

# Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis

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## Purpose of review

Anaphylactic cardiovascular collapse can be resistant to treatment with epinephrine (adrenaline) and, in some cases, diagnostic uncertainty compromises follow-up care. The purpose of this review is to examine recent studies relevant to the management and diagnosis of this condition.

## Recent findings

Nausea, vomiting, incontinence, diaphoresis, dyspnoea, hypoxia, dizziness and collapse are associated with hypotension. Relative bradycardia (falling heart rate despite hypotension) is a consistent feature of hypotensive insect sting anaphylaxis and may represent a non-specific physiological response to severe hypovolaemia in conscious individuals. Upright posture has been found to be associated with death from anaphylaxis. Animal studies have found the intramuscular route for epinephrine is ineffective, intravenous boluses temporarily effective, but intravenous infusions of epinephrine are able to reverse anaphylactic shock. In one animal model, antihistamines were found to be harmful. A prospective human study provides evidence for the efficacy of treatment with intravenous epinephrine infusion and fluid (volume) resuscitation. Case reports support the use of the vasoconstrictors metaraminol, methoxamine and vasopressin if adrenaline is ineffective. Repeated measurements of mast cell tryptase are more sensitive and specific than a single measurement for the diagnosis of anaphylaxis.

## Summary

Current evidence supports use of the supine/Trendelenburg position, epinephrine by intravenous infusion and aggressive volume resuscitation. If these fail, atropine should be considered for severe bradycardia and potent vasoconstrictors may be useful. To confirm the diagnosis of anaphylaxis, serial measurements of mast cell tryptase may be preferable to a single measurement.

## Keywords

anaphylactic shock, anaphylaxis, antihistamines, atropine, epinephrine (adrenaline), mast cell tryptase, vasoconstrictors

## Abbreviations

**LOC** loss of consciousness  
**MCT** mast cell tryptase

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## Introduction

Most episodes of anaphylaxis respond to treatment with a single dose of epinephrine; however, severe anaphylaxis can be associated with cardiovascular collapse that is resistant to treatment. The diagnosis of anaphylaxis can be uncertain if cardiovascular collapse occurs in the absence of other signs of anaphylaxis. Although test results will not be available in time to influence emergency care, they may influence subsequent care by increasing the certainty of diagnosis. An understanding of the symptoms associated with severe anaphylaxis is also useful when assessing episodes retrospectively. This paper will review recent studies, published from 2003 onwards, that have significant implications for the way that anaphylactic cardiovascular compromise is diagnosed and managed.

## Cardiovascular manifestations of anaphylaxis

A recent study from Canton Bern, Switzerland reported an annual incidence of anaphylaxis with circulatory compromise of 7.9–9.6 per 100 000 population, with 10% of these due to food, 18% due to drugs and 59% due to insect venoms [1]. This is comparable with an earlier study from Olmstead County, USA, which found an annual incidence of anaphylaxis with cardiovascular features of 8 per 100 000 population [2]. A lower incidence (less than 1 per annum per 100 000 population) has been reported from the United Kingdom; however, that study was flawed because it was based on a general practitioner database that did not capture emergency department presentations or in-hospital events [3].

## Clinical features

The cardinal clinical feature of cardiovascular compromise during anaphylaxis is hypotension. This may be associated with clinically obvious vasodilation (erythema) or a rapid onset of shock with peripheral circulatory failure; pale, clammy and cool skin; and occasionally cardiac arrest. In a logistic regression analysis of 1149 generalized hypersensitivity reactions, nausea, vomiting, incontinence, diaphoresis, dyspnoea, hypoxia, dizziness,

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**Table 1. Grading system for generalized hypersensitivity reactions [4\*]**

Grade	Defined by:
1 <b>Mild</b> (skin and subcutaneous tissues only)	Generalized erythema, urticaria, periorbital oedema or angioedema
2 <b>Moderate</b> (features suggesting respiratory, cardiovascular or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (pre-syncope), diaphoresis, chest or throat tightness, or abdominal pain
3 <b>Severe</b> (hypoxia, hypotension or neurological compromise)	Cyanosis or SpO <sub>2</sub> ≤ 92% at any stage, hypotension (SBP < 90 mmHg in adults), confusion, collapse, LOC or incontinence

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collapse and loss of consciousness (LOC) were found to be the minimum set of predictors of hypotension [4\*]. From a pathophysiological perspective, this makes sense; hypotension with brain and gastrointestinal ischaemia may directly cause many of these features, or they may reflect the degree of multiple organ involvement that is characteristic of anaphylaxis. Dyspnoea, wheeze, stridor and confusion were associated with documented hypoxia. Again, these findings make sense in terms of cause and effect. From these results, a simple grading system was devised (Table 1).

### Extravasation, vasodilation and cardiac anaphylaxis

The main cardiovascular changes during anaphylaxis are fluid extravasation and vasodilation, causing a mixed distributive–hypovolaemic shock pattern. Circulating blood volume may decrease by as much as 35% within 10 minutes due to extravasation [5], and severe vasodilation resistant to epinephrine (adrenaline) and responding only to potent vasoconstrictors has been described [6,7\*]. Severe reversible cardiac dysfunction associated with non-specific electrocardiogram changes and normal coronary arteries has also been described during human anaphylaxis [8,9,10] and mast cells are present around cardiac blood vessels and between myocardial fibres in humans [11]. A number of case reports have indicated that intravenous glucagon [12], the phosphodiesterase inhibitor amrinone [13] and intra-aortic balloon pump support [9] may be useful for treating resistant anaphylactic shock when cardiac dysfunction is a problem due to beta-blockade, pre-existing impairment of left ventricular function, or cardiac anaphylaxis. We have also observed global ST segment changes in a patient without any cardiovascular instability, suggesting a direct mediator effect on the human heart [14\*\*].

Despite these observations, it is difficult to dissect the contribution of cardiac dysfunction in humans with anaphylaxis when the usual cause of poor cardiac output is poor venous return, and myocardial ischaemia and dysfunction may itself result from the low diastolic blood pressure and hypoxaemia that accompany severe anaphylaxis. Furthermore, high catecholamine levels (either therapeutic or due to endogenous release) can have an adverse effect in the myocardium, including significant reductions

in cardiac output, ischaemic chest pain and ECG changes in the absence of coronary artery disease [15].

Therefore, although a number of animal studies and human observations support the concept of anaphylactic mediators' having direct effects on the myocardium [16\*], the contribution of this 'cardiac anaphylaxis' to morbidity and mortality remains to be defined.

### Allergic acute coronary syndrome

An allergic acute coronary syndrome has been proposed based on case reports of patients with underlying fixed coronary artery disease presenting with acute myocardial infarction beginning within 48 hours of an allergic event [17,18]. Although mediators released by mast cells might cause significant vasospasm and plaque ulceration, triggering angina or infarction, such case series are inherently selective and may represent chance occurrences; large series of anaphylaxis have so far failed to identify this syndrome of delayed infarction or ischaemia [4\*,5,19]. Myocardial ischaemia and infarction can also occur due to diastolic hypotension and hypoxia, perhaps contributed to by underlying cardiac disease.

### Relative bradycardia and the importance of posture

While performing a randomized–controlled trial of venom immunotherapy, we observed eight hypotensive anaphylactic sting reactions, two of which were associated with severe bradycardia and treated with intravenous atropine [20]. A careful review of these eight reactions revealed that hypotension was preceded by a fall in diastolic blood pressure (indicating vasodilation) with a compensatory tachycardia. Following this, in every case, the onset of hypotension was accompanied by a *relative* bradycardia. That is, rather than the heart rate further increasing to compensate for falling blood pressure, it fell as the blood pressure fell. We postulated that this may have been due to a neurocardiogenic reflex, triggered by cardiac mechanoreceptors, and enhanced by increased levels of serotonin, catecholamines, prostaglandins and nitric oxide that are known to potentiate this reflex and are elevated during anaphylaxis [14\*\*].

Bradycardia may also be a non-specific feature of severe hypovolaemic–distributive shock in awake animals.

**Table 2. An epinephrine and fluids protocol validated for use in ADULTS [14\*\*]****1. Epinephrine infusion**

- 1 mg in 100 ml (1:100 000, 10 µg/ml) intravenously by infusion pump
- commence at 30–100 ml/h (5–17 µg/min) according to reaction severity
  - titrate up or down according to response and side effects, aiming for lowest effective infusion rate
  - tachycardia, tremor and pallor in the setting of a normal or raised blood pressure are signs of epinephrine toxicity; consider a reduction in infusion rate
  - stop infusion 30 min after resolution of all symptoms and signs
  - continue observation for at least 2 h after ceasing infusion (longer for severe or complicated reactions); discharge only if remains symptom-free

**2. Normal saline rapid infusion**

- 1000 ml (pressurized) infused over 1–3 min and repeat as necessary
- give if hypotension is severe or does not respond promptly to epinephrine

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Physiological studies of awake mammals have identified two phases of response to hypovolaemia – an initial phase of blood pressure maintenance by tachycardia and peripheral vasoconstriction, followed by a second phase with more severe hypovolaemia characterized by bradycardia, reduced peripheral vascular tone and a profound fall in blood pressure [21]. Bradycardia has not been reported as a feature of anaphylaxis under anaesthesia, when tachycardia is the norm, except when there has been prior beta blockade or severe hypoxia [5]. This may be explained by the blunting of central reflexes that occurs under anaesthesia or different allergen routes and dosage.

We cannot be sure whether bradycardia during anaphylaxis is maladaptive, potentiated by various mediators, or an adaptive process that triggers collapse to a supine position and a slower heart rate to allow the heart to adequately fill between contractions when there is a severe reduction in preload. Nevertheless, the observations reviewed here further support the need for aggressive rapid volume resuscitation to prevent cardiac arrest. It is often forgotten that this can be initiated by laying a patient flat and elevating their legs (or Trendelenburg position, if a tilting trolley is available) while obtaining intravenous access and initiating the rapid infusion of isotonic crystalloid. Conversely, the upright position, by further enhancing blood pooling in the lower extremities, can be lethal [22]. Although unproven, treatment with intravenous atropine should also be considered in situations in which bradycardia is severe and unresponsive to first-line treatments.

### Epinephrine, intravenous fluids and peripheral vasoconstrictors

Epinephrine (adrenaline) has been considered useful in the treatment of anaphylactic shock since as early as 1925 [23] and retrospective analyses have indicated that epinephrine and fluid resuscitation are effective treatments for anaphylaxis occurring under anaesthesia [5,24]. However, the benefits of intravenous boluses of epinephrine can be marginal and short-lived, leading to concerns as to the efficacy of this treatment in severe reactions [10].

In 2004, our jack jumper ant sting anaphylaxis research programme produced the first prospective study of a protocol for treating anaphylaxis in humans [14\*\*]. The approach to using intravenous epinephrine and fluids to treat hypotension is presented in Table 2. Nineteen patients were treated with epinephrine, of whom eight were hypotensive, five received additional fluid resuscitation and two were given intravenous atropine for severe bradycardia. All except one responded within 5 minutes without any adverse effects. One patient took 15 minutes to respond, receiving epinephrine at 30 µg/min (180 ml/h by the protocol in Table 2), 3 l of saline and 600 µg atropine; the slow response in this case may have in part been caused by a delay detecting that a cannula had tissued. In nine cases, signs of anaphylaxis recurred when the epinephrine infusion was stopped, requiring the infusion to be restarted. In patients with hypotension, the mean total dose and duration of infusion were 762 µg and 169 min, respectively.

Two recent studies performed in anaesthetized ragweed-sensitized dogs further support the use of epinephrine by intravenous infusion. In the first of these, intravenous (IV) boluses of epinephrine produced only transient improvements in haemodynamic parameters, whereas intramuscular (IM) and subcutaneous (SC) doses had no measurable beneficial effect [25]. The same group then went on to compare epinephrine given by IV infusion, IV bolus, IM bolus and SC bolus. Again, epinephrine by IM and SC routes was ineffective in preventing haemodynamic collapse. IV boluses produced only transient improvements in blood pressure, apparently through temporary increases in venous return, cardiac stroke work and afterload. By comparison, a titrated intravenous infusion produced a sustained improvement and appeared to act only by increasing cardiac stroke work [26\*\*].

These differences may represent a concentration-dependent difference in  $\alpha_1$  receptor versus  $\beta_1$  receptor activation, with sustained epinephrine concentrations in the infusion group activating  $\beta_1$  receptors, and higher (but transient) epinephrine concentrations in the IV bolus group having additional  $\alpha_1$  effects temporarily

reversing vasodilation. It is important to note that sensitized animals were given doses of antigen that had previously been titrated to produce the desired hypotensive effect, thus avoiding the overwhelming anaphylactic reactions that can result from large doses of antigen; dogs allocated to no treatment survived, with a return of normal haemodynamic parameters within 60 min [26<sup>••</sup>]. In more severe reactions, e.g. after large doses of intravenous antibiotic boluses and anaesthetic agents, a reasonable hypothesis is that very high infusion rates of epinephrine or other vasoconstrictors might be required to reverse peripheral vasodilation.

A number of recent case reports have added to anecdotal evidence for the use of potent peripheral vasoconstrictors to resuscitate patients with overwhelming anaphylaxis. Agents successfully used have included the  $\alpha_1$ -agonists methoxamine [27] and metaraminol [7<sup>•</sup>], and the pituitary hormone vasopressin [6,28]. One of these recent reports is particularly compelling in light of the preceding discussion of epinephrine; aggressive fluid resuscitation, multiple intravenous boluses of epinephrine and high-dose infusions of epinephrine were ineffective in two cases, but blood pressure responses to intravenous boluses of metaraminol (2 mg in one case and 10 mg in the other) were immediate and sustained [7<sup>•</sup>].

### Antihistamines and other mediator blockers

In the early twentieth century, histamine was thought to be the principal mediator of anaphylaxis; however, we now understand that a variety of mediators are involved and in human anaphylaxis, histamine levels peak early and return rapidly to normal, despite the persistence of severe physiological compromise [10]. Guinea-pig studies indicate that although antihistamine pre-treatment may ameliorate some early changes, they have little effect after the first 10 min [29]. In a canine model, treatment with antihistamines appears to be ineffective in the treatment of anaphylactic shock [30]. In a rat model, pre-treatment with  $H_1$ -receptor blockade with or without concurrent  $H_2$ -receptor blockade worsens hypotension and decreases survival time [31]. In the same model, combined blockade

of multiple vasodilator mediators (histamine, serotonin and nitric oxide) slows reductions in blood pressure but does not improve survival [31].

### Diagnosis

Because the diagnosis of anaphylaxis can be uncertain, e.g. if cardiovascular collapse is rapid without other diagnostic features such as urticaria, angioedema or wheeze, serum mast cell tryptase (MCT) assay has been recommended to confirm the diagnosis of anaphylaxis in one authoritative guideline [32]. However, MCT may increase significantly during anaphylaxis without exceeding the stated upper limit of normal [33<sup>•</sup>]. Conversely, a proportion of patients will normally have levels above the normal range. In any given individual, MCT remains steady even over a period of up to 3 months and one study has found that repeated measurements during an episode of suspected anaphylaxis may increase sensitivity and specificity [33<sup>•</sup>]. However, this study was performed on sting anaphylaxis induced under controlled conditions – further studies in a general clinical setting and for other forms of anaphylaxis are required. It is also possible that measuring only mature tryptase (released in negligible amounts in the absence of anaphylaxis) could improve diagnostic performance, although this hypothesis remains to be tested.

### Clinical context

Myocardial and cerebral ischaemia need to be prevented by maintaining adequate venous return and blood pressure. In this context, the contribution of various mediators, possible contributions of cardiac anaphylaxis or allergic angina are irrelevant when initially managing a case of anaphylactic shock. Major interventions should therefore be early adoption of a supine posture with legs elevated, epinephrine, and aggressive fluid resuscitation. Basic airway management and high-flow oxygen must not be forgotten, both to reverse hypoxaemia and to ensure the lungs are full of oxygen to provide a ‘head start’ for resuscitation should cardiac arrest supervene. As with any resuscitation, severe bradycardia – whether due to anaphylaxis or tissue hypoxia – should be managed according to standard resuscitation principles.

**Table 3. Suggested management of anaphylactic shock**

1. Lie flat, elevate legs/Trendelenburg position, high-flow oxygen, support airway and assist ventilation as required.
2. Administer IM epinephrine 0.01 mg/kg (max 0.5 mg) into the anterolateral thigh and proceed to obtain wide-bore intravenous access. *(If IV access is present and patient is in an appropriate environment, may omit IM epinephrine and proceed directly to intravenous infusion of epinephrine.)*
3. Once IV access is available, commence rapid volume resuscitation with Normal Saline or Hartmann's Solution (20 ml/kg stat under pressure, repeated as necessary).
4. If remains hypotensive despite above steps, consider in the following sequence:
  - (a) Intravenous infusion of epinephrine using an infusion pump (Table 2)
  - (b) Intravenous bolus of atropine, if there is significant bradycardia
  - (c) Intravenous bolus of vasoconstrictor (e.g. Metaraminol, Methoxamine, Vasopressin)
  - (d) Further investigation/monitoring (central/pulmonary artery cannulation, echocardiography) to monitor intravascular volume and cardiac function
  - (e) Intravenous glucagon, milrinone/amrinone and/or mechanical support (intra-aortic balloon pump) if remains hypotensive with a suspicion of cardiac failure rather than volume depletion/vasodilation. Cardiac support may be more likely to be required if there is coexisting beta-blockade or underlying cardiac disease.

Most anaphylactic reactions are unanticipated and occur outside a well equipped and well staffed hospital environment. Initial interventions therefore need to be simple. Although an intravenous infusion of epinephrine may be the most efficacious, an intramuscular injection is easier in the first instance and less severe reactions may respond. This should be given in the anterolateral thigh, from where absorption is greatest [34]. Intravenous access can then be obtained, volume resuscitation initiated and an intravenous infusion of epinephrine prepared.

A significant issue faced by clinicians is how to proceed if epinephrine and fluid resuscitation are unsuccessful. In the setting of profound hypotension, a decision needs to be made promptly, usually without the benefit of invasive haemodynamic monitoring. The available evidence, although largely anecdotal, is compelling for the empirical addition of a potent vasoconstrictor bolus in this setting. Even if vasodilation is not a major problem, this intervention will maintain the perfusion of vital organs until further investigation can be initiated.

A proposed approach to managing anaphylactic shock based on these practical considerations is presented in Table 3.

## Conclusions

Nausea, vomiting, incontinence, diaphoresis, dyspnoea, hypoxia, dizziness and collapse are strongly associated with hypotension in the setting of anaphylaxis and, along with the other reaction features associated with hypoxia, may be used to define reaction severity. For hypotensive patients, immediate adoption of the supine/Trendelenburg position, epinephrine and aggressive fluid (volume) resuscitation are the cornerstones of management. Although it is usually recommended to first give epinephrine by the intramuscular route, epinephrine by intravenous infusion is more likely to be effective in severe reactions. Potent vasoconstrictors should be tried if epinephrine and fluid resuscitation are ineffective. The diagnosis of anaphylactic shock is usually straightforward; however, when the diagnosis is uncertain, serial serum tryptase measurements may be more useful than a single measurement.

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- of special interest
- of outstanding interest

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