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Low end-tidal carbon dioxide as a marker of severe anaesthetic anaphylaxis: the missing piece of the puzzle?

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Perioperative anaphylaxis has assumed increased prominence in recent times with the Royal College of Anaesthetists of Great Britain and Ireland focusing on this topic for the 6th National Audit Project "NAP6".[1] The reporting period for cases has recently closed and as a result analysis from this audit will provide large amounts of data that will help our understanding of the incidence, causes and sequelae of anaphylaxis in 2017.

This issue of The *British Journal of Anaesthesia* contains an original article by Gouel-Chéron and colleagues,[2] suggesting that a decrease in exhaled end tidal carbon dioxide is a useful independent marker of a severe anaphylactic reaction. Could this be true? Could one of the most ubiquitous and continuously measured parameters during anaesthesia have been pointing us towards the early diagnosis and treatment of severe intraoperative reactions all this time?

Before answering that question, it is worth reviewing the definition of anaphylaxis. Once regarded as a pathological entity,[3] anaphylaxis was an acute reaction that was "severe, life-threatening generalized or systemic hypersensitivity reaction". It was further subdivided into allergic causes (IgE vs IgG) or non-allergic causes. This classification is entirely unhelpful to the anaesthetist dealing with an unstable patient post induction with many differential diagnoses to consider. A further

consensus classification by the NIAID/FAAN in 2006[4] redefined anaphylaxis as a clinical entity, which meant that a diagnosis of anaphylaxis could be made and treatment begun if a cluster of signs occurred in an asleep patient (not known or suspected to be allergic to agents used) of skin signs (hives, itch-flush, swollen lips-tongue-uvula) with either respiratory compromise (hypoxaemia, wheeze-bronchospasm, stridor) or reduced bp. Other signs (such as syncope, collapse and gastrointestinal signs) are mentioned, but are only relevant to the awake patient.

There is no mention of reduced end tidal CO_2 (E'_{CO_2}) in these definitions, and it has always been presumed that low E'_{CO_2} is a secondary sign of either a low perfusion state (such as hypotension) or severe bronchospasm.

In the general anaesthetic setting, it is extremely common to record some post-induction hypotension as most of our induction agents cause hypotension, particularly in the setting of patient pathology (cardiac failure, ischaemic heart disease, hypovolaemia) and increasingly elderly surgical populations.[5] It is up to the anaesthetist to judge whether the hypotension is "within expected levels" or aberrant. Adding to the poor specificity of bp measurement as an early marker of severe anaphylaxis is the fact that most general anaesthesia is conducted with non-invasive intermittent bp monitoring rather than continuous

invasive arterial bp monitoring. The first measurement of hypotension post induction may be several min after the beginning of the anaphylactic reaction, particularly in patients with atrial fibrillation or where the bp is too low for the machine to obtain a reading. The diagnostic attractiveness of a continuously measured and ubiquitous parameter ((E'_{CO_2})) is obvious if proved to be associated with severe anaphylaxis.

Other classically described signs of anaphylaxis such as skin rashes are often not seen during the hypotensive phase of anaphylaxis, may be covered up by drapes or may not be present at all.[6] Bronchospasm may or may not be present and the importance to the diagnosis is particularly difficult to ascertain in heavy smokers, brittle asthmatics and those with concomitant upper respiratory tract infections.

If we accept the premise that end tidal CO_2 is an independent predictor of a severe anaphylactic reaction, then what are the implications for treatment? The first and most obvious implication is that an early diagnosis of severe anaphylaxis should trigger the early implementation of a perioperative anaphylaxis treatment algorithm, which will inevitably lead to the administration of epinephrine (adrenaline). Whilst there are no randomized-controlled trials indicating benefit of epinephrine in anaphylaxis (for ethical reasons), it remains a mainstay of treatment in anaphylaxis.[7] The diagnosis should also lead to the discontinuation of probable triggers such as colloid fluids running

at the time of reaction, chlorhexidine (particularly if administered mucosally or intravenously, such as a chlorhexidine-impregnated central line, though this may be needed until alternative i.v. access is obtained by rewiring the line) or neuromuscular blocker infusions. Depending on whether cardiovascular or respiratory features are most prominent, it may also lead to boluses of i.v. fluids, bronchodilators, alternate vasopressors and even extracorporeal membrane oxygenation in severe refractory cases.[8]

At present, there are several internationally developed guidelines on the treatment of perioperative anaphylaxis. The Scandinavian Guidelines were published in 2007,[9] the Association of Anaesthetists of Great Britain and Ireland published their current edition in 2009[6] and more recently the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) in association with the Australian and New Zealand College of Anaesthetists (ANZCA) group published their most recent edition in 2017.[8] There are many similarities between these guidelines, but some differences exist in doses of epinephrine and other adjuncts to treatment. One of the biggest discrepancies is in the recommendation to administer antihistamines. All three guidelines have these agents as second-line therapy, but since the British and Scandinavian guidelines have been released it has been shown that parenteral antihistamines are not only ineffective in severe anaphylaxis

Table 1 Differences in Epinephrine (Adrenaline), Antihistamine and Steroid administration recommendations of major perioperative anaphylaxis guidelines. (see references for full guidelines)

AAGBI Pharmacological Immediate Management (adult doses only)[5]	**SSAI** Pharmacological Immediate Management (adult doses only)[8]	**ANZAAG/ANZCA** Pharmacological Immediate Management (adult doses only)[9]
First line Epinephrine (adrenaline): 50 µg i.v. Epinephrine infusion if repeat doses necessary	**First Line** Epinephrine (adrenaline): Mild-moderate reaction: 10–50 µg i.v.	**First line** Epinephrine (adrenaline): Moderate reaction: 20 µg i.v. Severe reaction: 100–200 µg i.v.
Cardiac arrest: Follow ALS guidelines Full monitoring assumed but no i.m. epinephrine advocated in adults	Circulatory collapse: 100 µg–1 mg i.v. If no i.v. access: 500–800 µg intramuscular	Cardiac arrest: 1mg i.v. and follow ALS guidelines If no i.v. access/monitoring: 500 µg intramuscular q5min prn
Refractory cases: Repeat i.v. epinephrine doses as necessary). If several doses of epinephrine are needed consider i.v. infusion	Refractory cases: Titrate epinephrine to response. If large doses needed, use i.v. infusion	Refractory cases: Repeat epinephrine doses 1–2 min prn, increase doses if unresponsive. Start i.v. infusion if > 3 doses needed
Consider: Alternate i.v. vasopressor e.g. metaraminol	*Consider:* Noradrenaline Vasopressin Glucagon	*Consider:* Norepinephrine/Noradrenaline Vasopressin Glucagon Metaraminol/Phenylephrine ECMO
Antihistamines and steroids: Secondary management: Chlorpheniramine 10 mg i.v.	Antihistamines and steroids: Secondary treatment: Cimestin 2 mg i.v. or Desklorfeniramin 5 mg i.v. or Promethazine 50 mg i.v.	Antihistamines and steroids: Post-crisis management: I.V./I.M. antihistamines not recommended because of risk of hypotension, consider oral antihistamines when able to take oral meds
Hydrocortisone 200 mg i.v.	Hydrocortisone 200 mg i.v. or Methylprednisolone 80 mg i.v.	Hydrocortisone 2–4 mg kg^{-1} i.v. or Dexamethasone 0.1–0.4 mg kg^{-1}

but may cause harm through worsening of hypotension.[10] This new recommendation is incorporated into the Australian and New Zealand guidelines and evidence would support adoption worldwide.

Revision of guidelines is paramount as new evidence becomes available. The AAGBI guidelines are the third revision of this document. The ANZCA/ANZAAG guidelines are the second edition of these guidelines and used feedback from the first edition to improve the quality of the document. A feature unique to the ANZAAG/ANZCA guidelines is a background paper[11] explaining levels of evidence and rationale for recommendations. Incorporation of human factors was identified as an integral part of the design of the guidelines. As a result, management cards are downloadable as PDF files ready for theatre use and have been refined by extensive research of approaches in simulation settings.[11]

Table 1 compares the recommendations of these three important treatment guidelines with respect to recommendations on epinephrine administration, antihistamine and steroid administration. It should be noted that only these parts of the guidelines are compared, for full recommendations of management the full guidelines should be consulted. It should also be noted that all three guidelines make recommendations on treatment of paediatric anaphylaxis associated with anaesthesia. For simplicity, only adult management is compared in Table 1.

In their paper in this current issue, Gouel-Chéron and colleagues have analysed patients presenting to a group of 11 allergy investigation centres in France over an almost two-yr period from October 2012 to June 2014. All patients with suspected intraoperative anaphylaxis to neuromuscular blockers (NMBAs) were assessed and included if they satisfied criteria for anaphylaxis as described by Ring and Messmer[13] in 1977 in relation to colloid anaphylaxis. Severe reactions were defined as those fitting grades 3 (shock, life-threatening spasm of smooth muscles (bronchi, uterus etc.) and 4 (cardiac arrest) of this classification. 50% of the 86 patients were classified as suffering severe reactions in this study.

These authors were able to show a statistically significant difference in decrease of E'_{CO_2} values in severe (grade 3 $P<0.04$, grade 4 $P<0.005$) anaphylaxis, that were greater in magnitude than the decreases in systolic arterial pressure and oxygen saturation. If this is true, a sudden, severe decrease in E'_{CO_2} shortly post-induction could prove a valuable sign of early severe anaphylaxis. The particular benefit that E'_{CO_2} has is that it is readily and continuously measured throughout routine general anaesthesia. In such situations, pulse oximetry often displays poor or no trace and noninvasive blood pressure measurements may not cycle for several minutes and is known to be unreliable at low pressures.

So, should we re-write our diagnostic algorithms immediately and regard E'_{CO_2} as the gold standard for diagnosing acute, severe post induction anaphylaxis? Certainly not yet. This paper by Gouel-Chéron and colleagues has several limitations that limit it being considered worthy of changing practice at this stage.

The numbers of patients included in this study are relatively small. The total number of patients included in the final analysis is 86, and whilst the authors found statistical significance in the analysis, a small number of individual results could easily have changed this outcome. Of the patients included, all were suspected by the attending anaesthetist of having reactions to NMBAs, though not all were confirmed as such in the final diagnosis after investigation. Eight patients were diagnosed with antibiotic anaphylaxis, and another with gelatin fluid allergy.

Whilst these patients remain valid inclusions in a study looking at markers of acute early anaphylaxis, the intentional inclusion of other patients suspected to have had anaphylaxis to other substances in the study design that suffered early anaphylaxis post-induction may have provided greater numbers for analysis.

Similarly, questions exist over the final diagnosis of anaphylaxis for some of the patients. A relatively low proportion of these patients tested positive on skin test (60%), not all had a positive tryptase and there were no supplementary laboratory investigations (such as specific IgE analysis) to add extra weight to the diagnoses. Of course, at the present time there is no way to conclusively identify non-IgE causes of anaphylaxis. This will hopefully change in the near future with further investigation of the roles and variations in the MGRPRX2 receptor and its subtypes after the seminal publication of by McNeil and colleagues in 2015[14] identifying it as a major target for substances with the propensity to initiate non IgE mediated mediator release (including NMBAs).

Finally, this study's classification system of severity of anaphylaxis is imprecise, after the 40 yr old work of Ring and Messmer.[13] This classification system has served us well over the years, but current definitions of anaphylaxis exclude Ring and Messmer grade 1 reactions altogether (skin only) as they are not systemic hypersensitivity reactions. Grades 2 and 3 provide general and subjective descriptions of moderate and severe derangements in respiratory and cardiovascular systems. A new classification system has recently been described in the *British Journal of Anaesthesia*[15] that addresses this imprecision by removing rash only reactions and better defining moderate (grade A) from severe (grade B) by physiological variables at common "tipping points". Cardiac arrest is self-defining and is now Grade C.

It will take a while for studies to begin to collect data in a way that allows them to report results with greater precision, indeed the authors of this study found their data collection insufficiently detailed to use the new classification. The results of NAP6 studies may well help the debate concerning the way that data should best be collected to answer the questions of how to optimally treat perioperative anaphylaxis in the future.[1]

The ability to accurately and rapidly diagnose the severity of perioperative anaphylaxis is pivotal in applying treatment guidelines that invariably suggest treatment according to the severity of the reaction. Whilst all authors agree that early diagnosis and treatment of severe anaphylaxis with epinephrine is vital to the survival of our patients, it must be recognized that epinephrine is a drug with a low therapeutic index, particularly when administered intravenously. Accurate matching of severity of anaphylaxis to treatment will most likely occur when the grades of anaphylaxis are optimally defined.

Whilst it is too early to suggest that a rapid decrease in E'_{CO_2} is sufficiently diagnostic to make a diagnosis of post-induction anaphylaxis, the routine use of this real-time measurement may prove to be a valuable addition to our ability to detect and treat perioperative anaphylaxis. In the meantime, this work calls for larger studies to confirm or refute this finding as we work towards a near-zero mortality rate for perioperative anaphylaxis.

Declaration of interest

M.A.R. is a member of the Australian and New Zealand Anaesthetic Allergy Group, a not-for-profit organization involved in producing treatment guidelines for perioperative anaphylaxis and facilitating research in this area. M.A.R. has served as

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Getting the dose right: anaesthetic drug delivery and the posological sweet spot

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Posology, a scientific term not in common usage, is the science of drug dosage; it is thus a branch of clinical pharmacology (or perhaps a synonym of sorts). Combining the Greek words 'posos' (how much) and 'logos' (science), posology can be thought of more simply as 'dosology'. In the posology of anaesthesia, the fundamental question anaesthetists must answer each day is: 'What is the right anaesthetic dosing strategy for my next patient?'

In this issue of the *British Journal of Anaesthesia*, van den Berg and colleagues[1] report a novel approach to optimizing posology in anaesthesia. Their study was an attempt to personalize target-controlled infusion (TCI) therapy with a single observation from the patient. Taking a Bayesian approach, the authors started with pharmacokinetic (PK) parameters from a population model[2] and then adjusted them based on the difference between the predicted drug concentration and the observed drug concentration measured in real time from a single blood sample from the patient.

Bayesian estimations of PK model parameters have a decades-long history since their introduction by Sheiner and colleagues in 1979.[3] Bayesian methods are intuitively appealing, in part because the approach is somewhat similar to how humans solve problems: start with information that is available *a priori*, and adjust based on the difference between the *a priori* information and the observation, normalized by their variability. This moves the adjusted system from the *a priori* starting point

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Low end-tidal CO_2 as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions

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Abstract

Background: Prompt diagnosis of intra-anaesthetic acute hypersensitivity reactions (AHR) is challenging because of the possible absence and/or difficulty in detecting the usual clinical signs and because of the higher prevalence of alternative diagnoses. Delayed epinephrine administration during AHR, because of incorrect/delayed diagnosis, can be associated with poor prognosis. Low end-tidal CO_2 (etCO_2) is known to be linked to low cardiac output. Yet, its clinical utility during suspected intra-anaesthetic AHR is not well documented.
Methods: Clinical data from the 86 patients of the Neutrophil Activation in Systemic Anaphylaxis (NASA) multicentre study were analysed. Consenting patients with clinical signs consistent with intra-anaesthetic AHR to a neuromuscular blocking agent were included. Severe AHR was defined as a Grade 3–4 of the Ring and Messmer classification. Causes of AHR were explored following recommended guidelines.
Results: Among the 86 patients, 50% had severe AHR and 69% had a confirmed/suspected IgE-mediated event. Occurrence and minimum values of arterial hypotension, hypocapnia and hypoxaemia increased significantly with the severity of AHR. Low etCO_2 was the only factor able to distinguish mild [median 3.5 (3.2;3.9) kPa] from severe AHR [median 2.4 (1.6;3.0) kPa], without overlap in inter-quartile range values, with an area under the receiver operator characteristic curve of 0.92 [95% confidence interval: 0.79–1.00]. Among the 41% of patients who received epinephrine, only half received it as first-line therapy despite international guidelines.
Conclusions: An etCO_2 value below 2.6 kPa (20 mm Hg) could be useful for prompt diagnosis of severe intra-anaesthetic AHR, and could facilitate early treatment with titrated doses of epinephrine.
Clinical trial registration: NCT01637220.

Key words: anaesthesia, general; anaphylaxis; cardiac output; hypocapnia; neuromuscular blocking agents

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Editor's key points

- Prompt diagnosis and epinephrine injection are widely recognized as critical to successful treatment of anaphylaxis.
- Data from the NASA multicentre study were retrospectively analysed to identify perioperative management of acute hypersensitivity reactions.
- Low end-tidal CO$_2$ was the most useful measure for early differentiation of severe from mild reactions, and could facilitate rapid diagnosis and early treatment.

Anaphylaxis is defined as 'a serious allergic reaction that is rapid in onset and may cause death'.[1–3] The usual clinical criteria have limitations for Anaphylaxis occurring during anaesthesia (intra-anaesthetic anaphylaxis), which is often severe and life-threatening.[4] Indeed, intra-anaesthetic acute hypersensitivity reactions (AHR) may be difficult to diagnose because of the impossibility to detect classic signs such as erythema (because of surgical dressing) and/or absence of other clinical signs (such as anxiety, dyspnoea and abdominal pain). Finally, major signs of AHR (e.g. arterial hypotension, tachycardia) can have many other causes induced by anaesthesia and surgery, which occur with much higher prevalence, leading to high diagnostic uncertainty and incorrect/delayed therapy.

Although there are no human trials establishing the benefit of epinephrine or its preferred route of administration in AHR, prompt epinephrine infusion is a key element recommended by experts to improve prognosis,[5] based mainly on animal models or epidemiological studies in patients with food allergy[6–8] or perioperative anaphylaxis.[4 9 10] Inappropriate or delayed diagnosis of intra-anaesthetic AHR, because of the difficulties enumerated above, can result in delayed or inadequate epinephrine infusion (given as the second line treatment for example).[4 11 12]

From clinical experience and based on published case reports,[13 14] we hypothesized that end-tidal CO$_2$ (etCO$_2$), a nearly universally available clinical parameter in the operating room (OR) and with a time constant for changes of dozens of seconds could improve clinical reasoning when AHR is a possible diagnosis in patients under general anaesthesia (GA).[15] The main objective of this work was to evaluate the potential value of etCO$_2$ to help in the early diagnosis of severe intra-anaesthetic AHR in a prospective cohort of patients with suspected AHR to neuromuscular blocking agents (NMBA). Simultaneously, we evaluated the haemodynamic management of intra-anaesthetic AHR in order to estimate whether low etCO$_2$ could be used to facilitate early diagnosis and thereby early epinephrine treatment in severe AHR.

Methods

Study design

The multicentre Neutrophil Activation in Systemic Anaphylaxis (NASA) study involved 11 anaesthesia departments in the Ile-de-France region of France (https://clinicaltrials.gov/ct2/show/NCT01637220). Its purpose was to evaluate the role of neutrophils during AHR to NMBA (which is the culprit agent in ~60% of intra-anaesthetic AHR cases)[16 17] in humans through a case–control design, with 6–8 weeks follow-up of case patients. The study was approved by the appropriate local ethics authority

(committee for the protection of Individuals 'Ile-de-France 1', reference 2012-avril-12880), and prospectively registered at ClinicalTrials.gov (Identifier: NCT01637220). Diagnosis of AHR/anaphylaxis was defined as a reaction involving the cutaneous (rash or angioedema), the respiratory and/or the cardiovascular system, based on the Ring and Messmer classification.[18] From October 2012 to June 2014, we included any patient aged >17 yr with clinical signs consistent with intra-anaesthetic AHR to NMBA regardless of the grade of the reaction (flowchart of the NASA study in Fig. 1). Inclusion criteria were thus based only on clinical criteria and not on immunological testing. The only patient aged <18 yr had parental consent. As case patients were not in a medical or psychological state to provide study consent during the AHR, their consent was obtained as soon as they were judged able. If patients did not recover the day after the AHR, consent was obtained from a next of kin. Exclusion criteria included absence of consent. As recommended by guidelines,[19] case patients benefited from an allergist-anaesthetist visit 6–8 weeks following the AHR in order to identify the culprit agent.

We took advantage of this cohort to analyse clinical data associated with NMBA-induced AHR. Clinical and biological data were collected, including patient (age and sex) and anaesthesia/surgery characteristics (procedure, NMBA used, infection status, scheduled or urgent surgery) and medical information [history of atopic events, asthma, allergy to food, drugs or other compounds, comorbidities and surgeries, previous chronic drug treatments, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers, drugs known to alter the response to AHR]. All observable clinical signs of AHR, their chronology and outcome were recorded. Interventions/drugs initiated in the OR, before occurrence of the first clinical sign(s) of AHR were noted (nature of antiseptic, volume expansion, anaesthetic and other drugs used) in order to identify the culprit agent, as well as the specific treatment of the AHR. AHR was graded according to the Ring and Messmer classification[18] by two independent evaluations of clinician experts. Severe AHR was defined as Grade 3 or 4 (i.e. severe organ failure or cardiac/respiratory arrest). A recently reported severity classification of AHR has been also investigated,[20] but we were unable to use it in our cohort because some required data were unavailable.

Immunological investigations of intra-anaesthetic AHR were performed as recommended by international/national guidelines.[19 21 22] A venous blood sample was collected within 30 min following onset of AHR when the patient's condition had been stabilized, 2 h after the AHR and during the allergist-anaesthetist visit 6–8 weeks post-AHR. At that time, immediate reading intra-dermal tests against suspected culprit agents were performed on the forearms and arms of the patients. The following circulating parameters were assessed as described:[23] histamine (EIA, Immunotech, Beckman Coulter Brea, California, USA), tryptase (FEIA, ImmunoCAP 250 Phadia, Thermofisher Waltham, Massachusetts, USA) and anti-quaternary ammonium-specific IgE (N < 0.35 kU litre^{-1}) (FEIA, ImmunoCAP 250 Phadia, Thermofisher Waltham, Massachusetts, USA). Tryptase levels 2 h following AHR were considered elevated when above (1.2 × [baseline tryptase level] + 2 µg litre^{-1} as recently recommended.[24] Histamine concentration above 20 nmol litre^{-1} at 30 min following AHR was considered elevated.[25] Because it was published after the end of the current study, the recently suggested threshold for histamine concentration was not used.[16] However, only two patients had a histamine concentration between 20 and 27.9 nmol litre^{-1}, which would not have changed our results. Classifications of AHR according to

Fig 1 Flowchart of case patients of the NASA study.
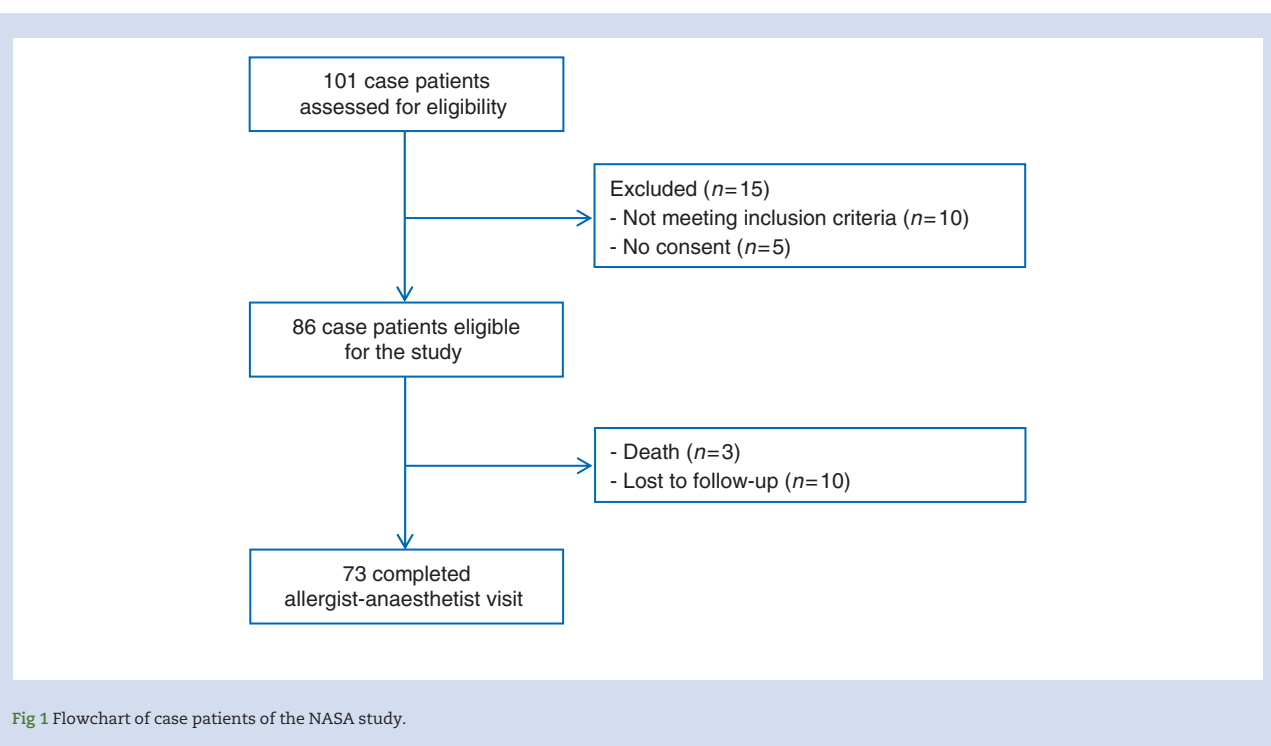
suspected mechanism (IgE-mediated reaction confirmed, suspected or absent) were retrospectively established by six experts, who were unaware of etCO$_2$ values.

Clinical signs and management during the hypersensitivity allergic reaction

Anaesthesia procedures were left to the individual physicians. However, all patients received tracheal intubation and volume-controlled ventilation at a standardized fraction of inspired oxygen (FiO$_2$) of 100% during the first minutes following induction. All clinical signs occurring during the AHR were recorded by the physician in charge. Whereas systolic arterial pressure (SAP) could be measured either continuously or intermittently, all other parameters [i.e. heart rate (HR), etCO$_2$ and SpO$_2$] were monitored continuously in addition to visual inspection of their tracings. Arterial hypotension, bradycardia and tachycardia were defined as recommended as SAP or HR under or above 20% of baseline, respectively. Hypocapnia and hypoxaemia were defined, respectively, as etCO$_2$ <4.5 kPa (34 mm Hg) and SpO$_2$ <94%. Bronchospasm was defined as increased airway pressure or ventilation difficulties as reported by the clinicians on the anaesthesia record. Upon first observation of a clinical sign consistent with AHR, the minimum or maximum numeric value of the studied variables was noted (i.e. minimum etCO$_2$ for hypocapnia, minimum/maximum HR for bradycardia/tachycardia, lowest SAP for arterial hypotension, minimum SpO$_2$ for hypoxemia). Additional values were retrospectively obtained from patients included in two of the centres (corresponding to 12 patients). Finally, we were able to record 77%, 82% and 73% of the numerical values during AHR of minimum SAP, etCO$_2$ and SpO$_2$, respectively. All patients who had an

AHR were treated following French[15] [19] [21] and international guidelines.[26]

Statistical analyses

The number of patients to include in the NASA study was calculated based on the primary endpoint (i.e. the difference in activated neutrophils between case and control patients), with a type II error of 10% and a type I error of 5%, leading to a minimum number of patients per group of 79. We finally included 86 case patients. No statistical power calculation was performed for the relationship between etCO$_2$ and the severity of AHR mainly because no data were available in the literature for such calculations. Variables are described according to their distribution as appropriate [i.e. median and interquartile range (IQR) for variables with non-Gaussian distributions, frequency and percentage for category criteria]. Only age was described as median and range. Comparisons were, respectively, performed with Mann–Whitney *U*-test or Fisher's exact test. To compare sub-groups defined by the severity of the AHR, we used a Kruskal–Wallis test followed by a *post hoc* analysis by Dunn's test for continuous data, or Fisher's exact test for categorical data. The ability of minimum etCO$_2$ and SAP to diagnose mild from severe AHR used the area under the receiver operator characteristic curve (AUCROC), with the pROC package.[27] Comparisons of two AUCROCs used the DeLong method. Sensitivity and specificity were calculated with standard formulae: true positive/(true positive + false negative) and true negative/(false positive + true negative), respectively. Confidence intervals (CI) for the difference between AUCROCs and threshold values were calculated with bootstrap resampling (B = 2000) with replacement and the percentiles method.

Statistical tests were bilateral and a type I error was fixed at 5%. Statistical analyses were performed with R version 3.0.2 software (R foundation for Statistical Computing, Vienna, Austria).

Results

Patient inclusion and clinical presentation

We included 86 case patients. The characteristics of these patients are presented in Table 1 (some patients may have received two NMBA during anaesthesia). Of note, seven (8%) were classified Grade 1, 36 (42%) Grade 2, 33 (38%) Grade 3 and 10 (12%) Grade 4. The clinical features of the AHR are described in Table 2. The AHR occurred with a median delay of 5 min following anaesthesia induction (defined as injection of the first anaesthetic drug) independently of the grade of AHR reaction. Three patients died between day 1 and day 5 after anaesthesia (Table 3).

Immunological investigation

Of the 86 cases, 59 (69%) had evidence of IgE-dependent anaphylaxis (classified as confirmed or highly suspected), based on elevated tryptase and/or elevated histamine and/or positive skin tests (data not shown), of which 73 had an allergist-anaesthetist visit (10 patients were lost to follow-up and three died, Fig. 1). Of the 73, 44 patients (60%) had a positive skin test, 35 (48%) to one or several NMBA, eight (11%) to β-lactams, and one (1%) to modified fluid gelatin. When comparing patients according to the evidence of an IgE-dependent mechanism, there were no differences in patient and surgery characteristics. Patients with evidence of an IgE-dependent pathway had more severe reactions

Table 1 Patient and surgery characteristics. Values are expressed as percentages or as median (minimum, maximum). ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin II receptor antagonist; BB, beta-blocker; CI, calcium channel inhibitor; NMBA, neuromuscular blocking agent

Variable	All patients (n=86)
Female sex (%)	62
Age (yr)	57 (17;92)
Previous general anaesthesia (%)	84
Medication (ACEI/ARA/BB/CI) (%)	37
History of allergy (%)	
Drugs	13
Latex	2
Food	7
Hymenoptera venom	3
Pollen/moth/animals/mold	15
Asthma (%)	12
Atopy (%)	20
Type of surgery (%)	
Cardiothoracic, vascular	20
Maxillofacial	8
Orthopaedic, neurosurgery	20
Visceral, urological, gynaecological	52
Scheduled surgery (%)	92
Surgery with a context of infection (%)	2.3
NMBA used during surgery (%)	
Succinylcholine	56
Atracurium	55
Rocuronium	4

that were more likely to be induced by succinylcholine, whereas non-IgE-mediated AHR were more frequently induced by atracurium (data not shown).

Analysis of haemodynamic and respiratory variables

The occurrence of clinical signs was significantly different among the four grades of AHR severity: hypotension, hypocapnia and hypoxaemia were significantly more frequent in severe AHR compared with lower severity grades (Table 2). The minimum values of SAP and etCO$_2$ were both significantly different between mild and severe AHR (P=0.01 for arterial hypotension; P=0.002 for hypocapnia), although the difference in etCO$_2$ was of higher magnitude and with no overlap between IQR values of mild vs severe AHR (Fig. 2). Nevertheless, performing a comparison with Dunn's post hoc test, only a low etCO$_2$ could distinguish Grade 2 from Grade 3 (P=0.04) and Grade 4 (P=0.005) AHR. Of note, analyses could not be performed for minimum SpO$_2$, as only two data points were available in the mild AHR group. The ability of etCO$_2$ to discriminate mild from severe AHR assessed with AUCROC was 0.92 (95% CI: 0.79–1.0) and 0.72 (95% CI: 0.57–0.87) for SAP (P=0.06 for comparison between the two AUCROCs) (Fig. 3). The etCO$_2$ and SAP thresholds to identify severe AHR for fixed specificity and their associated sensitivity values are presented in Table 4.

Bronchospasm occurrence

Twenty-eight (32%) patients presented with bronchospasm, of which 43% had mild and 57% severe AHR (Table 2), with no statistical difference between groups (P=0.5). Among those patients, half of patients classified as mild and all severe AHR patients had haemodynamic signs. Half of these had hypocapnia, with no difference between groups (P=0.06).

Therapeutic management

Thirteen patients, who all presented with increased airway pressure, received β-2-adrenergic agonists mainly by inhalation (only one had an i.v. injection). Twenty (23%) patients received an i.v. injection of glucocorticoids as second-line treatment, 40% of which presented as Grade 2 and 45% as Grade 3 AHR (Table 2). Among the 23 (27%) patients who did not receive any vasoconstrictors during the AHR reaction, seven had Grade 1 and 16 had Grade 2 AHR. The 19 (22%) patients who received only ephedrine and/or phenylephrine suffered from Grade 2 AHR (Table 2). Epinephrine was given to 35 (41%) of patients; all but one presented with severe AHR. Injection of epinephrine was preceded by ephedrine and/or phenylephrine injection in 19 (54%) patients. For only 13 (37%) patients was epinephrine injected as the first-line treatment, and it was given with norepinephrine for three (9%) patients. The sequence of injection of vasoconstrictors varied significantly among patients grouped per severity grade (P<0.0001).

Fluid resuscitation was more frequent and the total volume infused was higher with severe AHR: 1500 ml (1000;2000) compared with mild AHR: 1000 ml (500;1000), regardless of the type of solution used (Table 2). Although the use of both crystalloids and colloids was significantly different between groups of severity grade, the median volume infused did not differ. The characteristics of the three deceased patients and their risk factors are presented in Table 3.

Table 2 Clinical signs and therapeutic interventions during acute hypersensitivity reactions, according to severity grade. Values are expressed as percentages or as median (25th–75th percentile) when appropriate. The numbers of observations and missing values varied according to the numeric value analysed: maximum HR (43/17), minimum HR (14/6), minimum SAP (70/21), minimum SpO_2 (24/9), minimum $etCO_2$ (33/7). Analyses were performed with a *post hoc* Dunn test with Bonferroni correction. *Indicates a significant difference between Grade 2 and Grade 3. †Indicates a difference between Grade 3 and Grade 4. $etCO_2$, end-tidal CO_2; HR, heart rate; ICU, Intensive Care Unit; NA, non-available; ND, non-done; SAP, systolic arterial pressure; SpO_2, photoplethysmographic oxygen saturation. ‡Kruskal Wallis test. ¶Fisher's exact test

| Clinical/haemodynamic signs	All patients (n=86)	Grade 1 (n=7)	Grade 2 (n=36)	Grade 3 (n=33)	Grade 4 (n=10)	P
Erythema (%)	72	100	75	70	50	0.2¶
Tachycardia (%)	51	14	50	70	20	0.006¶
Maximum HR (beats min^{-1})	130 (119;136)		130 (115;137)	130 (124;131)	170 (170;170)	0.2‡
Bradycardia (%)	16	0	8	21	40	0.06¶
Minimum HR (beats min^{-1})	47 (40;50)		52 (51;54)	40 (39;45)	45 (42;48)	0.3‡
Arrhythmia (%)	13	0	3	15	50	0.002¶
Arterial hypotension (%)	81	0	75	100	100	<0.0001¶
Minimum SAP value (kPa)	7.7 (6.4;8.7)		8.7 (7.7;9.7)	6.7 (6.4;8)*	6 (5.3;9.7)	0.03‡
Bronchospasm (%)	32	0	33	30	60	0.07¶
Hypoxemia (%)	28	0	8	48	50	0.0001¶
Minimum SpO_2 (%)	85 (82;89)		91 (90;92)	87 (82;89)	76 (70;82)†	0.04‡
Hypocapnia (%)	38	0	17%	57%	80%	<0.0001¶
Minimum $etCO_2$ (kPa)	2.7 (1.9;3.3)		3.5 (3.2;3.9)	2.5 (2.3;3.2)*	1.5 (1.3;2.4)†	0.01‡
Cardiac arrest (%)	12	0	0	0	100	<0.0001¶
Delay of resuscitation						
Delay between anaesthesia induction and first signs of the reaction (min)	5 (5;10)	5 (2;5)	10 (5;10)	5 (5;15)	5 (3;17)	0.3‡
Delay between first signs of the reaction and treatment initiation (min)	0 (0;2)	0 (0;2)	0 (0;0)	1 (0;2)	1 (0;4)	0.06‡
Therapeutic interventions						
Epinephrine i.v. alone (%)	17	0	0	30	50	<0.0001¶
Cumulative doses of epinephrine (mg)	2.5 (0.9;6)	NA	NA	1.3 (0.5;2)	8 (3;11)	0.04‡
Norepinephrine i.v. alone (%)	2	0	0	6	0	0.5¶
Cumulative doses of norepinephrine i.v. (mg)	1.7 (1.6;1.8)	NA	NA	1.7 (1.6;1.9)	NA	ND
Epinephrine i.v. and norepinephrine i.v. (%)	6	0	0	12	10	0.1¶
Cumulative doses of epinephrine i.v. (mg)	5 (2;5)	NA	NA	3.7 (1.5;16)	5 (5;5)	1‡
Ephedrine and/or phenylephrine i.v. alone	22	0	53	0	0	<0.0001¶
Ephedrine and/or phenylephrine i.v., then epinephrine and/or norepinephrine i.v.	26	0	3	51	40	<0.0001¶
Cumulative doses of epinephrine i.v. (mg)	0.5 (0.3;3)	NA	0.1 (0.1;0)	0.45 (0.3;1)	10.6 (1;27)	0.1‡
Atropine i.v. (%)	8	0	5	9	20	0.4¶
Cumulative doses of atropine i.v. (mg)	1 (1;1)	NA	1 (1;1)	1 (1;1)	NA	ND
β-2-adrenergic agonist i.v./inhaled (%)	13	0	14	12	20	0.8¶
Glucocorticoids (%)	23	28	22	27	20	0.7¶
Histamine receptor antagonists (%)	1	14	0	0	0	0.08¶
Fluid resuscitation with crystalloids (%)	55	14	47	70	70	0.02¶
Cumulative volume of crystalloids (litre)	1 (0.7;1.8)	2 (2;2)	0.7 (0.5;1)	1.5 (1;2)	1 (1;1.38)	0.05‡
Fluid resuscitation with colloids (%)	22	0	11	42	10	0.006¶
Cumulative volume of colloids (ml)	0.5 (0.5;1)	NA	650 (500;850)	500 (500;1000)	500 (500;500)	0.7‡
Evolution						
Surgery cancelled (%)	55	0	23	82	78	1¶
Admission to ICU (%)	55	40	23	73	89	0.7¶

Discussion

The incidence of intra-anaesthetic AHR is estimated between 1/6000 and 1/20 000 procedures.[28] Translated to individual practice, when performing 1500 anaesthetic procedures a year, an anaesthesiologist has a probability of seeing a case of AHR in his/her practice every 4–15 yr. Acquisition and preservation of clinical skills to manage such rare events are challenging. The delayed

diagnosis/treatment of AHR during anaesthesia is attributable to its rarity and to the higher prevalence of differential diagnoses (e.g. arterial hypotension of other more frequent causes).

We took opportunity of the NASA study to analyse the clinical/monitoring signs of intra-anaesthetic AHR. The clinical results presented herein demonstrate that patients with severe AHR had a significantly lower $etCO_2$ value immediately

Table 3 Characteristics of the three fatal cases. AHR, acute hypersensitivity reaction; etCO$_2$, end-tidal CO$_2$; NA, not applicable. Please note that Patient 2 who died on day 5 had been scheduled for cardiac surgery and benefited from an extracorporeal life support as soon as the severe AHR was considered refractory to conventional therapy. Patient 3 received 1000ml of crystalloids plus 500ml of colloid.

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Female
Age (yr)	90	76	67
Urgent surgery	No	No	Yes
Beta-blocker treatment	Yes	No	Yes
Clinical signs			
Erythema	No	Yes	No
Tachycardia	No	No	No
Bradycardia	No	No	No
Arrhythmia	No	Yes	No
Arterial hypotension	Yes	Yes	Yes
Bronchospasm	No	No	Yes
Hypoxaemia	No	Yes	Yes
Hypocapnia	Yes	Yes	Yes
Minimum value of etCO$_2$ (kPa)	2	1.3	1.3
Delay between anaesthesia induction and first signs of the reaction (min)	20	3	10
Delay between first signs of the reaction and treatment initiation (min)	0	0	0
Therapeutic interventions			
Epinephrine i.v. alone	Yes	No	No
Cumulative doses of epinephrine i.v. (mg)	8	NA	NA
Ephedrine and/or phenylephrine i.v., then epinephrine i.v.	No	Yes	Yes
Cumulative doses of epinephrine i.v. (mg)	NA	20	1.3
β-2 agonist i.v.	No	No	No
Glucocorticoids i.v.	No	No	No
Volume expansion	No	No	Yes
Delay between shock and death (day post-shock)	1 day	5 days	2 days
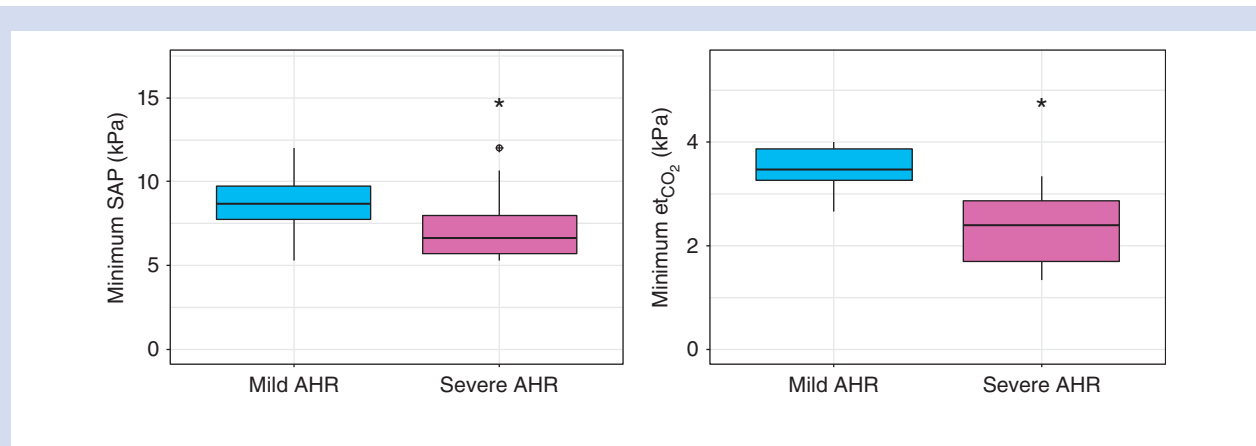
Fig 2 Clinical variables of patients with mild *vs* severe acute hypersensitivity reactions (AHR). Boxplot representations of systolic arterial pressure (SAP) and end-tidal CO$_2$ (etCO$_2$). Although there was a statistically significant difference between groups for minimum SAP (P=0.01), only etCO$_2$ could distinguish between mild and severe groups (P=0.002) with a very low overlap. *P<0.05; Mann–Whitney *U*-test.

following tracheal tube placement than patients with mild AHR. It is difficult for the anaesthetic practitioner to estimate in real time the severity of AHR and therefore decide rapidly if epinephrine must be injected first. A low etCO$_2$ value could accelerate the diagnosis of both the AHR and its severity, and thus contribute to earlier injection of titrated doses of epinephrine, as recommended by international guidelines.[19 29]

Among the cases included, 62% were female patients with a median age of 57, which is in accordance with previous epidemiological studies.[17] In this study, 86% of patients presented haemodynamic changes. When comparing mild to severe AHRs, only the minimum values of SAP and etCO$_2$ were significantly different (Fig. 2). It is possible that a lack of statistical power contributed to the lack of discrimination by SAP values.

However, SAP is usually only available discontinuously and SpO_2 measures can be impaired in the acute phase of shock when peripheral vasoconstriction leads to uninterpretable or absent photoplethysmographic signals. Moreover, there is a large overlap in the IQR values for minimum SAP and SpO_2 values, reducing the value of these parameters in rapid decision-making for diagnosis and management of individual patients. In contrast, $etCO_2$ values were decreased in severe compared with mild AHR without major overlap. Although there was no statistical difference between SAP and $etCO_2$ AUCROC, the ability of $etCO_2$ to identify severe AHR displays higher sensitivity for closed specificities (Table 4). Furthermore, given the fact that $etCO_2$ is displayed continuously as compared with the longer time constant for non-invasive blood pressure, one can assert that a low $etCO_2$ is a clinically more valuable sign to discriminate between patients with mild *vs* severe AHR during general anaesthesia.
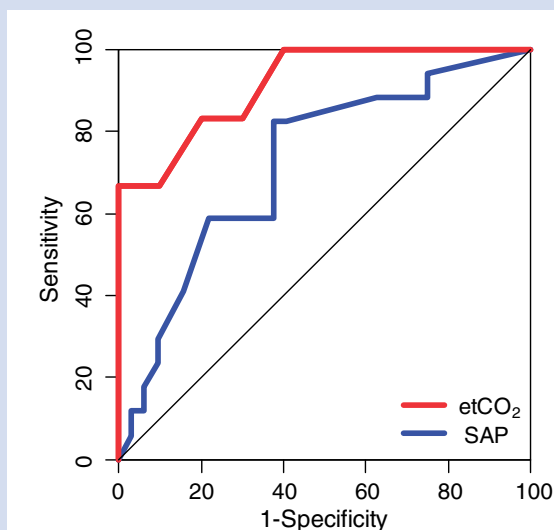

Fig 3 ROC curve of minimum end-tidal CO_2 ($etCO_2$ red line) and minimum systolic arterial pressure (SAP blue line) for categorization of patients between mild and severe acute hypersensitivity reactions. Area under curves for minimum $etCO_2$ and minimum SAP were, respectively, 0.92 (95% CI 0.79–1.00) and 0.72 (95% CI 0.57–0.87).

A sudden drop of $etCO_2$, without any changes in ventilation parameters or cell metabolism, in intubated and ventilated patients, reflects a drop in cardiac output (CO), and can precede arterial hypotension.[30] Correlation between these two parameters during acute haemodynamic changes has been demonstrated in both animal models and human studies.[31 32] In a pig model, $etCO_2$ was a reliable marker of CO in circulatory shock (i.e. haemorrhagic, septic and cardiogenic shock). Although arterial hypotension secondary to AHR was associated with a proportional decrease in CO,[33 34] nicardipine-induced arterial hypotension of similar amplitude and timing was associated with preserved CO in rats.[35] Importantly, the majority of arterial hypotension episodes during anaesthesia involve anaesthetic drug overdose,[36–39] preserved/moderately decreased CO and therefore normal/moderately decreased $etCO_2$ values. In ovalbumin-sensitized rats, anaphylaxis was characterized by rapid metabolic modifications leading to anaerobic glycolysis, possibly contributing to reduced CO_2 released in the circulation and to failure of cellular energy.[35] Therefore, low $etCO_2$ reflects changes in CO, yet remains relatively independent of other triggers of arterial hypotension that commonly occur during GA.

Even if the number of patients included is small, this is probably one of the largest prospective studies on the subject. Although both low CO and low $etCO_2$ are expected in a shock state that develops within minutes, we believe our findings are of major importance for clinical decision-making. Indeed, among the differential diagnoses of arterial hypotension or tachycardia occurring after induction of anaesthesia, AHR is the least prevalent and difficult to diagnose. This underscores why a low $etCO_2$ could help establish an AHR diagnosis upon occurrence of severe arterial hypotension during GA.

The clinical value of low $etCO_2$ to diagnose severe AHR upon arterial hypotension may be limited for patients who present only with bronchospasm as the major sign of AHR. In these patients, there is increased airway pressure and possibly no plateau on the $etCO_2$ curve. If there is no arterial hypotension, this situation is easy to recognize. A more difficult situation is for those patients in whom both severe bronchospasm and arterial hypotension are present. The capnogram will be altered but the association of severe bronchospasm and arterial hypotension is highly consistent with severe AHR. In our study, only six patients displayed moderate bronchospasm without haemodynamic impairment, all classified as Grade 2. This small number of patients may thus not alter the results of our study. Finally, when arterial hypotension is the major clinical sign, low $etCO_2$ is most important to discriminate severe from non-severe forms of AHR.

Among the 86 patients with AHR included in the NASA study, 69% were identified as involving an IgE-dependent mechanism, a proportion that is in accordance with previous

Table 4 Minimum end-tidal CO_2 and systolic arterial pressure thresholds for three selected specificities for severe AHR identification. The first column corresponds to the Youden Index (i.e. that maximizes both sensitivity and specificity). AHR, acute hypersensitivity reaction; CI, confidence interval; $etCO_2$, end-tidal CO_2; SAP, systolic arterial pressure

		Specificity 67%	Specificity 83%	Specificity 100%
Minimum $etCO_2$	$etCO_2$ threshold (kPa) (95% CI)	3.4 (3.3; 3.7)	3 (2.6; 3.3)	2.6 (2.1; 3)
	Sensitivity	100%	80%	60%
		Specificity 82%	Specificity 88%	Specificity 94%
Minimum SAP	SAP threshold (kPa) (95% CI)	7 (6.8; 8.3)	6.2 (5.4; 6.8)	5.9 (5.4; 6.5)
	Sensitivity	62%	37.5%	25%

epidemiological studies.[16 40] Although these authors agree with milder manifestations of non-IgE-dependent AHR, they emphasize the existing discrepancy between endotype and phenotype of shock, with a 22% rate of severe AHR among patients without evidence of an IgE-dependent mechanism.[40] On the other hand, minor manifestations, such as skin rash, can be seen in patients with documented IgE-dependent AHR. Taken together, there are several lines of evidence that challenge the importance of formally documenting an IgE-mediated mechanism regarding decisions on re-administration of a drug suspected to have caused a severe AHR during anaesthesia.[41]

In the NASA study, despite recommendations, epinephrine was administered as the first-line therapy in only 51% of severe AHR cases. Risk factors associated with fatal AHR induced by NMBA described by Reitter and colleagues[42] include: male sex, emergency setting, previous history of cardiovascular disease and beta-blocker treatment. These risk factors are close to those described in emergency settings.[43] In this study, the three deceased patients had at least one of these risk factors.[42] Before cardiac arrest, they presented with arterial hypotension and hypocapnia with very low etCO₂ values, and two received epinephrine as a second-line therapy. This underscores the major diagnostic uncertainty and difficulty in evaluating reaction severity in real time. Severity of AHR is often assessed a posteriori mainly by the magnitude of haemodynamic changes, lack of response to ephedrine and/or phenylephrine and requirement for epinephrine, illustrated here with 48% of patients with severe AHR receiving ephedrine before epinephrine. There is weak evidence for all recommended therapeutic measures to treat AHR (reviewed in[29]). The beneficial effects of very early epinephrine (minutes following onset of clinical signs) are supported by in vitro findings.[44] Several studies of severe or fatal cases of anaphylaxis report that less than one-third of patients received appropriate treatment,[7 45–48] leading the authors to conclude that 'failure to recognize the severity of these reactions and to administer epinephrine promptly increases the risk of a fatal outcome'.[7] However, this is not in accordance with analyses of fatal cases of AHR induced by NMBA where all patients benefited in prompt epinephrine infusion at a dose adapted to the initial form of the reaction (except for two of 31).[42] In the OR, in the absence of other causes of (acute) shock, a sudden and massive decrease of etCO₂ after anaesthesia induction, with a value below 2.6 kPa (20 mm Hg), could be the sign that would allow clinicians to estimate in real-time the severity of AHR, and thus facilitate early use of titrated epinephrine doses.[49]

Aggressive volume expansion is a key point in the management of severe AHR. In an ovalbumin-sensitized rat model, capillary leakage started within 2 min after onset of anaphylaxis and increased in severity over time.[50] In humans, this can lead to a volume loss representing 73% of total blood volume within 15 min.[51] An animal model suggested a combined effect of epinephrine and use of a specific colloid fluid to restore haemodynamics after ovalbumin-induced anaphylaxis.[52] However, the choice of fluid for fluid resuscitation during a state of shock is debated, mainly because some studies in humans have suggested an increased risk of mortality induced by colloids.[19 53 54] In France, crystalloids are first recommended, followed if necessary by colloids.[19] In the study herein, only 63% of patients benefited from fluid resuscitation with a significant difference between groups. Even if severe AHR benefited more often than mild AHR from volume expansion therapy, the proportion of fluid-resuscitated patients was surprisingly low, especially considering that there was no difference between groups regarding

volume administered. This reflects difficulties in maintaining clinical skills for rare events. Analysis of fatal cases of AHR induced by NMBA reported a fluid resuscitation rate far below those set by international guidelines,[41] which could have contributed to the death of those patients, as observed for patients in our study.

An important limitation of this study is related to the fact that the statistical power calculations were performed for the NASA study and not for the analyses related to the possibility of low etCO₂ values to discriminate between patients with mild vs severe AHR. The lack of statistical power might explain why the difference of the AUCROC was not significant ($P=0.06$) between low etCO₂ and arterial hypotension. Despite these limitations, we estimate that this study has one of the largest numbers of patients for whom clinical data were gathered prospectively with such a detailed phenotyping of the AHR.

Conclusions

The diagnosis and treatment of severe intra-anaesthetic AHR represent a significant challenge. Among standard measured parameters during GA, etCO₂ might be the most easily available and valuable parameter to efficiently differentiate, in real-time, patients between mild and severe AHR. A low value of etCO₂—below 2.6 kPa (20 mm Hg)—could be a useful diagnostic criterion for severe perioperative AHR, excluding during haemorrhage or sepsis. It should be part of the clinical reasoning to establish the diagnosis of severe intra-anaesthetic AHR and be a strong indication for early administration of titrated doses of epinephrine, as stipulated by national and international guidelines, with foreseeable improved outcomes and reduced mortality. To draw firmer conclusions and to modify diagnostic/treatment algorithms worldwide, the results of this study should be replicated by further adequately powered work, such as the ongoing UK Sixth National Audit Project[55] or as the French GERAP cohort.[16]

Authors' contributions

Data analysis, data collection, patient recruitment, writing up of the first draft of the paper script: A.G.-C.
Study design, data collection, drafting the article: L.D.C. and F.J.
Study design, data collection: P.N.-R.
Data collection, drafting the article: V.G.
Patient recruitment: A.S.
Patient recruitment, data collection: M.-T.G.
Study design, drafting the article: S.C.-M. and P.B.
Study design, patient recruitment, data collection: C.N.
Study design, data analysis, writing up of the first draft of the paper: D.L.

Declaration of interest

None declared.

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