High-Flow nasal cannula oxygen therapy with or without non-invasive ventilation (NIV) during the weaning period: a multicenter randomized controlled trial.

Oxygénothérapie à haut débit nasal avec ou sans ventilation non-invasive en post-extubation : Etude randomisée contrôlée multicentrique.

HIGH-WEAN STUDY
2016-A01078-43
Version n°4, 17 of October 2017

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CLINICAL TRIAL PROTOCOL	
SHORT TITLE	**High-Wean Study**
N° ID-RCB	2016-A01078-43
TITLE	**High-Flow nasal cannula oxygen therapy with or without non-invasive ventilation (NIV) during the weaning period: a multicenter randomized controlled trial.** Oxygénothérapie à haut débit nasal avec ou sans ventilation non-invasive en post-extubation : étude randomisée contrôlée multicentrique.
INDICATION	Post-Extubation
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ETHICAL COMMITTEE APROVAL	*Date20/09/2016* By the « Comité de Protection des Personnes Ouest III »

SOMMAIRE

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SIGNATURES

Signature de l'Investigateur Principal du Centre

J'ai lu l'ensemble des pages du protocole version n° 4 du 17/10/2017 de l'essai clinique dont le CHU de Poitiers est le promoteur.
Je confirme qu'il contient toutes les informations nécessaires à la conduite de l'essai.
Je m'engage à réaliser l'essai en respectant le protocole et les termes et conditions qui y sont définis. Je m'engage à réaliser l'essai en respectant :

- les principes de la "Déclaration d'Helsinki",
- les règles et recommandations de bonnes pratiques cliniques internationales (ICH-E6) et française (règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain - décisions du 24 novembre 2006)
- la législation nationale et la réglementation relative aux essais cliniques,
- la conformité avec la Directive Essais Cliniques de l'UE [2001/20/EC]

Je m'engage également à ce que les investigateurs et les autres membres qualifiés de mon équipe aient accès aux copies de ce protocole et des documents relatifs à la conduite de l'essai pour leur permettre de travailler dans le respect des dispositions figurant dans ces documents.

Nom de l'Investigateur Principal du Centre:

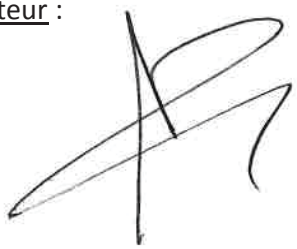
Date :

Signature :

Signature du Directeur Surveillant

Nom Investigateur Coordonnateur :
Pr Arnaud W THILLE

Signature



Date : 17/10/2017

Signature du Promoteur

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CHU de Poitiers représenté par son Directeur Général,
NOM : M. Jean-Pierre DEWITTE
Pour le Directeur Général et par délégation
Le Directeur de la Recherche et de l'Innovation
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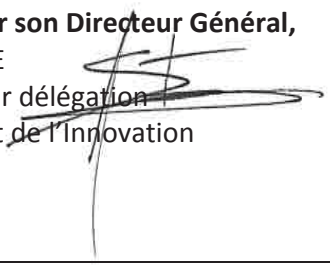

Date : 17/10/2017

LIST OF ABBREVIATIONS

Abréviations	
ARC	**C**linical **R**esearch **A**ssociated
BPC	**B**onnes **P**ratiques **C**liniques
CNIL	**C**ommission **N**ationale de l'**I**nformatique et des **L**ibertés
CPP	**C**omité de **P**rotection des **P**ersonnes
CCTIRS	**C**omité **C**onsultatif sur le **t**raitement de l'**i**nformation en matière de **r**echerche dans le domaine de la **s**anté
TEC	**T**echnicien d'**E**tude **C**linique
eCRF	**E**lectronique **C**ase **R**eport **F**orm
SAP	**S**ystolique **A**rterial **P**ressure
MAP	**M**edian **A**rterial **P**ressure
BMI	**B**ody **M**ass **I**ndex
HFNC	**H**igh **F**low **N**asal **C**annula
OHD	**O**xygènothérapie à **H**aut débit **N**asal
NIV	**N**on **I**nvasive **V**entilation
VNI	**V**entilation **N**on **I**nvasive
PaO_2	**P**artial **P**ressure of **D**ioxide
$PaCO_2$	**P**artial **P**ressure of **C**arbon **D**ioxide
RASS	**R**ichmond **A**gitation **S**edation **S**cale
COPD	**C**hronic **O**bstructive **P**ulmonary **D**esease
FiO2	**D**ioxyde **F**raction
SpO2	**D**ioxygene **s**aturation
ARF	**A**cute **R**espiratory **F**Ailure
ICU	**I**ntensive **C**are **U**nit
PPC	**Pression Positive Continue**
CPAP	**Continuous Positive Airway Pressure**

SYNOPSIS

Version n°4 du 17/10/2017

2016-A01078-43

TITRE DE L'ETUDE	Oxygénothérapie à haut débit nasal avec ou sans ventilation non-invasive en post-extubation : étude randomisée contrôlée multicentrique. **Etude High-Wean**
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JUSTIFICATION / CONTEXTE	L'extubation en réanimation est une décision difficile car la mortalité est particulièrement élevée en cas d'échec. En effet, la mortalité des patients qui nécessitent une réintubation atteint 25 à 50%. Parmi tous les patients extubés en réanimation, le taux de réintubation global est de l'ordre de 15% mais il peut dépasser 20 à 25% chez les patients les plus à risque. Jusqu'à récemment, la majorité des patients étaient traités par de l'oxygène standard en post-extubation. L'oxygène à haut débit nasal (OHD) est un dispositif d'oxygénation alternatif, bien toléré, qui améliore les échanges gazeux et réduit le travail respiratoire. Cette stratégie d'oxygénation est en pleine expansion et en voie de remplacement de l'oxygène standard aussi bien dans l'insuffisance respiratoire aigüe qu'en post-extubation. Plusieurs études récentes suggèrent que l'utilisation de l'OHD pourrait réduire le taux de réintubation en réanimation. Une grande étude multicentrique (en cours de publication) suggère également que l'OHD pourrait être équivalent à la ventilation non-invasive (VNI) chez les patients à risque. Compte tenu de ces résultats récents, l'OHD pourrait constituer le traitement de référence en post-extubation dans les années à venir. Plusieurs études suggèrent également que la VNI prophylactique pourrait réduire le risque de détresse respiratoire en post-extubation, notamment chez les patients hypercapniques. Cependant, les résultats sur la réintubation sont contradictoires et seulement 2 études ont retrouvé une

	réduction significative du taux de réintubation. En pratique, selon une enquête récente réalisée en France, environ 20 à 25% des patients à risque reçoivent de la VNI en postextubation. Un grand nombre de patients sont pourtant à risque d'échec d'extubation et pourraient bénéficier de la VNI, notamment les patients les plus âgés ou ceux ayant une maladie cardiaque ou respiratoire chronique sous jacente. Ces patients, faciles à identifier, ont un risque de réintubation élevé, et représentent près de la moitié des patients extubés en réanimation. Dans cette population, nous avons observé une réduction du taux de réintubation lorsque la VNI était utilisée en plus de l'oxygène standard. Afin d'améliorer encore les échanges gazeux et le travail respiratoire, l'OHD pourrait remplacer l'oxygène standard entre les séances de VNI, avec l'hypothèse qu'un traitement associant VNI et OHD pourrait être supérieur au traitement par OHD seul, et permettre une réduction de réintubation chez les patients les plus à risque.
OBJECTIF PRINCIPAL	Comparer le taux de réintubation dans les 7 jours suivant l'extubation entre un traitement associant VNI et OHD versus OHD seule chez les patients considérés à haut risque d'échec d'extubation en réanimation.
OBJECTIFS SECONDAIRES	**Objectifs secondaires** 1. Comparer le taux de réintubation à 48h, à 72h et jusqu'à la sortie de réanimation. 2. Comparer le taux de patients qui ont présenté des critères d'insuffisance respiratoire dans les 7 jours suivant l'extubation 3. Comparer le taux de patients chez qui le traitement a été poursuivi au delà des 48 premières heures suivant l'extubation 4. Comparer le nombre de jours sans intubation, sans VNI et sans OHD dans les 2 semaines suivant l'extubation. 5. Comparer la durée d'hospitalisation en réanimation et à l'hôpital entre les deux groupes 6. Comparer la survie en réanimation, à l'hôpital, à J28 et à J90 entre les deux groupes.
CRITERE D'EVALUATION PRINCIPAL	Réintubation dans les 7 jours suivant l'extubation programmée.
CRITERES D'EVALUATION SECONDAIRES	1. Taux de réintubation à 48h, à 72h et jusqu'à la sortie de réanimation. 2. Nombre de patients ayant présenté des critères d'insuffisance respiratoire aigüe dans les 7 jours suivant l'extubation 3. Nombre de patients chez qui le traitement a été poursuivi au delà des 48 premières heures 4. Nombre de jours sans intubation, VNI ou OHD 14 jours après l'extubation

	5. Durée de séjour en réanimation et à l'hôpital 6. Mortalité en réanimation et à l'hôpital, mortalité à J28 et J90.
METHODOLOGIE / SCHEMA DE L'ETUDE	Etude de soins courants, prospective, randomisée, contrôlée, ouverte, comparant 2 stratégies de ventilation en post-extubation chez des patients à haut risque de réintubation en réanimation. Les patients répondant aux critères d'inclusion seront randomisés après un test de sevrage puis assignés à l'un des 2 groupes OHD ou OHD plus VNI.
CRITERES D'INCLUSION DES SUJETS	Les patients présentant tous les critères suivants seront éligibles : 1. Durée de ventilation mécanique d'au moins 24 h avant l'extubation 2. Extubation programmée après réussite d'une épreuve de sevrage. 3. Patients à haut risque de réintubation présentant au moins 1 des critères suivants : patients âgés de plus de 65 ans ou ayant une maladie cardiaque ou respiratoire sous-jacente. <u>Les patients seront considérés comme ayant une maladie cardiaque sous-jacente et potentiellement incluables s'ils présentent une des maladies suivantes :</u> (1) Une dysfonction ventriculaire gauche quelle que soit son origine avec une fraction d'éjection du ventricule gauche ≤ 45%, (2) Une cardiopathie ischémique documentée, (3) Une fibrillation auriculaire chronique, ou (4) Des antécédents connus d'œdème pulmonaire cardiogénique. <u>Les patients seront considérés comme ayant une maladie respiratoire sous-jacente et potentiellement incluables s'ils présentent une des maladies suivantes :</u> (1) Une maladie respiratoire chronique obstructive, (2) Un syndrome obésité-hypoventilation, (3) Ou une maladie respiratoire restrictive. *Concernant la maladie respiratoire sous-jacente, le patient pourra être inclus si la maladie est documentée ou fortement suspectée par le médecin en charge, c'est à dire chez un patient intubé pour une insuffisance respiratoire hypercapnique ($PaCO_2$ > 45 mm Hg) et ayant :* - *(1) des antécédents de tabagisme avec une PEP intrinsèque sous ventilation mécanique et/ou de l'emphysème sur la radiographie pulmonaire ou le scanner faisant suspecter une BPCO.*

	- *(2) Une obésité (BMI >30 kg/m^2) avec hypoventilation alvéolaire ($PaCO_2$> 45 mm Hg) faisant suspecter un syndrome obésité-hypoventilation.* - *(3) Une anomalie de la cage thoracique (exemple cyphoscoliose) faisant suspecter un syndrome restrictif.*
CRITERES DE NON INCLUSION DES SUJETS	1. Patients admis pour un traumatisme crânien 2. Pathologie neuromusculaire périphérique chronique ayant conduit à l'intubation (type myopathie ou myasthénie) 3. Traitement au long cours par VNI pour une maladie respiratoire chronique 4. Traitement au long cours par Pression Positive Continue (PPC ou CPAP) pour un syndrome d'apnées du sommeil 5. Contre-indication à la VNI 6. Extubation non programmée (autoextubation volontaire ou accidentelle). Les patients réintubés suite à une extubation non programmée pourront être inclus dans le cas d'une prochaine extubation programmée. 7. Limitation thérapeutique avec une décision de non réintubation en cas d'échec d'extubation 8. Patient non affilié ou bénéficiaire d'un régime de sécurité sociale 9. Personnes bénéficiant d'une protection renforcée à savoir les mineurs, les femmes enceintes, qui allaitent, les personnes privées de liberté par une décision judiciaire ou administrative, les majeurs sous protection juridique. 10. Patient ou proche ayant exprimé son opposition à participer
NOMBRE DE PATIENTS	**650 patients**
DUREE DE LA RECHERCHE	▪ Durée de la période d'inclusion : 36 mois ▪ Durée de la participation pour chaque patient : 3 mois ▪ Durée totale de l'étude : 51 mois avec 39 mois pour l'étude et 12 mois pour l'analyse ▪ Date de début théorique : 2ème trimestre 2017 ▪ Date de fin théorique : 2ème trimestre 2020

1 RESPONSIBILITIES

1.1 STUDY TITLE

High-Flow nasal cannula oxygen therapy with or without non-invasive ventilation (NIV) during the weaning period: a multicenter randomized controlled trial.

Oxygénothérapie à haut débit nasal avec ou sans ventilation non-invasive en post-extubation : Etude randomisée contrôlée multicentrique.

HIGH-WEAN Study

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2 BACKGROUND AND RATIONALE OF THE STUDY

Extubation is usually decided after a weaning readiness test involving spontaneous breathing on a T-piece or low levels of ventilatory assist. The day of extubation is a critical time during an intensive care unit (ICU) stay because in case of extubation failure, mortality can reach 30 to 50% [1, 2]. The overall rate of extubation failure is around 15% but it may exceed 20-25% in some subsets of patients considered at high-risk. Up until now, the majority of the patients have been treated with standard oxygen after extubation. High flow nasal cannula oxygen therapy (HFNC) is a well-tolerated device for oxygenation that at once improves gas exchange [3] and reduces the work of breathing [4]. Recently, several studies showed a significant reduction in the reintubation rate after planned extubation for patients treated with HFNC as compared to standard oxygen [5, 6]. Furthermore, several studies also suggest that prophylactic NIV could reduce the risk of acute respiratory failure, particularly in hypercapnic patients [7-9]. However, a large population may benefit from NIV, especially patients older than 65 years and those with any underlying chronic cardiac or respiratory disease. Easy to identify and at high risk of reintubation, these patients represent around half of those extubated in an ICU [10]. In this subset of patients, we have recently reported a significant reduction in the reintubation rate when prophylactic was systematically applied after extubation and interspersed with standard oxygen [11]. In order to further improve gas exchange and the work of breathing, HFNC may replace standard oxygen between NIV sessions. We are hypothesizing that treatment associating NIV with HFNC between NIV sessions may be more effective than HFNC alone, and may reduce the reintubation rate in patients at high risk of extubation failure in the ICU

2.1 USE OF PROPHYLACTIC NIV AFTER PLANNED EXTUBATION IN THE ICU

Prophylactic NIV used to prevent respiratory failure after extubation must be clearly distinguished from therapeutic NIV used to treat post-extubation respiratory distress. Therapeutic NIV has no proven benefit in the overall population of patients with post-extubation acute respiratory failure [12] and can even increase the risk of death by delaying reintubation [13]. By contrast, prophylactic NIV is applied immediately after a planned extubation, in the absence of respiratory failure. The switch from mechanical ventilation to spontaneous breathing can unmask latent left ventricular dysfunction [14], and positive pressure delivered by NIV represents the reference treatment of cardiogenic pulmonary edema [15, 16]. NIV is also particularly effective in patients with chronic obstructive pulmonary disease (COPD) by reducing work of breathing [17, 18], in patients with obesity-hypoventilation syndrome (OHS) [19], and in case of obstructive sleep apneas. Thus, prophylactic NIV may be beneficial in patients with cardiac heart failure and those chronic lung disease or diaphragmatic dysfunction.

Results of clinical studies

Several RCTs have evaluated the use of prophylactic NIV immediately after extubation in patients having successfully passed a weaning readiness test, and ready for extubation [7-9, 20-22]**.** The results of all randomized controlled studies indexed in Medline are given in the **Table 1.** As compared to standard oxygen, several studies suggest that prophylactic NIV could reduce the risk of post-extubation respiratory failure in patients at high-risk for reintubation, particularly in hypercapnic patients [7-9]. In the first study, 97 patients considered at high-risk according to heterogeneous criteria (hypercapnic patients,

comorbidities, chronic cardiac failure, weak cough, stridor, or failure of more than one spontaneous breathing trial before extubation) were included [7]. Prophylactic NIV, applied at least 8 hours per day during the first 48h following extubation, enabled to significantly reduce the rate of reintubation from 24% to 8% (p=0.027). In another study [8], 162 patients considered at high-risk for reintubation according to other criteria (age >65 years, high severity score at the beginning of the weaning, or intubation for cardiac failure) were included. Prophylactic NIV was applied during the first 24h following extubation and enabled to reduce the risk of post-extubation respiratory failure and to decrease in-ICU mortality although the reintubation rate was surprisingly not significantly decreased. A subgroup analysis suggested that NIV was chiefly beneficial in hypercapnic patients with chronic respiratory disorders [8]. Therefore, the same group conducted a second trial including 106 patients with hypercapnia ($PaCO_2$> 45 mm Hg) at the end of the spontaneous breathing trial before extubation [9]. The results confirmed the previous study, and the use of prophylactic NIV avoided post-extubation respiratory failure and reduced day-90 mortality [9]. Once again, the rate of reintubation was not significantly different with prophylactic NIV or standard oxygen, and the rates of mortality in ICU or in hospital were also similar. Two others studies assessed the impact of prophylactic NIV on outcome. The largest multicenter trial nowadays included 400 patients intubated more than 48h in the ICU [21]. In this study no difference was found neither for the reintubation rate nor for the mortality rate. However, the patients included were not really at high-risk for reintubation with an overall reintubation rate relatively low around 10% [21]. Another study used prophylactic NIV in patients intubated at least 3 days for acute respiratory failure [22]. The authors found positive results with a decrease in reintubation rate in the group receiving NIV (5% vs. 39%, p=0.016). However, only 38 patients were included and the rate of reintubation reported in this monocentric study was abnormally high in the control group receiving standard oxygen [22].

How to interpret these results and which recommendations can be proposed?

These findings suggest that prophylactic NIV could be effective to prevent post-extubation respiratory failure in hypercapnic patients or those at high-risk for reintubation but probably useless in patients at low-risk for reintubation. However, all questions are not resolved by these studies. First, the first three positive studies were conducted in specialized pulmonary units [7-9]. Therefore, the majority of the patients had underlying chronic pulmonary disease and more than 30% of them were hypercapnic at time of extubation [7, 8]. In our recent prospective cohort study assessing risk factors for reintubation in a general ICU only 15% of the patients were hypercapnic at time of extubation, and hypercapnia was not a variable independently associated with reintubation [23]. Second, in the study by Ferrer et al. including hypercapnic patients [9], the mortality at day 90 was significantly lower in patients receiving prophylactic NIV but neither in-ICU mortality nor in-hospital mortality were different and it seems difficult to attribute so long long-term benefit to the use of NIV immediately after extubation. The rate of reintubation was not significantly different while it is well shown that extubation failure is the major event independently associated [24]. Finally, most of the factors used as inclusion criteria to start prophylactic NIV are not variables clearly associated with reintubation (comorbidities, high severity score, hypercapnia, failure of a weaning trial…) and, therefore, research efforts must focus in better identifying high-risk patients who may benefit from NIV [25]. In view with this literature, Canadian guidelines suggested that 1) NIV be used after planned extubation in

patients who are considered to be at high risk of respiratory failure, but only in centres that have expertise in NPPV (grade 2B) and 2) NIV not be used after planned extubation in patients who are considered to be at low risk of respiratory failure (2C). This means that its interest is not established with certainty and that this strategy could probably be discussed for some patients at high-risk of reintubation but that it cannot be routinely recommended in clinical practice.

2.2 USE OF HFNC AFTER PLANNED EXTUBATION IN THE ICU

High-flow oxygen therapy through nasal cannula (HFNC) is a recent technique that delivers heated and humidified oxygen at high flow rates [26]. Several physiological studies have showed that HFNC was better tolerated than standard oxygen delivered through a mask [4, 27, 28]. High-flow rates of fresh gas enable to increase the fraction of inspired oxygen (FiO_2) [29], to generate low levels of positive end-expiratory pressure [30], and to decrease physiological dead space by flushing expired carbon dioxide in the upper airways [31]. The result is a decrease in work of breathing [32] and dyspnea [28] while the heating and humidification of inspired gases might prevent thick secretions and atelectasis. HFNC could offer an alternative to standard oxygen in hypoxemic patients and could even avoid intubation in patients with acute respiratory failure or reintubation during the post-extubation period. In a multicentre randomized controlled trial we recently found that mortality in patients with acute respiratory failure treated with HFNC alone was significantly lower than those treated with standard oxygen or NIV [33]. During the post-extubation period a recent study showed a significant reduction in the reintubation rate for hypoxemic patients treated with HFNC as compared to standard oxygen [5]. The results of 2 large-scale randomised controlled trials carried out in Spain suggest that (1) in low-risk patients HFNC could reduce the reintubation rate compared to standard oxygen [6], and that (2) in high-risk patients HFNC could be equivalent to non-invasive ventilation (NIV) (This last suty is not published yet). Given the findings reported in these recent studies, HFNC may be considered as the reference therapy during the post-extubation period.

Table 1: Use of prophylactic non-invasive ventilation (NIV) applied immediately after extubation to prevent respiratory distress in ICU

Randomised controlled trials *Inclusion criteria	**Main results: NIV vs. Standard Oxygen (O_2)** *Main End Point
Nava et al. 2005 [7] 3 centers: NIV (n=48) vs. O_2 (n=49) *Patients considered at high risk for reintubation	*Reintubation: n=4 (8%) vs. n=12 (24%), p=0.027 In-ICU Mortality: n=3 (6%) vs. n=9 (18%), p=0.064
Ferrer et al. 2006 [8] 2 centers: NIV (n=79) vs. O_2 (n=83) *Age>65, APACHE II>12, or intubation for cardiac heart failure	*Postextubation ARF: n=13 (16%) vs. n=27 (33%), p=0.029 Reintubation: n=9 (11%) vs. n=18 (22%), p=0.12 Nosocomial Infections: 18 (23%) vs. 27 (33%), p=NS In-ICU Mortality: NIV n=2 (3%) vs. n=12 (14%), p=0.015
Ferrer et al. 2009 [9] 3 centers: NIV (n=54) vs. O_2 (n=52) *PCO_2 >45 mm Hg at the end of weaning trial	* Postextubation ARF: n=8 (15%) vs. n=25 (48%), p<0.0001 Reintubation: n=6 (11%) vs. n=10 (19%), p=0.37 Pneumonias: 3 (6%) vs. 9 (17%), p=0.12 In-ICU Mortality: n=3 (6%) vs. n=4 (8%), p=0.71 *Mortality at day-90: n=6 (11%) vs. n=16 (31%), p=0.024
Khilnani et al. 2011 [20] 1 single center : NIV (n=20) vs. O_2 (n=20) *COPD patients	*Reintubation: n=5 (25%) vs. n=3 (15%), p=0.44 Length of ICU stay: 18.3±7.9 j vs. 16.1±6.3, p=0.34
Su et al. 2012 [21] 3 centers : NIV (n=202) vs. O_2 (n=204) *Intubation ≥ 48h	*Extubation failure: n=30 (15%) vs. n=27 (13%), p=0.62 Reintubation: n=21 (10%) vs. n=16 (8%), p=0.37 In-ICU Mortality: n=3 (1.5%) vs. n=2 (1%), p=0.64
Ornico et al. 2013 [22] 1 single centre: NIV (n=20) vs. O_2 (n=18) *Intubation ≥ 3 days for ARF	*Reintubation: n=1 (5%) vs. n=7 (39%), p=0.016 In-Hospital Mortality: 0% vs. n=4 (22%), p=0.041

Abbreviations in the table: NIV: Non-Invasive Ventilation, ARF: Acute Respiratory Failure, COPD: Chronic Obstructive Pulmonary Disease; APACHE: Acute Physiology and Chronic Health Evaluation

2.3 When and how to define extubation failure?

Extubation failure is usually defined as a need for reintubation within hours or days following planned extubation. In the literature, the time interval used in the definition varies from 48 hours [34-36] to 72 hours [10, 37-39], or 1 week [23, 40, 41]. A consensus conference on weaning defined success as absence of ventilatory support during the first 48 hours after extubation [42]. However, the use of prophylactic NIV may delay reintubation, and the time interval needed to assess extubation failure when NIV is used should probably be longer than 48 hours. We therefore decided to consider extubation failure in case of reintubation within the 7 days following planned extubation in order not underestimate the rate of extubation failure in case de prophylactic NIV.

2.4 Who are the most at-risk patients for reintubation?

Unfortunately, the exact reason for extubation failure often escapes identification. Reintubation is usually performed because of an apparently new episode of respiratory distress, which may be related to primary respiratory failure, congestive heart failure, aspiration, ineffective cough with airway secretion build-up, or upper airway obstruction. Other reasons for reintubation include the onset of new sepsis, surgical complications, acute coronary syndrome, and neurological impairment. This multiplicity of causative factors contributes to explain the clinical difficulties raised by extubation and the persistent uncertainties about the pathophysiology of extubation failure. Many factors have been implicated in extubation failure and the main factors studied are the following:

- In several studies, neurological disorders [36] or impaired neurological status [43, 44] were independently associated with extubation failure. Cough strength [45-47] and amount of secretions [44, 46] seem to be good predictors of extubation failure, especially in patients with impaired neurological status [48].
- The usual severity scores measured at ICU admission are poor predictors of extubation failure [39, 43, 46, 47] even when measured at the time of extubation [10, 44].
- The primary reason for intubation may help to predict the extubation outcome, but the available results are conflicting [37, 39].
- Several studies showed higher extubation failure rates in older patients [10, 39]. It has been shown that patients older than 65 years with underlying chronic cardiac or respiratory diseases had reintubation rates above 30% compared to less than 10% in the other patients [10].
- In another study, a positive fluid balance on the day before extubation was associated with an increased risk of extubation failure [39].
- A minimal oxygenation threshold is among the key criteria used to select patients for extubation, and readiness testing is usually not performed in severely hypoxemic patients. This point may explain the low predictive value of pre-extubation blood gas values for the outcome of extubation. One study showed that PaO_2/FiO_2 below 200 mmHg was associated with an increased risk of extubation failure in neurosurgical patients [43], but most studies found no differences in terms of oxygenation between patients who succeeded and those who failed extubation [10, 37, 39, 44, 46].
- Unlike hypoxemia, hypercapnia per se may predict weaning outcomes [44, 49]. However, only one study found that hypercapnia during the SBT was independently associated with extubation failure [44].
- An international consensus panel on weaning suggested that ventilated patients be categorized into three groups according to the difficulty of their weaning process [42]. Although prolonged weaning is independently associated with increased mortality [49-52] the rate of reintubation is not different between patients with simple weaning and those with difficult weaning. Thus, the classification scheme is of only moderate usefulness for predicting extubation failure.

2.5 What inclusion criteria should we use in our study?

In previous studies that assessed prophylactic NIV several inclusion criteria are not clearly associated with an increased risk of reintubation.

In order to 1) identify a subset of patients at high-risk for reintubation and 2) assess the impact of NIV on outcome, we performed two observational prospective studies including more than 800 intubated patients [10, 23]. Our first study aimed to identify the patients most at-risk for reintubation [10]. Of 168 planned extubations (26 episodes of extubation failure) the risk of reintubation was markedly higher in patients aged of more than 65 years old (29%) and in those with any underlying cardiac or respiratory disease (23%). The rate of reintubation even reached 34% in patients having these 2 risk factors while it was only 9% in patients without any of these 2 risk factors. The main interest of this study is to easily identify a population of patients at high-risk for reintubation with a rate ranging from 20 to 30%. In our second study all patients intubated more than 24h and considered at high-risk for reintubation based on our previous study, i.e. those with an age > 65y or with underlying chronic cardiac or respiratory disease, systematically received prophylactic NIV at least 8h a day until recovery of reintubation [23]. Our results are encouraging since the reintubation rate within the 7 days following planned extubation was significantly reduced between the 2 cohorts from 28% to 15%, p=0.03 [11].

2.6 Which standard treatment should we use for the control group?

The usual treatment after planned extubation includes standard oxygen alone through a facemask or nasal cannula. However, it has recently been found that the use of HFNC after planned extubation decreased the rate of reintubation as compared to standard oxygen [5, 6]. In another study not published yet, the rate of reintubation was similar in high-risk patients treated with HFNC alone than with prophylactic NIV interspaced by standard oxygen. Concerning the use of prophylactic NIV few recommendations are available. Recent Canadian guidelines recommended the use of NIV prophylactic in at-risk patients with moderate evidence (grade 2A). In clinical practice, a recent survey performed in France reported that only 11% of the patients extubated in the ICU received NIV during the post-extubation period [6]. Given around half of the patients could be considered at high-risk for extubation failure according to our criteria; it means that around 20 to 25% of at-risk patients are treated with prophylacticNIV after planned extubation in France.
Given the recent studies we strongly believe, although the data are still limited, that HFNC may be considered as the reference therapy during the post-extubation period.

2.7 Which treatment should we use for the interventional group

The combination of the two techniques, i.e. prophylactic NIV interspaced by HFNC could seem the best strategy to improve blood gases, to reduce work of breathing and to avoid subsequent respiratory failure. The majority of the studies that assessed prophylactic NIV after extubation applied NIV during the first 24 after planned extubation. In our recent study, NIV was prolonged beyond the first 24h in more than 20% of the cases [11, 23] and NIV could be prolonged according to patient's respiratory status in the absence of criteria for reintubation.
Therefore, whatever the group of randomization, all patients will receive HFNC alone or NIV interspaced with HFNC during at least 48h whereas this strategy may be continued beyond the first 48h in the absence of complete recovery.

2.8 Originality and Innovative Aspects of our study

- HFNC had never previously been used as a reference therapy. When administered to a control group, this treatment has seemed highly innovative and in agreement with the recent literature.
- The study addresses a large population of patients considered to be at high-risk for reintubation. Patients intubated more than 24h older than 65y or with an underlying chronic cardiac or respiratory disease are easy to identify in clinical practice and, based on our preliminary results, they represent around half of the patients who are extubated in the ICU. By contrast, hypercapnic patients represent only 15% of the patients in a general ICU.
- The ventilatory strategy used in the interventional group associating NIV and HFNC has never been assessed.
- This is the largest study assessing the use of prophylactic NIV in the post-extubation period

2.9 Ethical Considerations: equipoise of 2 treatment groups

The clinician must offer at any time the best possible treatment for the patient. If a clinician is convinced of the superiority of one treatment over another, then it has no reason to propose a randomized study comparing these two treatments. But if the efficacy of the two treatments appear equivalent, a priori, according to his knowledge of findings from the literature, the randomization is an acceptable option (individual perspective) and desirable for all patients (collective view). The opinions concerning the use of prophylactic NIV are very different from a unit to another and from a country to another. NIV is more widely used in Europe than in North America and the majority of the studies on prophylactic NIV after extubation have been performed in Europe. Clinical practice is also heterogeneous in France and in recent survey around 20% of the patients at high-risk received NIV in the post-extubation period [53].

2.10 References

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3 STUDY OBJECTIVES AND OUTCOMES

3.1 HYPOTHESIS:

A treatment associating NIV and HFNC may reduce the reintubation rate in patients at high risk of extubation failure in the ICU.

3.2 PRIMARY OBJECTIVE

To compare the reintubation rate within the 7 days following planned extubation between HFNC alone and HFNC with NIV in patients at high risk of extubation failure in the ICU.

3.3 SECONDARY OBJECTIVES

The secondary objectives of the study are:

1. To compare the rates of reintubation at 48h, 72h and up to ICU discharge
2. To compare the number of patients who meet the criteria for acute respiratory failure within the 7 days following extubation
3. To compare the number of patients in whom the treatment (HFNC or HFNC/NIV) is continued beyond the first 48h following extubation
4. To compare the number of ventilatory support-free days (including intubation, NIV or HFNC) within the 14 days following extubation
5. To compare the length of stay in ICU and in hospital between the 2 groups
6. To compare mortality in ICU, in hospital, at day 28 and at day 90 between the 2 groups.

3.4 PRIMARY OUTCOME

Reintubation within the 7 days following planned extubation

3.5 SECONDARY OUTCOMES

1. Reintubation at 48h, 72h and up to ICU discharge
2. Criteria for acute respiratory failure within the 7 days following extubation
3. Number of patients in whom the treatment (HFNC or HFNC/NIV) is continued beyond the first 48h following extubation
4. Number of ventilatory support-free days (including intubation, NIV or HFNC) within the 14 days following extubation
5. Length of stay in ICU and in hospital stay
6. Mortality in ICU, in hospital, at day 28 and at day 90

4 CRITERIA FOR INCLUSION AND RECRUITMENT OF THE PATIENTS

4.1 INCLUSION CRITERIA

Patient who meet the following criteria will be eligible for inclusion:

1. Duration of mechanical ventilation prior to extubation > 24h
2. Planned extubation after weaning trial success.
3. Patients at high risk of reintubation having at least one of the following criteria [10] : patients older than 65 years, or those having any underlying chronic cardiac or lung disease.

   Underlying chronic cardiac diseases include
   (1) Left ventricular dysfunction whatever the cause defined by left ventricular ejection fraction ≤ 45%,
   (2) Documented ischemic cardiopathy
   (3) Chronic auricular fibrillation
   (4) history of cardiogenic pulmonary edema

   Chronic lung diseases include
   (1) the existence of any underlying chronic obstructive pulmonary disease (COPD),
   (2) obesity-hypoventilation syndrome (OHS) or
   (3) restrictive pulmonary disease.

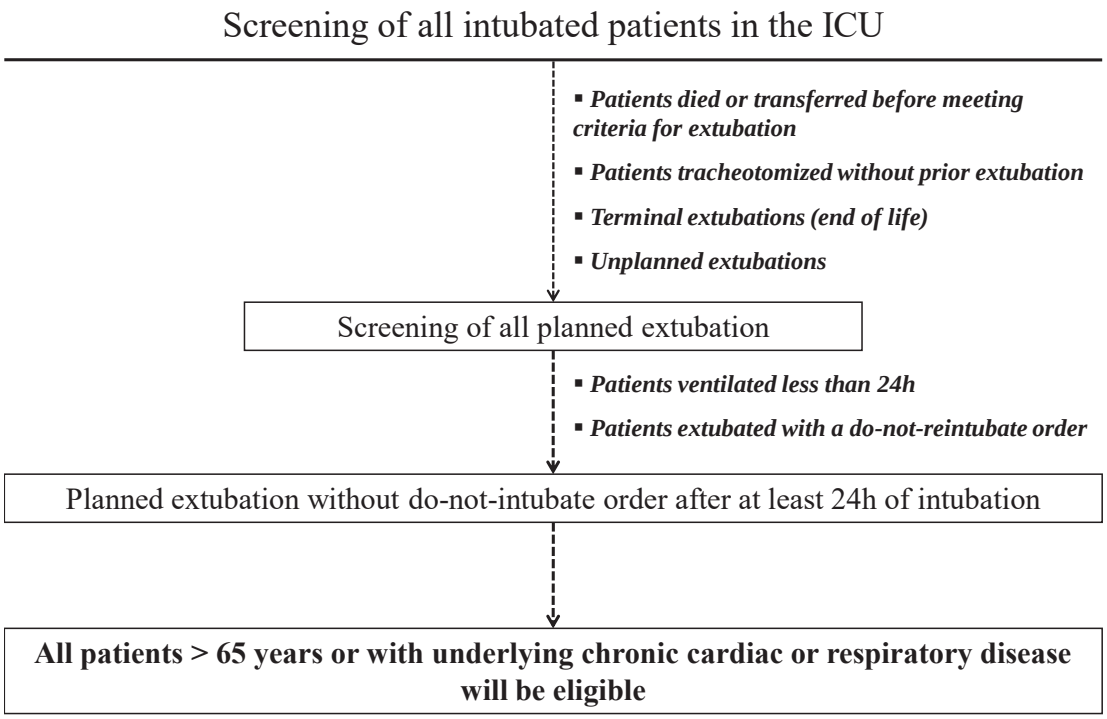
   The underlying lung disease will be either documented or highly suspected by the physician in a patient intubated for acute hypercapnic respiratory failure ($PaCO_2$ > 45 mm Hg) and having:
   1) a history of smoking with intrinsic positive end-expiratory pressure (PEEP) under mechanical ventilation and/or emphysema on chest X-ray or scanner suggesting underlying COPD,
   2) obesity (BMI > 30 kg/m^2) with alveolar hypoventilation ($PaCO_2$> 45 mm Hg) suggesting OHS,
   or 3) rib cage deformation suggesting restrictive pulmonary disease.

4.2 NON INCLUSION CRITERIA

1. Patients admitted for traumatic brain injury
2. Peripheral neuromuscular disease as reason for intubation (Underlying myopathy or myasthenia gravis)
3. Usual long-term treatment with NIV for chronic lung disease
4. Usual long-term treatment with CPAP for obstructive apneas syndrome
5. Contraindication to NIV
6. Unplanned extubation (accidental or self extubation). Intubated patients following an unplanned extubation may be included in the case of a next scheduled extubation.
7. Do-not-reintubate order at time of extubation
8. No Health insurance coverage
9. People under protection: Pregnant or breastfeeding women, minor patients, subjects with guardianship. Inhability to freely provide consent through judiciary or administrative condition.
10. Opposition to participation

4.3 SCREENING AND RECRUITMENT OF THE PATIENTS

All intubated patients will be screened and recruitment procedure for eligible patients will be done as following:



WEANING PROCEDURE

An international consensus panel on weaning insisted on the need to perform the first weaning test as soon as the patient meets the following criteria [42]:

- Resolution of the initial reason for intubation,
- Cardiovascular stability with minimal or no need for vasopressors,
- Patient awake with a RASS between +1 and -2 according the Richmond Assessment Sedation Scale,
- No continuous sedation,
- Respiratory rate ≤ 35 breaths per minute and adequate oxygenation defined as SpO_2 > 90 % on FiO_2 ≤ 40% or PaO_2/FiO_2 ≥ 150 mm Hg with PEEP up to 8 cmH_2O.

Early identification of patients who are able to breathe spontaneously results in better outcomes and it has clearly demonstrated that the use of a weaning protocol, including daily screening followed by weaning trial and systematic extubation if successful, shortened intubation time without increased risk of reintubation [54, 55]. In absence of a weaning protocol in the ICU, the weaning protocol used in our ICU will be proposed to manage weaning **(Appendix n°2)**. The first weaning trial will be performed as soon as the patient meets weaning criteria above-mentioned and patients will be categorized into three groups according to the difficulty of their weaning process.

As recommended by the international conference consensus on weaning the weaning test will be performed according to the usual practice in each unit either using the T-tube by simply disconnecting the patient from the ventilator and providing additional oxygen or using a low level of pressure support (PS) of 7 cm H_2O without PEEP. In a large multicenter randomized controlled trial, the rate of patients who were extubated after 48h was similar when the weaning trial was performed using T-tube or PS trial [34]. Regardless the strategy, the weaning test will be performed over a period of 30 min to 2h and PEEP will be systematically removed in order to avoid masking latent left ventricular dysfunction [56]. Blood gas will be systematically assessed at the end of the weaning trial prior to extubation in order to stratify on $PaCO_2$ and to include the same number of hypercapnic patients ($PaCO_2$> 45 mm Hg) in the 2 groups.

5 STUDY DESIGN

This is a prospective multicenter randomized controlled open-label trial comparing 2 strategies of oxygenation during the post-extubation period in patients at high risk of extubation failure in an ICU. Patients will randomly be assigned to one of the two groups, with a 1:1 ratio.

5.1 INCLUSION

Patients may be included after verification of the eligibility criteria (inclusion criteria and non-inclusion criteria are detailed above) and obtained non-opposition to participation from the patients or their proxy. In all cases, the patient will be informed as soon as possible by the investigator of his participation in the study and his consent to continue to participate in the study will be requested. A duplicate copy will be given to the patient. A copy addressed to the project manager will be placed in a sealed envelope. The investigator will indicate in the patient's medical records his or her participation in the research project and the means through which informed consent and relevant information were obtained.

5.2 RANDOMIZATION

The randomization will be centrally organized and stratified on $PaCO_2$ and center. As NIV may be more effective in hypercapnic patients ($PaCO_2$ > 45 mm Hg) stratification on $PaCO_2$ will permit to well-balanced the 2 treatments among the 2 subgroups of hypercapnic and non hypercapnic patients. $PaCO_2$ will be measure at the end of the weaning trial. If not possible, $PaCO_2$ measured during the last blood gas under mechanical ventilation will be used.

Randomization will be carried out through an Internet site dedicated to clinical trials and accessible to investigators through user identification and a personal password. The randomization will become effective following verification of the criteria of inclusion and exclusion. Patients included will be randomized at time of decision of planned extubation and assigned to one of the 2 following groups: 1) The patients assigned to control group will receive continuously HFNC alone; 2) The patients assigned to interventional group will receive NIV during at least 12 hours a day with HFNC between NIV sessions. In the 2 groups, patients will be treated for at least 48h after planned extubation.

5.3 GROUPS OF TREATMENT

Given the characteristics of the two methods under evaluation, a double blind trial is not possible.

Control group: HFNC alone

Immediately after planned extubation the patients assigned to the control group will be continuously treated by HFNC for at least 48h with a flow of 50 L/min and FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$).

In the absence of ARF symptoms 48h after planned extubation, treatment can be stopped and switched to standard oxygen therapy, after a weaning test using HFNC with a flow of 30L/min and FiO_2 of 30%.

In case of occurrence or persistence of ARF symptoms at H48, HFNC will be continued or re-initiated by periods of 24h until disparition of symptoms.

NB: The use of curative NIV to treat acute respiratory failure is not encouraged.

Interventional group: HFNC and NIV

NIV will be immediately initiated after planned extubation by prolonged sessions during the 48h following extubation: a first session of at least 4h, and then sessions of at least 2 hours, during all the night (continuous NIV from 10 P.M. to 6 A.M.) if it is possible, for a total duration of at least 12 hours a day. NIV will be performed with a ventilator dedicated for NIV (ICU ventilator with NIV mode or NIV ventilator) in pressure-support ventilation using the following ventilator settings:

- Minimal pressure-support level of 5 cm H_2O targeting a tidal volume around 6 to 8 ml/kg,
- A PEEP level between 5 and 10 cmH_2O
- A FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$).
- A pressure ramp slope between 0.1 and 0.2 s and a cycling off criterion at 25-30% of peak inspiratory flow

Between NIV sessions, HFNC will be delivered with a flow of 50 l/min and a FiO_2 to achieve adequate oxygenation ($SpO_2 \geq 92\%$).

The treatment including HFNC and NIV will be delivered for at least 48h after planned extubation.

In the absence of ARF symptoms 48h after planned extubation, treatment can be stopped and switched to standard oxygen therapy, after a weaning test using HFNC with a flow of 30L/min and FiO_2 of 30%.

In case of occurrence or persistence of ARF symptoms at H48, NIV and HFNC will be continued or re-initiated by periods of 24h until disparition of symptoms.

NB: The use of curative NIV to treat acute respiratory failure is not encouraged.

Duration of the treatment

In the 2 groups, patients will be treated for a minimal duration of 48h.

In the absence of ARF symptoms 48h after planned extubation, treatment can be stopped and switched to standard oxygen therapy.

If acute respiratory failure (see ARF criteria below) appears or persists 48h after extubation, the treatment will be continued for periods of 24 hours until complete respiratory recovery.

Acute respiratory failure will be defined by at least 2 criteria among the following:

1. Respiratory rate > 25 breaths/min during at least 2 hours
2. Clinical signs suggesting respiratory distress with increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles,
3. pH < 7.35 units with $PaCO_2$ > 45 mm Hg
4. Need for $FiO_2 \geq 50\%$ to maintain $SpO_2 \geq 92\%$ or $PaO_2/FiO_2 \leq 150$ mmHg

If a patient present newly criteria for ARF beyond the first 48h after extubation, the treatment will be resume according to initial randomization.

5.4 DEFINITIONS OF EVENTS AND CRITERIA OF EVALUATION

Reintubation will be performed according to one of the following criteria:

1. Respiratory failure defined by at least 2 ARF criteria among the following: (1) Respiratory rate > 35/min, (2) Clinical signs suggesting respiratory distress with

increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles, (3) Respiratory acidosis defined as pH < 7.35 units and $PaCO_2$ > 45 mm Hg, (4) Need for $FiO_2 \geq 80\%$ to maintain $SpO_2 \geq 92\%$ or $PaO_2/FiO_2 \leq 100$ mmHg.

2. Hemodynamic failure defined as SAP < 90 mm Hg or MAP < 65 mm Hg with the need for vasopressors
3. Neurological failure: altered consciousness (Glasgow <12) or agitation.
4. Cardiac or respiratory arrest

In case of criteria for reintubation, the patient should be immediately intubated. However, according to the clinical practice in each center, the patients can be treated by therapeutic NIV in case of respiratory distress. In case of persistence of ARF criteria 2 hours after NIV initiation, the patient should be immediately intubated and NIV should not be continued beyond this delay of 2h.

5.5 PATIENT FOLLOW-UP AND DATA COLLECTION

At time of inclusion/extubation:

- Age, gender, height, weight.
- Severity score indicated by the SAPS II and the SOFA score
- Underlying chronic cardiac or respiratory disease
- Date and reason for admission
- Date and reason for intubation
- Duration of intubation prior to extubation
- Classification according to the weaning difficulty: “simple weaning” refers to patients who succeed the first weaning test and are extubated without difficulty, “difficult weaning” to patients who fail the first weaning test and require up to 3 tests or 7 days to achieve successful weaning, and “prolonged weaning” to patients who require more than 7 days of weaning after the first test.
- Type of weaning trial performed before extubation: T-tube or pressure-support trial
- Qualitative assessment of cough strength and amount of secretions
- Steroids at before extubation
- Vital parameters at the end of the weaning trial at the time of inclu: systolic and diastolic arterial pressure, heart rate, respiratory rate and SpO_2.
- Before and at the end of the weaning trial: Blood Gas and ventilatory parameters.

Post-Extubation H1:

- Vital parameters: systolic and diastolic arterial pressure, heart rate, respiratory rate and SpO_2.
- Ventilatory settings and parameters: Gas flow and FiO_2 using HFNC, pressure-support, PEEP, FiO_2 and expiratory tidal volume with NIV.
- Blood gas with HFNC in the control group and with NIV in the interventional group.
- Criteria for acute respiratory failure and for reintubation
- Need for reintubation

Post-Extubation H6, H12-H24, H24-H48:

- Vital parameters: systolic and diastolic arterial pressure, heart rate, respiratory rate and SpO_2.
- Ventilatory settings and parameters: Gas flow and FiO_2 using HFNC, pressure-support, PEEP, FiO_2 and expiratory tidal volume with NIV.
- At H6, H12-H24 and H24-H48: Blood gas with HFNC in the control group and with NIV in the interventional group.
- Number and duration of NIV sessions and HFNC
- Criteria for acute respiratory failure and for reintubation
- Need for reintubation
- Death

Each day from day 3 to Day 7:

- Vital parameters: systolic and diastolic arterial pressure, heart rate, respiratory rate and SpO_2.
- Ventilatory settings and parameters: Gas flow and FiO_2 using HFNC, pressure-support, PEEP, FiO_2 and expiratory tidal volume with NIV.
- Blood gas with HFNC in the control group and with NIV in the interventional group if available, if applicable.
- Number and duration of NIV sessions and HFNC
- Criteria for acute respiratory failure and for reintubation
- Need for reintubation
- Death

At Day 14:

- Duration and etiology of Reintubation or tracheotomy
- Duration of NIV and reintubation
- Length of ICU stay
- Death

At ICU discharge and day 90 (By phone):

- Inform consent
- withdrawal or withholding of life-sustaining treatment
- Length of hospital stay
- Death

5.6 DURATION OF THE STUDY

Duration of participation of each patient: 3 months
Anticipated duration of recruitment: 36 months
Total study duration: 51 months with 36 months for the study and 12 months for analysis

Total number of scheduled patients to be recruited: 650 patients

6 STATISTICS

All analyses will be performed by a methodologist-biostatistician (Dr Stéphanie Ragot) using the SAS statistical package version 9.2 (SAS Institute Cary, NC)
The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion and exclusion criteria for each patient.

6.1 DESCRIPTIVE ANALYSIS

The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality.
Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as those lost to follow-up subjects will be described. Deviations from the protocol will be described and analyzed on a case-by-case basis.

6.2 ANALYSIS PERTAINING TO THE MAIN CRITERION OF EVALUATION

The percentages of patients having needed reintubation within the 7 days following planned extubation will be compared between the 2 groups by means of the Chi2 test.
The different parameters that would be potentially predictive of reintubation will be considered by means of the Student's t-Test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the Chi^2 test (or Fisher's exact test) for qualitative variables and by means of univariate logistic regressions. Results will be expressed as odds ratio and 95% confidence interval.
The analysis will subsequently be completed by multivariate logistic regression after testing for interactions. The maximal model will include all the variables associated with the dependent variable ($p<0.20$) as well as the relevant variables according to the data collected in the literature (forced variables). The model will be simplified according to a step-by-step procedure of elimination in descending order; only the variables associated with the dependent variable (threshold limit value: 5%) and the forced variables will be conserved.
Kaplan–Meier curves will be plotted to assess the time from enrollment to reintubation and will be compared by means of the log-rank test. The variables associated with reintubation with a p value <0.20 will be assessed by means of a Cox proportional-hazard regression analysis with the use of a backward-selection procedure. The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and hazard ratio with 95% confident interval.

6.3 ANALYSIS PERTAINING TO THE SECONDARY CRITERIA OF EVALUATION

Reintubation rates at the various pre defined times, acute respiratory failure rates will be compared between the 2 groups according to the same statistical methodology than the main outcome.
Number of ventilator-free days and lengths of stay be compared between the two treatment groups by means of the Student's t-Test (or the Mann-Whitney U test, if necessary) .

Regarding mortality criteria (in ICU, in-hospital, at day 28 and at day 90, Kaplan–Meier curves will be plotted to assess the time from enrollment to death and will be compared between the 2 treatment groups by means of the log-rank test. In absence of interaction between variables, the variables associated with mortality with a p value <0.20 in univariate Cox models will be considered in a maximal model. A Cox proportional-hazard regression analysis will be performed using a backward manual procedure. The final model will include variables significantly associated with mortality with a P value of less than 0.05 and will be expressed using adjusted relative risk and hazard ratio with 95% confident interval.

6.4 PREDERTMINED SUBGROUP ANALYSIS

Randomization will be stratified according to the $PaCO_2$ value before extubation in order to have the same proportion of hypercapnic patients defined as a $PaCO_2$ > 45 mm Hg at the end of the spontaneous breathing trial. Therefore, a subgroup analysis will be performed for main and secondary criteria of evaluation in hypercapnic patients with $PaCO_2$ > 45 mm Hg before extubation and non hypercapnic patients.
Moreover, subgroup analysis will be performed for main and secondary criteria of evaluation in patients with underlying cardiac or respiratory disease and according to the weaning test performed before extubation (T-piece versus minimal pressure-support).

6.5 EXPECTED NUMBER OF PATIENTS TO BE INCLUDED IN THE STUDY: STATISTICAL JUSTIFICATION

This study is based on the recent literature using HFNC in the postextubation period and on our 2 preliminary studies that have allowed us to accurately assess the number of subjects to include [10, 23]. In keeping with our results, we determined that enrollment of 590 patients would provide a power of 80% to show an absolute difference of 8% in the rate of reintubation between the control group using HFNC alone (rate of reintubation estimated to 18%) as compared with the interventional group using HFNC and NIV (rate of reintubation estimated to 10%) at a two-sided alpha level of 0.05.
So as to be certain to cover the secondary exclusions, we would like to increase the number of patients included by 10%, ie **650 patients**.

6.6 EXPECTED RATE OF REINTUBATION IN THE 2 GROUPS

The expected rates of reintubation in the two groups are based on the literature and on our 2 preliminary studies.

Interventional group:
In our preliminary study the reintubation rate in patients treated with NIV and standard oxygen was 15% within the 7 days following extubation. This rate was only 10% within the 48 hours following extubation which is strictly similar to the rates reported in the literature [7-9]. Although no study to date has evaluated this ventilatory strategy combining NIV and HFNC in the interventional group, we can expect a decreased reintubation rate as compared to NIV and standard oxygen from 15% to 10% within the 7 days following extubation.

Control group:

In our preliminary study the reintubation rate in patients treated with standard oxygen was particularly high reaching 28% within the 7 days following extubation. Using HFNC, the rate of reintubation should be markedly reduced. In a recent monocentric study this rate was only 4% within the 48h following extubation [5] whereas it was nearly 20% in a recent Spanish study not published yet. In these 2 studies the rate of reintubation was underestimated for two reasons: first, because the rate of reintubation was assessed within the 48 first hours following extubation and not at day 7 as in our study, and second because hypercapnic patients considered at high-risk for reintubation were excluded. Therefore, we expect a rate of reintubation at day 7 around 15-20% in the control group treated by HFNC alone.

7 DATA MANAGEMENT, STUDY MONITORING

7.1 DEFINITION OF SOURCE DATA

Source data is all information, original records of clinical findings, observations, or other activities in clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

All protocol-required information collected during the study must be recorded by the investigator or other study personnel in the source documentation for the study. The source documentation will be used to enter the protocol required information into the e-CRF. No data should therefore be directly entered into the e-CRF.

7.2 STUDY MONITORING

7.2.1 Responsibilities of the supervisor

The supervisors and delegate supervisors, staff undertakes to perform the clinical trial in accordance with this clinical protocol, ICH guidelines for GCP and the applicable regulatory requirements.

The supervisors are required to ensure compliance with all procedures required with the clinical trial protocol and with all study procedures provided by he sponsor including security rules.

The supervisors agree to provide reliable data and all information request by the study protocol (with the help of the e-CRF, discrepancy resolution form (DRF) or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives.

The supervisors may appoint such other individuals as he/she may deem appropriate as sub supervisors to assist in the conduct of the study. All supervisors shall be appointed and listed in a timely manner. All supervisors will be supervised by and work under the responsibility of the supervisors.

For the purpose of ensuing compliance with the clinical trial protocol, good clinical practice and applicable regulatory requirements, the supervisor should permit auditing by or on the behalf of the sponsor and inspection by regulatory authorities

The investigator agrees to allow the auditors/inspectors to have direct access to the study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

7.2.2 Responsibilities of the sponsor

The sponsor of this study is responsible of the health authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, trial protocol compliance, integrity and invalidity of the data recorded on the e-CRF. The main duty of the monitoring team is to help the supervisors and the sponsor maintain a high level of ethical, scientific technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the study, the site will be contacted, through monitoring visits and Newsletters, by a representative of the monitoring team to review study progress, supervisor’s compliance with study protocol requirements and any emergent problems. These monitoring visits will include review of the following aspects: patient’s information and non-opposition, patient’s recruitment and follow-up and quality of data.

7.2.3 Source document requirement

According to the ICH guidelines for the Good Clinical Practice, the monitoring team must check the e-CRF entries against source documents. The personnel bound by professional secret, must maintain the confidentiality of all personal identity or personal medical information (according to the confidentiality and personal data protection rules).

7.2.4 Use and completion of Case Report Form (CRFs) and additional request

Electronic CRF will be used for this study. It is the responsibility of the supervisor to maintain adequate and accurate e-CRF and to record all observations and other data pertinent in source documents. All e-CRFs should be completed in their entirety in a legible manner to ensure accurate interpretation of data.

The computerized handling of the data by the sponsor when available in the e-CRF may generate additional requests (DRF) to which the investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

7.3 CNIL

Data collected during the study will be stored in a computer file within the law "informatique et libertés" du 6 janvier 1978 modifiée en 2004.

A notice concerning the implementation of data processing necessary for the realization of the study will be asked to "*Comité Consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS*)", and will be followed by an application to the *"Commission Nationale Informatique et Liberté (CNIL)"* for the processing of personal data.

7.4 MANAGEMENT OF INTERCURRENT EVENTS DURING THE STUDY

Intercurrent events occur during the study and are part of the assessment criteria will be notified in the eCRF and analyzed at end of study.

7.5 ARCHIVE

Sponsor documents will be completed CHU of Poitiers on the archive site for a period of 15 years and any movement must be declared to the manager.

Investigators documents will be archived in each center for a period of 15 years and the place will be indicated to the sponsor.

8 ETHICAL CONSIDERATIONS AND REGULATORY STANDARDS

8.1 ETHICAL PRINCIPLES, LAWS AND REGULATION

This study will be conducted by the supervisors and the sponsor,

- In accordance with Good Clinical Practice (GCP).
- In accordance to the ethical principles that have their origin in the Declaration of Helsinki and with respect to the European clinical practice (**Appendix n°3**),
- In compliance with all international guidelines and national laws and regulation in France.

The clinical trial will be recorded in the public registry website clinicaltrials.gov.

8.2 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

The protocol, the informed consent document must be submitted to the Institutional review board/ Independent ethics Committee IRB/IEC (Comité de Protection des Personnes Ouest III.) for review, and will receive IRB/IEC approval / favorable opinion before initiation of the study.

During the clinical trial, any amendments to the protocol must also be approved by IRB/IEC (Comité de Protection des Personnes Ouest III).
The IRB/IEC should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety.
A progress report is sent to the IRB /IEC at least annually and a summary of the clinical trial's outcome at the end of the study.

8.3 PATIENT INFORMATION AND NON-OPPOSITION

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding the study.
Freely given non-opposition must be obtained from every subject (or their legal representantative) before clinical study participation.
The investigator must provide the subject a copy of the information form and non-opposition about the study in the language in which the subject is more proficient. The patient will be informed of his right to refuse to participate, and to retract at any time.

9 INSURANCE

Because the research is qualified such as routine care after CPP autorization, the insurance will be that of the institution responsible of care.

10 CONFIDENTIALITY AND PROPERTY RIGHTS

All information disclosed or provided by the sponsor, or produced during the clinical trial including but not limited to the clinical trial protocol, the e-CRFs, and the results obtained during the course of the clinical trial is confidential prior to the publication results. The investigator and any person under his authority agree to undertake to keep confidential and not to disclose the information to a third party without the prior written approval of the sponsor.
The sub-investigators shall be bound to the same obligation as the investigator

All information, documents provided by the sponsor or its designee are and remain the sole property of the sponsor.
Results of the clinical trial are also the property of the sponsor, who may use or exploit them without any limitation.

11 PUBLICATION AND COMMUNICATION

11.1 End of study report

The end of study report will be established by the biostastitician of the study, including row data and results of statistical analysis.
This report should be approved and signed by the executive committee and principal supervisors.
A summary of the results of the study will performed and provided on request of the participating patients.

11.2 Publication

Communications, reports and publication of the results of the study will be under the responsibility of the principal investigator-coordinator of the study and the executive committee.
Co-authors of report and publication will include the coordinator and principal co-investigators, the investigators according to their participation to the study, the biostatistician and other associated researchers. Rules of publication will follow the international recommendation according to (N Engl J Med, 1997; 336: 309-315).

12 STUDY FEASIBILITY

The feasibility of this project is based on the 5 following points:

1. The high skill of our centre to conduct this randomized controlled trial: Our center is in an excellent position to coordinate such a trial after having been the main investigator of the FLORALI study (300 patients included) [33], which aimed to compare standard oxygen, HFNC and NIV in patients with de novo acute respiratory failure. The FLORALI study was performed in a shorter than expected time and the

results have been recently in the New England Journal of Medicine [33]. The majority of the centers participating to our new study on the weaning, and thus, have high expertise in the use of NIV and HFNC. An overwhelming majority of the centers participating in our new trial on weaning has already participated to the FLORALI study and consequently possess considerable experience in the use of both NIV and HFNC. Moreover, the vast majority of the centers are ICU within teaching hospitals highly skilled to participate in randomized controlled trials.

2. We verified capacity for inclusion from our two preliminary results. Based on our preliminary studies more than half of the patients meet the inclusion criteria at time of extubation in ICU, and therefore, around 8 patients per center and per month could be eligible. We expect only one patient included per month and per centre to be sure to conduct the study with certainty.
3. Data collection was simplified so as to be adapted to the collection of clinical and laboratory data usually carried out in cases of extubation and to maximize the support of co-investigating centers and physicians. The data collection period is short and occurs primarily during the week following extubation Furthermore, inclusion criteria are easily identified based on the age and medical history, and the time to inclusion is predictable given the decision of extubation is planned by the physician in charge of the patient.
4. The project benefits from the expertise for scientific support of the European network REVA (Research in Artificial Ventilation) directed by Laurent Brochard (Toronto, Canada) and Pr Alain Mercat (Angers, France).
5. Fisher&Paykel provides logistical support and consumables, and lends the devices necessary to carry out HFNC oxygen therapy in all participating centers

13 BENEFITS EXPECTED

At the individual level, the decision of reintubation in the ICU is clearly defined according to criteria of acute respiratory failure, allowing for avoidance of the deleterious effects of a delayed reintubation whatever the group of randomization. Indeed, it has been found that a delayed reintubation could worsen the patient's condition and increase mortality [13]. Moreover, the individual risk of reintubation may be reduced through this strategy of oxygenation, which could be beneficial in the 2 groups using HFNC as the standard therapy of oxygenation.

Nowadays, there is no recommendation concerning the use of NIV or HFNC in the post-extubation period. Although several studies have reported beneficial effects of NIV in hypercapnic patients, prophylactic NIV is underused after extubation. A recent survey in France and Belgium reported that only 10% of the patients extubated in a ICU received NIV in the post-extubation period [53]. Clinical practice differs not only between ICUs but also between countries. Our study would be the largest multicenter trial on the use of NIV or HFNC in the post-extubation period, and could consequently change clinical practice and contribute to the establishment of recommendations on extubation. If the results were positive in terms of reintubation or mortality, this optimal strategy might possibly be applied as a standard treatment in post-extubation for all patients at high risk of reintubation. If effective, this strategy could help to reduce mortality in a population of severely ill patients. From an economic standpoint, a reduced intubation rate would be likely to diminish the subsequent duration of mechanical ventilation, ICU stay and the overall costs of prolonged hospitalization.

APPENDIX

Appendix 1. STUDY FLOW CHART

Actions	Avant épreuve de sevrage	Inclusion / Extubation	H1	Post-Extubation H6, H12-H24, H24-H48	J3 à J7	J14, Sortie de réanimation	J28, J90 (par téléphone)
Critères inclusion et non-inclusion	X						
Information et non opposition Proche/Patient	X	X	X	X	X	X	X
Randomisation		X					
Données démographiques, antécédents	X	X					
SOFA, IGS II		X					
Examen Clinique (PAS, PAD, FC, FR, SpO2)		X	X	X	X		
Traitements, données sur le sevrage	X	X					
Paramètres ventilatoires			X	X	X		
Gaz du sang artériel	X	X (fin sevrage)	X	X	X		
Critères d'insuffisance respiratoire aigue et de réintubation			X	X	X		
Statut, durée de séjour			X	X	X	X	X

Appendix 2. WEANING PROTOCOL

PROTOCOLE DE SEVRAGE DE LA VENTILATION MECANIQUE

Date : **Nom et signature de l'IDE :**

A faire tous les matins pour tous les patients intubés sans sédation continue quelque soit le mode ventilatoire

1ère étape : Le patient peut-il respirer sans le ventilateur ?

1 - Ventilation : FR ≤ 35/min **et** SpO_2 ≥ 92% avec FiO_2 ≤ 40% **et** PEEP ≤ 8 cmH_2O oui ❒ non ❒

2 - Hémodynamique : absence de vasopresseurs (Noradrénaline/Adrénaline) oui ❒ non ❒

3 - Neurologique : patient réveillé, réponse adaptée à la commande (+1≥ RASS ≥-2) oui ❒ non ❒

4 - Pas de sédation continue (arrêt hypnovel, propofol, sufentanil) oui ❒ non ❒

Si les 4 critères de sevrage sont présents → réaliser une épreuve de sevrage ventilatoire au nez artificiel après le nursing du matin *(Cf. procédure)* : durée 1 heure

Régler le débit d'oxygène selon la FiO_2 du ventilateur (oxygène à 3 L/min si FiO_2 30%, oxygène à 6 L/min si FiO_2 40%)

Critères de mauvaise tolérance de l'épreuve	Avant l'épreuve	5 min après le début	Fin de l'épreuve (H1 ou échec)
Heure de début de l'épreuve : - - h - -			Durée :
Débit d'O_2 : > 6L/min			
SpO_2 : < 90%			
FR : > 35/min			
FC : > 140/min			
PAS : < 90 ou > 180 mm Hg			
Détresse : **T**irage (**T**), **S**ueurs (**S**), Agitation (**A**), **M**arbrures (**M**)		**T - S - A - M**	**T - S - A - M**

Arrêt de l'épreuve : à H1 ou en cas de survenue d'un seul critère de mauvaise tolérance

- ► Relever l'ensemble des constantes avant rebranchement et noter la durée de l'épreuve
- ► Entourer le ou les critères de mauvaise tolérance en cas d'échec
- ► Réaliser un gaz du sang avant rebranchement si un cathéter artériel est en place
- ► Reconnecter le patient au ventilateur avec les paramètres ventilatoires préalables

Conclusion : L'épreuve de ventilation spontanée au nez artificiel est un succès **oui ❒** **non ❒**

Si oui ► 2ème étape : Le patient est-il extubable ?

Toux	Absente = 0	Faible = 1	Bonne = 2	Très bonne = 3
Sécrétions	Absente = 0	Peu abondantes =1	Abondantes = 2	Très abondantes = 3
Risque d'encombrement	Non	Oui (Si sécrétions = 2 ou 3 **ET** toux = 0 ou 1)		
Risque d'œdème laryngé évalué par le test de fuite ***(Risque évalué uniquement par un kiné, un médecin ou un interne)***	Non ❒		Oui ❒	

3ème étape : Extubation sur décision médicale (cf. procédure)

Extubation ce jour: Oui ❒

Non ❒ **Motif** ----------

Service de réanimation médicale – Version N°1 – Mai 2014

Appendix 3. HELSINKI DECLARATION

ASSOCIATION MEDICALE MONDIALE

Déclaration d'Helsinki de L'AMM - Principes éthiques applicables à la recherche médicale impliquant des êtres humains

Adoptée par la 18e Assemblée générale de l'AMM, Helsinki, Finlande, Juin 1964 et amendée par les :
29e Assemblée générale de l'AMM, Tokyo, Japon, Octobre 1975
35e Assemblée générale de l'AMM, Venise, Italie, Octobre 1983
41e Assemblée générale de l'AMM, Hong Kong, Septembre 1989
48e Assemblée générale de l'AMM, Somerset West, Afrique du Sud, Octobre 1996
52e Assemblée générale de l'AMM, Edimbourg, Ecosse, Octobre 2000
53e Assemblée générale de l'AMM, Washington DC, Etats Unis, Octobre 2002 (ajout d'une note de clarification)
55e Assemblée générale de l'AMM, Tokyo, Japon, Octobre 2004 (ajout d'une note de clarification)
59e Assemblée générale de l'AMM, Séoul, République de Corée, Octobre 2008
64e Assemblée générale de l'AMM, Fortaleza, Brésil, Octobre 2013

Préambule

1. L'Association Médicale Mondiale (AMM) a élaboré la Déclaration d'Helsinki comme un énoncé de principes éthiques applicables à la recherche médicale impliquant des êtres humains, y compris la recherche sur du matériel biologique humain et sur des données identifiables.
La Déclaration est conçue comme un tout indissociable. Chaque paragraphe doit être appliqué en tenant compte de tous les autres paragraphes pertinents.

2. Conformément au mandat de l'AMM, cette Déclaration s'adresse en priorité aux médecins. L'AMM invite cependant les autres personnes engagées dans la recherche médicale impliquant des êtres humains à adopter ces principes.

Principes généraux

3. La Déclaration de Genève de l'AMM engage les médecins en ces termes: «La santé de mon patient prévaudra sur toutes les autres considérations » et le Code International d'Ethique Médicale déclare qu'un «médecin doit agir dans le meilleur intérêt du patient lorsqu'il le soigne».

4. Le devoir du médecin est de promouvoir et de sauvegarder la santé, le bien-être et les droits des patients, y compris ceux des personnes impliquées dans la recherche médicale. Le médecin consacre son savoir et sa conscience à l'accomplissement de ce devoir.

5. Le progrès médical est basé sur la recherche qui, en fin de compte, doit impliquer des êtres humains.

6. L'objectif premier de la recherche médicale impliquant des êtres humains est de comprendre les causes, le développement et les effets des maladies et d'améliorer les interventions préventives, diagnostiques et thérapeutiques (méthodes, procédures et traitements). Même les meilleures interventions éprouvées doivent être évaluées en permanence par des recherches portant sur leur sécurité, leur efficacité, leur pertinence, leur accessibilité et leur qualité.

7. La recherche médicale est soumise à des normes éthiques qui promeuvent et assurent le respect de tous les êtres humains et qui protègent leur santé et leurs droits.

8. Si l'objectif premier de la recherche médicale est de générer de nouvelles connaissances, cet objectif ne doit jamais prévaloir sur les droits et les intérêts des personnes impliquées dans la recherche.

9. Il est du devoir des médecins engagés dans la recherche médicale de protéger la vie, la santé, la dignité, l'intégrité, le droit à l'auto-détermination, la vie privée et la confidentialité des informations des personnes impliquées dans la recherche. La responsabilité de protéger les personnes impliquées dans la recherche doit toujours incomber à un médecin ou à un autre professionnel de santé et jamais aux personnes impliquées dans la recherche même si celles-ci ont donné leur consentement.

10. Dans la recherche médicale impliquant des êtres humains, les médecins doivent tenir compte des normes et standards éthiques, légaux et réglementaires applicables dans leur propre pays ainsi que des normes et standards internationaux. Les protections garanties par la présente Déclaration aux personnes impliquées dans la recherche ne peuvent être restreintes ou exclues par aucune disposition éthique, légale ou réglementaire, nationale ou internationale.

11. La recherche médicale devrait être conduite de sorte qu'elle réduise au minimum les nuisances éventuelles à l'environnement.

12. La recherche médicale impliquant des êtres humains doit être conduite uniquement par des personnes ayant acquis une éducation, une formation et des qualifications appropriées en éthique et en science. La recherche impliquant des patients ou des volontaires en bonne santé nécessite la supervision d'un médecin ou d'un autre professionnel de santé qualifié et compétent.

13. Des possibilités appropriées de participer à la recherche médicale devraient être offertes aux groupes qui y sont sous-représentés.

14. Les médecins qui associent la recherche médicale à des soins médicaux devraient impliquer leurs patients dans une recherche uniquement dans la mesure où elle se justifie par sa valeur potentielle en matière de prévention, de diagnostic ou de traitement et si les médecins ont de bonnes raisons de penser que la participation à la recherche ne portera pas atteinte à la santé des patients concernés.

15. Une compensation et un traitement adéquats doivent être garantis pour les personnes qui auraient subi un préjudice en raison de leur participation à une recherche.

Risques, contraintes et avantages

16. Dans la pratique médicale et la recherche médicale, la plupart des interventions comprennent des risques et des inconvénients.
Une recherche médicale impliquant des êtres humains ne peut être conduite que si l'importance de l'objectif dépasse les risques et inconvénients pour les personnes impliquées.

17. Toute recherche médicale impliquant des êtres humains doit préalablement faire l'objet d'une évaluation soigneuse des risques et des inconvénients prévisibles pour les personnes et les groupes impliqués, par rapport aux bénéfices prévisibles pour eux et les autres personnes ou groupes affectés par la pathologie étudiée.
Toutes les mesures destinées à réduire les risques doivent être mises en œuvre. Les risques doivent être constamment surveillés, évalués et documentés par le chercheur.

18. Les médecins ne peuvent pas s'engager dans une recherche impliquant des êtres humains sans avoir la certitude que les risques ont été correctement évalués et pourront être gérés de manière satisfaisante.
Lorsque les risques s'avèrent dépasser les bénéfices potentiels ou dès l'instant où des conclusions définitives ont été démontrées, les médecins doivent évaluer s'ils continuent, modifient ou cessent immédiatement une recherche.

Populations et personnes vulnérables

19. Certains groupes ou personnes faisant l'objet de recherches sont particulièrement vulnérables et peuvent avoir une plus forte probabilité d'être abusés ou de subir un préjudice additionnel.
Tous les groupes et personnes vulnérables devraient bénéficier d'une protection adaptée.

20. La recherche médicale impliquant un groupe vulnérable se justifie uniquement si elle répond aux besoins ou aux priorités sanitaires de ce groupe et qu'elle ne peut être effectuée sur un groupe non vulnérable. En outre, ce groupe devrait bénéficier des connaissances, des pratiques ou interventions qui en résultent.

Exigences scientifiques et protocoles de recherche

21. La recherche médicale impliquant des êtres humains doit se conformer aux principes scientifiques généralement acceptés, se baser sur une connaissance approfondie de la littérature scientifique, sur d'autres sources pertinentes d'informations et sur des expériences appropriées en laboratoire et, le cas échéant, sur les animaux. Le bien-être des animaux utilisés dans la recherche doit être respecté.

22. La conception et la conduite de toutes les recherches impliquant des êtres humains doivent être clairement décrites et justifiées dans un protocole de recherche.
Ce protocole devrait contenir une déclaration sur les enjeux éthiques en question et indiquer comment les principes de la présente Déclaration ont été pris en considération. Le protocole devrait inclure des informations concernant le financement, les promoteurs, les affiliations institutionnelles, les conflits d'intérêts potentiels, les incitations pour les personnes impliquées dans la recherche et des informations concernant les mesures prévues pour

soigner et/ou dédommager celles ayant subi un préjudice en raison de leur participation à la recherche.
Dans les essais cliniques, le protocole doit également mentionner les dispositions appropriées prévues pour l'accès à l'intervention testée après l'essai clinique.

Comités d'éthique de la recherche

23. Le protocole de recherche doit être soumis au comité d'éthique de la recherche concerné pour évaluation, commentaires, conseils et approbation avant que la recherche ne commence. Ce comité doit être transparent dans son fonctionnement, doit être indépendant du chercheur, du promoteur et de toute autre influence indue et doit être dûment qualifié. Il doit prendre en considération les lois et réglementations du ou des pays où se déroule la recherche, ainsi que les normes et standards internationaux, mais ceux-ci ne doivent pas permettre de restreindre ou exclure l'une des protections garanties par la présente Déclaration aux personnes impliquées dans la recherche.
Le comité doit avoir un droit de suivi sur les recherches en cours. Le chercheur doit fournir au comité des informations sur le suivi, notamment concernant tout évènement indésirable grave. Aucune modification ne peut être apportée au protocole sans évaluation et approbation par le comité. A la fin de la recherche, les chercheurs doivent soumettre au comité un rapport final contenant un résumé des découvertes et des conclusions de celle-ci.

Vie privée et confidentialité

24. Toutes les précautions doivent être prises pour protéger la vie privée et la confidentialité des informations personnelles concernant les personnes impliquées dans la recherche.

Consentement éclairé

25. La participation de personnes capables de donner un consentement éclairé à une recherche médicale doit être un acte volontaire. Bien qu'il puisse être opportun de consulter les membres de la famille ou les responsables de la communauté, aucune personne capable de donner un consentement éclairé ne peut être impliquée dans une recherche sans avoir donné son consentement libre et éclairé.

26. Dans la recherche médicale impliquant des personnes capables de donner un consentement éclairé, toute personne pouvant potentiellement être impliquée doit être correctement informée des objectifs, des méthodes, des sources de financement, de tout éventuel conflit d'intérêts, des affiliations institutionnelles du chercheur, des bénéfices escomptés et des risques potentiels de la recherche, des désagréments qu'elle peut engendrer, des mesures qui seront prises après à l'essai clinique et de tout autre aspect pertinent de la recherche. La personne pouvant potentiellement être impliquée dans la recherche doit être informé de son droit de refuser d'y participer ou de s'en retirer à tout moment sans mesure de rétorsion. Une attention particulière devrait être accordée aux besoins d'informations spécifiques de chaque personne pouvant potentiellement être impliquée dans la recherche ainsi qu'aux méthodes adoptées pour fournir les informations. Lorsque le médecin ou une autre personne qualifiée en la matière a la certitude que la personne concernée a compris les informations, il doit alors solliciter son consentement libre et éclairé, de préférence par écrit. Si le consentement ne peut pas être donné par écrit, le consentement non écrit doit être formellement documenté en présence d'un témoin.

Toutes les personnes impliquées dans des recherches médicales devraient avoir le choix d'être informées des conclusions générales et des résultats de celles-ci.

27. Lorsqu'il sollicite le consentement éclairé d'une personne pour sa participation à une recherche, le médecin doit être particulièrement attentif lorsque cette dernière est dans une relation de dépendance avec lui ou pourrait donner son consentement sous la contrainte. Dans ce cas, le consentement éclairé doit être sollicité par une personne qualifiée en la matière et complètement indépendante de cette relation.

28. Lorsque la recherche implique une personne incapable de donner un consentement éclairé, le médecin doit solliciter le consentement éclairé de son représentant légal. Les personnes incapables ne doivent pas être incluses dans une recherche qui n'a aucune chance de leur être bénéfique sauf si celle-ci vise à améliorer la santé du groupe qu'elles représentent, qu'elle ne peut pas être réalisée avec des personnes capables de donner un consentement éclairé et qu'elle ne comporte que des risques et des inconvénients minimes.

29. Lorsqu'une personne considérée comme incapable de donner un consentement éclairé est en mesure de donner son assentiment concernant sa participation à la recherche, le médecin doit solliciter cet assentiment en complément du consentement de son représentant légal. Le refus de la personne pouvant potentiellement être impliquée dans la recherche devrait être respecté.

30. La recherche impliquant des personnes physiquement ou mentalement incapables de donner leur consentement, par exemple des patients inconscients, peut être menée uniquement si l'état physique ou mental empêchant de donner un consentement éclairé est une caractéristique nécessaire du groupe sur lequel porte cette recherche.
Dans de telles circonstances, le médecin doit solliciter le consentement éclairé du représentant légal. En l'absence d'un représentant légal et si la recherche ne peut pas être retardée, celle-ci peut être lancée sans le consentement éclairé. Dans ce cas, le protocole de recherche doit mentionner les raisons spécifiques d'impliquer des personnes dont l'état les rend incapables de donner leur consentement éclairé et la recherche doit être approuvée par le comité d'éthique de la recherche concerné. Le consentement pour maintenir la personne concernée dans la recherche doit, dès que possible, être obtenu de la personne elle-même ou de son représentant légal.

31. Le médecin doit fournir des informations complètes au patient sur la nature des soins liés à la recherche. Le refus d'un patient de participer à une recherche ou sa décision de s'en retirer ne doit jamais nuire à la relation patient-médecin.

32. Pour la recherche médicale utilisant des tissus ou des données d'origine humaine, telles que les recherches sur tissus et données contenues dans les biobanques ou des dépôts similaires, les médecins doivent solliciter le consentement éclairé pour leur analyse, stockage et/ou réutilisation. Il peut se présenter des situations exeptionnelles où il est impraticable, voire impossible d'obtenir le consentement. Dans de telles situations, la recherche peut être entreprise uniquement après évaluation et approbation du comité d'éthique de la recherche concerné.

<u>Utilisation de placebo</u>

33. Les bénéfices, les risques, les inconvénients, ainsi que l'efficacité d'une nouvelle intervention doivent être testés et comparés à ceux des meilleures interventions avérées, sauf dans les circonstances suivantes :

Lorsqu'il n'existe pas d'intervention avérée, l'utilisation de placebo, ou la non intervention, est acceptable ; ou

Lorsque pour des raisons de méthodologie incontournables et scientifiquement fondées l'utilisation de toute intervention moins efficace que la meilleure éprouvée, l'utilisation d'un placebo, ou la non intervention, est nécessaire afin de déterminer l'efficacité ou la sécurité d'une intervention,

et lorsque les patients recevant une intervention moins efficace que la meilleure éprouvée, un placebo, ou une non intervention, ne courent pas de risques supplémentaires de préjudices graves ou irréversibles du fait de n'avoir pas reçu la meilleure intervention éprouvée.

Le plus grand soin doit être apporté afin d'éviter tout abus de cette option

Conditions de l'accès à l'intervention testée après l'essai clinique

34. En prévision d'un essai clinique, les promoteurs, les chercheurs et les gouvernements des pays d'accueil devraient prévoir des dispositions pour que tous les participants qui ont encore besoin d'une intervention identifiée comme bénéfique dans l'essai puissent y accéder après celui-ci. Cette information doit également être communiquée aux participants au cours du processus de consentement éclairé.

Enregistrement des recherches, publication et dissémination des résultats

35. Toute recherche impliquant des êtres humains doit être enregistrée dans une banque de données accessible au public avant que ne soit recrutée la première personne impliquée dans la recherche.

36. Les chercheurs, auteurs, promoteurs, rédacteurs et éditeurs ont tous des obligations éthiques concernant la publication et la dissémination des résultats de la recherche. Les chercheurs ont le devoir de mettre à la disposition du public les résultats de leurs recherches impliquant des êtres humains. Toutes les parties ont la responsabilité de fournir des rapports complets et précis. Ils devraient se conformer aux directives acceptées en matière d'éthique pour la rédaction de rapports. Les résultats aussi bien négatifs et non concluants que positifs doivent être publiés ou rendus publics par un autre moyen. La publication doit mentionner les sources de financement, les affiliations institutionnelles et les conflits d'intérêts. Les rapports de recherche non-conformes aux principes de la présente Déclaration ne devraient pas être acceptés pour publication.

Interventions non avérées dans la pratique clinique

37. Dans le cadre du traitement d'un patient, faute d'interventions avérées ou faute d'efficacité de ces interventions, le médecin, après avoir sollicité les conseils d'experts et avec le consentement éclairé du patient ou de son représentant légal, peut recourir à une intervention non avérée si, selon son appréciation professionnelle, elle offre une chance de sauver la vie, rétablir la santé ou alléger les souffrances du patient. Cette intervention devrait par la suite faire l'objet d'une recherche pour en évaluer la sécurité et l'efficacité. Dans tous les cas, les nouvelles informations doivent être enregistrées et, le cas échéant, rendues publiques.