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INTERMITTENT RECRUITMENT WITH HIGH-FREQUENCY OSCILLATION/TRACHEAL GAS INSUFFLATION IN ARDS

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ABSTRACT

Background: In acute respiratory distress syndrome (ARDS), recruitment sessions of high-frequency oscillation (HFO) and tracheal-gas insufflation (TGI) with short-lasting recruitment maneuvers (RMs) may improve oxygenation, and enable reduction of subsequent conventional mechanical ventilation (CMV) pressures. We determined the effect of adding HFO-TGI sessions to lung-protective CMV on early/severe ARDS outcome.

Methods: We conducted a prospective, clinical trial, subdivided in a first, single-center period and a second, two-center period. We enrolled 125 (first period, n=54) patients with PaO_2/inspired O_2 fraction (FiO_2)<150 mmHg for >12 consecutive hours at end-expiratory pressure≥8 cmH_2O. Patients were randomly assigned to HFO-TGI-group (n=61, receiving HFO-TGI sessions with RMs, interspersed with lung-protective CMV) or CMV-group (n=64, receiving lung-protective CMV and RMs). Primary outcome was survival to hospital-discharge.

Results: Pre-enrollment ventilation-duration was variable. During days 1-10 post-randomization, PaO_2/FiO_2, oxygenation index, plateau-pressure and respiratory compliance were improved in HFO-TGI-group vs. CMV-group (P<0.001 for group*time). Within days 1-60, HFO-TGI-group vs. CMV-group had more ventilator-free days {31.0 (0.0-42.0) vs. 0.0 (0.0-23.0), P<0.001}, and more days without respiratory, circulatory, renal, coagulation, and liver failure (P≤0.003). Survival to hospital-discharge was higher in HFO-TGI-group vs. CMV-group (38/61, 62.3% vs. 23/64, 35.9%, P=0.004).

Conclusions: Intermittent recruitment with HFO-TGI and RMs may improve survival in early/severe ARDS.

Trial Registration: *ClinicalTrials.gov identifiers: First period: NCT00416260; Second period: NCT00637507.*

INTRODUCTION

High-frequency oscillation (HFO) is suggested for adults with severe acute respiratory distress syndrome (ARDS) [1,2]. During HFO, tidal volumes of <3.5 mL/kg predicted body weight are administered at ≥3 Hz [1-3]; mean airway pressure (mPaw) ranges within 22-40 cmH_2O [1-3]. Animal lung injury data favor HFO over lung-protective, conventional mechanical ventilation (CMV) [4]. The low HFO tidal volumes minimize volutrauma, and the high HFO-mPaw limits atelectrauma [2,5].

When combined with 40-s-lasting recruitment maneuvers (RMs), HFO improves oxygenation vs. lung-protective CMV, likely through lung recruitment [6-8]. The short-term addition of tracheal gas insufflation (TGI) to HFO may further improve oxygenation vs. HFO without TGI and lung-protective CMV [7,8]. TGI may promote

lung recruitment by exerting a positive end-expiratory pressure (PEEP) effect and augmenting HFO-dependent, distal gas-mixing [7-10].

We reasoned that a lung-protective, CMV-based ventilatory strategy employing extended (i.e. ≥6 hours) and repetitive (according to pre-specified criteria) recruitment sessions of HFO-TGI with RMs could result in a progressively sustained oxygenation improvement, with minimal, concurrent risk of long-term HFO-TGI-related adverse effects [2,7,10]. This should enable rapid reduction of subsequent CMV pressures to non-injurious levels [11]. A reduced lung end-inspiratory stretch could attenuate ventilator-associated lung injury [12,13], and improve outcome [14]. Thus, we compared the effect of 2 recruitment strategies during lung-protective CMV, namely HFO-TGI sessions with short-lasting RMs vs. solely short-lasting RMs, on the survival of patients with early/severe ARDS.

METHODS

Patients

The study was approved by the Scientific Committees of Evaggelismos hospital and Larissa University hospital. Informed, written next-of-kin consent was obtained for patients fulfilling the eligibility criteria presented in eTable 1 of the electronic supplement (eSupplement). Patients had early (onset within ≤72 hours) ARDS [15] and severe oxygenation-disturbances: PaO_2/inspired O_2 fraction (FiO_2)<150 mmHg for >12 consecutive hours with positive end-expiratory pressure (PEEP)≥8 cmH_2O; ARDS mortality increases at PaO_2/FiO_2<150 mmHg [16]. We employed deep sedation and intermittent neuromuscular blockade with cisatracurium [12]. The sedation/paralysis and weaning (from CMV) protocols are detailed in eSupplement.

Study Design and Randomization

We conducted a prospective, randomized, unblinded, parallel-group, controlled trial, temporally subdivided in a first, single-center and a second, two-center period for feasibility reasons (eSupplement). The 37-bed intensive care unit (ICU) of Evaggelismos hospital participated in both periods. The 10-bed ICU of Larissa hospital participated in the second period. Following consent, patients were allocated to the intervention (HFO-TGI) or control (CMV) group according to computer-generated, odd and even random numbers, respectively.

HFO-TGI group received recruitment sessions of HFO-TGI with RMs according to pre-specified oxygenation criteria. HFO-TGI sessions were interspersed with lung-protective CMV without RMs (Table 1). CMV group received lung-protective CMV, and RMs for days 1-4 post-randomization (Table 1); the likelihood of sustained, RM-induced oxygenation improvement decreases and the risk of RM-hemodynamic complications increases with CMV-time [17]. In HFO-TGI group, RMs were used after day 4 as part of the HFO-TGI protocol; RM-related, oxygenation benefits are maintained when RMs are followed by HFO, even when HFO-time exceeds 4 days [6]. During days 1-4, minimum RM frequency was 4/day in both groups. Figure 1 illustrates the study protocol.

HFO-TGI recruitment protocol

HFO was provided by the 3100B high-frequency ventilator (Sensormedics, Yorba Linda, CA). The goal of each HFO-TGI session was to increase PaO_2/FiO_2 to >150 mmHg by using a high initial mPaw (recruitment period), and then maintain the oxygenation benefit during a gradual mPaw reduction to 6 cmH_2O below its initial

value (stabilization period) and during weaning from TGI and HFO (weaning period). Additional protocol features are described in eSupplement.

Recruitment period-initial setting of HFO-mPaw. A rigid-wall catheter (inner diameter=1.0 mm, outer diameter=2.0 mm) was introduced during CMV. In each patient, catheter length was tailored to catheter tip placement at 0.5-1.0 cm beyond tracheal tube tip. CMV-mean tracheal pressure was determined through the catheter with Direc218B (Raytech Instruments, Canada) over 3-min periods preceding transition to HFO. Patients were connected to the high-frequency ventilator, and an RM was performed. Subsequently, a tracheal tube cuff-leak of 3-5 cmH_2O was placed, and mean tracheal pressure was re-measured**.** High-frequency ventilator-displayed mPaw (HFO-mPaw) was titrated to an HFO-mean tracheal pressure that exceeded preceding CMV-mean tracheal pressure by 3 cmH_2O. This resulted in an average HFO-mPaw of 8-9 cmH_2O above the preceding average CMV-mPaw, because the average, high inspiratory flow-related drop [8] in HFO-mPaw along the tracheal tube was approximately 6 cmH_2O.

TGI initiation. Following setting of initial HFO-mPaw, the catheter was proximally connected to a variable-orifice O_2 flowmeter providing pure, humidified O_2 at room temperature. Continuous, forward-thrust TGI was initiated through the catheter {TGI-flow=50% of preceding CMV minute ventilation [10]}. TGI initiation caused a 1-2-cmH_2O increase in HFO-mPaw, which was reversed by adjusting mPaw valve [10].

Recruitment period duration. If at 60-90 min after HFO-TGI initiation PaO_2/FiO_2 exceeded 150 mmHg, we proceeded to stabilization period. Otherwise, the "additional recruitment algorithm" was applied, and the recruitment period extended until

PaO_2/FiO_2 exceeded 150 mmHg and/or mPaw reached 40 cmH_2O (Figure 1). High-frequency ventilator FiO_2 was kept at 100% throughout this period.

Stabilization period-targeted HFO-mPaw reduction. mPaw was gradually (rate=1-2 cmH_2O/h) reduced to 3 cmH_2O below its initially-set value. If PaO_2/FiO_2 remained >150 mmHg, an RM was performed and mPaw was decreased by another 3 cmH_2O at 1-2 cmH_2O/h. If PaO_2/FiO_2 was still >150 mmHg, we proceeded to weaning period. Whenever these downward mPaw-titrations resulted in PaO_2/FiO_2<150 mmHg, the "additional recruitment algorithm" was followed (Figure 1). The pre-specified minimum duration of stabilization period was 240 min.

Ventilator-FiO_2 was reduced to 80%, 70%, and 60% if the PaO_2/FiO_2 of the immediately preceding physiologic measurement was 150-200, 200-300, and >300 mmHg, respectively. Prior to and during each subsequent physiologic measurement, ventilator-FiO_2 was set at 100% (for 20 min). This enabled precise determination of PaO_2/FiO_2 during ongoing TGI.

Weaning period-discontinuation of TGI and HFO. An RM was performed and TGI was discontinued over 30 min; the associated HFO-mPaw reduction of 1-2 cmH_2O was reversed by adjusting mPaw valve. Patients were ventilated with standard HFO for another 30 min, and if PaO_2/FiO_2 was >150 mmHg, they were returned to CMV. If PaO_2/FiO_2 was <150 mmHg, patients were returned to the "additional recruitment algorithm" (Figure 1).

HFO-TGI session duration. The minimum time from HFO initiation to HFO termination was 6 hours. Each transition to "additional recruitment algorithm" (Figure 1) extended the session by ≥2-3 hours. After every 12-24 hours of HFO-TGI, a brief

bronchoscopic inspection of the carina was performed to rule out TGI-induced tracheal mucosal damage.

Return to HFO-TGI. The criterion was PaO_2/FiO_2<150 mmHg sustained for >12 consecutive hours, while on CMV. Patients were assessed for return to HFO-TGI at 12 and 24 hours after return to CMV, and then, on the beginning of each day until day 10 post-randomization.

Definitions

Definitions of organ/system failures according to corresponding sequential organ failure assessment (SOFA) subscore≥3 [18], infections, and other complications are provided in eSupplement. Multiple organ failure (MOF) was defined as ≥3 concurrent organ/system failures [19].

Follow-up

Baseline patient data were recorded within 2 hours pre-randomization. Daily recordings included physiologic/laboratory data (days 1-28 post-randomization), intervention-associated complications (days 1-10; examples: RM-induced hypotension or desaturation), mechanical ventilation-associated barotrauma [study-independent radiologists assessed chest radiographs for pathologic gas collection(s), e.g. pneumothorax], data on organ/system failures and medication (days 1-60), episodes of failure to maintain unassisted breathing and various complications (until hospital-discharge or death; examples: infections, heparin-induced thrombocytopenia). Investigators were unblinded to patient outcomes. Adherence to protocol was overseen by the Data Monitoring Committee.

During days 1-10, sets of physiologic measurements were obtained as follows: 1) CMV group: 3 measurements/day, starting at 9 a.m. 2) HFO-TGI group: just before,

during, and 6 hours after HFO-TGI, and as in CMV group if no longer requiring HFO-TGI. Measurements included arterial/central-venous blood-gas analysis, hemodynamics, and respiratory mechanics while on CMV [7,12]. For between-group comparisons, we used CMV-data obtained within 9-10 a.m. in both groups.

Outcome Measures

Primary: survival to hospital-discharge, i.e. "patient discharged home, while breathing without assistance."

Secondary: ventilator-free and organ/system failure-free days to day 28 and 60, i.e., follow-up days within days 1-28 and 1-60 minus days on ventilator or days with organ/system failure (for survivors, minimum follow-up days=60); mechanical ventilation-associated barotrauma; TGI-related tracheal mucosal injury; evolution of oxygenation, plateau pressure, and respiratory compliance during the period of HFO-TGI use.

Statistical Analysis

Additional details are provided in eSupplement. According to pilot cohort data, the predicted survival-rate to hospital-discharge was 66% and 40% for the HFO-TGI group and CMV group, respectively. For alpha=0.05 and power=0.80 a total sample size of 124 patients was required. Interim analyses were conducted at the completion of the follow-up of the 84th and 104th patient; stopping rules were $P<0.001$ for efficacy and $P>0.1$ for futility. All study personnel were masked from interim analyses results.

An intention-to-treat analysis was performed with SPSS version 12.0 (SPSS, Illinois, USA) and SAS version 9.0 (SAS Institute, North Carolina, USA). Data are reported as mean±SD, or median (interquartile range), or number (percentage), unless

otherwise specified. Dichotomous and categorical variables were compared by Fisher's exact test. Continuous variables were compared by two-tailed, independent-samples t-test or Mann-Whitney exact *U*-test. The Bonferroni correction was used for multiple comparisons. For days 1-10, the effects of group, time, and group∗time, on physiological variables were determined by mixed-model analysis. Survival was analyzed with the Kaplan-Meier method and survival data were compared by Fisher's exact test and log-rank test. Cox regression was used to determine independent predictors of death. The effect of center was assessed by between-center comparisons for study endpoints. Reported P-values are two-sided. Significance was accepted at $P<0.05$.

RESULTS

The study was conducted from July 1, 2006 to September 29, 2007 (first period, n=54) and from March 10, 2008 to May 30, 2009 (second period, n=71). From 171 potentially eligible patients, 125 were randomized (HFO-TGI group, n=61; CMV group, n=64) and their data analyzed (Figure 2). Sixteen of the 46 (34.8%) excluded patients survived to hospital discharge.

Table 2 displays baseline characteristics. Eighty five patients (68.0%; HFO-TGI group, n=40) had MOF. The HFO-TGI intervention period extended to day 10 post-randomization. Table 3 displays data on daily HFO-TGI; session duration ranged within 6.0-102.2 hours.

Physiological variables during intervention period

Results are summarized in Table 4. There was no significant between-group difference in hemodynamics, arterial-blood lactate, and hemodynamic support. Measures of oxygenation (PaO_2/FiO_2 and oxygenation index) and lung mechanics

(plateau pressure and respiratory compliance) improved substantially over days 1-10 in HFO-TGI group (Table 4 and Figure 3A-3D).

Response to HFO-TGI. Pre-session PaO_2/FiO_2 rose from 110.6±32.0 mmHg to 256.1±93.1 mmHg during the recruitment period (maximum duration=8.5 hours). Oxygenation improvement was primarily due to the high mPaws, RMs, and TGI [7,8] (Figure 1). Subsequently, PaO_2/FiO_2 fell to 221.0±82.3 mmHg (end of stabilization period), and to 172.2±33.4 mmHg (weaning period, 30 min after TGI discontinuation; eFigure 5 of eSupplement). The initial mPaw was reduced by 6 cmH_2O within 5.5±0.6 and 16.3±14.4 hours in 124 and 93 of 223 HFO-TGI sessions, respectively. HFO-TGI resulted in significant improvements in post-session vs. pre-session oxygenation and lung mechanics, and did not affect hemodynamics or $PaCO_2$ vs. preceding CMV (details provided in the text and eFigure 6 of eSupplement). Intervention failure (Figure 1) occurred in 6 sessions (eSupplement).

Intervention-associated complications

Within days 1-4, HFO-TGI group and CMV group patients received 4.7±3.5 and 4.7±1.5 RMs/day, respectively (P=0.79); RM-abort rates due to hypotension or desaturation (eSupplement) were ~6% in both groups. Within days 5-10, 19 HFO-TGI group patients received 2.0±2.2 RMs/day, and RM-abort rate was 16.5%; this exclusive RM-use had no significant effect on study outcomes (eSupplement). On HFO-TGI initiation, 10 patients (16.7%) experienced once RM-associated, major drops in systolic pressure to 75.1±5.4 mmHg (average drop=28.0±7.2%) and cardiac index to 2.4±0.6 L/min/m^2 (average drop=26.0±11.4%). In 9 patients, hemodynamic status was restored within ≤10 min with fluids and vasopressors. In 1 patient, a chest tube was inserted for tension pneumothorax. Five patients (HFO-TGI group, n=3)

experienced once an RM-associated, prolonged (duration=3-5 min) desaturation (maximum absolute drop in oxygen saturation=7-17%), which was reversed within ≤5 min after RM discontinuation. In 1 patient, day-10 bronchoscopy revealed a hemorrhagic posterior tracheal mucosa, suggesting TGI-induced mucosal damage (eSupplement).

Clinical course data

Within days 1-60, HFO-TGI group vs. CMV group had more ventilator-free days {31.0 (0.0-42.0) vs. 0.0 (0.0-23.0), P<0.001}, and more days without respiratory {46.0 (2.0-54.0) vs. 5.0 (0.0-33.8), P=0.001}, coagulation {60.0 (21.5-60.0) vs. 17.0 (5.3-60.0), P=0.003}, liver {60.0 (28.5-60.0) vs. 24.5 (6.3-60.0), P=0.003}, circulatory {43.0 (2.0-55.0) vs. 6.5 (0.0-39.0), P=0.001}, renal {60.0 (12.0-60.0) vs. 15.5 (2.0-60.0), P=0.001}, and nonpulmonary organ failure {29.0 (0.0-46.5) vs. 0.0 (0.0-30.8), P=0.001}; results were similar for days 1-28 (eSupplement).

During days 1-10, SOFA score improved in HFO-TGI group (Table 4 and Figure 3E). Within days 1-60, HFO-TGI group vs. CMV group had more follow-up days {60.0 (28.5-60.0) vs. 24.5 (7.0-60.0), P=0.001}, lower proportions of follow-up days with MOF {11.7% (1.7-69.1) vs. 51.0% (11.3-100.0), P=0.002}, less frequent MOF occurrence in patients without MOF at baseline {7/21 (33.3%) vs. 15/19 (78.9%), P=0.005; respective times of occurrence 4.7±5.1 vs. 8.5±6.6 days post-randomization, P=0.20}, similar absolute number of days on ventilator (20.1±13.3 vs. 20.4±15.9, P=0.90), and more patients {42/61 (68.9%) vs. 26/64 (40.6%), P=0.002} achieving unassisted breathing for ≥48 hours (i.e. successful weaning) in shorter time {21.4±10.0 vs. 30.9±12.8 days, P=0.001 (Figure 3F)}.

Throughout study period, HFO-TGI group vs. CMV group had 24.3±20.9 vs. 22.3±20.0 total days on ventilator (P=0.60), and 35.0 (18.0-61.5) vs. 21.0 (7.0-57.3) total days of inhospital follow-up (P=0.07). HFO-TGI group vs. CMV group had comparable percentages of patients with occurrence of barotrauma as new pneumothorax {6/61 (9.8%) vs. 9/64 (14.1%), P=0.59}, and ≥1 episode of ventilator-associated pneumonia {(VAP) 49.2% vs. 50.0%, P>0.99}, catheter-related bacteremia (21.3% vs. 18.8%, P=0.82), Gram negative sepsis (59.0% vs. 48.4%, P=0.28), renal (32.8% vs. 37.5%, P=0.71), coagulation (24.6% vs. 26.6%, P=0.84), hepatic (9.8% vs. 9.4%, P>0.99), and neurologic failure (52.5% vs. 46.9%, P=0.59), heparin-induced thrombocytopenia (16.4% vs. 18.8%, P=0.82), failure to maintain unassisted breathing (47.5% vs. 32.8%, P=0.10), and paresis (18.0% vs. 15.6%, P=0.81). VAP-occurrence was not a predictor of successful weaning but prolonged the mean time to its achievement by ~8-9 days in both groups (eSupplement). Further details on complications, and data on administered medication and rescue oxygenation {used in 6/64 CMV group patients (9.4%)} are provided in eSupplement.

During days 1-28, CMV protocol violations corresponded to 6.3% vs. 3.8% of the follow-up time in HFO-TGI group and CMV group, respectively, P=0.004. The HFO-TGI algorithm was applied without deviation in 202 sessions (90.1%). The CMV group RM protocol was accurately applied in 98.8% of the corresponding patient-days. There was no between-group crossover. Study center did not affect study outcomes (data not shown).

Survival

Survival to hospital-discharge was higher in HFO-TGI group vs. CMV group {38/61, 62.3% vs. 23/64, 35.9%, P=0.004 by Fisher's exact test; (Figure 4)}. There

was no significant, between-group difference in the ICU and hospital stays of survivors and non-survivors (Figure 4, inset), or the survival of patients with pulmonary contusion-associated ARDS {HFO-TGI group vs. CMV group: 13/22 (59.1%) vs. 8/12 (66.7%), P=0.72 (eSupplement)}. Death attributable to MOF [19] was less frequent in HFO-TGI group vs. CMV group {8/61 (13.1%) vs. 22/64 (34.4%), P=0.006 (eSupplement)}. Independent predictors of in-hospital mortality included assignment to CMV group {hazard ratio (HR)=2.64, 95% confidence interval (CI)=1.51-4.61; P=0.001}, baseline arterial-blood lactate (HR=1.16, 95% CI=1.06-1.28; P=0.002), and baseline simplified acute physiology score (SAPS) II (HR=1.04, 95% CI=1.00-1.06; P=0.003).

DISCUSSION

We showed an increased efficacy of intermittent HFO-TGI recruitment sessions in early (exhibiting high likelihood of lung-recruitability) and severe ARDS. During the recruitment period, the 2.3-fold average PaO_2/FiO_2 rise is consistent with enhanced lung recruitment [6-10,20]. This enabled reduction of the initial respiratory system distending pressure by 6 cmH_2O (stabilization period), with maintenance of approximately 85% of the oxygenation benefit. The evolution of compliance (Figure 3D) suggests progressive increase in aerated lung volume [20], which explains the concurrent plateau-pressure reduction (Figure 3C). These changes imply prompt inhibition of the injurious mechanical stresses to the lung [13,21], leading to prevention of biotrauma-associated organ injury [21], and improved survival.

In CMV group, the absence of physiological improvements (Figures 3A-3D) was associated with prolonged and multiple organ dysfunction during follow-up and a long-term mortality of 64.1% [19]. In a recent multicenter study [22], ARDS patients with similar baseline SAPS II scores and oxygenation disturbances had similar evolution of their respiratory variables and SOFA scores during early follow-up and a long-term mortality of 63.2%.

Prior trials evaluated continuous HFO [23,24], prone positioning [22,25,26], and high PEEP with/without recruitment maneuvers [27-29]. Positive findings comprised improved oxygenation [22,24-29], improved respiratory mechanics [26,27,29], lower rates of refractory hypoxemia [28,29], and more ventilator-free and organ failure-free days [29]. However, results on mortality were inconclusive. In contrast, our results on both physiology and outcome favor intermittent recruitment with HFO-TGI and RMs. This suggests improved lung protection throughout the early phase of ARDS through a more effective method of periodic lung recruitment.

We compared a recruitment strategy of combined HFO, TGI and short-lasting RMs to short-lasting RMs alone during lung-protective CMV. Theoretically, longer-lasting RMs could have produced different results. However, the best way to perform RMs still remains undetermined. Also, TGI usefulness is still unproven, and similar outcome results might have been obtained with an HFO-RMs recruitment protocol. Nevertheless, 3 physiological studies suggest a TGI-related, gas-exchange and/or lower lung recruitment benefit [7,8,30]. Furthermore, the present study's potentially non-protective HFO settings may augment lung base recruitment [8,30].

During days 1-10, the study protocol was applied by subgroups of 2 investigators assigned to each patient of each group on a rotating 12-hour basis. There was tighter

tidal volume control (Table 4) and accurate RM-protocol application in the CMV group. Medical treatment (including sedation/paralysis) was similar in both groups (eSupplement). Notable but promptly/effectively treated complications occurred in 13 (i.e. 5.8%) of the 223 HFO-TGI sessions (see Results).

Limitations

Sample size was relatively small, but the study was adequately powered to detect a substantial survival benefit. Study design was unblinded and results originate from just 2 centers, thus warranting further multicenter confirmation. Also, the study was conducted in 2 periods, primarily due to feasibility reasons (eSupplement). Lastly, although the high CMV group mortality and small number of ventilator-free days may be justifiable by disease severity, a selection bias in favor of the HFO-TGI group cannot be totally excluded.

Another limitation was the lack of measurement of proinflammatory cytokines during the intervention period. However, the causal link among persistence of ARDS, systemic inflammation, and development of multiple organ dysfunction/failure is well-established [31]. Furthermore, our physiological and SOFA score results (Figure 3) are consistent with this sequence of events occurring more frequently in the CMV group, with a consequent increase in the probability of death [19].

Pre-enrollment duration of mechanical ventilation (DMV) was variable (Table 2), with a potentially unpredictable impact on patient outcomes [30,32]. Indeed, although pre-enrollment DMV exceeded 7 days [33] in just 12 patients (9.6%; HFO-TGI group, n=8), the results of a recent multicenter trial imply that any difference in the overall management strategy of early ARDS might affect results on mortality [34].

Conclusions

Our two-center results suggest that in early/severe ARDS, the addition of recruitment sessions of HFO-TGI with RMs to lung-protective CMV may improve survival to hospital-discharge. This is supported by the associated improvements in respiratory physiology, ventilator free days, and nonpulmonary organ function.

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Study Organization. *Study Chairpersons:* Spyros D. Mentzelopoulos (principal investigator); Sotiris Malachias (principal investigator); Spyros G. Zakynthinos (study director), Charis Roussos (study chair), Zakynthinos E (collaborating center principal investigator). *Independent Main Endpoint and Safety Monitoring Committee:* Evaggelismos hospital: Panagiotis Politis, MD, Elissavet Stamataki, MD, PhD, and Zafiria Mastora, MD; Larissa University hospital: Zoi Daniil, MD, PhD. *Overall-study and data quality assurance:* Panagiotis Politis, MD, Elissavet Stamataki, MD, PhD, Zafiria Mastora, MD, Zoi Daniil, MD, PhD.

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FIGURE LEGENDS

Figure 1. Algorithmic representation of the study protocol. CMV, conventional mechanical ventilation; I:E, inspiratory-to-expiratory time ratio; pHa, arterial-blood pH; FiO_2, inspired O_2 fraction; SpO_2, peripheral O_2 saturation; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; CPAP, continuous positive airway pressure; mPaw, mean airway pressure; ΔP, oscillatory pressure amplitude; mPtr, mean tracheal pressure; iNO, inhaled nitric oxide. During HFO-TGI, recruitment maneuvers were performed with TGI turned off and the tracheal tube cuff inflated. Target SpO_2 was >95% for all periods (see also eSupplement); at any period, an SpO_2 of <88% for >5 min was to trigger immediate transition to the Additional Recruitment Algorithm, or to its next step if the desaturation occurred during its application.

Note that any transition to the Additional Recruitment Algorithm resulted in mPaw increase of ≥2cmH_2O, which had to be reversed after the subsequent transition to the stabilization period. This resulted in extension of the stabilization period by ≥1 hour.

*, Corresponds to the timing of the first set of daily physiologic measurements performed during CMV, prior to HFO-TGI initiation. By design, these measurements were to be performed at 9 a.m., unless the patient was already on HFO-TGI at that particular time (see also eSupplement).

†, Frequency and ΔP were adjusted to maintain a pHa of ≥7.20 by means of 2 consecutive arterial blood gas analyses performed within the first 30 min of the recruitment period.

‡, High-frequency ventilator FiO_2 was initially set at 100%; for further details regarding the management of FiO_2 see Methods.

§, Corresponds to the timing of physiologic measurements during the HFO-TGI session. In HFO-TGI sessions exceeding 6 hours, 1 additional set of physiologic measurements was obtained for every additional 2-4 hours.

‖, Corresponds to the timing of physiologic measurements performed during CMV, after weaning from TGI and HFO.

**, The corresponding, pre-specified management technique is presented in detail in the subsection "Additional features of the HFO-TGI protocol" of the eMethods of the eSupplement; recruitment maneuvers were not performed at mPaws of >40 cmH_2O. One recruitment maneuver was performed every 1-2 hours during periods with mPaws of 35-40 cmH_2O.

#, The temporal distance between any measurement and a preceding recruitment maneuver was ≥2 hours.

1 cmH_2O=0.098 kPa; 1 mmHg=0.133 kPa.

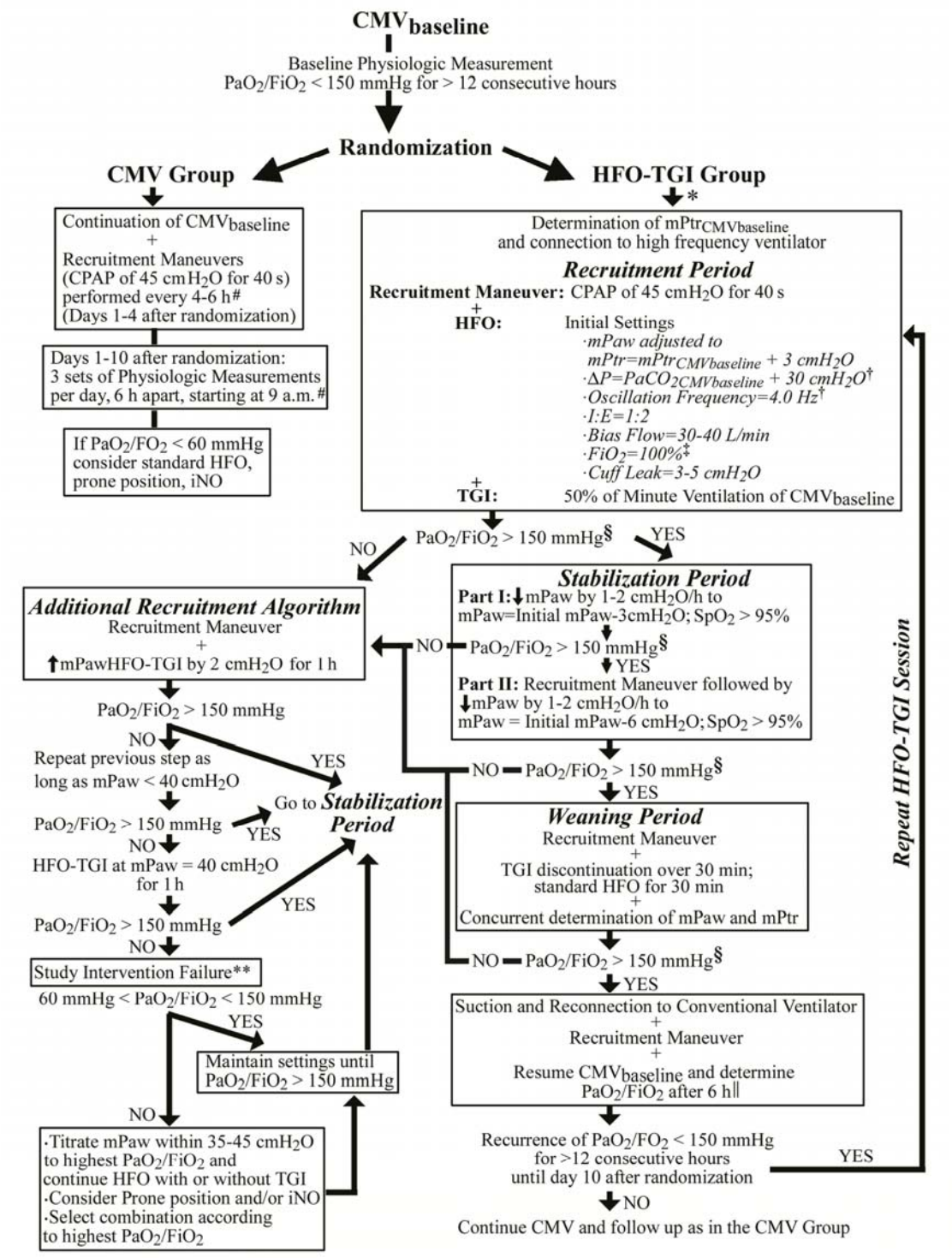
CMVbaseline
Baseline Physiologic Measurement
PaO2/FiO2 < 150 mmHg for > 12 consecutive hours
Randomization
CMV Group
HFO-TGI Group *
Continuation of CMVbaseline + Recruitment Maneuvers (CPAP of 45 cmH2O for 40 s) performed every 4-6 h# (Days 1-4 after randomization)
Days 1-10 after randomization: 3 sets of Physiologic Measurements per day, 6 h apart, starting at 9 a.m.#
If PaO2/FO2 < 60 mmHg consider standard HFO, prone position, iNO
Determination of mPtrCMVbaseline and connection to high frequency ventilator
Recruitment Period
Recruitment Maneuver: CPAP of 45 cmH2O for 40 s
+
HFO: Initial Settings
·mPaw adjusted to mPtr=mPtrCMVbaseline + 3 cmH2O
·ΔP=PaCO2CMVbaseline + 30 cmH2O†
·Oscillation Frequency=4.0 Hz†
·I:E=1:2
·Bias Flow=30-40 L/min
·FiO2=100%‡
·Cuff Leak=3-5 cmH2O
+
TGI: 50% of Minute Ventilation of CMVbaseline
PaO2/FiO2 > 150 mmHg§
NO
YES
Stabilization Period
Part I: ↓mPaw by 1-2 cmH2O/h to mPaw=Initial mPaw-3cmH2O; SpO2 > 95%
NO — PaO2/FiO2 > 150 mmHg§
YES
Part II: Recruitment Maneuver followed by ↓mPaw by 1-2 cmH2O/h to mPaw = Initial mPaw-6 cmH2O; SpO2 > 95%
NO — PaO2/FiO2 > 150 mmHg§
YES
Weaning Period
Recruitment Maneuver
+
TGI discontinuation over 30 min; standard HFO for 30 min
+
Concurrent determination of mPaw and mPtr
NO — PaO2/FiO2 > 150 mmHg§
YES
Suction and Reconnection to Conventional Ventilator
+
Recruitment Maneuver
+
Resume CMVbaseline and determine PaO2/FiO2 after 6 h‖
Recurrence of PaO2/FO2 < 150 mmHg for >12 consecutive hours until day 10 after randomization
YES
NO
Continue CMV and follow up as in the CMV Group
Repeat HFO-TGI Session
Additional Recruitment Algorithm
Recruitment Maneuver
+
↑mPawHFO-TGI by 2 cmH2O for 1 h
PaO2/FiO2 > 150 mmHg
NO
YES
Repeat previous step as long as mPaw < 40 cmH2O
PaO2/FiO2 > 150 mmHg
YES
Go to Stabilization Period
NO
HFO-TGI at mPaw = 40 cmH2O for 1 h
PaO2/FiO2 > 150 mmHg
YES
NO
Study Intervention Failure**
60 mmHg < PaO2/FiO2 < 150 mmHg
YES
Maintain settings until PaO2/FiO2 > 150 mmHg
NO
·Titrate mPaw within 35-45 cmH2O to highest PaO2/FiO2 and continue HFO with or without TGI
·Consider Prone position and/or iNO
·Select combination according to highest PaO2/FiO2

Figure 1

Figure 2. Study flow chart.

ARDS, acute respiratory distress syndrome; CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal-gas insufflation; RMs, recruitment maneuvers.

*, Definition provided in the footnote of eTable 1 of the eSupplement; additional pre-specified exclusion criteria not met by anyone of the 171 potentially eligible patients were active air leak or recent severe air leak, obstructive or interstitial lung disease, lung surgery on current admission, pregnancy, and dependency on prone positioning or inhaled nitric oxide (see eTable 1); the lower limits for age and body weight were 18 years and 40 kg, respectively.

†, The patient was transferred to another hospital not participating in the study on day 31 post-randomization. The data from this patient were included in the intention-to-treat analysis assuming that he died, because at the time point of transfer the patient was not discharged home and was not breathing without assistance (see also text for definition of "Hospital Discharge").

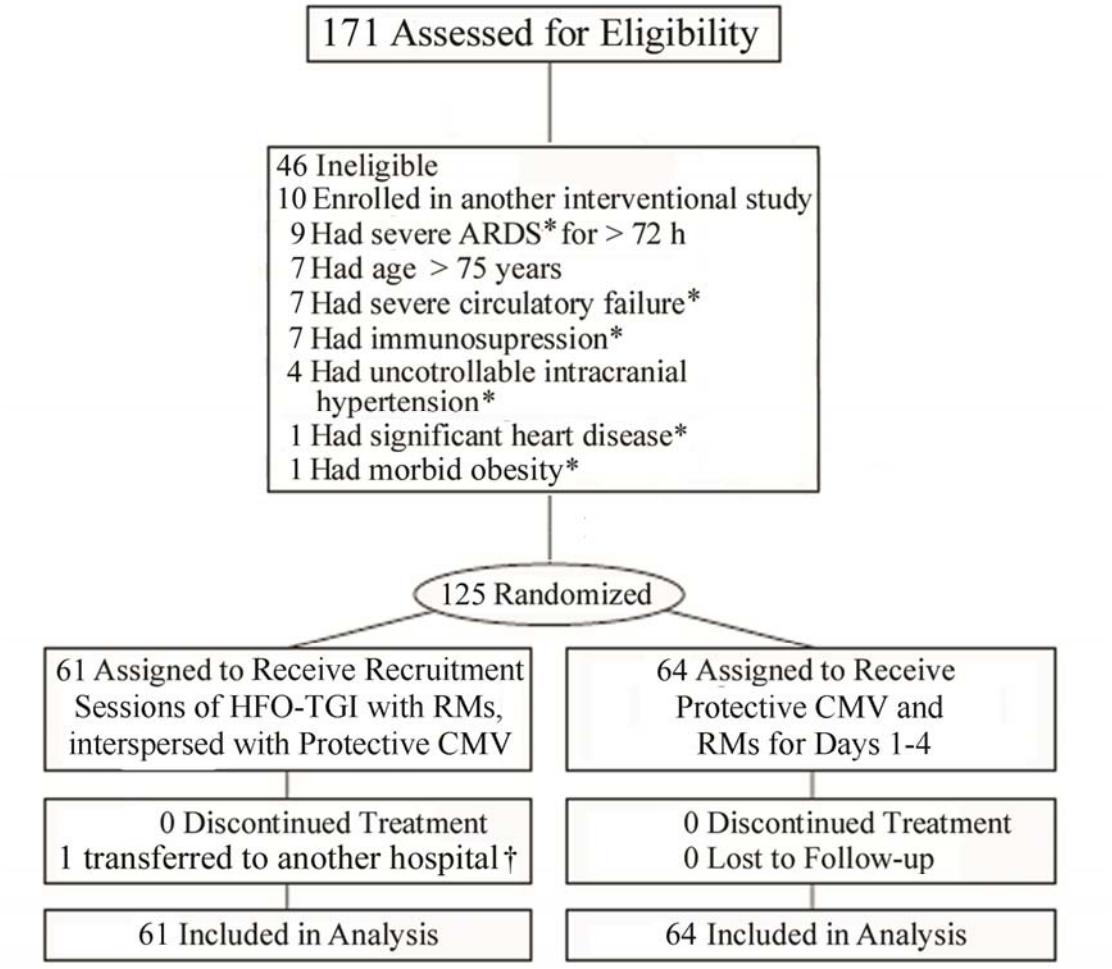

Figure 2

Figure 3. Results on major physiological variables (A-D), sequential organ failure assessment (SOFA) score (E), and probability of achieving unassisted breathing for ≥48 hours (F).

FiO_2, inspired O_2 fraction CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal-gas insufflation; BL, baseline.

A-D: Dots represent means of measurements obtained during CMV, within 2 hours before randomization (baseline), and within 9:00 and 10:00 a.m. of days 1-10 post-randomization. **E:** Dots represent the mean SOFA score at baseline, and at the time

points of the aforementioned physiological measurements; numbers represent surviving patients; 1 CMV group patient achieved unassisted breathing from day 6 and onward; 1, 2, 2, and 1 HFO-TGI group patients achieved respectively unassisted breathing from days 4, 7, 9, and 10 and onward, and 1 and 1 HFO-TGI group patients achieved respectively unassisted breathing for 72 hours starting from day 9 and unassisted breathing solely during day 9 (see also Table 3); the significant between-group difference observed on days 9 and 10 was partly due to the more frequent development of postrandomization multiple organ failure in the CMV group (see also text). **A-E:** Error bars represent SD. Summary results on PaO_2/FiO_2, oxygenation index, plateau pressure, compliance, and SOFA score are presented in Table 4. Between-group and within-group comparisons were subjected to the Bonferroni correction (see also footnote of Table 4 and the eSupplement).

Between-group comparisons:

*, P<0.05 vs. CMV-group at that particular time point.

Within-group comparisons:

†, P<0.05 vs. baseline.

‡, P<0.05 vs. baseline maintained from this point onward.

§, P<0.05 vs. day 2 maintained from this point onward.

1 mmHg = 0.133 kPa; 1 cmH_2O = 0.098 kPa.

F: Displayed P value corresponds to the results of the log rank test, which compares the probability of achieving unassisted breathing for ≥48 hours within days 1-60 post-randomization. Independent predictors of unassisted breathing for ≥48 hours within days 1-60 were assignment to CMV group (hazard ratio=0.37, 95% confidence interval (CI)=0.22-0.61; P<0.001).

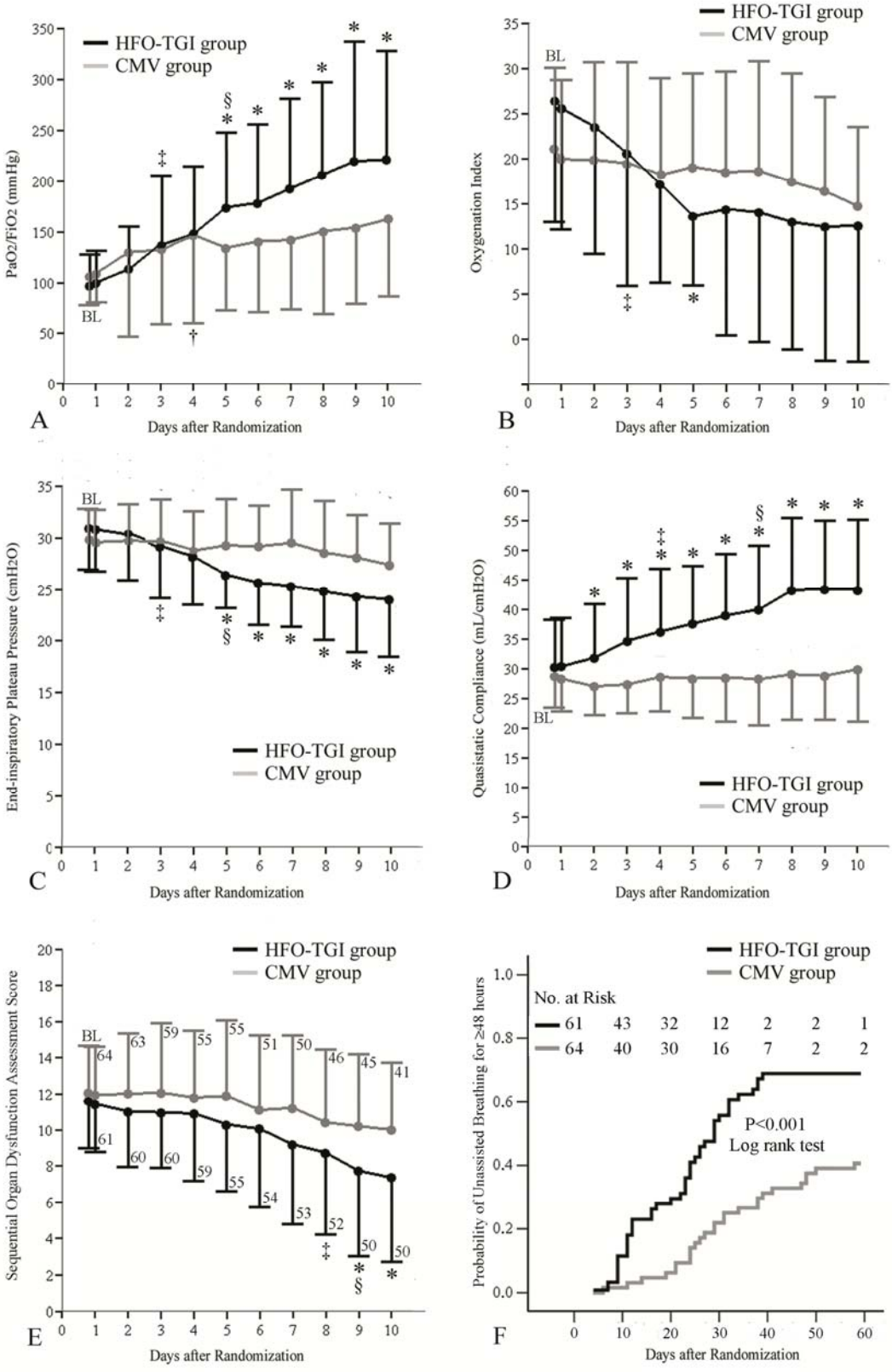
HFO-TGI group
CMV group
PaO2/FiO2 (mmHg)
BL
Days after Randomization
A
Oxygenation Index
B
End-inspiratory Plateau Pressure (cmH2O)
C
Quasistatic Compliance (mL/cmH2O)
D
Sequential Organ Dysfunction Assessment Score
E
No. at Risk
61 43 32 12 2 2 1
64 40 30 16 7 2 2
P<0.001
Log rank test
Probability of Unassisted Breathing for ≥48 hours
F

Figure 4. Results on survival.

CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal-gas insufflation; ICU, intensive care unit. The inset displays mean±SD data and corresponding P values for ICU and hospital stay of survivors and non-survivors

Regarding survival, P values correspond to the results of 1) the Fisher's exact test for the time point of hospital discharge; and 2) the log rank test, which compares the probability of death between the 2 groups throughout the follow-up period.

*, P=0.002 by Fisher's exact test for the 28-day survival.

†, P=0.001 by Fisher's exact test for the 60-day survival.

§, For patients with hospital stays of ≥60 days, follow-up was terminated at the time point of hospital discharge; the actual range of hospital stay was 17-137 days; patients discharged before day 60 (HFO-TGI group, n=25; CMV group, n=11) were followed as outpatients until day 60; the "surviving status" of all the 61 discharged patients at 150 days post-randomization was reconfirmed through telephone communication.

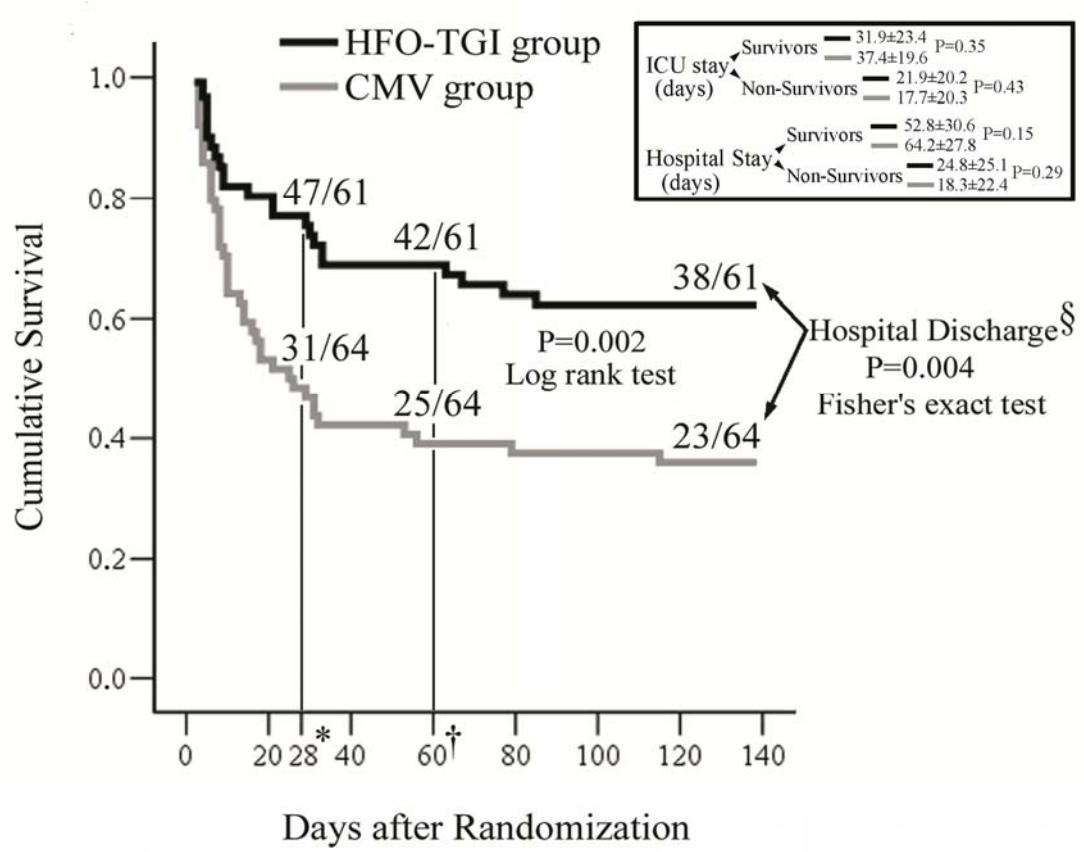
HFO-TGI group
CMV group
ICU stay (days)
Survivors 31.9±23.4 37.4±19.6 P=0.35
Non-Survivors 21.9±20.2 17.7±20.3 P=0.43
Hospital Stay (days)
Survivors 52.8±30.6 64.2±27.8 P=0.15
Non-Survivors 24.8±25.1 18.3±22.4 P=0.29
47/61
42/61
38/61
31/64
25/64
23/64
P=0.002
Log rank test
Hospital Discharge§
P=0.004
Fisher's exact test
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
28*
40
60†
80
100
120
140
Days after Randomization

Figure 4

Table 1. The conventional mechanical ventilation (CMV) 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 (cmH_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 (cmH_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 (mmHg)	60-80
Recruitment maneuver (RM) §,**,††	CPAP of 45 cmH_2O for 40 s

FiO_2, inspired O_2 fraction; PEEP, positive end-expiratory pressure; SpO_2, peripheral O_2 saturation; CPAP, continuous-positive airway pressure. Apart from the protocolized use of RMs, the presented CMV strategy reflects mainly standard clinical practice in both study centers.

*, 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 cmH_2O/h (and accordingly adjust FiO_2) until reaching an SpO_2 of ≤95% and/or a PaO_2 of ≤80 mmHg. 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 cmH_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 mmHg.

§, Perform in the control, i.e. the CMV group, during the first 4 days after randomization at a rate of 1 every 4-6 hours; increase post-RM PEEP by 2 cmH_2O, whenever the plateau pressure target of 30 cmH_2O is still achievable; within the following 60 min, if applicable, re-titrate PEEP and FiO_2 to the oxygenation targets as described above.

**, In the intervention, i.e. the high-frequency oscillation (HFO) and tracheal gas insufflation (TGI) group, identical RMs are to be used solely during sessions of HFO-TGI (see also Methods and Figure 1).

††, In both groups, before each RM, pre-oxygenate the patient by using an FiO_2 of 100% for ≥5 min to reduce the risk of RM-associated desaturation [6]; for additional details, see eSupplement.

Table 2. Patient characteristics just prior to randomization.

	HFO-TGI Group (n=61)	CMV Group (n=64)
Age – yr	50.7 ± 17.7	52.9 ± 17.1
Male Gender – no. (%)	46 (75.4)	47 (73.4)
Body-mass index - kg/m^2	26.4 ± 4.3	25.4 ± 2.5
Predicted body weight – kg *	71.2 ± 8.9	69.7 ± 7.7
Comorbid Conditions – no. (%) †		
Hypertension	18 (29.5)	19 (29.7)
Diabetes Mellitus	7 (11.5)	7 (10.9)
Neoplasm	7 (11.5)	9 (14.1)
Other ‡	5 (8.2)	6 (9.4)
Surgical operations during current hospitalization – no. (%)		
Major elective operation	5 (8.2)	10 (15.6)
Emergency operation	24 (39.3)	16 (25.0)
DMV before enrollment in the total study population (days) §	3.0 (1.0-5.5)	2.0 (1.0-5.0)
ALI / ARDS diagnosis established within 1 hour of ICU admission– no. (%) §/	48 (78.7) /	55 (85.9) /
DMV before enrollment (days) §	2.5 (1.0-3.0)	2.0 (1.0-5.0)
Tracheostomized before enrollment – no. (%)	8 (13.1)	8 (12.5)
Simplified acute physiology score II (Predicted death rate - %)	43.5 ± 12.3 (35.2 ± 2 3.4)	43.6 ± 10.9 (34.4 ± 20.2)
Presence of at least 2 / at least 3 organ/system failures – no (%)	61 (100.0) / 40 (65.6)	63 (98.4) / 45 (70.3)
Circulatory failure; septic etiology– no. (%)	46 (75.4)	46 (71.9)
non-septic etiology-no. (%)	9 (14.8)	11 (17.2)
Primary ARDS – no. (%)	50 (82.0)	50 (78.1)
Etiology of ARDS		
Hospital-acquired pneumonia – no. (%)‖,**, §§	20 (32.8)	22 (34.4)
Community-acquired pneumonia – no. (%) ††	7 (11.5)	10 (15.6)
Bilateral pulmonary contusions – no. (%) **, ‡‡	22 (36.1)	12 (18.9)
Polytransfusion – no. (%) ‡‡, §§	5 (8.2)	8 (12.5)
Aspiration pneumonia – no. (%)	5 (8.2)	4 (6.3)
Intraabdominal sepsis – no. (%)	5 (8.2)	4 (6.3)
Other – no. (%) #	9 (14.8)	9 (14.1)

Values are mean±SD, or number (percentage), or median (interquartile range). CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; DMV, duration of mechanical ventilation; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

*, The corresponding calculation formula is provided in the footnote of Table 1.

†, Some patients had more than 1 comorbid condition.

‡, Includes 6 cases of alcohol abuse (3 in each group), 2 cases of chronic atrial fibrillation (1 in each group), 2 cases of intravenous drug abuse (1 in each group), 2 cases of major depression (1 in each group), and 1 case of cerebrovascular disease (HFO-TGI group) and schizophrenic disorder (CMV group).

§, On ICU admission, all patients were receiving mechanical ventilation for acute respiratory failure; also, within 1, 24, and 36 hours of ICU admission, 103, 7, and 3 patients (respectively) were confirmed of fulfilling the criteria of ALI/ARDS [15]; note: pre-enrollment DMV reflects time elapsed from DMV initiation to the onset of ALI/ARDS plus time elapsed from the latter time point to the time point of the fulfilment of the present study's criterion of "severe oxygenation disturbance" plus the time needed for the obtainment of the next-of-kin consent (see also text); pre-enrollment DMV was less than 7 days in 53 patients of the HFO-TGI group (86.9%) and 60 patients of the CMV group (93.8%).

‖, Caused by *Acinetobacter baumannii* (12 cases in the HFO-TGI group, and 11 cases in the CMV group) *Klebsiella pneumoniae* (6 cases in the HFO-TGI group, and 6 cases in the CMV group), and *Pseudomonas aeruginosa* (2 cases in the HFO-TGI group, and 5 cases in the CMV group); 17 HFO-TGI group patients and 20 CMV group patients had concurrent circulatory failure.

**, Both factors were simultaneously present in 7 patients of the HFO-TGI group, and 2 patients of the CMV group.

††, Caused by *Streptococcus pneumoniae* (2 cases in the HFO-TGI group, and 4 cases in the CMV group), *Legionella pneumoniophila* (3 cases in the HFO-TGI group, and 2 cases in the CMV group), methicillin-resistant *Staphylococcus aureus* (1 case in the HFO-TGI group, and 2 cases in the CMV group), and *Klebsiella pneumoniae* (1 case in the HFO-TGI group); unknown etiology: 1 case in the CMV group; 6 HFO-TGI group patients and 8 CMV group patients had concurrent circulatory failure.

‡‡, Both factors were simultaneously present in 1 patient of the HFO-TGI group, and 1 patient of the CMV group.

§§, Both factors were simultaneously present in 1 patient of the HFO-TGI group.

#, Includes 3 cases of acute interstitial pneumonia (1 in the HFO-TGI group, and 2 in the CMV group), 3 cases of necrotizing fasciitis (1 in the HFO-TGI group, and 2 in the CMV group; 1 patient from each group also received a massive blood transfusion), 2 cases of thermal injury (1 in each group), and 1 case of urosepsis due to *Proteus mirabilis* (HFO-TGI group), sepsis due to *Serratia marcescens* (HFO-TGI group), cerebral ventriculitis and sepsis due to *Acinetobacter baumannii* (HFO-TGI-group), necrotizing gram-negative pneumonia (HFO-TGI group; the patient also had bilateral pulmonary contusions), necrotizing pancreatitis (CMV group; the patient had also suffered an episode of pulmonary aspiration), alveolar hemorrhage (CMV group), submersion injury (HFO-TGI-

group), toxic epidermal necrolysis (HFO-TGI group; the patient also had aspiration pneumonia), postoperative mediastinitis (CMV group), and surgical wound infection (CMV group).

Table 3. Daily duration and employed settings of high-frequency oscillation (HFO) and tracheal-gas insufflation (TGI).

Day No.	No. treated with HFO-TGI *- No. returned to CMV † / No. treated with CMV alone ‡ - No. breathing without assistance / No. died §	Duration of daily HFO-TGI (hours) ‖	HFV FiO_2 (%) **	mPaw (cmH_2O) ††	mPaw drop along Tracheal Tube (cmH_2O) ‡‡,§§	Bias Flow (L/min) ††	TGI flow (L/min) ***	Frequency (Hz) ††	ΔP (cmH_2O) ††
1	61 - 51 / 0 - 0 / 0	11.5 ± 6.6	85.7 ± 8.7	29.9 ± 4.2	6.2 ± 1.5	40.9 ± 9.3	6.4 ± 0.9	4.1 ± 0.7	84.7 ±7.5
2	56 - 48 / 5 – 0 / 1	10.1 ± 5.9	84.7 ± 9.2	29.5 ± 3.4	6.1 ± 1.6	40.6 ± 8.8	6.5 ± 0.7	4.2 ± 0.9	84.8 ± 7.8
3	42 - 38 / 18 – 0 / 0	9.9 ± 6.2	84.5 ± 8.9	30.0 ± 4.2	6.7 ± 1.7	40.8 ± 9.2	6.6 ± 0.9	3.9 ± 0.6	85.7 ± 7.9
4	37 - 30 / 21- 1 / 1	10.9 ± 6.8	84.8 ± 9.0	29.2 ± 4.5	6.6 ± 1.2	42.1 ± 10.2	6.6 ± 0.9	4.0 ± 0.7	85.7 ± 7.0
5	17 - 15 / 37 – 1 / 4	12.7 ± 7.2	87.3 ± 8.6	30.2 ± 4.5	6.2 ± 1.7	46.3 ± 10.5	6.6 ± 0.7	4.2 ± 0.8	86.0 ± 5.9
6	15 - 10 / 38 – 1 / 1	11.9 ± 6.8	89.1 ± 8.3	31.4 ± 5.4	6.2 ± 1.7	47.3 ± 10.8	6.6 ± 0.8	4.3 ± 0.9	87.3 ± 5.4
7	11 - 7 / 39 - 3 / 1	14.2 ± 7.5	90.9 ± 7.1	32.0 ± 4.0	6.0 ± 1.9	47.1 ± 10.2	6.6 ± 0.7	3.9 ± 0.7	87.6 ± 6.5
8	8 - 5 / 41 - 3 / 1	13.5 ± 7.7	89.7 ± 7.9	30.4 ± 5.7	4.8 ± 1.9	49.7 ± 11.1	6.4 ± 0.8	4.1 ± 1.0	87.8 ± 5.2
9	5 - 2 / 38 - 7 / 2	12.0 ± 5.6	88.9 ± 5.3	31.0 ± 3.8	4.8 ± 1.7	48.0 ± 11.0	6.3 ± 0.7	4.2 ± 0.7	87.7 ± 2.6
10	3 - 3 / 40 – 7 / 0	17.0 ± 5.1	90.0 ± 3.3	32.0 ± 4.4	4.7 ± 2.3	53.3 ± 11.6	6.3 ± 0.6	4.4 ± 1.0	84.1 ± 4.2

Data are presented as number, number (percentage), or mean±SD. CMV, conventional mechanical ventilation; HFV, high-frequency ventilator; FiO_2, inspired oxygen fraction; mPaw, mean airway pressure; ΔP, oscillatory pressure amplitude. .

*, Refers to the total number of patients treated with HFO-TGI; 19 and 19 patients received intermittent HFO-TGI for ≤3 days and ≥5 days, respectively.

†, Refers to the total number of patients treated with HFO-TGI and then returned to CMV, after fulfilling the criteria for weaning from HFO-TGI (see also Methods and Figure 1).

‡, Refers to the total number of patients treated with CMV alone, because they did not fulfil the criterion for return to HFO-TGI (see also Methods and Figure 1.

§, On days 2, 4, 5, and 9, 5 patients (1 still on HFO-TGI and 4 on post-HFO-TGI CMV) died of multiple organ failure after achieving "PaO_2/FiO_2>150 mmHg" during their last HFO-TGI session; within days 5-9, 6 patients died (4 of multiple organ failure, 1 of hypoxemia, and 1 of iatrogenic pneumothorax not related to any study protocol intervention) while still on HFO-TGI and without achieving "PaO_2/FiO_2>150 mmHg" during that particular HFO-TGI session (see also "Study Intervention Failures" in pages 22 and 23 of eResults of eSupplement).

‖, 124/223 (55.6%), 65/223 (29.1%), and 34/223 (15.2%) of HFO-TGI sessions lasted <8, 8-18, and >18 hours, respectively; in 16 patients, the maximum uninterrupted use of HFO-TGI ranged in-between 30.1 and 102.2 hours; 177 of the 223 sessions (79.4%) were administered to all the 61 patients (100%) during days 1-4; after the morning of day 5, the remaining 46 sessions (20.6%) were administered to 19 patients (31.1%).

**, Refers to HFV-set FiO_2 averaged over the duration of the daily HFO-TGI sessions; actually delivered FiO_2 was further increased by the use of the 100% O_2 flow of TGI; HFV FiO_2 was set at 100% during 1) the recruitment period; 2) the application of the additional recruitment algorithm (see also Figure 1); and 3) the 15-min periods preceding and 5-min periods corresponding to the physiologic measurements of the stabilization period.

††, Parameter value averaged over the duration of daily HFO-TGI.

‡‡, Refers to the average pressure drop determined by measuring the mean tracheal pressure just prior to TGI initiation and after TGI discontinuation (see also Methods, Figure 1, and "mPaw and mean tracheal pressure" in pages 19 and 20 of eResults of eSupplement); pressure drop ranged within 2.0-10.4 cmH_2O (depending on tracheal tube size, HFO-frequency and ΔP, and presence of secretions); recent data [8] showed that under similar HFV settings and tracheal tube cuff leak, the addition of a TGI flow similar to that used in the present study results in an average increase of 1.5 cmH_2O in mean tracheal pressure (see also eSupplement).

§§, Eight patients were already tracheostomized before study entry, whereas another 5 patients were tracheostomized during the study intervention period; during 176 of the 223 HFO-TGI sessions (78.9%), 53 of the 61 patients (86.9%) were ventilated through orotracheal tubes (inner diameter = 8.19±0.04 mm, range = 7.50-9.00 mm); during 47 of the 223 HFO-TGI sessions (21.1%), 13 of the 61 patients (21.3%) were ventilated through tracheostomy tubes (inner diameter = 8.58±0.11 mm, range = 8.00-9.00 mm).

***,** equals to 50.6±2.2% (range=45.0-55.2%) of the minute ventilation of the pre-session CMV; TGI flow ranged within 4.5-8.5 L/min.

1 cmH_2O=0.098 kPa.

Table 4. Physiological variables, hemodynamic support, and organ failure assessment during days 1-10 post-randomization.

VARIABLE	BASELINE	DAY 1	DAY 5	DAY 10	MISSING VALUES (%)	P-VALUES, EFFECT OF Group	Time	Group*Time
Tidal volume – L / mL/kg PBW; HFO-TGI Group	0.46±0.05 / 6.5±0.6	0.46±0.05 / 6.4±0.6	0.47±0.06 / 6.7±0.7 ‡	0.50±0.07 / 7.2±1.2 *,†,‡,§	15.2	<0.001	<0.001	<0.001
CMV Group	0.45±0.06 / 6.5±0.5	0.44±0.06 / 6.4±0.5	0.45±0.05 / 6.3±0.4	0.46±0.07 / 6.4±0.6	18.2			
Vent. Rate – breaths/min; HFO-TGI Group	27.6±4.3	27.8±4.4	27.6±4.3	26.0±5.2	15.2	0.046	<0.001	0.003
CMV Group	27.2±5.3	27.2±5.3	28.2±3.8	27.6±5.5	18.2			
Peak pressure - cmH_2O; HFO-TGI Group	43.4±6.1	42.5±5.5 *	39.6±7.4 †,‡	35.3±9.5 †,‡	15.2	0.46	<0.001	<0.001
CMV Group	41.2±5.6	39.5±5.3 †	39.8±6.0	37.2±7.0	18.2			
Mean airway pressure - cmH_2O; HFO-TGI Group	21.7±2.9	21.6±2.9 *	18.9±2.8 †,‡	16.7±4.2 *,†,‡	15.2	0.41	<0.001	0.001
CMV Group	20.3±3.3	19.7±3.0	19.6±3.2	17.9±3.1	18.8			
Plateau pressure - cmH_2O; HFO-TGI Group	**30.9**±4.2	**30.7±4.2**	**26.3±3.2** *,†,‡	**24.0±5.6** *,†,‡	15.2	**<0.001**	**<0.001**	**<0.001**
CMV Group	**29.9**±3.0	**29.7±3.1**	**29.3±4.5**	**27.4±4.1**	18.2			
External PEEP - cmH_2O; HFO-TGI Group	14.3±2.5	14.2±2.5	12.0±2.6 †,‡	10.1±3.0 †,‡,§	15.2	0.81	<0.001	0.03
CMV Group	13.1±3.0	12.9±3.3	12.1±3.2	10.5±2.8 †,‡	18.2			
Compliance – mL/cmH_2O; HFO-TGI Group	**30.3±8.1**	**30.4±8.2**	**37.6±9.8** *,†,‡	**43.3±11.8** *,†,‡	15.2	**<0.001**	**<0.001**	**<0.001**
CMV Group	**28.8±5.3**	**28.3±5.5**	**28.4±6.6**	**30.0±8.9**	18.2			
FiO2 - (%); HFO-TGI Group	**81.9±13.9**	**81.6±13.8** *	**65.0±12.7** †,‡	**57.2±15.8** †,‡	8.3	**0.57**	**<0.001**	**0.007**
CMV Group	**76.1±14.2**	**74.1±14.8**	**69.5±17.3**	**61.3±17.9**†,‡	15.8			
PaO2 – mmHg; HFO-TGI Group	**75.5±17.7**	**77.9±19.5**	**108.0±37.4** *,†,‡	**114.8±37.9** *,†,‡	8.3	**<0.001**	**<0.001**	**<0.001**
CMV Group	**78.2±12.7**	**78.5±12.7**	**85.4±22.8**	**90.1±28.6**	15.8			

Table 4. Physiological variables, hemodynamic support, and organ failure assessment during days 1-10 post-randomization (continued).

VARIABLE	BASELINE	DAY 1	DAY 5	DAY 10	MISSING VALUES (%)	*P*-VALUES, EFFECT OF Group	Time	Group*Time
PaO_2/FiO_2– mmHg; HFO-TGI Group	**96.5±31.3**	**99.5±31.6**	**175.2±74.1 *,†,‡**	**222.9±108.1 *,†,‡**	8.3	**0.007**	**<0.001**	**<0.001**
CMV Group	**106.9±27.7**	**110.5±28.2**	**135.0±61.6**	**163.5±76.1**	15.8			
Oxygenation index; HFO-TGI Group	**26.4±13.5**	**25.6±13.4**	**13.6±7.7 *,†,‡**	**12.6±15.1 †,‡**	15.2	**0.21**	**<0.001**	**0.01**
CMV Group	**21.1±8.9**	**19.9±8.8**	**19.1±10.3**	**14.7±8.8**	18.8			
$PaCO_2$ – mmHg; HFO-TGI Group	47.6±8.4	47.2±8.2	46.9±8.3	46.3±10.7	8.3	0.03	0.048	0.14
CMV Group	47.5±8.0	47.4±8.0	50.0±9.9	50.3±18.9 †,‡	15.8			
Arterial pH; HFO-TGI Group	7.33±0.07	7.33±0.07	7.39±0.07 †,‡	7.40±0.07 *,†,‡	8.3	0.001	<0.001	<0.001
CMV Group	7.30±0.08	7.31±0.08	7.36±0.09 †,‡	7.36±0.08	15.8			
Shunt fraction; HFO-TGI Group	0.46±0.12	0.45±0.13	0.29±0.12 *,†	0.26±0.15 *,†	8.3	0.02	<0.001	<0.001
CMV Group	0.42±0.09	0.42±0.09	0.37±0.13	0.33±0.13	15.8			
MAP – mmHg; HFO-TGI Group	81.7±13.2	79.9±13.5	81.5±11.9	83.4±9.5	8.3	0.16	0.02	<0.001
CMV Group	77.3±11.0	79.1±11.9	82.4±9.7	80.1±12.8	15.8			
CVP – mmHg; HFO-TGI Group	10.8±4.1	11.7±4.2 †	11.3±3.4	10.3±3.1	8.3	0.89	<0.001	0.63
CMV Group	10.1±3.4	10.8±3.6 †	11.8±4.2	11.4±4.5	15.8			
Heart Rate – beats/min; HFO-TGI Group	98.9±18.9	96.6±19.8	90.1±17.4 †	95.9±14.9	8.3	0.58	0.02	0.31
CMV Group	98.9±16.7	97.7±16.6	92.3±14.2	93.4±15.4	15.8			
Cardiac index – L/min/m^2; HFO-TGI Group	4.0±1.03	4.0±1.0	3.7±0.9	3.8±0.5	12.9	0.12	<0.001	0.65
CMV Group	4.1±0.9	4.2±0.8	4.0±0.7	4.1±1.0	21.1			

Table 4. Physiological variables, hemodynamic support, and organ failure assessment during days 1-10 post-randomization (continued).

VARIABLE	BASELINE	DAY 1	DAY 5	DAY 10	MISSING VALUES (%)	*P*-VALUES, EFFECT OF Group	Time	Group*Time
DO_2I - mL/min/m^2; HFO-TGI Group	460.0±122.7	475.3±133.5 †	431.3±105.5	443.3±116.8	12.9	0.46	<0.001	0.18
CMV Group	489.8±134.8	495.7±130.0	444.9±81.6 ‡	419.8±78.1 †,‡	21.1			
$ScvO_2$ - (%); HFO-TGI Group	70.7±8.8	71.4±8.5	72.8±5.8	71.6±8.7	8.3	0.14	0.09	0.30
CMV Group	70.7±6.6	71.0±6.7	71.0±6.0	71.9±4.3	15.8			
Lactate – mmol/L; HFO-TGI Group	2.5±1.8	2.3±1.8	1.9±1.1	1.5±0.8	8.3	0.12	<0.001	0.32
CMV Group	2.8±2.8	2.8±2.5	2.2±2.1	1.6±0.8	15.8			
Fluid balance – L/day; HFO-TGI Group‖	2.03±1.65	2.34±2.34	1.04±1.48 ‡	0.81±1.73 ‡	8.3	0.63	<0.001	0.47
CMV Group‖	2.07±1.71	2.56±2.04	1.07±1.55 ‡	0.72±1.68 ‡	15.8			
Norepinephrine - µg/kg/min; HFO-TGI Group**	0.19±0.16	0.22±0.23	0.15±0.13	0.09±0.11	8.3	0.38	0.03	0.12
CMV Group**	0.19±0.16	0.19±0.17	0.15±0.15	0.12±0.16	15.8			
SOFA score – mmHg; HFO-TGI Group	**11.7±2.7**	**11.5±2.7**	**10.4±3.7**	**7.4±4.6 *,†,‡,§**	**8.3**	**0.02**	**<0.001**	**0.03**
CMV Group	**12.1±2.6**	**11.9±2.7**	**11.9±4.2**	**10.0±3.8**	**15.8**			

Values are mean±SD. Data originate from physiologic measurements performed during conventional mechanical ventilation in each one of the 125 patients (intention-to-treat analysis), within 2 hours before randomization (baseline), and in-between 9:00 and 10:00 a.m. of days 1-10 post-randomization.

PBW, predicted body weight; CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; PEEP, positive end-expiratory pressure; MAP, mean arterial pressure; CVP, central-venous pressure; DO_2I, oxygen delivery index; $ScvO_2$, central-venous oxygen saturation; SOFA, sequential organ failure assessment.

Detailed data on physiological endpoints and SOFA score (highlighted in bold script) are presented in Figure 3. Pressure, volume, and respiratory rate values were those displayed by the ventilator. Respiratory compliance was calculated as tidal volume divided by the end-inspiratory-to-end-expiratory plateau airway pressure difference [7,12]. For both groups, analyzed data corresponded to 11 consecutive time points, i.e., the baseline and the morning of each one of the first 10 days post-randomization. For between-group comparisons at each time point, we used the Bonferroni correction, i.e., we multiplied the obtained P values by 11. The 11 time points resulted in a total of 55 within-group pairwise comparisons; thus, we multiplied P values from within-group comparisons by 55. The handling of missing values is summarized in eSupplement.

*, P<0.05 versus CMV group at that particular time point.

†, P<0.05 versus baseline.

‡, P<0.05 versus Day 1.

§, P<0.05 versus Day 5.

‖, Baseline values correspond to the fluid balance of the preceding 24 hours; other values correspond to the fluid balance of days 1, 5, and 10.

**, Baseline infusion rate was the infusion rate recorded just prior to randomization; other infusion rates are the average infusion rates of days 1, 5, and 10; during days 1-10, all patients of both groups required a norepinephrine infusion for ≥1 hour to maintain a mean arterial pressure of ≥70 mmHg.

1 cmH_2O=0.098 kPa; 1 mmHg=0.133 kPa.