on the first of the two potentially fatal items – shock and laryngeal edema and begin with the notion that we have not definitively identified the vasoactive substance responsible for either of these. Further, if epinephrine treats them, it is a non-proven assumption although delay in its administration has been reported to increase the risk of a fatality<sup>2</sup>.

Histamine is the most obvious candidate and we do recommend administration of antihistamines such as IV diphenhydramine as soon as possible. Platelet activating factor is another consideration but has no clinically useful antagonist, despite human and animal data suggesting a major role for it for many years<sup>3,4</sup>. The best evidence in patients is indirect i.e. low plasma acetylhydrolase, required to metabolize PAF, is associated with a predisposition to anaphylactic episodes. By contrast, bradykinin is an excellent alternative consideration as a cause of hypotension and laryngeal edema, with multiple possible agents available that could be used to block its action or prevent its formation, and none are used. Steroids have no effect on the most

acute symptoms and are often given to prevent later biphasic reactions, yet the most recent commentary<sup>5</sup> suggests that steroids may actually be harmful to the overall outcome.

Bradykinin is the key mediator of laryngeal edema in many non-anaphylactic situations including types I and II hereditary angioedema (C1 inhibitor deficiency), some of the forms of hereditary angioedema with normal C1 inhibitor (e.g. mutant factor XII or plasminogen), ACE-inhibitor angioedema, acquired C1 inhibitor deficiency, and a subpopulation of patients with non-histaminergic idiopathic angioedema. Chronic spontaneous urticaria with angioedema, a far more common disorder, does not cause laryngeal edema even though histamine is a key mediator and mast cell degranulation initiates the process. While none of these forms of angioedema are associated with hypotension, other situations in which bradykinin levels are high enough to survive degradation during lung passage to elevate blood levels on the arterial site of the circulation, do cause hypotension. Blood pressure measurement is actually used as a semi-quantitative assay for bradykinin blood levels in rodent experiments. The first circumstance to suggest that humans are no different was infusion of albumin preparations for volume expansion in an ER setting which then caused profound shock because they were contaminated with factor XII<sub>f</sub> ( $\beta$ XII<sub>a</sub>), an active enzyme that produces bradykinin<sup>6</sup>. Then mast cell heparin (oversulfated compared to commercial heparin) was shown to be a potent activator of factor XII leading to bradykinin formation<sup>7</sup> the consequences of which became evident when oversulfated mucopolysaccharides contaminating heparin anticoagulant preparations caused anaphylactoid reactions in vivo by activation of the contact (bradykinin-forming) cascade<sup>8</sup>.

Finally, two clinical studies support the concept; one old and one new. During a double-blind, placebo-controlled study of the efficacy of whole-body bee extract vs purified bee venom as an immunotherapeutic agent for insect sting anaphylaxis, one patient, when stung in an intensive care unit setting had anaphylaxis with severe hypotension. Multiple injections of epinephrine failed to affect the blood pressure and he apparently survived due to massive fluid replacement<sup>9</sup>. Plasma studies revealed that multiple plasma proteins had been cleaved including all of his high molecular weight kininogen suggesting massive and sudden release of bradykinin<sup>9</sup>. We know, from therapeutic studies of C1 inhibitor deficiency, that epinephrine cannot be relied upon to reverse the effects of bradykinin. Finally, a recent study of the plasma of patients with anaphylaxis of diverse etiologies provided evidence of activation of each step of the bradykinin-forming cascade<sup>10</sup>.

My thesis is: The hypotension and laryngeal edema of anaphylaxis is primarily due to bradykinin formation and we have drugs that could be administered intravenously which may well be a requirement for action within a few minutes, or subcutaneously if no venous access, that will work pharmacologically including a bradykinin B-2 receptor antagonist and a plasma kallikrein inhibitor. If fatalities due to shock and laryngeal edema are due to bradykinin, we are in a similar situation regarding epinephrine and fatal anaphylaxis as when whole body extract was used to treat insect sting anaphylaxis and was shown to be of no value. Epinephrine may treat many anaphylactic symptoms but might not work for some of those that kill. We ought to find out.

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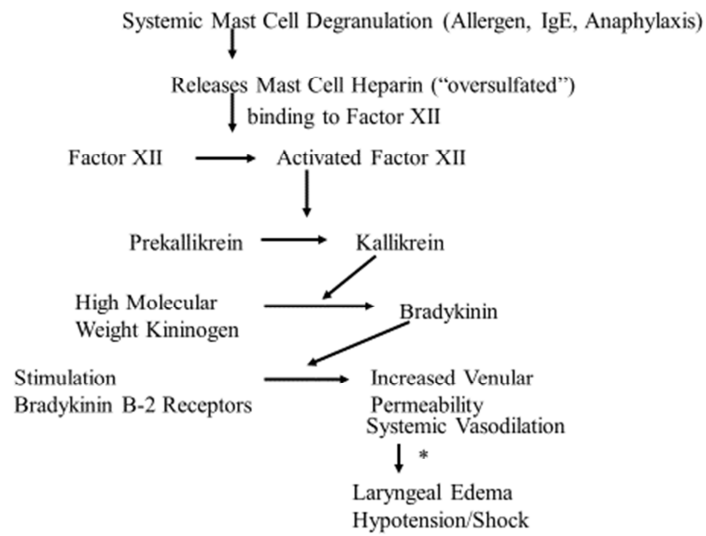
### Table of Major Points

- Profound hypotension and laryngeal edema are causes of fatalities due to anaphylaxis.
- Bradykinin mediated diseases are particularly associated with laryngeal edema.
- Elevated arterial levels of bradykinin cause hypotension and shock.
- Prominent activation of the plasma bradykinin-forming cascade is seen in anaphylaxis.

- Antagonists of the bradykinin B2 receptor and bradykinin formation are available for clinical use.

**Figure 1 Legend:** Proposal linking mast cell activation not only with bradykinin formation (known), but also with laryngeal edema and hypotension/shock as manifestation of anaphylaxis

Figure 1



\* Proposed as manifestations due primarily to bradykinin