Title of Proposed Clinical Trial: Effect of the Combination of High-Frequency Oscillation and Tracheal Gas Insufflation on the Survival of Patients with Severe Acute Respiratory Distress Syndrome

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Note: Red Script Text corresponds to subsequent Protocol Revisions

Introduction to the Objective and Rationale of the Trial

In the past 5 years, there is a growing number of published articles showing the suitability and benefits of the use of high frequency oscillation (HFO) in patients with acute respiratory distress syndrome (ARDS) (1-4). In 2002, Derdak and associates published the results of a randomized controlled trial comparing HFO and conventional mechanical ventilation (CMV) in patients with ARDS. The CMV group did not receive lung protective CMV (1). There was a trend toward a significant decrease in 30-day mortality in the HFO group (37% vs. 52% in the CMV group, P=0.102). The HFO group mortality was comparable to the mortality reported by the ARDSnet trial published in the year 2000; in this trial, patients received low tidal volume CMV (5). It should be noted that Derdak et al employed "moderate" tidal volumes (6-9), the use of which was subsequently supported by the results of the meta-analysis of Eichacker et al (10). However, as Levy points out (11), the mortality of 26-31% in a total of 1000 patients treated with low tidal volumes [if one combines the data of the 2 ARDSnet studies (5,12)] indicates that the open lung-low tidal volume ventilation is the most effective CMV strategy in ARDS.

During HFO, the proposed mechanisms of gas-exchange include 1) bulk convection, 2) pendelluft effect, 3) asymmetric velocity profiles, 4) Taylor dispersion and turbulence, 5) cardiogenic mixing, 6) molecular diffusion, and 7) collateral ventilation (13).

Tracheal gas insufflation (TGI) constitutes an interesting adjunct to CMV for patients with severe ARDS. Conventional forward thrust TGI improves CO_2 elimination (14). Two theories have been developed, in order to explain the efficacy of TGI (14-16). The first theory proposes the washout of the anatomic deadspace, and the second theory supports the augmentation of alveolar ventilation. The removal of CO_2 – rich gas from the anatomic deadspace and its O_2 – rich and CO_2 – free gas prevents the reentry of CO_2 into the alveoli during the subsequent inspiration (deadspace washout mechanism). Alveolar ventilation may also be augmented by 1) the increase in the mixing of the gases distally to the central airways due to the high-velocity and probably turbulent TGI flow, and 2) the enhancement of collateral ventilation.

In our preceding study (paper submitted to Crit Care Med), we showed that the combination of HFO with TGI (HFO-TGI) improves gas-exchange as compared to lung protective CMV. In the present study, we intend to determine the effect of HFO-TGI on the survival of patients with severe ARDS. Our main hypotheses are that 1) HFO-TGI will improve oxygenation and lung recruitment, thus resulting in reduced ventilation pressures during the subsequent CMV, and 2) this reduction in the injurious mechanical stresses to the lung may attenuate ventilator-associated lung injury and thus improve survival. This is also the major proposed mechanism of survival improvement by low-stretch, low-volume CMV (5).

METHODS

Patients

Study participants must fulfill the following eligibility criteria: 1) early ARDS (establishment of the diagnosis within the preceding 72 hours) according to the criteria of the American-European Consensus Conference (18), 2) severe oxygen disturbance [defined as ratio of partial pressure of arterial oxygen (PaO_2) to inspired oxygen fraction (FiO_2)<150mmHg, while they are on CMV with positive end-expiratory pressure (PEEP) set at ≥8cmH_2O, 3) age 18-75 years, body weight >40 Kg, and 4) absence of a) severe air leak (more than one chest tubes per hemithorax with persistent air leak for more than 72 hours), b) systolic blood pressure lower than 90 mmHg, despite maximum support with fluids and vasopressor drugs (i.e., norepinephrine infusion rate exceeding 0,5 μg/kg/min, c) significant heart disease (e.g. ejection fraction lower than 40%, history of pulmonary edema and active ischemic disease or myocardial infarction), d) severe chronic obstructive pulmonary disease (COPD) or asthma (e.g. previous admission for COPD/asthma, chronic treatment with corticosteroids for COPD/asthma, and chronic CO_2 retention more than 50 mmHg), e) intracranial pathology with intracranial pressure >20mmHg, not responsive to conservative treatment (e.g. hemorrhage, head injury, tumor, infection or acute ischemic stroke), f) chronic interstitial lung disease with bilateral lung infiltrates, g) lung biopsy or incision during the current admission, h) previous lung transplantation or bone marrow transplantation, i) pregnancy, j) immunosuppression, and k) participation in another clinical study.

Randomization will result in assignment to either the control group (treatment with CMV) or the HFO-TGI group (treatment with CMV and HFO-TGI sessions, as described in the following paragraphs). The randomization technique will comprise the use of computer-generated sequence(s) of random numbers and a "sealed envelope technique", in order to achieve concealment until patient study entry.

Continuous monitoring of patients will include electrocardiographic lead II, intraarterial pressure [and/or cardiac index (PICCO plus, Pulsion Medical Systems, Munich, Germany)] and peripheral oxygen saturation (SpO_2). Maintenance of anesthesia will be achieved with intravenous midazolam or propofol and/or fentanyl or remifentanyl. Neuromuscular blockade (cisatracurium) will be used in concordance with recent recommendations (19), and/or as part of the treatment prescribed by the attending physicians. The sedation protocol is illustrated in Figure 1, and reflects mainly our standard clinical practice.

Conventional Mechanical Ventilation Strategy

Patients eligible for the study will be initially on CMV ([Siemens 300C ventilator (Siemens, Berlin, Germany), or Galileo Gold ventilator (Hamilton Medical, Bonaduz, Switzerland)] with the following FiO_2/PEEP combinations: 0.6/10 cm H_2O, 0.7/10-14 cm H_2O, 0.8/14 cm H_2O, 0.9/16 cm H_2O, 1.0/16-20 cm H_2O. The tidal volume will be 5.5-7.5ml/kg predicted body weight with a maximum plateau pressure of 35 cmH_2O. The goals for tidal volume and plateau pressure will be 6.0 ml/Kg predicted body weight and 30 cmH_2O, respectively, provided that the below-mentioned gas exchange goals are achievable. Respiratory rate will be adjusted so that arterial pH (pHa) will be maintained from 7.20-7.30 to 7.45 and the inspiratory to expiratory time (I/E) ratio will be 1:2. Oxygenation targets will be as follows: SaO_2=90-95% or PaO_2=60-80 mmHg. The target pHa will be >7.20. Recruitment maneuvers (RM) [continuous-positive airway pressure of 45 cmH_2O (40-50) for 20-40 sec depending on patient tolerance] will be performed every 4-6 hours for the first 4 days after randomization in the control group. The CMV strategy is summarized in Table 1.

HFO-TGI strategy-main study intervention protocol

Recently published recommendations regarding HFO use (Sensormedics 3100B ventilator, Sensormedics, Yorba Linda, CA, USA) include the following steps (20).

1) Sufficient level of sedation for the abolishment of respiratory muscles activity, with or without neuromuscular blockade, so that patient-ventilator dyssynchrony is avoided (21-24).
2) Confirmation of endotracheal tube patency and placement of the tube at 3-4 cm above carina.
3) RMs: immediately after patient-oscillator connection, an RM will be performed [increase in the circuit pressure to 45 (40-50) cmH_2O for 20-40 sec depending on patient tolerance, with the oscillator's piston off]. RMs will be repeated every 2-12 hours approximately.
4) FiO_2 will initially be set at 1.0.
5) Bias flow will be set at 30-40 L/min.
6) According to the data of our preceding study (paper submitted to Crit Care Med), TGI will be equal to 50% of the preceding CMV minute ventilation; this is also consistent with an earlier study of our group (25).
7) Initial oscillation frequency will be 4 Hz, and will be titrated according to pHa>7.20-7.30, with a minimum value of 3 Hz. Oscillatory pressure amplitude (ΔP) will be set within 60-100 cmH_2O and will be titrated according to pHa>7.20-7.30.
8) A tracheal tube cuff leak will be placed to facilitate CO_2 elimination. The associated reduction in mean airway pressure (mPaw) of 3-5 cmH_2O will be immediately reversed by using the corresponding control knob.
9) I:E ratio will be maintained at 1:2.
10) **Initial adjustments and the subsequent de-escalation of mPaw (and TGI will be conducted as follows: A] Initial mPaw = mPaw CMV + 8-10 cm H_2O (depending on CMV tracheal pressure), or approximate equivalent, i.e. mPaw = 2-3 cmH_2O above the point of maximal curvature of the expiratory pressure-volume curve (if the curve is constructed) B] mPaw reduction by 1-2 cmH_2O every 1-2 hours, with a final target to reduce initial mPaw by 6 cmH_2O and maintain a PaO_2/FiO_2 of >150 mmHg, C] discontinuation of TGI over 30 min, and reconfirmation that PaO_2/FiO_2 remains at >150 mmHg after another 30 min, D] return to CMV. The main indication for return to HFO-TGI will be a PaO_2/FiO_2 of <150 mmHg with PEEP ≥ 8 cmH_2O for > 12 hours. The minimum total time of HFO-TGI will be 12 hours.**

A study protocol schema is provided in Figure 2, whereas the proposed intervention failure algorithm is illustrated in Figure 3. The HFO-TGI protocol will be based on the simple principle of "Recruit – Stabilize – and Wean, and Re-recruit if necessary". The minimum duration of the recruitment period will be 60 min; the minimum duration of the stabilization period will be 4 hours; the minimum duration of the weaning period will be 60 min; and the minimum duration of the HFO-TGI session will be 6 hours. HFO-TGI sessions will be extended according to the need of use of the Additional Recruitment Algorithm. The maximum duration of application of the HFO-TGI intervention will be 10 days.

Patient Safety Features

The lowest allowable SpO_2 will be 88% for the whole duration of the HFO-TGI protocol. An SpO_2 of <88% for ≥5 min will trigger immediate transition to the Additional Recruitment Algorithm [and/or its subsequent step(s) if still persisting for

another 5 min (Figure 2)]. During HFO-TGI sessions, the maximum set mPaw will never exceed 40 cmH_2O (allowance may be made up to 45 cmH_2O for the case of intervention failure). In addition, systolic blood pressure value will be maintained at >90 mmHg, mean blood pressure will be maintained at >60 mmHg, and reductions in cardiac output/index of >10% will be treated with fluids and vasopressors. RMs resulting in any of the immediately aforementioned hemodynamic perturbations will be aborted and withheld for 12 hours; the same action will be undertaken if RMs result in desaturation (i.e., SpO_2 <85% or absolute SPO_2 decrease of >5%). At the end of the HFO-TGI sessions, a brief fiberoptic inspection of the trachea will be carried out (by a study-independent physician), in order to exclude or confirm the presence of TGI-related mucosal damage; the proposed grading of endoscopic findings is presented in Table 2; TGI-related mucosal damage in a patient will result in discontinuation of TGI use in that particular patient. Lastly, during HFO-TGI and in the presence of a tracheal tube cuff leak, the nasogastric tube will be placed on drainage to minimize any potential risk of aspiration of gastric contents.

Weaning from CMV

The corresponding proposed protocol is presented in Figure 4.

Patient Follow-up

Data on demographic, physiologic, and radiographic characteristics, coexisting conditions, and medication will be recorded within 4 hours prior to randomization. For the first 10 days post-randomization, at least 3 sets physiologic measurements (blood-gas analysis, hemodynamics, and respiratory mechanics during CMV) will be obtained daily. Laboratory, radiographic/imaging (with special emphasis on barotrauma; assessments to be carried out by study-independent radiologists), and physiologic data will be collected daily until weaning from CMV and/or intensive care unit (ICU) discharge or death. Patients will be monitored daily for signs of failure of nonpulmonary organs and systems. Patient clinical course will be documented until hospital discharge or death.

Outcome Measures

Primary:

- Survival to days 28 and 60 post-randomization, and to Hospital Discharge (patient discharged home while breathing without assistance).

Secondary:

- Evolution of Gas-exchange, Hemodynamics, and Respiratory Mechanics during the Study Intervention Period.
- Ventilator Free Days during days 1-28 and 1-60 post-randomization (defined as in reference 5).
- Organ or System Failure Free Days during days 1-28 and 1-60 post-randomization (organ failures will be defined on the basis of a corresponding sequential organ dysfunction assessment score of 3 or 4).
- Occurrence of Barotrauma (i.e., any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or pneumatocele > 2 cm).
- Occurrence of Tracheal Mucosal Injury due to use of TGI.

Power Analysis and Study Periods

Based on pilot data, we estimate an absolute HFO-TGI related improvement of 26% in the survival to hospital discharge. For the determination of a 26% absolute difference in hospital mortality with alpha=0.05 and power=0.80, a total sample size of 124 patients will be required.

Based on pilot data, we wish to provide the following estimates for the study: 1) a minimum investigator-to-patient ratio of 1:1 for days 1-10 post-randomization (i.e. the intervention period): 2 investigators have to be assigned to each patient of each group on a rotating 12-hour basis to apply either the HFO-TGI protocol, or the lung-protective CMV strategy, and the RM protocol of the CMV group; in each 12-hour study shift, each investigator may apply the study protocol in up to 2 patients simultaneously; 2) for days 1-10: in Evaggelismos hospital, 1 of the 3 supervising investigators will be available on a rotating basis for advice and/or assistance with respect to the application of the study protocol; 3) a minimum investigator-to-patient ratio of 1:3 for day 11 to hospital discharge: 1 investigator will be concurrently assigned to a maximum of 3 patients for daily collection of the follow-up data and confirmation of the application of the standardized lung-protective CMV strategy, and/or application of the weaning protocol; 4) a maximum and average predicted enrollment rate for Evaggelismos hospital of 6 and 4.2 patients per month, respectively; 5) a maximum predicted concurrent presence of 3 patients in the intervention period and 6 patients in the post-intervention follow-up period, requiring a total of 5 assigned investigators; 6) a projected temporary reduction in the actually available investigator manpower of 7 (with supervising investigators included) of Evaggelismos hospital to 5 in-between October 2007 and February 2008; 7) a maximum and average predicted enrollment rate for Larissa hospital of 2 and 1 patients per month, respectively, requiring at least 2 investigators; and 8) a requirement of ≥50 hours of prior, principal investigator-guided use of HFO-TGI for each one of the investigators of the Larissa hospital (50 hours correspond to approximately 50% of the average time of HFO-TGI use per investigator during the pilot period). The predictions for Evaggelismos hospital were based on organization experience gained from the period of the pilot data collection. The predictions for Larissa hospital were based on the 1.0:3.7 bed ratio of its ICU vs. the ICU of Evaggelismos.

After considering the above-mentioned factors of study feasibility, we propose to conduct the trial in 2 periods: a single-center first period of at least 50 patients (average estimate=52 patients, maximum=54 patients), starting on July 2006 and having a projected duration of 12-13 months; and a two-center final period of at least 70 patients, starting on March 2008 and having a projected duration of 14-15 months.

First study period planning

An interim analysis assessing safety data will be conducted after the enrolment of 20 patients. Following the (probable in our opinion) establishment of patient safety, we will be able to extend the study until the enrolment and follow-up completion of 50-54 patients. Based on our pilot period data, we have estimated an HFO-TGI-related improvement in compliance of 25% within days 5-10 (improvement most likely to be confirmed within days 5-8). For alpha = 0.05 and power = 0.80, we will have to enroll 52 patients, whereas the enrollment of 54 patients will raise power to 0.82." Consequently, provided that our pilot data-based prediction is confirmed in the first 20 participants of the first study period, we will conclude that this study period will be adequately powered to assess the evolution of respiratory physiology during

the study intervention period. As according to our original hypothesis the evolution of respiratory physiology is a prerequisite for an HFO-TGI-associated improvement in survival, following the aforementioned confirmation, we will add this "intermediate" outcome to the (registered with Clinicaltrials.gov) primary outcome measures of the first study period.

The other primary outcome measure for the first study period will be (as for the whole study) survival to hospital discharge; additional survival assessment time points may include days 28 and 60 post-randomization. The current study period will not be sufficiently powered to reliable assess in-hospital mortality. Nevertheless, regarding 28-day survival, a possible, large chi-square effect size of 0.5-0.6 would result in alpha ≤ 0.04 and power ≥ 0.81. This will correspond to a between-group, 28-day survival difference similar to that determined in the Amato trial [i.e. 34% (26)]. However, in such a case, a large difference in 28-day survival will also likely be reflected by a concurrent difference in ventilator-free days (26), which in turn will be explained by early improvements in the respiratory physiology of the HFO-TGI group. Regarding the potential for TGI-associated tracheal mucosal damage (14), this will be assessed as feasible (feasibility to be confirmed during the first period) according to the pre-specified grading of Table 2.

BIBLIOGRAPHY

1. Derdak S, Mehta S Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults. A randomized controlled trial. Am J Respir Crit Care Med 2002; 166: 801-808.
2. Mehta S, Granton J, MacDonald RJ, et al. High-frequency oscillatory ventilation in adults. The Toronto experience. Chest 2004; 126: 518-527.
3. Ferguson N, Chiche JD, Kacmarek RM, et al. Combining high-frequency oscillatory ventilation and recruitment in adults with early acute respiratory distress syndrome: The Treatment with Oscillation and an Open Lung Strategy (TOOLS) Trial pilot study. Crit Care Med 2005; 33: 479-486.
4. Sadeek KA, Takeuchi M, Suchodolski K, et al. Open-lung protective ventilation with pressure control ventilation, high frequency oscillation, and intratracheal pulmonary ventilation results in similar gas exchange, hemodynamics, and lung mechanics. Anesthesiology 2003; 99: 1102-1111.
5. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301-1308,.
6. Thompson BT, Hayden D, Matthay MA, et al. Clinicians' approaches to mechanical ventilation in acute lung injury and ARDS. Chest 2001; 120: 1622-1627.
7. Esteban A, Anzueto A, Alia I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000; 161: 1450-1458.
8. Carmichael LC, Dorinsky PM, Higgins SB, et al. Diagnosis and treatment of acute respiratory distress syndrome in adults: an international survey. J Crit Care 1996; 11: 9-18.

9. Esteban A, Anzueto A, Frutos F, et al, and the Mechanical Ventilation Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287: 345-355.
10. Eichacker PQ, Gerstenberger ER, Banks SM, et al. Meta-analysis of acute lung injury and acute respirtory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med 2002; 166: 1510-1514.
11. Levy MM. PEEP in ARDS-How Much is Enough? N Enl J Med 2004; 351: 389-381.
12. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressure in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351: 327-336.
13. Pillow JJ. High-frequency oscillatory ventilation: Mechanisms of gas exchange and lung mechanics. Crit Care Med 2005; 33 [Suppl.]: S135-S141.
14. Nahum A, Ravenscraft SA, Nakos G, et al: Tracheal gas insufflation during pressure-control ventilation. Am Rev Respir Dis 1992; 146:1411-1418.
15. Burke WC, Nahum A, Ravenscraft SA, et al: Modes of tracheal gas insufflation. Am Rev Respir Dis 1993; 148:562-568.
16. Nahum A, Ravenscraft SA, Nakos G, et al: Effect of catheter flow direction on CO_2 removal during tracheal gas insufflation in dogs. J Appl Physiol 1993; 75:1238-1246.
17. Dolan S, Derdak S, Solomon D, et al. Tracheal gas insufflation combined with high-frequency oscillatory ventilation. Crit Care Med 1996; 24: 456-465.
18. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Le Call JR, Morris A, Spragg R, and the Consensus Committee. The American-European Consensus Conference on ARDS. Definition, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-824.
19. Elsasser S, Schachinger H, Strobel W. Adjunctive drug treatment in severe hypoxic respiratory failure. Drugs 1999; 58: 429-446.
20. Derdak S. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. Crit Care Med 2003; 31 [Suppl]: S317-S323.
21. Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position reduces lung stress and strain in severe ARDS. Eur Respir J 2005; 25: 534-544.
22. Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position improves expiratory airway mechanics severe chronic bronchitis. Eur Respir J 2005; 25: 259-268.
23. Prechter GC, Nelson SB, Hubmayr RD. The ventilatory recruitment threshold for carbon dioxide. Am Rev Respir Dis 1990; 141: 758-764.
24. Kondili E, Alexopoulou C, Prinianakis G, et al. Pattern of lung emptying and expiratory resistance in mechanically ventilated patients with chronic obstructive pulmonary disease. Intensive Care Med 2004; 30: 1311-1318.
25. Nakos G, Zakynthinos S, Kotanidou A, Roussos C. Tracheal gas insufflation reduces the tidal volume while $PaCO_2$ is maintained constant. Intensive Care Med 1994; 20: 407–413.
26. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998; 338:347-354.

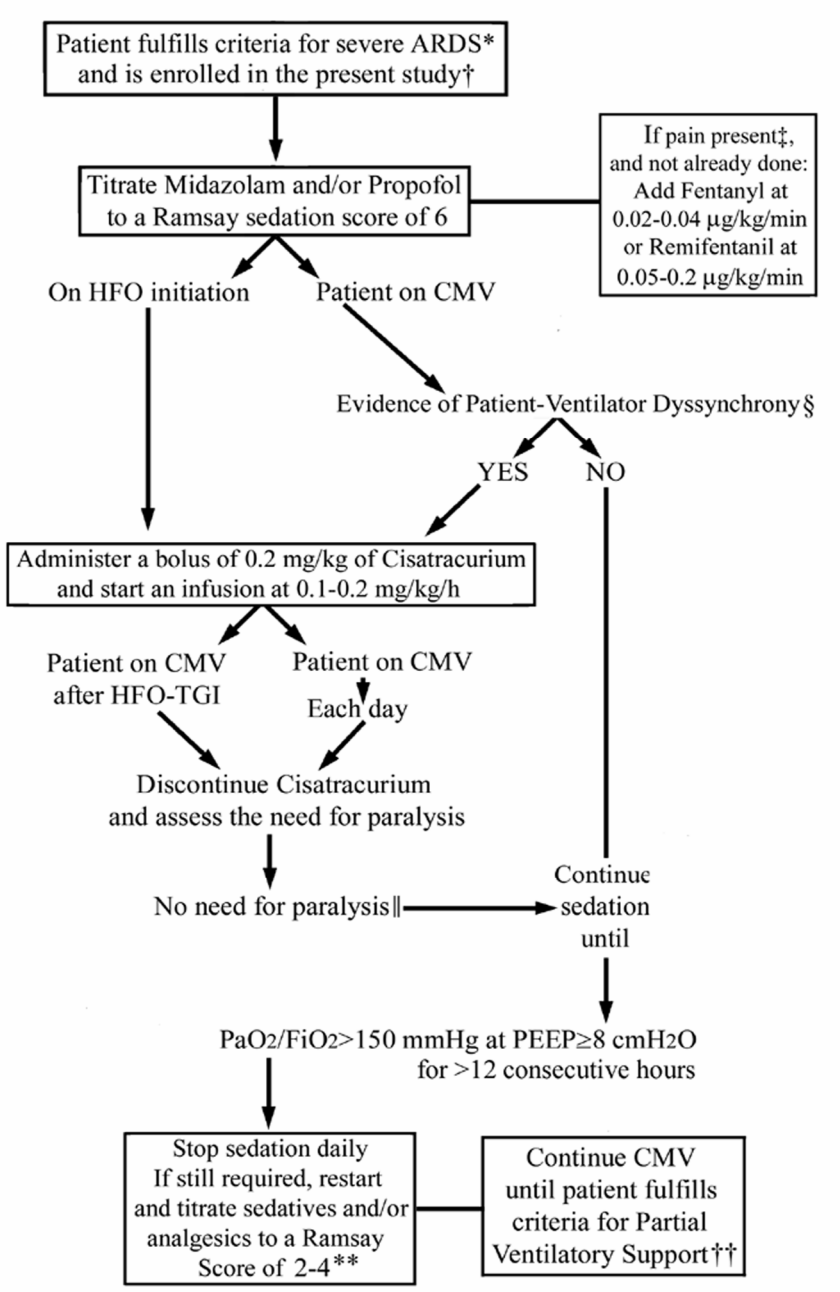

Figure 1. The proposed sedation protocol. ARDS, acute respiratory distress syndrome; HFO, high-frequency oscillation; CMV, conventional mechanical ventilation; TGI, tracheal gas insufflation; FiO_2, inspired O_2 fraction; PEEP, positive end-expiratory pressure.

*, PaO_2/FiO_2<150 mmHg, despite being ventilated at PEEP≥8 cmH_2O for >12 consecutive hours.

†, In both study centers, the standard management of sedation and paralysis of patients with ARDS is similar to the presented protocol.

‡, Refers mainly to trauma patients, and/or patients subjected to major surgery.

§, Defined as presence of spontaneous breathing efforts associated with increases in peak pressure of ≥5 cmH_2O.

‖, At the current ventilatory settings, the pre-specified gas exchange and plateau pressure targets of CMV (see text and Table 1) are achievable for ≥60 min after the discontinuation of cisatracurium; in addition, there is no patient-ventilator dyssynchrony.
**, Restart intravenous sedation according to the fulfillment of ≥1 of the following criteria: 1) Ramsay score=1; 2) respiratory rate rises to >40/min for >30 min due to patient-triggered breaths; and 3) patient-ventilator dyssynchrony ensues, with or without failure to achieve the pre-specified gas exchange targets of CMV (see text) at the current ventilatory settings.
††, These criteria are presented in Figure 4.

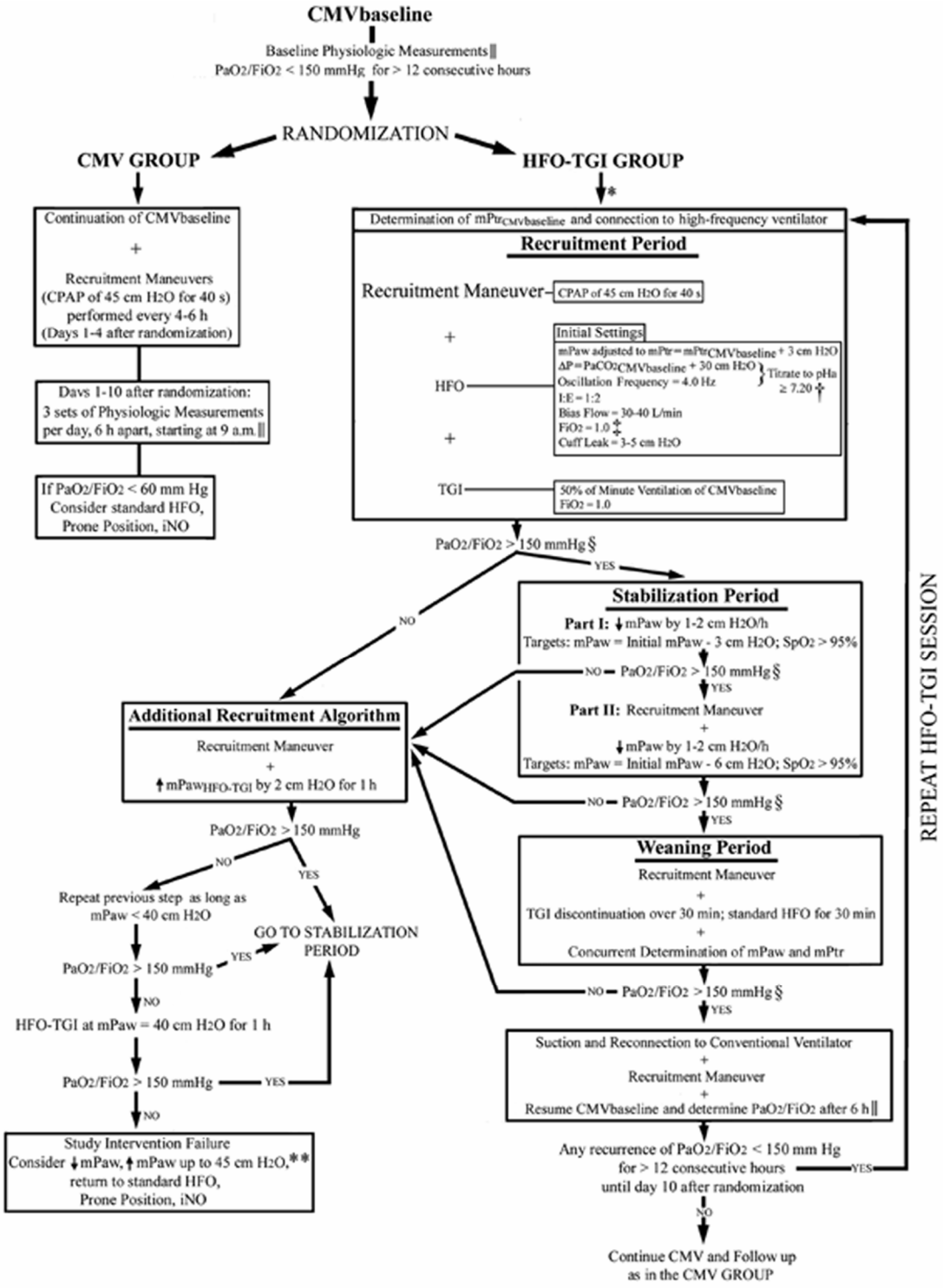

Figure 2 (please see next page for dedicated legend)

*, Initiate HFO-TGI if patient fullfils the pre-specified criterion for severe oxygenation disturbance.

†, Perform 2 ABG analyses within 30 min of HFO-TGI initiation and titrate f and ΔP to a pHa of at least 7.20.

‡, High Frequency Ventilator FiO2=1.0 during the Recruitment Period, during the Application of the Additional Recruitment Algorithm, during the 15-min periods that preceded physiologic measurements, and during the 5-min periods of the physiologic measurements.
During the Stabilization Period, FiO2 = 80%, 70%, 60% if PaO2/FiO2 of immediately preceding physiologic measurement = 150-200, 200-300, and > 300 mmHg (respectively).

§, Perform physiologic measurements (arterial and central-venous blood gas analysis and hemodynamics) at that time-point.

‖, Perform physiologic measurements (blood-gas analyses, hemodynamics, and respiratory mechanics with end-inspiratory/expiratory airway occlusion) at that time-point.

**, Consult immediately with a supervising investigator on how to proceed with the Intervention Failure Algorithm.

ABORT RECRUITMENT MANEUVER IN CASE OF 1) HYPOTENSION: SYSTOLIC PRESSURE < 90 MMHG; MEAN PRESSURE <60 MMHG; 2) DESATURATION: SPO2 <85% OR ABSOLUTE SPO2 DROP >5%.
IF NECESSARY, TREAT HYPOTENSION AND/OR ASSOCIATED DROP IN CARDIAC OUTPUT WITH FLUIDS AND VASOPRESSORS.
JUST PRIOR TO RETURN TO CMV, A BRIEF ENDOSCOPIC INSPECTION OF THE TRACHEA WILL BE CARRIED OUT.

Abbreviations: CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; CPAP, continuous positive airway pressure; mPaw, mean airway pressure; mPtr, mean tracheal pressure; ΔP, oscillatory pressure amplitude; I:E, inspiratory-to-expiratory time ratio; FiO2, inspired oxygen fraction; ABG=arterial blood gas; SpO2, peripheral oxygen saturation; iNO, inhaled nitric oxide.

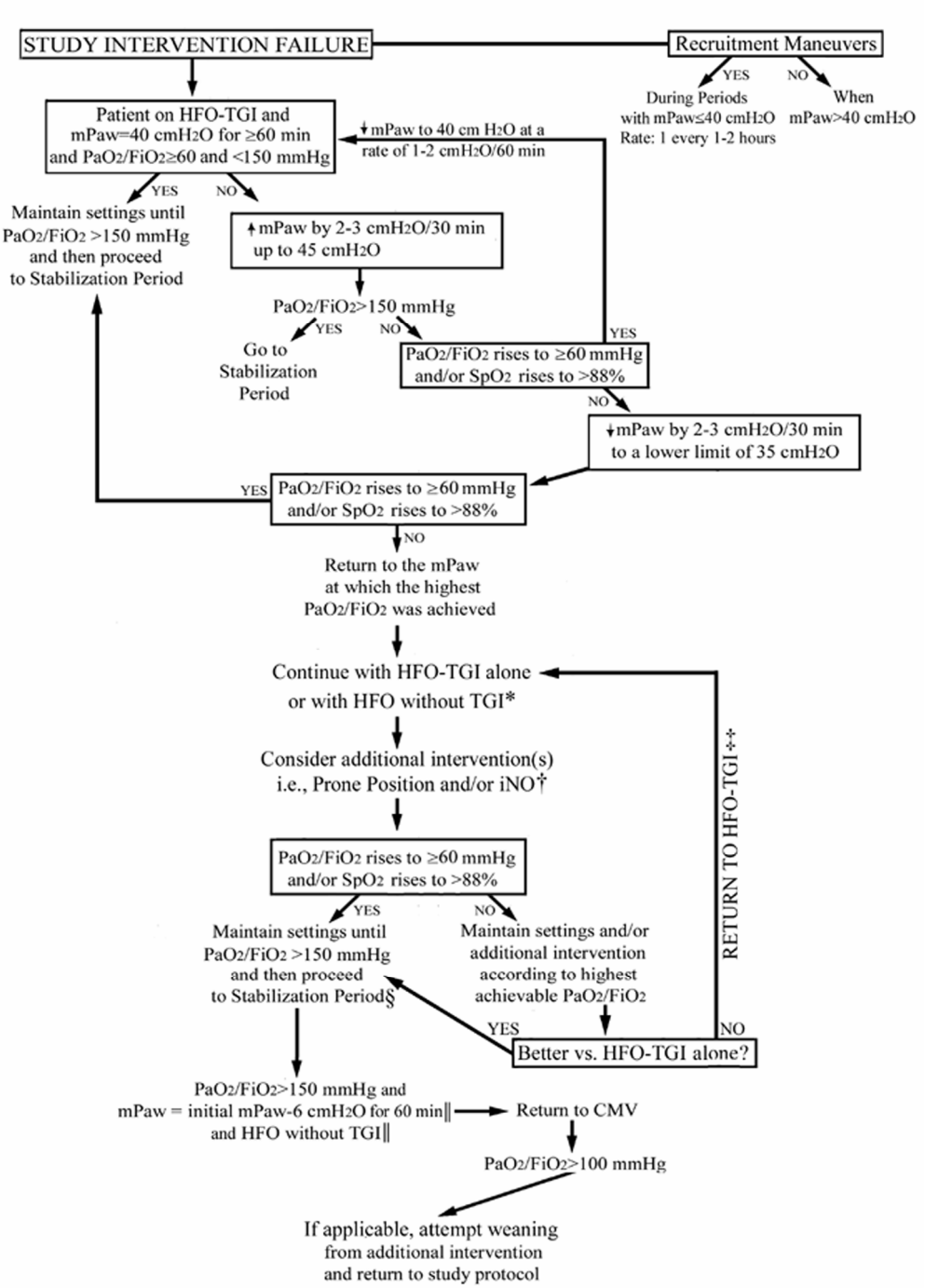

Figure 3. Proposed algorithmic actions and options for the case of Study Intervention Failure. HFO, high-frequency oscillation; TGI, tracheal gas insufflation; mPaw, mean airway pressure; FiO_2, inspired O_2 fraction; SpO_2, peripheral O_2 saturation; iNO, inhaled nitric oxide. An arterial blood gas analysis will be performed and hemodynamic data will be recorded at 30 min after every change in high-frequency ventilator mPaw, or TGI, or use of an additional intervention.

*, If applicable, consider HFO without TGI after taking into account the oxygenation response to TGI discontinuation during the weaning period of the preceding HFO-TGI session.

†, Defined as additional interventions; the use of these interventions will have to be approved by the attending physicians.

‡, If applicable, return to the supine position from prone, or discontinue iNO, or both; if on HFO without TGI, restart TGI at its initial setting of 50% of the minute ventilation of the conventional mechanical ventilation that preceded the HFO-TGI session.
§, If on HFO without TGI, follow all steps of the HFO-TGI protocol (apart from the discontinuation of TGI) as presented in Figure 2.
‖, This time point corresponds to the end of the weaning period of the HFO-TGI session, i.e., 60 min after the reaching of the protocol-pre-specified target mPaw, which is 6 cmH_2O lower than the initial mPaw used at the start of the HFO-TGI session (see also Figure 2).

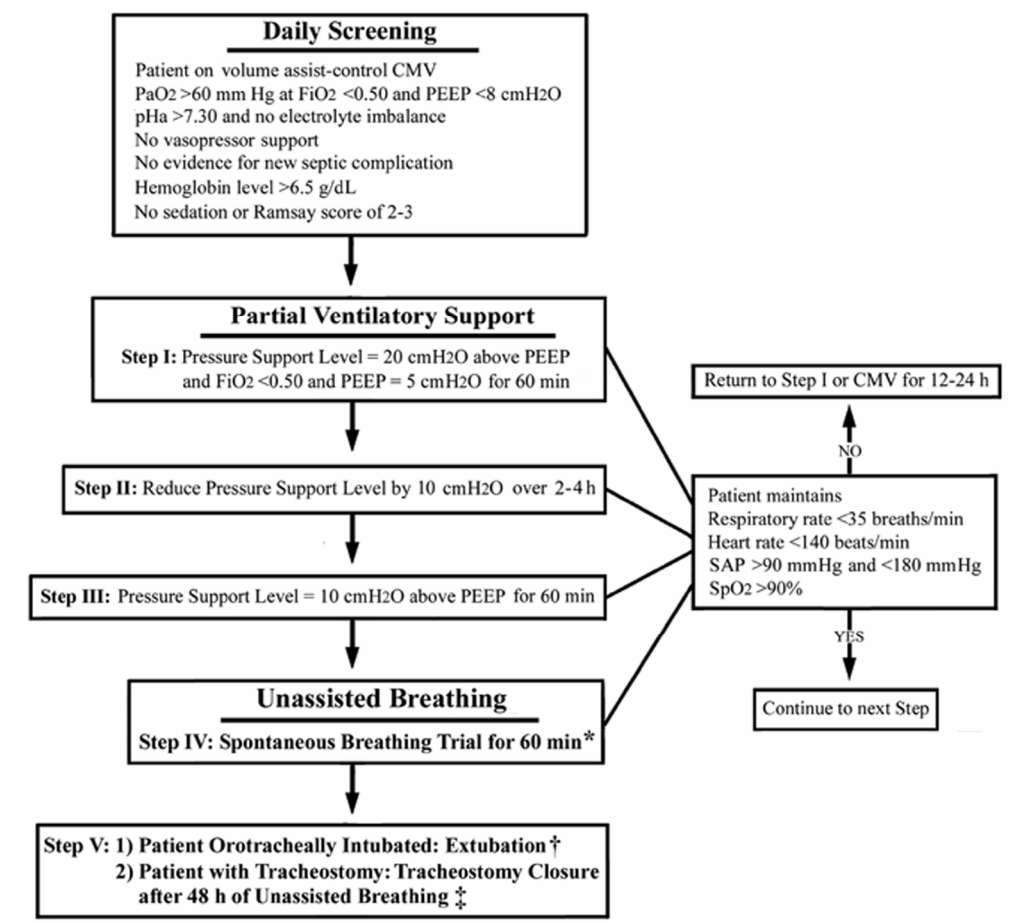

Figure 4. Schematic representation of the proposed weaning protocol. CMV, conventional mechanical ventilation; FiO_2, inspired O_2 fraction; PEEP, positive end-expiratory pressure; pHa, arterial-blood pH; SAP, systolic arterial pressure; SpO_2, peripheral O_2 saturation. Continuous lines correspond to the clinical evaluation detailed in the dedicated box. For steps I-III, the "transition to the next step" corresponds to successful gradual withdrawal of ventilatory support. The transition from step IV to step V corresponds to a successful spontaneous breathing trial.

*, At the end of a successful spontaneous breathing trial confirm that PaO_2>60 mmHg and pHa>7.30 by arterial blood gas analysis.

†, In case of recurrence of respiratory failure, reintubate and consider tracheostomy.

‡, In case of patient failure to tolerate spontaneous breathing for 48 consecutive hours, return to Step I or CMV for 12-24 hours; following tracheostomy decannulation, consider interim placement of a minitracheostomy tube to facilitate suctioning of secretions.

TABLE 1. THE CONVENTIONAL VENTILATION STRATEGY

Ventilator mode	Volume assist-control
Target tidal volume (mL/kg predicted body weight) *	6.0 (with allowances from 5.5 to 7.5)
Target end-inspiratory plateau pressure (cm H_2O)	≤30 (with allowance of up to 35 †)
Ventilator rate (breaths/min) / Target pHa	16-35 / 7.20-7.45
Inspiratory-to-expiratory time ratio	1:2
Combinations of FiO_2 (%) / PEEP (cm H_2O) ‡	40 / 5-8; 50 / 8; 60 / 10; 70 / 10-14; 80 / 14; 90 / 16; 100 / 16-20
Target SpO_2 (%)	90-95
Target PaO_2 (mm Hg)	60-80
Recruitment maneuver §	CPAP of 45 cm H_2O for 20-40 s

FiO_2, inspired O_2 fraction; PEEP, positive end-expiratory pressure; SpO_2, peripheral O_2 saturation; CPAP, continuous-positive airway pressure. Patients will be ventilated through a 25-26-cm long endotracheal tube with an inner diameter of 8.0-9.0 mm.

*, Calculate as " = 50 + [Height (cm) – 152.4] x 0.91" and as " = 45.5 + [Height (cm) – 152.4] x 0.91" for males and females, respectively.

†, Whenever deemed necessary for achieving the lowest target pHa and/or SpO_2/PaO_2; in such cases, use tidal volumes of 5.5-6.0 mL/kg.

‡, Whenever the upper limit of the oxygenation targets is exceeded, reduce PEEP at a rate of 1-2 cm H_2O/hour (and accordingly adjust FiO_2) until reaching an SpO_2 of ≤95% and/or a PaO_2 of ≤80 mm Hg. During the first 10 days post-randomization, reverse and suspend (for 12 hours) the downward titrations if 1) starting plateau pressure and FiO_2 is ≤30 cm H_2O and ≤70%, respectively; and 2) they are associated with a PaO_2/FiO_2 decrease of >25% and a PaO_2/FiO_2 of <150 mm Hg.

§, Perform in the control (i.e., the conventional mechanical ventilation) group during the first 4 days after randomization at a rate of 1 every 3-6 hours.

Table 2. Proposed grading of bronchoscopic findings

Grade	Bronchoscopic Findings	Interpretation	Action
I	Pink and glistening tracheal mucosa	Normal; No TGI-related complication	None
II	Reddened and/or swollen mucosa with/without presence of purulent secretions	Probable respiratory infection during mechanical ventilation; No TGI-related complication	None
III	A. Hemorrhagic mucosa and/or presence of thrombotic material* B. Limited localized necrosis, especially at the carina †, and/or presence of necrotic mucosal slough C. Extensive localized necrosis, especially at the carina †, and/or presence of necrotic mucosal slough	Possible mucosal pealing, in conjunction with mechanical erosion of the submucosal vessels by the TGI jet stream; Suggests TGI-related complication §	Dicontinue TGI §

TGI, tracheal gas insufflation.

*, Any concurrent bleeding diathesis / coagulopathy could constitute an independent contributory factor.

†, Predicted to be probable site of impact of the TGI jet stream.

§, Exception: Grade IIIA findings attributable to tracheostomy performed within the preceding 6-24 hours.