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# The effect of high-frequency oscillatory ventilation combined with tracheal gas insufflation on extravascular lung water in patients with acute respiratory distress syndrome: A randomized, crossover, physiologic study☆,☆☆

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ABSTRACT

*Purpose:* High-frequency oscillation combined with tracheal gas insufflation (HFO-TGI) improves oxygenation in patients with acute respiratory distress syndrome (ARDS). There are limited physiologic data regarding the effects of HFO-TGI on hemodynamics and pulmonary edema during ARDS. The aim of this study was to investigate the effect of HFO-TGI on extravascular lung water (EVLW).

*Materials and methods:* We conducted a prospective, randomized, crossover study. Consecutive eligible patients with ARDS received sessions of conventional mechanical ventilation with recruitment maneuvers (RMs), followed by HFO-TGI with RMs, or vice versa. Each ventilatory technique was administered for 8 hours. The order of administration was randomly assigned. Arterial/central venous blood gas analysis and measurement of hemodynamic parameters and EVLW were performed at baseline and after each 8-hour period using the single-indicator thermodilution technique.

*Results:* Twelve patients received 32 sessions. $Pao_2$/fraction of inspired oxygen and respiratory system compliance were higher ($P < .001$ for both), whereas extravascular lung water index to predicted body weight and oxygenation index were lower ($P = .021$ and .029, respectively) in HFO-TGI compared with conventional mechanical ventilation. There was a significant correlation between $Pao_2$/fraction of inspired oxygen improvement and extravascular lung water index drop during HFO-TGI ($Rs = -0.452$, $P = .009$).

*Conclusions:* High-frequency oscillation combined with tracheal gas insufflation improves gas exchange and lung mechanics in ARDS and potentially attenuates EVLW accumulation.



## 1. Introduction

Intermittent high-frequency oscillation combined with tracheal gas insufflation (HFO-TGI), tracheal tube cuff leak, and recruitment maneuvers (RMs) improves gas exchange and lung mechanics in patients with acute respiratory distress syndrome (ARDS) [1-4]. Underlying mechanisms may include (1) high-frequency oscillation–recruitment maneuvers lung recruitment, likely augmented by tracheal gas insufflation's (TGI's) positive end-expiratory pressure (PEEP) effect [1-3], (2) preferential recruitment of previously nonaerated, dependent lung regions [4], (3) enhancement of high-frequency oscillation (HFO)-related gas transport mechanisms [5] by the TGI jet stream, and (4) improved washout of the anatomical dead space and $CO_2$ elimination [6].

An unstudied, to date, but plausible beneficial mechanism of HFO-TGI could comprise a reduction in pulmonary edema. The role of extravascular lung water (EVLW) measurement has been recently proposed to be central in the diagnosis, monitoring, and decision making in ARDS, and it is feasible by the single thermodilution technique [7-10]. In the present study, we tested the hypothesis that HFO-TGI with RMs reduces EVLW compared with CMV with RMs, without adversely affecting other hemodynamic parameters.

## 2. Patients and methods

The study was conducted from June to December 2011 in the intensive care unit of Evaggelismos Hospital, which is a 30-bed multidisciplinary unit, admitting medical and surgical patients, including trauma. The study

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protocol was approved by the Evaggelismos Hospital Scientific and Ethics Committee. Written next-of-kin consent was obtained for all patients.

### 2.1. Study subjects

Patients who met the following criteria were considered eligible for enrollment: (1) ages of 18 to 75 years, (2) body weight more than 40 kg, (3) ARDS diagnosis established within preceding 96 hours [11], (4) endotracheal intubation and mechanical ventilation, (5) oxygenation disturbances with $Pao_2$/fraction of inspired oxygen ($Fio_2$) ratio less than 200 mm Hg at PEEP at least 5 cm $H_2O$. Exclusion criteria were in accordance with previously published exclusion criteria for HFO-TGI use [3]: (1) active air leak or recent persistent (for >72 hours) air leak, (2) severe hemodynamic instability (systolic arterial pressure <90 mm Hg despite volume loading with up to 30 mL/kg crystalloid to target a central venous pressure [CVP] of 12 mm Hg and norepinephrine infusion ≥0.5 μg/kg per minute), (3) significant heart disease (left ventricular ejection fraction <40% and/or history of pulmonary edema, active coronary ischemia, or myocardial infarction), (4) significant chronic obstructive pulmonary disease (COPD) or asthma (previous hospital admissions for COPD/asthma, chronic corticosteroid therapy for COPD/asthma, and/or documented chronic $CO_2$ retention with baseline $Paco_2$ >45 mm Hg), (5) chronic interstitial lung disease, (6) lung biopsy or resection at current admission, (7) known or suspected thromboembolic disease, (8) intracranial hypertension (intracranial pressure ≥20 mm Hg despite deep sedation, analgesia, hyperosmolar therapy, and minute ventilation titrated to $Paco_2$ ≤35 mm Hg), (9) pregnancy, (10) morbid obesity with body mass index more than 40 kg/m$^2$, and (11) enrollment in another interventional study.

### 2.2. Protocol

After study enrollment, baseline measurements were obtained while patients were ventilated with lung-protective volume-assist CMV with constant inspiratory flow as prescribed by the attending physicians (Table 1). Subsequently, patients received either a session comprising 8 hours of CMV followed by 8 hours of HFO-TGI (HF-1) or vice versa (HF-2) (Fig. 1A). A schematic presentation of the study protocol is detailed in Fig. E1 in the electronic supplementary material (ESM). We used constrained randomization [12] to ensure equal number of HF-1 and HF-2 sessions and equal representation of each patient in the 2 groups. Each patient could receive at least 2 sessions, the first session being randomly assigned to 1 of the 2 groups, HF-1 or HF-2, and the second session to the opposite group. If oxygenation criteria were met for at least 6 hours after the second session and the 96-hour criterion was also met, a patient could additionally receive 2 more sessions.

The 8-hour duration of each ventilatory technique was chosen because we know from previous studies that application of HFO-TGI for more than 6 hours is associated with significant improvement in oxygenation and lung mechanics [3]. In between consecutive sessions, patients were ventilated with CMV, whereas ventilation settings, sedation, and analgesia were adjusted by the attending physicians. Any episodes of hypotension related to RMs or HFO-TGI application were to be treated with norepinephrine and a 300 to 500 mL bolus of crystalloid [3]. In the event of pneumothorax, severe hemodynamic instability, or intracranial hypertension at any point during the study period, the patient was withdrawn from the study.

### 2.3. CMV application

During every CMV period, patients were ventilated with the square-wave inspiratory flow, volume-assist control mode. Ventilatory settings were as follows: tidal volume 6 to 8 mL/kg predicted body weight (PBW), combinations of PEEP (centimeters of water), and $Fio_2$ according to the ARDSnet PEEP/$Fio_2$ protocol (10/0.6, 10-14/0.7, 14/0.8, 14-18/0.9, and 18-24/1.0) [13]; and inspiratory-to-expiratory time ratio 1:2, target pH 7.20-7.45, and target end-inspiratory plateau airway pressure less than 30 cm $H_2O$. Target $Pao_2$ was 60 to 80 mm Hg, except in patients with traumatic brain injury, where we aimed at $Pao_2$ more than 90 mm Hg. Recruitment maneuvers were administered during CMV by applying continuous positive airway pressure at 40 cm $H_2O$ for 40 seconds (see also Fig. E1 in the ESM).

Patients were sedated with midazolam and/or propofol to a Ramsay score of 4 to 6. If patient-ventilator dyssynchrony [14] was observed despite a Ramsay score of 6, continuous infusion of cis-atracurium was initiated at 0.1 to 0.2 mg/kg per hour. A bolus dose of cis-atracurium was administered 30 minutes before each RM. Continuous infusion of fentanyl at 1 to 3 μg/kg per hour was used for analgesia in the presence of clinically obvious factors mandating pain control, for example, cases of trauma or surgery within the preceding 48 to 72 hours.

### 2.4. HFO-TGI application

Before HFO-TGI initiation, orotracheal tubes (inner diameter, 8.0-9.0 mm) were cut down to 26 cm; correct positioning of tracheal tube tip (approximately 4 cm above the carina) was verified by chest radiography, and tracheal tube patency was confirmed by a less than or equal to 10-second-lasting bronchoscopy [1]. A 4.8-cm-long circuit adapter with angled side arms (Smiths Medical International, Watford, UK) was introduced in between the tracheal tube connector and the Y-piece of the ventilator breathing circuit. A rigid wall catheter (Vygon, Ecouen, France; inner diameter, 1.0 mm; outer diameter, 2.0 mm) was passed through the side arm of the adapter and was used for the administration of TGI. The TGI catheter length was tailored to the placement of its tip at 0.5 to 1.0 cm beyond the tip of the tracheal tube.

Patients were sedated with midazolam and/or propofol to a Ramsay score of 6 and paralyzed with cis-atracurium. High-frequency oscillation was provided using a 3100B high-frequency ventilator (Sensormedics, Yorba Linda, CA). Patients were connected to the high-frequency ventilator, and a 40-second RM was performed by pressurizing the HFO breathing circuit at 40 cm $H_2O$ with the oscillator piston off. We then resumed HFO and placed a 3 to 5 cm $H_2O$ tracheal tube cuff leak. We returned mean airway pressure (mPaw) to its preleak level by adjusting the mPaw valve, and mPaw was set 6 to 8 cm $H_2O$ above its value during the preceding CMV [2]. Subsequently, we connected the TGI catheter to a variable orifice $O_2$ flowmeter providing humidified $O_2$ at room temperature and started TGI at a flow equal to 50% of the preceding CMV minute ventilation. Tracheal gas insufflation initiation caused a 1 to 2 cm $H_2O$ rise in mPaw, which we reversed by adjusting the mPaw valve. Fraction of inspired oxygen was set at 1, oscillatory pressure amplitude was set at 65 to 90 cm $H_2O$ (30 cm $H_2O$ above the preceding CMV $Paco_2$ value), and oscillation frequency at 3.5 to 5.5 Hz. Oscillatory pressure amplitude and oscillation frequency were further adjusted to achieve a target arterial pH of 7.20 to 7.45. The catheter used for TGI administration was removed when switching to the conventional ventilator.

### 2.5. Measurements

Patients underwent 3 assessments in every session: at baseline, after 8 hours of CMV, and after 8 hours of HFO-TGI (Fig. 1A and Fig. E1, ESM). Each assessment lasted 10 to 15 minutes while the patient remained on CMV or HFO-TGI, respectively. Extravascular lung water, hemodynamic parameters, respiratory system mechanics, arterial and central venous blood gases, and the cumulative fluid balance over the preceding 8 hours (8-hour fluid intake minus 8-hour fluid output) were documented for each assessment.

The single-indicator transpulmonary thermodilution technique (PiCCOplus; Pulsion Medical Systems, Munich, Germany) was used for EVLW measurement and hemodynamic monitoring. This technique correlates well with the criterion standard gravimetric method in