Evaluation of the risk of hyperoxia –induced hypercapnia in obese cardiac surgery patients

A crossover comparison of two different oxygen saturation targets achieved by manual versus automatic titration

PROTOCOL

Registration number: NCT02917668

Authors :

Denault, Marie-Hélène, MD

Ruel, Carolanne, MD

Bouchard, Pierre-Alexandre, research asst. and respiratory therapist

Simon, Mathieu, MD

Lellouche, François, MD, PhD

Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec.

2725, chemin St-Foy, Québec, QC, Canada, GIV 4G5

Tél.: 418-656-8711

Fax: 418-656-4762

marie-helene.denault.1@ulaval.ca

Authors' contributions:

MHD designed the protocol, recruited patients, collected data, coordinated the study and will write the manuscript. CR and PAB recruited patients and collected data. MS helped with protocol design. FL supervised the whole process and will review the manuscript.

Amendments: sample size enlargement from 15 to 30 patients (July 2017)

Support:

No financial support was obtained for this study.

July 13th 2017

1. INTRODUCTION

1.1 Rationale

Oxygen is one of the most widely used drugs in acute care settings, with 34 % and 13,8 % of patients receiving some in ambulances and in hospitals, respectively [1, 2]. It is used to correct hypoxemia (35 %), and to relieve chest pain (35%) and dyspnea (40%)[3], even if numerous studies demonstrate that oxygen has no use in treating respiratory distress in normoxic patients [3-5]. Interestingly, a prescription is found for oxygen therapy in only 55 % of cases, with a saturation target specified in barely 52 % of those[2].

While hypoxemia seems to be a daily preoccupation for health care professionals, oxygen therapy carries some risks, which have been known for more than 60 years[6]. It is the pulmonary consequences of hyperoxia that have been studied the most. Of note, airway inflammation and cellular lung damage through reactive oxygen species production have been related to hyperoxia. In COPD patients, the risk of hyperoxia-induced hypercapnia has led international guidelines to recommend a target peripheral oxygen saturation of 88-92 % in these patients[5, 7, 8], but they are still receiving too much oxygen.

Obese people are also at risk for hyperoxia-induced hypercapnia[5, 7], but literature is sparse. Obesity is defined by WHO as a body mass index (BMI) superior to 30 kg/m^2, affecting more than 600 million adults in 2014, a number that had doubled since 1980 and corresponded to 13 % of world population [9]. In Canada, 28,7 % of women and 26,8 % of men were obese, percentages as high as 34,8 % and 33,6 % respectively in the United States [10]. Obesity-hypoventilation syndrome (OHS), originally named Pickwickian syndrome, is defined by the combination of obesity and daytime hypercapnia ($PaCO_2$ > 45 mmHg) after exclusion of other causes [11, 12]. It is found in 10 to 20 % of obese patients treated in sleep disorders clinics and in 50% of hospitalized obese patients having a BMI higher than 50 kg/m^2 [11, 13, 14]. Several pathophysiologic mechanisms belonging to respiratory centers, ventilator mechanics and sleep-disordered breathing have been proposed. Kaw and al. Have recently

shown that obese patients with obstructive sleep apnea syndrome (OSA) meeting the criteria for OHS were at increased risk for postoperative complications-respiratory or heart failure, intubation, ICU transfer, prolonged hospital stay- than those with isolated OSA [15]. Now, concerning the effect of hyperoxia, Wijesinghe and al. have shown that, in stable OHS patients, breathing a FiO_2 of 100 % for 20 minutes leaded to an elevation in $PtCO_2$ of 5 mmHg compared to ambient air. Moreover, 43,5 % of patients had majored their $PtCO_2$ of more than 4 mmHg while breathing a FiO_2 of 100% and the study had to stop in 3 patients because of a worrisome rise of more than 10 mmHg [16] . Hollier and al. have compared the effects of FiO_2 of 28% and 50 % on a 20 minutes time lapse, but observed a smaller pCO_2 difference [17]. Recent international practice guidelines recommend a SpO_2 target of 88-92 % in morbidly obese patients (BMI > 40 kg/m^2), but do not address this matter for obese patients with a lower BMI [5, 7]. In light of contemporary available evidence, many questions remain unanswered. What is the effect of hyperoxia on obese patients in an acute setting? Is there, in obese patients not previously known for OHS, a risk of hyperoxia-induced hypercapnia in this clinical context?

1.2 Objectives and hypotheses

This study aimed to evaluate the risk of hyperoxia-induced hypercapnia in obese patients after coronary artery bypass grafting, by comparing a SpO_2 target $\geq$ 95 % achieved by manual titration (usual care) and a more conservative target of 90 % achieved by automatic titration in the post-extubation period.

2. METHODS

15 obese patients will be recruited at Quebec's heart and lung Institute. Informed written consent will be obtained from each included patient. The protocol will be submitted to the establishment's ethics committee for approval.

2.1 Inclusion criteria

• Age ≥ 18 years

• BMI $\geq$ 30 kg / m^2

• Procedure: coronary artery bypass grafting (CABG) only

• SpO2 $\geq$ 95% before extubation

2.2 Exclusion criteria

• Comorbidities:

- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Restrictive syndrome other than that associated with obesity (interstitial lung disease, neuromuscular disease, etc.)
- OSA requiring CPAP therapy

• No FreeO_2 device available at the time of the study

• Patient enrolled in another study that does not allow co-enrollment

2.3 Sample size

Since there are few data in the literature regarding the effect of hyperoxia in the obese population, and these data are for patients known to have hypoventilation syndrome and in the stable state, it is difficult for us to estimate the magnitude of the possibly observable change in PaCO_2. Based on previous studies on stable OHS patients[16, 17], empirical sample size will be set at 15 patients to detect a PaCO_2 difference of 5 mmHg between groups.

2.4 Study process

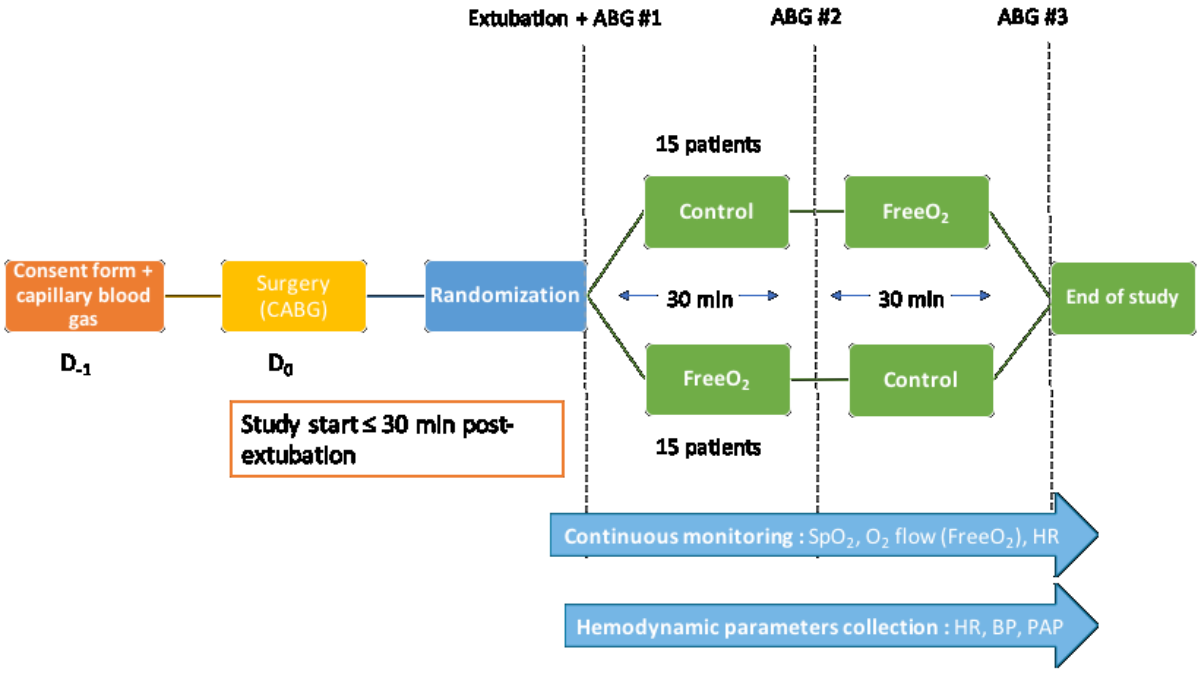
We will compare the effect of two modes of oxygenation on capnia in post-CABG obese patients , immediately after extubation:

A. FreeO_2 mode : oxygen via nasal cannulas or mask (if O_2 flow rate> 5l / min for more than 5 minutes), automatically titrated by FreeO_2 for a SpO_2 of 90 $\pm$ 2%

B. Control mode : oxygen via ventimask, manually adjusted by nurses for $SpO_2 \geq 95\%$ (routine care according to the local protocol in which extubation is done with a FiO_2 equal to FiO_2 before extubation + 10%).

Patients meeting all inclusion criteria will be randomized postoperatively. After being extubated, they will be oxygenated for 30 minutes according to FreeO_2 or control mode, in a randomized order. They will then be oxygenated according to the second mode of administration for 30 minutes. Each patient will act as his own control (crossover design)(see figure 1).

Figure 1 Study process



The study will last 1h for each patient, and should begin within 30 minutes after extubation. A resource person will be at the bedside for the duration of data

collection to ensure protocol compliance and integrity. We expect to be able to complete the data collection within a 12-month period.

2.5 Parameters collected

The usual demographic data (age, sex, weight, height, BMI, waist size) will be collected during the recruitment of patients as well as the type of surgery (number of grafts, extracorporeal circulation duration), intraoperative and postoperative narcotic doses, left ventricular function and preoperative renal function. Continuous monitoring of oxygen flow, peripheral oxygen saturation and heart rate by FreeO_2 will be achieved throughout both periods. During the control period, FreeO_2 will collect data, but will not deliver oxygen. The respiratory rate will also be measured manually and on the monitor. When patients are oxygenated with FreeO_2, they will record the flow of oxygen delivered; with the usual mode, we will note the FiO_2 used. At the end of each period, hemodynamic measurements will be taken: heart rate, systemic arterial pressure, pulmonary artery pressure, vasopressor dosage. A total of four blood gases will be collected for each patient : a capillary blood gas the day before surgery (baseline), and arterial blood gases before extubation, after the first period and after the second period.

2.6 Outcomes

The primary endpoint will be end-of-period $PaCO_2$. Secondary endpoints will include end-of-period pH and PaO_2 and percentage of time spent in hypoxemia (SpO2 <88%), in severe hypoxemia (SpO_2 <85%) and in hyperoxemia (SpO_2> 96%). We will compare the respiratory rate data with 2 measurements (manual and monitor). We will also compare the hemodynamic data.

2.7 Statistics

Mean differences will be used for all of the outcomes since they are continuous, taking into account the crossover design (analyses with four groups). Univariate and

multivariate analyses will be used to identify factors of response and nonresponse. Analyses to assess period, time and carryover effects will be done.

3. AMENDMENT

Analysis of the primary outcome after inclusion of 15 patients showed a trend towards a higher end-of-period $PaCO_2$ in control mode, but the study lacked statistical power. We thus decided, following the recommendation of our statistician, to make an amendment to the protocol in order to enlarge sample size to 30 patients. This amendment was accepted by our institution's board on July 13th, 2017.

REFERENCES

1. Hale, K.E., C. Gavin, and B.R. O'Driscoll, *Audit of oxygen use in emergency ambulances and in a hospital emergency department.* Emerg Med J, 2008. **25**(11): p. 773-6.
2. O'Driscoll, B.R. *British Thoracic Society Emergency Oxygen Audit 2013 (National Audit Period 15 August – 1 November 2013)*. 2014; Available from: https://www.brit-thoracic.org.uk/document-library/audit-and-quality-improvement/audit-reports/bts-emergency-oxygen-audit-report-2013/.
3. Branson, R.D. and J.A. Johannigman, *Pre-hospital oxygen therapy.* Respir Care, 2013. **58**(1): p. 86-97.
4. Iscoe, S., R. Beasley, and J.A. Fisher, *Supplementary oxygen for nonhypoxemic patients: O2 much of a good thing?* Crit Care, 2011. **15**(3): p. 305.
5. Beasley, R., et al., *Thoracic Society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'.* Respirology, 2015. **20**(8): p. 1182-1191.
6. Beasley, R., et al., *High-concentration oxygen therapy in COPD.* Lancet, 2011. **378**(9795): p. 969-70.
7. O'Driscoll, B.R., et al., *BTS guideline for oxygen use in adults in healthcare and emergency settings.* Thorax, 2017. **72**(Suppl 1): p. ii1-ii90.
8. Rabe, K.F., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* Am J Respir Crit Care Med, 2007. **176**(6): p. 532-55.
9. OMS. *Obésité et surpoids (aide-mémoire No 311)*. 2016 Juin 2016; Available from: http://www.who.int/mediacentre/factsheets/fs311/fr/.
10. Collaboration, N.C.D.R.F., *Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants.* Lancet, 2016. **387**(10026): p. 1377-96.
11. Piper, A.J. and R.R. Grunstein, *Obesity hypoventilation syndrome: mechanisms and management.* Am J Respir Crit Care Med, 2011. **183**(3): p. 292-8.
12. Piper, A.J. and R.R. Grunstein, *Current perspectives on the obesity hypoventilation syndrome.* Curr Opin Pulm Med, 2007. **13**(6): p. 490-6.
13. Nowbar, S., et al., *Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome.* Am J Med, 2004. **116**(1): p. 1-7.
14. Mokhlesi, B., et al., *Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea.* Sleep Breath, 2007. **11**(2): p. 117-24.
15. Kaw, R., et al., *Postoperative Complications in Patients With Unrecognized Obesity Hypoventilation Syndrome Undergoing Elective Noncardiac Surgery.* Chest, 2016. **149**(1): p. 84-91.

16. Wijesinghe, M., et al., *The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study.* Chest, 2011. **139**(5): p. 1018-24.
17. Hollier, C.A., et al., *Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study.* Thorax, 2014. **69**(4): p. 346-53.