22 Suspected perioperative anaphylaxis associated with cardiac arrest

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Key findings

- A little over half of cases reported to NAP7 as anaphylaxis were considered to be so by the review panel. Other causes included isolated severe hypotension, bronchospasm and oesophageal intubation.
- Severe bronchospasm leading to cardiac arrest was uncommon, but in one case it led to a reported flat capnograph despite cardiovascular stability.
- Perioperative anaphylaxis leading to cardiac arrest occurred with a similar frequency and patterns of presentation, location, initial rhythm and suspected triggers in NAP7 as in NAP6.
- Perioperative anaphylaxis was managed with low-dose intravenous adrenaline most often and this was without complications in the cases reviewed.
- Outcomes in NAP7 were generally better than for equivalent cases in NAP6. There was only one death and survival rate was 97%.
- The most common failing during management of perioperative anaphylaxis was not starting chest compressions when systolic blood pressure had fallen to below 50 mmHg and occasionally even when it was unrecordable. The Baseline Survey provided further evidence of reluctance to initiate early cardiopulmonary resuscitation (CPR).
- The one death occurred in a relatively young patient in whom chest compressions were delayed and who, despite surviving resuscitation, died later after developing multiorgan failure.
- The management of cases was generally good. Care was judged good more often in NAP7 than it had been in NAP6, and poor less often than it had been in NAP6.

What we already know

NAP7 provides an opportunity to compare data and reflect on changes that may have occurred since NAP6 (Harper 2018a, 2018b). NAP6 studied life-threatening (grade 3–5) anaphylaxis (Cook 2018a) and required confirmation of allergy by a specialist allergy/immunology specialist before it could be reported (Cook 2018a). Conversely, in NAP7 there was a requirement for a cardiac arrest (a minimum of five chest compressions and/or defibrillation) for the case to be included and therefore NAP7 only included patients meeting the criteria for grade 4–5 anaphylaxis as defined in NAP6.

The NAP7 cohort of cases therefore includes unverified cases with a presumed diagnosis of anaphylaxis and not all will be correctly diagnosed by the reporter. Conversely, it is plausible that not all cases of anaphylaxis occurring in the NAP6 window were referred for specialist follow-up, correctly diagnosed and therefore included. Thus, it is likely that NAP6 will have underestimated cases of anaphylaxis and NAP7 may have overestimated the number of cases. NAP6 estimated the incidence of life-threatening (grades 3–5) perioperative anaphylaxis as 1 in 11,752 and noted that delayed or incomplete reporting meant the incidence may be up to 70% higher: around 1 in 7000 (Harper 2018c).

Since NAP6 was published, there have been international consensus guidelines published on the management of perioperative anaphylaxis (Garvey 2019, Hopkins 2019) and the Resuscitation Council UK (RCUK) has published more general guidelines on management of anaphylaxis (RCUK 2021), whereas the Association of Anaesthetists has withdrawn its guideline, although the topic is included in the *Quick Reference Handbook* (QRH; Association of Anaesthetists 2022).

Whether adrenaline should be administered intramuscularly or intravenously for perioperative anaphylaxis is a matter of some discussion. It is recognised that adrenaline is a key drug for the treatment of anaphylaxis but there have been concerns about the risk of dose-related complications when it is used intravenously, especially in the elderly (Kawano 2017). Early use of intravenous

adrenaline is recommended in the NAP6 report (Cook 2018b). It is also recommended in the consensus statement from the International Suspected Perioperative Allergic Reaction Group (Garvey 2019) and in the most recent version of the QRH (Association of Anaesthetists 2022). Conversely, the RCUK (2021) guidelines, which are not specifically for perioperative care, emphasise intramuscular use stating that 'Intramuscular adrenaline is the first-line treatment for anaphylaxis (even if intravenous access is available)'. The guidance goes on to describe intravenous administration of adrenaline by those expert in its use. In NAP6 there were no complications attributed to excessive intravenous dosing or drug error with adrenaline.

Intravenous dosing, in the absence of cardiac arrest, is usually recommended in the range of 10–50 µg, increasing in resistant cases to 100–200 µg (Garvey 2019, Association of Anaesthetists 2022). In the event of cardiac arrest, recommendations from all sources align with the Advanced Life Support guidelines including administration of intravenous adrenaline (Chapter 15 Controversies).

The RCUK has collaborated with the newly formed Perioperative Allergy Network (https://www.bsaci.org/about-bsaci/bsaci-council-and-executive/bsaci-subcommittees/perioperative-allergy-network) and, although not published at the time of writing, this will include a specific perioperative algorithm which promotes early use of IV adrenaline by anaesthetists in cases of suspected anaphylaxis (personal communication, J Soar).

The administration of drugs other than vasopressors in the treatment of anaphylaxis has been deemphasised in recent years and this includes progressive de-emphasis of the importance of both antihistamines and corticosteroids in the initial resuscitation phase (Harper 2018d, Garvey 2019, RCUK 2021).

The threshold blood pressure at which chest compressions should be started was discussed in NAP6 and a threshold of a systolic blood pressure (sBP) of 50 mmHg was recommended (Cook 2018c). It was emphasised that this should be in concert with, and not to the detriment, of other treatments. This threshold has subsequently been adopted by others (Garvey 2019, Harper 2020, RCUK 2021).

In NAP6, in 130 cases (51% of all cases) sBP fell to below 50 mmHg during an episode of perioperative anaphylaxis. There were 40 cardiac arrests and 10 of these patients died (Cook 2018c).

Patients reported in NAP6 who developed cardiac arrest from perioperative anaphylaxis were female in two thirds of cases; half developed cardiac arrest in the anaesthetic room and 81% before surgery started. Cardiovascular presenting features (63%) were more common than respiratory (28%) including hypotension in 40% of cases and bronchospasm in 20%.

The rhythm at cardiac arrest was pulseless electrical activity (PEA) in 85% (often preceded by bradycardia), ventricular fibrillation or tachycardia in 10% (all preceded by tachycardia) and asystole in 5%. There were no episodes of airway compromise, although in many cases airway management was complete before signs of anaphylaxis developed.

The mean dose of adrenaline administered was 5 mg. The median duration of cardiac arrest was five minutes in survivors but much longer in those who died. Five patents died without return of spontaneous circulation and five later (overall 25% mortality rate). Half of survivors required a catecholamine infusion and 90% were admitted to ICU. There were no episodes of recurrence of symptoms. ICU stay was an average of two days. Of 31 survivors, 32% were judged to have been harmed. Care was judged good in 75% of cases.

In NAP6, compared with patients who survived perioperative anaphylaxis (including those who survived cardiac arrest), patients who died were older (50% aged > 65 years, vs 35%), had a higher ASA score (80% ASA 3–5 vs 28%), were more likely to be obese (50% vs 34%), have coronary artery disease (50% vs 14%) and to be taking a beta blocker (60% vs 17%) or ACE inhibitor (60% vs 17%) (Cook 2018c). In some ways, perioperative cardiac arrest may be considered a physiological stress test. Presenting features, rhythm at cardiac arrest and dose of adrenaline differed little between those who died and those who had a cardiac arrest but survived. Care for six patients was judged as good and none as poor.

What we found

Baseline Survey

In the Baseline Survey, anaesthetists estimated that anaphylaxis is one of the top four causes of perioperative cardiac arrest (Chapter 10 Anaesthetists survey). Among the perioperative cardiac arrests they had most recently attended, anaesthetists reported anaphylaxis as the second most common cause, accounting for 10% of cases. The median sBP at which anaesthetists reported they would start chest compressions was 41–50 mmHg, with a tendency to initiate compressions earlier in a patient graded ASA 3 than ASA 2 (Chapter 15 Controversies).

Activity Survey

In the Activity Survey, nine cases of suspected anaphylaxis were reported (1 in ≈2700), eight during general anaesthesia and one regional anaesthesia, including seven cases of severe hypotension and two of severe bronchospasm. Two cases included cardiac arrest (cardiac arrest rate 1 in ≈12,000), both of whom survived. As these cases were reported at the point of care and not subject to classification or verification by clinical review or investigation, it is likely this estimated incidence is significantly higher than the true rate.

Case reports

In the registry phase, there were 59 cases in which the reporter either reported anaphylaxis as the cause of the cardiac arrest or considered it as a differential diagnosis. Of these 59, the panel considered 35 (54%) to be a case of anaphylaxis and panel

confidence in this diagnosis was high in 19, moderate in 14 and low in 2. Other diagnoses included isolated severe hypotension (eight cases; 12%), severe hypoxaemia in seven cases (12%), bronchospasm or obstructive ventilation in five cases (8.4%) and high neuraxial block in one case (1.5%).

Bronchospasm

There were four cases in which severe bronchospasm was considered the primary diagnosis rather than anaphylaxis. All patients recovered after a brief cardiac arrest and did not require prolonged specific management of bronchospasm or anaphylaxis. In one case, a patient with airway disease was reported to have a flat capnograph trace despite initially no cardiovascular disturbance; this resolved with treatment of bronchospasm with adrenaline, without removal of the tube. In another case, oesophageal intubation was a possibility as a flat capnograph, difficult ventilation and cardiac arrest resolved with reintubation. All patients survived the cardiac arrest. Three were discharged without harm or delay and one patient died postoperatively but it was not clear whether that was related to the event: this would probably have been an unexpected death. It was not clear in all cases that tracheal intubation was a necessary part of general anaesthesia.

A patient with morbid obesity who had multiple comorbidities developed high airway pressures and difficult lung ventilation after receiving rocuronium and tracheal intubation. This was presumed to have been caused by severe bronchospasm caused by anaphylaxis to rocuronium. The capnography trace was flat. The patient became hypoxic and hypotensive. Chest compressions were started when the systolic blood pressure was less than 50 mmHg. The patient was reintubated and a total dose of 100 µg adrenaline was administered. The patient was successfully resuscitated and survived to hospital discharge. The NAP7 panel opinion was that this patient's deterioration was most likely due to a misplaced tracheal tube and not anaphylaxis.

Non-anaphylaxis

In the 26 cases with an erroneous or unlikely diagnosis of anaphylaxis, care before cardiac arrest was judged good by the panel in seven (27%) cases and poor in three (23%). Overall care was judged good in 45% of cases but 35% had elements of poor care and there were further high levels of uncertainty. Three (12%) of these patients died and four (15%) were harmed: 27% in all were harmed or died. None of the deaths were judged inevitable. In 16 of these cases, panel confidence in diagnosis was low.

A middle-aged healthy patient having elective surgery became profoundly hypotensive and bradycardic with a rash following spinal and general anaesthesia. Anaphylaxis was suspected and the patient was treated with incremental doses of adrenaline and required an adrenaline infusion. Chest compressions were started after about 10 minutes and the patient was resuscitated successfully and survived to go home. The patient's mast cell tryptase level was not raised, and the Local Coordinator's view was that this was a case of severe vasodilatory hypotension caused by the anaesthetic.

Anaphylaxis

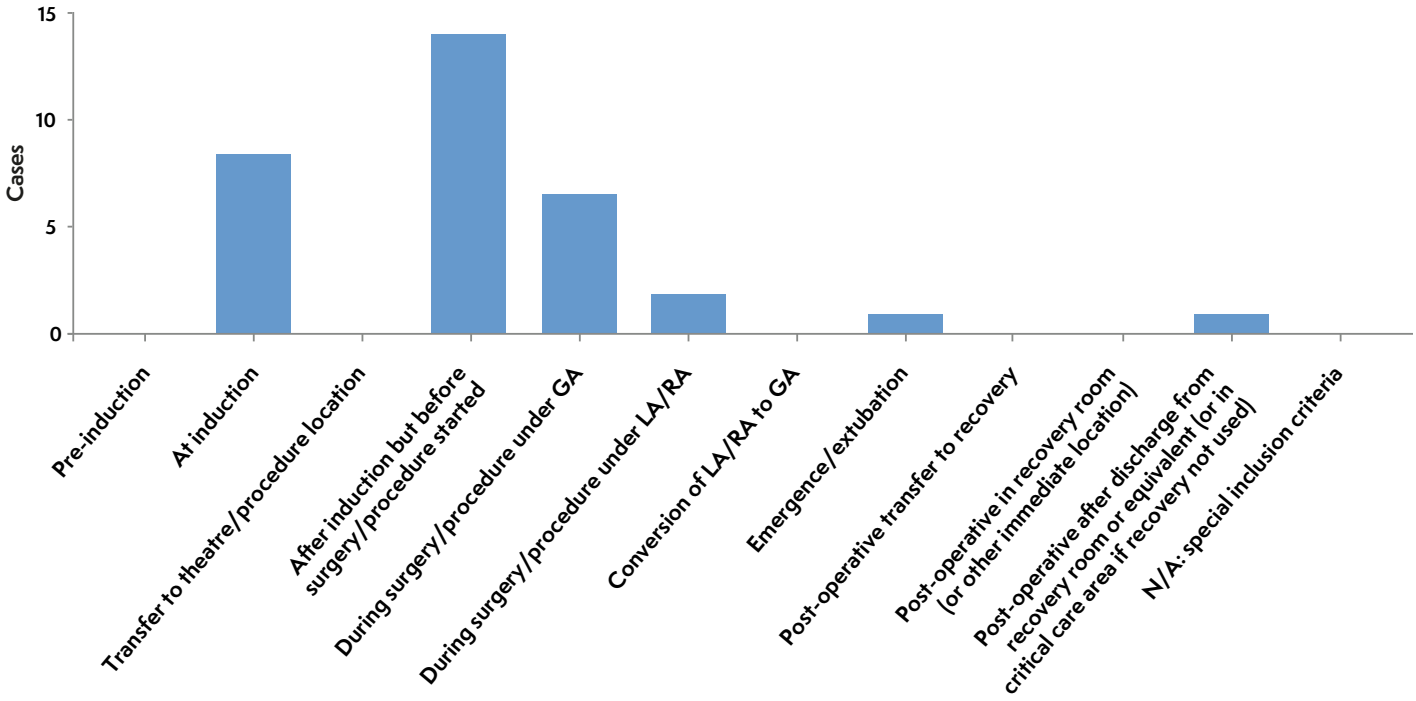
The 33 cases judged to be anaphylaxis with high or moderate confidence form the basis of further analysis in this chapter. For 12 cases, a confirmatory tryptase result was available at the time of reporting and for 21 it was not.

A patient undergoing elective surgery had a PEA cardiac arrest following a dose of co-amoxiclav. Chest compressions were started due to a very low end-tidal CO_2 value, and the airway was changed to a tracheal tube. A total dose of intravenous adrenaline 1–2 mg was given during cardiac arrest. The patient required ICU admission and made a good recovery. The patient's mast cell tryptase was raised. The NAP7 panel judged that the management of the cardiac arrest and the patient follow up was good.

Compared with the Activity Survey, patients experiencing anaphylaxis were more likely to be obese, aged 66–75 years, without frailty and undergoing elective surgery but these may be statistical quirks. There was no particular pattern in terms of patient sex, ethnicity, ASA score or timing of surgery. The cases were spread across 15 different surgical specialties, with none especially prominent.

Twenty-four (72%) cases presented at induction or soon after, before surgery started (Figure 22.1). Three cases (9%) occurred in the absence of general anaesthesia. One case (3%) occurred after surgery. Anaphylaxis was more likely to occur in the anaesthetic room than were other causes of cardiac arrest (30% vs 10%) and four (13%) occurred in potentially isolated locations.

Figure 22.1 Perioperative timing of cardiac arrest due to anaphylaxis. GA, general anaesthetic; LA, local anaesthetic; RA, regional anaesthetic.



In 31 (94%) cardiac arrests the initial rhythm was PEA (compared with 52% of all NAP7 cardiac arrests), with one (3%) each of severe bradycardia and pulseless ventricular tachycardia: a distribution very similar to NAP6. Four patients received defibrillation. Duration of cardiac arrest was similar to that of the whole NAP7 population with 21 (64%) lasting less than 10 minutes and 15% longer than 20 minutes. In a small number of cases there was a delay in starting chest compressions when the systolic blood pressure was less than 50 mmHg and once even when it was unrecordable.

Dosing of adrenaline varied significantly, but in most cases was given in 50–100 μg aliquots with good effect. Doses of up to 9 mg were required. Total doses ranged 0.8–9 mg, median 2 mg (interquartile range 1.5–3 mg). There were no reports of arrhythmias or other complications of the administration of intravenous adrenaline for management of perioperative anaphylaxis. In one case, a relatively healthy patient showed signs of anaphylaxis shortly after induction of anaesthesia. The patient received intramuscular adrenaline but this did not prevent decline to cardiac arrest. When modest dose intravenous adrenaline was administered recovery was prompt and the panel judged that earlier intravenous adrenaline might have prevented the cardiac arrest.

All 33 patients were successfully resuscitated. All patients were admitted to a high-dependency care area after the event, the vast majority with an unplanned admission to ICU. Duration of ICU stay was most commonly one to three days but in several cases it exceeded a week. Physical consequences of perioperative anaphylaxis were relatively few, although reports included cases of prolonged ICU stay, acute kidney injury, the need for coronary stenting and mood changes requiring psychological support. Recovery was generally good; only two patients were reported to have an increase in their Modified Rankin Scale of disability at discharge.

The one death occurred in a moderately healthy patient: CPR was not started immediately when systolic blood pressure fell below 50 mmHg. The patient survived resuscitation but required vasopressor support, admission to ICU and died of complications of multiorgan support.

Compared with other causes of cardiac arrest, anaphylaxis had a higher rate of survival both at initial resuscitation (100% vs 75%) and (when these data were available) at discharge from hospital (24 of 25; 96%, vs 52% overall). Cases of anaphylaxis induced cardiac arrest had a higher survival rate in NAP7 than in NAP6: in NAP7 33 (100%) patients were resuscitated successfully and 32 (97%) survived to the point of reporting to NAP7, compared with, in NAP6, 85% and 75%, respectively.

Of 24 patients with a final reported outcome, 20 (83%) experienced no harm beyond delayed discharge, which is a similar proportion to all cases in NAP6 (79%). Of these 24 with a final reported outcome, one patient died and three came to harm (total 16%) whereas among NAP6 patients who experienced cardiac arrest 50% came to harm or died, as did 53% of all cases reported to NAP7.

Care was rated good or poor, before cardiac arrest in 79% and 0%, respectively, during the arrest in 88% and 0%, respectively, and after cardiac arrest in 88% and 0%, respectively. Overall quality of care was rated as good in 79% and poor in 0%. Overall care during anaphylaxis cases was rated good more often than in all NAP7 cases (52%) and poor in fewer cases than in all NAP7 cases (2%).

In 16 cases, a trigger agent was proposed: an antibiotic in 62% (co-amoxiclav in six, teicoplanin in three cases), a neuromuscular blocking drug in 31% (most commonly rocuronium) and sugammadex in one (6.2%).

No cases occurred due to drug error (eg administering a drug to a patient known to be allergic to that drug). In one case, after a previous collapse following administration of an antibiotic, an elevated tryptase was recorded but this was not acted on. Subsequent administration of a related antibiotic led to perioperative anaphylaxis and cardiac arrest requiring relatively brief CPR. In another case, administration of an antibiotic was followed by anaphylaxis, cardiac arrest and a hospital admission lasting more than a week. A previous antibiotic-related rash was not declared by the patient before surgery but was subsequently identified in general practice notes.

Debriefing after cardiac arrest due to anaphylaxis was completed in 57% of cases and planned for a later date in 17%, compared with all NAP7 cases, 52% and 8.5%, respectively.

Discussion

The case registry identified 33 cases of cardiac arrest due to suspected perioperative anaphylaxis in NAP7 over the one-year reporting period, which is highly consistent with the 40 cases reported to NAP6, when taking account of the estimated 15% fall in surgical activity between the NAP6 Activity Survey (Kemp 2018) and the NAP7 Activity Survey (Chapter 11 The NAP7 Activity Survey). Anaphylaxis accounted for 33 (3.7%) of 881 cases of perioperative cardiac arrest and in the review panel's causes of cardiac arrest was the seventh most common cause.

The panel disagreed with the reporter's opinion that cardiac arrest was caused by anaphylaxis in about half of reported cases. We used panel consensus to determine this and did not use a formal diagnostic likelihood score (eg Hopkins 2019) as the data available in the case review form was sometimes insufficiently complete for this. In all of the cases not judged to be anaphylaxis, the panel identified another significantly more likely cause of the patient's deterioration and cardiac arrest and in these cases quality of care was notably poorer than in other NAP7 cases.

Anaesthetists appear to overestimate the frequency of anaphylaxis as a cause of perioperative cardiac arrest. In the Baseline Survey, anaesthetists ranked it among the top four most common causes, but in cases reported to NAP7 it was the seventh most frequent cause. In the Activity Survey anaesthetists suggested anaphylaxis accounted for 10% of perioperative cardiac arrests but the panel judged it was a cause of only 3.7% of cases reported to NAP7. It is likely hypotension due to anaesthetic technique and patient status, isolated bronchospasm and airway complications may be incorrectly diagnosed as anaphylaxis. This highlights the importance of considering other diagnoses at the time of perioperative cardiac arrest and of serial measurement of mast cell tryptase to confirm or refute the presumed diagnosis.

Similarities in patterns of timing, location, initial cardiac rhythm and precipitants between cases of perioperative cardiac arrest reported to NAP7 and those reported in NAP6, suggest consistency between projects.

Anaphylaxis leading to cardiac arrest occurred in the absence of general anaesthesia, postoperatively and in isolated locations where anaesthetists may work as solo operator, reminding us that all anaesthetists should be expert in the management of both anaphylaxis and cardiac arrest.

Two cases of anaphylaxis appear to have been avoidable. In one case, better processes and follow-up should have identified the cause of a previous anaphylactic event and elevated mast cell tryptase. Had this been followed up, it is likely that investigation would have led to identification of a trigger agent and avoidance of a cardiac arrest during a subsequent anaesthetic. In the second case, information about allergies differed between hospital and general practice notes, highlighting the potential value of integrated digital notes accessible across healthcare sectors.

Before cardiac arrest occurred, adrenaline was generally administered intravenously in doses ranging from 50 to 100 µg. Intramuscular adrenaline was sometimes co-administered. During prolonged cardiac arrest, standard dosing for that situation was the norm. There were no complications associated with intravenous adrenaline administration, but there was one case of anaphylaxis progressing from moderate hypotension to cardiac arrest when only intramuscular adrenaline was administered. In this case, the panel judged that cardiac arrest would likely have been avoided by early use of intravenous adrenaline. A recent Japanese study of less severe perioperative anaphylaxis (43 cases, only 2 with cardiac arrest) reported more rapid and sustained improvements in cardiovascular parameters when adrenaline was given intravenously rather than intramuscularly (Suigiyama 2023). The accompanying editorial also advocated for intravenous over intramuscular administration (Savic 2023).

Although care was generally rated as good, delays in starting CPR were relatively common and drew criticism from the panel. These included not starting CPR when the systolic blood pressure was less than 50 mmHg and even occasionally when it was unrecordable. Although this has echoes of NAP6, which reported poor care in 24% of patients with profound hypotension, care was not reported as poor in any NAP7 cases. Of note, for the one patient who died of perioperative anaphylaxis in this series there was delay in starting CPR and despite initial resuscitation being successful, the patient died after developing multiorgan failure. The topic of when to start CPR is also discussed in Chapter 10 Anaesthetists' Baseline Survey and Chapter 15 Controversies.

Rating of care quality in NAP7 was generally improved compared to NAP6: with 80% good care (NAP6 43%) and 0% poor care (NAP6 16%). Outcomes from perioperative cardiac arrest due to anaphylaxis also appeared better in NAP7 than in NAP6, with a 97% survival rate in NAP7 compared with 75% in NAP6.

Overall, compared with NAP6, NAP7 data suggests improvements in care of patients with cardiac arrest due to anaphylaxis and improved outcomes.

Recommendations

National

- National guidance should be coordinated so that guidance from the Resuscitation Council UK, the Quick Reference Handbook of the Association of Anaesthetists, and Perioperative Allergy Network are consistent for the route and initial dose of adrenaline to administer for perioperative anaphylaxis.

Institutional

- Organisations should have a mechanism to ensure abnormal tryptase results are flagged to the requesting clinician, to minimise the risk of avoidable anaphylaxis in the future.
- Digital solutions should ensure recording of all allergies is consistent across all healthcare records and accessible to clinical staff.
- Departments of anaesthesia should have protocols for the detection, management and referral for investigation of perioperative anaphylaxis. These should be readily accessible to all departmental members, widely disseminated and kept up to date.

Individual

- All clinical staff who deliver anaesthesia should be skilled in management of perioperative anaphylaxis and cardiac arrest.
- All clinical staff who deliver anaesthesia should be expert in the administration of intravenous adrenaline, both in low dose bolus and as an infusion, for the management of perioperative anaphylaxis.
- Chest compressions should be started if the systolic blood pressure falls and remains below 50 mmHg during anaesthesia in an adult, in addition to standard treatments for anaphylaxis.

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