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Complete List of Authors:	Ferrando, Carlos; Hospital Clínico Universitario Valencia, Anesthesiology and Critical Care Romero, Carolina; Consorci Hospital General Universitari de Valencia Tusman, Gerardo; Hospital Privado de Comunidad Suarez-Sipmann, Fernando ; Uppsala Universitet Canet, Jaume; Hospital Universitari Germans Trias i Pujol Dosdá, Rosa; Hospital Clinico Universitario valencia Valls, Paola; Hospital Clinico Universitario Valencia Villena, Abigail; Hospital Clínico Universitario Valencia Serralta, Ferran; Hospital Clínico Universitario Valencia Jurado, Ana; Hospital Clínico Universitario Valencia Carrizo, Juan; Hospital Clínico Universitario Valencia Navarro, Jose; Hospital Clínico Universitario Valencia Parrilla, Cristina; Hospital Clínico Universitario Valencia Romero, Jose; ITACA Institute (Group IBIME), Universidad Politécnica Pozo, Natividad; INCLIVA Clinical Research Institute Soro, Marina; Hospital Clínico Universitario Valencia Villar, Jesús; Instituto de Salud Carlos III, CIBER de Enfermedades Respiratorias; Hospital Universitario Dr. Negrin, Research Unit
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Title: Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery –
a prospective, diagnostic pilot study.

¹Carlos Ferrando, ²Carolina Romero, ³Gerardo Tusman, ^{4,5}Fernando Suarez-Sipmann, ⁶Jaume Canet, ⁷Rosa Dosdá, ¹Paola Valls, ¹Abigail Villena, ¹Ferran Serralta, ¹Ana Jurado, ¹Juan Carrizo, ¹Jose Navarro, ⁷Cristina Parrilla, ⁸Jose E. Romero, ⁹Natividad Pozo, ¹Marina Soro, ^{4,10,11}Jesus Villar, ¹Francisco Javier Belda.

(1) Department of Anesthesiology and Critical Care, Hospital Clínico Universitario, Valencia, Spain; (2) Department of Anesthesiology, Hospital General Universitario, Valencia, Spain; (3); Department of Anesthesiology, Hospital Privado de Comunidad, Mar de Plata, Buenos Aires, Argentina; (4) CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; (5) Section of Anesthesiology and Critical Care, Uppsala University Hospital Uppsala, Uppsala, Sweden; (6) Department of Anesthesiology and Critical Care, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; (7) Department of Radiology, Hospital Clínico Universitario, Valencia, Spain; (8) ITACA Institute (Group IBIME), Universidad Politécnica, Valencia, Spain; (9) INCLIVA Clinical Research Institute, Hospital Clínico Universitario, Valencia, Spain; (10) Keenan Research Center for Biomedical Science at the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; (11) Spain Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Las Palmas, Spain.

Corresponding Author: Carlos Ferrando

Department of Anesthesiology and Critical Care
Hospital Clínico Universitario
Av. Blasco Ibañez, 17
46010 Valencia. SPAIN
Phone: (+34) 963862600 Fax: (+34) 963862680
Email: cafeoranestesia@gmail.com

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Abstract

Objective To assess the diagnostic accuracy of SpO₂ while breathing room air for 5 min (“the Air-Test”) in detecting postoperative atelectasis.

Design Prospective, cohort study. Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standar computed tomography scan.

Setting Postanesthetic care unit in a terciary Hospital in Spain.

Participants 350 patients from January 12 to February 7, 2015. 170 patients scheduled for surgery under general anesthesia admitted into the postsurgical unit were included.

Intervention The Air-Test was performed in awake extubated patients after a 30 min stabilization period receiving supplemental oxygen therapy via a Venturi mask. The Air-Test was defined positive when SpO₂ was $\leq 96\%$ and negative when $\geq 97\%$. Arterial blood gases were measured in all patients at the end of the Air-Test. Within the next 25 min, the presence of atelectasis was evaluated by computed tomography scan in 59 randomly selected patients.

Main Outcomes Measures The primary study outcome was the accuracy of the Air-Test for the detection of postoperative atelectasis assess by reference standar. The secondary outcome was incidence of positive Air-Test.

Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scan in all patients (30/30) with positive and in 5 patients (17%) with negative Air-Test. Based on the Air-Test, postoperative atelectasis were present in 36% of the patients (62 out of 170).

Conclusion The Air Test is an accurate, simple, inexpensive and noninvasive method to diagnose postoperative atelectasis.

Trial Registration ClinicalTrials.gov Identifier: NCT02650037.

Keywords: Postoperative, atelectasis, oxygenation, SpO₂

Strengths and limitations of this study

- This study used a simple and brief room-air breathing trial (Air-Test) in the early postoperative period to diagnose atelectasis.
- Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standard computed tomography scan.
- This study was a pilot study and a large external validation study is needed.
- The Air-Test had several limitations not only related to the pulse-oximeter but also to the test which could limit the clinical application in some cases.

Introduction

An estimated 234 million major surgical procedures are undertaken each year worldwide¹. Atelectasis may develop in nearly 90% of patients submitted to general anesthesia and may persist not only during the immediate postoperative period but up to several days after surgery²⁻⁵. Persistence of atelectasis after surgery is potentially associated with postoperative pulmonary complications such as pneumonia, acute lung injury, extubation failure and reintubation³⁻⁷. Hypoxemia, a direct consequence of atelectasis⁸ may also promote systemic complications such as acute myocardial ischemia or impaired wound healing, among others⁹.

Oxygen therapy is usually applied in the postoperative period to alleviate hypoxemia¹⁰, which develops in most patients after general anesthesia. As a result, most atelectasis in the postoperative period may not be diagnosed at the bedside precluding the application of any corrective measure and thus potentially increasing the risk of atelectasis-related postoperative complications. In the other hand, the use of low FIO₂ (0.21) could better categorize lung function through SpO₂ values, as it forces SpO₂ to operate at the steep portion of the oxygen-hemoglobin dissociation curve, and thus it can be used to estimate the alveolar shunt using the SpO₂-FIO₂ diagram described by Jones et al¹¹. This may help to unmask underlying oxygenation deficits due to shunt and thus the presence of atelectasis when SpO₂ is low, assuming a linear relationship between shunt and atelectasis. Thus, a combination of oxygen therapy with transitory decreases of FIO₂ to 0.21 during a 5 minutes period, which is enough to achieve a steady state condition of the expired fraction of oxygen (FEO₂)^{12,13} may allow to estimate shunt and to unmask the presence of atelectasis during the immediate postoperative period.

We hypothesized that changes in arterial oxygen saturation induced by a short maneuver of FIO₂ reduction to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO₂ recorded by pulse oximetry after breathing room-air for 5 min ("the Air-Test") can reveal the presence of atelectasis and to establish the relation of the SpO₂ value to the presence of atelectasis assessed by CT-scan.

Methods

Study design

We performed a prospective, cohort study at the post-surgical recovery unit of the Hospital Clínico Universitario, Valencia, Spain, from January 12 to February 7, 2015. The study was approved by the Local Ethics Committee for Clinical Research in accordance with the Declaration of Helsinki (Chairperson: Dr. Antonio Peláez), and registered on December 28, 2015 at <http://www.clinicaltrials.gov> with identification no. NCT02650037. Written informed consent was obtained from all patients. The complete and original protocol is described in this section.

Elegibility criteria

The study included consecutive patients with an American Society of Anaesthesiologists physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical unit. Exclusion criteria were: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, and (v) preoperative SpO₂ ≤ 97% on room-air. Postoperatively patients who gave their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin <10g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale >1 or <-1, and (vi) pain >4 evaluated with the visual analogue scale after the first 30 min in the PACU (Figure 1).

Monitoring

Intraoperative anesthesia management followed standard clinical routines. The study started on arrival into the Postsurgical Unit. A multi-parameter monitor IntelliVue MX450 (Philips Healthcare, Boeblingen, Germany) was used in all patients to monitor electrocardiogram, non-invasive systemic arterial pressure, and SpO₂. The finger probe pulse-oximeter of the MX450 monitor uses the Fourier Artifact Suppression Technology (FAST) SpO₂. Pulsi-oximeter characteristics are described in the Supplement digital content 1.

Index Test for postoperative atelectasis

Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO₂ of 0.5 during the first 30 min. The Air-Test was performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO₂ monitoring with a finger probe pulse-oximeter. The Air-Test was considered positive when the recorded SpO₂ was ≤ 96% and negative when SpO₂ was ≥ 97%. The selected cut-off value to diagnose atelectasis was based in the SpO₂-FIO₂ diagram¹⁰ described by Jones which showed that a SpO₂ was ≤ 96% corresponds to a shunt effect >10% which defines alveolar collapse. Recently,

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3 Tusman et al.¹⁴ used a similar approach by using a FIO₂ of 0.21 to define an open-lung condition in anesthetized
4 patients while ventilated.

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6 The selected 5 min was based on the results we obtained in our pilot study in ten healthy volunteers
7 showing that the mean time needed from mask removal to the stabilization of the FEO₂ was 56 (7) seconds. Our
8 pilot study was performed in ten healthy and nonsmoker volunteers in the Hospital Privado de Comunidad, Mar
9 de Plata (Argentina) to establish the mean time from Venturi mask removal with oxygen supplementation to the
10 stabilization of the expiratory fraction of Oxygen (FEO₂) signal. Interventions and results are described in the
11 Supplement digital content 1. Also, the selected time was based in the results found by Howe et al.¹² in
12 spontaneously breathing patients and Fildissis et al.¹³ in mechanically ventilated patients. Both studies showed
13 that the oxygen (PaO₂) measured 5 min after discontinuation of supplementary oxygen represents steady state
14 conditions in lung-healthy patients.

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16 The Air-Test was performed 30 min after PACU admission for safety reasons. As a number of the
17 included patients were randomized to perform the reference standar test for postoperative atelectasis (CT-scan)
18 as soon as possible after the Air-Test to minimize bias, we arbitrarily decided that the minimal time required to
19 ensure a safety discharge from the PACU after a general anesthesia and after meeting all the discharge criteria
20 should be the defined 30 min.

21
22 In addition, we evaluated the prevalence of having a positive Air-Test. Once the Air-Test was completed, an
23 arterial blood gas sample was drawn while breathing room-air from each patient (ABL 520, Radiometer,
24 Copenhagen, Denmark). The oxygen mask was placed back whenever SpO₂ fell to 92% for more than one
25 minute during the Air-Test and until the end of the protocol after the Air-Test was completed.

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **Randomization of patients for references standard test (CT scan)**

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43 Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold
44 standard technique. It was used an adaptive randomization which allowed us to minimize the exposure to CT-
45 scans in patients not expected to have atelectasis but having sufficient number of patients on each arm to conduct
46 comparisons¹⁵.

47 48 49 50 51 52 **Reference standard test for postoperative atelectasis (CT scan)**

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54 For the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered
55 negligible (negative) based in previous data¹⁴ because it does not cause a clinically relevant shunt^{16,17}. CT-scans
56 were obtained with 16-detector row/ 32 slices Aquillion LB (Toshiba). Scans (120 kV, 100-140 mA and 0.5 sec
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rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5mm thickness slices with 5mm interval and a depth of 12 bits per pixel. Each right and left surface of normally aerated tissue and atelectasis were semi automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchi and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to 100). After this correction, separation between normally aerated lung and atelectasis was automatically corrected. An example of the segmentation steps can be seen in Figure 2. Quantitative analysis of CT densities was performed using previously validated methods^{18,19}. The atelectatic area was expressed in cm² as mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROI) were calculated using equation 1:

$$VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$$

Where V is the set of voxels inside the ROI and x , y and z the voxel sizes in the three dimensions given in millimeters. Volumes are given in milliliters.

Mass of lung tissue for the different ROIs were calculated as previously described²⁰. See equation 2:

$$MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$$

Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V , HU_i represents the CT value for voxel i and VOL_{voxel} represents the voxel volume for the image being processed given in milliliters. The atelectatic mass was expressed in grams as mean \pm standard deviation (SD) and as a percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but performed at the region presenting the largest amount of atelectasis in each lung independently. All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.

Diagnostic test of the index test (Air-Test)

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3 A 2×2 table (table 2) was used for the assessment of sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP +$
4 $TN)] \times 100$; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$; where *TP* is true positive, *TN*
5 is true negative, *FP* is false positive, and *FN* is false negative.
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8 9 **Statistical analysis**

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11 The total sample size was not calculated as this is a cohort study. The sample size for patients randomized for
12 CT-scan was also not calculated as this is preliminary pilot study. Thus, we arbitrarily decided that the minimum
13 sample size was at least 50 patients (25 patients with positive Air-Test and 25 with negative). Data were
14 analysed using the statistical software R version 3.1.1²¹. All the analysis performed were pre-specified.
15 Statistical description of the baseline demographics were obtained with the *library (Rmisc)* and *library*
16 *(PropCIs)*. We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous
17 variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for
18 ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median
19 (interquartil range). A simple linear regression model was used with the variables SpO₂ and the total area of
20 atelectasis following the formula: Area of atelectasis ~ SpO₂ + ε, where ε is the error. A regression line was built
21 in the scatterplot with the function *lm()*. The diagnostic accuracy and sensitivity analysis were conducted in R
22 with the *library pROC*. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values
23 were computed with bootstrap resampling and the averaging methods described by Fawcett²². Bootstrap has
24 shown to generate unbiased optimism-adjusted estimates of the CIs statistic. In all bootstrap CIs, patients were
25 resampled and the modified curve was built before the statistics of interest were computed. As in the bootstrap
26 comparison test, the resampling was done in a stratified manner²³. For all comparisons, a two-sided value of
27 p<0.05 was considered significant.
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Results

A total of 181 out of 350 eligible patients scheduled for surgery were enrolled, from whom 170 underwent the Air-Test in the Post-operative Unit. Thirty randomly assigned patients from the 62 with positive and 29 from 108 with a negative Air-Test were assessed with CT (Figure 1).

Baseline demographic and clinical characteristics of all patients

Demographic, surgical, intraoperative ventilatory management data and clinical variables after the completion of the Air-Test are shown in Table 1. Patients with a positive Air-Test were older, predominantly male and had a higher ARISCAT score (The Assess Respiratory Risk in Surgical Patients in Catalonia)²⁴ with a larger weight as compared with those with a negative test. There were no significant differences regarding intraoperative management, type and duration of surgery between both groups. Oxygenation (PaO₂) was 25% lower in patients with a positive test (p<0.001). Also, the SpO₂ was placed in the steep portion of the oxygen-hemoglobin dissociation curve as compared with patients with a negative test. All the patients were hemodynamically stable and normothermic.

Table 1. Study variables of patients.

	Positive Air Test (n=62)	Negative Air Test (n=108)	p-value
Demographic data			
Age, yr	65 (11)	56 (17)	<0.001
Women, %	33 (6)	56 (9)	0.01
Height, cm	164 (9)	166 (9)	0.06
Body weight, kg	84 (21)	73 (15)	<0.001
ARISCAT score	26 (14)	16 (15)	0.01
Preoperative SpO ₂ , %	98 (1)	98 (2)	0.12
Lower Abdominal surgery	24 (38)	34 (31)	0.20
Upper Abdominal surgery	9 (14)	13 (12)	0.11
Peripheral surgery	29 (46)	60 (55)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volumen, ml	470 (52)	460 (88)	0.33
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FIO ₂	0.6 (0.2)	0.7 (0.3)	0.88
SpO₂ and arterial blood gases at PACU at the end of the Air-Test			
Postoperative SpO ₂ , %	91 (3)	99 (1)	0.01
PaO ₂ , mmHg	66 (10)	87 (12)	0.01
PaCO ₂ , mmHg	41 (6)	42 (6)	0.29
pH	7.37 (0.04)	7.38 (0.03)	0.06
MAP, mmHg	79 (12)	85 (15)	0.07
Lactate, mmol/L	1.1 (0.4)	1.0 (0.7)	0.32
Hb, g/dl	12.6 (1.7)	12.9 (1.1)	0.09
Temperature, C°	36.4 (1.9)	36.1 (2.1)	0.41
VAS	1 (1)	1 (1)	1.00

Table 1. Data are described as mean (SD) or number/total number (%). ARISCAT score to predict postoperative pulmonary complications²², PEEP: positive end-expiratory pressure; FIO₂: inspiratory oxygen fraction; PACU: Post-Anesthetic Care Unit; SpO₂: pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial pressure; PaCO₂: carbon dioxide partial pressure; pH: acid base state; MAP: mean arterial pressure; Hb: Hemoglobin, VAS: visual analogue scale.

Baseline demographic and clinical characteristics of patients with reference standard (CT scan)

As shown in table 2, the differences found between patients with positive and negative Air-Test (table 1) were maintained in those patients in whom the CT-scan was performed.

Table 2. Study variables of patients with reference standard CT-scan.

	Positive Air Test (n=30)	Negative Air Test (n=29)	p-value
Demographic data			
Age, yr	62 (13)	53 (15)	0.045
Women, n (%)	12 (40)	11 (37)	0.57
Height, cm	165 (10)	163 (12)	0.32
Body weight, kg	88 (29)	75 (17)	<0.001
ARISCAT score	28 (14)	14 (15)	<0.001
Preoperative SpO ₂ , %	98 (2)	98 (2)	0.28
Lower Abdominal surgery	39 (10)	29 (5)	0.20
Upper Abdominal surgery	6 (3)	4 (3)	0.11
Peripheral surgery, %	55 (11)	67 (7)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volumen, ml	472 (50)	466 (92)	0.56
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FIO ₂	0.7 (0.2)	0.7 (0.3)	0.90
SpO₂ and arterial blood gases at PACU at the end of the Air Test			
Postoperative SpO ₂ , %	92 (3)	99 (1)	0.01
PaO ₂ , mmHg	78 (21)	90 (10)	<0.001
PaCO ₂ , mmHg	40 (6)	42 (6)	0.34
pH	7.37 (0.04)	7.38 (0.03)	0.09
MAP, mmHg	81 (12)	76 (15)	0.72
Lactate, mmol/L	1.1 (0.4)	1.0 (0.6)	0.52
Hb, g/dl	12.5 (1.2)	12.3 (1.6)	0.41
Temperature, C°	36.2 (1.9)	36.2 (2.3)	0.68
VAS	1 (1)	1 (1)	1.00

Table 2. Data are described as mean (SD) or number/total number (%). ARISCAT score to predict postoperative pulmonary complications²², PEEP: positive end-expiratory pressure; FIO₂: inspiratory oxygen fraction; PACU: Post-Anesthetic Care Unit; SpO₂: pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial pressure; PaCO₂: carbon dioxide partial pressure; pH: acid base state; MAP: mean arterial pressure; Hb: Hemoglobin, VAS: visual analogue scale.

Diagnostic accuracy

Of the 59 patients evaluated with a CT-scan, all those with a positive Air-Test and 5 of those with a negative Air-Test (17%) had measurable atelectasis (area >2% of the whole lung) on the CT-scan. When mass analysis was used to diagnose atelectasis, 27 patients with positive Air-Test and only 3 patients with negative Air-Test had measurable atelectasis (mass >2% of the whole lung). None of the patients with negative Air-Test and atelectasis on the CT-scan had a SpO₂ >98% and an atelectatic area or mass >4%. ROC analysis showed that a positive Air-Test (SpO₂ ≤96%) was adequate to diagnose postoperative atelectasis (Table 3).

Table 3. Diagnostic accuracy, Sensitivity, Specificity and area under the curve (AUC) to detect atelectasis with the Air-Test assessed with the reference standar (CT-scan).

	AUC (95%CI)	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Air-Test (N = 59)	0.90 (0.82-0.98)	82.6	87.8	91.5

Sensitivity analysis

Since the Air-Test could be affected by several factors such as dyshemoglobinemias, low perfusion state, motion artifact, and hypothermia, we performed two additional analyses to confirm our results. First, the PaO₂ threshold value confirming the diagnosis of atelectasis was 78 mmHg, with a sensitivity of 82.6% and a specificity of 78.7% and an area under the ROC curve of 0.86 (95%CI: 76.6 to 96.1%). Second, looking for the suitability of the SpO₂ to diagnose atelectasis, we performed a ROC test for correlated data between SpO₂-ROC and PaO₂-ROC. The ROC *test* showed no differences between both tests (p=0.10).

Secondary outcome

We found a 36% prevalence of positive Air-Test in our population (62 of the 170 patients).

Adverse events

No adverse events were reported during the study period.

Discussion

The main result of this diagnostic pilot study was the high accuracy of the postoperative Air-Test to diagnose atelectasis. This test, performed 30 minutes after surgery, identified a high prevalence postoperative atelectasis. This simple, noninvasive and inexpensive test at bedside may be used in healthy patients with a preoperative SpO₂ between 97 to 100% while breathing room-air.

The Air-Test helped to unmask underlying oxygenation deficits and the presence of atelectasis when SpO₂ ≤ 96%. As previous studies have described, shunt-induced by atelectasis is the main cause of oxygenation impairment during the postoperative period¹⁵. In fact, Rothen et al.²⁶ showed that 75% of the impairment in PaO₂ is related to atelectasis and airway closure in patients with healthy lungs. Based on this statement, our results are in line with the findings of Witting et al.²⁵ who found that a SpO₂ ≤ 96% in patients breathing room-air confirmed the diagnosis of hypoxemia (defined as PaO₂ < 70 mmHg in their study) with a sensitivity of 100% and a specificity of 54% and an area under the ROC curve of 0.91 (95%CI: 0.78 to 0.94).

We found a 17% of false negative Air-Test in patients who presented an area of atelectasis higher than 2% in the CT images that was reduced to 10% when mass was used to diagnose atelectasis. Potential reasons for this decreased sensitivity could be related to several factors. First, the duration of the Test; five minutes might not be enough to achieve a steady state condition of the FEO₂ in some patients. Some authors in mechanically ventilated patients found slightly higher times: 5.5 (4.8) minutes in healthy patients²⁷ or 7.1 (2.1) in mechanically ventilated COPD patients²⁸. Another potential cause for the false negatives might be the percentage of error of pulse-oximeter measurement. A difference in bias up to 2% and a precision up to 3% compared to the reference standard (CO-oximeter) has been described²⁹. Although we did not find false positives when the area was used to diagnose postoperative atelectasis, 3 of the 30 patients with positive Air-Test did not have a mass of atelectasis > 2%. Potential causes are a certain overestimation of the shunt-induced by atelectasis based on the SpO₂-FIO₂ diagram due to the presence of low V/Q zones, as these may appear during mechanically ventilated patients¹³ and the difference in bias and precision as discussed above.

We found a 36% prevalence of postoperative atelectasis based on the Air-Test. Our findings are in agreement with previous studies. Akca et al.³⁰ found a similar prevalence using CT-scan in 30 patients after colon surgery. Our findings also match with the prevalence of postoperative SpO₂ ≤ 96% found by Severgnini et al. where 12 of the 27 patients in the control group and 8 of the 28 patients in the study group (36% prevalence of the total population) had a SpO₂ ≤ 96% while breathing room-air (unpublished data), but no atelectasis were diagnosed by chest radiography³¹. Recently, an observational study including 833 nonselected postoperative

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2 patients with 48h continuous SpO₂ monitoring, demonstrated a 37% prevalence of hypoxemia (SpO₂<90%)⁹.
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4 However, in general, the rate of atelectasis usually reported is much lower^{24,32}. Two recent trials together
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6 including more than 1200 patients reported a prevalence around 15% when diagnosed by chest radiography^{33,34}.
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8 This low prevalence might be explained by the low sensitivity and specificity of chest radiographs. When
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10 compared to the prevalence observed in our study using CT-scan, it suggests that atelectasis are usually
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12 underestimated.

13 14 **Limitations**

15 We must acknowledge several limitations. First, the Air-Test can only be applied to patients with a preoperative
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17 SpO₂ ≥ 97% on room-air, since it is not possible to differentiate whether the postoperative SpO₂ indicates the
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19 presence of postoperative atelectasis or previous lung disease. However, a high percentage of patients scheduled
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21 for surgery have a SpO₂ ≥ 97%²⁴. Second, intraoperative respiratory complications that decrease low V/Q zones
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23 and therefore decrease SpO₂, such as lung edema or pneumothorax, may overestimate shunt-induced by
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25 atelectasis based on the SpO₂-FIO₂. However, these postoperative complications in the immediate postoperative
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27 period rarely appear³⁴. Third, compensatory mechanisms in the presence of atelectasis such as the hypoxic
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29 pulmonary vasoconstriction decreases shunt and therefore may increase SpO₂, which would underestimate
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31 atelectasis based on the SpO₂-FIO₂ diagram. This last two limitations may decrease the sensitivity and specificity
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33 of the Air-Test. Fourth, temporal factors could have affected our results because of time delays among the Air-
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35 Test, arterial blood gases, and the CT-scan. However, if at all, results would have been affected in a negative
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37 sense since a time-dependent reduction of postoperative atelectasis occurs as patients improve their breathing
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39 capacity. Fifth, erroneous readings of the pulse-oximeter may underestimate postoperative atelectasis in the
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41 presence of dyshemoglobinemias or overestimate them in the presence of anemia, low perfusion state, motion
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43 artifacts or hypothermia²⁹. Some of these limitations are not only related to the pulse-oximeter but also to the
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45 Air-Test itself as shifts of the oxy-hemoglobin dissociation curve can affect the principle used by Jones et al. to
46
47 describe the SpO₂-FIO₂ diagram¹¹. However, this limitation was well controlled as shown in tables 1 and 2.
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49 Finally, for the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered
50
51 negligible. Although this percentage is not clinically relevant, these atelectasis which are not diagnosed with the
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53 Air-Test could potentially trigger an inflammatory response³⁵ which at last would affect the rationale of using this
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55 test.

56 57 **Implications for practice**

58 First, this is a pilot study and a powered large external validation study is needed in a more heterogeneous
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3 surgical population such as obese, patients without previously normal lung function or patients with a
4 preoperative SpO₂ <97%. Such a study may also analyze the Air-Test at different time points, with different
5 pulse-oximeter technologies and in patients without previously supplemental oxygen delivery during the
6 postoperative period with the aim to validate the test as a surrogate of postoperative atelectasis; and its severity if
7 it is found a correlation between the SpO₂ values during the Air-Test and the area of atelectasis measured by CT-
8 scan. Second, the Air-Test may become a standardized screening test before leaving the PACU to evaluate
9 postoperative oxygenation. It may contribute to a higher patient flow in PACU without losing high care quality
10 as it may discriminate those patients without postoperative lung derecruitment (negative Air-Test) from those
11 (positive Air-Test) with an increased risk of postoperative hypoxemia³⁶, whom should ideally be surveyed more
12 closely during this period and would likely benefit from measures to revert atelectasis, which may have a
13 potential positive impact on healthcare costs³⁷. Despite the benefits in outcomes of these measures remain
14 uncertain³⁸, several studies showed the potential benefits³⁹ and currently is ongoing a clinical trial which uses the
15 Air-Test to individually apply the use of a postoperative continuous positive end-expiratory pressure⁴⁰.

28 **Conclusions**

29
30 We have demonstrated that the Air-Test is an accurate, simple, inexpensive, noninvasive and readily
31 available method for diagnosing postoperative atelectasis.
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Footnotes:**Contributors**

Dr. Ferrando (MD, PhD) and Prof. Belda (MD, PhD) had full access to all data and are responsible for the integrity and the accuracy of the data analysis. *Study design:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD) and Prof. Belda (MD, PhD). *Acquisition and analysis of data:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Dosdá, (MD, PhD), Dr. Tusman (MD), Dr. Soro (MD, PhD), Dr. Valls (MD), Dr. Villena (MD), Dr. Serralta (MD), Dr. Jurado (MD), Dr. Carrizo (MD), Dr. Navarro (MD), Dr. Parrilla (MD), Dr. Pozo (PhD), Dr. Romero (BSc), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD). *Interpretation of data:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), Dr. Canet (MD, PhD). *Drafting of the manuscript:* Dr. Ferrando (MD, PhD), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD). *Critical revision of the manuscript for intellectual content:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD), Dr. Canet (MD, PhD), Dr. Suarez-Sipmann (MD, PhD), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD).

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Declaration of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Ethical approval

Approved by the Local Ethics Committee for Clinical Research. Written informed consent was obtained from all patients.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

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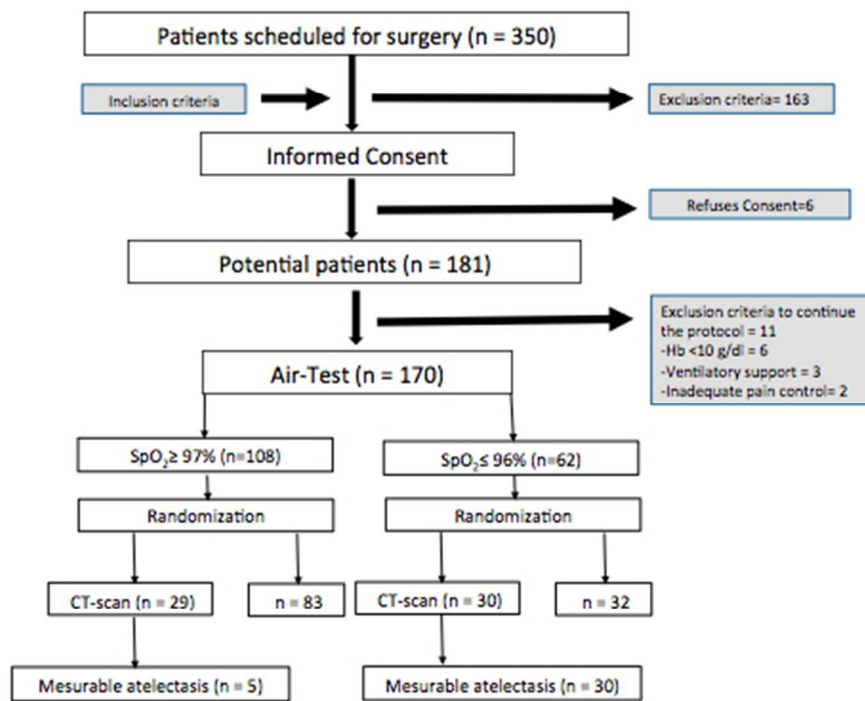


Figure 1. Flow diagram of the Air-Test study.

185x134mm (72 x 72 DPI)

Supplementary file

Title: Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.

Carlos Ferrando, Carolina Romero, Gerardo Tusman, Fernando Suarez-Sipmann, Jaume Canet, Rosa Dosdá, Paola Valls, Abigail Villena, Ferran Serralta, Ana Jurado, Juan Carrizo, Jose Navarro, Cristina Parrilla, Jose E. Romero, Natividad Pozo, Marina Soro, Jesus Villar, Francisco Javier Belda.

Corresponding Author: Carlos Ferrando

Department of Anesthesiology and Critical Care

Hospital Clínico Universitario

Av. Blasco Ibañez, 17

46010 Valencia. SPAIN

Phone: (+34) 963862600 Fax: (+34) 963862680

Email: cafeoranestesia@gmail.com

Methods

Procedures

We performed a pilot study in ten healthy and non-smoker volunteers in the Hospital Privado de Comunidad, Mar de Plata (Argentina) to establish the mean time from Venturi mask removal with oxygen supplementation to the stabilization of the expiratory fraction of Oxygen (FEO₂) signal. The volunteers were breathing spontaneously through a Venturi mask at 4 L/min with a jet adjusted to a theoretical FiO₂ of 0.5 during 10 min before the Air-Test was performed. Nasal oxygen and carbon dioxide concentrations were measured using a 1 mm ID cannula placed 1 cm inside the right nostril and connected to the side-stream capnograph S5 (GE Healthcare/Datex-Ohmeda, Helsinki, Finland). Time-base oximetry and capnography were recorded with the Datex Collect software (GE Healthcare/Datex-Ohmeda, Helsinki, Finland) and analyzed off-line. We measured mean time needed from mask removal to the stabilization of the FEO₂.

The FAST SpO₂ algorithm derives SpO₂ using the absorption of red and infrared light. But unlike the traditional algorithm, the FAST algorithm examines the strength of the different frequency components that make up the signals. This approach allows to distinguish the physiological signal from the noise artifacts increasing measurement accuracy¹. Nevertheless, the SpO₂ measurement was considered qualitatively optimal only when a plethysmography waveform stable and normal was seen during the average time period of 10 seconds given by the monitor. The conventional finger probe pulse oximetry is an accurate reflection of SaO₂ values measured by the reference standard (CO-oximeter) with a bias of 2% and with a standard deviation (precision) of less than 3%².

Results

Demographic data of the 10 volunteers are described in the were age: 31 (7) years old, weight 71 (9) kg and height: 173 (4) cm. The mean time for the stabilization of the expired O₂ fraction once supplementary oxygen therapy was removed was 56 (7) seconds.

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Selection of topic	Item	Description
Title, abstract	1	Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.
	2	<p>Objective To assess the diagnostic accuracy of SpO₂ while breathing room air for 5 min (“the Air-Test”) in detecting postoperative atelectasis.</p> <p>Design Prospective, cohort study. Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standar computed tomography scan.</p> <p>Setting Postanesthetic care unit in a terciary Hospital in Spain.</p> <p>Participants 350 patients from January 12 to February 7, 2015. 170 patients scheduled for surgery under general anesthesia admitted into the postsurgical unit were included.</p> <p>Intervention The Air-Test was performed in awake extubated patients after a 30 min stabilization period receiving supplemental oxygen therapy via a Venturi mask. The Air-Test was defined positive when SpO₂ was ≤96% and negative when ≥97%. Arterial blood gases were measured in all patients at the end of the Air-Test. Within the next 25 min, the presence of atelectasis was evaluated by computed tomography scan in 59 randomly selected patients.</p> <p>Main Outcomes Measures The primary study outcome was the accuracy of the Air-Test for the detection of postoperative atelectasis assess by reference standar. The secondary outcome was incidence of positive Air-Test.</p> <p>Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scan in all patients (30/30) with positive and in 5 patients (17%) with negative Air-Test. Based on the Air-Test, postoperative atelectasis were present in 36% of the patients (62 out of 170).</p> <p>Conclusion The Air Test is an accurate, simple, inexpensive and noninvasive method to diagnose postoperative atelectasis.</p> <p>Trial Registration ClinicalTrials.gov Identifier: NCT02650037.</p>
Introduction	3	<p>Oxygen therapy is usually applied in the postoperative period to alleviate hypoxemia¹⁰, which develops in most patients after general anesthesia. As a result, most atelectasis in the postoperative period may not be diagnosed at the bedside precluding the application of any corrective measure and thus potentially increasing the risk of atelectasis-related postoperative complications. In the other hand, the use of low FIO₂ (0.21) could better categorize lung function through SpO₂ values, as it forces SpO₂ to operate at the steep portion of the oxygen-hemoglobin dissociation curve, and thus it can be used to estimate the alveolar shunt using the SpO₂-FIO₂ diagram described by Jones et al¹¹. This may help to unmask underlying oxygenation deficits due to shunt and thus the presence of atelectasis when SpO₂ is low, assuming a linear relationship between shunt and atelectasis. Thus, a combination of oxygen therapy with transitory decreases of FIO₂ to 0.21 during a 5 minutes period, which is enough to achieve a steady state condition of the expired fraction of oxygen (FEO₂)^{12,13} may allow to estimate shunt and to unmask the presence of atelectasis during the immediate postoperative period.</p>
	4	<p>We hypothesized that changes in arterial oxygen saturation induced by a short maneuver of FIO₂ reduction to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO₂ recorded by pulse oximetry after breathing room-air for 5 min (“the Air-Test”) can reveal the presence of atelectasis and to establish the relation of the SpO₂ value to the presence of atelectasis assessed by CT-scan.</p>
Methods		
Participants	5	<p>We performed a prospective, cohort study at the post-surgical recovery unit of the Hospital Clínico Universitario, Valencia, Spain, from January 12 to February 7, 2015.</p>

	6,7,8,9	The study included consecutive patients with an American Society of Anaesthesiologists physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical unit. Exclusion criteria were: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, and (v) preoperative SpO ₂ ≤97% on room-air. Postoperatively patients who gave their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin <10 g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale > 1 or < -1, and (vi) pain > 4 evaluated with the visual analogue scale after the first 30 min in the PACU (Figure 1).
Test□Methods	10a	Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO ₂ of 0.5 during the first 30 min. The Air-Test was performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO ₂ monitoring with a finger probe pulse-oximeter
	10b	<p>CT-scans were obtained with 16-detector row/ 32 slices Aquillion LB (Toshiba). Scans (120 kV, 100-140 mA and 0.5 sec rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5 mm thickness slices with 5 mm interval and a depth of 12 bits per pixel. Each right and left surface of normally aerated tissue and atelectasis were semi automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchi and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to 100). After this correction, separation between normally aerated lung and atelectasis was automatically corrected. An example of the segmentation steps can be seen in Figure 2. Quantitative analysis of CT densities was performed using previously validated methods^{18,19}. The atelectatic area was expressed in cm² as mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROI) were calculated using equation 1:</p> $VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$ <p>Where V is the set of voxels inside the ROI and x, y and z the voxel sizes in the three dimensions given in millimeters. Volumes are given in milliliters. Mass of lung tissue for the different ROIS were calculated as previously described²⁰. See equation 2:</p> $MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$ <p>Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V, HU_i represents the CT value for voxel i and VOL_{voxel} represents the voxel volume for the image being processed given in milliliters. The atelectatic mass was expressed in grams as mean ± standard deviation (SD) and as a percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but performed at the region presenting the largest amount of atelectasis in each lung independently. All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.</p>
	11	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique. It was used an adaptive randomization which allowed us to minimize the exposure to CT-scans in patients not expected to have atelectasis but having sufficient number of patients on each arm to conduct comparisons

	12a	The Air-Test was considered positive when the recorded SpO ₂ was ≤96% and negative when SpO ₂ was ≥97%. The selected cut-off value to diagnose atelectasis was based in the SpO ₂ -FIO ₂ diagram ¹⁰ described by Jones which showed that a SpO ₂ was ≤96% corresponds to a shunt effect >10% which defines alveolar collapse. Recently, Tusman et al. ¹⁴ used a similar approach by using a FIO ₂ of 0.21 to define an open-lung condition in anesthetized patients while ventilated.
	12b	For the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible (negative) based in previous data because it does not cause a clinically relevant shunt
	13	All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.
	12	Data were analysed using the statistical software R version 3.1.1. All the analysis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i> . We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro-Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range).
Analysis		
	14	<p>Diagnostic test of the index test (Air-Test)</p> <p>A 2×2 table (table 2) was used for the assessment of sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP + TN)] \times 100$; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$; where <i>TP</i> is true positive, <i>TN</i> is true negative, <i>FP</i> is false positive, and <i>FN</i> is false negative.</p> <p>Statistical analysis</p> <p>The total sample size was not calculated as this is a cohort study. The sample size for patients randomized for CT-scan was also not calculated as this is preliminary pilot study. Thus, we arbitrarily decided that the minimum sample size was at least 50 patients (25 patients with positive Air-Test and 25 with negative). Data were analysed using the statistical software R version 3.1.1²¹. All the analysis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i>. We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro-Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range). A simple linear regression model was used with the variables SpO₂ and the total area of atelectasis following the formula: Area of atelectasis ~ SpO₂ + ε, where ε is the error. A regression line was built in the scatterplot with the function <i>lm()</i>. The diagnostic accuracy and sensitivity analysis were conducted in R with the <i>library pROC</i>. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values were computed with bootstrap resampling and the averaging methods described by Fawcett²². Bootstrap has shown to generate unbiased optimism-adjusted estimates of the CIs statistic. In all bootstrap CIs, patients were resampled and the modified curve was built before the statistics of interest were computed. As in the bootstrap comparison test, the resampling was done in a stratified manner²³. For all comparisons, a two-sided value of p<0.05 was considered significant.</p>
	17	All the analysis performed were pre-specified
Results		
Participants	19	Figure 1

	20	Table 1
	21	Table 2
	22	Table 2
	22	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique.
Test Results	23	Table 3
	24	Table 3
	25	Adverse events No adverse events were reported during the study period.
Discussion		
	26	Limitations We must acknowledge several limitations. First, the Air-Test can only be applied to patients with a preoperative SpO ₂ ≥97% on room-air, since it is not possible to differentiate whether the postoperative SpO ₂ indicates the presence of postoperative atelectasis or previous lung disease. However, a high percentage of patients scheduled for surgery have a SpO ₂ ≥97% ²⁴ . Second, intraoperative respiratory complications that decrease low V/Q zones and therefore decrease SpO ₂ , such as lung edema or pneumothorax, may overestimate shunt-induced by atelectasis based on the SpO ₂ -FIO ₂ . However, these postoperative complications in the immediate postoperative period rarely appear ³⁴ . Third, compensatory mechanisms in the presence of atelectasis such as the hypoxic pulmonary vasoconstriction decreases shunt and therefore may increase SpO ₂ , which would underestimate atelectasis based on the SpO ₂ -FIO ₂ diagram. This last two limitations may decrease the sensitivity and specificity of the Air-Test. Fourth, temporal factors could have affected our results because of time delays among the Air-Test, arterial blood gases, and the CT-scan. However, if at all, results would have been affected in a negative sense since a time-dependent reduction of postoperative atelectasis occurs as patients improve their breathing capacity. Fifth, erroneous readings of the pulse-oximeter may underestimate postoperative atelectasis in the presence of dyshemoglobinemias or overestimate them in the presence of anemia, low perfusion state, motion artifacts or hypothermia ²⁹ . Some of these limitations are not only related to the pulse-oximeter but also to the Air-Test itself as shifts of the oxy-hemoglobin dissociation curve can affect the principle used by Jones et al. to describe the SpO ₂ -FIO ₂ diagram ¹¹ . However, this limitation was well controlled as shown in tables 1 and 2. Finally, for the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible. Although this percentage is not clinically relevant, these atelectasis which are not diagnosed with the Air-Test could potentially trigger an inflammatory response ³⁵ which at last would affect the rationale of using this test.
	27	Implications for practice First, this is a pilot study and a powered large external validation study is needed in a more heterogeneous surgical population such as obese, patients without previously normal lung function or patients with a preoperative SpO ₂ <97%. Such a study may also analyze the Air-Test at different time points, with different pulse-oximeter technologies and in patients without previously supplemental oxygen delivery during the postoperative period with the aim to validate the test as a surrogate of postoperative atelectasis; and its severity if it is found a correlation between the SpO ₂ values during the Air-Test and the area of atelectasis measured by CT-scan. Second, the Air-Test may become a standardized screening test before leaving the PACU to evaluate postoperative oxygenation. It may contribute to a higher patient flow in PACU without losing high care quality as it may discriminate those patients without postoperative lung derecruitment (negative Air-Test) from those (positive Air-Test) with an increased risk of postoperative hypoxemia ³⁶ , whom should ideally be surveyed more closely during this period and would likely benefit from measures to revert atelectasis, which may have a potential positive impact on healthcare costs ³⁷ . Despite the benefits in outcomes of these measures remain uncertain ³⁸ , several studies showed the potential benefits ³⁹

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		and currently is ongoing a clinical trial which uses the Air-Test to individually apply the use of a postoperative continuous positive end-expiratory pressure ⁴⁰ .
	28	Trial Registration ClinicalTrials.gov Identifier: NCT02650037.
	29	The complete and original protocol is described in this section.
	30	The work was not supported

For peer review only

DOCUMENTACIÓN PROYECTO DE INVESTIGACIÓN

1. Carta de presentación al Comité Ético
2. Memoria del Proyecto de investigación
3. Hoja de Información al Paciente y Consentimiento Informado según modelo del Hospital Clínico Universitario de Valencia.
4. Compromiso del Investigador, según modelo propio del Comité.
5. Autorización del Jefe de Servicio según modelo propio del Comité.
6. Autorización del Jefe de Servicio Implicado según modelo propio del Comité
7. Currículum Vitae del Investigador Principal y sus Colaboradores
8. Memoria Económica

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5 Hospital Clínico Universitario De Valencia
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11 Valencia, 4 de Abril de 2014
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16 **Ref: Proyecto Investigación**
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18 Estimados Señores;
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21 En referencia al protocolo titulado: **Estudio de validación de la pulsioximetría como**
22 **método diagnóstico no invasivo de atelectasia durante el postoperatorio;** con el **Dr.**
23 **Carlos Ferrando** como investigador principal, adjunto les remito la siguiente
24 documentación para que sea evaluado por el Comité Ético:
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29 - Memoria del Proyecto de investigación.
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31 - Hoja de Información al Paciente y Consentimiento Informado según modelo del
32 Hospital Clínico Universitario de Valencia.
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40 - Currículum Vitae del Investigador Principal y sus Colaboradores.
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44 - Memoria Económica.
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56 Fdo.: Dr. Carlos Ferrando
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1. Introducción y justificación:

La complicación postoperatoria más frecuente tras una anestesia general es la hipoxemia [1]. La hipoxemia es consecuencia de la aparición de atelectasias [2]. La anestesia general lleva implícita la formación de atelectasias, y éstas mayoritariamente se producen durante la inducción y los primeros minutos de la ventilación mecánica (VM)[3]. La no apertura de estas atelectasias durante la VM hace que persistan durante el postoperatorio [4]. A las atelectasias producidas durante el intraoperatorio pueden sumarse nuevas que aparecen en el postoperatorio inmediato como consecuencia de la hipoventilación generada por los efectos residuales de la anestesia general, dolor, encamamiento, disfunción diafragmática o disminución del aclaramiento mucociliar [5]. La presencia de las atelectasias durante el postoperatorio incrementa la incidencia de complicaciones pulmonares postoperatorias (CPP) tales como hipoxemia y neumonía. La aparición de estas CPP como atelectasias, hipoxemia y neumonía aumentan la necesidad y los días de VM en el postoperatorio, aumenta los reingresos no programados y los días de estancia en las unidades de cuidados críticos [1,6].

La primera manifestación clínica de la atelectasia es la hipoxemia. Para que esta se manifieste clínicamente (hipoxemia) el porcentaje de shunt intrapulmonar que debe producir la atelectasia ha de ser superior al 15% respirando aire ambiente (fracción inspiratoria de oxígeno (FiO_2) 0.21) y superior a 0.5 a las concentraciones de oxígeno habitualmente administrada durante el postoperatorio de estos pacientes (FiO_2 0.5). Sin embargo, las atelectasias pueden pasar desapercibidas si no se manifiestan clínicamente como hipoxemia, aumentando el riesgo de neumonía postoperatoria, aumentando los requerimientos de VM y la estancia hospitalaria.

A día de hoy el diagnóstico de atelectasia requiere de la realización de técnicas de imagen como la radiografía de tórax o la tomografía, pero ambas técnicas tienen limitaciones. La tomografía es considerada el "gold standar", sin embargo no es clínicamente factible realizarla debido a la carga que supondría para el sistema sanitario por el volumen de pacientes diarios intervenidos quirúrgicamente con anestesia general, y porque generaría un gasto sanitario no sostenible. A día de hoy, la

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3 radiografía de tórax es la técnica de imagen más frecuentemente utilizada a pie de
4 cama, pero ha demostrado una baja sensibilidad y especificidad para el diagnóstico de
5 la atelectasia con una mala correlación con la tomografía [7]. Una alternativa cada día
6 más frecuentemente utilizada es la ultrasonografía pulmonar. Estudios previos han
7 demostrado que esta técnica tiene una sensibilidad del 90% y especificidad del 95%
8 para el diagnóstico de la atelectasia [8]. Sin embargo, la ultrasonografía pulmonar
9 también tiene una serie de limitaciones para la práctica clínica diaria como son la
10 disponibilidad de un ecógrafo, la curva de aprendizaje de la técnica y de la
11 interpretación de los resultados y el consumo de tiempo necesario para realizarla, que
12 hace que la técnica no pueda realizarse a todos los pacientes durante el
13 postoperatorio.
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23 Como se ha comentado previamente, la atelectasia genera shunt, y el shunt una
24 disminución de la presión arterial de oxígeno (PaO_2). La caída de la PaO_2 producirá una
25 disminución de la saturación periférica de oxígeno (SpO_2). Tomando como referencia el
26 comportamiento de la curva de disociación de la hemoglobina en pulmón normal, un
27 punto de corte de una $SpO_2 \geq 97\%$ con una FiO_2 de 0.21 define una condición de
28 pulmón abierto (ausencia de atelectasia). Por tanto, una $SpO_2 \leq 96\%$ a una FiO_2 de 0.21
29 diagnosticaría la presencia de atelectasia [9]. Sin embargo, este método no ha sido
30 validado a día de hoy con técnicas de imagen consideras como el "gold standar" para
31 el diagnóstico de la atelectasia.
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40 De entre las técnicas que han demostrado disminuir las complicaciones pulmonares
41 postoperatorias al disminuir las atelectasias está la maniobra de capacidad vital [10].
42 Esta maniobra consiste en la realización de una inspiración profunda. Sin embargo, el
43 último meta-análisis concluye que debido a una heterogeneidad estadísticamente
44 significativa los resultados no son concluyentes [4].
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50 Por todo esto está justificada la realización de un estudio clínico durante el
51 postoperatorio inmediato en pacientes sometidos a anestesia general que: valide la
52 utilización de la SpO_2 como método diagnóstico de atelectasia utilizando la
53 ultrasonografía pulmonar y que valide la utilización de la maniobra de capacidad vital
54 como maniobra efectiva para el tratamiento de las atelectasias.
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2. Hipótesis

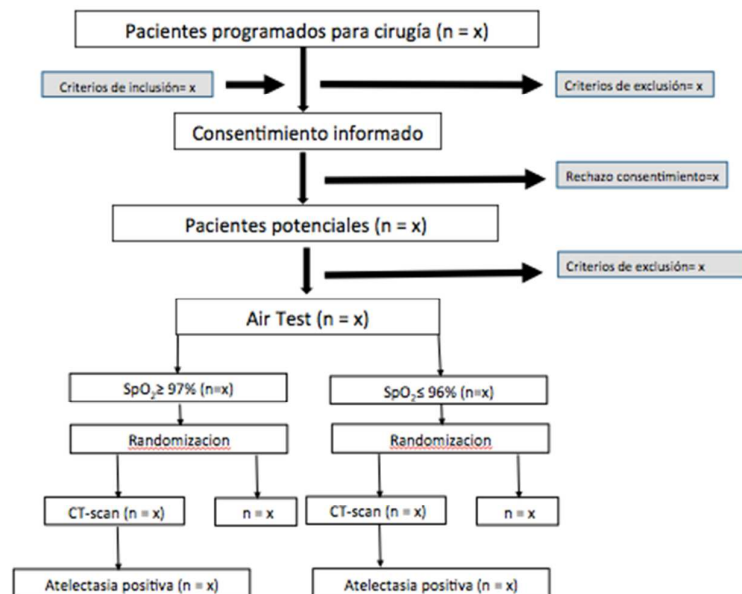
La monitorización de la SpO_2 durante la oxigenación con FiO_2 de 0.21 y utilizando como punto de corte una $SpO_2 \leq 96\%$ es un método efectivo y sensible para el diagnóstico de atelectasia. La realización de una maniobra de capacidad vital durante el postoperatorio inmediato es un método efectivo para el tratamiento de la atelectasia. La reversión de la atelectasia con la maniobra de capacidad vital es evaluado de manera sensible y específica mediante la monitorización de la SpO_2 .

3. Objetivos

1. Validar la utilización de una $SpO_2 \leq 96\%$ durante la oxigenación con FiO_2 de 0.21 como método para el diagnóstico de atelectasia en pacientes postoperados mediante la tomografía axial computerizada (TAC).

4. Metodología

Figura 1. Diagrama de Flujo del estudio.



4.1 Tipo de estudio

Prospectivo, observacional.

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3 4.2 El estudio comenzará tras la aprobación por el CEIC del HCUV, con una duración
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4.2 El estudio comenzará tras la aprobación por el CEIC del HCUV, con una duración
estimada de 3 meses.

4.3 Población

Pacientes postoperados en ventilación espontánea con SpO₂ ≤96% durante los
primeros minutos de ingreso en la unidad de recuperación postanestésica (URPA).

Número de pacientes: x pacientes.

4.4 Criterios de inclusión

- Pacientes con clasificación ASA I-IV
- Edad > 18 años
- Aceptación y firma del consentimiento informado

4.5. Criterios de exclusion

- Edad < 18 años
- Pacientes postoperados de cirugía de resección pulmonar.
- Pacientes con patología pulmonar previa que pudiera dificultar la
interpretación de las técnicas de imagen.
- Pacientes que requieran soporte ventilatorio invasivo o no invasivo en el momento
de ingreso en URPA
- Mujeres embarazadas o en fase de lactancia.
- SpO₂ < 92% con FiO₂ de 0.50.

4.6 Criterios de retirada del estudio: Pacientes en los que una vez incluidos en el
estudio se incumpla el protocolo por cuestiones médicas o porque el paciente retire su
consentimiento.

4.7 Protocolo de estudio

El manejo anestésico, hemodinámico, respiratorio y analgésico intraoperatorio y
postoperatorio se realizará según la práctica clínica habitual, siguiendo los protocolos
de manejo anestésico del servicio de Anestesiología y Reanimación.

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3 Una vez el paciente llegue a la URPA se iniciará la monitorización y cuidados médicos y
4 de enfermería protocolizados. Se iniciará oxigenoterapia con una mascarilla Venturi a
5 una de FiO_2 0.50.
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9 Durante los primeros 15 y 30 minutos tras el ingreso en la URPA, cuando el paciente
10 esté colaborativo, con un estado neurológico aceptable (Richmonn de entre -1 y +1),
11 con fuerza conservada y con un nivel analgésico adecuado (EVA <3) se le retirara la
12 mascarilla Venturi y se oxigenará al paciente con una FiO_2 de 0.21 durante 5 minutos.
13 Si la $SpO_2 \leq 96\%$ se diagnosticará al paciente de atelectasia. Si la $SpO_2 \geq 97\%$ se
14 diagnosticará de ausencia de atelectasia.
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20 Tras los 5 min de oxigenación con una FiO_2 de 0.21 se extraerá una gasometría arterial
21 para la evaluación de gases arteriales en sangre.
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25 Técnica de la tomografía axial computerizada

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27 Para la realización de la tomografía computarizada se utilizará un equipo multicorte de
28 16 coronas de detectores (Aquilion LB, Toshiba) con el paciente en decúbito supino, en
29 apnea, sin contraste intravenoso y en sentido craneocaudal en un rango que incluye
30 los ápices pulmonares y las glándulas suprarrenales. Se emplean los siguientes
31 parámetros de adquisición: 120 kV, 100-140 mA, tiempo de rotación de gantry 0,5 s.
32 Para la interpretación de las imágenes los datos se reconstruyen con un grosor de
33 corte de 5 mm a intervalos de 5 mm. Cada una de las secciones tiene una profundidad
34 de 12 bits por pixel.
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42 Las imágenes se interpretan con la amplitud y nivel de ventana adecuados (1500
43 unidades Hounsfield (UH), -600 UH).
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46 La atelectasia se definirá la atenuación en el TAC > de - 100 a +100 HU.
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49 Variables de estudio:

50 Las variables se agruparán del siguiente modo:
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- 53 • Variables demográficas: Edad, sexo, talla, peso corporal ideal (PBW), comorbilidad,
54 tipo de cirugía, tiempo de ventilación mecánica.
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- Variables farmacológicas: Hipnótico, mórfoico, relajante neuromuscular, analgesia epidural o intravenosa.
- Variables del intercambio gaseoso y otros valores de la gasometría arterial: PaO₂, PaCO₂, pH y Bicarbonato, serán recogidas del analizador de gases i-stat (Abbott Laboratorios). La SpO₂ será recogida del monitor hemodinámico Dash 3000 (GE Healthcare).

La sangre arterial será recogida a través de la cánula de la arterial radial. Se extraerán 0,5 ml tras desechar los primeros 5ml.

- Variable de volumen pulmonar: Se medirá el volumen pulmonar atelectasiado con la ecografía pulmonar y la tomografía axial computerizada.

Tiempos de estudio:

T₁: 15-30 min tras el ingreso en la URPA. SpO₂, gasometría arterial, ultrasonografía

T₂: A alta de la Unidad de Recuperación Postanestésica. SpO₂, tomografía.

5. Estudio estadístico

Los datos serán recogidos en tablas diseñadas de forma específica para cada fase del estudio, componiendo un cuaderno de recogida de datos para cada paciente. Se procesaran en el programa estadístico statistical software R version 3.1.1.

Inicialmente se hará un estudio demográfico de la población (sexo, edad, peso, IMC), comprobando la homogeneidad de sus variables, y una comparativa con la bibliografía de que la muestra es representativa de la población a estudio.

Se comprobará la hipótesis de normalidad de las distribuciones mediante el test de Kolmogorov-Smirnov, en el caso de variables continuas y la prueba de bondad de ajuste de Test Chi-cuadrado para variables categóricas.

Los resultados de la variables cuantitativas continuas se expresaran como media más desviación estándar para las variables con una distribución normal y como mediana más rango intercuartílico para las variables con una distribución no normal.

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3 Para el análisis de la variable principal del estudio como es la pulsioximetría con SpO₂
4 ≤96% con FiO₂ 0.21, y su asociación con la presencia de atelectasia en TAC (> de -
5 100HU), realizaremos el. Test Chi-cuadrado para comparación de las proporciones. Al
6 igual que el análisis mediante Curva COR de la cuantificación de grado de atelectasia
7 en TAC y la pulsioximetría, como parámetro clínico.
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12 En los casos en que rechace tal hipótesis de homogeneidad de varianzas (p- valor del
13 test < 0,05), se aplicará el test estadístico para K muestras independientes (T Kruskal
14 Wallis) o el Test estadístico de la U de Mann Whitney cuando la comparación sea de
15 dos grupos. Si la hipótesis nula no se rechaza, las técnicas utilizadas seran el test de la
16 T de Student realizando previamente Test de Levene para igualdad de varianzas, o
17 ANOVA cuando se trate de tres grupos. Se utilizará la prueba de Chi-cuadrado y el test
18 exacto de Fisher para analizar la diferencia entre proporciones.
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25 26 **6. Bibliografía**

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28 **7. Fortalezas del estudio**

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30 La complicación postoperatoria más frecuente es la atelectasia, pero muchas de ellas
31 pueden pasar desapercibidas debido al uso de FiO₂ elevada durante el postoperatorio.
32 El tratamiento de la atelectasia ha demostrado disminuir la aparición de
33 complicaciones postoperatorias más graves como hipoxemia, neumonía,
34 requerimientos de ventilación mecánica e incluso complicaciones sistémicas como SIRS
35 y Sepsis. Sin embargo, las atelectasias no suelen tratarse ni prevenirse de manera
36 rutinaria hasta que no se manifiestan como hipoxemia debido a que a día de hoy solo
37 pueden diagnosticarse mediante técnicas de imagen. Técnicas que por otra parte no se
38 realizan de manera rutinaria.
39

40 Si se concluye el estudio con éxito, podremos diagnosticar de manera inmediata y no
41 invasiva la presencia de atelectasias durante el postoperatorio inmediato. El
42 diagnóstico temprano permitirá un tratamiento adecuado y precoz disminuyendo la
43 aparición de complicaciones postoperatorias, disminuirá la utilización de recursos
44 sanitarios y la estancia hospitalaria. Además, el diagnóstico de atelectasia con un
45 método no invasivo supondrá un ahorro en el coste al evitar la realización de técnicas
46 de imagen como radiografía de tórax o tomografía.
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8. Impacto esperado

Si nuestra hipótesis es correcta, los beneficios esperables de diagnosticar de manera no invasiva y temprana la presencia de atelectasias para la salud pública incluyen:

- Menos probabilidades de que se desarrollen complicaciones pulmonares graves postoperatorias, pudiéndose trasladar la técnica a cualquier paciente.
- Alta temprana de la Unidad de recuperación postanestésica (URPA)
- Alta temprana del hospital
- Reducción significativa de los costes sanitarios

HOJA DE INFORMACIÓN AL PACIENTE

Se le ofrece la posibilidad de participar en el proyecto de investigación titulado **“Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia pulmonar durante el postoperatorio”** que está siendo realizado por el Dr. Carlos Ferrando del Servicio de Anestesiología y Reanimación y que ha sido ya evaluado y aprobado por el Comité Ético de Investigación Clínica del Hospital Clínico Universitario de Valencia.

Antecedentes:

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3 Después de una intervención quirúrgica la complicación que aparece con mayor
4 frecuencia es la disminución de la cantidad de oxígeno existente en la sangre (lo que se
5 denomina hipoxemia), debido a una disminución del volumen de los pulmones
6 (denominado atelectasia). La existencia de atelectasias pasa muchas veces
7 desapercibida debido a que al paciente se le administra oxígeno después de la cirugía y
8 por lo tanto la cantidad de oxígeno medida en la sangre llega a estar en muchas
9 ocasiones dentro de la normalidad.

10
11 Sin embargo, diagnosticar y tratar las atelectasias es importante ya que si se
12 mantienen, se incrementa la aparición de complicaciones postoperatorias tales como
13 neumonía o reingresos. Un motivo de que no se traten es que hoy en día solo pueden
14 diagnosticarse mediante técnicas de imagen (radiografía de tórax, ecografía, TAC) que
15 no se realizan de manera rutinaria. Nuestro equipo de trabajo propone un método
16 sencillo y nada invasivo de diagnosticar y tratar las atelectasias nada más que el
17 paciente sale del quirófano. Este método hay que aplicarlo a un grupo de pacientes y
18 comprobar que efectivamente es útil. Por este motivo se plantea el presente estudio y
19 se le pide su colaboración.

20 21 **¿Cuál es el objetivo de este estudio?**

22 El objetivo del estudio es validar la utilización de la medida de la cantidad de
23 oxígeno en sangre periférica sin administrar oxígeno suplementario al paciente como
24 método diagnóstico de las atelectasias, y validar la utilización de la maniobra de
25 capacidad vital (realizar una inspiración profunda) como maniobra efectiva para el
26 tratamiento de las atelectasias.

27 28 **¿Por qué se le ha pedido que participe?**

29 Se le ha pedido que participe en este estudio, porque usted va ser intervenido
30 quirúrgicamente bajo anestesia general y cuando salga de quirófano está previsto que
31 permanezca unas horas en la Unidad de Recuperación Postanestésica (URPA).

32 33 **¿En qué consiste su participación? ¿Qué tipo de pruebas o procedimientos se le 34 realizarán?**

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3 El inicio de la participación en el estudio es el día de su intervención quirúrgica.
4 Antes de iniciar el estudio, se revisarán sus antecedentes personales médicos y
5 quirúrgicos, su situación clínica, y los resultados de los últimos análisis realizados en la
6 visita de preanestesia, para determinar si cumple los criterios para poder participar en
7 el estudio. Si cumple los criterios y decide participar, cuando salga de quirófano
8 ingresará como es habitual en la Unidad de Recuperación Postanestésica donde
9 permanecerá unas horas. Allí se recogerán datos relacionados con su contenido de
10 oxígeno en la sangre por medio del análisis de muestras de sangre arterial (2
11 muestras), y se valorarán sus pulmones por medio de una ecografía. De vez en cuando
12 le pediremos que haga una respiración lo más profunda que pueda.
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20
21 Una vez que su médico responsable de el alta de la URPA, antes de trasladarlo a
22 su habitación se le realizará un TAC (Tomografía axial computerizada).
23

24 Todas estas determinaciones las realizará el médico investigador o la persona del
25 equipo por él designada.
26
27
28

29
30 Es importante que usted sepa que su participación en el estudio no supone la
31 necesidad de recibir más medicación ni la realización de analíticas adicionales o
32 mediciones de parámetros diferentes a los habituales. La participación en el presente
33 proyecto no supone ninguna alteración del tratamiento que esté llevando (si lo tiene) y
34 todo tratamiento que se le pueda poner a partir de los estudios clínico-bioquímicos
35 que se le realicen será siempre bajo criterio médico.
36
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40 41 **¿Cuáles son los riesgos generales de participar en este estudio?** 42

43
44 Los riesgos adicionales por su participación en el estudio son los relacionados
45 con la punción para la extracción de muestra de sangre en el caso de que no tenga un
46 catéter colocado en la arteria cuando salga de quirófano, y los relacionados con la
47 realización del TAC.
48
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51
52 La punción en la arteria puede ocasionarle dolor, y en raras ocasiones hematoma. La
53 realización de una prueba de TAC aislada produce en el paciente una mínima
54 irradiación clínicamente no significativa y que no acarrea complicación alguna.
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58 **¿Cuáles son los beneficios de la participación en este estudio?** 59 60

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3 Basado en conocimientos y observaciones previas parece que la aplicación de la
4 maniobra de inspiración profunda puede reducir la aparición de atelectasias
5 postoperatorias, sin embargo, no podemos garantizar que obtenga beneficios clínicos
6 directos por su participación en el estudio, ya que es precisamente lo que queremos
7 averiguar. En todo caso su participación ayudará a conocer mejor el resultado de
8 diferentes estrategias de ventilación y así mejorar el tratamiento y pronóstico de
9 futuros pacientes.
10

11 **¿Qué pasará si decido no participar en este estudio?**

12 Su participación en este estudio es totalmente voluntaria. En caso de que
13 decida no participar en el estudio, esto no modificará el trato y seguimiento que de su
14 enfermedad realicen ni su médico ni el resto del personal sanitario que se ocupa de su
15 enfermedad. Así mismo, podrá retirarse del estudio en cualquier momento, sin tener
16 que dar explicaciones.
17

18 **Manejo clínico alternativo**

19 La alternativa a entrar en este estudio es recibir también oxígeno a la
20 concentración y el tiempo que su médico responsable considere necesario, y puede
21 incluir o no las maniobras de respiración profunda.
22

23 **¿A quién puedo preguntar en caso de duda?**

24 Es importante que comente con cualquiera de los investigadores de este
25 proyecto los pormenores o dudas que surjan antes de firmar el consentimiento para su
26 participación.
27

28 Así mismo, podrá solicitar cualquier explicación que desee sobre cualquier
29 aspecto del estudio y sus implicaciones a lo largo del mismo contactando con el
30 investigador principal del proyecto, el Dr. Carlos Ferrando en el teléfono 963862600
31 (Extensión 62653).
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Confidencialidad:

Todos sus datos, así como toda la información médica relacionada con su enfermedad será tratada con absoluta confidencialidad por parte del personal encargado de la investigación. Así mismo, si los resultados del estudio fueran susceptibles de publicación en revistas científicas, en ningún momento se proporcionarán datos personales de los pacientes que han colaborado en esta investigación.

Tal y como contempla la Ley de Protección de Datos de Carácter Personal, podrá ejercer su derecho a acceder, rectificar o cancelar sus datos contactando con el investigador principal de este estudio.

Otra información relevante

Durante su participación en este estudio, se le extraerán muestras de sangre de un catéter arterial durante la intervención quirúrgica y en el periodo posterior a la intervención. La muestra de sangre será analizada inmediatamente después de su extracción y lo que pueda sobrar se eliminará inmediatamente. Esta muestra será siempre utilizada con fines científicos

CONSENTIMIENTO INFORMADO

Título del Proyecto titulado: **“Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia pulmonar durante el postoperatorio”**

Investigador principal: Carlos Ferrando Ortola

Servicio: Anestesiología y Reanimación

Yo, _____ he sido informado por el
Dr. _____, colaborador del proyecto de investigación arriba mencionado,
y declaro que:

- 1
2
3 - He leído la Hoja de Información que se me ha entregado
4
5 - He podido hacer preguntas sobre el estudio
6
7 - He recibido respuestas satisfactorias a mis preguntas
8
9 - He recibido suficiente información sobre el estudio

10
11 Comprendo que mi participación es voluntaria

12
13 Comprendo que todos mis datos serán tratados confidencialmente

14
15 Comprendo que puedo retirarme del estudio:

- 16
17
18 - Cuando quiera
19
20 - Sin tener que dar explicaciones
21
22 - Sin que esto repercuta en mis cuidados médicos
23

24 Con esto doy mi conformidad para participar en este estudio,
25
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32 Firma del paciente:

Firma del Investigador:

33
34 Fecha:

Fecha

35
36
37 **TITULO:** Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia
38 pulmonar y de la efectividad de la maniobra de capacidad vital para la reversión de la atelectasia
39 durante el postoperatorio

40 **INVESTIGADOR PRINCIPAL:** Carlos Ferrando

41
42 **COMPROMISO DEL INVESTIGADOR PRINCIPAL Y AUTORIZACIÓN JEFE DE SERVICIO**

43
44 Carlos Ferrando como Investigador Principal del Proyecto, DECLARA:

- 45
46 - Que conoce y acepta su participación.
47 - Que se compromete a que cada sujeto sea tratado y controlado siguiendo lo establecido en el
48 protocolo autorizado por el Comité Ético de Investigación Clínica del Hospital Clínico Universitario de
49 Valencia.
50 - Que respetará las normas éticas aplicables a este tipo de estudios.
51 - Que dicho estudio se llevará a cabo contando con la colaboración de:
52
 - 53 • CarolinaRomero
 - 54 • Paola Valls
 - 55 • Angels Lozano
 - 56 • Irene León
 - 57 • Marina Soro
 - 58 • Francisco Martí

59
60

- Rosa Dosda
- Francisco Javier Belda

FIRMADO:

Dr. Carlos Ferrando
Investigador principal

Dra. Carolina Romero
Investigador colaborador

Dra. Paola Valls
Investigador colaborador

Dra. Angels Lozano
Investigador principal

Dra. Marina Soro
Investigador colaborador

Dra. Irene León
Investigador colaborador

Dr. Francisco Martí
Investigador colaborador

Dr. Francisco Javier Belda
Investigador colaborador

Dra. Rosa Dosda
Investigador colaborador

Cristina Parrilla
Investigador colaborador

Dr. Francisco Javier Belda como Jefe de Servicio de (Anestesiología y Reanimación), DECLARO:

Que conozco cuanta documentación da base al trabajo del Proyecto, que el investigador principal y el resto del equipo, reúne las características de competencia necesarias para realizar este proyecto, así como la metodología específica del Proyecto de referencia.

Que autorizo la realización de este Proyecto en el Servicio que dirijo.

En _____, a __ de _____ de 20__

Fdo: Anestesiología y Reanimación

TITULO: Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia pulmonar y de la efectividad de la maniobra de capacidad vital para la reversión de la atelectasia durante el postoperatorio.

INVESTIGADOR PRINCIPAL: Carlos Ferrando

INFORME DEL INVESTIGADOR PRINCIPAL

Carlos Ferrando como Investigador Principal del Proyecto, CERTIFICA que:

¿Existen pruebas extraordinarias y/o colaboración a realizar por otros servicios? SI

Indicar cual:

¿Se ha comunicado a dicho servicio y se dispone de la correspondiente autorización? SI

¿La realización del estudio supone una modificación de la Práctica Clínica Habitual? SI

La realización de la tomografía no es una práctica clínica habitual durante el postoperatorio inmediato en pacientes con sospecha de atelectasia. Sin embargo, si es utilizada como método diagnóstico durante la aparición de complicaciones pulmonares postoperatorias. Muchas de las complicaciones aparecen como consecuencia de no diagnosticar y tratar la atelectasia. Una atelectasia no tratada puede tener consecuencias como hipoxemia, neumonía, lesión pulmonar, aumento de la respuesta inflamatoria pudiendo llegar a producir sepsis/shock séptico.

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9 La realización del estudio, ¿implica algún uso extraordinario de los medios del HCUV? SI

10 El coste secundario a la realización de la tomografía. Sin embargo, la validación de un método no
11 invasivo como la pulsioximetría como método diagnóstico de atelectasia supondrá un mejor
12 tratamiento inmediato con menor probabilidad de que se desarrollen complicaciones y a la postre un
13 ahorro del coste sanitario.
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22 En _____, a __ de _____ de 20__
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30 Fdo: Dr. Carlos Ferrando
31 Investigador Principal
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39 **TITULO:** Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia
40 pulmonar y de la efectividad de la maniobra de capacidad vital para la reversión de la atelectasia
41 durante el postoperatorio

42 **INVESTIGADOR PRINCIPAL:** Carlos Ferrando

43 **PRUEBAS EXTRAORDINARIAS Y /O COLABORACION.**

44 **CONFORMIDAD DE SERVICIO IMPLICADO**

45 Cumplimentar únicamente si existen pruebas extraordinarias o colaboraciones con otros servicios.

46 Indicar Nombre del Servicio Colaborador
47
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PRUEBAS EXTRAORDINARIAS	NOMBRE	Nº PRUEBAS	IMPORTE UNITARIO
	Tomografía axial computerizada	30	0 €
		€	
		€	
		€	
		€	
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PAGOS POR COLABORACIÓN (*)	SERVICIO	IMPORTE UNITARIO
	Radiología	0 €
		€
		€
		€
		€
		€

(*) INCLUIDOS EN EL IMPORTE TOTAL POR EL PACIENTE Y/O COMO PAGOS EXTRA

En _____, a __ de _____ de 20__

Fdo: Dr. Carlos Ferrando
Investigador Principal

Fdo: Dr. Julio Palmero
Jefe de Servicio de Radiología

TITULO: Estudio de validación de la pulsioximetría como método diagnóstico no invasivo de atelectasia pulmonar durante el postoperatorio

INVESTIGADOR PRINCIPAL: Carlos Ferrando

MEMORIA ECONOMICA PROYECTO INVESTIGACIÓN

RESUMEN ECONOMICO TOTAL

1. GASTOS ADMINISTRACION Y GESTION: 0 €/paciente

2. GASTOS PARA EL DESARROLLO DEL PROYECTO: 0 €/paciente

CONCEPTO	IMPROTE UNITARIO	IMPORTE TOTAL

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11 Fdo: Dr. Carlos Ferrando
12 Investigador Principal

Fdo: Dr. Francisco Javier Belda
Servicio de Anestesiología y Reanimación

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38 **Methods**

39 **Study design**

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41 Prospective, cohort study at the post-surgical recovery unit of the Hospital Clínico Universitario,
42 Valencia, Spain. The study will start after approval by the Local Ethics Committee for Clinical Research
43 in accordance with the Declaration of Helsinki (Chairperson: Dr. Antonio Peláez).
44

45
46 Written informed consent will be obtained from all patients.
47

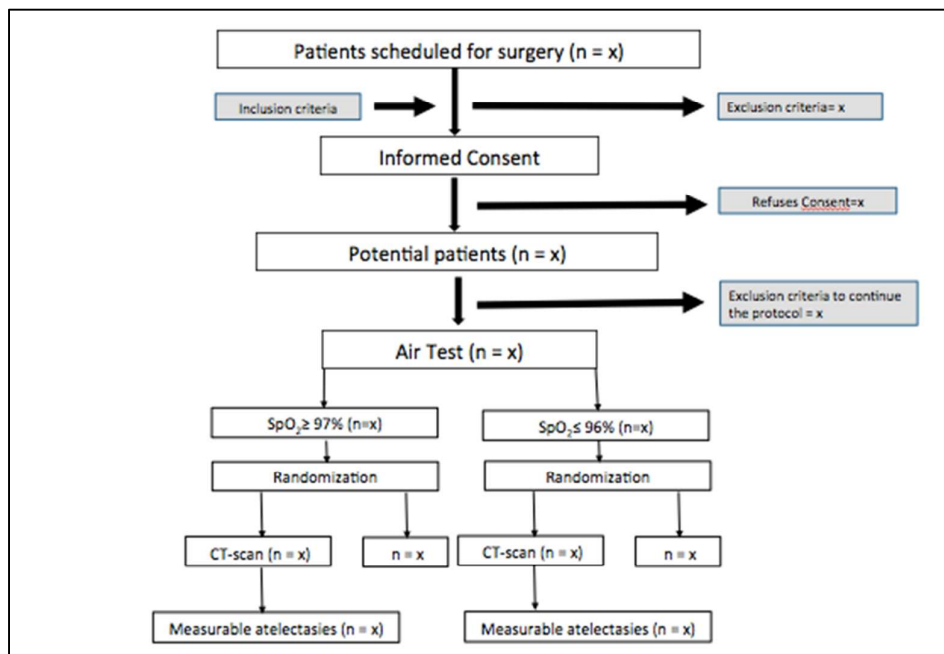
48
49 **Elegibility criteria**

50
51 The study will include consecutive patients with an American Society of Anaesthesiologists
52 physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical
53 unit.
54

55
56 Exclusion criteria are: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung
57 resection surgery, and (v) preoperative SpO₂ ≤ 97% on room-air.
58
59
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Postoperatively patients who give their consent will be excluded if they meet any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin $<10\text{g/dL}$, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale >1 or <-1 , and (vi) pain >4 evaluated with the visual analogue scale after the first 30 min in the PACU.

Figure 1. STARD Flowchart.



Monitoring

Intraoperative anesthesia management will follow standard clinical routines. The study will start on arrival into the Postsurgical Unit. A multi-parameter monitor IntelliVue MX450 (Philips Healthcare, Boeblingen, Germany) will be used to monitor electrocardiogram, non-invasive systemic arterial pressure, and SpO₂. The finger probe pulse-oximeter of the MX450 monitor uses the Fourier Artifact Suppression Technology (FAST) SpO₂.

Index Test for postoperative atelectasis

Patients will receive supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO₂ of 0.5 during the first 30 min.

The Air-Test: It will be performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO₂ monitoring with a finger probe pulse-oximeter. If SpO₂ drops $<92\%$ for more than 1 minute, the oxygen mask (FiO₂ 0.5) will be placed.

1
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3 Positive Air-Test: SpO₂ ≤96%

4
5 Negative Air-Test: SpO₂ ≥97%.

6
7 The Air-Test will be performed 30 min. This time has been arbitrarily decided by the researchers.

8
9 Once the Air-Test is complete, an arterial blood gas sample will be drawn while breathing room-air from
10 each patient (ABL 520, Radiometer, Copenhagen, Denmark).

11 12 13 **Randomization of patients for reference standard test (CT scan)**

14
15
16 25 min later, patients will be randomly allocated to perform a CT-scan evaluation which is the gold
17 standard technique.

18
19
20 Adaptive randomization which allowed us to minimize the exposure to CT-scans in patients not expected
21 to have atelectasis but having sufficient number of patients on each arm to conduct comparisons will be
22 performed.
23
24
25

26 27 **Reference standard test for postoperative atelectasis (CT scan)**

28
29 For the purpose of this study, an atelectatic area of less than 2% in the CT-scan is not considered
30 negligible (negative).

31
32
33 CT-scans will be obtained with 16-detector row/ 32 slices Aquilion LB (Toshiba). Scans (120 kV,
34 100-140 mA and 0.5 sec rotation time) The images were reconstructed in 5mm thickness slices with 5mm
35 interval and a depth of 12 bits per pixel.
36

37
38 All CT images will be analyzed by the same radiologist (RD) and computer engineer blinded to the
39 purpose of the study.
40
41
42

43 **Statistical analysis**

44
45 Data will be analysed using the statistical software R version 3.1.1. Statistical description of the baseline
46 demographics will be obtained with the *library (Rmisc)* and *library (PropCIs)*. We will compare
47 postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test,
48 depending on the variables (the Shapiro-Wilk test used to assess normality), Friedman test for ordinal
49 and binomial test for proportional variables. Data will be expressed as mean (standard deviation) or median
50 (interquartile range). The diagnostic accuracy and sensitivity analysis were conducted in R with the *library*
51 *pROC*. For all comparisons, a two-sided value of p<0.05 was considered significant.
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For peer review only

BMJ Open

Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Postoperative, atelectasis, oxygenation, SpO ₂ , Adult anaesthesia < ANAESTHETICS, Adult intensive & critical care < ANAESTHETICS

SCHOLARONE™
Manuscripts

Title: Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery –
a prospective, diagnostic pilot study.

¹Carlos Ferrando, ²Carolina Romero, ³Gerardo Tusman, ^{4,5}Fernando Suarez-Sipmann, ⁶Jaume Canet, ⁷Rosa Dosdá, ¹Paola Valls, ¹Abigail Villena, ¹Ferran Serralta, ¹Ana Jurado, ¹Juan Carrizo, ¹Jose Navarro, ⁷Cristina Parrilla, ⁸Jose E. Romero, ⁹Natividad Pozo, ¹Marina Soro, ^{4,10,11}Jesus Villar, ¹Francisco Javier Belda.

(1) Department of Anesthesiology and Critical Care, Hospital Clínico Universitario, Valencia, Spain; (2) Department of Anesthesiology, Hospital General Universitario, Valencia, Spain; (3); Department of Anesthesiology, Hospital Privado de Comunidad, Mar de Plata, Buenos Aires, Argentina; (4) CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; (5) Section of Anesthesiology and Critical Care, Uppsala University Hospital Uppsala, Uppsala, Sweden; (6) Department of Anesthesiology and Critical Care, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; (7) Department of Radiology, Hospital Clínico Universitario, Valencia, Spain; (8) ITACA Institute (Group IBIME), Universidad Politécnica, Valencia, Spain; (9) INCLIVA Clinical Research Institute, Hospital Clínico Universitario, Valencia, Spain; (10) Keenan Research Center for Biomedical Science at the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; (11) Spain Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Las Palmas, Spain.

Corresponding Author: Carlos Ferrando

Department of Anesthesiology and Critical Care
Hospital Clínico Universitario
Av. Blasco Ibañez, 17
46010 Valencia. SPAIN
Phone: (+34) 963862600 Fax: (+34) 963862680
Email: cafeoranestesia@gmail.com

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Abstract

Objective To assess the diagnostic accuracy of pulse oximetry hemoglobin saturation (SpO₂) while breathing room air for 5 min (“the Air-Test”) in detecting postoperative atelectasis.

Design Prospective, cohort study. Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standar computed tomography scan.

Setting Postanesthetic care unit in a terciary Hospital in Spain.

Participants Of the 350 patients scheduled for surgery from January 12 to February 7, 2015,170 patients with all the inclusion and none of the exclusion criteria who give their consent were included.

Intervention The Air-Test was performed in awake extubated patients after a 30 min stabilization period receiving supplemental oxygen therapy via a Venturi mask. The Air-Test was defined positive when SpO₂ was ≤96% and negative when ≥97%. Arterial blood gases were measured in all patients at the end of the Air-Test. Within the next 25 min, the presence of atelectasis was evaluated by computed tomography scan in 59 randomly selected patients.

Main Outcomes Measures The primary study outcome was the accuracy of the Air-Test for the detection of postoperative atelectasis assess by reference standar. The secondary outcome was incidence of positive Air-Test.

Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scan in all patients (30/30) with positive and in 5 patients (17%) with negative Air-Test in which CT-scan was performed. Based on the Air-Test, postoperative atelectasis were present in 36% of the patients (62 out of 170).

Conclusion The Air Test is an accurate, simple, inexpensive and noninvasive method to diagnose postoperative atelectasis.

Trial Registration ClinicalTrials.gov Identifier: NCT02650037.

Keywords: Postoperative, atelectasis, oxygenation, SpO₂

Strengths and limitations of this study

- This study used a simple and brief room-air breathing trial (Air-Test) in the early postoperative period to diagnose atelectasis.
- Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standard computed tomography scan.
- This study was a pilot study and a large external validation study is needed.
- The Air-Test had several limitations not only related to the pulse-oximeter but also to the test which could limit the clinical application in some cases.

Introduction

An estimated 234 million major surgical procedures are undertaken each year worldwide¹. Atelectasis may develop in nearly 90% of patients submitted to general anesthesia and may persist not only during the immediate postoperative period but up to several days after surgery²⁻⁵. Persistence of atelectasis after surgery is potentially associated with postoperative pulmonary complications such pneumonia, acute lung injury, extubation failure and reintubation³⁻⁷. Hypoxemia, a direct consequence of atelectasis⁸ may also promote systemic complications such acute myocardial ischemia or impaired wound healing, among others⁹.

Oxygen therapy is usually applied in the postoperative period to alleviate hypoxemia¹⁰, which develops in most patients after general anesthesia. As a result, most atelectasis in the postoperative period may not be diagnosed at the bedside precluding the application of any corrective measure and thus potentially increasing the risk of atelectasis-related postoperative complications. In the other hand, the use of low inspiratory fraction of oxygen (FIO₂) (0.21) could better categorize lung function through pulse oximetry hemoglobin saturation (SpO₂) values, as it forces SpO₂ to operate at the steep portion of the oxygen-hemoglobin dissociation curve, and thus it can be used to estimate the alveolar shunt using the SpO₂-FIO₂ diagram described by Jones et al¹¹. This may help to unmask underlying oxygenation deficits due to shunt and thus the presence of atelectasis when SpO₂ is low, assuming a linear relationship between shunt and atelectasis. Thus, a combination of oxygen therapy with transitory decreases of FIO₂ to 0.21 during a 5 minutes period, which is enough to achieve a steady state condition of the expired fraction of oxygen (FEO₂)^{12,13} may allow to estimate shunt and to unmask the presence of atelectasis during the immediate postoperative period.

We hypothesized that changes in arterial oxygen saturation induced by a short maneuver of FIO₂ reduction to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO₂ recorded by pulse oximetry after breathing room-air for 5 min ("the Air-Test") can reveal the presence of atelectasis and to establish the relation of the SpO₂ value to the presence of atelectasis assessed by computed tomography (CT)-scan.

Methods

Study design

We performed a prospective, cohort study at the post-surgical recovery unit of the Hospital Clínico Universitario, Valencia, Spain, from January 12 to February 7, 2015. The study was approved by the Local Ethics Committee for Clinical Research in accordance with the Declaration of Helsinki (Chairperson: Dr. Antonio Peláez), and registered on December 28, 2015 at <http://www.clinicaltrials.gov> with identification no. NCT02650037. Written informed consent was obtained from all patients. The complete and original protocol is described in this section.

Elegibility criteria

The study included consecutive patients with an American Society of Anaesthesiologists physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical unit. Exclusion criteria were: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, and (v) preoperative $SpO_2 \leq 97\%$ on room-air. Postoperatively patients who gave their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin <10g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale >1 or <-1, and (vi) pain >4 evaluated with the visual analogue scale after the first 30 min in the postanesthetic care unit (PACU) (Figure 1).

Monitoring

Intraoperative anesthesia management followed standard clinical routines. The study started on arrival into the PACU. A multi-parameter monitor IntelliVue MX450 (Philips Healthcare, Boeblingen, Germany) was used in all patients to monitor electrocardiogram, non-invasive systemic arterial pressure, and SpO_2 . The finger probe pulse-oximeter of the MX450 monitor uses the Fourier Artifact Suppression Technology (FAST) SpO_2 . Pulsi-oximeter characteristics are described in the Supplement digital content 1.

Index Test for postoperative atelectasis

Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO_2 of 0.5 during the first 30 min. The Air-Test was performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO_2 monitoring with a finger probe pulse-oximeter. The Air-Test was considered positive when the recorded SpO_2 was $\leq 96\%$ and negative when SpO_2 was $\geq 97\%$. The selected cut-off value to diagnose atelectasis was based in the SpO_2 - FIO_2 diagram¹⁰ described by Jones which showed that a SpO_2 was $\leq 96\%$ corresponds to a shunt effect >10% which defines alveolar collapse. Recently,

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3 Tusman et al.¹⁴ used a similar approach by using a FIO₂ of 0.21 to define an open-lung condition in anesthetized
4 patients while ventilated.

5
6 The selected 5 min was based on the results we obtained in our pilot study in ten healthy volunteers
7 showing that the mean time needed from mask removal to the stabilization of the FEO₂ was 56 (7) seconds. Our
8 pilot study was performed in ten healthy and nonsmoker volunteers in the Hospital Privado de Comunidad, Mar
9 de Plata (Argentina) to establish the mean time from Venturi mask removal with oxygen supplementation to the
10 stabilization of the expiratory fraction of Oxygen (FEO₂) signal. Interventions and results are described in the
11 Supplement digital content 1. Also, the selected time was based in the results found by Howe et al.¹² in
12 spontaneously breathing patients and Fildissis et al.¹³ in mechanically ventilated patients. Both studies showed
13 that the oxygen (PaO₂) measured 5 min after discontinuation of supplementary oxygen represents steady state
14 conditions in lung-healthy patients.

15
16 The Air-Test was performed 30 min after PACU admission for safety reasons. As a number of the
17 included patients were randomized to perform the reference standar test for postoperative atelectasis (CT-scan)
18 as soon as possible after the Air-Test to minimize bias, we arbitrarily decided that the minimal time required to
19 ensure a safety discharge from the PACU after a general anesthesia and after meeting all the discharge criteria
20 should be the defined 30 min.

21
22 In addition, we evaluated the prevalence of having a positive Air-Test. Once the Air-Test was
23 completed, an arterial blood gas sample was drawn while breathing room-air from each patient (ABL 520,
24 Radiometer, Copenhagen, Denmark). The oxygen mask was placed back whenever SpO₂ fell to 92% for more
25 than one minute during the Air-Test and until the end of the protocol after the Air-Test was completed.

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **Randomization of patients for references standard test (CT scan)**

42
43 Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is
44 the gold standard technique. It was used an adaptive randomization which allowed us to minimize the exposure
45 to CT-scans in patients not expected to have atelectasis following FDA recommendations¹⁵ but having sufficient
46 number of patients on each arm to conduct comparisons¹⁶. In this study we set a maximun sample size of 60
47 patients with CT-scan and a maximun sample size of 30 per arm (positive and negative Air-Test). We equally
48 assigned the first 15 patients of each arm to two groups (CT-scan or no CT-scan) and started using the adaptive
49 randomization at the next 16th patient on each arm.

50 51 52 53 54 55 56 57 58 **Reference standard test for postoperative atelectasis (CT scan)**

For the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible (negative) based in previous data¹⁴ because it does not cause a clinically relevant shunt^{17,18}. CT-scans were obtained with 16-detector row/ 32 slices Aquillion LB (Toshiba) located at the Radiology Department. Scans (120 kV, 100-140 mA and 0.5 sec rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5mm thickness slices with 5mm interval and a depth of 12 bits per pixel, which is considered adequate for the analysis we performed¹⁹. Each right and left surface of normally aerated tissue and atelectasis were semi automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchi and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to 100). After this correction, separation between normally aerated lung and atelectasis was automatically corrected. Quantitative analysis of CT densities was performed using previously validated methods^{20,21}. The atelectatic area was expressed in cm² as mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROI) were calculated using equation 1:

$$VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$$

Where V is the set of voxels inside the ROI and x , y and z the voxel sizes in the three dimensions given in millimeters. Volumes are given in milliliters.

Mass of lung tissue for the different ROIS were calculated as previously described²². See equation 2:

$$MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$$

Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V , HU_i represents the CT value for voxel i and VOL_{voxel} represents the voxel volume for the image being processed given in milliliters. The atelectatic mass was expressed in grams as mean \pm standard deviation (SD) and as a percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but performed at the region presenting the largest amount of atelectasis in each lung independently. All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.

Diagnostic test of the index test (Air-Test)

A 2×2 table (table 2) was used for the assessment of sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP + TN)] \times 100$; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$; where *TP* is true positive, *TN* is true negative, *FP* is false positive, and *FN* is false negative.

Statistical analysis

The total sample size was not calculated as this is a cohort study. The sample size for patients randomized for CT-scan was also not calculated as this is preliminary pilot study. Thus, we arbitrarily decided that the minimum sample size was at least 50 patients (25 patients with positive Air-Test and 25 with negative). Data were analysed using the statistical software R version 3.1.1²³. All the analysis performed were pre-specified. Statistical description of the baseline demographics were obtained with the *library (Rmisc)* and *library (PropCIs)*. We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range). A simple linear regression model was used with the variables SpO₂ and the total area of atelectasis following the formula: Area of atelectasis ~ SpO₂ + ε, where ε is the error. A regression line was built in the scatterplot with the function *lm()*. The diagnostic accuracy and sensitivity analysis were conducted in R with the *library pROC*. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values were computed with bootstrap resampling and the averaging methods described by Fawcett²⁴. Bootstrap has shown to generate unbiased optimism-adjusted estimates of the CIs statistic. In all bootstrap CIs, patients were resampled and the modified curve was built before the statistics of interest were computed. As in the bootstrap comparison test, the resampling was done in a stratified manner²⁵. For all comparisons, a two-sided value of p<0.05 was considered significant.

Results

A total of 181 out of 350 eligible patients scheduled for surgery were enrolled, from whom 170 underwent the Air-Test in the PACU. Thirty randomly assigned patients from the 62 with positive and 29 from 108 with a negative Air-Test were assessed with CT (Figure 1).

Baseline demographic and clinical characteristics of all patients

Demographic, surgical, intraoperative ventilatory management data and clinical variables after the completion of the Air-Test are shown in Table 1. Patients with a positive Air-Test were older, predominantly male and had a higher ARISCAT score (The Assess Respiratory Risk in Surgical Patients in Catalonia)²⁶ with a larger weight as compared with those with a negative test. There were no significant differences regarding intraoperative management, type and duration of surgery between both groups. Oxygenation (PaO₂) was 25% lower in patients with a positive test (p<0.001). Also, the SpO₂ was placed in the steep portion of the oxygen-hemoglobin dissociation curve as compared with patients with a negative test. All the patients were hemodynamically stable and normothermic.

Table 1. Study variables of patients.

	Positive Air-Test (n=62)	Negative Air-Test (n=108)	p-value
Demographic data			
Age, yr	65 (11)	56 (17)	<0.001
Women, %	33 (6)	56 (9)	0.01
Height, cm	164 (9)	166 (9)	0.06
Body weight, kg	84 (21)	73 (15)	<0.001
ARISCAT score	26 (14)	16 (15)	0.01
Preoperative SpO ₂ , %	98 (1)	98 (2)	0.12
Lower Abdominal surgery	24 (38)	34 (31)	0.20
Upper Abdominal surgery	9 (14)	13 (12)	0.11
Peripheral surgery	29 (46)	60 (55)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volumen, ml	470 (52)	460 (88)	0.33
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FIO ₂	0.6 (0.2)	0.7 (0.3)	0.88
SpO₂ and arterial blood gases at PACU at the end of the Air-Test			
Postoperative SpO ₂ , %	91 (3)	99 (1)	0.01
PaO ₂ , mmHg	66 (10)	87 (12)	0.01
PaCO ₂ , mmHg	41 (6)	42 (6)	0.29
pH	7.37 (0.04)	7.38 (0.03)	0.06
MAP, mmHg	79 (12)	85 (15)	0.07
Lactate, mmol/L	1.1 (0.4)	1.0 (0.7)	0.32
Hb, g/dl	12.6 (1.7)	12.9 (1.1)	0.09
Temperature, C°	36.4 (1.9)	36.1 (2.1)	0.41
VAS	1 (1)	1 (1)	1.00

Table 1. Data are described as mean (SD) or number/total number (%). ARISCAT score to predict postoperative pulmonary complications²⁶, PEEP: positive end-expiratory pressure; FIO₂: inspiratory oxygen fraction; PACU: Post-Anesthetic Care Unit; SpO₂: pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial pressure; PaCO₂: carbon dioxide partial pressure; pH: acid base state; MAP: mean arterial pressure; Hb: Hemoglobin, VAS: visual analogue scale.

Baseline demographic and clinical characteristics of patients with reference standard (CT-scan)

As shown in table 2, the differences found between patients with positive and negative Air-Test (table 1) were maintained in those patients in whom the CT-scan was performed.

Table 2. Study variables of patients with reference standard CT-scan.

	Positive Air-Test (n=30)	Negative Air-Test (n=29)	p-value
Demographic data			
Age, yr	62 (13)	53 (15)	0.045
Women, n (%)	12 (40)	11 (37)	0.57
Height, cm	165 (10)	163 (12)	0.32
Body weight, kg	88 (29)	75 (17)	<0.001
ARISCAT score	28 (14)	14 (15)	<0.001
Preoperative SpO ₂ , %	98 (2)	98 (2)	0.28
Lower Abdominal surgery	39 (10)	29 (5)	0.20
Upper Abdominal surgery	6 (3)	4 (3)	0.11
Peripheral surgery, %	55 (11)	67 (7)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volumen, ml	472 (50)	466 (92)	0.56
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FIO ₂	0.7 (0.2)	0.7 (0.3)	0.90
SpO₂ and arterial blood gases at PACU at the end of the Air-Test			
Postoperative SpO ₂ , %	92 (3)	99 (1)	0.01
PaO ₂ , mmHg	78 (21)	90 (10)	<0.001
PaCO ₂ , mmHg	40 (6)	42 (6)	0.34
pH	7.37 (0.04)	7.38 (0.03)	0.09
MAP, mmHg	81 (12)	76 (15)	0.72
Lactate, mmol/L	1.1 (0.4)	1.0 (0.6)	0.52
Hb, g/dl	12.5 (1.2)	12.3 (1.6)	0.41
Temperature, C°	36.2 (1.9)	36.2 (2.3)	0.68
VAS	1 (1)	1 (1)	1.00

Table 2. Data are described as mean (SD) or number/total number (%). ARISCAT score to predict postoperative pulmonary complications²⁶, PEEP: positive end-expiratory pressure; FIO₂: inspiratory oxygen fraction; PACU: Post-Anesthetic Care Unit; SpO₂: pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial pressure; PaCO₂: carbon dioxide partial pressure; pH: acid base state; MAP: mean arterial pressure; Hb: Hemoglobin, VAS: visual analogue scale.

Diagnostic accuracy

Of the 59 patients evaluated with a CT-scan (29 with positive and 30 with negative Air-Test), all those with a positive Air-Test and 5 of those with a negative Air-Test (17%) had measurable atelectasis (area >2% of the whole lung) on the CT-scan. When mass analysis was used to diagnose atelectasis, 27 patients with positive Air-Test and only 3 patients with negative Air-Test had measurable atelectasis (mass >2% of the whole lung). None of the patients with negative Air-Test and atelectasis on the CT-scan had a SpO₂ >98% and an atelectatic area or mass >4%. Receiving Operating Curve (ROC) analysis showed that a positive Air-Test (SpO₂ ≤96%) was adequate to diagnose postoperative atelectasis (Table 3).

Table 3. Diagnostic accuracy, Sensitivity, Specificity and area under the curve (AUC) to detect atelectasis with the Air-Test assessed with the reference standar (CT-scan).

	AUC (95%CI)	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Air-Test (N = 59)	0.90 (0.82-0.98)	82.6	87.8	91.5

Sensitivity analysis

Since the Air-Test could be affected by several factors such as dyshemoglobinemias, low perfusion state, motion artifact, and hypothermia, we performed two additional analyses to confirm our results. First, the PaO₂ threshold value confirming the diagnosis of atelectasis was 78 mmHg, with a sensitivity of 82.6% and a specificity of 78.7% and an area under the ROC curve of 0.86 (95%CI: 76.6 to 96.1%). Second, looking for the suitability of the SpO₂ to diagnose atelectasis, we performed a ROC test for correlated data between SpO₂-ROC and PaO₂-ROC. The ROC *test* showed no differences between both tests (p=0.10).

Secondary outcome

We found a 36% prevalence of positive Air-Test in our population (62 of the 170 patients).

Adverse events

No adverse events were reported during the study period.

Discussion

The main result of this diagnostic pilot study was the high accuracy of the postoperative Air-Test to diagnose atelectasis. This test, performed 30 minutes after surgery, identified a high prevalence postoperative atelectasis. This simple, noninvasive and inexpensive test at bedside may be used in healthy patients with a preoperative SpO₂ between 97 to 100% while breathing room-air.

The Air-Test helped to unmask underlying oxygenation deficits and the presence of atelectasis when SpO₂ ≤ 96%. As previous studies have described, shunt-induced by atelectasis is the main cause of oxygenation impairment during the postoperative period¹⁵. In fact, Rothen et al.²⁷ showed that 75% of the impairment in PaO₂ is related to atelectasis and airway closure in patients with healthy lungs. Based on this statement, our results are in line with the findings of Witting et al.²⁸ who found that a SpO₂ ≤ 96% in patients breathing room-air confirmed the diagnosis of hypoxemia (defined as PaO₂ < 70 mmHg in their study) with a sensitivity of 100% and a specificity of 54% and an area under the ROC curve of 0.91 (95%CI: 0.78 to 0.94).

We found a 17% of false negative Air-Test in patients who presented an area of atelectasis higher than 2% in the CT images that was reduced to 10% when mass was used to diagnose atelectasis. Potential reasons for this decreased sensitivity could be related to several factors. First, the duration of the test; five minutes might not be enough to achieve a steady state condition of the FEO₂ in some patients. Some authors in mechanically ventilated patients found slightly higher times: 5.5 (4.8) minutes in healthy patients²⁹ or 7.1 (2.1) in mechanically ventilated patients with chronic obstructive pulmonary disease³⁰. Another potential cause for the false negatives might be the percentage of error of pulse-oximeter measurement. A difference in bias up to 2% and a precision up to 3% compared to the reference standard (CO-oximeter) has been described³¹. Although we did not find false positives when the area was used to diagnose postoperative atelectasis, 3 of the 30 patients with positive Air-Test did not have a mass of atelectasis > 2%. Potential causes are a certain overestimation of the shunt-induced by atelectasis based on the SpO₂-FIO₂ diagram due to the presence of low ventilation/perfusion (V/Q) zones, as these may appear during mechanically ventilated patients¹³ and the difference in bias and precision as discussed above.

We found a 36% prevalence of postoperative atelectasis based on the Air-Test. Our findings are in agreement with previous studies. Akca et al.³² found a similar prevalence using CT-scan in 30 patients after colon surgery. Our findings also match with the prevalence of postoperative SpO₂ ≤ 96% found by Severgnini et al. where 12 of the 27 patients in the control group and 8 of the 28 patients in the study group (36% prevalence of the total population) had a SpO₂ ≤ 96% while breathing room-air (unpublished data), but no atelectasis were

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3 diagnosed by chest radiography³³. Recently, an observational study including 833 nonselected postoperative
4 patients with 48h continuous SpO₂ monitoring, demonstrated a 37% prevalence of hypoxemia (SpO₂<90%)⁹.
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6 However, in general, the rate of atelectasis usually reported is much lower^{26,34}. Two recent trials together
7 including more than 1200 patients reported a prevalence around 15% when diagnosed by chest radiography^{35,36}.
8
9 This low prevalence might be explained by the low sensitivity and specificity of chest radiographs. When
10 compared to the prevalence observed in our study using CT-scan, it suggests that atelectasis are usually
11 underestimated.
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14 15 **Limitations**

16 We must acknowledge several limitations. First, the Air-Test can only be applied to patients with a preoperative
17 SpO₂ ≥ 97% on room-air, since it is not possible to differentiate whether the postoperative SpO₂ indicates the
18 presence of postoperative atelectasis or previous lung disease. However, a high percentage of patients scheduled
19 for surgery have a SpO₂ ≥ 97%²⁵. Second, intraoperative respiratory complications that decrease low V/Q zones
20 and therefore decrease SpO₂, such as lung edema or pneumothorax, may overestimate shunt-induced by
21 atelectasis based on the SpO₂-FIO₂. However, these postoperative complications in the immediate postoperative
22 period rarely appear³⁶. Third, compensatory mechanisms in the presence of atelectasis such as the hypoxic
23 pulmonary vasoconstriction decreases shunt and therefore may increase SpO₂, which would underestimate
24 atelectasis based on the SpO₂-FIO₂ diagram. These last two limitations may decrease the sensitivity and
25 specificity of the Air-Test. Fourth, temporal factors could have affected our results because of time delays
26 among the Air-Test, arterial blood gases, and the CT-scan. However, if at all, results would have been affected in
27 a negative sense since a time-dependent reduction of postoperative atelectasis occurs as patients improve their
28 breathing capacity. Fifth, erroneous readings of the pulse-oximeter may underestimate postoperative atelectasis
29 in the presence of dyshemoglobinemias or overestimate them in the presence of anemia, low perfusion state,
30 motion artifacts or hypothermia³¹. Some of these limitations are not only related to the pulse-oximeter but also to
31 the Air-Test itself as shifts of the oxy-hemoglobin dissociation curve can affect the principle used by Jones et al.
32 to describe the SpO₂-FIO₂ diagram¹¹. However, this limitation was well controlled as shown in tables 1 and 2.
33
34 Sixth, for the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible.
35 Although this percentage is not clinically relevant, these atelectasis which are not diagnosed with the Air-Test
36 could potentially trigger an inflammatory response³⁷ which at last would affect the rationale of using this test.
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38 Finally, as sample size calculation was not performed, this study can only be considered as a pilot study.
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56 **Implications for practice**

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3 First, this is a pilot study and a powered large external validation study is needed in a more heterogeneous
4 surgical population such as obese, patients without previously normal lung function or patients with a
5 preoperative SpO₂ <97%. Such a study may also analyze the Air-Test at different time points, with different
6 pulse-oximeter technologies and in patients without previously supplemental oxygen delivery during the
7 postoperative period with the aim to validate the test as a surrogate of postoperative atelectasis; and its severity if
8 it is found a correlation between the SpO₂ values during the Air-Test and the area of atelectasis measured by CT-
9 scan. Second, the Air-Test may become a standardized screening test before leaving the PACU to evaluate
10 postoperative oxygenation. It may contribute to a higher patient flow in PACU without losing high care quality
11 as it may discriminate those patients without postoperative lung derecruitment (negative Air-Test) from those
12 (positive Air-Test) with an increased risk of postoperative hypoxemia³⁸, whom should ideally be surveyed more
13 closely during this period and would likely benefit from measures to revert atelectasis, which may have a
14 potential positive impact on healthcare costs³⁹. Despite the benefits in outcomes of these measures remain
15 uncertain⁴⁰, several studies showed the potential benefits⁴¹ and currently is ongoing a clinical trial which uses the
16 Air-Test to individually apply the use of a postoperative continuous positive end-expiratory pressure⁴².

30 **Conclusions**

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32 We have demonstrated that the Air-Test is an accurate, simple, inexpensive, noninvasive and readily
33 available method for diagnosing postoperative atelectasis.
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38 **Figure legends**

39 Figure 1. STARD Flow diagram
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Footnotes:**Contributors**

Dr. Ferrando (MD, PhD) and Prof. Belda (MD, PhD) had full access to all data and are responsible for the integrity and the accuracy of the data analysis. *Study design:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD) and Prof. Belda (MD, PhD). *Acquisition and analysis of data:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Dosdá, (MD, PhD), Dr. Tusman (MD), Dr. Soro (MD, PhD), Dr. Valls (MD), Dr. Villena (MD), Dr. Serralta (MD), Dr. Jurado (MD), Dr. Carrizo (MD), Dr. Navarro (MD), Dr. Parrilla (MD), Dr. Pozo (PhD), Dr. Romero (BSc), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD). *Interpretation of data:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), Dr. Canet (MD, PhD). *Drafting of the manuscript:* Dr. Ferrando (MD, PhD), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD). *Critical revision of the manuscript for intellectual content:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD), Dr. Canet (MD, PhD), Dr. Suarez-Sipmann (MD, PhD), Dr. Villar (MD, PhD) and Prof. Belda (MD, PhD).

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Declaration of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Ethical approval

Approved by the Local Ethics Committee for Clinical Research. Written informed consent was obtained from all patients.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

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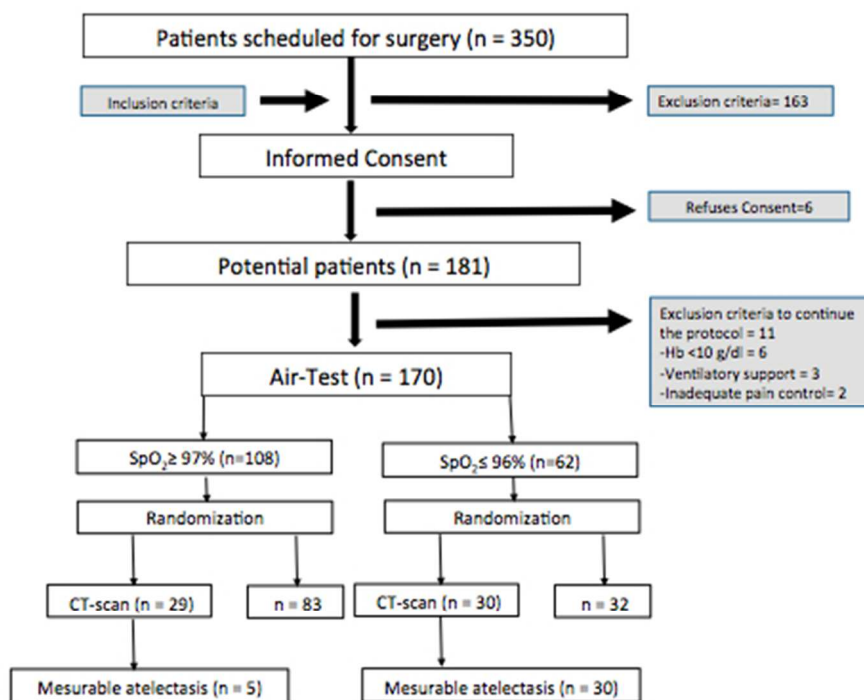


Figure 1. Flow diagram of the Air-Test study.

185x134mm (72 x 72 DPI)

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3 **Supplementary file**
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5 **Title:** Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after
6 surgery – a prospective, diagnostic pilot study.
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9 Carlos Ferrando, Carolina Romero, Gerardo Tusman, Fernando Suarez-Sipmann, Jaume Canet, Rosa
10 Dosdá, Paola Valls, Abigail Villena, Ferran Serralta, Ana Jurado, Juan Carrizo, Jose Navarro, Cristina
11 Parrilla, Jose E. Romero, Natividad Pozo, Marina Soro, Jesus Villar, Francisco Javier Belda.
12
13

14
15
16 Corresponding Author: Carlos Ferrando

17 Department of Anesthesiology and Critical Care

18 Hospital Clínico Universitario

19 Av. Blasco Ibañez, 17

20 46010 Valencia. SPAIN

21 Phone: (+34) 963862600 Fax: (+34) 963862680

22 Email: cafeoranestesia@gmail.com
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Methods

Procedures

We performed a pilot study in ten healthy and non-smoker volunteers in the Hospital Privado de Comunidad, Mar de Plata (Argentina) to establish the mean time from Venturi mask removal with oxygen supplementation to the stabilization of the expiratory fraction of Oxygen (FEO₂) signal. The volunteers were breathing spontaneously through a Venturi mask at 4 L/min with a jet adjusted to a theoretical FiO₂ of 0.5 during 10 min before the Air-Test was performed. Nasal oxygen and carbon dioxide concentrations were measured using a 1 mm ID cannula placed 1 cm inside the right nostril and connected to the side-stream capnograph S5 (GE Healthcare/Datex-Ohmeda, Helsinki, Finland). Time-base oximetry and capnography were recorded with the Datex Collect software (GE Healthcare/Datex-Ohmeda, Helsinki, Finland) and analyzed off-line. We measured mean time needed from mask removal to the stabilization of the FEO₂.

The FAST SpO₂ algorithm derives SpO₂ using the absorption of red and infrared light. But unlike the traditional algorithm, the FAST algorithm examines the strength of the different frequency components that make up the signals. This approach allows to distinguish the physiological signal from the noise artifacts increasing measurement accuracy¹. Nevertheless, the SpO₂ measurement was considered qualitatively optimal only when a plethysmography waveform stable and normal was seen during the average time period of 10 seconds given by the monitor. The conventional finger probe pulse oximetry is an accurate reflection of SaO₂ values measured by the reference standard (CO-oximeter) with a bias of 2% and with a standard deviation (precision) of less than 3%².

Results

Demographic data of the 10 volunteers are described in the were age: 31 (7) years old, weight 71 (9) kg and height: 173 (4) cm. The mean time for the stabilization of the expired O₂ fraction once supplementary oxygen therapy was removed was 56 (7) seconds.

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1. Baker SJ, "Motion Resistant" pulse oximetry: A comparison of new and old models. *Anesth Analg* 2002; 95: 967-72.
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Selection of topic	Item	Description
Title, abstract	1. Page 1, lines 3-5	Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.
	2. Page 2, lines 2-42	<p>Objective To assess the diagnostic accuracy of SpO₂ while breathing room air for 5 min (“the Air-Test”) in detecting postoperative atelectasis.</p> <p>Design Prospective, cohort study. Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standar computed tomography scan.</p> <p>Setting Postanesthetic care unit in a terciary Hospital in Spain.</p> <p>Participants 350 patients from January 12 to February 7, 2015. 170 patients scheduled for surgery under general anesthesia admitted into the postsurgical unit were included.</p> <p>Intervention The Air-Test was performed in awake extubated patients after a 30 min stabilization period receiving supplemental oxygen therapy via a Venturi mask. The Air-Test was defined positive when SpO₂ was ≤96% and negative when ≥97%. Arterial blood gases were measured in all patients at the end of the Air-Test. Within the next 25 min, the presence of atelectasis was evaluated by computed tomography scan in 59 randomly selected patients.</p> <p>Main Outcomes Measures The primary study outcome was the accuracy of the Air-Test for the detection of postoperative atelectasis assess by reference standar. The secondary outcome was incidence of positive Air-Test.</p> <p>Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scan in all patients (30/30) with positive and in 5 patients (17%) with negative Air-Test. Based on the Air-Test, postoperative atelectasis were present in 36% of the patients (62 out of 170).</p> <p>Conclusion The Air Test is an accurate, simple, inexpensive and noninvasive method to diagnose postoperative atelectasis.</p> <p>Trial Registration ClinicalTrials.gov Identifier: NCT02650037.</p>
Introduction	3. Page 4, lines 16-34	Oxygen therapy is usually applied in the postoperative period to alleviate hypoxemia ¹⁰ , which develops in most patients after general anesthesia. As a result, most atelectasis in the postoperative period may not be diagnosed at the bedside precluding the application of any corrective measure and thus potentially increasing the risk of atelectasis-related postoperative complications. In the other hand, the use of low FIO ₂ (0.21) could better categorize lung function through SpO ₂ values, as it forces SpO ₂ to operate at the steep portion of the oxygen-hemoglobin dissociation curve, and thus it can be used to estimate the alveolar shunt using the SpO ₂ -FIO ₂ diagram described by Jones et al ¹¹ . This may help to unmask underlying oxygenation deficits due to shunt and thus the presence of atelectasis when SpO ₂ is low, assuming a linear relationship between shunt and atelectasis. Thus, a combination of oxygen therapy with transitory decreases of FIO ₂ to 0.21 during a 5 minutes period, which is enough to achieve a steady state condition of the expired fraction of oxygen (FEO ₂) ^{12,13} may allow to estimate shunt and to unmask the presence of atelectasis during the immediate postoperative period.
	4. Page 4, lines 36-44	We hypothesized that changes in arterial oxygen saturation induced by a short maneuver of FIO ₂ reduction to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO ₂ recorded by pulse oximetry after breathing room-air for 5 min (“the Air-Test”) can reveal the presence of atelectasis and to establish the relation of the SpO ₂ value to the presence of atelectasis assessed by CT-scan.
Methods		
Participants	5.	We performed a prospective, cohort study at the post-surgical recovery unit of

	Page 5, lines 6-8	the Hospital Clínico Universitario, Valencia, Spain, from January 12 to February 7, 2015.
	6,7,8,9. Page 5, lines 19-33	The study included consecutive patients with an American Society of Anaesthesiologists physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical unit. Exclusion criteria were: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, and (v) preoperative SpO ₂ ≤97% on room-air. Postoperatively patients who gave their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin <10 g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale > 1 or < -1, and (vi) pain > 4 evaluated with the visual analogue scale after the first 30 min in the PACU (Figure 1).
Test Methods	10a. Page 5, lines 48-51	Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO ₂ of 0.5 during the first 30 min. The Air-Test was performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO ₂ monitoring with a finger probe pulse-oximeter
	10b. Page 6, lines 64-60 and 7, lines	<p>CT-scans were obtained with 16-detector row/ 32 slices Aquillion LB (Toshiba). Scans (120 kV, 100-140 mA and 0.5 sec rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5 mm thickness slices with 5 mm interval and a depth of 12 bits per pixel. Each right and left surface of normally aerated tissue and atelectasis were semi automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchi and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to 100). After this correction, separation between normally aerated lung and atelectasis was automatically corrected. An example of the segmentation steps can be seen in Figure 2. Quantitative analysis of CT densities was performed using previously validated methods^{18,19}. The atelectatic area was expressed in cm² as mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROI) were calculated using equation 1:</p> $VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$ <p>Where V is the set of voxels inside the ROI and x, y and z the voxel sizes in the three dimensions given in millimeters. Volumes are given in milliliters. Mass of lung tissue for the different ROIS were calculated as previously described²⁰. See equation 2:</p> $MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$ <p>Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V, HU_i represents the CT value for voxel i and VOL_{voxel} represents the voxel volume for the image being processed given in milliliters. The atelectatic mass was expressed in grams as mean ± standard deviation (SD) and as a percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but performed at the region presenting the largest amount of atelectasis in each lung independently. All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.</p>
	11. Page 6,	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique. It was used an

	lines 2-49	adaptive randomization which allowed us to minimize the exposure to CT-scans in patients not expected to have atelectasis but having sufficient number of patients on each arm to conduct comparisons
	12a. Page 5, lines 51 to 57 and page 6, lines 2-5	The Air-Test was considered positive when the recorded SpO ₂ was ≤96% and negative when SpO ₂ was ≥97%. The selected cut-off value to diagnose atelectasis was based in the SpO ₂ -FIO ₂ diagram ¹⁰ described by Jones which showed that a SpO ₂ was ≤96% corresponds to a shunt effect >10% which defines alveolar collapse. Recently, Tusman et al. ¹⁴ used a similar approach by using a FIO ₂ of 0.21 to define an open-lung condition in anesthetized patients while ventilated.
	12b. Page 6, lines 54-56	For the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible (negative) based in previous data because it does not cause a clinically relevant shunt
	13. Page 7, lines 47-49	All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.
	12. Page 8, lines 18-26	Data were analysed using the statistical software R version 3.1.1. All the analisis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i> . We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range).
Analysis		
	14. Page 8, lines 2-6 and lines 11-41	<p>Diagnostic test of the index test (Air-Test)</p> <p>A 2×2 table (table 2) was used for the assessment of sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP + TN)] \times 100$; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$; where <i>TP</i> is true positive, <i>TN</i> is true negative, <i>FP</i> is false positive, and <i>FN</i> is false negative.</p> <p>Statistical analysis</p> <p>The total sample size was not calculated as this is a cohort study. The sample size for patients randomized for CT-scan was also not calculated as this is preliminary pilot study. Thus, we arbitrarily decided that the minimum sample size was at least 50 patients (25 patients with positive Air-Test and 25 with negative). Data were analysed using the statistical software R version 3.1.1²¹. All the analisis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i>. We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range). A simple linear regression model was used with the variables SpO₂ and the total area of atelectasis following the formula: Area of atelectasis ~ SpO₂ + ε, where ε is the error. A regression line was built in the scatterplot with the function <i>lm()</i>. The diagnostic accuracy and sensitivity analysis were conducted in R with the <i>library pROC</i>. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values were computed with bootstrap resampling and the averaging methods described by Fawcett²². Bootstrap has shown to generate unbiased optimism-adjusted estimates of the CIs statistic. In all bootstrap CIs, patients were resampled and the modified curve was built before the statistics of interest were computed. As in the bootstrap comparison test, the resampling was done in a stratified manner²³. For all comparisons, a two-sided value of p<0.05 was</p>

		considered significant.
	17. Page 8, line 17	All the analysis performed were pre-specified
Results		
Participants	19	Figure 1
	20	Table 1
	21	Table 2
	22	Table 2
	22. Page 6, line 44	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique.
Test Results	23	Table 3
	24	Table 3
	25. Page 11, line 46	Adverse events No adverse events were reported during the study period.
Discussion		
	26. Page 13, lines 15-54	Limitations We must acknowledge several limitations. First, the Air-Test can only be applied to patients with a preoperative SpO ₂ ≥ 97% on room-air, since it is not possible to differentiate whether the postoperative SpO ₂ indicates the presence of postoperative atelectasis or previous lung disease. However, a high percentage of patients scheduled for surgery have a SpO ₂ ≥ 97% ²⁴ . Second, intraoperative respiratory complications that decrease low V/Q zones and therefore decrease SpO ₂ , such as lung edema or pneumothorax, may overestimate shunt-induced by atelectasis based on the SpO ₂ -FIO ₂ . However, these postoperative complications in the immediate postoperative period rarely appear ³⁴ . Third, compensatory mechanisms in the presence of atelectasis such as the hypoxic pulmonary vasoconstriction decreases shunt and therefore may increase SpO ₂ , which would underestimate atelectasis based on the SpO ₂ -FIO ₂ diagram. This last two limitations may decrease the sensitivity and specificity of the Air-Test. Fourth, temporal factors could have affected our results because of time delays among the Air-Test, arterial blood gases, and the CT-scan. However, if at all, results would have been affected in a negative sense since a time-dependent reduction of postoperative atelectasis occurs as patients improve their breathing capacity. Fifth, erroneous readings of the pulse-oximeter may underestimate postoperative atelectasis in the presence of dyshemoglobinemias or overestimate them in the presence of anemia, low perfusion state, motion artifacts or hypothermia ²⁹ . Some of these limitations are not only related to the pulse-oximeter but also to the Air-Test itself as shifts of the oxy-hemoglobin dissociation curve can affect the principle used by Jones et al. to describe the SpO ₂ -FIO ₂ diagram ¹¹ . However, this limitation was well controlled as shown in tables 1 and 2. Sixth , for the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible. Although this percentage is not clinically relevant, these atelectasis which are not diagnosed with the Air-Test could potentially trigger an inflammatory response ³⁵ which at last would affect the rationale of using this test. Finally, as sample size calculation was not performed, this study can only be considered as a pilot study.
	27. Page 15, lines 1-25	Implications for practice First, this is a pilot study and a powered large external validation study is needed in a more heterogeneous surgical population such as obese, patients without previously normal lung function or patients with a preoperative SpO ₂ < 97%. Such a study may also analyze the Air-Test at different time points, with different pulse-oximeter technologies and in patients without previously supplemental oxygen delivery during the postoperative period with the aim to validate the test as a surrogate of postoperative atelectasis; and its severity if it is

		found a correlation between the SpO ₂ values during the Air-Test and the area of atelectasis measured by CT-scan. Second, the Air-Test may become a standardized screening test before leaving the PACU to evaluate postoperative oxygenation. It may contribute to a higher patient flow in PACU without losing high care quality as it may discriminate those patients without postoperative lung derecruitment (negative Air-Test) from those (positive Air-Test) with an increased risk of postoperative hypoxemia ³⁶ , whom should ideally be surveyed more closely during this period and would likely benefit from measures to revert atelectasis, which may have a potential positive impact on healthcare costs ³⁷ . Despite the benefits in outcomes of these measures remain uncertain ³⁸ , several studies showed the potential benefits ³⁹ and currently is ongoing a clinical trial which uses the Air-Test to individually apply the use of a postoperative continuous positive end-expiratory pressure ⁴⁰ .
	28. Page 2, line 44	Trial Registration ClinicalTrials.gov Identifier: NCT02650037.
	29. Page 5, lines 14-16	The complete and original protocol is described in this section.
	30. Page 15, lines 26-28	The work was not supported

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The accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.

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Title: The accuracy of postoperative noninvasive Air-Tests to diagnose atelectasis in healthy patients after surgery — a prospective diagnostic pilot study

¹Carlos Ferrando, ²Carolina Romero, ³Gerardo Tusman, ^{4,5}Fernando Suarez-Sipmann, ⁶Jaume Canet, ⁷Rosa Dosdá, ¹Paola Valls, ¹Abigail Villena, ¹Ferran Serralta, ¹Ana Jurado, ¹Juan Carrizo, ¹Jose Navarro, ⁷Cristina Parrilla, ⁸Jose E. Romero, ⁹Natividad Pozo, ¹Marina Soro, ^{4,10,11}Jesus Villar, and ¹Francisco Javier Belda.

(1) Department of Anesthesiology and Critical Care, Hospital Clínico Universitario, Valencia. Spain; (2) Department of Anesthesiology, Consorci Hospital General Universitari, Valencia, Spain; (3); Department of Anesthesiology, Hospital Privado de Comunidad, Mar de Plata, Buenos Aires, Argentina; (4) CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; (5) Section of Anesthesiology and Critical Care, Uppsala University Hospital Uppsala, Uppsala, Sweden; (6) Department of Anesthesiology and Critical Care, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; (7) Department of Radiology, Hospital Clínico Universitario, Valencia, Spain; (8) ITACA Institute (Group IBIME), Universidad Politécnica, Valencia, Spain; (9) INCLIVA Clinical Research Institute, Hospital Clínico Universitario, Valencia, Spain; (10) Spain Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Las Palmas, Spain.

Corresponding Author: Carlos Ferrando

Department of Anesthesiology and Critical Care
Hospital Clínico Universitario
Av. Blasco Ibañez, 17
46010 Valencia. SPAIN
Phone: (+34) 963862600 Fax: (+34) 963862680
E-mail: cafeoranestesia@gmail.com

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Abstract

Objective To assess the diagnostic accuracy of peripheral capillary oxygen saturation (SpO₂) while breathing room air for 5 minutes (the “Air-Test”) in detecting postoperative atelectasis.

Design Prospective cohort study. Diagnostic accuracy was assessed by measuring the agreement between the index-test and the reference-standard computed tomography scan images.

Setting Postanesthetic care unit in a tertiary hospital in Spain.

Participants 350 patients from January 12 to February 7, 2015; 170 patients scheduled for surgery under general anesthesia who were admitted into the postsurgical unit were included.

Intervention The Air-Test was performed in conscious extubated patients after a 30 min stabilization period during which they received supplemental oxygen therapy via a Venturi mask. The Air-Test was defined as positive when SpO₂ was $\leq 96\%$ and negative when $\geq 97\%$. Arterial blood gases were measured in all patients at the end of the Air-Test. In the subsequent 25 minutes, the presence of atelectasis was evaluated by performing a computed tomography scan in 59 randomly-selected patients.

Main outcome measures The primary study outcome was assessment of the accuracy of the Air-Test for detecting postoperative atelectasis compared to the reference standard. The secondary outcome was the incidence of positive Air-Test results.

Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scans in all patients (30/30) and was positive and in 5 patients (17%) with negative Air-Test results. Based on the Air-Test, postoperative atelectasis was present in 36% of the patients (62 out of 170).

Conclusion The Air-Test may represent an accurate, simple, inexpensive, and noninvasive method for diagnosing postoperative atelectasis.

Trial Registration ClinicalTrials.gov Identifier: NCT02650037.

Keywords: Postoperative, atelectasis, oxygenation, SpO₂

Strengths and limitations of this study

- This study used a simple and fast room-air breathing trial (the “Air-Test”) in the early postoperative period to diagnose atelectasis.
- Diagnostic accuracy was assessed by measuring agreement between the index-test and the reference-standard computed tomography scan images.
- This study was a pilot study and a large external validation study is now needed.
- The Air-Test had several limitations, not only related to the pulse-oximeter, but also to the test itself, which could limit its clinical application in some cases.

Introduction

An estimated 234 million major surgical procedures are undertaken each year worldwide¹. Atelectasis may develop in nearly 90% of patients put under general anesthesia and can persist not only during the immediate postoperative period, but up to several days after surgery²⁻⁵. Persistence of atelectasis after surgery is potentially associated with postoperative pulmonary complications such pneumonia, acute lung injury, and extubation failure requiring reintubation³⁻⁷. Hypoxemia, a direct consequence of atelectasis⁸, may also promote systemic complications such acute myocardial ischemia or impaired wound healing, among others⁹.

Oxygen therapy is usually given in the postoperative period to alleviate hypoxemia¹⁰, which develops in most patients after general anesthesia. As a result, the majority of atelectasis cases in the postoperative period cannot be diagnosed at the bedside, thus precluding the application of any corrective measures and potentially increasing the risk of atelectasis-related postoperative complications. On the other hand, using a low (0.21) fraction of inspired oxygen (FiO_2) may improve lung function categorization as measured by peripheral capillary oxygen saturation (pulse oximetry hemoglobin saturation; SpO_2) values, because it forces SpO_2 to operate in the steep section of the oxygen-hemoglobin dissociation curve, and can therefore be used to estimate the alveolar shunt using the SpO_2 - FiO_2 diagram described by Jones et al¹¹. This could help to unmask underlying oxygenation deficits caused by this shunt and thus, the presence of atelectasis when SpO_2 is low, although this does assume that there is a linear relationship between the alveolar shunt and atelectasis. Consequently, a combination of oxygen therapy with transitory decreases in FiO_2 to 0.21 over a 5-minute period, is enough to achieve a steady-state in the expired fractional oxygen concentration (FEO_2)^{12,13} and thus, may allow estimation of the alveolar shunt in addition to revealing the presence of atelectasis in the immediate postoperative period.

We hypothesized that changes in arterial oxygen saturation induced by a short FiO_2 maneuver to reduce it to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO_2 recorded by pulse oximetry after breathing room-air for 5 min (the "Air-Test") can reveal the presence of atelectasis and to establish the relationship between SpO_2 and the presence of atelectasis, as assessed by a computed tomography (CT) scan.

Methods

Study design

We performed a prospective, cohort study in the post-surgical recovery unit at the University Clinical Hospital (*Hospital Clínico Universitario*) in Valencia (Spain), from January 12 to February 7, 2015. The study was approved by the Local Ethics Committee for Clinical Research (Chairperson: Dr. Antonio Peláez), is in accordance with the Declaration of Helsinki on human experimentation, and was registered on December 28, 2015 at <http://www.clinicaltrials.gov> with identification no. NCT02650037. Written informed consent was obtained from all the patients involved in the study. The complete and original protocol is described in this section.

Eligibility criteria

The study included consecutively recruited patients with an American Society of Anesthesiologists physical status of I-III who were scheduled for elective surgery with general anesthesia and admitted to the post-surgical unit. Exclusion criteria were: (i) age < 18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, or (v) preoperative SpO₂ ≤ 97% on room air. Postoperatively, patients who had given their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room, (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin < 10 g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale > 1 or < -1, and (vi) pain > 4, (evaluated with the visual analogue scale), after the first 30 min in the post-anesthesia care unit (PACU; Figure 1).

Monitoring

Intraoperative anesthesia management followed standard clinical routines and the study started upon arrival at the post-surgical unit. A multi-parameter IntelliVue MX450 (Philips Healthcare, Böblingen, Germany) monitor was used for all patients to monitor the patient's heart activity (via electrocardiogram), systemic arterial pressure (non-invasively), and SpO₂. The MX450 monitor pulse-oximeter finger probe uses Fourier artifact-suppression technology (FAST) to measure SpO₂; its characteristics are described in Supplement 1 of this article's supporting digital content.

Index-test for postoperative atelectasis

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3 Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FiO_2
4 of 0.5 for the first 30 min. The Air-Test was then performed by removing the oxygen mask and leaving the
5 patients breathing room-air for at least 5 minutes while continuously monitoring SpO_2 with a pulse-oximeter
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Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FiO_2 of 0.5 for the first 30 min. The Air-Test was then performed by removing the oxygen mask and leaving the patients breathing room-air for at least 5 minutes while continuously monitoring SpO_2 with a pulse-oximeter finger probe. The Air-Test result was considered positive when the recorded SpO_2 was $\leq 96\%$ and negative when SpO_2 was $\geq 97\%$. We selected this cut-off value to diagnose atelectasis based on the SpO_2 - FiO_2 diagram¹⁰ described by Jones showing that $\text{SpO}_2 \leq 96\%$ corresponds to a shunt effect of more than 10% and defines alveolar collapse. Recently, Tusman et al.¹⁴ used a similar approach by using a FiO_2 of 0.21 to define an open-lung condition in anesthetized patients while ventilated.

We used a 5-minute time interval based on the results we obtained in our pilot study performed with 10 healthy nonsmoker volunteers at the Private Community Hospital (*Hospital Privado de Comunidad* in its original Spanish) in Mar del Plata (Argentina), to establish the mean time from removal of a Venturi mask providing oxygen supplementation to detection of a FEO_2 stabilization signal — in this case, 56 (± 7) seconds. Interventions and results are described in Supplement 1 of our additional digital content. Furthermore, the selected time was also based on results from spontaneously-breathing patients published by Howe et al.¹² and in mechanically-ventilated patients described by Fildissis et al.¹³. Both studies showed that the partial-pressure of oxygen in arterial blood (PaO_2) measured 5 minutes after discontinuation of supplementary oxygen represents a steady-state condition in lung-healthy patients.

The Air-Test was performed 30 min after PACU admission for safety reasons. This arbitrary time restraint was set to provide sufficient time for staff to carry out all the necessary tests and to check that patients met all the discharge criteria, thus ensuring their safe release from the PACU after having received general anesthesia. The reference-standard test for postoperative atelectasis (a CT scan) was performed in a random selection of these patients as soon as possible after completing the Air-Test (in order to minimize bias). In addition, we evaluated the prevalence of positive Air-Test results. Once the Air-Test was completed, a blood sample was drawn from each patient while breathing room-air in order to perform an arterial blood gas analysis (Radiometer ABL 520 blood gas analyzer, Radiometer, Copenhagen, Denmark). The oxygen mask was placed back whenever their SpO_2 fell to 92% for more than one minute during the Air-Test and until the end of the protocol after the Air-Test was completed.

Randomization of patients for the reference-standard test (computed tomography scan)

Approximately 25 min later, patients were randomly selected to undergo a CT-scan evaluation — the gold standard technique used for diagnosing atelectasis. We used adaptive randomization which allowed us to minimize the CT-scan exposure in patients not expected to have atelectasis while maintaining a sufficient number of patients on each arm to be able to conduct adequate statistical comparisons¹⁵.

Postoperative atelectasis (computed tomography scan) reference-standard test

For the purpose of this study and based on previous data¹⁴, the presence of an atelectatic area of less than 2% in the CT-scan was considered negligible (negative) because it does not cause a clinically relevant alveolar shunt^{16,17}. CT-scans were acquired with 16 detectors per row and 32 slices using an Aquilion LB scanner (Toshiba). Scans (120 kV, 100-140 mA, and 0.5 sec rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5 mm-thickness slices with 5 mm intervals, and with a depth of 12 bits per pixel. Each right and left surface of normally-aerated tissue and atelectasis were semi-automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchus, and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to +100). After this correction, normally-aerated lung and atelectasis tissue separation was automatically corrected. An example of the segmentation steps is shown in Figure 2. CT densities were quantitatively analyzed using previously validated methods^{18,19}. The atelectatic area was expressed in cm² as the mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROIs) were calculated using equation 1:

$$VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$$

Where V is the set of voxels inside the ROI and x , y , and z are the voxel sizes in the three dimensions, in millimeters. Volumes are given in milliliters.

The lung tissue masses for the different ROIs were calculated as previously described²⁰. See equation 2:

$$MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$$

Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V , HU_i represents the CT value for voxel i , and VOL_{voxel} represents the voxel volume for the image being processed, in

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3 milliliters. The atelectatic mass was expressed in grams as the mean \pm standard deviation (SD) and as a
4 percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but was performed
5 at the region presenting the largest amount of atelectasis, independently in each lung. All CT images were
6 analyzed by the same radiologist and computer engineer who were blinded to the purpose of the study.
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10 11 **Index-test (Air-Test) diagnostic test**

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14 A 2 \times 2 table (table 2) was used to assess the sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP + TN)] \times$
15 100; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$ of the Air Test; where *TP* is true
16 positive, *TN* is true negative, *FP* is false positive, and *FN* is false negative.
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20 21 **Statistical analysis**

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23 The total sample size was not calculated because this was a cohort study. Similarly, the sample size for the
24 randomized CT-scan group was not calculated because this was preliminary pilot study. Thus, we arbitrarily
25 decided that the minimum sample size should be at least 50 patients (25 patients each with positive or negative
26 Air-Test results). Data were analyzed using the statistical software R, version 3.1.1²¹. All the analyses performed
27 were pre-specified and statistical description of the baseline demographics were obtained from the *Rmisc* and
28 *PropCIs* libraries. We compared postoperative variables either using the Student *t* or Mann–Whitney U tests for
29 continuous variables, depending on their characteristics: the Shapiro–Wilk test was used to assess normality, the
30 Friedman test for ordinal variables, and the binomial test for proportional variables. Data are expressed as the
31 mean (\pm standard deviation) or median (interquartile range).
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40 We used a simple linear regression model with the SpO₂ and total atelectasis area variables using the following
41 formula: Area of atelectasis \sim SpO₂ + ϵ , where ϵ is the error and a regression line was built on the resulting
42 scatterplot using the *lm()* function. The diagnostic accuracy and sensitivity analysis were conducted in R with the
43 *pROC* library. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values were
44 computed with bootstrap resampling and averaging methods, as described by Fawcett²², which have been shown
45 to generate unbiased optimism-adjusted estimates of the CI statistics. The patients were resampled for all
46 bootstrap CIs and the modified curve was built before the statistics of interest were computed. As in the
47 bootstrap comparison test, the resampling was stratified²³. For all comparisons, a two-sided value of $p < 0.05$
48 was considered significant.
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Results

A total of 181 out of 350 eligible patients scheduled for surgery were enrolled; 170 of these underwent the Air-Test in the post-operative unit; 30 randomly-assigned patients from the 62 positive Air-test results and 29 from the 108 negative Air-Test results, were also assessed with CT imaging (Figure 1).

Baseline demographic and clinical characteristics of all the patients

The demographic, surgical, intraoperative ventilatory management data, and clinical variables after the completion of the Air-Test are shown in Table 1. Patients with positive Air-Test results were older, predominantly male, had a higher ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia)²⁴ score, and weighted more compared to those with negative test results. There were no significant differences regarding intraoperative management, type, and surgery duration between either group. Oxygenation (i.e. PaO₂) was 25% lower in patients with a positive test result ($p < 0.001$). In addition, SpO₂ fell in the steep section of the oxygen-hemoglobin dissociation curve for positive test-result patients but not for patients with a negative test result. All the patients were hemodynamically stable and normothermic.

Table 1. Patient study variables in the positive and negative Air-Test results groups

	Positive Air Test Result (n = 62)	Negative Air Test Result (n = 108)	<i>p</i> -value
Demographic data			
Age, yrs.	65 (11)	56 (17)	< 0.001
Women, n (%)	33 (6)	56 (9)	0.01
Height, cm	164 (9)	166 (9)	0.06
Body weight, kg	84 (21)	73 (15)	< 0.001
ARISCAT score	26 (14)	16 (15)	0.01
Preoperative SpO ₂ , %	98 (1)	98 (2)	0.12
Lower Abdominal surgery	24 (38)	34 (31)	0.20
Upper Abdominal surgery	9 (14)	13 (12)	0.11
Peripheral surgery	29 (46)	60 (55)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volume, ml	470 (52)	460 (88)	0.33
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FiO ₂	0.6 (0.2)	0.7 (0.3)	0.88
SpO₂ and arterial blood gases in PACU at the end of the Air-Test			
Postoperative SpO ₂ , %	91 (3)	99 (1)	0.01
PaO ₂ , mmHg	66 (10)	87 (12)	0.01
PaCO ₂ , mmHg	41 (6)	42 (6)	0.29
pH	7.37 (0.04)	7.38 (0.03)	0.06
MAP, mmHg	79 (12)	85 (15)	0.07
Lactate, mmol/L	1.1 (0.4)	1.0 (0.7)	0.32
Hb, g/dl	12.6 (1.7)	12.9 (1.1)	0.09
Temperature, °C	36.4 (1.9)	36.1 (2.1)	0.41
VAS	1 (1)	1 (1)	1.00

Table 1. Data are described as the mean (\pm SD) or number/total number (%). The ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) score was used to predict postoperative pulmonary complications²², PEEP: positive end-expiratory pressure; FiO₂: inspiratory oxygen fraction; PACU: post-anesthetic care unit; SpO₂: pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial-pressure; PaCO₂: carbon dioxide partial-pressure; pH: acid-base status; MAP: mean arterial pressure; Hb: hemoglobin, VAS: visual analogue scale.

Baseline demographic and clinical characteristics of patients in the reference-standard (computed tomography scan) group

As shown in table 2, the differences found between patients with positive and negative Air-Test results (table 1) were maintained in patients who also underwent a CT-scan.

Table 2. Study variables of patients in the positive and negative Air-Test results groups also assessed with a reference-standard CT-scan

	Positive Air Test Result (n = 30)	Negative Air Test Result (n = 29)	<i>p</i> -value
Demographic data			
Age, yrs.	62 (13)	53 (15)	0.045
Women, n (%)	12 (40)	11 (37)	0.57
Height, cm	165 (10)	163 (12)	0.32
Body weight, kg	88 (29)	75 (17)	< 0.001
ARISCAT score	28 (14)	14 (15)	< 0.001
Preoperative SpO ₂ , %	98 (2)	98 (2)	0.28
Lower Abdominal surgery	39 (10)	29 (5)	0.20
Upper Abdominal surgery	6 (3)	4 (3)	0.11
Peripheral surgery, %	55 (11)	67 (7)	0.06
Duration of surgery, min	137 (62)	119 (63)	0.27
Intraoperative ventilatory management			
Tidal volume, ml	472 (50)	466 (92)	0.56
Respiratory rate, breaths/min	12 (1)	12 (2)	1.00
PEEP, cmH ₂ O	6 (1)	6 (2)	1.00
FiO ₂	0.7 (0.2)	0.7 (0.3)	0.90
SpO₂ and arterial blood gases at PACU at the end of the Air Test			
Postoperative SpO ₂ , %	92 (3)	99 (1)	0.01
PaO ₂ , mmHg	78 (21)	90 (10)	< 0.001
PaCO ₂ , mmHg	40 (6)	42 (6)	0.34
pH	7.37 (0.04)	7.38 (0.03)	0.09
MAP, mmHg	81 (12)	76 (15)	0.72
Lactate, mmol/L	1.1 (0.4)	1.0 (0.6)	0.52
Hb, g/dl	12.5 (1.2)	12.3 (1.6)	0.41
Temperature, °C	36.2 (1.9)	36.2 (2.3)	0.68
VAS	1 (1)	1 (1)	1.00

Table 2. Data are described as mean (SD) or number/total number (%). The ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) score was used to predict postoperative pulmonary complications²², PEEP: positive end-expiratory pressure; FiO₂: inspiratory oxygen fraction; PACU: post-anesthetic care unit; SpO₂:

pulse oximetry hemoglobin saturation; PaO₂: arterial oxygen partial-pressure; PaCO₂: carbon dioxide partial-pressure; pH: acid base state; MAP: mean arterial pressure; Hb: Hemoglobin, VAS: visual analogue scale.

Diagnostic accuracy

Of the 59 patients evaluated with a CT-scan, all those with a positive Air-Test and 5 of those with a negative Air-Test result (17%) had a measurable atelectasis (area > 2% of the whole lung) on their CT-scan. When mass analysis was used to diagnose atelectasis, 27 patients with a positive Air-Test result and only 3 patients with a negative Air-Test result had measurable atelectasis (mass > 2% of the whole lung). None of the patients with a negative Air-Test result and atelectasis on their CT-scan had a SpO₂ > 98% and an atelectatic area or mass > 4%. ROC analysis showed that a positive Air-Test (SpO₂ ≤ 96%) result was adequate to diagnose postoperative atelectasis (Table 3).

Table 3. Diagnostic accuracy, sensitivity, specificity and area under the curve (AUC) for detecting atelectasis with the Air-Test, as assessed against a reference-standard (computed tomography scans).

	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Air-Test (N = 59)	0.90 (0.82-0.98)	82.6	87.8	91.5

Sensitivity analysis

Since the Air-Test could be affected by several factors such as dyshemoglobinemia, low-perfusion status, motion artifact, and hypothermia, we performed two additional analyses to confirm our results. First, the PaO₂ threshold value confirming the diagnosis of atelectasis was 78 mmHg, with a sensitivity of 82.6%, a specificity of 78.7%, and an area under the ROC curve of 0.86 (95% CI: 76.6-96.1%). Second, to check the suitability of SpO₂ for diagnosing atelectasis, we performed a ROC test for correlated data between SpO₂-ROC and PaO₂-ROC. The ROC test showed no differences between either test ($p = 0.10$).

Secondary outcome

We found a prevalence of positive Air-Test results of 36% in our population (62 of the 170 patients).

Adverse events

No adverse events were reported during the study period.

Discussion

This diagnostic pilot study showed that performing a postoperative Air-Test 30 minutes after surgery could accurately diagnose atelectasis and identified a high prevalence postoperative atelectasis. This simple, noninvasive, and inexpensive bedside test can be used in healthy patients with a preoperative SpO₂ between 97 and 100% while breathing room-air and helped to unmask underlying oxygenation deficits and the presence of atelectasis when SpO₂ ≤ 96%. As previous studies have described, the alveolar shunt induced by atelectasis is the main cause of oxygenation impairment during the postoperative period¹⁵. In fact, Rothen et al.²⁵ showed that 75% of PaO₂ impairment is related to atelectasis and airway closure in patients with healthy lungs. Based on this statement, our results are in line with those of Witting et al.²⁶ who found that a SpO₂ ≤ 96% in patients breathing room-air was synonymous with a diagnosis of hypoxemia (defined as PaO₂ < 70 mmHg in their study) with a sensitivity of 100%, a specificity of 54%, and an area under the ROC curve of 0.91 (95% CI: 0.78 to 0.94).

We found a rate of 17% false-negative Air-Test results in patients who presented an atelectasis area higher than 2% in their CT images, which reduced to 10% when mass was used to diagnose atelectasis. There are several potential reasons for this decreased sensitivity. First, the test duration: perhaps five minutes is insufficient time to achieve a steady state FEO₂ in some patients. Some authors found that slightly longer times (5.5 [4.8] minutes in healthy patients²⁷ or 7.1 [2.1] in COPD patients) were required in mechanically-ventilated patients²⁸. Another potential cause for the false negatives might be the percentage of pulse-oximeter measurements because an error bias of up to 2% and differences in precision of up to 3% compared to the reference standard (CO-oximeter) have been described for these data²⁹. Although we did not find false positives when the area was used to diagnose postoperative atelectasis, three of the 30 patients with a positive Air-Test result did not present an atelectasis mass > 2%. In addition to the bias and variation in precision discussed above, this error could also potentially be caused by overestimation of the atelectasis-induced alveolar shunt (based on the SpO₂-FiO₂ diagram¹¹), because of the presence of low ventilation-perfusion (V/Q) zones which can appear during mechanical ventilation¹³.

In agreement with previous studies, the Air-Test indicated a 36% prevalence of postoperative atelectasis: Akca et al. found a similar prevalence using CT-scans in 30 patients after colon surgery³⁰. Our findings also correlate with the prevalence of postoperative SpO₂ ≤ 96% found by Severgnini et al. where 12 of the 27 patients in the control group and 8 of the 28 patients in the study group (representing a prevalence of 36% in the total population) had a SpO₂ ≤ 96% while breathing room-air (unpublished data), but no atelectasis was diagnosed by

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3 chest radiography³¹. Recently, an observational study which continuously monitored SpO₂ in 833 unselected
4 postoperative patients for 48 h, demonstrated a 37% prevalence of hypoxemia (SpO₂ < 90%)⁹. However, in
5 general, the rate of atelectasis usually reported is much lower^{24,32}. Two recent trials, which together included
6 more than 1200 patients, reported an atelectasis prevalence of around 15% when diagnosed by chest
7 radiography^{33,34}. However, this low prevalence might be explained by the low sensitivity and specificity of chest
8 radiographs, and when compared to the prevalence observed in our study using CT-scans, suggests that
9 atelectasis is usually underestimated.

16 Limitations

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18 There are several limitations to our study which we would like to acknowledge and expand upon here. First, the
19 Air-Test can only be applied to patients with a preoperative SpO₂ ≥ 97% on room-air because at lower
20 percentages it is impossible to differentiate whether the postoperative SpO₂ measured indicates the presence of
21 postoperative atelectasis or of previous lung disease. However, a high percentage of patients scheduled for
22 surgery have a SpO₂ ≥ 97%²⁴. Second, intraoperative respiratory complications that decrease low V/Q zones and
23 therefore decrease SpO₂ (e.g. lung edema or pneumothorax) may overestimate the atelectasis-induced alveolar
24 shunt when this measurement is based on SpO₂-FiO₂. However, these postoperative complications in the
25 immediate postoperative period rarely appear³⁴. Third, compensatory mechanisms which come into play in the
26 presence of atelectasis, such as hypoxic pulmonary vasoconstriction, decrease this shunt and therefore may also
27 increase SpO₂ and thus, based on the SpO₂-FiO₂ chart¹¹, would underestimate atelectasis. These latter two
28 limitations may decrease the sensitivity and specificity of the Air-Test.

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30 Fourth, temporal factors could have also affected our results because of potential time delays between testing the
31 arterial blood gases, and performing the Air-Test and CT-scans. However, even if this represents a problem, the
32 results would have been negatively affected because a time-dependent reduction in postoperative atelectasis
33 occurs as patients improve their breathing capacity. Fifth, it is possible that the pulse-oximeter may have
34 underestimated postoperative atelectasis in the presence of dyshemoglobinemia or overestimated it in the
35 presence of anemia, a low perfusion state, motion artifacts, or hypothermia²⁹. Some of these limitations are
36 related not only to the pulse-oximeter, but also to the Air-Test itself, because shifts on the oxy-hemoglobin
37 dissociation curve can affect the principle used by Jones et al. to describe the SpO₂-FiO₂ diagram¹¹. However,
38 this limitation was well controlled, as shown in tables 1 and 2. Finally, for the purpose of this study, an
39 atelectatic area of less than 2% in the CT-scan was considered negligible; although this percentage is not
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3 clinically relevant, these atelectasis, which are not diagnosed with the Air-Test, could potentially trigger an
4 inflammatory response³⁵ which would therefore affect the rationale behind using this test.
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7 **Implications for practice**

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9 First, this is a pilot study and an adequately powered large external validation study looking at a more
10 heterogeneous surgical population (e.g. including obese patients without previous normal lung function or
11 patients with a preoperative SpO₂ < 97%) is still needed. This study should aim to validate the Air-Test as a
12 surrogate for the presence of postoperative atelectasis and could also analyze it at different time points, with
13 different pulse-oximeter technologies, and in patients who had not previously received supplemental oxygen
14 delivery during the postoperative period, in order to check if there is any correlation between the SpO₂ values
15 during the Air-Test and the area of atelectasis measured by the index-test CT-scan.
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19 Second, the Air-Test could be used as a standardized screening test which could be applied in order to evaluate
20 postoperative oxygenation before allowing patients to leave the PACU; its use could therefore contribute to
21 speeding up the flow of patients through the PACU without jeopardizing the provision of high-quality care
22 because it might be able to more accurately identify patients without postoperative lung derecruitment (negative
23 Air-Test results) from those with an increased risk of postoperative hypoxemia (positive Air-Test results)³⁶ and
24 thus, those who should, ideally, be more closely monitored during this period and would likely benefit from
25 measures to revert atelectasis. Thus, this non-invasive and inexpensive discriminatory test may have the
26 potential to positively impact healthcare costs³⁷. Despite the potential benefits of employing this test, as shown
27 by several studies³⁹, its more mainstream use remains uncertain³⁸. However, a clinical trial which uses the Air-
28 Test to individually indicate the application of postoperative continuous positive end-expiratory pressure is
29 currently ongoing⁴⁰.
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43 **Conclusions**

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45 We have demonstrated that the Air-Test can be used as an accurate, simple, inexpensive, noninvasive, and
46 readily available method for diagnosing postoperative atelectasis, although these results should be confirmed in
47 further, adequately-powered studies.
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Footnotes:**Contributors**

Dr. Ferrando (MD, PhD) and Prof. Belda (MD, PhD) had full access to all the data and are responsible for the integrity and the accuracy of the data analysis. *Study design:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD), and Prof. Belda (MD, PhD). *Acquisition and analysis of the data:* Dr. Ferrando (MD, PhD), Dr. Romero (MD), Dr. Dosdá, (MD, PhD), Dr. Tusman (MD), Dr. Soro (MD, PhD), Dr. Valls (MD), Dr. Villena (MD), Dr. Serralta (MD), Dr. Jurado (MD), Dr. Carrizo (MD), Dr. Navarro (MD), Dr. Parrilla (MD), Dr. Pozo (PhD), Dr. Romero (BSc), Dr. Villar (MD, PhD), and Prof. Belda (MD, PhD). *Interpretation of the data:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), and Dr. Canet (MD, PhD). *Drafting of the manuscript:* Dr. Ferrando (MD, PhD), Dr. Villar (MD, PhD), and Prof. Belda (MD, PhD). *Critical revision of the manuscript for intellectual content:* Dr. Ferrando (MD, PhD), Dr. Tusman (MD), Dr. Suarez-Sipmann (MD, PhD), Dr. Canet (MD, PhD), Dr. Suarez-Sipmann (MD, PhD), Dr. Villar (MD, PhD), and Prof. Belda (MD, PhD).

Language edition

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Declaration of interests

All the authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare they received/have: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Ethical approval

This work was approved by the Local Ethics Committee for Clinical Research. Written informed consent was obtained from all the participating patients.

Data Sharing Statement**Transparency declaration**

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3 The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being
4 reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as
5 planned (and, if relevant, registered) have been explained.
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9 *The manuscript's guarantor.

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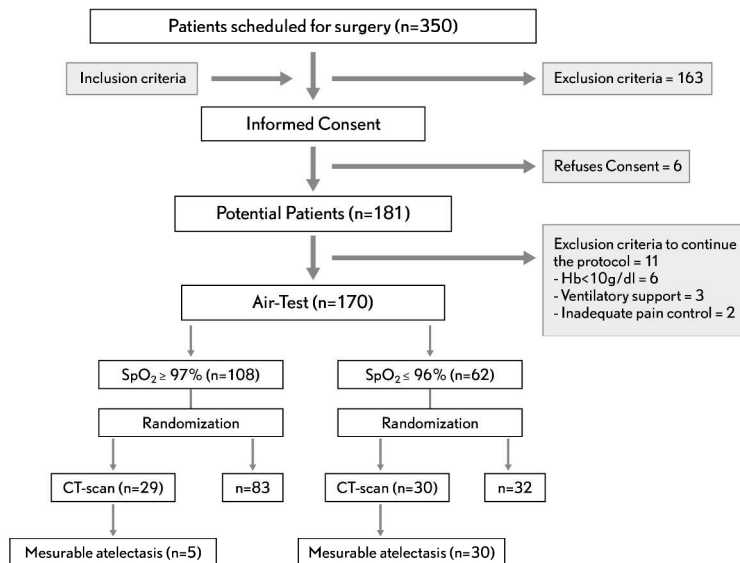
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Figure Legends

Figure 1: START Flow diagram

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START Flow diagram

297x210mm (300 x 300 DPI)

Review only

Supplementary file

Title: The accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.

Carlos Ferrando, Carolina Romero, Gerardo Tusman, Fernando Suarez-Sipmann, Jaume Canet, Rosa Dosdá, Paola Valls, Abigail Villena, Ferran Serralta, Ana Jurado, Juan Carrizo, Jose Navarro, Cristina Parrilla, Jose E. Romero, Natividad Pozo, Marina Soro, Jesus Villar, Francisco Javier Belda.

Corresponding Author: Carlos Ferrando

Department of Anesthesiology and Critical Care

Hospital Clínico Universitario

Av. Blasco Ibañez, 17

46010 Valencia. SPAIN

Phone: (+34) 963862600 Fax: (+34) 963862680

Email: cafeoranestesia@gmail.com

Methods

Procedures

We performed a pilot study in ten healthy and non-smoker volunteers in the Hospital Privado de Comunidad, Mar de Plata (Argentina) to establish the mean time from Venturi mask removal with oxygen supplementation to the stabilization of the expiratory fraction of Oxygen (FEO₂) signal. The volunteers were breathing spontaneously through a Venturi mask at 4 L/min with a jet adjusted to a theoretical FiO₂ of 0.5 during 10 min before the Air-Test was performed. Nasal oxygen and carbon dioxide concentrations were measured using a 1 mm ID cannula placed 1 cm inside the right nostril and connected to the side-stream capnograph S5 (GE Healthcare/Datex-Ohmeda, Helsinki, Finland). Time-base oximetry and capnography were recorded with the Datex Collect software (GE Healthcare/Datex-Ohmeda, Helsinki, Finland) and analyzed off-line. We measured mean time needed from mask removal to the stabilization of the FEO₂.

The FAST SpO₂ algorithm derives SpO₂ using the absorption of red and infrared light. But unlike the traditional algorithm, the FAST algorithm examines the strength of the different frequency components that make up the signals. This approach allows to distinguish the physiological signal from the noise artifacts increasing measurement accuracy¹. Nevertheless, the SpO₂ measurement was considered qualitatively optimal only when a plethysmography waveform stable and normal was seen during the average time period of 10 seconds given by the monitor. The conventional finger probe pulse oximetry is an accurate reflection of SaO₂ values measured by the reference standard (CO-oximeter) with a bias of 2% and with a standard deviation (precision) of less than 3%².

Results

Demographic data of the 10 volunteers are described in the were age: 31 (7) years old, weight 71 (9) kg and height: 173 (4) cm. The mean time for the stabilization of the expired O₂ fraction once supplementary oxygen therapy was removed was 56 (7) seconds.

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1. Baker SJ, "Motion Resistant" pulse oximetry: A comparison of new and old models. *Anesth Analg* 2002; 95: 967-72.
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Selection of topic	Item	Description
Title, abstract	1. Page 1, lines 3-5	Accuracy of postoperative, noninvasive Air-Test to diagnose atelectasis in healthy patients after surgery – a prospective, diagnostic pilot study.
	2. Page 2, lines 2-42	<p>Objective To assess the diagnostic accuracy of SpO₂ while breathing room air for 5 min (“the Air-Test”) in detecting postoperative atelectasis.</p> <p>Design Prospective, cohort study. Diagnostic accuracy was assessed by measuring agreement of the index test with the reference standar computed tomography scan.</p> <p>Setting Postanesthetic care unit in a terciary Hospital in Spain.</p> <p>Participants 350 patients from January 12 to February 7, 2015. 170 patients scheduled for surgery under general anesthesia admitted into the postsurgical unit were included.</p> <p>Intervention The Air-Test was performed in awake extubated patients after a 30 min stabilization period receiving supplemental oxygen therapy via a Venturi mask. The Air-Test was defined positive when SpO₂ was ≤96% and negative when ≥97%. Arterial blood gases were measured in all patients at the end of the Air-Test. Within the next 25 min, the presence of atelectasis was evaluated by computed tomography scan in 59 randomly selected patients.</p> <p>Main Outcomes Measures The primary study outcome was the accuracy of the Air-Test for the detection of postoperative atelectasis assess by reference standar. The secondary outcome was incidence of positive Air-Test.</p> <p>Results The Air-Test diagnosed postoperative atelectasis with an area under the receiving operating curve of 0.90 (95% confidence interval: 0.82 to 0.98) with a sensitivity of 82.6% and a specificity of 87.8%. The presence of atelectasis was confirmed by computed tomography scan in all patients (30/30) with positive and in 5 patients (17%) with negative Air-Test. Based on the Air-Test, postoperative atelectasis were present in 36% of the patients (62 out of 170).</p> <p>Conclusion The Air Test is an accurate, simple, inexpensive and noninvasive method to diagnose postoperative atelectasis.</p> <p>Trial Registration ClinicalTrials.gov Identifier: NCT02650037.</p>
Introduction	3. Page 4, lines 16-34	<p>Oxygen therapy is usually applied in the postoperative period to alleviate hypoxemia¹⁰, which develops in most patients after general anesthesia. As a result, most atelectasis in the postoperative period may not be diagnosed at the bedside precluding the application of any corrective measure and thus potentially increasing the risk of atelectasis-related postoperative complications. In the other hand, the use of low FIO₂ (0.21) could better categorize lung function through SpO₂ values, as it forces SpO₂ to operate at the steep portion of the oxygen-hemoglobin dissociation curve, and thus it can be used to estimate the alveolar shunt using the SpO₂-FIO₂ diagram described by Jones et al¹¹. This may help to unmask underlying oxygenation deficits due to shunt and thus the presence of atelectasis when SpO₂ is low, assuming a linear relationship between shunt and atelectasis. Thus, a combination of oxygen therapy with transitory decreases of FIO₂ to 0.21 during a 5 minutes period, which is enough to achieve a steady state condition of the expired fraction of oxygen (FEO₂)^{12,13} may allow to estimate shunt and to unmask the presence of atelectasis during the immediate postoperative period.</p>
	4. Page 4, lines 36-44	<p>We hypothesized that changes in arterial oxygen saturation induced by a short maneuver of FIO₂ reduction to 0.21 can be used to detect the shunt related to postoperative atelectasis. Thus, the aim of this study was to determine whether SpO₂ recorded by pulse oximetry after breathing room-air for 5 min (“the Air-Test”) can reveal the presence of atelectasis and to establish the relation of the SpO₂ value to the presence of atelectasis assessed by CT-scan.</p>
Methods		
Participants	5.	We performed a prospective, cohort study at the post-surgical recovery unit of

	Page 5, lines 6-8	the Hospital Clínico Universitario, Valencia, Spain, from January 12 to February 7, 2015.
	6,7,8,9. Page 5, lines 19-33	The study included consecutive patients with an American Society of Anaesthesiologists physical status I-III scheduled for elective surgery with general anesthesia admitted to the post-surgical unit. Exclusion criteria were: (i) age <18 years, (ii) pregnancy, (iii) previous lung resection, (iv) cardiac and lung resection surgery, and (v) preoperative SpO ₂ ≤97% on room-air. Postoperatively patients who gave their consent were excluded if they met any of the following criteria: (i) patients not extubated in the operating room (OR), (ii) patients requiring any kind of ventilatory support, (iii) postoperative hemoglobin <10 g/dL, (iv) need for continuous vasopressor or inotropic support, (v) agitation/sedation Richmond scale > 1 or < -1, and (vi) pain > 4 evaluated with the visual analogue scale after the first 30 min in the PACU (Figure 1).
Test Methods	10a. Page 5, lines 48-51	Patients received supplemental oxygen through a Venturi mask with a jet and flow adjusted to a theoretical FIO ₂ of 0.5 during the first 30 min. The Air-Test was performed removing the oxygen mask and leaving the patients breathing room-air for at least 5 min under continuous SpO ₂ monitoring with a finger probe pulse-oximeter
	10b. Page 6, lines 64-60 and 7, lines	<p>CT-scans were obtained with 16-detector row/ 32 slices Aquillion LB (Toshiba). Scans (120 kV, 100-140 mA and 0.5 sec rotation time) were obtained during an expiratory hold after a normal inspiration. The images were reconstructed in 5 mm thickness slices with 5 mm interval and a depth of 12 bits per pixel. Each right and left surface of normally aerated tissue and atelectasis were semi automatically delineated. To this aim a customized MATLAB script was used to automatically select the normally aerated lung surface with a window setting of -1000 to +100 Hounsfield units (HU). Segmentation was manually corrected by an expert to remove the heart, the major vessels, the bronchi and artifacts and to delineate the atelectatic tissue. Finally, an automatic thresholding was applied to the atelectasis regions (HU from -100 to 100). After this correction, separation between normally aerated lung and atelectasis was automatically corrected. An example of the segmentation steps can be seen in Figure 2. Quantitative analysis of CT densities was performed using previously validated methods^{18,19}. The atelectatic area was expressed in cm² as mean and standard deviation (SD) and as a percentage of the total lung area. Volumes for the different segmented regions of interest (ROI) were calculated using equation 1:</p> $VOL_{ROI} = \sum_V x * y * z * 0.001 \quad (1)$ <p>Where V is the set of voxels inside the ROI and x, y and z the voxel sizes in the three dimensions given in millimeters. Volumes are given in milliliters. Mass of lung tissue for the different ROIS were calculated as previously described²⁰. See equation 2:</p> $MASS_{ROI} = \sum_{i \in V} \frac{(HU_i + 1000) * VOL_{voxel}}{1000} \quad (2)$ <p>Where V represents the set of voxels inside the ROI under study, i represents the voxel index from V, HU_i represents the CT value for voxel i and VOL_{voxel} represents the voxel volume for the image being processed given in milliliters. The atelectatic mass was expressed in grams as mean ± standard deviation (SD) and as a percentage of the total lung mass. The thoracic level for CT-scan analysis was not predefined but performed at the region presenting the largest amount of atelectasis in each lung independently. All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.</p>
	11. Page 6,	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique. It was used an

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60		lines 2-49	adaptive randomization which allowed us to minimize the exposure to CT-scans in patients not expected to have atelectasis but having sufficient number of patients on each arm to conduct comparisons
	12a.	Page 5, lines 51 to 57 and page 6, lines 2-5	The Air-Test was considered positive when the recorded SpO ₂ was ≤96% and negative when SpO ₂ was ≥97%. The selected cut-off value to diagnose atelectasis was based in the SpO ₂ -FIO ₂ diagram ¹⁰ described by Jones which showed that a SpO ₂ was ≤96% corresponds to a shunt effect >10% which defines alveolar collapse. Recently, Tusman et al. ¹⁴ used a similar approach by using a FIO ₂ of 0.21 to define an open-lung condition in anesthetized patients while ventilated.
	12b.	Page 6, lines 54-56	For the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible (negative) based in previous data because it does not cause a clinically relevant shunt
	13.	Page 7, lines 47-49	All CT images were analyzed by the same radiologist (RD) and computer engineer blinded to the purpose of the study.
	12.	Page 8, lines 18-26	Data were analysed using the statistical software R version 3.1.1. All the analisis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i> . We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range).
	Analysis		
	14.	Page 8, lines 2-6 and lines 11-41	<p>Diagnostic test of the index test (Air-Test)</p> <p>A 2×2 table (table 2) was used for the assessment of sensitivity = $[TP/(TP + FN)] \times 100$; specificity = $[TN/(FP + TN)] \times 100$; and diagnostic accuracy = $[(TP + TN)/(TP + TN + FP + FN)] \times 100$; where <i>TP</i> is true positive, <i>TN</i> is true negative, <i>FP</i> is false positive, and <i>FN</i> is false negative.</p> <p>Statistical analysis</p> <p>The total sample size was not calculated as this is a cohort study. The sample size for patients randomized for CT-scan was also not calculated as this is preliminary pilot study. Thus, we arbitrarily decided that the minimum sample size was at least 50 patients (25 patients with positive Air-Test and 25 with negative). Data were analysed using the statistical software R version 3.1.1²¹. All the analisis performed were pre-specified. Statistical description of the baseline demographics were obtained with the <i>library (Rmisc)</i> and <i>library (PropCIs)</i>. We compared postoperative variables with either Student's t or the Mann-Whitney U for continuous variables test, depending on the variables (the Shapiro–Wilk test was used to assess normality), Friedman test for ordinal and binomial test for proportional variables. Data are expressed as mean (standard deviation) or median (interquartil range). A simple linear regression model was used with the variables SpO₂ and the total area of atelectasis following the formula: Area of atelectasis ~ SpO₂ + ε, where ε is the error. A regression line was built in the scatterplot with the function <i>lm()</i>. The diagnostic accuracy and sensitivity analysis were conducted in R with the <i>library pROC</i>. The Confidence intervals (CIs) of the thresholds or the sensitivity and specificity values were computed with bootstrap resampling and the averaging methods described by Fawcett²². Bootstrap has shown to generate unbiased optimism-adjusted estimates of the CIs statistic. In all bootstrap CIs, patients were resampled and the modified curve was built before the statistics of interest were computed. As in the bootstrap comparison test, the resampling was done in a stratified manner²³. For all comparisons, a two-sided value of p<0.05 was</p>

		considered significant.
	17. Page 8, line 17	All the analysis performed were pre-specified
Results		
Participants	19	Figure 1
	20	Table 1
	21	Table 2
	22	Table 2
	22. Page 6, line 44	Approximately 25 min later, patients were randomly allocated to perform a CT-scan evaluation which is the gold standard technique.
Test Results	23	Table 3
	24	Table 3
	25. Page 11, line 46	Adverse events No adverse events were reported during the study period.
Discussion		
	26. Page 13, lines 15-54	Limitations We must acknowledge several limitations. First, the Air-Test can only be applied to patients with a preoperative SpO ₂ ≥ 97% on room-air, since it is not possible to differentiate whether the postoperative SpO ₂ indicates the presence of postoperative atelectasis or previous lung disease. However, a high percentage of patients scheduled for surgery have a SpO ₂ ≥ 97% ²⁴ . Second, intraoperative respiratory complications that decrease low V/Q zones and therefore decrease SpO ₂ , such as lung edema or pneumothorax, may overestimate shunt-induced by atelectasis based on the SpO ₂ -FIO ₂ . However, these postoperative complications in the immediate postoperative period rarely appear ³⁴ . Third, compensatory mechanisms in the presence of atelectasis such as the hypoxic pulmonary vasoconstriction decreases shunt and therefore may increase SpO ₂ , which would underestimate atelectasis based on the SpO ₂ -FIO ₂ diagram. This last two limitations may decrease the sensitivity and specificity of the Air-Test. Fourth, temporal factors could have affected our results because of time delays among the Air-Test, arterial blood gases, and the CT-scan. However, if at all, results would have been affected in a negative sense since a time-dependent reduction of postoperative atelectasis occurs as patients improve their breathing capacity. Fifth, erroneous readings of the pulse-oximeter may underestimate postoperative atelectasis in the presence of dyshemoglobinemias or overestimate them in the presence of anemia, low perfusion state, motion artifacts or hypothermia ²⁹ . Some of these limitations are not only related to the pulse-oximeter but also to the Air-Test itself as shifts of the oxy-hemoglobin dissociation curve can affect the principle used by Jones et al. to describe the SpO ₂ -FIO ₂ diagram ¹¹ . However, this limitation was well controlled as shown in tables 1 and 2. Sixth , for the purpose of this study, an atelectatic area of less than 2% in the CT-scan was considered negligible. Although this percentage is not clinically relevant, these atelectasis which are not diagnosed with the Air-Test could potentially trigger an inflammatory response ³⁵ which at last would affect the rationale of using this test. Finally, as sample size calculation was not performed, this study can only be considered as a pilot study.
	27. Page 15, lines 1- 25	Implications for practice First, this is a pilot study and a powered large external validation study is needed in a more heterogeneous surgical population such as obese, patients without previously normal lung function or patients with a preoperative SpO ₂ < 97%. Such a study may also analyze the Air-Test at different time points, with different pulse-oximeter technologies and in patients without previously supplemental oxygen delivery during the postoperative period with the aim to validate the test as a surrogate of postoperative atelectasis; and its severity if it is

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16		found a correlation between the SpO ₂ values during the Air-Test and the area of atelectasis measured by CT-scan. Second, the Air-Test may become a standardized screening test before leaving the PACU to evaluate postoperative oxygenation. It may contribute to a higher patient flow in PACU without losing high care quality as it may discriminate those patients without postoperative lung derecruitment (negative Air-Test) from those (positive Air-Test) with an increased risk of postoperative hypoxemia ³⁶ , whom should ideally be surveyed more closely during this period and would likely benefit from measures to revert atelectasis, which may have a potential positive impact on healthcare costs ³⁷ . Despite the benefits in outcomes of these measures remain uncertain ³⁸ , several studies showed the potential benefits ³⁹ and currently is ongoing a clinical trial which uses the Air-Test to individually apply the use of a postoperative continuous positive end-expiratory pressure ⁴⁰ .
17 18 19 20 21 22 23 24 25 26 27	28. Page 2, line 44	Trial Registration ClinicalTrials.gov Identifier: NCT02650037.
28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	29. Page 5, lines 14-16	The complete and original protocol is described in this section.
	30. Page 15, lines 26-28	The work was not supported