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## **Successful use of high-flow nasal cannula to treat hemoptysis and acute global respiratory failure in two cystic fibrosis bronchiectasis patients and review of the current literature**

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## **Abstract**

Cystic fibrosis (CF) is a multisystemic disease, and despite the continuous improvement in understanding its pathophysiology and the present therapeutic possibilities, complications may occur. Indeed, literature shows that the onset of hemoptysis is a common complication reported in CF patients: in this context, the high-flow nasal cannula (HFNC) respiratory support has recently gained more importance because it helps increase the hygroscopic degree in the bronchial secretions by improving ciliary function and mucus hydration; thus, it reduces the patients' work of breathing, and through high air flow, it reduces dead space in hyperinflated patients, and we carefully review the current literature on this topic. In this manuscript, we describe two cases of HFNC use for the successful treatment of global respiratory failure and hemoptysis in patients affected by CF bronchiectasis on chronic home oxygen therapy. This could add more treatment possibilities in this patient population to cure life-threatening complications related to severe CF disease.

**Key words:** acute global respiratory failure, bronchiectasis, cystic fibrosis, hemoptysis, high flow nasal cannula, non-invasive respiratory support.

## Introduction

Cystic fibrosis (CF) is a recessive genetic disease characterized by with multisystemic disease manifestations, the most prominent of which occur in the respiratory system where sits a severe reduction of the airway surface liquid and impaired mucociliary clearance [1]. Therefore, individuals with CF have extreme difficulty clearing pathogens from the lung, experiencing chronic pulmonary infections and often show bronchiectasis because of the vicious cycle of infection- inflammation and bronchial remodelling [1]. Thus, patients with CF often present with exacerbations of diverse ethiopathology characterized by the need of in hospital admission. Among the most severe complications encountered there are pneumothorax, hemoptysis, and acute respiratory failure which can be hypoxic and/or combined hypoxic-hypercapnic (global) respiratory failure (ARF). Those complications long have been known to be associated with older age greater than 18 y/o and more severe airways disease. The onset of hemoptysis is indeed a common complication reported in CF patients with lower FEV1% of predicted, affected by diabetes and presence of infection with *Pseudomonas Aeruginosa* and *Staphylococcus aureus* [2,3]. Based on the current literature, haemoptysis has been reported to occur in 1 of 115 patients with CF (0.87%) each year and based the severity of the bleeding small (0-5 mL) moderate (5-240 mL), and massive (> 240 mL in a 24-h period or > 100 mL per day over several days) should be admitted to the hospital for urgent treatment which in case of massive hemoptysis consists in Bronchial artery embolization (BAE) [3,4].

In the past few years the High Flow Nasal Cannula HFNC respiratory support has gained an increasing attention related to its success in the treatment of hypoxic acute respiratory failure which further pushes its use during COVID19 pandemics waves [5-9]. However, recently its successful application have been described in the literature during acute exacerbation of patients affected by chronic obstructive diseases such as COPD, CF and lung cancer patients. Few reports have described HFNC use at home for long term intermittent treatment. In those reports, the HFNC helps increasing humidification in the bronchial secretions, by improving ciliary function and mucus hydration, thus it reduces work of breathing and through high flow it reduces dead space in hyperinflated patients. There are few manuscript in the literature which focuses on the topic and describe the successful use of HFNC in patients with bronchiectasis or during hemoptysis in no CF patients [10-12].

We report for the first time two cases of global ARF complicated with hemoptysis in patients with CF bronchiectasis that was successfully resolved after High Flow Nasal Cannula (HFNC) use and we discuss the pathophysiologic mechanism behind the resolution of the acute event with the related literature revision.

## **Case Reports**

### ***Case Report 1***

A 48 year-old-patient affected by FC, he received home oxygen therapy (O<sub>2</sub> 2L/m). He presented to the Emergency Department (ED) with fever, moderate haemoptysis (5-240 mL of fresh red blood) and global respiratory failure related to a CF exacerbation.

At the arrival at Time 1 (T1) Arterial blood gas (ABG) analysis was performed in oxygen support (FiO<sub>2</sub> 50%) showing: pH 7,31 pO<sub>2</sub> 59 pCO<sub>2</sub> 52 SpO<sub>2</sub> 90% HCO<sub>3</sub><sup>-</sup> 33 ( FiO<sub>2</sub> 50%). An Angio CT scan was performed which showed no active bleeding form bronchial arteries. The patient was transferred from ED to the CF unit where the HFNC (myAIRVO) support was promptly initiated set with the following parameters: Flow 55 L/m, FiO<sub>2</sub> 50% , Temperature 31C°. After one hour of HFNC use (T1), an ABG was repeated showing: pH 7,43 pO<sub>2</sub> 123 pCO<sub>2</sub> 48 SpO<sub>2</sub> 97%. Further ABG evaluation at 24h distance in HFNC (T2) (flow 40 l/m , FiO<sub>2</sub> 30%) showed pH 7,39 pO<sub>2</sub> 85 pCO<sub>2</sub> 48 HCO<sub>3</sub><sup>-</sup> 32,1 SpO<sub>2</sub> 96% (FiO<sub>2</sub> 30%) (Figures 1 and Table 1). Antibiotics and antifibrinolytic agents were initiated as per standard haemoptysis protocol. Indeed, the haemoptysis gradually reduced over the course of the following 24hours, stopping at 48 hours completely. The microbiological analysis of sputum did not highlight any infection detection.

During the following 48 hours the HFNC was continually used 24hours /day and the FiO<sub>2</sub> was gradually reduced monitoring the improvement of the SpO<sub>2</sub> continuous monitoring. The patient did not express any discomfort on its use nor he experienced any related complications. After five days from the admission, the patient was discharged on home oxygen therapy 2.5 l/m similar to his home previous standard prescription with improved clinical conditions. The functional tests performed at admission (AD) and discharge (DI) demonstrated a slight improvement (FVC 38% vs 43%,FEV1 23% vs 27%,PEF 33% vs 43%) .

### ***Case Report 2***

A 61-year-old patient affected by CF, on nocturnal home oxygen therapy at the rate of 1.5 L/ min. In anamnesis: chronic atelectasis of right inferior lobe, gallbladder stones, bladder stones. Radical prostatectomy . Embolization of the right bronchial artery in 2009 and 2021 for previous moderate haemoptysis. He was started on genetic therapy with Trikafta.

He presented at the ED with acute disease's exacerbation complicated by global respiratory failure and moderate haemoptysis (5-240 mL of blood). At the arrival in ED, (T1) the ABG in Venturi Mask with FiO<sub>2</sub> 60% showed: pH 7,33 pO<sub>2</sub> 42 pCO<sub>2</sub> 55 hcO<sub>3</sub><sup>-</sup> 31,1 SpO<sub>2</sub> 83%. The patient performed Angio Thorax CT scan with mdc which excluded active bleeding. Therefore the patient was transferred to the CF Unit.

At first HFNC (myAIRVO) was set with the following parameters: flow 50 L/m, FiO<sub>2</sub> 45% e T 31 C°; After 2 hours of HFNC (T2) set with 31°C temperature, air flow of 50 l/m and FiO<sub>2</sub> at

65% to adjust for desaturation, the improvement in the ABG was evident: pH 7,39 pO<sub>2</sub> 96 pCO<sub>2</sub> 50 HCO<sub>3</sub><sup>-</sup> 29,5 SpO<sub>2</sub> 98,6% . The HFNC support as with the previous case was constantly used 24hours /day, the patient expressed comfort during its use and did not experience any related complications. The FiO<sub>2</sub> was gradually tapered down as per the monitoring of the improvement at the SpO<sub>2</sub> continuous monitoring.

The microbiological analysis of sputum evidenced an infection caused by *Pseudomonas aeruginosa*.

During the admission, two further scant episodes of haemoptysis occurred and they completely stopped at 48 hours from admission. Antibiotics and antifibrinolytics EV together with cautious respiratory physical therapy was offered to the patient during the entire admission. He was then discharged after twenty-six days (T3) of admission on home oxygen therapy 1,5 l/m his ABG was the following: pH 7,41 pO<sub>2</sub> 96 pCO<sub>2</sub> 43 HCO<sub>3</sub><sup>-</sup> 26,6 SpO<sub>2</sub> 98,5% (Figure 2 and Table 2). The respiratory functional tests at the discharge were also improved: AD FEV<sub>1</sub> 36% vs DC FVC 55%with IT 68% PEF 5,28 (67%) . The comparison of before and during HFNC treatment for both patients described above are plotted in Table 1 and 2.

## **Discussion**

This study for the first time in the literature describes the successful use of HFNC during the admission for exacerbation of two patients affected by CF and severe disease presented to the ED with Haemoptysis and global respiratory failure. Both cases reflects the current literature which describes CF patients who presents with haemoptysis being older than 18yo, with advanced disease and affected by infection (one of the 2 cases) typical *P. Aeruginosa* or *S Aureus* [3] .

The use of HFNC was successful in both cases described in improving and resolving both the haemoptysis episodes and the global ARF.

In the past decade, the HFNC has become an increasingly used form of noninvasive respiratory support both in the acute as well in the chronic settings. Wide use has been described to treat acute hypoxic and acute and chronic global respiratory failure before and during COVID19 pandemic waves with variable results [5-13].

Both our patients were on home oxygen therapy before the exacerbation described in the present manuscript. Chronic hypoxia produces a mixture of permanent and reversible structural changes in the pulmonary vasculature, dryness and reduced mucociliary clearance. It results in hypertrophy of the muscular media of small pulmonary arteries, muscularization of pulmonary arterioles, and fibrosis of the intimal layer. In stable disease, initiation of oxygen therapy causes some pulmonary artery vasodilatation in areas of the lung with poor ventilation; this causes a small increase in the ratio of dead space to tidal volume [14].

The continuous use of home oxygen therapy is associated with dry and damaged bronchial mucosa and a small increase in dead space which consequent increase work of breathing together with bronchial obstruction and mucoid impaction in these so fragile patients.

All these side effects of oxygen home therapy make HFNC one of the most suitable device in CF bronchiectasis patients [15-17].

From a review of the literature, different pathways are described to be involved in the effective results related to the HFNC use. First, the humidification via HFNC offers a promising management approach for patients with bronchiectasis because it improves mucociliary clearance. This is vital for breaking the “vicious cycle” of recurrent infections and airway inflammation which classically characterized CF patients. Also, the combined synergic function of heating and humidification improve ciliary function and mucus hydration, thus it balances better mucociliary clearance. An ERS post hoc analysis demonstrated that HFNC significantly reduce exacerbation rates and improve quality of life in stable bronchiectasis [16]. Second, the air high flow delivered by HFNC (greater than 40 l/m) exerts positive airway pressure of 3-4 cmH<sub>2</sub>O, which improve alveolar recruitment, tidal volume, dead-space washout and reduce work of breathing in the upper airways and main bronchi [16-18]. Third, warm and humidified air may have stabilized the desiccated and damaged bronchial mucosa optimizing its function, thus reducing cough, mucosal bleeding, and finally improving gas exchange. Indeed, recent ERS guidelines describes HFNC use in ARF; it is described successfully both in hypoxemic and global ARF [9]. Both patients described in this manuscript presented to the ED with Haemoptysis and global respiratory failure during CF exacerbation with increasing mucus secretion and rise in the inflammatory markers. Therefore, from one hand HFNC use it certainly played an important role from the hygroscopic side increasing the percentage of water within the thick mucus of those remodeled airways facilitating its removal; while on the other hand the greater fraction of O<sub>2</sub> delivered helped improving the hypoxic ARF by better penetration within the smallest airway below.

However, the HFNC played also the role of reducing the amount of dead space in the upper airways washing out the stagnant CO<sub>2</sub> located there while lessening the work of breathing and respiratory rate, therefore improving the hypercapnic ARF. Despite it is well established that optimal cilia movements occur at core temperature and high humidity, data on HFNC effectiveness in patients with severe bronchiectasis management is still small [2-3]. One of the most serious complications of bronchiectasis exacerbation is haemoptysis: this can occur when a section of one of the blood vessels supplying the lungs suddenly splits open due to mucosa dryness and long term oxygen use. Depending on the size of the broken vessel, haemoptysis may become a potentially life-threatening emergency and requires rapid diagnosis and treatment. However, current guidelines for the clinical management of

haemoptysis in CF bronchiectasis (not requiring BAE) suggest the following: when a patient is hospitalized, to start IV antibiotics and procoagulant therapies (eg, tranexamic and aminocaproic acid) together with discontinuation of aerosolized therapies. This, indeed, was promptly initiated for both patients admitted [3].

The Bronchial artery embolization (BAE) is the therapy of choice when moderate or massive haemoptysis persists or if clinical instability occurs.

However, minor adverse events following BAE may occur including transient and typically self-limiting chest, esophageal, or thoracic back discomfort, or a combination of multiple small episodes, or in some unfortunate cases, more significant complications including transverse myelitis, spinal cord ischemia, vascular injury, and vascular access site thrombosis have been reported [3]. For major bleeding there are no better option than BAE, however for small, intermittent haemoptysis episodes, without any CT evidence of bleeding like in these two cases, HFNC respiratory support may be considered as a first line option under continuous monitoring to check whether it can contribute to the haemoptysis improvement, and the global patients' clinical condition. In order to best take advantage from the HFNC treatment, the right setting of the HFNC machine should be organized to kick off the right treatment start.

The literature suggests it should be used at the lowest temperature (31°C) with medium flow (equal or above 40 l/min) as initiation of treatment. This was indeed put in practice to attempt to solve the haemoptysis episodes in both cases described. There is a recent study which evaluated the comfort of patients affected by acute hypoxemic respiratory failure (AHRF) ( $\text{PaO}_2/\text{FiO}_2 \leq 300$  + pulmonary infiltrates + exclusion of cardiogenic edema) supported by HFNC. The study showed that patient comfort was reported as significantly higher during steps at the lower temperature of 31 °C in comparison to 37 °C, with the HFNC set at both 30 and 60 l/min ( $p < 0.0001$ ). Higher flow, however, was not associated with poorer comfort [19]. The comfort should very much guide the clinical decision on which respiratory support to start in these patients as the Noninvasive ventilation (NIV) may also be beneficial paying great attention to the use of the continuous humidification and mostly to the interface of choice during the treatment which could play a pivotal role in the success on the NIV treatment itself [20]. In our two CF cases lower temperature at 31°C was accepted with comfort allowing the HFNC continuous use 24h/day. Thus successfully resolving the global ARF and the haemoptysis. The use of a humidified warm respiratory support may be found controversial in theory in these two patients, given the ongoing presence of airways haemoptysis/ bleeding. Theoretically, it could be argued that the opposite treatment should be offered such as ice block applied to the chest or cold mixture of air and oxygen via either Ventury mask or supported via NIV to induce vasoconstriction in the chest bleeding vessels causing the ongoing bleeding. In actual fact, this issue has never been explored with a proper

study and there is no evidence in the literature that this can be harmful for the patient. On the contrary, a previous case report reported the successful use of HFNC support in a patient with haemoptysis due to a large endo-bronchial lung tumour mass resulting in the complete resolution of the respiratory distress and the bleeding without any embolization [21].

Moreover, it is also important to notice that the temperature set up in the HFNC machine was on purpose lower (31°C ) than the actual body temperature thus not favoring further vasodilatation and bleeding. On the opposite it is the idea of the authors that this setting from one side, may optimize the status of the damaged lung mucosa and on the other side, may adjust the hygroscoy of the airway mucus which is usually severely impaired in patients with chronic respiratory disease and in particular CF patients.

To our knowledge, indeed, this is the first case of CF bronchiectasis haemoptysis in which HFNC have been used. In a previous described case in the literature, a patient in hypoxic ARF due to a large mass partly obstructing the right main bronchus experiencing several moderate haemoptysis episodes [21]. After medical and physical therapy, another episode of haemoptysis occurred in the first 24hours of the recovery so HFNC was started (T 31 degree C, flow 40 l/m FiO<sub>2</sub> 60%). There was a rapid improvement of the respiratory rate, dyspnea, haemoptysis, and the oxygen saturation. The reasons for its success maybe similar to those found in the two CF cases described being: first, optimizing mucus water dilution; second, the reduced dry mucosa may have contributed to improving the cough and mucus clearance, possibly stopping the mucosal bleeding. Third, further improvement could be possible be related to the abovementioned mechanisms of upper airways dead-space air clearance and gas exchange amelioration. The latter mechanism was difficult to be demonstrated in vivo due to the anatomical complexity and inability to visualize the gas flow in the upper airways. Thus, Winfried Möller elaborated two models in order to study the phenomenon in the upper nasal airways showing effective clearance of the tracer gas, demonstrating similar dynamic characteristics despite the very different geometries of the upper airway models; the clearance of the nasal component of the anatomical dead-space with HFNC therapy is a rapid process, which may significantly reduce CO<sub>2</sub> rebreathing [17].

## **Conclusions**

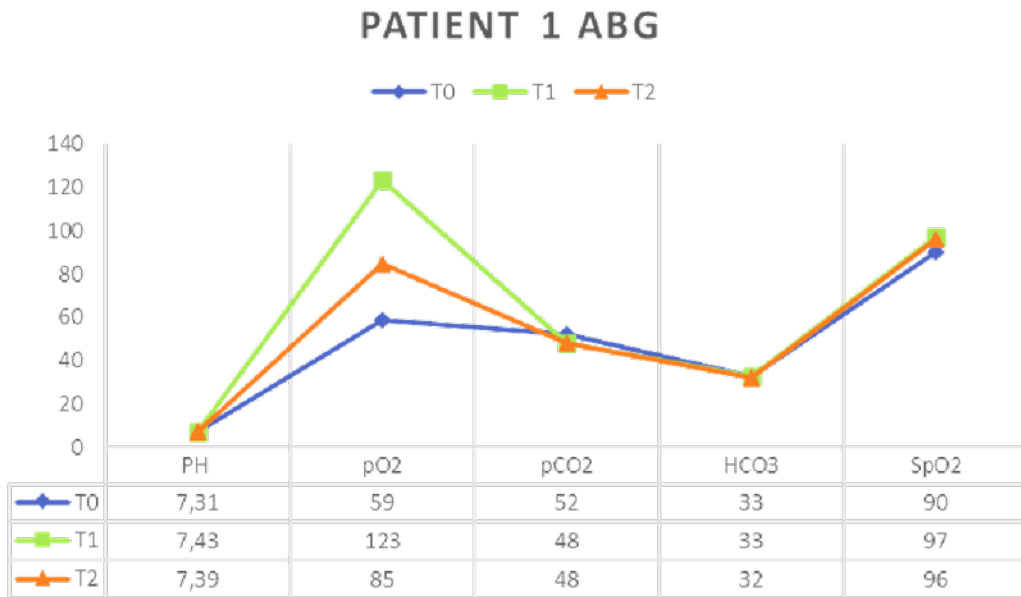
This manuscript described the successful treatment via the use of HFNC of two patients affected by CF bronchiectasis with global ARF complicated by haemoptysis. These patients did not require BAE nor have active bleeding on Angio ChestCT scan. The HFNC once again demonstrated being a valuable first line non-surgical add-on therapeutic respiratory support which helped the resolution of the haemoptysis and the improvement of global ARF. Different pathophysiologic mechanism may have been implicated in the successful results and they have been described in this manuscript. Further studies would be warranted with

larger number of patients to confirm these results and to fully elucidate the mechanisms behind the scenes in similar patients' populations.

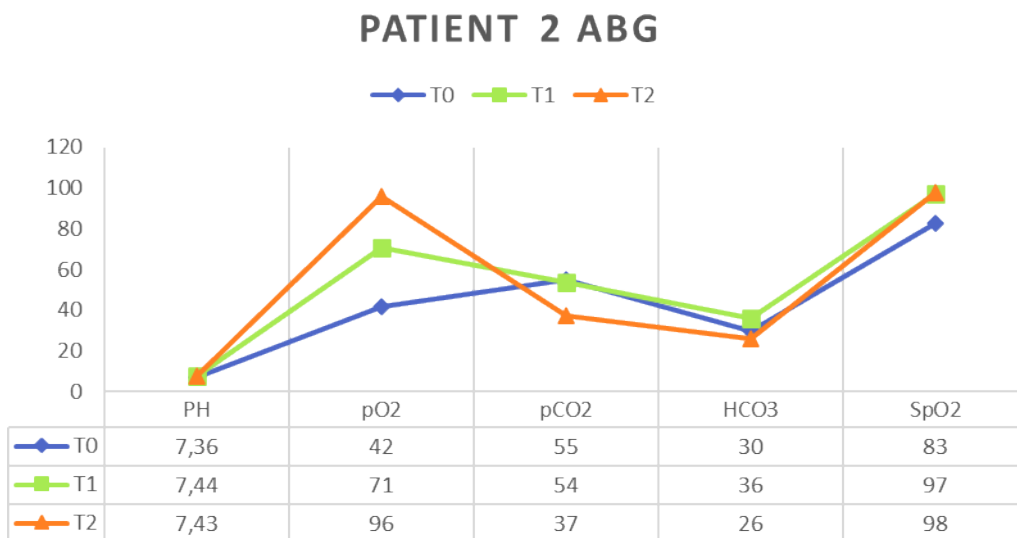
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**Figure 1. Amelioration of arterial blood gas in patient 1 at T0, T1 and T2.**



**Figure 2. Amelioration of arterial blood gas in patient 2 at T0, T1 and T2.**

**Table 1. Oxygentherapy setting in patient 1 at T0, T1 and T2.**

PT 1	FLOW	FIO2	TEMPERATURE	OXYGEN
T0		50%		COT
T1	55 (l/m)	50%	31 degrees	HFNC
T2	40 (l/m)	30%	31 degrees	HFNC

**Table 2. Oxygentherapy setting in patient 2 at T0, T1 and T2.**

PT 2	FLOW	FIO2	TEMPERATURE	OXYGEN
T0		60%		Venturi mask
T1	50 (l/m)	45%	31 degrees	HFNC
T2		28%		COT