Table 1
Results at 1 year and 2 years and time effect.

Variable	Baseline			12 months			24 months			Time effect[a]	
	Cases $n=32$	Control $n=12$	p-value	Cases $n=26$	Control $n=9$	p-value	Cases $n=24$	Control $n=9$	p-value	Cases $n=24$	Control $n=9$
Age	69.9 ± 7.2	71.0 ± 5.2	0.8	70.3 ± 7.8	72.5 ± 5.6	0.4	70.9 ± 7.7	73.8 ± 5.8	0.3	–	–
BMI (kg/m^2)	28.4 ± 4.5	28.5 ± 7.1	0.8	28.8 ± 4.8	27.6 ± 7.4	0.4	28.4 ± 4.7	26.7 ± 7.5	0.4	0.4	0.2
FVC	77.0 ± 12.2	75.7 ± 21	0.6	75.8 ± 11.5	71.1 ± 18.1	0.6	76.4 ± 16.6	81.1 ± 17.5	0.5	0.9	0.1
FEV_1	51.5 ± 14.2	50.2 ± 12.5	0.9	52.7 ± 15.2	48.6 ± 14.7	0.4	51.7 ± 16.4	52.6 ± 15.1	0.8	0.4	0.4
FEV_1/FVC	47.5 ± 11.5	48.3 ± 9.1	0.8	48.9 ± 13.2	49.2 ± 12.6	0.9	47.7 ± 11.9	48.8 ± 11.5	0.8	0.07	0.2
6MWT	478.3 ± 66.5	473.5 ± 79.5	0.8	474.2 ± 100.4	470.4 ± 78.2	0.6	481.1 ± 96.6	466.7 ± 110	0.7	0.6	0.9
mMRC	2.1 ± 0.3	2 ± 0	0.1	1.7 ± 0.7	1.5 ± 0.5	0.5	1.7 ± 0.7	1.6 ± 0.7	0.7	0.008	0.1
BODE	2.7 ± 1.1	2.6 ± 1	0.8	2.2 ± 1.5	2.2 ± 1.2	0.7	2.2 ± 1.6	2.3 ± 1.7	0.8	0.1	0.7
CAT	11.4 ± 5	11.9 ± 3	0.6	6.8 ± 5.5	14.1 ± 4.9	0.001	7.9 ± 5.4	10.7 ± 3.9	0.16	0.002	0.2
Exacerbations	2 ± 3.1	2.2 ± 2.5	0.9	--	–	–	1.6 ± 2.1	3.8 ± 3.7	0.03	0.5	0.04
No. of steps	8470 ± 3826	6643 ± 4198	0.2	8060 ± 4552	5253 ± 3103	0.1	7419 ± 5301	4394 ± 2410	0.07	0.1	0.9
Strength (kg)	195.7 ± 76.7	196.1 ± 82.1	0.9	233.3 ± 68.5	172.5 ± 19.9	0.015	248.2 ± 86.8	177.0 ± 36.5	0.046	0.003	0.2

6MWT: 6-minute walk test; BMI, body mass index; BODE: Body mass index, airflow obstruction, Dyspnea and Exercise capacity; CAT: COPD Assessment Test; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified British Medical Council dyspnea scale; No. of steps: daily steps quantified with accelerometer (ActiGraph, the accelerometer was analyzed with ≥4 days of ≥10 h/day recording); Strength: maximum lower limb strength (maximum 1 repetition) in leg press exercise.
[a] p-value between baseline and 24 months.

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1579-2129/

Chlorine Inhalation Challenge in Humans: Development of a New Closed-Circuit Methodology

Prueba de provocación bronquial con cloro en humanos: desarrollo de una nueva metodología con circuito-cerrado

Dear Editor:

Depending on the concentrations, the inhalation of chlorine can cause conditions of various severity such as acute respiratory distress syndrome (ARDS),[1] reactive airway dysfunction syndrome (RADS),[2] or low dose irritant-induced asthma (LDIIA).[3] Mice models of chlorine exposure have used high levels of chlorine ranging from 400 to 800 ppm for 5•30 min. The chlorine exposure was performed by diluting Cl_2 gas in a chamber using a nose-only exposure chamber or even full-body cylindrical chambers.[4,5] In humans although allergen[6] or occupational sensitizer[7] exposures have been fairly well standardized, few chlorine exposure methods have been reported: (1) painting a dilution of sodium hypochlorite onto a cardboard[8]; (2) Dilution of chlorine gas with humidified medical grade air in a mixing chamber to the concentration of 0.4 and 1 ppm[9]; (3) nebulization of 30 ml of commercial bleach (5% sodium hypochlorite) to reach a chlorine concentration of 0.4 ppm.[10] However, the reliability, accuracy and safety of these chlorine inhalation methods have not been reported, which probably has prevented further performance of chlorine challenges.

The aim of this study was to describe a closed-circuit apparatus designed to expose humans to chlorine gas in a safe manner.

The chlorine-generating closed-circuit inhalation challenge apparatus has four main components (Fig. 1): (1) a chlorine generation system; (2) an exposure chamber with a pressure control system; (3) a monitoring device; and (4) a delivery device. Chlorine is generated in a gaseous form by a portable electrochemical gas generator CAL 2000 LT (Advanced Calibration Designs, Inc., Tucson, Arizona, USA), able to deliver a concentration up to 50 ppm at 0.5 L/min. This type of generator is versatile, has a very stable gas output that can be adjusted to different outlet concentrations and

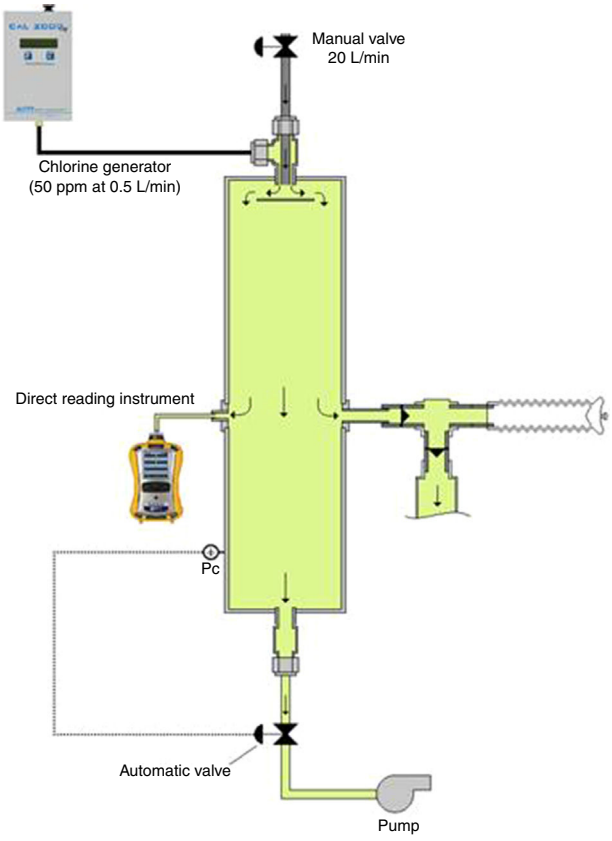

Fig. 1. Components of the closed-circuit apparatus.

is available for a multitude of products; hydrogen sulfide, hydrogen cyanide or chlorine dioxide. The 0.5 L/min chlorine gas mixture produced by this generator was mixed with a fresh-air airflow at the inlet of an exposure chamber. This airflow needed to be adjusted at 20 L/min in order to allow the production of the targeted 1 ppm concentration of chlorine in the chamber. The value of this airflow was roughly established by mass balance calculation and was finely tuned through experimentations. The exposure chamber consisted of a vertical stainless steel cylinder (size = 15 cm diameter í 0.5 m long); an exhaust pump is connected to the outlet of this exposure chamber through an electro pneumatic proportional valve VEF (SMC Inc.). The opening of this valve is controlled by an automated regulation system in order to keep the pressure in the exposure chamber slightly under the ambient pressure in order to avoid the contamination of the surroundings. At equilibrium, the airflow coming in the chamber is almost the same as the one exiting it.

Three opening ports were located at mid-length of the exposure chamber. One port was connected to a MultiRAE monitor (RAE Systems by Honeywell, San Jose, CA, USA) equipped internally with a sampling pump that continuously monitored chlorine concentrations. Another port was connected to a piezo-resistive pressure sensor, which continuously monitored the pressure in the chamber. This sensor sends a signal to the automated regulating system that controls the opening of the outlet valve. When the subjects breathed from the exposure chamber, they reduced the pressure in the chamber. Automatically, this lower pressure is sensed by the regulating system that reacts by closing the outlet valve in order to maintain the pressure in the chamber around its set point (slightly negative, ∧0.2 cm H_2O). The last port allows the inhalation of the chlorine mixture through a mouthpiece by a system of unidirectional valves. Expired air by the subject is evacuated out of the laboratory through a venting system.

The delivered concentrations of chlorine gas were continuously monitored and recorded.

The chlorine inhalation challenge was tested in four healthy subjects with normal respiratory function and normal airway responsiveness who were exposed to 1 ppm of chlorine gas for 15 min. This level of exposure corresponds to the threshold limit value-short-term exposure level in Canada. A stabilized chlorine concentration of 1 ppm was reached after 1 h. The study was approved by the Research Ethics Committee of Sacrèc)-Coeur Hospital and all subjects signed an informed consent form.

The mean chlorine concentration obtained for the four subjects was 1.01 ± 0.034 ppm.

No subject reported any smell of chlorine or any respiratory symptoms following the chlorine exposure. FEV_1 and airway responsiveness did not change after exposure to chlorine.

This study is the first to describe a closed-circuit system designed for generating chlorine at low concentrations, delivering highly stable concentrations of chlorine under secure conditions.

D'tm)Alessandro et al.[9] performed chlorine exposure by diluting chlorine gas with medical air, which has a potential risk of gas leaking.

No data describing the variability of the delivered chlorine concentrations was reported in a study using a nebulization of commercial bleach for generating chlorine exposure.[10] The monitoring of chlorine levels and their stability were not reported after painting chlorine onto a cardboard.[8]

The chlorine closed-circuit system described here has several advantages over the few chlorine exposure methods previously reported. It produces very stable chlorine concentrations without leaking risks and allows a continued monitoring of the chlorine concentrations with great accuracy. The results obtained in the four tested patients showed highly reproducible values with no variability, once the targeted chlorine concentrations were achieved.

The main limitation of this apparatus is related to the building of the automated control system that controls the pressure in the chamber and the opening of the outlet valve that might require trained personnel. This may restrict its accessibility to centers with the resources for such purposes. Another limitation relates to the costs of the different commercially available devices used to build the system. However, the same apparatus can be used to generate other types of irritants agents such as ammonia.

In conclusion, we describe for the first time the closed-circuit methodology for a safe, accurate and reproducible exposure to chlorine gas. This system will be very useful to investigate the pathophysiology of irritant-induced asthma in humans. Whether test maybe useful in cases of occupational caused by chloramines will need to be investigated in the future.

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Nebulized Tranexamic Acid as a Therapeutic Alternative in Pulmonary Hemorrhage☆

Ácido tranexámico nebulizado como alternativa de tratamiento en la hemorragia pulmonar

Dear Editor,

Pulmonary hemorrhage is a potentially life-threatening condition that sometimes requires immediate intervention to stop the bleeding. When the source of the bleeding is not identifiable, for example, in alveolar hemorrhage, therapeutic options are limited and include correction of the coagulation defects, along with life-sustaining treatment as needed.[1–3]

In this context, tranexamic acid (TA), a synthetic antifibrinolytic agent, has been approved for the oral or intravenous treatment or prophylaxis of bleeding episodes in patients with coagulation disorders. Based on its effectiveness in the control of local mucosal bleeding (nose, colon, rectum, and mouth), it has been evaluated for use in pulmonary hemorrhage of different etiologies.[4–6]

We report the case of an 18-year-old man, diagnosed with idiopathic pulmonary hemosiderosis, who had received several lines of treatment, and who was currently receiving corticosteroids, hydroxychloroquine, and immunoglobulins.

He was admitted to the ICU with a clinical picture of dyspnea and frank hemoptysis, requiring orotracheal intubation due to global respiratory failure. Chest X-ray showed bilateral infiltrates, and anemia with a 2 g/dL decrease in hemoglobin from baseline was detected. Fiberoptic bronchoscopy was performed, showing the bronchial mucosa covered with red blood, surging up from both lower lobes. Antimicrobial treatment began with a wide-spectrum antimicrobial and the corticosteroid dose was increased to 1 mg/kg/12 h.

The patient's progress in the following hours was poor, and collection of bloody fluid from the orotracheal tube persisted. Anemia developed again with a fall in hemoglobin levels of 1.5 g/dL, and ventilation and oxygenation became more difficult, with reduced lung compliance. Chest X-ray showed increased patchy bilateral consolidations. Fiberoptic bronchoscopy was repeated, showing aspiration of fresh blood from both lower lobes.

The patient's clinical status continued to worsen and diffuse alveolar hemorrhage was suspected. Treatment began with nebulized TA on day 3 of admission, and antimicrobial treatment, sedation, and analgesia were maintained. A 22 mm Cirrus®2 nebulizer breathing kit was used for nebulization. Using this system and a gas flow of 8 L/min, 77% of the output volume contains particles at least 5 μm in diameter with a mean mass diameter of 2.7 μm.[7]

We used a TA dose of 500 mg/5 mL/12 h, during which time the patient remained on mechanical ventilation.

A significant improvement was observed in the following days, with no new episodes of bleeding or anemia, and the patient's respiratory status improved, so sedation could be discontinued. He awakened correctly and was weaned from mechanical ventilation, with extubation on day 9 of hospitalization. Figure 1 describes the course of the event, in terms of lung compliance, PaO_2/FiO_2, anemia, and need for transfusion during the first 7 days in the ICU, at which time mechanical ventilation weaning maneuvers were initiated.

Diffuse alveolar hemorrhage, whether idiopathic or associated with hematological disorders is an entity with a mortality rate ranging between 70% and 90%.[8,9]

TA, a synthetic derivative of the amino acid lysine, has antifibrinolytic activity, as it binds with plasminogen, thus inhibiting fibrin binding and subsequent plasmin activation.[4]

A Cochrane review identifies two clinical trials which evaluate the use of oral and intravenous TA (Anchafibrin®).[10] There is insufficient evidence to recommend its use, but some small studies suggest that it may reduce hemorrhage duration. However, a review article[33] of the published series concludes that, while a recommendation with strong evidence cannot be given, TA can reduce both bleeding duration and volume, with a low short-term risk of thromboembolic disease (weak recommendation, 2B).[11]

The recommendation to administer nebulized TA in pulmonary hemorrhage may be based on pathophysiological evidence that it increases the activity of anti-fibrinolytic factors that are depleted in sites of continuous bleeding throughout the bronchial tree. Studies indicate that the drug is more effective when administered locally rather than systemically, suggesting that local administration provides improved, more durable inhibition of fibrinolysis, with less systemic absorption, thus reducing the risk of thrombosis associated with the latter. Indeed, the local application of TA has proven

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