



RESEARCH ARTICLE

High Frequency Jet Ventilation during stereotactic ablation of liver tumours: an observational study on blood gas analysis as a measure of lung function during general anaesthesia [version 1; peer review: 3 approved]

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Abstract

Background: Stereotactic ablation of tumours in solid organs is a promising curative procedure in clinical oncology. The technique demands minimal target organ movements to optimise tumour destruction and prevent injury to surrounding tissues. High frequency jet ventilation (HFJV) is a novel option during these procedures, reducing the respiratory-associated movements of the liver. The effects of HFJV via endotracheal catheter on gas exchange during liver tumour ablation is not well studied.

Methods: The aim of this explorative study was to assess lung function and the effects on blood gas and lactate during HFJV in patients undergoing stereotactic liver ablation. Blood gases were analysed in 25 patients scheduled for stereotactic liver ablation under general anaesthesia pre-induction, every 15 minutes during HFJV and following extubation in the recovery room. The HFJV was set at fixed settings.

Results: None of the patients developed hypoxia or signs of increased lactate production but a great variation in PaO₂/FiO₂ ratio was found; from 13.1 to 71.3. An increase in mean PaCO₂ was observed, from a baseline of 5.0 to a peak of 7.1 at 30 minutes (p <0.001) and a decrease was found in median pH, from a baseline of 7.44 to 7.31 at 15 minutes (p=0.03). We could not see any clear association between a decrease in PaO₂/FiO₂ ratio and PaCO₂ elevation.

Conclusions: HFJV during general anaesthesia in patients undergoing stereotactic liver ablation is feasible and it did not cause hypoxemia or signs of increased lactate production. A reversible mild to moderate impairment of gas exchange was found during HFJV.

Keywords

High-Frequency Jet Ventilation, Blood Gas Analysis, Anesthesia, General, Liver Neoplasms, Stereotactic Techniques, Surgery, Computer-Assisted/methods

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Introduction

Stereotactic ablation of tumours in solid organs is a promising, dynamically developing and potentially curative procedure in clinical oncology. High precision in targeting malignant lesions with the use of image fusion for pre-interventional diagnostic imaging is highly dependent on immobilisation of the operation field. Respiratory movements cause diaphragmatic shifts, displacing abdominal organs during stereotactic-guided procedures. Biro *et al.*¹ observed that breathing-related liver motion decreased from 20mm to 5mm using high frequency jet ventilation (HFJV) as compared to conventional ventilation.

HFJV is an attractive novel ventilatory strategy, minimizing movements in proximity to the lungs and keeping the abdominal and extraperitoneal target organ immobilised². The surgical ablation procedure usually requires at least 30 to 45 minutes to be performed and as the patient is anaesthetised before ablation begins and a CT-scan is performed before the procedure can start, HFJV will thus be applied for up to at least an hour not uncommonly in elderly ASA Class 2-3 patients (ASA Class: American Association of Anesthesiologists Classification, ASA 2 being a patient with mild systemic disease and ASA 3 being a patient with severe systemic disease). The effects on oxygenation, carbon dioxide elimination, pH and lactate formation are not well-studied in this patient category during HFJV with the jet catheter placed through the endotracheal tube during liver ablation.

The primary aim of this explorative observational study was to study changes over time in arterial oxygenation, carbon dioxide elimination, pH and lactate formation in adult patients undergoing liver ablation under general anaesthesia who are ventilated with HFJV. The secondary aim was to describe the PaO₂/FiO₂ ratio and its relation to PaCO₂ during HFJV.

Methods

Ethics

This study conforms to the standard of the Declaration of Helsinki and the study was approved by the Regional Ethics Committee in Stockholm (Dnr 2016/1124-32, June 7th, 2016) and the local Radiation Protection Committee at Danderyd University Hospital (Project number 2016-1, June 1st, 2016). Written informed consent for participation and publication was obtained from all subjects.

Patient population

Twenty-five consecutive patients (age ≥ 50 years) with primary or secondary malignant liver tumours accepted for elective stereotactic ablation were included in this study after obtaining their written and oral informed consent. Exclusion criteria applied before inclusion of the 25 patients were pregnancy, recent pneumothorax or severe, poorly controlled lung disease. Patient demographics are presented in Table 1. The study was conducted October-December 2017 at Danderyd University Hospital, Stockholm, Sweden.

Anaesthetic methods

All patients had total intravenous anaesthesia based on propofol (Propofol-Lipuro®, B. Braun Melsungen AG, Melsungen,

Table 1. Demographics. Study population demographics.

Variables		Overall series
Age (years)	Median	70
	Mean	68 (9.649 SD)
Gender, n (%)	Male	17 (68)
	Female	8 (32)
BMI (kg/m ²)	Mean	26.7
ASA-score	ASA 1	1*
	ASA 2	6
	ASA 3	18
Smoking	Yes	3 (12)
	No	22 (88)**
Lung disease	Yes	6 (24)***
	No	19 (76)
Time in HFJV	Median (min)	75

* number of patients in each ASA-classification group

** 8 patients with previous smoking habits

***2 patients with mild asthma, 2 patients with lung metastasis, 1 patient with pulmonary hypertension and Sjogren's disease, 1 patient with earlier postoperative pulmonary embolism.

Germany) 3–12 mg/kg/min and remifentanyl (Ultiva®, Glaxo-SmithKline AB, Solna, Sweden) 0,05–2 mikrgr/kg/min for induction and maintenance. Neuromuscular block was achieved by IV injection of rocuronium (Esmeron®, MSD, Haarlem, Netherlands) 0,6 mg/kg at induction.

The patients were preoxygenated with FiO₂ of 0.8 at induction and intubated with an endotracheal tube (ETT) one size larger than the standard (i.e. size 8 for women and size 9 for men) to create sufficient space for the jet cannula and allow passive exhalation. An alveolar recruitment maneuver was performed following endotracheal intubation and confirmation of correct ETT placement and, subsequently, initiation of conventional ventilation was carried out while preparing for the HFJV.

The HFJV was performed with a Monsson III device (*Acutronic, Switzerland*). A jet cannula (*Laserjet 40, double lumen jet catheter acc Biro, Acutronic Medical System AG, Hirzel, Germany*) was put through the ETT. The jet ventilator was initiated with standardised settings on the jet ventilator; driving pressure (DP) between 1.2-1.4 bar, frequency of 220 min⁻¹, oxygen 80% throughout the procedure. The ventilator had pre-set limits for ventilatory pressures at which ventilation is aborted and an alarm sound is activated.

The following protocol for a raise in PaCO₂ was used. When PaCO₂ rises above 10 kPa, DP is increased. If this does not lead to an acceptable level of PaCO₂, the frequency is decreased. If still not a satisfactory PaCO₂, HFJV is aborted and conventional ventilation is started. All these steps are carried out in close communication with the surgeon.

Monitoring consisted of 3-lead ECG, oxygen saturation via pulse oximetry on a finger, invasive blood pressure via an arterial line in radial artery and level of muscle relaxation through train of four (TOF), recorded every 5 minutes in accordance with routine practice.

Blood gas analysis

All patients had an arterial line inserted in accordance with routine practice for patients having HFJV. In 19 patients it was placed before anaesthesia and in 6 patients right after induction. Blood gas and lactate were sampled at baseline, after the start of HFJV, every 15 minutes (15', 30' and 45') during the procedure and when extubated in the recovery room. No further follow-up was done; the study protocol ended with the postoperative blood gas analysis.

Blood gases were analysed with a standard ABL 90 FLEX (*Radiometer Medical Aps, Brønshøj, Denmark*) in a standard blood gas syringe and was analysed immediately after the blood was taken from the patient (approximately 1–3 minutes).

PaCO₂ was categorised in three groups; <6 kPa, 6-8 kPa and >8 kPa. PaO₂/FiO₂ ratio was categorised in three groups; <20, 20-40 and >40.

Statistics

This is an observational study thus; no power analysis or statistical plan has been conducted and we planned for 25 patients to target the primary outcomes. Data is presented as mean and SD for normal distributed data and median and range for non-normal distributed data. Data was tested for normality with the Shapiro-Wilk test. Repeated measures one-way ANOVA was used on normally distributed data and repeated measures ANOVA on ranks was used when data was non-normally distributed. The Bonferroni or Tukey Test was used in all pairwise multiple comparison procedures. Missing data; calculations are made on available data only. A p<0.05 was considered statistically significant. All statistical tests were conducted with SigmaPlot (*version 14, Software Inc., San Jose, California, USA*).

Results

All 25 patients had an uncomplicated perioperative course. Anaesthesia, surgery and early recovery was uneventful apart from one patient who experienced a minor pneumothorax associated with the surgical procedure and was left with no further intervention. Changes in the HFJV settings per the protocol for increasing PaCO₂ had to be initiated in one patient. HFJV did not need to be discontinued in any patients. One patient had a DP of 1,6 during the whole procedure. In one patient, oxygen was raised from 80% to 100% after 5 min of HFJV as saturation dropped to 93%. Saturation was then normalised.

A total number of 131 blood gases were analysed in this study.

Mean PaO₂ at baseline was 11.6 kPa (SD 2.3). All patients had a PaO₂ above the normal lower limit of 8 kPa except for one patient (7.9 kPa). The PaO₂ increased during HFJV and all patients had perioperative PaO₂>10 kPa (see [Table 2](#)). An

Table 2. PaO₂. PaO₂ at baseline, during high frequency jet ventilation (HFJV) and after extubation in the recovery room. No hypoxemia was seen during HFJV. At recovery 3 patients required additional oxygen.

Group	N	Missing	Mean	SD	Range
Baseline	25	6	11.6	2.3	7.9–16.9
at t=1 st CT	25	1	29.2	10.7	10.5–57
at t=15' later	25	1	30.7	11.4	13–53.9
at t=30' later	25	3	29.7	12.4	13.3–56
at t=45' later	25	6	29.8	11.8	12.4–50.5
Recovery	25	5	11.4	3.0	8.45–17.8

inter-individual variation was seen in oxygenation during HFJV and the PaO₂/FiO₂ ratio significantly decreased but was restored at recovery (see [Figure 1](#)). During the stay in the recovery room, three patients required supplementary oxygen and in two cases values were not accessible. All remaining 20 patients breathing room air had a PaO₂ above the normal lower limit of 8 kPa (see [Table 2](#)).

Mean PaCO₂ at baseline was 5.0 (SD 0.4). None of the patients had a PaCO₂ above the normal limit of 6 kPa. A significant raise was seen in mean PaCO₂ from baseline to t=1st CT; 5.0 to 6.1 kPa (p=0.003). The mean PaCO₂ value increased further to peak mean PaCO₂ 7.1 kPa at 45' (see [Figure 2](#)). The number of patients with a PaCO₂ >6 kPa was 14/24 at t=1st CT, 15/24 at t=15', 18/22 at t=30', 15/19 patients at t=45'. Mean PaCO₂ during recovery (5,6 kPa) was not significantly different from the mean baseline. Five out of 23 patients had a PaCO₂ value >6 kPa at recovery, the highest value being 8.03 kPa.

Median pH decreased from baseline 7.44 to 7.31 at t=15' (p=0.03). There was a small further drop in pH but with no statistical difference between time points (see [Figure 3](#)). Fourteen out of 24 patients had a pH <7.35 at t=1st CT, 18/24 patients at t=15', 17/22 at t=30' and 14/19 at t=45'. Median pH during recovery (7.37) was not significantly different from the median baseline. Four out of 23 patients had a pH<7.35 at recovery, with the lowest value being 7.24 (see [Figure 3](#)).

All lactate values were within normal range during HFJV. One patient had a minor increase (2.3 mmol L⁻¹) during recovery.

There was no clear correlation between decrease in PaO₂/FiO₂ ration and the PaCO₂ increase (see [Figure 4](#)). Ten out of 16 blood gas analyses (62%) with a PaCO₂>8 had a PaO₂/FiO₂ ratio of >40. Thirteen out of 39 (33%) of the blood gas analyses with normal PaCO₂ had PaO₂/FiO₂ ratio <40.

Discussion

There is sparse information about arterial blood gas changes during HFJV during abdominal surgery. No previous study has

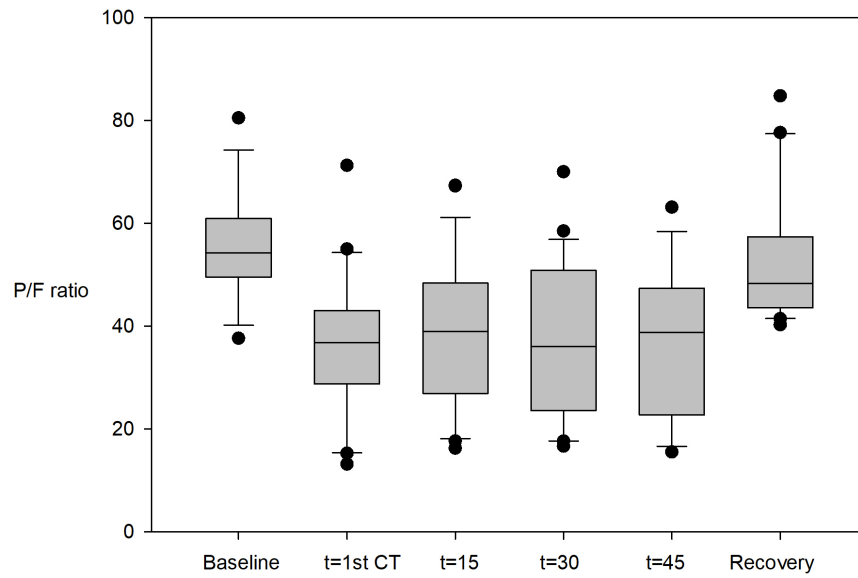


Figure 1. PaO₂/FiO₂ ratio. PaO₂/FiO₂ ratio at baseline, during high frequency jet ventilation and after extubation in the recovery room. An inter-individual variation was seen in oxygenation during HFJV and the PaO₂/FiO₂ ratio significantly decreased but was restored at recovery.

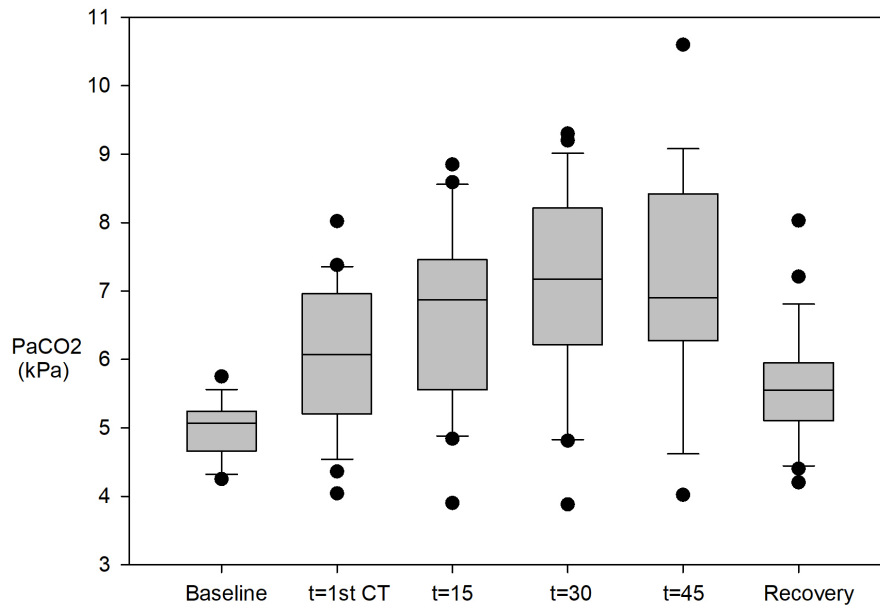


Figure 2. PaCO₂. PaCO₂ at baseline, during high frequency jet ventilation and after extubation in the recovery room. A significant raise was seen in mean PaCO₂ from baseline to 1st CT. Five out of 23 patients had a PaCO₂ value >6 kPa at recovery, the highest value being 8.03 kPa.

explicitly assessed oxygenation and carbon dioxide elimination during CT-guided stereotactic liver ablation with the jet ventilation catheter placed inside an ETT. Our study showed that this technique, high frequency jet ventilation by a catheter placed through the ETT, maintained adequate oxygenation in all patients. The gas exchange, the ratio of arterial oxygen partial

pressure to fractional inspired oxygen (PaO₂/FiO₂), decreased and varied considerably. The carbon dioxide tension increased and pH decreased reasonably as an effect of the CO₂ retention. Furthermore, the impairment in oxygenation, decrease in PaO₂/FiO₂ ratio and CO₂ elimination was found somewhat surprisingly not to correlate, showing a scattered pattern. There

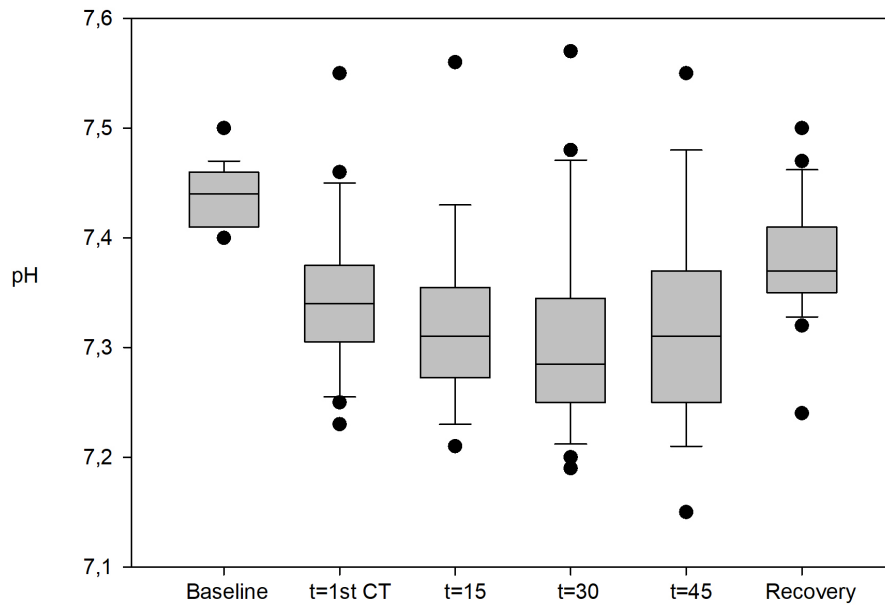


Figure 3. pH. pH at baseline, during high frequency jet ventilation and after extubation in the recovery room. There was a significant drop in pH from baseline during HFJV. Four out of 23 patients had a pH<7.35 at recovery, with the lowest value being 7.24.

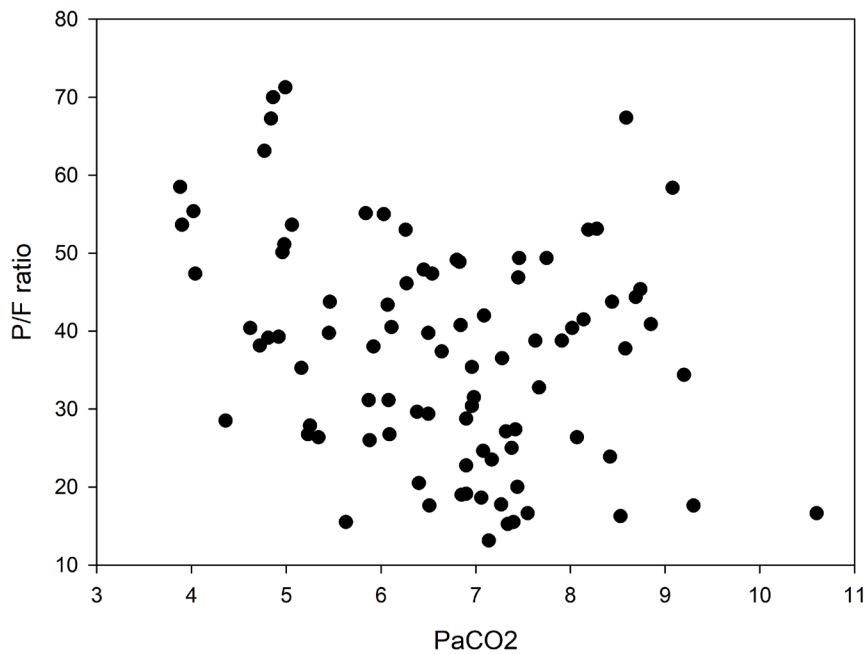


Figure 4. PaO₂/FiO₂ ratio vs PaCO₂. Plotted blood gas pairs of PaO₂/FiO₂ ratio vs PaCO₂ in the 25 patients studied. No clear correlation could be seen.

was also only modest residual impairment of gas exchange during early recovery.

High frequency ventilation is not new³. However, most HFJV use is for airway interventions, for example during a bronchoscopy or laryngoscopy. This may not entirely translate to its use in

abdominal surgery, in this case during puncture of the liver under CT-guidance, with the jet catheter placed through an endotracheal in patients who are under general anaesthesia and receiving muscle relaxants. The HFJV catheter in our study was inserted into the endotracheal tube and thus the explicit effective inspired oxygen fraction cannot be defined. The PaO₂/FiO₂ findings may

thus not be entirely true. The open system may also impact the expired pressure as well as gas elimination. Pause pressure was measured via the tip of the jet cannula, providing the pressure at tracheal level between the jet inspirations. This is not a fully representative pressure for the whole lung but may still be seen as an indicator for built-up auto positive end expiratory pressure (PEEP). The HFJV technique is dependent on passive outflow, contrary to high frequency oscillation that possibly has a more active exhalation. There is indeed, with HFJV, an obvious risk of carbon dioxide retention as well as a potential for a build-up of intrinsic PEEP and subsequent risk for barotrauma.

All patients had total intravenous anaesthesia because of the open airway system and all had muscle relaxation to promote the stereotactic liver ablation, both factors that impact on lung function⁴. Age and supine position are also factors known to impair the lung function during anaesthesia⁵. In the present study a FiO_2 of 0.8 was used during the entire procedure except for one patient who had a FiO_2 of 1.0. High oxygen fraction may cause rapid absorption atelectasis and anaesthesia *per se* causes loss of muscle tone and reduced lung volume, factors having a negative effect on ventilation/perfusion matching⁶. It should also be acknowledged that preoxygenation was performed before induction, thus further promoting lung collapse when the high oxygen fraction is maintained⁷. Several of the patients had a history of pulmonary disease, further impairing ventilation/perfusion matching during anaesthesia⁸. The oxygenation as well as the arterial carbon dioxide tension was somewhat surprisingly restored by the arterial blood gas measurement in the recovery room. Lung recruitment manoeuvre is standard procedure following intubation but not during emergencies.

Comparison with previous studies

Bickel *et al.*⁹ found that HFJV during laparoscopy in ASA 1-2 patients lessened the cardiovascular effects of pneumoperitoneum as compared to conventional ventilation. They only briefly commented on the effects on blood gases. Contrary to the present findings, they state that PaO_2 , PaCO_2 and pH was similar during all phases and between the study groups. Explicit values were, however, not presented. They used the same type of HFJV apparatus, with an average ventilator frequency of 150 cycles/min. In an earlier study, transtracheal HFJV was started with 100% oxygen at 30 to 35 pounds per square inch of driving pressure (equals 2.1-2.4 bar), 100 cycles per minute and an I:E ratio of 25%. An increase in CO_2 was noted at 10 minutes, similar to the present findings¹⁰. There is also a risk for hypercapnia and/or hypoxia when HFJV is used during airway surgery as shown by Fernandez-Bustamante *et al.*¹¹. Their study included 316 patients who underwent an interventional rigid bronchoscopy under general anaesthesia and HFJV. The most common complications were hypoxia, hypercapnia and hemodynamic instability. Sutterlin *et al.*¹² found that increasing frequency raised arterial carbon dioxide, possibly by reducing the gas elimination time. The carbon dioxide and pH normalised after awakening. It would indeed be of value to be able to monitor the inspired alveolar oxygen pressure and carbon dioxide tension as well as PEEP during HFJV.

Alternative methods and future studies

Alternative lung ventilation modes could be considered during liver tumour ablation instead of HFJV. Various forms of high flow systems for apnoeic oxygenation have recently gained interest, including THRIVE (transnasal humidified rapid-insufflation ventilatory exchange). Several reports show the feasibility of THRIVE during general anaesthesia in the difficult airway situation¹³ and in laryngeal surgery¹⁴. In the difficult airway situation, THRIVE is a way of prolonging the apnoeic time until a definitive airway is secured. Whether this technique could have a place in anaesthetic management for stereotactic liver ablation needs to be investigated.

Limitations of the study

There are several limitations that should be considered. We have not included any control group having conventional ventilation as this would jeopardise intervention safety and accuracy, increasing the risk for bleeding and tissue damage. As pointed out, only one HFJV setting was used. Pressure and frequency was not adjusted, except in one patient when pressure was slightly adjusted according to a raise in PaCO_2 . Likewise, a fixed oxygen fraction was used throughout the procedure and, as mentioned, oxygen concentration reaching the alveoli and PEEP levels cannot be assessed. The focus of our study was gas exchange during HFJV, following arterial blood gases under steady state jet ventilation. We did not include any further follow-up after the recovery phase.

Conclusion

This study shows the feasibility of using HFJV through an ETT with an FiO_2 of 0.8 during liver tumour ablation. It did not cause any hypoxia or increase in lactate. It was associated with mild to moderate impairment in gas exchange that was restored during early recovery.

Data availability

Underlying data

Harvard Dataverse: Replication Data for; High Frequency Jet Ventilation during stereotactic ablation of liver tumours – an observational study on blood gas analysis as a measure of lung function during general anaesthesia. <https://doi.org/10.7910/DVN/MXHFWW>¹⁵

This project contains the following underlying data:

- Blood gas HFJV F1000_data_190401.tab (Blood gas data associated to HFJV)

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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HFJV causes minor movement of liver tissue and is thus advantageous in liver ablation, compared to standard mechanical ventilation. This study shows that gas exchange can be maintained at a reasonable level for an hour-long anesthesia/surgery. A successive fall in PaO₂ was seen but in no patient was hypoxemia seen. Similarly, PaCO₂ rose during the hour-long observation period, but not to any critical level. The authors found no correlation between fall in PaO₂ and increase in PaCO₂. Thus, hypoventilation was not the major or only cause of impaired oxygenation. FIO₂ was in most patients 0.8, but in an open system, as here, the alveolar FO₂ may be different and also vary between patients. The authors discuss a certain degree of auto-PEEP but have not been able to make measurements of it. Atelectasis may be reduced with increase in auto-PEEP, as inferred by the authors. One may speculate in varying distance between catheter tip and carina with effects on ventilation of each lung. Impairment in lung perfusion, possibly reflected by decrease in cardiac output, might be an additional cause of varying oxygenation.

However, all these comments are speculations and need not be in a paper.

On the whole, the study is well performed in a simple and straightforward way. Results are clear and show a reasonably maintained gas exchange under the studied conditions.

My only minor criticism is that the ventilatory technique is mentioned in different parts of the paper and could be brought together in the Methods section.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Respiratory physiology, in particular gas exchange and lung morphology during anesthesia and in acute lung injury.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 18 September 2019

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The authors address the question if high frequency jet ventilation (HFJV) affects blood gases when applied during stereotactic ablation of liver tumours. This procedure has evolved as an auspicious treatment in the field of hepatic oncology. It is crucial to minimize the movement of the liver to establish optimal conditions for the surgeon throughout the intervention. Hence, HFJV has evolved as a promising method. No data are available so far on the effects of HFJV on gas exchange during stereotactic ablation of liver tumours. Therefore, 25 patients have been involved in this observational study. Blood gases were assessed before induction and every 15 minutes during HFJV and finally in the recovery area after extubation. No hypoxia could be observed in any of the patients even though paO_2/F_1O_2 showed a wide range. $PaCO_2$ increased during HFJV and returned to baseline levels after extubation. pH decreased due to CO_2 retention during HFJV. There was no correlation between paO_2/F_1O_2 and CO_2 . The authors conclude that HFJV does not cause hypoxaemia during stereotactic liver ablation under general anaesthesia but that gas exchange is slightly impaired during the procedure.

This article makes an important contribution to the anaesthetic practice during stereotactic ablation of liver tumours. Working conditions for the surgeon can be optimised by HFJV without compromising the patient's gas exchange and metabolic status.

The manuscript is well written and attractive. The abstract fulfils its purpose in giving a clear overview of the whole study. The background of the intervention as well as the importance in the oncological field and the problems associated with ventilation are clearly pictured in the introduction. A sound description of the

aims of the study are also provided. The study population, anaesthetic methods and blood gas analysis are soundly described in the methods section. The presentation of the results is clear and straightforward with well-designed graphs and tables to illustrate the outcome parameters. Every result is discussed and literature in the field is cited and compared with the findings of this study. A perspective for future studies is given and the promising conclusion is drawn that HFJV is feasible to use during liver tumour ablation without causing hypoxia or an increase in lactate although a moderate impairment in gas exchange was observed during the procedure.

All in all, I think that this paper is an important addition to the literature with a well-thought-out protocol, clear results and a promising conclusion. It is scientifically sound and should be accepted for indexing.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anaesthesia in cardiac and thoracic surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 03 July 2019

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High frequency jet ventilation (HFJV) is an alternative method to conventional ventilation which is known to minimize movement of the thorax and abdomen what finally could facilitate surgical procedures. The aim of the study of the revised manuscript was to analyze usefulness, efficacy and safety of HFJV during stereotactic ablation of liver tumors with particular emphasis on gas exchange. The study was performed on 25 patients with malignant liver tumors. In conclusions, authors demonstrated possibility and benefits of HFJV's usage during the liver's surgical procedures. However, influence of some disadvantages on patients' gas exchange was also critically discussed.

In general the work presents interesting results and, in my opinion, could be accepted.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: oncology, ophthalmology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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