

Low end-tidal CO₂ as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions

A. Gouel-Chéron^{1,2,3}, L. de Chaisemartin^{4,5,†}, F. Jönsson^{1,2,†}, P. Nicaise-Roland⁴, V. Granger^{4,5}, A. Sabahov³, M.-T. Guinnepain⁶, S. Chollet-Martin^{4,5}, P. Bruhns^{1,2}, C. Neukirch^{7,8,‡} and D. Longrois^{3,8,*,‡}; and the NASA Study Group[¶]

¹Institut Pasteur, Department of Immunology, Unit of Antibodies in Therapy and Pathology, Paris, France,

²INSERM, U1222, Paris, France, ³Département d'Anesthésie-Réanimation, Hôpital Bichat, HUPNVS, APHP, Paris, France, ⁴Département d'immunologie, UF Auto-immunité et Hypersensibilités, Hôpital Bichat, HUPNVS, APHP, Paris, France, ⁵Inflammation Chimiotiques et Immunopathologie, INSERM, Faculté de pharmacie, Université Paris-Sud, Université Paris-Saclay, Châtenay-Malabry, France, ⁶Département de médecine interne, Hôpital Foch, Suresnes, France, ⁷Département de pneumologie. Hôpital Bichat, HUPNVS, APHP, DHU FIRE, Paris, France and ⁸INSERM U1152, Université Paris Diderot Paris 7, Paris, France

*Corresponding author. E-mail: dan.longrois@aphp.fr

†Equal contribution.

‡Co-senior authorship.

¶Members of the NASA Study Group are listed in the Appendix.

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 CO₂ (etCO₂) 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 etCO₂ 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 etCO₂ 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 CO₂ 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 CO₂ (etCO₂), 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 etCO₂ 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 etCO₂ 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 classification¹⁸ 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 $(1.2 \times [\text{baseline tryptase level}] + 2 \mu\text{g litre}^{-1})$ 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

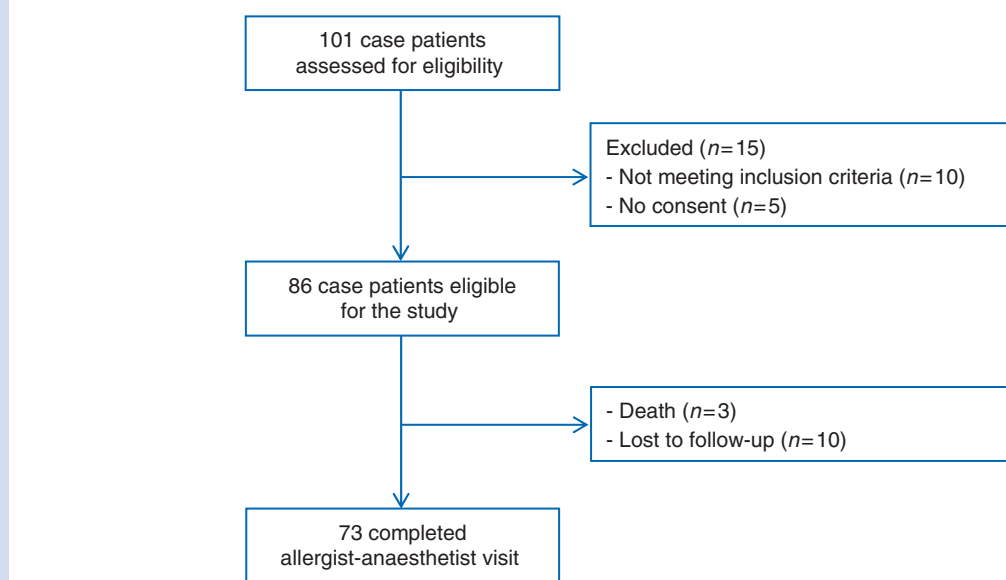


Fig 1 Flowchart of case patients of the NASA study.

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 $\text{etCO}_2 < 4.5 \text{ kPa}$ (34 mm Hg) and $\text{SpO}_2 < 94\%$. 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

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 etCO₂ were both significantly different between mild and severe AHR ($P=0.01$ for arterial hypotension; $P=0.002$ for hypocapnia), although the difference in etCO₂ 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 etCO₂ 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 SpO₂, as only two data points were available in the mild AHR group. The ability of etCO₂ 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 etCO₂ 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 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

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 SpO₂ (24/9), minimum etCO₂ (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. etCO₂, end-tidal CO₂; HR, heart rate; ICU, Intensive Care Unit; NA, non-available; ND, non-done; SAP, systolic arterial pressure; SpO₂, 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 1/20000 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 etCO₂ value immediately

Table 3 Characteristics of the three fatal cases. AHR, acute hypersensitivity reaction; etCO₂, end-tidal CO₂; 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

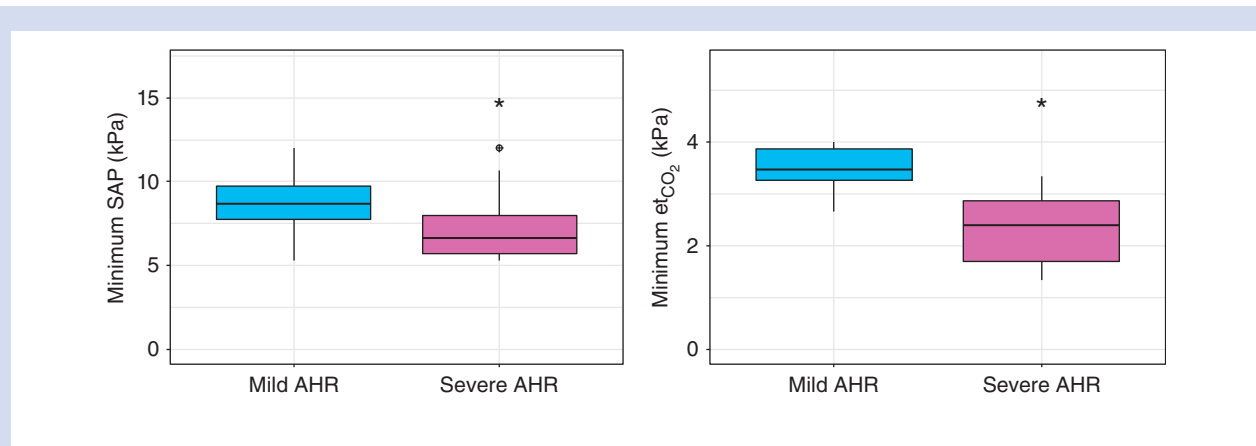


Fig 2 Clinical variables of patients with mild vs severe acute hypersensitivity reactions (AHR). Boxplot representations of systolic arterial pressure (SAP) and end-tidal CO₂ (etCO₂). Although there was a statistically significant difference between groups for minimum SAP ($P=0.01$), only etCO₂ could 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 etCO₂ 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 etCO₂ 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 SpO₂ 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 SpO₂ values, reducing the value of these parameters in rapid decision-making for diagnosis and management of individual patients. In contrast, etCO₂ values were decreased in severe compared with mild AHR without major overlap. Although there was no statistical difference between SAP and etCO₂ AUCROC, the ability of etCO₂ to identify severe AHR displays higher sensitivity for closed specificities (Table 4). Furthermore, given the fact that etCO₂ is displayed continuously as compared with the longer time constant for non-invasive blood pressure, one can assert that a low etCO₂ is a clinically more valuable sign to discriminate between patients with mild vs severe AHR during general anaesthesia.

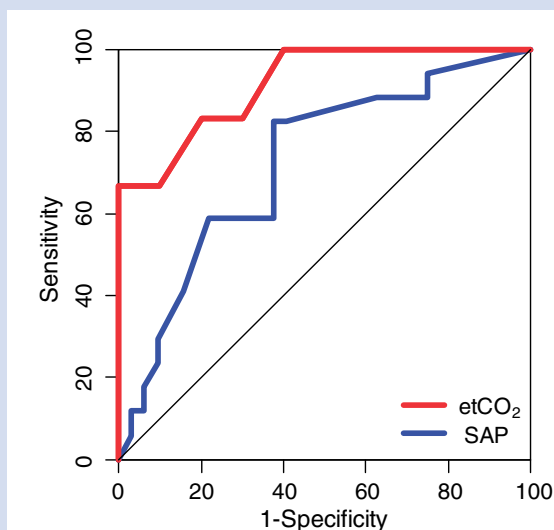


Fig 3 ROC curve of minimum end-tidal CO₂ (etCO₂ red line) and minimum systolic arterial pressure (SAP blue line) for categorization of patients between mild and severe acute hypersensitivity reactions. Area under curves for minimum etCO₂ and minimum SAP were, respectively, 0.92 (95% CI 0.79–1.00) and 0.72 (95% CI 0.57–0.87).

A sudden drop of etCO₂, 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, etCO₂ 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 etCO₂ values. In ovalbumin-sensitized rats, anaphylaxis was characterized by rapid metabolic modifications leading to anaerobic glycolysis, possibly contributing to reduced CO₂ released in the circulation and to failure of cellular energy.³⁵ Therefore, low etCO₂ 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 etCO₂ 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 etCO₂ could help establish an AHR diagnosis upon occurrence of severe arterial hypotension during GA.

The clinical value of low etCO₂ 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 etCO₂ 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 etCO₂ 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 CO₂ 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; etCO₂, end-tidal CO₂; 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 colleagues⁴² 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 in²⁹). 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 Project⁵⁵ 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.

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Declaration of interest

None declared.

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Appendix

NASA study group

Philippe Montravers MD PhD¹, Caitlin M. Gillis PhD², David A. Mancardi PhD², Michel Aubier MD PhD^{3,4}, Caroline Sauvan MD⁴, Marc Fischler MD PhD⁵, Julie Bresson MD⁵, Catherine Paugam-Burtz MD PhD⁶, Skander Necib MD⁶, Alexandre Mebazaa MD PhD⁷, Matthieu Le Dorze MD⁷, Laurent Jacob MD PhD⁸, Carole Chahine MD⁸, Hawa Keita-Meyer MD PhD⁹, Valentina Faitot MD⁹, Olivier Langeron MD PhD¹⁰, Sabrine Roche MD¹⁰, Bernard Cholley MD PhD¹¹ and Jean Mantz MD PhD^{11,*}

*Deceased

¹Département d'anesthésie-réanimation, Hôpital Bichat, AP-HP, Paris, France, ²Unit of Antibodies in Therapy & Pathology, INSERM U1222, Institut Pasteur, Paris, France, ³INSERM U1152, Université Paris Diderot Paris 7, Paris, France, ⁴Service de pneumologie et d'allergologie, Hôpital Bichat, AP-HP, DHU FIRE, Paris, France, ⁵Département d'anesthésie-réanimation, Hôpital Foch, Suresnes, France, ⁶Département d'anesthésie-réanimation, Hôpital Beaujon, AP-HP, Clichy, France, ⁷Département d'anesthésie-réanimation, Hôpital Lariboisière, AP-HP, Paris, France, ⁸Département d'anesthésie-réanimation, Hôpital Saint Louis, AP-HP, Paris, France, ⁹Département d'anesthésie-réanimation, Hôpital Louis Mourier, AP-HP, Colombes, France, ¹⁰Département d'anesthésie-réanimation, Hôpital Pitié Salpêtrière, AP-HP, Paris, France, and ¹¹Département d'anesthésie-réanimation, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

Handling editor: Hugh C Hemmings Jr

Supplementary data

NASA study group

Pr. Philippe Montravers MD PhD (Département d'anesthésie-réanimation, Hôpital Bichat, AP-HP, Paris, France); Caitlin M. Gillis PhD & David A. Mancardi PhD (Unit of Antibodies in Therapy & Pathology, INSERM U1222, Institut Pasteur, Paris, France); Pr. Michel Aubier MD PhD & Dr. Caroline Sauvan MD (Service de pneumologie et d'allergologie, Hôpital Bichat, AP-HP, Paris, France); Pr. Marc Fischler MD PhD & Dr. Julie Bresson MD (Département d'anesthésie-réanimation, Hôpital Foch, Suresnes, France); Pr. Catherine Paugam-Burtz MD PhD & Dr. Skander Necib MD (Département d'anesthésie-réanimation, Hôpital Beaujon, AP-HP, Clichy, France); Pr. Alexandre Mebazaa MD PhD & Dr. Matthieu Le Dorze MD (Département d'anesthésie-réanimation, Hôpital Lariboisière, AP-HP, Paris, France); Pr. Laurent Jacob MD PhD & Dr. Carole Chahine MD (Département d'anesthésie-réanimation, Hôpital Saint Louis, AP-HP, Paris, France); Pr. Hawa Keita-Meyer MD PhD & Dr. Valentina Faitot MD (Département d'anesthésie-réanimation, Hôpital Louis Mourier, AP-HP, Colombes, France); Pr. Olivier Langeron MD PhD & Dr. Sabine Roche MD (Département d'anesthésie-réanimation, Hôpital Pitié Salpêtrière, AP-HP, Paris, France); Pr. Bernard Cholley MD PhD & Pr. Jean Manz* MD PhD (Département d'anesthésie-réanimation, Hôpital Européen Georges Pompidou, AP-HP, Paris, France).

*Deceased