ANESTHESIOLOGY

End-tidal Carbon Dioxide for Diagnosing Anaphylaxis in Patients with Severe Postinduction Hypotension

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Anaphylaxis in the anesthetized patient can be challenging to diagnose as hypotension, the most common manifestation, has multiple causes postinduction. In addition to hypotension, low end-tidal carbon dioxide has also been suggested to be helpful in the diagnosis.

What This Article Tells Us That Is New

- From a retrospective single-center case-control study comparing low end-tidal carbon dioxide ($ETCO_2$) postinduction in hypotensive patients due to anaphylaxis compared to other causes, a low $ETCO_2$ contributed to the diagnosis of anaphylaxis. The results therefore suggest that in mechanically ventilated patients with severe postinduction hypotension, $ETCO_2$ should be considered as one of the means of distinguishing between anaphylaxis and other potential causes.

ABSTRACT

Background: Perioperative hypersensitivity reactions may be difficult to diagnose during general anesthesia. Postinduction hypotension is the most common sign but is not specific. It was recently suggested that low end-tidal carbon dioxide ($ETCO_2$) might be a marker of anaphylaxis (Ring and Messmer grades III to IV immediate hypersensitivity reactions) in hypotensive patients under mechanical ventilation. To test this hypothesis, the authors compared $ETCO_2$ in patients with a diagnosis of anaphylaxis and in patients with severe hypotension from any other cause after the induction of anesthesia.

Methods: This was a retrospective single-center case-control study in which two groups were formed from an anesthesia data warehouse. The anaphylaxis group was formed on the basis of tryptase/histamine assay data and allergy workup data recorded over the period 2010 to 2018. The control (hypotension) group consisted of all patients having experienced severe hypotension (mean arterial pressure less than 50 mmHg for 5 min or longer) with a cause other than anaphylaxis after anesthesia induction in 2017.

Results: The anaphylaxis and hypotension groups comprised 49 patients (grade III: n = 38; grade IV: n = 11) and 555 patients, respectively. The minimum $ETCO_2$ value was significantly lower in the anaphylaxis group (median [interquartile range]: 17 [12 to 23] mmHg) than in the hypotension group (32 [29 to 34] mmHg; $P < 0.001$). The area under the receiver operating characteristic curve (95% CI) for $ETCO_2$ was 0.95 (0.91 to 0.99). The sensitivity and specificity (95% CI) for the optimal cutoff value were 0.92 (0.82 to 0.98) and 0.94 (0.92 to 0.99), respectively. In multivariable analysis, minimum $ETCO_2$ was associated with anaphylaxis after adjusting for confounders and competing predictors, including arterial pressure, heart rate, and peak airway pressure (odds ratio [95% CI] for $ETCO_2$: 0.51 [0.38 to 0.68]; $P < 0.001$).

Conclusions: In case of severe hypotension after anesthesia induction, a low $ETCO_2$ contributes to the diagnosis of anaphylaxis, in addition to the classical signs of perioperative immediate hypersensitivity.

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Perioperative immediate hypersensitivity reactions are rare but must be recognized promptly and treated adequately.[1] They can be of either allergic or nonallergic origin. Life-threatening immediate hypersensitivity reactions define anaphylaxis.[1] Anaphylaxis is mainly related to allergic reactions occurring after induction of anesthesia, with neuromuscular blocking agents and antibiotics being the main causal agents.[1,2] Anaphylaxis is thus typically suspected when severe hypotension occurs within minutes of the induction of anesthesia. However, hypotension at induction can have several causes, the most frequent of which by far is an excessive dose of anesthetic.[2,3] It was recently suggested that a rapid decrease in end-tidal carbon dioxide ($ETCO_2$, known to be correlated with cardiac output during acute hemodynamic changes) is an early marker of anaphylaxis in a mechanically ventilated patient under general anesthesia.[3,4] Specifically, $ETCO_2$ was better than arterial pressure for distinguishing between anaphylaxis and mild immediate hypersensitivity reaction.[4] The ability of $ETCO_2$ to distinguish between anaphylaxis and

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nonhypersensitivity reactions in hypotensive patients has yet to be demonstrated.

To test this hypothesis, we thus compared $ETCO_2$ in adult patients with a diagnosis of anaphylaxis (either allergic or nonallergic) and in patients with severe hypotension from any other cause after the induction of anesthesia.

Materials and Methods

Study Design

This retrospective single-center study was carried out at Lille University Hospital (Lille, France). The research protocol was approved by the research ethics committee at the French Society of Anesthesia and Intensive Care (Paris, France), which confirmed that written informed consent was not required (reference: Institutional Review Board 00010254-2020-065). The study outcomes, data collection, and statistical analysis were established before the data were accessed, as described in the submission form to the research ethics committee. *Post hoc* analyses were also performed and are explicitly described as such in the Materials and Methods. In line with the French legislation, all datasets created specifically for the current work were registered with Lille University Hospital's Data Protection Officer and with the French National Data Protection Commission (Paris, France; reference: DEC19-533).

The study data were extracted from our anesthesia data warehouse, in which all intraoperative monitoring data (and particularly data from the DIANE anesthesia information management system, Bow Medical, France) have been stored since 2010.[5,6] The variables continuously monitored by DIANE (including $ETCO_2$) are measured every 30 s. Noninvasive arterial blood pressure values are measured and stored every 2.5 to 3.0 min during anesthesia induction. When necessary (see "Data Collection and Study Variables" section), additional data were directly retrieved from DIANE files and from the hospital's electronic patient records (Sillage, SIB, France).

Population

Adult (age 18 yr or older) patients having undergone general anesthesia with tracheal intubation and mechanical ventilation for surgery (including obstetric patients) were considered for inclusion in the current study (fig. 1). Emergency surgery (defined as "no delay to plan care")[7] was not included so as to avoid bias from preoperative hemodynamic instability. Two separate populations were constituted from the data warehouse.

The anaphylaxis (either allergic or nonallergic) group was formed by checking the database for the period between January 2010 and December 2018 against the study's inclusion criteria. We also checked the hospital's laboratory database for the presence of data from at least one plasma tryptase assay (ImmunoCAP Tryptase immunoassay; Thermo Fisher Scientific, Sweden) and plasma histamine assay (histamine radioimmunoassay; Beckman Coulter Inc., Immunotech, France) performed during the hospital stay that encompassed the patient's anesthesia procedure. Patients with a tryptase level above 1.2 × [basal tryptase level] + 2 $\mu g \cdot l^{-1}$ or a tryptase level greater than 25 $\mu g \cdot l^{-1}$ (when a basal level was not available) or a histamine level greater than 27.9 $nmol \cdot l^{-1}$ were selected.[8–11] Next, perioperative anaphylaxis was defined as the combination of suggestive clinical signs during anesthesia (grades III [life-threatening mono- or multivisceral signs] and IV [cardiac arrest] of the modified[1,2] Ring and Messmer[12] scale) with at least one positive assay (tryptase and/or histamine) for a blood sample taken within 2 h of the onset of the reaction. Only anaphylaxis with an available $ETCO_2$ recording during mechanical ventilation was selected for analysis. Last, skin test results were also systematically retrieved (when available) from the patients' medical records. Skin testing in our hospital is performed by prick tests, followed by intradermal tests, in accordance with the recommendations of the French Society of Anesthesia and Intensive Care and the French Society of Allergology.[13] Since our goal was to characterize anaphylaxis, whether allergic or nonallergic, a positive skin test was not required for patient inclusion.

The (nonanaphylaxis) hypotension group comprised patients with severe hypotension (mean arterial pressure [MAP] values less than 50 mmHg for at least 5 min) during the 30 min after induction of general anesthesia. This MAP cutoff was used to select hypotension episodes of the same order of magnitude as in patients with anaphylaxis. In addition, the 50-mmHg cutoff and the 5-min duration correspond to one of the best-validated definitions of severe intraoperative hypotension, based on its proven association with adverse postoperative outcomes.[14] Given that we had to examine each selected individual DIANE file to validate the study variables (see next section), we chose to extract warehouse data collected in a single year only (arbitrarily, 2017). Patients with hypotension due to anaphylaxis (thus already belonging to the anaphylaxis group) and patients for whom $ETCO_2$ recordings during mechanical ventilation were not available were excluded (fig. 1).

Data Collection and Study Variables

For all included patients, general characteristics (sex, age, weight, American Society of Anesthesiologists [ASA] Physical Status), the hypnotic used for induction and its dose, and the ventilation settings were directly obtained from the data warehouse. The time interval between induction and onset of hypotension (measured from the injection of the first induction drug to the first MAP less than 50 mmHg), the duration of hypotension (from the first MAP measurement less than 50 mmHg to the first measurement 50 mmHg or greater), and the recording of arterial blood pressure, heart rate (HR), peak airway pressure (P_{MAX}), and $ETCO_2$ during the hypotension episode (from 1 min before to 5 min after the start) were also obtained from the warehouse.

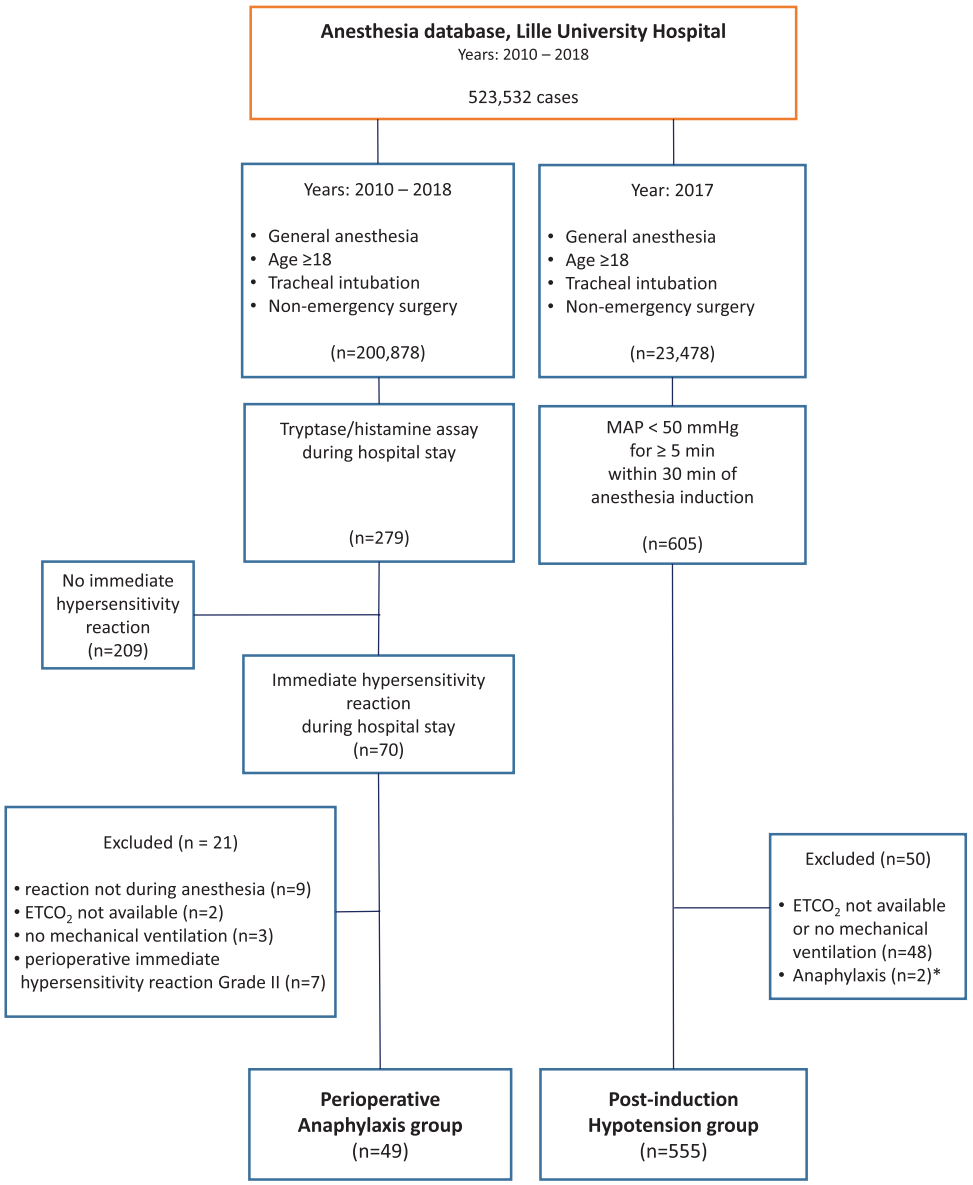

Fig. 1. Study flow chart. *Already in the anaphylaxis group. $ETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure.

We then validated the study data in order to avoid any misinterpretation of values of interest, especially of low $ETCO_2$ values—particularly when the patient was still being ventilated with a face mask or if the ventilator circuit had been disconnected. Hence, we reviewed the DIANE records of (1) all study participants in the anaphylaxis group, and (2) participants in the hypotension group for whom (i) at least one $ETCO_2$ value recorded during the episode of hypotension was less than 30 mmHg, (ii) the maximum HR value from electrocardiogram monitoring differed from maximum HR from oximetry monitoring by more than 5 beats/min, or (iii) the maximum P_{MAX} value differed by more than 5 cm H_2O from the mean of values recorded during the hypotension episode. The highest values of HR and P_{MAX} and the lowest values of MAP and $ETCO_2$ were then recorded for each patient in each group.

Statistical Analysis

We did not perform a power calculation because our goal was to analyze as many patients with intra-anesthetic anaphylaxis as possible. Quantitative variables were described as the mean ± SD or the median [interquartile range], depending on their distribution. The normality of the distributions was checked graphically and by applying the Shapiro–Wilk test. Qualitative variables were described as number

(percentage). Intergroup comparisons used a two-tailed independent *t* test or the Mann–Whitney U test for quantitative variables or the chi-square test or Fisher exact test for qualitative variables, depending on the data distribution and the sample size. The ability of $ETCO_2$ to differentiate between anaphylaxis and severe postinduction hypotension (of any other cause) was quantified by plotting a receiver operating characteristic curve from values obtained in patients with anaphylaxis and patients with severe postinduction hypotension. The area under the receiver operating characteristic curve (95% CI) was calculated, and the optimal cutoff was defined by maximization of the Youden index. The same analysis was performed for arterial blood pressure, and areas under the receiver operating characteristic curve were compared using DeLong's method.

In response to peer review, a model-based approach was performed *post hoc* to estimate the discriminant value of $ETCO_2$ adjusted for differences in group selection and competing covariates. The univariable association between potential confounding variables (demographics, ASA Physical Status, the hypnotic (with dose) used for induction, and ventilation settings), competing predictors (MAP, HR, P_{MAX}, duration of hypotension, and $ETCO_2$), and the outcome (anaphylaxis) was first assessed using binary logistic regression. Then, two separate multivariable predictive models of anaphylaxis were created with all covariables forced in the model, except (model 1) and with (model 2) $ETCO_2$, into backward stepwise logistic regressions. Backward selection was used to minimize the number of predictors, as the study focused on $ETCO_2$. Analysis was restricted to complete cases. For each model (with and without $ETCO_2$), the maximum Akaike information criterion was used to determine the final model. Odds ratios and their associated 95% CIs were reported for each covariable of the final logistic regression models. The two models were compared using the likelihood-ratio test, and the association between $ETCO_2$ and anaphylaxis adjusted on other covariables was obtained from model 2. As the variable "propofol dose" had a significant amount of missing data (mainly due to the use of other drugs or mode of anesthesia induction), an additional multivariable predictive model (model 3), excluding this covariable, was created. Sensitivity analyses were conducted by repeating the multivariable analyses with (1) variables selected on the basis of their univariable association with anaphylaxis ($P \leq 0.1$), and (2) all variables (except propofol dose) forced in the multivariable model.

Several *post hoc* analyses were also conducted after the results of the univariable analysis or in response to peer review. (1) To enhance the clinical relevance of the comparison of $ETCO_2$ and MAP between anaphylaxis and (nonanaphylaxis) hypotension, the anaphylaxis group was limited to patients without cardiac arrest (*i.e.*, Ring and Messmer grade III only). (2) Because the International Suspected Perioperative Allergic Reaction group consensus scoring for suspected anaphylaxis defined severe hypotension as systolic blood pressure (SBP) less than 60 mmHg,[15] the anaphylaxis group was also compared for $ETCO_2$ and SBP to the hypotension group restricted to patients with a minimal SBP less than 60 mmHg (instead of MAP less than 50 mmHg). (3) The minimum values of $ETCO_2$ and MAP were compared between the two groups, with the anaphylaxis group restricted to patients with a positive skin test (*i.e.*, proven allergic anaphylaxis).

The threshold for statistical significance was set to $P < 0.05$. Analyses were conducted using R software (version 3.6.3; R Core Team, Austria).[16]

Results

Study Participants in the Anaphylaxis Group

Of 523,532 patients anesthetized between 2010 and 2018 in our hospital, 200,878 met the criteria for further screening for anaphylaxis (fig. 1). Seventy of these patients had tryptase/histamine assay results for the hospital stay with the suspected immediate hypersensitivity reaction (all Ring and Messmer grades). After a data review, we considered that 61 patients had experienced a perioperative immediate hypersensitivity reaction. Data on $ETCO_2$ and mechanical ventilation were not available for 5 of the 61 patients, and 7 cases had a grade II hypersensitivity reaction (no grade I). Hence, 49 patients were included in the anaphylaxis group (grade III: n = 38; grade IV: n = 11, of which 2 were inaugural cardiac arrests). The characteristics of the 49 included patients are summarized in table 1, and the clinical and hemodynamic signs and the outcomes of anaphylaxis by severity are summarized in table 2. Median [interquartile range] plasma tryptase concentration was 67 [34 to 134] $\mu g \cdot l^{-1}$ (no missing data). The causal agent was identified in 34 patients (neuromuscular blocking agent: 26; antibiotic: 4; gelatin: 2; latex: 2). Detailed characteristics of the 49 cases are reported in Supplemental Digital Content 1 (http://links.lww.com/ALN/C774). All but three of the anaphylaxis cases occurred within 30 min of induction of anesthesia (the arbitrarily chosen time limit for inclusion in the hypotension group).

Hypotension Group

Of the 23,478 patients meeting the inclusion criteria for further screening for hypotension in 2017, 605 (2.6%) were found to have experienced severe postinduction hypotension. Forty-eight of these were excluded because hypotension occurred before tracheal intubation and mechanical ventilation, and two were excluded because the hypotension was due to anaphylaxis (these patients were already included in the anaphylaxis group, according to the design of the study; minimum $ETCO_2$ for the two patients: 11 and 24 mmHg). Hence, $ETCO_2$ was analyzed in 555 patients (fig. 1). The characteristics of these patients are presented in table 1.

Univariable Analysis of $ETCO_2$ and MAP in Patients with Anaphylaxis and Patients with Postinduction Hypotension

The minimum values of both $ETCO_2$ and MAP were significantly lower in the anaphylaxis group than in the

Table 1. Characteristics of Patients with Anaphylaxis and Postinduction Hypotension

Variable	Missing Values Anaphylaxis	Missing Values Hypotension	Anaphylaxis (n = 49)	Hypotension (n = 555)	*P* Value
Age (yr)	—	—	57 ± 14	57 ± 16	0.997
Men, n (%)	—	—	23 (47%)	257 (46%)	> 0.999
Weight (kg)	1	16	80 ± 19	75 ± 20	0.106
ASA Physical Status, n (%)	—	—			0.075
I			4 (8%)	131 (24%)	
II			26 (53%)	270 (49%)	
III			18 (37%)	146 (26%)	
IV			1 (2%)	8 (1%)	
Induction agent (propofol [bolus]/propofol target controlled infusion/other)	—	—	41/6/2	456/83/16	0.748
Propofol (mg · kg^{-1})*	1	16	2.3 ± 1.0	2.6 ± 1.2	0.074
Induction-hypotension delay (min)	3†	—	11 [7–18]	15 [9–21]	0.076
Duration of hypotension (min)	—	—	10 [5–15]	8 [7–12]	0.300
Minute volume (l)	1	3	6.4 ± 1.2	6.1 ± 1.2	0.116
Tidal volume (ml)	1	2	469 ± 65	445 ± 68	0.019
Ventilatory frequency (cycles · min^{-1})	0	1	14 ± 2	14 ± 2	0.823
Minimum MAP (mmHg)	—	—	34 [26–42]	42 [38–45]	< 0.001
Maximum HR (beats · min^{-1})	2‡	1	108 ± 28	73 ± 17	< 0.001
Maximum P_{MAX} (cm H_2O)	2	1	33 ± 10	20 ± 6	< 0.001
Minimum $ETco_2$ (mmHg)	—	—	17 [12–23]	32 [29–34]	< 0.001

Data are quoted as the number (percentage), mean ± SD, or median [interquartile range].

*From 41 (anaphylaxis), and 456 (hypotension) patients who received a bolus of propofol at induction. †Three intraoperative anaphylaxis cases not included in the analysis. ‡Two inaugural cardiac arrests not included in the analysis.

ASA, American Society of Anesthesiologists Physical Status; $ETco_2$, end-tidal carbon dioxide; HR, heart rate; MAP, mean arterial pressure; P_{MAX}, peak airway pressure.

hypotension group ($ETco_2$: 17 [12 to 23] *vs.* 32 [29 to 34] mmHg, respectively; $P < 0.001$; MAP: 34 [26 to 42] *vs.* 42 [38 to 45] mmHg, respectively; $P < 0.001$), as shown in figure 2. The receiver operating characteristic curves representing the ability of $ETco_2$ and MAP to discriminate between anaphylaxis and postinduction hypotension are shown in figure 3. The resulting areas under the receiver operating characteristic curve (95% CI) for $ETco_2$ was high (0.95 [0.91 to 0.99]) and was significantly higher ($P < 0.001$) than that obtained for MAP (0.71 [0.61 to 0.81]). The best $ETco_2$ cutoff value for identifying anaphylaxis was 25 mmHg (sensitivity [95% CI], 0.92 [0.82 to 0.98]; specificity, 0.94 [0.92 to 0.99]). The best MAP cutoff value for identifying anaphylaxis was 37 mmHg (sensitivity, 0.63 [0.45 to 0.80]; specificity, 0.80 [0.66 to 0.93]).

Table 2. Clinical and Hemodynamic Signs, and Outcomes in Patients with an Intraoperative Anaphylaxis, by Severity

Signs/Outcomes	Grade III (n = 38)	Grade IV (n = 11)
Erythema, n (%)	9 (24%)	0 (0%)
Maximum HR (beats · min^{-1})*	112 ± 28	97 ± 26
Minimum MAP (mmHg)	36 [30–45]	0 [0–24]
Maximum P_{MAX} (cm H_2O)†	31 ± 10	37 ± 8
Minimum $ETco_2$ (mmHg)	19 [14–24]	9 [7–12]
Surgery canceled, n (%)	35 (92%)	10 (91%)
Admission to the ICU, n (%)	30 (79%)	10 (91%)
Death, n (%)	0 (0%)	1 (9%)
Plasma tryptase (µg · l^{-1})	64 [33–111]	132 [43–157]

Data are quoted as the number (percentage), mean ± SD, or median [interquartile range].

*After exclusion of two inaugural cardiac arrests. †One missing value in each group.

$ETco_2$, end-tidal carbon dioxide; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; P_{MAX}, peak airway pressure.

Multivariable Analysis of the Association between $ETco_2$ and Anaphylaxis

Univariable associations between potential confounders, predictors, and anaphylaxis are shown in table 3. Covariables, except for $ETco_2$, were entered into a backward stepwise logistic regression to create a first predictive model (model 1). Predictors retained in this first model significantly associated with anaphylaxis were minimum MAP, maximum HR, and maximum P_{MAX}, as shown in table 3. A second model was created by adding $ETco_2$ to the variables entered in the model 1. In this second model, low $ETco_2$ was found to be an independent predictor of anaphylaxis (odds ratio [95% CI] for $ETco_2$: 0.51 [0.38 to 0.68]; $P < 0.001$) as well as duration of hypotension and maximum HR (table 3). The two models were compared using the likelihood ratio test, and model 2 (including $ETco_2$) fit the data significantly better than model 1 (without $ETco_2$; $P < 0.001$). A model of multivariable logistic regression analysis excluding the "propofol dose" variable (to minimize missing data [131/604, mainly due to agents or modes of induction other than bolus propofol; table 1]) also found low $ETco_2$ to be an independent predictor of anaphylaxis (odds ratio [95% CI] for $ETco_2$: 0.61 [0.50 to 0.74];

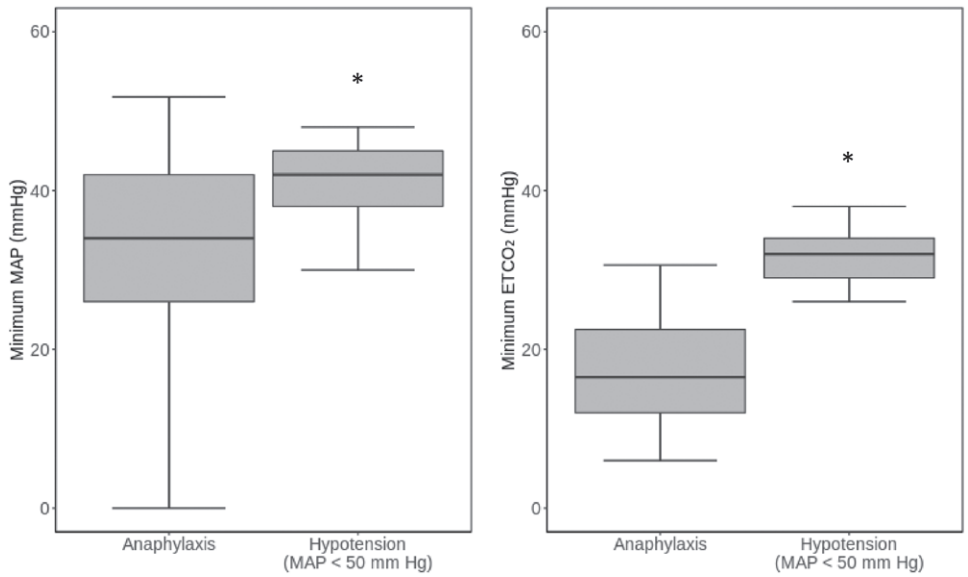

Fig. 2. The minimum mean arterial pressure (MAP, in mmHg) and minimum end-tidal carbon dioxide ($ETco_2$, in mmHg) in patients with anaphylaxis (n = 49) *versus* patients with postinduction hypotension (MAP less than 50 mmHg, n = 555). MAP value used for grade IV reactions was 0 mmHg in 7 of 11 patients. In the four remaining patients, the lowest value was 21, 26, 31, and 36 mmHg. *Box plots* represent the median [interquartile range]. *Upper and lower whiskers* represent 10th and 90th percentiles. *$P < 0.001$ *versus* anaphylaxis.

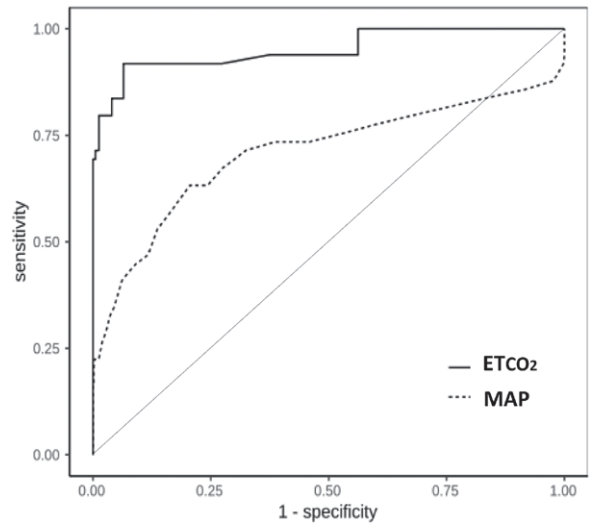

Fig. 3. Receiver operating characteristic curves representing the respective abilities of the minimum end-tidal carbon dioxide ($ETco_2$) and the minimum mean arterial pressure (MAP) to differentiate between anaphylaxis (n = 49) and postinduction hypotension (n = 555). The area under the receiver operating characteristic curve (95% CI) was 0.95 (0.91 to 0.99) for $ETco_2$ and 0.71 (0.61 to 0.81) for MAP ($P < 0.001$ *vs.* $ETco_2$).

$P < 0.001$; missing data: n = 24 of 604; table 3). Additional models restricted to variables that had a P value 0.1 or less through univariable analyses found similar results for $ETco_2$ (odds ratio [95% CI]: 0.51 [0.38 to 0.68]; $P < 0.001$ [missing data: n = 131 of 604 observations]; same model without propofol: odds ratio [95% CI]: 0.65 [0.56 to 0.76]; $P < 0.001$ [missing data: n = 7 of 604 observations]). A final analysis with all variables (except propofol dose) forced in the same model found an odds ratio (95% CI) for $ETco_2$ of 0.60 (0.49 to 0.73); $P < 0.001$ (missing data: n = 24 of 604 observations; Supplemental Digital Content 2, http://links.lww.com/ALN/C775).

Sensitivity Analyses

The minimum values of both $ETco_2$ and MAP were lower in the anaphylaxis group limited to patients without circulatory arrest (*i.e.*, grade 3 anaphylaxis only, n = 38) than in the hypotension group ($ETco_2$: 19 [14 to 24] *vs.* 32 [29 to 34] mmHg, respectively; $P < 0.001$; MAP: 36 [30 to 45] *vs.* 42 [38 to 45] mmHg, respectively; $P = 0.007$).

The anaphylaxis group was compared to the hypotension group restricted to patients with a minimal SBP less than 60 mmHg (n = 226). As with MAP, the minimum values of both $ETco_2$ and SBP were lower in the anaphylaxis group than in the hypotension group ($ETco_2$: 17 [12 to 23] *vs.* 30 [27 to 33] mmHg, respectively; $P < 0.001$; SBP: 44 [38 to 55] *vs.* 53 [48 to 57] mmHg, respectively;

Table 3. Risk Factors for Anaphylaxis and Backward Stepwise Logistic Regression Models

	Univariate Odds Ratio (95% CI)	*P* Value	Model 1 (without $ETCO_2$) Odds Ratio (95% CI)	*P* Value	Model 2 (with $ETCO_2$) Odds Ratio (95% CI)	*P* Value	Model 3 (without Propofol) Odds Ratio (95% CI)	*P* Value
Age (yr)	1.00 (0.98–1.02)	0.997						
Men	1.03 (0.57–1.84)	0.932						
Weight (kg)	1.01 (1.00–1.02)	0.113						
ASA Physical Status								
I								
II	3.15 (1.08–9.22)	0.036						
III	4.04 (1.33–12.24)	0.014						
IV	4.09 (0.41–41.02)	0.231						
Propofol (mg · kg^{-1})*	0.76 (0.55–1.05)	0.102						
Tidal volume (ml)	1.00 (1.00–1.01)	0.022						
Duration of hypotension (min)	1.03 (1.00–1.06)	0.080	1.00 (0.95–1.06)	0.995	1.13 (1.02–1.24)	0.014	1.06 (1.00–1.13)	0.036
Minimum MAP (mmHg)	0.90 (0.87–0.93)	< 0.001	0.95 (0.91–1.00)	0.041	1.09 (0.99–1.21)	0.088		
Maximum HR (beats · min^{-1})†	1.07 (1.05–1.09)	< 0.001	1.06 (1.04–1.08)	< 0.001	1.06 (1.02–1.11)	0.004	1.04 (1.01–1.06)	0.009
Maximum P_{MAX} (cm H_2O)	1.19 (1.14–1.24)	< 0.001	1.13 (1.07–1.19)	< 0.001	1.08 (0.98–1.19)	0.116	1.10 (1.02–1.18)	0.014
Minimum $ETCO_2$ (mmHg)	0.58 (0.51–0.67)	< 0.001			0.51 (0.38–0.68)	< 0.001	0.61 (0.50–0.74)	< 0.001

Model 1: all covariates forced in the model, except end-tidal carbon dioxide ($ETCO_2$). Model 2: with all covariates. Model 3: with all covariates, except propofol (see Materials and Methods). Models 1 and 2: 131 of 604 observations deleted due to missingness. Model 3: 24 of 604 observations deleted due to missingness.

*n = 40 (anaphylaxis), and 440 (hypotension) patients who received a bolus of propofol at induction. †After exclusion of two inaugural cardiac arrests.

ASA, American Society of Anesthesiologists Physical Status; HR, heart rate; MAP, mean arterial pressure; P_{MAX}, peak airway pressure.

$P = 0.001$). The area under the receiver operating characteristic curve (95% CI) for $ETCO_2$ (0.93 [0.88 to 0.98]) was also significantly higher ($P < 0.001$) than that obtained for SBP (0.65 [0.54 to 0.76]).

The minimum values of both $ETCO_2$ and MAP were lower in the anaphylaxis group restricted to patients with a positive skin test (n = 34) than in the hypotension group ($ETCO_2$: 18 [12 to 24] *vs.* 32 [29 to 34] mmHg, respectively; $P < 0.001$; MAP: 34 [29 to 45] *vs.* 42 [38 to 45] mmHg, respectively; $P = 0.001$). The corresponding area under the receiver operating characteristic curve (95% CI) for $ETCO_2$ was high (0.95 [0.90 to 0.99]) and significantly higher ($P < 0.001$) than that obtained for MAP (0.67 [0.54 to 0.80]).

Discussion

Our current results demonstrated that low $ETCO_2$ is a sensitive marker of anaphylaxis in adult patients having developed postinduction hypotension during nonemergency surgery. Moreover, low $ETCO_2$ was associated with anaphylaxis after adjusting for MAP, HR, and P_{MAX}. The results therefore suggest that when postinduction hypotension arises in a mechanically ventilated patient, $ETCO_2$ should be considered, in addition to classical signs of anaphylaxis, as a means of distinguishing an anaphylaxis from the other most frequent causes of hypotension and thus helping to initiate appropriate, early treatment.

Gouel-Chéron *et al.* first hypothesized in 2017 that a low $ETCO_2$ could be a useful, early, independent marker of anaphylaxis.[4] In fact, the researchers showed that $ETCO_2$ distinguished between grades III to IV and grades I to II immediate hypersensitivity reaction without an overlap of the interquartile ranges and an area under the receiver operating characteristic curve (95% CI) of 0.92 (0.79 to 1.0). Our study extended these results to a comparison with patients with hypotension due to other causes after anesthesia induction. Interestingly, the $ETCO_2$ values recorded during anaphylaxis are similarly low in the two studies (grade III: 19 [17 to 24] and 19 [14 to 24] mmHg, respectively; grade IV: 11 [10 to 18] and 9 [7 to 12] mmHg, respectively). It should be noted, however, that the best cutoff value determined in the current work should not be used to discriminate anaphylaxis from nonanaphylaxis in the general population, because it was obtained in the specific setting of isolated case–control groups.

In this study, severe hypotension was defined as MAP less than 50 mmHg for at least 5 min.[14] However, the literature on anaphylaxis is often based on SBP values, and the International Suspected Perioperative Allergic Reaction group consensus scoring for suspected anaphylaxis recently defined severe hypotension as SBP less than 60 mmHg.[15] We used MAP values because they are considered to be more accurate than SBP when measured with an oscillometric technique—by far the most widely used technique for measuring arterial pressure during anesthesia induction in routine practice.[17] In any case, the sensitivity analysis conducted using SBP (less than 60 mmHg) provided results similar to those obtained with MAP less than 50 mmHg. This is consistent with previous data showing that changes in SBP or MAP (measured invasively) induced by volume expansion or vasopressors are similarly correlated with simultaneous changes in cardiac output.[18,19]

Our results show that most episodes of severe hypotension after anesthesia induction are—at least in the context of elective surgery—accompanied by normal or moderately decreased $ETCO_2$ values (fig. 2) and, presumably, by unaffected or moderately reduced cardiac output. Indeed, rapid changes in $ETCO_2$ in the absence of acute modifications in ventilation or cell metabolism are highly suggestive of parallel variations in cardiac output.[20,21] Tidal volume, but not minute ventilation, was slightly higher in patients with *versus* without anaphylaxis (table 1), but the difference appears too small to be of clinical significance. It has repeatedly been shown that changes in $ETCO_2$ are correlated with changes in cardiac output during fluid challenges and passive leg raising in mechanically ventilated patients.[22] This hemodynamic profile—severe hypotension with relatively unaffected cardiac output—has recently been shown to be typical of postinduction hypotension,[23] and contrasts with that suspected in anaphylaxis in most of our patients, *i.e.*, a severe decrease in cardiac output. Observations in human anaphylaxis showed that hypotension is initially associated with a reduction in systemic vascular resistance. With compensatory tachycardia, cardiac output is maintained or increased.[24,25] However, with increasing severity of anaphylaxis, maldistribution and hypovolemia lead to reduced venous return and cardiac output. Raised intrathoracic pressures from positive pressure ventilation, with or without bronchospasm, further impair cardiac filling in this setting.[24] Myocardial depression may also occur during anaphylaxis but is not the primary mechanism in humans.[24,25] A reduction in $ETCO_2$ has been proposed as a clinical feature suggesting inadequate perfusion during anaphylaxis.[24] The main value of low $ETCO_2$ in this setting may therefore be to prompt adequate treatment of anaphylaxis.

Any severe decrease in cardiac output, whatever the cause, is expected to result in a profound drop in $ETCO_2$ Our study design prevented us from drawing definitive conclusions about potential confounders. Our results showed that of the 23,478 anaesthetized patients meeting our inclusion criteria in 2017, there were 557 patients with hypotension at induction and interpretable $ETCO_2$ data (fig. 1). After reviewing (*post hoc* analysis) all cases with $ETCO_2$ less than 30 mmHg (N = 154 of 557 [27.6%]), we found no evidence for any "specific" diagnosis (with the exception of the two patients with anaphylaxis). These episodes were thus likely "nonspecific" postinduction hypotension related to relative anesthesia overdose. A sudden, profound drop in both MAP and $ETCO_2$ after induction of anesthesia is therefore a very unusual event. Even though other causes of severe hypotension, including other life-threatening complications, cannot be ruled out, our data show that in case of severe postinduction hypotension, a low $ETCO_2$ dramatically increases the likelihood of anaphylaxis.

Bronchospasm is another frequent manifestation of anaphylaxis and usually alters the capnogram. By impairing expiratory flow, bronchospasm may accentuate the decrease in $ETCO_2$ because the latter no longer reflects the alveolar carbon dioxide concentration.[26] Conversely, severe bronchospasm leads to alveolar hypoventilation and then hypercapnia. A marked increase in airway resistance usually translates into an increase in P_{MAX} during mechanical ventilation. Accordingly, P_{MAX} in patients with anaphylaxis was higher than in the hypotension group. This may have contributed to decreased $ETCO_2$ in some patients. Importantly, the multivariable logistic regression analyses showed that both increased P_{MAX} and decreased $ETCO_2$ were independently associated with anaphylaxis.

Anaphylaxis may occur very early after the beginning of anesthesia induction. Accordingly, in our study, hypotension occurred before the onset of mechanical ventilation in some patients. This situation limits the clinical relevance of our results, as shown in figure 1; three anaphylaxis cases were excluded from the main analysis because manual ventilation interfered with our interpretation of the $ETCO_2$ values. This phenomenon was also observed in a similar proportion of the hypotension group, as shown in figure 1.

Our study's main limitation was its retrospective, single-center design. Hence, the sample size was not prespecified, and we sought to include as many patients as possible in the anaphylaxis group while achieving the best compromise between sensitivity and specificity of diagnosis. Baseline tryptase levels were not available for all patients; the presence of "false-positive" anaphylaxis in our study group cannot therefore be entirely ruled out. However, this possibility was minimized by our definition of an elevated isolated serum tryptase (greater than 25 $\mu g \cdot l^{-1}$)—a cutoff associated with low sensitivity but high specificity (from 74 to 100%) in previous studies of immediate hypersensitivity reactions.[11] Histamine concentration was dramatically increased in some patients, which was likely due to hemolysis of the collected blood. However, this did not affect the selection of patients since they were all included on tryptase concentration alone. Of the 49 patients in the study, skin tests were unavailable in 12, and inconclusive in 3. Our study thus characterizes anaphylaxis, not specifically allergic anaphylaxis. We did not compare the doses of vasoactive drugs used to treat hypotension. A poor or unsustained response of hypotension to standard doses of sympathomimetics is a component of the clinical score system recently proposed by the International Suspected Perioperative Allergic Reaction group for postevent diagnostic evaluation.[15] In fact, such a comparison was difficult to model: most patients in the hypotensive group received various doses of ephedrine and/or phenylephrine and/or norepinephrine, whereas most patients in the anaphylaxis group received epinephrine (as the first vasoactive drug or after ephedrine), precisely because anaphylaxis was suspected. The association between duration of hypotension and anaphylaxis in our study likely reflects poor response to vasoactive drugs.

In conclusion, the clinical diagnosis of a perioperative anaphylaxis may be challenging because the symptoms are nonspecific. The most common scenario for suspected anaphylaxis is the occurrence of severe hypotension in the minutes after induction of anesthesia. In the current study, low $ETCO_2$ was a sensitive, specific, independent marker of anaphylaxis. Our results therefore suggest that in mechanically ventilated patients with severe postinduction hypotension, $ETCO_2$ should be considered as one of the means of distinguishing between anaphylaxis and other potential causes of hypotension.

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Competing Interests

The authors declare no competing interests.

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