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Letter to the Editor

Overweight and bronchospasm during general anaesthesia: An association with heterogeneous mechanisms

Dear Editor,

Anaphylaxis during anaesthesia is a life-threatening condition with an estimated incidence of approximately 1:10,000.¹ Bronchospasm during general anaesthesia is classically associated with an IgE-mediated reaction but other underlying mechanisms have been described during general anaesthesia.² It is well known that being overweight is associated with an increased risk of airway hyperresponsiveness (AHR). The aim of this study is to determine whether being overweight is associated with an increased risk of bronchospasm or non-IgE-mediated bronchospasm during general anaesthesia and describe the clinical characteristics of patients with bronchospasm.

A retrospective study was conducted between 2014 and 2018 at the University Hospital Centre of Toulouse. The inclusion criteria were: 1. A history of adverse reactions compatible with anaphylaxis during general anaesthesia, 2. Skin tests performed with the drugs used during general anaesthesia and 3. Body mass index (BMI) appearing on their medical record. The study was approved by the Institutional Review Board of the French society for Respiratory Medicine – Société de Pneumologie de Langue Française – (CEPRO# 2019-004).

Skin tests were performed according to the EAACI guidelines.³ Allergy to drugs was defined as a positive skin test and/or specific IgE ≥ 0.35 kU/ml. Bronchospasm was based on wheezing detected by auscultation. Additionally, bronchospasm was further confirmed by an increase in peak airway pressure >30 cmH₂O with visible up-slope on the capnogram due to increased airway resistance, particularly in cases with non-audible bronchospasm. Isolated bronchospasm was defined as bronchospasm with no skin symptoms and no haemodynamic impairment. Non-IgE mediated bronchospasm was established when skin tests and specific IgE were negative for all the drugs. The severity of the reaction was graded according to Ring and Messmer classification.⁴ A significant increase in serum tryptase during the reaction was calculated as at least $2 + 1.2 \times$ baseline tryptase level.^{5,6} Study participants were divided into two groups based on their BMI. Overweight and normal weight were defined as BMI ≥ 25 kg/m² and BMI <25 kg/m², respectively.

Data were expressed as numbers and percentages for categorical data and median and interquartile range [IQR] for continuous data. Continuous data and categorical data were compared using the Mann-Whitney U test and Fisher's exact test, respectively. Logistic

regression analyses were carried out, using bronchospasm as the dependent variable. A p-value of <0.05 was considered significant.

Among the 115 patients who met the inclusion criteria, 62 (53.9%) patients were overweight and 53 (46.1%) were normal weight (Table 1). The number of patients with bronchospasm during anaesthesia was statistically higher in the overweight group (31 (50%)) compared to the normal-weight group (12 (22.6%)) ($p = 0.0036$). As a result, overweight patients were more likely to be treated with short-acting beta agonists (SABAs) during general anaesthesia compared to normal-weight patients (14 [22.6%] patients vs 4 [8.3%] patients, respectively; $p = 0.038$). Skin symptoms were observed more frequently in normal-weight patients (38 [71.7%]) compared to overweight patients (31 [50.0%]) ($p = 0.02$). Time to reaction was similar between groups and reaction mainly occurred at induction.

In univariate analysis, skin symptoms were inversely associated with bronchospasm (odds ratio [OR] 0.4 [95% confidence interval (CI) 0.2–0.89] [$p = 0.024$]) (Table 2). In logistic regression, no association was observed between skin symptoms and bronchospasm. Although there was no association between NMBD use and bronchospasm in univariate analysis, a statistically significant association was observed between NMBD use and bronchospasm in logistic regression (OR: 4.0 [1.1–14.1]; $p = 0.03$). Being overweight was heavily associated with bronchospasm with an OR of 3.4 [1.5–7.7] in both univariate ($p = 0.0031$) and 3.0 [1.3–7.0] multivariate analysis ($p = 0.01$). Interestingly, only the overweight group was associated with non-IgE mediated bronchospasm (OR of 9.6 [2.1–44.0] in both univariate [$p = 0.0035$] and 11.5 [2.4–55.3] multivariate analysis [$p = 0.0023$]).

This study has identified that being overweight is an independent risk factor of bronchospasm, particularly non-IgE-mediated bronchospasm, during general anaesthesia. In a prospective study, Tassoudis *et al.* found that the incidence of bronchospasm was higher in obese patients compared to non-obese patients undergoing elective laparoscopic surgery.⁷ However, no skin tests were performed. In NAP6, a large prospective study of anaphylaxis related to anaesthesia, the authors also highlighted that bronchospasm is more frequent in obese/morbidly obese patients.¹ However, an association between bronchospasm and overweight patients is not described in this study. In the NAP6 study, a high frequency of bronchospasm during general anaesthesia is observed but the underlying mechanism is not specifically studied. Mechanical causes such as aspiration with airway irritation and ventilator problems could explain bronchospasm during anaesthesia in obese patients. However, a difficult intubation does not contribute to an increased rate of bronchospasm in obese patients.⁸ In the NAP6 study, the authors

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Table 1

Patients' characteristics recorded for a reaction during general anaesthesia based on body mass index (BMI).

	BMI <25 kg/m ² n = 53	BMI ≥25 kg/m ² n = 62	p
Age	50.0 [34.5–65.5]	54 [43.3–65.8]	0.40
Female	34 (64.2)	37 (59.7)	0.70
Active and former smokers	18 (34.0)	21 (33.9)	1.00
Atopy	17 (32.1)	20 (32.3)	1.00
History of asthma	9 (17.0)	14 (22.6)	0.49
Details of anaesthesia			
Emergency surgery	11 (20.7)	12 (19.3)	1.00
NMBD use	43 (81.1)	51 (82.2)	1.00
Propofol use	42 (79.2)	49 (79.0)	1.00
Benzodiazepine use	47 (88.7)	53 (85.5)	0.57
Morphine use	45 (84.9)	52 (83.9)	1.00
Antibiotics use	29 (54.7)	32 (51.6)	0.85
Characteristics of the reaction			
Grades [†]			0.15
1	13 (24.5)	10 (16.1)	
2	20 (37.7)	17 (27.4)	
3	18 (34.0)	34 (54.8)	
4	2 (3.8)	1 (1.6)	
Bronchospasm	12 (22.6)	31 (50.0)	0.0036
Bronchospasm at induction	10/12 (83.3)	25 (80.6)	1.00
Isolated bronchospasm	0/12 (0.0)	4/31 (12.9)	0.56
Skin symptoms	38 (71.7)	31 (50.0)	0.022
SABA use	4 (8.3)	14 (22.6)	0.038
Adrenaline use	23 (43.4)	32 (51.6)	0.60
Time to reaction	n = 48	n = 51	0.18
Induction	31 (64.6)	42 (82.4)	
During surgery	9 (18.8)	3 (5.9)	
Recovery room	4 (8.3)	3 (5.9)	
After surgery	4 (8.3)	3 (5.9)	
Allergy investigation			
Allergy to drugs	21 (39.6)	32 (51.6)	0.26
Allergy to NMBD	10 (18.9)	20 (32.2)	0.14
Allergy to propofol	0 (0.0)	1 (1.6)	1.00
Allergy to morphine	1 (1.9)	2 (3.2)	1.00
Allergy to antibiotics	8 (15.1)	9 (14.5)	1.00
Allergy to latex	2 (3.7)	0 (0)	1.00
Baseline serum tryptase	4.2 [3.2–5.7]	4.9 [3.4–6.7]	0.29
Significant increase in serum tryptase	n = 23	n = 29	0.74
‡(total population)	17 (73.9)	23 (79.3)	
Significant increase in serum tryptase	n = 9	n = 18	0.63
‡(patients with bronchospasm)	8 (88.9)	14 (77.8)	

[†] According to Ring and Messmer.⁴

[‡] A significant increase in serum tryptase during the reaction was calculated as at least 2 + 1.2 × baseline tryptase level. SABA, short-acting beta agonist; NMBD, neuromuscular blocking drug. Values in bold indicate significant difference.

Table 2

Univariate analysis and logistic regression according to the presence of bronchospasm during general anaesthesia.

	Univariate analysis n = 115			Logistic regression n = 115		
	OR	95% CI	p	OR	95% CI	p
Bronchospasm (n = 43)						
History of asthma	1.7	0.7–4.3	0.25	1.7	0.6–4.7	0.29
Overweight	3.4	1.5–7.7	0.0031	3.0	1.3–7.0	0.01
NMBD use	3.0	0.9–9.7	0.06	4.0	1.1–14.1	0.03
Skin symptoms	0.4	0.2–0.89	0.024	0.4	0.2–1.0	0.06
Non-IgE mediated bronchospasm (n = 19)						
History of asthma	2.9	0.99–8.6	0.051	3.2	1.0–10.5	0.06
Overweight	9.6	2.1–44.0	0.0035	11.5	2.4–55.3	0.0023
NMBD use	1.2	0.3–4.7	0.76	1.4	0.3–5.9	0.69
Skin symptoms	1.2	0.4–3.2	0.76	2.0	0.7–6.3	0.22

95%CI, 95% confidence interval; NMBD, neuromuscular blocking drug; OR, odds ratio. Values in bold indicate significant difference.

suggest that suxamethonium is associated with bronchospasm/high airway pressure and rocuronium with both bronchospasm and haemodynamic impairment in the general population. Gouel-Chéron *et al.* also described NMBDs involvement in bronchospasm with both IgE- and non-IgE-mediated reactions.²

Previous data on NMBDs suggests that these drugs drive bronchospasm in overweight patients via an IgE-mediated mechanism or via an effect on airway reactivity. However, our study shows that being overweight is associated with non-IgE mediated bronchospasm and that a majority of overweight patients with non-IgE mediated bronchospasm display skin symptoms and/or haemodynamic impairment. Interestingly, among the 17 overweight patients with non-IgE mediated bronchospasm, only 3 patients had an isolated bronchospasm. The rest of the patients had skin symptoms and/or haemodynamic impairment associated with bronchospasm. Moreover, in overweight patients with non-IgE mediated bronchospasm 6 out of 9 patients had a significant increase in serum tryptase suggesting anaphylaxis but further investigations ruled allergy out. Given the presence of extra-respiratory symptoms in the patients with non-IgE mediated bronchospasm, a direct effect of NMBD on the airways is unlikely suggesting that an alternative mechanism drives the development of bronchospasm associated with skin symptoms and/or haemodynamic impairment in overweight patients.

The main limitation of our study is the small number of obese patients, whether or not being obese has a dose-response effect on bronchospasm could be determined with a larger cohort.

In conclusion, being overweight is a risk factor of bronchospasm and particularly non-IgE mediated bronchospasm. The underlying mechanisms involved in non-IgE mediated bronchospasm have to be clarified. Further studies with clinical, functional and biological data are warranted to determine different phenotypes of bronchospasm during general anaesthesia, similarly to that carried out for asthma.

Conflict of interest

The authors have no conflict of interest to declare.

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