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Intermittent recruitment with high-frequency oscillation/tracheal gas insufflation in acute respiratory distress syndrome

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ABSTRACT: **In acute respiratory distress syndrome (ARDS), recruitment sessions of high-frequency oscillation (HFO) and tracheal gas insufflation (TGI) with short-lasting recruitment manoeuvres (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.**

We conducted a prospective clinical trial, subdivided into a first single-centre period and a second two-centre period. We enrolled 125 (first period, n=54) patients with arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) of <150 mmHg for >12 consecutive hours at an end-expiratory pressure of ⩾8 cmH_2O. Patients were randomly assigned to an HFO-TGI group (receiving HFO-TGI sessions with RMs, interspersed with lung-protective CMV; n=61) or CMV group (receiving lung-protective CMV and RMs; n=64). The primary outcome was survival to hospital discharge.

Pre-enrolment ventilation duration was variable. During days 1–10 post-randomisation, $P_{a,O_2}/F_{I,O_2}$, oxygenation index, plateau pressure and respiratory compliance were improved in the HFO-TGI group *versus* the CMV group (p<0.001 for group × time). Within days 1–60, the HFO-TGI group had more ventilator-free days *versus* the CMV group (median (interquartile range) 31.0 (0.0–42.0) *versus* 0.0 (0.0–23.0) days; p<0.001), and more days without respiratory, circulatory, renal, coagulation and liver failure (p⩽0.003). Survival to hospital discharge was higher in the HFO-TGI group *versus* the CMV group (38 (62.3%) out of 61 *versus* 23 (35.9%) out of 64 subjects; p=0.004).

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

KEYWORDS: **Adult, clinical trial, high-frequency ventilation, respiratory distress syndrome**

High-frequency oscillation (HFO) is suggested for adults with severe acute respiratory distress syndrome (ARDS) [1, 2]. During HFO, tidal volumes of <3.5 $mL \cdot kg^{-1}$ predicted body weight are administered at ⩾3 Hz and mean airway pressure ($\bar{P}_{aw}$) ranges 22–40 cmH_2O [1–3]. Animal lung injury data favour HFO over lung-protective conventional mechanical ventilation (CMV) [4]. The low HFO tidal volumes minimise volutrauma and the high HFO $\bar{P}_{aw}$ limits atelectrauma [2, 5].

When combined with 40-s recruitment manoeuvres (RMs), HFO improves oxygenation *versus* lung-protective CMV, probably through lung recruitment [6–8]. The short-term addition of tracheal gas insufflation (TGI) to HFO may further improve oxygenation *versus* 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 h) 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 noninjurious levels [11]. A reduced lung end-inspiratory stretch could attenuate ventilator-associated lung injury [12, 13] and

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improve outcome [14]. Thus, we compared the effect of two recruitment strategies during lung-protective CMV, namely HFO-TGI sessions with short-lasting RMs *versus* short-lasting RMs alone, on the survival of patients with early/severe ARDS.

METHODS

Patients

The study was approved by the Scientific Committees of Evaggelismos Hospital (Athens, Greece) and Larissa University Hospital (Larissa, Greece). Informed, written next-of-kin consent was obtained for patients fulfilling the eligibility criteria presented in eTable 1 of the online supplementary material. Patients had early (onset within $\leqslant$72 h) ARDS [15] and severe oxygenation disturbances: arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) <150 mmHg for >12 consecutive hours with a PEEP of $\geqslant$8 cmH_2O; ARDS mortality increases at $P_{a,O_2}/F_{I,O_2}$ <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 the online supplementary material.

Study design and randomisation

We conducted a prospective, randomised, unblinded, parallel-group controlled trial, temporally subdivided into a first single-centre and a second two-centre period for feasibility reasons (online supplementary material). The 37-bed intensive care unit (ICU) of Evaggelismos Hospital participated during 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. The 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). The CMV group received lung-protective CMV and RMs for days 1–4 post-randomisation (table 1); the likelihood of sustained, RM-induced oxygenation improvement decreases and the risk of RM haemodynamic complications increases with CMV time [17]. In the 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 four per day in both groups. Figure 1 illustrates the study protocol.

HFO-TGI recruitment protocol

HFO was provided using a 3100B high-frequency ventilator (Sensormedics, Yorba Linda, CA, USA). The goal of each HFO-TGI session was to increase $P_{a,O_2}/F_{I,O_2}$ to >150 mmHg by using a high initial $\bar{P}_{aw}$ (recruitment period), and then maintain the oxygenation benefit during a gradual $\bar{P}_{aw}$ reduction to 6 cmH_2O below its initial value (stabilisation period) and during weaning from TGI and HFO (weaning period). Additional protocol features are described in online supplementary material.

Recruitment period: initial setting of HFO $\bar{P}_{aw}$

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 ($\bar{P}_{tr}$) was determined through the catheter with Direc218B (Raytech Instruments, Vancouver, 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

TABLE 1 Conventional mechanical ventilation (CMV) strategy

Ventilator mode	Volume assist control
Target tidal volume mL·kg^{-1} predicted body weight[#]	6.0 (with allowances from 5.5 to 7.5)
Target end-inspiratory plateau pressure cmH_2O	$\leqslant$30 (with allowance of $\leqslant$35[##])
Ventilator rate breaths·min^{-1}/target pH_a	16–35/7.20–7.45
Inspiratory-to-expiratory time ratio	1:2
Combinations of F_{I,O_2} %/PEEP cmH_2O[¶]	40/5–8, 50/8, 60/10, 70/10–14, 80/14, 90/16, 100/16–20
Target S_{p,O_2} %	90–95
Target P_{a,O_2} mmHg	60–80
RM[+,§,ƒ]	CPAP of 45 cmH_2O for 40 s

Apart from the protocolised use of recruitment manoeuvres (RMs), the presented CMV strategy mainly reflects standard clinical practice at both study centres. pH_a: arterial blood pH; F_{I,O_2}: inspiratory oxygen fraction; PEEP, positive end-expiratory pressure; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; P_{a,O_2}: arterial oxygen tension; CPAP: continuous positive airway pressure. [#]: calculated as 50 + (height (cm) − 152.4) × 0.91 and 45.5 + (height (cm) − 152.4) × 0.91 for males and females, respectively. [¶]: whenever the upper limit of the oxygenation targets was exceeded, PEEP was adjusted at a rate of 1–2 cmH_2O·h^{-1} (adjusting F_{I,O_2} accordingly) an S_{p,O_2} of $\leqslant$95% and/or an P_{a,O_2} of $\leqslant$80 mmHg was reached; during the first 10 days post-randomisation, the downward titrations were reversed and suspended (for 12 h) if 1) starting plateau pressure and F_{I,O_2} were $\leqslant$30 cmH_2O and $\leqslant$70%, respectively, and 2) they were associated with a $P_{a,O_2}/F_{I,O_2}$ decrease of >25% and a $P_{a,O_2}/F_{I,O_2}$ of <150 mmHg. [+]: performed in the control, *i.e.* the CMV group, during the first 4 days after randomisation at a rate of one every 4–6 h; post-RM PEEP was increased by 2 cmH_2O, whenever the plateau pressure target of 30 cmH_2O was still achievable; within the following 60 min, if applicable, we re-titrated PEEP and F_{I,O_2} to the oxygenation targets as described. [§]: in the intervention, *i.e.* the high-frequency oscillation (HFO) and tracheal gas insufflation (TGI) group, identical RMs were used solely during sessions of HFO-TGI (see Methods section and fig. 1). [ƒ]: in both groups, before each RM, we pre-oxygenated the patient by using an F_{I,O_2} of 100% for $\geqslant$5 min to reduce the risk of RM-associated desaturation [6]; for additional details, see the online supplementary material. [##]: whenever deemed necessary for achieving the lowest target pH_a and/or $S_{p,O_2}/P_{a,O_2}$; in such cases, tidal volumes of 5.5–6.0 mL·kg^{-1} were used.

tube cuff-leak of 3–5 cmH_2O was placed and $\bar{P}_{tr}$ was re-measured. High-frequency ventilator-displayed $\bar{P}_{aw}$ (HFO-$\bar{P}_{aw}$) was titrated to an HFO-$\bar{P}_{tr}$ that exceeded preceding CMV-$\bar{P}_{tr}$ by 3 cmH_2O. This resulted in an average HFO-$\bar{P}_{aw}$ of 8–9 cmH_2O above the preceding average CMV-$\bar{P}_{aw}$, because the average high-inspiratory flow-related drop [8] in HFO-$\bar{P}_{aw}$ along the tracheal tube was ~6 cmH_2O.

TGI initiation

Following setting of the initial HFO-$\bar{P}_{aw}$, the catheter was proximally connected to a variable-orifice oxygen flow meter providing pure, humidified oxygen 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-$\bar{P}_{aw}$, which was reversed by adjusting the $\bar{P}_{aw}$ valve [10].

Recruitment period duration

If, at 60–90 min after HFO-TGI initiation, $P_{a,O_2}/F_{I,O_2}$ exceeded 150 mmHg, we proceeded to the stabilisation period. Otherwise, the additional recruitment algorithm was applied, and the recruitment period extended until $P_{a,O_2}/F_{I,O_2}$ exceeded 150 mmHg and/or $\bar{P}_{aw}$ reached 40 cmH_2O (fig. 1). The high-frequency ventilator F_{I,O_2} was kept at 100% throughout this period.

Stabilisation period: targeted HFO-$\bar{P}_{aw}$ reduction

$\bar{P}_{aw}$ was gradually reduced (rate 1–2 $cmH_2O \cdot h^{-1}$) to 3 cmH_2O below its initially set value. If $P_{a,O_2}/F_{I,O_2}$ remained >150 mmHg, an RM was performed and $\bar{P}_{aw}$ was decreased by another 3 cmH_2O at 1–2 $cmH_2O \cdot h^{-1}$. If $P_{a,O_2}/F_{I,O_2}$ was still >150 mmHg, we proceeded to weaning period. Whenever these downward $\bar{P}_{aw}$ titrations resulted in a $P_{a,O_2}/F_{I,O_2}$ of <150 mmHg, the additional recruitment algorithm was followed (fig. 1). The pre-specified minimum duration of the stabilisation period was 240 min.

Ventilator F_{I,O_2} was reduced to 80, 70 or 60% if the $P_{a,O_2}/F_{I,O_2}$ of the immediately preceding physiological measurement was 150–200, 200–300 or >300 mmHg, respectively. Prior to and during each subsequent physiological measurement, ventilator F_{I,O_2} was set at 100% (for 20 min). This enabled precise determination of $P_{a,O_2}/F_{I,O_2}$ during ongoing TGI.

Weaning period: discontinuation of TGI and HFO

An RM was performed and TGI was discontinued over 30 min; the associated HFO-$\bar{P}_{aw}$ reduction of 1–2 cmH_2O was reversed by adjusting the $\bar{P}_{aw}$ valve. Patients were ventilated with standard HFO for a further 30 min and if $P_{a,O_2}/F_{I,O_2}$ was >150 mmHg, they were returned to CMV. If $P_{a,O_2}/F_{I,O_2}$ was <150 mmHg, patients were returned to the additional recruitment algorithm (fig. 1).

HFO-TGI session duration

The minimum time from HFO initiation to HFO termination was 6 h. Each transition to the additional recruitment algorithm (fig. 1) extended the session by ⩾2–3 h. After every 12–24 h 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 for return to HFO-TGI was $P_{a,O_2}/F_{I,O_2}$ <150 mmHg sustained for >12 consecutive hours, while on CMV. Patients were assessed for return to HFO-TGI at 12 and 24 h after return to CMV, and then at the beginning of each day until day 10 post-randomisation.

Definitions

Definitions of organ/system failures according to a corresponding Sequential Organ Failure Assessment (SOFA) subscore ⩾3 [18], infections and other complications are provided in the online supplementary material. Multiple organ failure (MOF) was defined as three or more concurrent organ/system failures [19].

Follow-up

Baseline patient data were recorded within 2 h pre-randomisation. Daily recordings included physiological/laboratory data (days 1–28 post-randomisation), intervention-associated complications (days 1–10; *e.g.* RM-induced hypotension or desaturation), mechanical ventilation-associated barotrauma (study-independent radiologists assessed chest radiographs for pathological 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; *e.g.* infections and heparin-induced thrombocytopenia). Investigators were unblinded to patient outcomes. Adherence to the protocol was overseen by the Data Monitoring Committee (see Acknowledgements section for details).

During days 1–10, sets of physiological measurements were obtained as follows. 1) CMV group: three measurements per day, starting at 09:00 h. 2) HFO-TGI group: just before, during and 6 h after HFO-TGI, and as in CMV group if no longer requiring HFO-TGI. Measurements included arterial/central-venous blood-gas analysis, haemodynamics and respiratory mechanics while on CMV [7, 12]. For between-group comparisons, we used CMV data obtained between 09:00 and 10:00 h in both groups.

Outcome measures

Primary

The primary outcome was survival to hospital-discharge, *i.e.* ''patient discharged home, while breathing without assistance.''

Secondary

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

Statistical analysis

Additional details are provided in the online supplementary material. According to the pilot cohort data, the predicted survival rate to hospital discharge was 66 and 40% for the HFO-TGI group and CMV group, respectively. For an α-value of 0.05 and a power of 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.

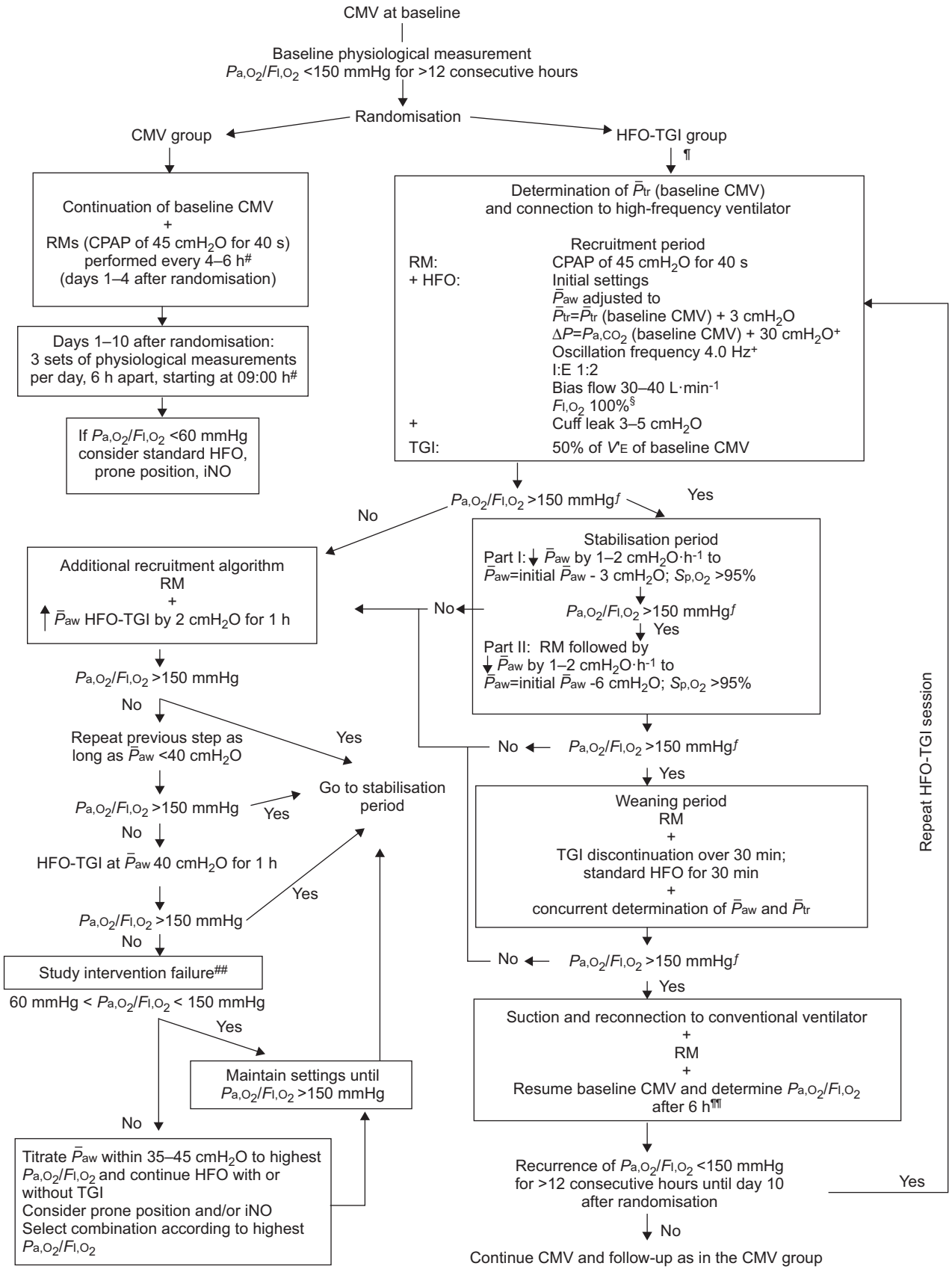
CMV at baseline
Baseline physiological measurement
$P_{a,O_2}/F_{I,O_2}$ <150 mmHg for >12 consecutive hours
Randomisation
CMV group
HFO-TGI group ¶
Continuation of baseline CMV
+
RMs (CPAP of 45 cmH_2O for 40 s)
performed every 4–6 h#
(days 1–4 after randomisation)
Days 1–10 after randomisation:
3 sets of physiological measurements
per day, 6 h apart, starting at 09:00 h#
If $P_{a,O_2}/F_{I,O_2}$ <60 mmHg
consider standard HFO,
prone position, iNO
Determination of $\bar{P}_{tr}$ (baseline CMV)
and connection to high-frequency ventilator
Recruitment period
RM: CPAP of 45 cmH_2O for 40 s
+ HFO: Initial settings
$\bar{P}_{aw}$ adjusted to
$\bar{P}_{tr}=\bar{P}_{tr}$ (baseline CMV) + 3 cmH_2O
$\Delta P=P_{a,CO_2}$ (baseline CMV) + 30 cmH_2O+
Oscillation frequency 4.0 Hz+
I:E 1:2
Bias flow 30–40 $L\cdot min^{-1}$
F_{I,O_2} 100%§
+ Cuff leak 3–5 cmH_2O
TGI: 50% of V'_E of baseline CMV
$P_{a,O_2}/F_{I,O_2}$ >150 mmHgf
Yes
No
Stabilisation period
Part I: ↓ $\bar{P}_{aw}$ by 1–2 $cmH_2O\cdot h^{-1}$ to
$\bar{P}_{aw}$=initial $\bar{P}_{aw}$ - 3 cmH_2O; S_{p,O_2} >95%
$P_{a,O_2}/F_{I,O_2}$ >150 mmHgf
Yes
Part II: RM followed by
↓ $\bar{P}_{aw}$ by 1–2 $cmH_2O\cdot h^{-1}$ to
$\bar{P}_{aw}$=initial $\bar{P}_{aw}$ -6 cmH_2O; S_{p,O_2} >95%
No
Additional recruitment algorithm
RM
+
↑ $\bar{P}_{aw}$ HFO-TGI by 2 cmH_2O for 1 h
$P_{a,O_2}/F_{I,O_2}$ >150 mmHg
No
Repeat previous step as
long as $\bar{P}_{aw}$ <40 cmH_2O
Yes
Go to stabilisation
period
$P_{a,O_2}/F_{I,O_2}$ >150 mmHg
Yes
No
HFO-TGI at $\bar{P}_{aw}$ 40 cmH_2O for 1 h
$P_{a,O_2}/F_{I,O_2}$ >150 mmHg
Yes
No
Study intervention failure##
60 mmHg < $P_{a,O_2}/F_{I,O_2}$ < 150 mmHg
Yes
Maintain settings until
$P_{a,O_2}/F_{I,O_2}$ >150 mmHg
No
Titrate $\bar{P}_{aw}$ within 35–45 cmH_2O to highest
$P_{a,O_2}/F_{I,O_2}$ and continue HFO with or
without TGI
Consider prone position and/or iNO
Select combination according to highest
$P_{a,O_2}/F_{I,O_2}$
No
$P_{a,O_2}/F_{I,O_2}$ >150 mmHgf
Yes
Weaning period
RM
+
TGI discontinuation over 30 min;
standard HFO for 30 min
+
concurrent determination of $\bar{P}_{aw}$ and $\bar{P}_{tr}$
No
$P_{a,O_2}/F_{I,O_2}$ >150 mmHgf
Yes
Suction and reconnection to conventional ventilator
+
RM
+
Resume baseline CMV and determine $P_{a,O_2}/F_{I,O_2}$
after 6 h¶¶
Recurrence of $P_{a,O_2}/F_{I,O_2}$ <150 mmHg
for >12 consecutive hours until day 10
after randomisation
Yes
Repeat HFO-TGI session
No
Continue CMV and follow-up as in the CMV group

FIGURE 1. Algorithmic representation of the study protocol. During high-frequency oscillation (HFO) tracheal gas insufflation (TGI), recruitment manoeuvres (RMs) were performed with TGI turned off and the tracheal tube cuff inflated. Target arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) was >95% for all periods (see online supplementary material); at any period, an S_{p,O_2} of <88% for >5 min was the trigger for 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 mean airway pressure ($\bar{P}_{aw}$) increase of $\geqslant$2 cmH_2O, which had to be reversed after the subsequent transition to the stabilisation period. This resulted in extension of the stabilisation period by $\geqslant$1 h. CMV: conventional mechanical ventilation; P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; CPAP: continuous positive airway pressure; iNO: inhaled nitric oxide; $\bar{P}_{tr}$: mean tracheal pressure; ΔP: oscillatory pressure amplitude; P_{a,CO_2}: arterial carbon dioxide tension; I:E, inspiratory-to-expiratory time ratio; V'_E: minute ventilation. #: temporal distance between any measurement and a preceding RM was $\geqslant$2 h. ¶: corresponds to the timing of the first set of daily physiological measurements performed during CMV, prior to HFO-TGI initiation; by design, these measurements were to be performed at 09:00 h unless the patient was already on HFO-TGI at that particular time (see online supplementary material). +: frequency and ΔP were adjusted to maintain an arterial blood pH of $\geqslant$7.20 by means of two consecutive arterial blood gas analyses performed within the first 30 min of the recruitment period. §: high-frequency ventilator F_{I,O_2} was initially set at 100%; for further details regarding the management of F_{I,O_2} see the Methods section. ƒ: corresponds to the timing of physiological measurements during the HFO-TGI session; in HFO-TGI sessions exceeding 6 h, one additional set of physiological measurements was obtained for every additional 2–4 h. ##: the corresponding, pre-specified management technique is presented in detail in the subsection ''Additional features of the HFO-TGI protocol'' of the eMethods in the online supplementary material; RMs were not performed at $\bar{P}_{aw}$ >40 cmH_2O; one RM was performed every 1–2 h during periods with $\bar{P}_{aw}$ of 35–40 cmH_2O. ¶¶: corresponds to the timing of physiological measurements performed during CMV, after weaning from TGI and HFO.

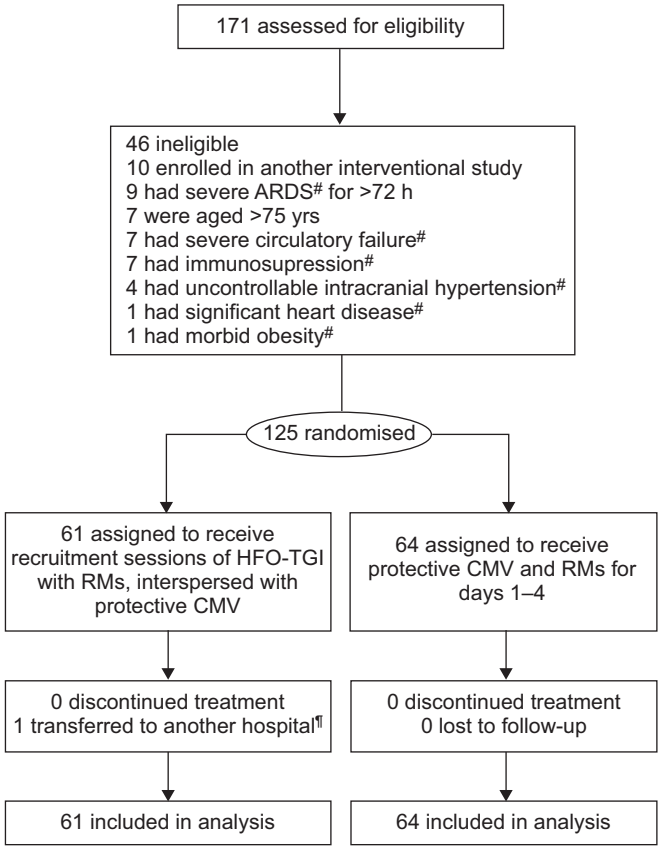

FIGURE 2. Study flow chart. ARDS: acute respiratory distress syndrome; HFO: high-frequency oscillation; TGI: tracheal gas insufflation; RM: recruitment manoeuvre; CMV: conventional mechanical ventilation. #: definition provided in the footnote of eTable 1 in the online supplementary material; additional 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 (eTable 1); the lower limits for age and body weight were 18 yrs and 40 kg, respectively. ¶: the patient was transferred to another hospital not participating in the study on day 31 post-randomisation; 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 the main text for the definition of ''hospital discharge'').

An intention-to-treat analysis was performed with SPSS version 12.0 (SPSS, Chicago, IL, USA) and SAS version 9.0 (SAS Institute, Cary, NC, USA). Data are reported as mean$\pm$SD, median (interquartile range) or n (%), unless otherwise specified. Dichotomous and categorical variables were compared using Fisher's exact test. Continuous variables were compared using a two-tailed, independent-samples t-test or the Mann–Whitney exact U-test. The Bonferroni correction was used for multiple comparisons. For days 1–10, the effects of group, time and group $\times$ time on physiological variables were determined by mixed-model analysis. Survival was analysed with the Kaplan–Meier method, and survival data were compared by Fisher's exact test and the log-rank test. Cox regression was used to determine independent predictors of death. The effect of centre was assessed by between-centre comparisons for study end-points. 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 randomised (HFO-TGI group, n=61; CMV group, n=64) and their data analysed (fig. 2). 16 (34.8%) out of the 46 excluded patients survived to hospital discharge.

Table 2 presents baseline characteristics. 85 (68.0%) patients (HFO-TGI group, n=40) had MOF. The HFO-TGI intervention period extended to day 10 post-randomisation. Table 3 presents data on daily HFO-TGI; session duration ranged 6.0–102.2 h.

Physiological variables during intervention period

Physiological variables during the intervention period are summarised in table 4. There were no significant between-group differences in haemodynamics, arterial blood lactate or haemodynamic support. Measures of oxygenation (($P_{a,O_2}/F_{I,O_2}$) and oxygenation index) and lung mechanics (plateau pressure and respiratory compliance) improved substantially over days 1–10 in the HFO-TGI group (table 4 and fig. 3a–d).

Response to HFO-TGI

Mean$\pm$SD pre-session $P_{a,O_2}/F_{I,O_2}$ rose from 110.6$\pm$32.0 to 256.1$\pm$93.1 mmHg during the recruitment period (maximum duration 8.5 h). Oxygenation improvement was primarily due to the high $\bar{P}_{aw}$, RMs and TGI (fig. 1) [7, 8]. Subsequently, $P_{a,O_2}/F_{I,O_2}$

TABLE 2 Patient characteristics just prior to randomisation

	HFO-TGI group	CMV group
Subjects n	61	64
Age yrs	50.7±17.7	52.9±17.1
Males	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[¶]		
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 hospitalisation		
Major elective operation	5 (8.2)	10 (15.6)
Emergency operation	24 (39.3)	16 (25.0)
DMV before enrolment in the total study population[§] days	3.0 (1.0–5.5)	2.0 (1.0–5.0)
ALI/ARDS diagnosis established within 1 h of ICU admission[§]	48 (78.7)	55 (85.9)
DMV before enrolment[§] days	2.5 (1.0–3.0)	2.0 (1.0–5.0)
Tracheotomised before enrolment	8 (13.1)	8 (12.5)
SAPS II (predicted death rate %)	43.5±12.3 (35.2±23.4)	43.6±10.9 (34.4±20.2)
Presence of ⩾2/⩾3 organ/system failures	61 (100.0)/40 (65.6)	63 (98.4)/45 (70.3)
Circulatory failure		
Septic aetiology	46 (75.4)	46 (71.9)
Nonseptic aetiology	9 (14.8)	11 (17.2)
Primary ARDS	50 (82.0)	50 (78.1)
Aetiology of ARDS		
Hospital-acquired pneumonia[f,##,¶¶]	20 (32.8)	22 (34.4)
Community-acquired pneumonia[++]	7 (11.5)	10 (15.6)
Bilateral pulmonary contusions[##,§§]	22 (36.1)	12 (18.9)
Polytransfusion[¶¶,§§]	5 (8.2)	8 (12.5)
Aspiration pneumonia	5 (8.2)	4 (6.3)
Intra-abdominal sepsis	5 (8.2)	4 (6.3)
Other[ff]	9 (14.8)	9 (14.1)

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. HFO: high-frequency oscillation; TGI: tracheal gas insufflation; CMV: conventional mechanical ventilation; DMV: duration of mechanical ventilation; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; SAPS: Simplified Acute Physiology Score. [#]: the corresponding calculation formula is provided in the footnote of table 1. [¶]: some patients had more than one comorbid condition. [+]: includes six cases of alcohol abuse (three in each group), two cases of chronic atrial fibrillation (one in each group), two cases of intravenous drug abuse (one in each group), two cases of major depression (one in each group), and one case each 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 h of ICU admission, 103, seven and three patients, respectively, were confirmed as fulfilling the criteria for ALI/ARDS [15]; pre-enrolment 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 for severe oxygenation disturbance plus the time needed to obtain next-of-kin consent (see also text); pre-enrolment DMV was <7 days in 53 (86.9%) patients of the HFO-TGI group and 60 (93.8%) patients of the CMV group. [f]: caused by *Acinetobacter baumannii* (12 cases in the HFO-TGI group and 11 cases in the CMV group), *Klebsiella pneumoniae* (six cases in the HFO-TGI group and six cases in the CMV group) and *Pseudomonas aeruginosa* (two cases in the HFO-TGI group and five 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 seven patients in the HFO-TGI group and two patients in the CMV group. [¶¶]: Both factors were simultaneously present in one patient in the HFO-TGI group. [++]: caused by *Streptococcus pneumoniae* (two cases in the HFO-TGI group and four cases in the CMV group), *Legionella pneumophila* (three cases in the HFO-TGI group and two cases in the CMV group), methicillin-resistant *Staphylococcus aureus* (one case in the HFO-TGI group and two cases in the CMV group) and *K. pneumoniae* (one case in the HFO-TGI group); one case in the CMV group was of unknown aetiology; six HFO-TGI group patients and eight CMV group patients had concurrent circulatory failure. [§§]: both factors were simultaneously present in one patient of the HFO-TGI group and one patient of the CMV group. [ff]: includes three cases of acute interstitial pneumonia (one in the HFO-TGI group and two in the CMV group), three cases of necrotising fasciitis (one in the HFO-TGI group and two in the CMV group; one patient from each group also received a massive blood transfusion), two cases of thermal injury (one in each group), and one case each of urosepsis due to *Proteus mirabilis* (HFO-TGI group), sepsis due to *Serratia marcescens* (HFO-TGI group), cerebral ventriculitis and sepsis due to *A. baumannii* (HFO-TGI group), necrotising Gram-negative pneumonia (HFO-TGI group; the patient also had bilateral pulmonary contusions), necrotising pancreatitis (CMV group; the patient had also suffered an episode of pulmonary aspiration), alveolar haemorrhage (CMV group), submersion injury (HFO-TGI-group), toxic epidermal necrolysis (HFO-TGI group; the patient also had aspiration pneumonia), post-operative 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	Treated with HFO-TGI[#]/ returned to CMV[¶]	Treated with CMV alone[+]/breathing without assistance	Died[§]	Duration of daily HFO-TGI[ƒ] h	HFV $F_{I,O2}$[##] %	$\bar{P}_{aw}$[¶¶] cmH_2O	$\bar{P}_{aw}$ drop along tracheal tube[++,§§] cmH_2O	Bias flow[¶¶] $L \cdot min^{-1}$	TGI flow[ƒƒ] $L \cdot min^{-1}$	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 n or mean±SD. CMV: conventional mechanical ventilation; HFV: high-frequency ventilator; F_{I,O_2}: inspiratory oxygen fraction; $\bar{P}_{aw}$: mean airway pressure; ΔP: oscillatory pressure amplitude; P_{a,O_2}: arterial oxygen tension; MOF: multiple organ failure; $\bar{P}_{tr}$: mean tracheal pressure. [#]: total number of patients treated with HFO-TGI; 19 and 19 patients received intermittent HFO-TGI for ⩽3 and ⩾5 days, respectively. [¶]: total number of patients treated with HFO-TGI and then returned to CMV, after fulfilling the criteria for weaning from HFO-TGI (see Methods section and fig. 1). [+]: total number of patients treated with CMV alone because they did not fulfil the criterion for return to HFO-TGI (see Methods section and fig. 1). [§]: on days 2, 4, 5 and 9, five patients (one still on HFO-TGI and four on post-HFO-TGI CMV) died of MOF after achieving $P_{a,O_2}/F_{I,O_2}$ >150 mmHg during their last HFO-TGI session; within days 5–9, six patients died (four of MOF, one of hypoxaemia and one of a iatrogenic pneumothorax not related to any study protocol intervention) while still on HFO-TGI and without achieving $P_{a,O_2}/F_{I,O_2}$ >150 mmHg during that particular HFO-TGI session (see eResults section in the online supplementary material). [ƒ]: 124 (55.6%), 65 (29.1%) and 34 (15.2%) out of 223 of HFO-TGI sessions lasted <8, 8–18 and >18 h, respectively; in 16 patients, the maximum uninterrupted use of HFO-TGI ranged from 30.1–102.2 h; 177 (79.4%) out of the 223 sessions were administered to all 61 (100%) patients on days 1–4; after the morning of day 5, the remaining 46 (20.6%) sessions were administered to 19 (31.1%) patients. [##]: HFV-set F_{I,O_2} averaged over the duration of the daily HFO-TGI sessions; actually delivered F_{I,O_2} was further increased by the use of 100% oxygen flow TGI; HFV F_{I,O_2} was set at 100% during 1) the recruitment period, 2) the application of the additional recruitment algorithm (fig. 1) and 3) the 15-min periods preceding and 5-min periods corresponding to the physiological measurements of the stabilisation period. [¶¶]: parameter value averaged over the duration of daily HFO-TGI. [++]: average pressure drop determined by measuring the $\bar{P}_{tr}$ just prior to TGI initiation and after TGI discontinuation (see Methods section, fig. 1 and the eResults section in the online supplementary material); pressure drop ranged from 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 conditions, 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 $\bar{P}_{tr}$ (see online supplementary material). [§§]: eight patients were already tracheotomised before study entry, whereas a further five patients were tracheotomised during the study intervention period; during 176 (78.9%) out of the 223 HFO-TGI sessions, 53 (86.9%) out of the 61 patients were ventilated through orotracheal tubes (inner diameter 8.19±0.30 mm, range 7.50–9.00 mm); during 47 (21.1%) out of the 223 HFO-TGI sessions, 13 (21.3%) out of the 61 patients were ventilated through tracheostomy tubes (inner diameter 8.58±0.11 mm, range 8.00–9.00 mm). [ƒƒ]: 50.6±2.2% (range 45.0–55.2%) of the minute ventilation of the pre-session CMV; TGI flow ranged 4.5–8.5 $L \cdot min^{-1}$.

TABLE 4 Physiological variables, haemodynamic support and organ failure assessment for days 1–10 post-randomisation

Variable	Baseline	Day 1	Day 5	Day 10	Missing values %	p-value		
						Group	Time	Group × time
Tidal volume						<0.001	<0.001	<0.001
L								
HFO-TGI group	0.46±0.05	0.46±0.05	0.47±0.06	0.50±0.07	15.2			
CMV group	0.45±0.06	0.44±0.06	0.45±0.05	0.46±0.07	18.2			
mL·kg^{-1} PBW								
HFO-TGI group	6.5±0.6	6.4±0.6	6.7±0.7§	7.2±1.2$^{*,+,\S,\ddagger}$	15.2			
CMV group	6.5±0.5	6.4±0.5	6.3±0.4	6.4±0.6	18.2			
Ventilation rate breaths·min^{-1}						0.046	<0.001	0.003
HFO-TGI group	27.6±4.3	27.8±4.4	27.6±4.3	26.0±5.2	15.2			
CMV group	27.2±5.3	27.2±5.3	28.2±3.8	27.6±5.5	18.2			
Peak pressure cmH$_2$O						0.46	<0.001	<0.001
HFO-TGI group	43.4±6.1	42.5±5.5*	39.6±7.4$^{+,\S}$	35.3±9.5$^{+,\S}$	15.2			
CMV group	41.2±5.6	39.5±5.3^{+}	39.8±6.0	37.2±7.0	18.2			
$\bar{P}_{aw}$ cmH$_2$O						0.41	<0.001	0.001
HFO-TGI group	21.7±2.9	21.6±2.9*	18.9±2.8$^{+,\S}$	16.7±4.2$^{*,+,\S}$	15.2			
CMV group	20.3±3.3	19.7±3.0	19.6±3.2	17.9±3.1	18.8			
Plateau pressure cmH$_2$O						<0.001	<0.001	<0.001
HFO-TGI group	30.9±4.2	30.7±4.2	26.3±3.2$^{*,+,\S}$	24.0±5.6$^{*,+,\S}$	15.2			
CMV group	29.9±3.0	29.7±3.1	29.3±4.5	27.4±4.1	18.2			
External PEEP cmH$_2$O						0.81	<0.001	0.03
HFO-TGI group	14.3±2.5	14.2±2.5	12.0±2.6$^{+,\S}$	10.1±3.0$^{+,\S,\ddagger}$	15.2			
CMV group	13.1±3.0	12.9±3.3	12.1±3.2	10.5±2.8$^{+,\S}$	18.2			
Compliance mL·cmH$_2$O^{-1}						<0.001	<0.001	<0.001
HFO-TGI group	30.3±8.1	30.4±8.2	37.6±9.8$^{*,+,\S}$	43.3±11.8$^{*,+,\S}$	15.2			
CMV group	28.8±5.3	28.3±5.5	28.4±6.6	30.0±8.9	18.2			
F_{I,O_2} %						0.57	<0.001	0.007
HFO-TGI group	81.9±13.9	81.6±13.8*	65.0±12.7$^{+,\S}$	57.2±15.8$^{+,\S}$	8.3			
CMV group	76.1±14.2	74.1±14.8	69.5±17.3	61.3±17.9$^{+,\S}$	15.8			
P_{a,O_2} mmHg						<0.001	<0.001	<0.001
HFO-TGI group	75.5±17.7	77.9±19.5	108.0±37.4$^{*,+,\S}$	114.8±37.9$^{*,+,\S}$	8.3			
CMV group	78.2±12.7	78.5±12.7	85.4±22.8	90.1±28.6	15.8			
$P_{a,O_2}/F_{I,O_2}$ mmHg						0.007	<0.001	<0.001
HFO-TGI group	96.5±31.3	99.5±31.6	175.2±74.1$^{*,+,\S}$	222.9±108.1$^{*,+,\S}$	8.3			
CMV group	106.9±27.7	110.5±28.2	135.0±61.6	163.5±76.1	15.8			
Oxygenation index						0.21	<0.001	0.01
HFO-TGI group	26.4±13.5	25.6±13.4	13.6±7.7$^{*,+,\S}$	12.6±15.1$^{+,\S}$	15.2			
CMV group	21.1±8.9	19.9±8.8	19.1±10.3	14.7±8.8	18.8			
P_{a,CO_2} mmHg						0.03	0.048	0.14
HFO-TGI group	47.6±8.4	47.2±8.2	46.9±8.3	46.3±10.7	8.3			
CMV group	47.5±8.0	47.4±8.0	50.0±9.9	50.3±18.9$^{+,\S}$	15.8			
pHa						0.001	<0.001	<0.001
HFO-TGI group	7.33±0.07	7.33±0.07	7.39±0.07$^{+,\S}$	7.40±0.07$^{*,+,\S}$	8.3			
CMV group	7.30±0.08	7.31±0.08	7.36±0.09$^{+,\S}$	7.36±0.08	15.8			
Shunt fraction						0.02	<0.001	<0.001
HFO-TGI group	0.46±0.12	0.45±0.13	0.29±0.12$^{*,+}$	0.26±0.15$^{*,+}$	8.3			
CMV group	0.42±0.09	0.42±0.09	0.37±0.13	0.33±0.13	15.8			
MAP mmHg						0.16	0.02	<0.001
HFO-TGI group	81.7±13.2	79.9±13.5	81.5±11.9	83.4±9.5	8.3			
CMV group	77.3±11.0	79.1±11.9	82.4±9.7	80.1±12.8	15.8			
CVP mmHg						0.89	<0.001	0.63
HFO-TGI group	10.8±4.1	11.7±4.2^{+}	11.3±3.4	10.3±3.1	8.3			
CMV group	10.1±3.4	10.8±3.6^{+}	11.8±4.2	11.4±4.5	15.8			
Heart rate beats·min^{-1}						0.58	0.02	0.31
HFO-TGI group	98.9±18.9	96.6±19.8	90.1±17.4^{+}	95.9±14.9	8.3			
CMV group	98.9±16.7	97.7±16.6	92.3±14.2	93.4±15.4	15.8			

TABLE 4 Continued

Variable	Baseline	Day 1	Day 5	Day 10	Missing values %	p-value		
						Group	Time	Group × time
Cardiac index L·min^{-1}·m^{-2}						0.12	<0.001	0.65
HFO-TGI group	4.0±1.03	4.0±1.0	3.7±0.9	3.8±0.5	12.9			
CMV group	4.1±0.9	4.2±0.8	4.0±0.7	4.1±1.0	21.1			
DO_2I mL·min^{-1}·m^{-2}						0.46	<0.001	0.18
HFO-TGI group	460.0±122.7	475.3±133.5^{+}	431.3±105.5	443.3±116.8	12.9			
CMV group	489.8±134.8	495.7±130.0	444.9±81.6§	419.8±78.1$^{+,\S}$	21.1			
S_{cv,O_2} %						0.14	0.09	0.30
HFO-TGI group	70.7±8.8	71.4±8.5	72.8±5.8	71.6±8.7	8.3			
CMV group	70.7±6.6	71.0±6.7	71.0±6.0	71.9±4.3	15.8			
Lactate mmol·L^{-1}						0.12	<0.001	0.32
HFO-TGI group	2.5±1.8	2.3±1.8	1.9±1.1	1.5±0.8	8.3			
CMV group	2.8±2.8	2.8±2.5	2.2±2.1	1.6±0.8	15.8			
Fluid balance$^{\#}$ L·day^{-1}						0.63	<0.001	0.47
HFO-TGI group	2.03±1.65	2.34±2.34	1.04±1.48§	0.81±1.73§	8.3			
CMV group	2.07±1.71	2.56±2.04	1.07±1.55§	0.72±1.68§	15.8			
Noradrenaline¶ μg·kg^{-1}·min^{-1}						0.38	0.03	0.12
HFO-TGI group	0.19±0.16	0.22±0.23	0.15±0.13	0.09±0.11	8.3			
CMV group	0.19±0.16	0.19±0.17	0.15±0.15	0.12±0.16	15.8			
SOFA score						0.02	<0.001	0.03
HFO-TGI group	11.7±2.7	11.5±2.7	10.4±3.7	7.4±4.6$^{*,+,\S,f}$	8.3			
CMV group	12.1±2.6	11.9±2.7	11.9±4.2	10.0±3.8	15.8			

Data are presented as mean±SD, unless otherwise stated. Data originate from physiological measurements performed during conventional mechanical ventilation in each one of the 125 patients (intention-to-treat analysis), within 2 h before randomization (baseline), and between 09:00 and 10:00 h on days 1–10 post-randomisation. Detailed data on physiological endpoints and the Sequential Organ Failure Assessment (SOFA) score are presented in fig. 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, analysed data corresponded to 11 consecutive time-points, *i.e.* at baseline and on the morning of each of the first 10 days post-randomisation. 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 summarised in the online supplementary material. HFO: high-frequency oscillation; TGI: tracheal gas insufflation; CMV: conventional mechanical ventilation; PBW: predicted body weight; $\bar{P}_{aw}$: mean airway pressure; PEEP: positive end-expiratory pressure; F_{I,O_2}: inspiratory oxygen fraction; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; pH_a: arterial pH; MAP: mean arterial pressure; CVP: central venous pressure; DO_2I: oxygen delivery index; S_{cv,O_2}: central venous oxygen saturation. $^{\#}$: baseline values correspond to the fluid balance of the preceding 24 h; other values correspond to the fluid balance of days 1, 5 and 10. ¶: baseline infusion rate was the infusion rate recorded just prior to randomisation; 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 noradrenaline infusion for ⩾1 h to maintain a MAP of ⩾70 mmHg. *: p<0.05 *versus* CMV group at that particular time-point; $^{+}$: p<0.05 *versus* baseline; §: p<0.05 *versus* day 1; ^{f}: p<0.05 *versus* day 5.

fell to 221.0±82.3 mmHg (end of stabilisation period) and to 172.2±33.4 mmHg (weaning period, 30 min after TGI discontinuation; eFigure 5 in the online supplementary material). The initial $\bar{P}_{aw}$ was reduced by 6 cmH_2O within 5.5±0.6 and 16.3±14.4 h in 124 and 93 out of 223 HFO-TGI sessions, respectively. HFO-TGI resulted in significant improvements in post- *versus* pre-session oxygenation and lung mechanics, and did not affect haemodynamics or arterial carbon dioxide tension *versus* the preceding CMV (details provided in the text and eFigure 6 of the online supplementary material). Intervention failure (fig. 1) occurred in six sessions (online supplementary material).

Intervention-associated complications

On days 1–4, HFO-TGI group and CMV group patients received 4.7±3.5 and 4.7±1.5 RMs per day, respectively (p=0.79); RM abort rates due to hypotension or desaturation were ~6% in both groups (online supplementary material). On days 5–10, 19 HFO-TGI group patients received 2.0±2.2 RMs per day and the RM abort rate was 16.5%; this exclusive RM use had no significant effect on study outcomes (online supplementary material). On HFO-TGI initiation, 10 (16.7%) patients experienced one RM-associated, major drop 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^{-1}·m^{-2} (average drop 26.0±11.4%). In nine patients, haemodynamic status was restored within ⩽10 min with fluids and vasopressors. In one patient, a chest tube was inserted for tension pneumothorax. Five patients (three of whom were in the HFO-TGI group) experienced one 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 one patient, day 10 bronchoscopy revealed a haemorrhagic posterior tracheal mucosa, suggesting TGI-induced mucosal damage (online supplementary material).

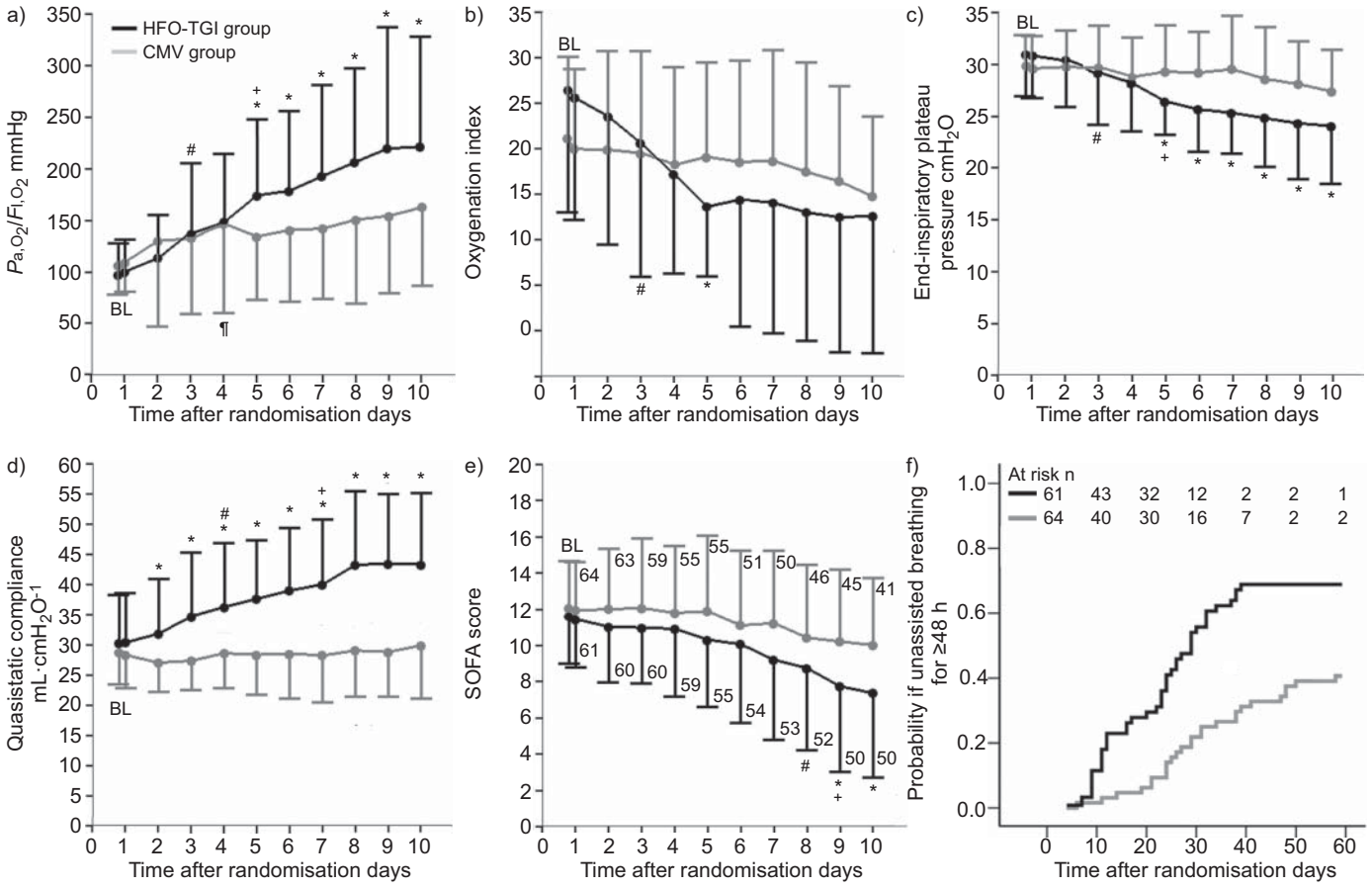

FIGURE 3. Data for a–d) major physiological variables, e) Sequential Organ Failure Assessment (SOFA) score and f) probability of achieving unassisted breathing for ⩾48 h. a–d) Circles represent means of measurements obtained during conventional mechanical ventilation (CMV), within 2 h before randomisation (baseline (BL)) and between 09:00 and 10:00 h on days 1–10 post-randomisation. e) Circles represent the mean SOFA score at baseline and at the time-points of the aforementioned physiological measurements, and numbers represent surviving patients. One CMV group patient achieved unassisted breathing from day 6 onward. One, two, two and one high-frequency oscillation (HFO) tracheal gas insufflation (TGI) group patients achieved unassisted breathing from days 4, 7, 9 and 10 onward, respectively, and one and one HFO-TGI group patients achieved unassisted breathing for 72 h starting from day 9 and unassisted breathing solely during day 9, respectively (table 3). The significant between-group difference observed on days 9 and 10 was partly due to the more frequent development of post-randomisation multiple organ failure in the CMV group (see main text for details). a–e) Error bars represent SD. Summary results for a) arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}), b) oxygenation index, c) plateau pressure, d) compliance and e) SOFA score are presented in table 4. Between-group (*) and within-group ($^{\#,\P,+}$) comparisons were subjected to the Bonferroni correction (see footnote of table 4 and the online supplementary material). *: $p<0.05$ *versus* CMV group at that particular time-point; $^{\#}$: $p<0.05$ *versus* baseline maintained from this point onward; ¶: $p<0.05$ *versus* baseline; $^{+}$: $p<0.05$ *versus* day 2 maintained from this point onward. f) $p<0.001$ by log-rank test, which compares the probability of achieving unassisted breathing for ⩾48 h within days 1–60 post-randomisation. Assignment to CMV group was an independent predictor of unassisted breathing for ⩾48 h within days 1–60 (hazard ratio 0.37, 95% CI 0.22–0.61; $p<0.001$).

Clinical course data

On days 1–60, the HFO-TGI group had more ventilator-free days *versus* the CMV group (median (interquartile range) 31.0 (0.0–42.0) *versus* 0.0 (0.0–23.0) days; $p<0.001$), and more days without respiratory (46.0 (2.0–54.0) *versus* 5.0 (0.0–33.8) days; $p=0.001$), coagulation (60.0 (21.5–60.0) *versus* 17.0 (5.3–60.0) days; $p=0.003$), liver (60.0 (28.5–60.0) *versus* 24.5 (6.3–60.0) days; $p=0.003$), circulatory (43.0 (2.0–55.0) *versus* 6.5 (0.0–39.0) days; $p=0.001$), renal (60.0 (12.0–60.0) *versus* 15.5 (2.0–60.0) days; $p=0.001$) and nonpulmonary organ failure (29.0 (0.0–46.5) *versus* 0.0 (0.0–30.8) days; $p=0.001$); results were similar for days 1–28 (online supplementary material).

On days 1–10, SOFA score improved in the HFO-TGI group (table 4 and fig. 3e). On days 1–60, the HFO-TGI group had more follow-up days *versus* the CMV group (60.0 (28.5–60.0) *versus* 24.5 (7.0–60.0) days; $p=0.001$), lower proportions of follow-up days with MOF (11.7% (1.7–69.1%) *versus* 51.0% (11.3–100.0%); $p=0.002$), less frequent MOF occurrence in patients without MOF at baseline (seven (33.3%) out of 21 *versus* 15 (78.9%) out of 19 subjects; $p=0.005$) (respective times of occurrence mean$\pm$SD 4.7$\pm$5.1 *versus* 8.5$\pm$6.6 days post-randomisation; $p=0.20$), similar absolute number of days on ventilator (20.1$\pm$13.3 *versus* 20.4$\pm$15.9 days; $p=0.90$), and more patients (42 (68.9%) out of 61 *versus* 26 (40.6%) out of 64 patients; $p=0.002$) achieving unassisted breathing for ⩾48 h (*i.e.* successful weaning) in a shorter time (21.4$\pm$10.0 *versus* 30.9$\pm$12.8 days; $p=0.001$) (fig. 3f).

Throughout the study period, the HFO-TGI group, *versus* the CMV group, had 24.3$\pm$20.9 *versus* 22.3$\pm$20.0 total days on a

ventilator (p=0.60) and 35.0 (18.0–61.5) *versus* 21.0 (7.0–57.3) total days of in-hospital follow-up (p=0.07). The HFO-TGI group had comparable percentages of patients with an occurrence of barotrauma as a new pneumothorax *versus* the CMV group (six (9.8%) out of 61 *versus* nine (14.1%) out of 61 patients; p=0.59), and one or more episodes of ventilator-associated pneumonia (VAP) (49.2% *versus* 50.0%; p>0.99), catheter-related bacteraemia (21.3% *versus* 18.8%; p=0.82), Gram-negative sepsis (59.0% *versus* 48.4%; p=0.28), renal (32.8% *versus* 37.5%; p=0.71), coagulation (24.6% *versus* 26.6%; p=0.84), hepatic (9.8% *versus* 9.4%; p>0.99) and neurological failure (52.5% *versus* 46.9%; p=0.59), heparin-induced thrombocytopenia (16.4% *versus* 18.8%; p=0.82), failure to maintain unassisted breathing (47.5% *versus* 32.8%; p=0.10), and paresis (18.0% *versus* 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 (online supplementary material). Further details on complications, and data on administered medication and rescue oxygenation (used in six (9.4%) out of 64 CMV group patients) are provided in the online supplementary material.

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

Survival

Survival to hospital discharge was higher in the HFO-TGI group *versus* the CMV group (38 (62.3%) out of 61 *versus* 23 (35.9%) out of 64 patients; 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 nonsurvivors (table 5), or the survival of patients with pulmonary contusion-associated ARDS (HFO-TGI group *versus* CMV group: 13 (59.1%) out of 22 *versus* eight (66.7%) out of 12 patients; p=0.72) (online supplementary material). Death attributable to MOF [19] was less frequent in the HFO-TGI group *versus* the CMV group (eight (13.1%) out of 61 *versus* 22 (34.4%) out of 64 patients; p=0.006) (online supplementary material). Independent predictors of in-hospital mortality included assignment to the CMV group (hazard ratio (HR) 2.64, 95% 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 $P_{a,O_2}/F_{I,O_2}$ rise was consistent with enhanced lung recruitment [6–10, 20]. This enabled reduction of the initial respiratory system distending pressure by 6 cmH_2O (stabilisation period), with maintenance of ~85% of the oxygenation benefit. The evolution of compliance (fig. 3d) suggests progressive increase in aerated lung volume [20], which explains the concurrent plateau-pressure reduction (fig. 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.

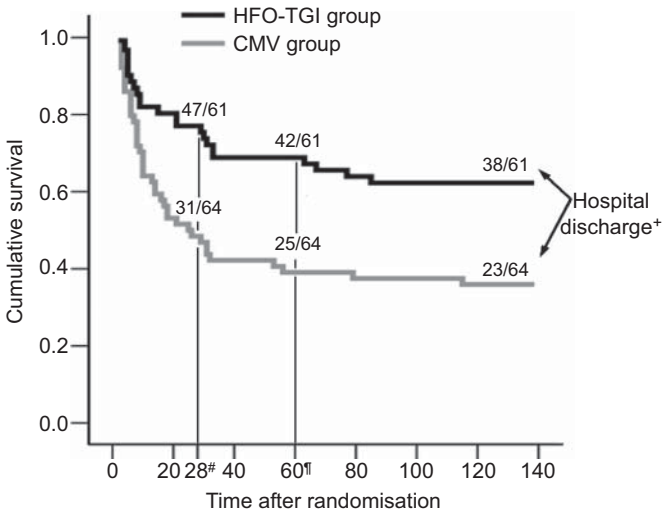

FIGURE 4. Survival to hospital discharge. p=0.002 by log-rank test; p=0.004 by Fisher's exact test. HFO: high-frequency oscillation; TGI: tracheal gas insufflation; CMV; conventional mechanical ventilation. #: p=0.002 by Fisher's exact test for 28-day survival. ¶: p=0.001 by Fisher's exact test for 60-day 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 61 discharged patients at 150 days post-randomisation was reconfirmed through telephone communication.

In the CMV group, the absence of physiological improvements (fig. 3a–d) was associated with prolonged and multiple organ dysfunction during follow-up and a long-term mortality of 64.1% [19].

TABLE 5 Length of intensive care unit (ICU) and hospital stay

	Length of stay days	p-value
ICU		
Survivors		0.35
HFO-TGI group	31.9±23.4	
CMV group	37.4±19.6	
Nonsurvivors		0.43
HFO-TGI group	21.9±20.2	
CMV group	17.7±20.3	
Hospital		
Survivors		0.15
HFO-TGI group	52.8±30.6	
CMV group	64.2±27.8	
Nonsurvivors		0.29
HFO-TGI group	24.8±25.1	
CMV group	18.3±22.4	

Data are presented as mean±SD, unless otherwise stated. HFO: high-frequency oscillation; TGI: tracheal gas insufflation; CMV: conventional mechanical ventilation.

In a recent multicentre 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%.

Previous trials evaluated continuous HFO [23, 24], prone positioning [22, 25, 26] and high PEEP with/without RMs [27–29]. Positive findings comprised improved oxygenation [22, 24–29], improved respiratory mechanics [26, 27, 29], lower rates of refractory hypoxaemia [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 favour 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-RM recruitment protocol. Nevertheless, three physiological studies suggest a TGI-related, gas-exchange and/or lower lung recruitment benefit [7, 8, 30]. Furthermore, the present study's potentially nonprotective HFO settings may augment lung base recruitment [8, 30].

During days 1–10, the study protocol was applied by subgroups of two investigators assigned to each patient of each group on a rotating 12-h 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 (online supplementary material). Notable, but promptly/effectively treated, complications occurred in 13 (5.8%) out of the 223 HFO-TGI sessions (see Results section).

Limitations

Our sample size was relatively small, but the study was adequately powered to detect a substantial survival benefit. The study design was unblinded and the results originate from just two centres, thus warranting further multicentre confirmation. Also, the study was conducted over two periods, primarily for feasibility reasons (online supplementary material). Lastly, although the high CMV group mortality and small number of ventilator-free days may be justifiable by disease severity, a selection bias in favour of the HFO-TGI group cannot be totally excluded.

Another limitation was the lack of measurement of pro-inflammatory cytokines during the intervention period. However, the causal link among persistence of ARDS, systemic inflammation and development of multiple organ dysfunction/MOF is well-established [31]. Furthermore, our physiological and SOFA score results (fig. 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-enrolment duration of mechanical ventilation (DMV) was variable (table 2), with a potentially unpredictable impact on patient outcomes [30, 32]. Indeed, although pre-enrolment DMV exceeded 7 days [33] in just 12 (9.6%) patients (eight in the HFO-TGI group), the results of a recent multicentre trial imply that any difference in the overall management strategy of early ARDS might affect results for mortality [34].

Conclusions

Our two-centre 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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CLINICAL TRIAL

This study is registered at www.clinicaltrials.gov with identifier numbers NCT00416260 (first period) and NCT00637507 (second period).

STATEMENT OF INTEREST

None declared.

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The Study Chairpersons were S.D. Mentzelopoulos (principal investigator), S. Malachias (principal investigator), S.G. Zakynthinos (study director), C. Roussos (study chair) and E. Zakynthinos (collaborating centre principal investigator). The members of the Independent Main Endpoint and Safety Monitoring Committee were P. Politis, E. Stamataki and Z. Mastora (all Evaggelismos Hospital), and Z. Daniil (Larissa University Hospital). Overall study and data quality assurance was performed by P. Politis, E. Stamataki, Z. Mastora and Z. Daniil.

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