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Nasal High Flow Reduces Dead Space

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ABSTRACT:

Recent studies show that nasal high flow (NHF) therapy can support ventilation in patients with acute or chronic respiratory disorders. Clearance of dead-space has been suggested as being the key mechanisms of respiratory support with NHF therapy.

The hypothesis of this study was that NHF in a dose-dependent manner can clear dead space of the upper airways from expired air and decrease re-breathing.

The randomized cross-over study involved 10 volunteers using scintigraphy with ^{81m}Krypton-gas (^{81m}Kr-gas) during a breath-holding maneuver with closed mouth and in three nasally breathing tracheotomized patients by volumetric capnography and oximetry through sampling CO_2 and O_2 in the trachea and measuring the inspired volume with inductance plethysmography following NHF rates of 15, 30 and 45 L/min.

The scintigraphy revealed a decrease in ^{81m}Kr-gas clearance half-time with an increase of NHF in the nasal cavities (cc = -0.55, $p < 0.01$), pharynx (cc = -0.41, $p < 0.01$) and the trachea (cc = -0.51, $p < 0.01$). Clearance rates in nasal cavities derived from time constants and MRI-measured volumes were 40.6 (SD 12.3), 52.5 (SD 17.7) and 72.9 (SD 21.3) mL/s during NHF (15-30-45L/min). Measurement of inspired gases in the trachea showed an NHF-dependent decrease of inspired CO_2 that correlated with an increase of inspired O_2 (cc = -0.77, $p < 0.05$). NHF clears the upper airways from expired air, which reduces dead space by a decrease of re-breathing making ventilation more efficient. The dead-space clearance is flow and time-dependent and it may extend below the soft palate.

Part of the study has been registered at www.clinicaltrials.gov (NCT01509703).

Keywords: nasal high flow, upper airways, dead space, re-breathing, Krypton, respiratory support

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66 **New and Noteworthy**

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68 Clearance of expired air in upper airways by nasal high flow (NHF) can be extended below
69 the soft palate and de facto causes a reduction of dead-space. Using scintigraphy the authors
70 found a relationship between NHF, time and the clearance. Direct measurement of CO_2 and
71 O_2 in the trachea confirmed a reduction of re-breathing, providing the actual data on
72 inspired gases and this can be used for the assessment of other forms of respiratory support.

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INTRODUCTION

Recent studies report that an open nasal cannula system that generates nasal high flow (NHF) with or without supplemental oxygen (O_2) can assist ventilation in patients with chronic respiratory failure (1, 5, 22, 24), sleep disorders (17, 21), in hypoxemic patients after cardiothoracic surgery and in those with acute hypoxemic respiratory failure (6, 25, 28). In addition, the use of this form of respiratory support in pediatrics and in newborns has proven clinical benefits (8, 11, 15). Delivering a high flow of gas through the open nasal cannula to generate airway pressure (27) has been tried in the past but developments in technology have now allowed efficiently heated and humidified respiratory gases to enable a wide range of flow rates from 2 L/min in preterm newborns to 60 L/min in adults (24, 28).

A number of clinically relevant benefits have been associated with NHF therapy: reduction in respiratory rate, a decrease of minute ventilation during sleep, improved alveolar ventilation, a reduction in wasted ventilation and the work of breathing (4, 11, 23, 28), although how NHF produces these effects is not yet understood. A mechanistic study on healthy volunteers suggested two different ventilatory responses to NHF, one when awake and another during sleep (19). In this study it was speculated that the reduction of dead-space ventilation due to clearance of anatomical dead-space in the upper airways could be the principal driver for the reduction of minute ventilation during sleep, which may potentially lead to a reduction in the work of breathing. In a previous study using upper airway models the authors demonstrated the fast-occurring flow dependent clearance of nasal cavities by NHF (18). The dead-space clearance is difficult to study *in vivo* due to the complexity in quantifying the respiratory gases in the airways. However, many have proposed it to be the major physiological mechanism, which improves respiratory support (20, 22, 26) and reduces arterial and tissue CO_2 (1, 7, 14).

The aim of this study was to measure upper airway dead-space reduction during NHF therapy to test a hypothesis that NHF in a dose-dependent manner can clear dead space in the upper airways and decrease re-breathing.

Clearance of ^{81m}Kr tracer gas from the upper airways by NHF was assessed in healthy volunteers using dynamic gamma camera imaging. Reduction of re-breathing was investigated in tracheotomized patients using volumetric capnography and oximetry by sampling gas from the trachea while the patients maintained nasal breathing during NHF therapy.

METHODS

Study participants

Ten healthy, non-smoking volunteers (age 55 +/- 14 years) participated in the tracer-gas scintigraphy study (Table 1). This part of the study was approved by the Ethics Committee of the Medical School of the Ludwig Maximilian University (Munich, Germany), and written consent was obtained from each subject.

In the second part, three male patients who did not require supplemental O_2 were included, each of whom had received long-time mechanical ventilation through a tracheostomy and then were admitted for weaning. Two of them had COPD (age 59 and 72 years), and the third patient was recovering from subarachnoid hemorrhage and pneumonia (age 72 years). This part of the study was approved by the Ethics Committee of Witten-Herdecke University, Germany, and registered under clinicaltrials.gov (NCT01509703).

Nasal high flow (NHF)

NHF rates of 15, 30 and 45 L/min without supplemental oxygen were delivered in a randomized order using the AIRVO™ blower-humidifier and the Optiflow™ nasal cannula (Fisher & Paykel Healthcare, New Zealand). In the scintigraphy study NHF was delivered for 30 s (during breath-holding). In the tracheotomized nasally-breathing patients NHF was delivered continuously for 10 min. Throughout all studies the mouth remained closed.

Scintigraphy

For these experiments the ^{81m}Kr-gas was generated and a planar gamma camera was used for imaging, as described in detail earlier (18). The volunteers filled their upper airways with

^{81m}Kr tracer gas through the nasal pillow, and the NHF cannula with the preset flow was inserted into the nose while the volunteer was holding their breath. ^{81m}Kr-gas activity-time profiles were assessed in five regions of interest (ROI): anterior nasal (Nasal1), posterior nasal (Nasal2), pharynx (space from the soft palate to the larynx), trachea and the upper lung (Figure 1A). ^{81m}Kr-gas clearance time constants and half-times were evaluated after correction with the natural ^{81m}Kr-gas decay ($T_{1/2}$ = 13 s). Nasal clearance rates were evaluated as the ratio of nasal volume (V_N) and clearance time constant. Nasal volume, comprising the nasal cavity and the nasopharynx (excluding sinuses) was assessed using individual MRI imaging.

Clearance of anatomical dead space in tracheotomized patients

Tracheotomized patients were included in order to assess re-breathing of expired gas from the upper airways. When the weaning from invasive mechanical ventilation was completed the tracheostomy tube was replaced with a tracheostomy retainer (2). A custom-made probe was placed through the retainer to measure O_2, CO_2 and pressure profiles for synchronization with breathing (ADInstruments, New Zealand). Inspiratory volume was assessed with calibrated respiratory inductance plethysmography (RIP; Viasys Services, USA), as described in detail previously (12, 19).

The effect of NHF on the volume of inspired O_2 and CO_2 was analyzed for every breath. Inspired O_2 was calculated in the first 100 mL of inspired volume. Inspired CO_2 was calculated in the total inspired volume and in the first 100 mL. Arterial blood oxygen saturation (SpO_2) and transcutaneous CO_2 (Tosca, Radiometer, Denmark) were monitored throughout the study.

Data analysis

All data is presented as mean +/- standard deviation (SD). Differences between groups or application modes were assessed by a two-sided t-test using a significance level of $p < 0.05$. Pearson's coefficient correlation (cc) analysis was then applied, to assess the correlation among the study variables.

RESULTS

^{81m}Kr-gas clearance in healthy volunteers

After filling the upper airways with ^{81m}Kr-gas the volunteer was holding his or her breath and the NHF cannula was attached to their nose; this caused immediate purging of the ^{81m}Kr-gas from the upper airways (Figure 1B and supplemental video). NHF caused rapid activity decay in the nasal cavity and, as shown in Figure 1B, the nasal cavity was cleared at 0.5 s after applying NHF at a rate of 45 L/min.

The half-times of ^{81m}Kr-gas clearance in nasal regions are shown in Table 2 and Figure 2A. For both the anterior (Nasal1) and the posterior (Nasal2) ROIs, there was a decrease in ^{81m}Kr-gas clearance half-time with an increase of NHF from 15 to 45 L/min ($cc = -0.55$, $p < 0.01$) in all subjects. Nasal1 ROI cleared faster compared to the Nasal2 ($p < 0.01$) and clearance half-times in both ROIs highly correlate ($cc = 0.55$, $p < 0.01$). There is no correlation between clearance half-times and individual nasal volumes V_N derived from MRI scans. Using the time constants for both ROIs and V_N, the clearance rate in the nasal cavities was calculated: 40.6 (SD 12.3), 52.5 (SD 17.7) and 72.9 (SD 21.3) mL/s during NHF of 15, 30 and 45 L/min, respectively. This demonstrates that there is a significant correlation between clearance rate and NHF ($cc = 0.61$, $p < 0.01$).

In the lower compartments beyond the soft palate, ^{81m}Kr-gas clearance was also NHF dependent but slower (pharynx: $cc = -0.41$, $p < 0.01$; trachea: $cc = -0.51$, $p < 0.01$; Table 2 and Figure 2B) and in some experiments only natural ^{81m}Kr-gas decay was recorded. Pharyngeal and tracheal clearance half-times correlated with the nasal half times ($cc = 0.4$, $p < 0.05$). There was no detected ^{81m}Kr-gas clearance in the lung ROI.

Re-breathing of expired air during NHF therapy in tracheotomized patients

An example of a single-breath analysis of inspired CO_2 and O_2 at baseline and during an NHF rate of 45 L/min is presented in Figures 3A and 3B. A summary of the effects of NHF on inspired CO_2 and O_2 in the first 100 mL is shown in Figure 4. In all three patients studied, NHF led to a decrease of inspired CO_2 and to an increase of inspired O_2 in a flow-dependent manner (Figure 4A and 4B). Linear regression analyses between a change (Δ) of total inspired

O_2 versus CO_2 in the first 100 mL per breath are presented in Figure 4C. An NHF-induced decrease of inspired CO_2 correlates with an increase of inspired O_2 (cc = -0.767; r^2 = 0.59, p = 0.016). A ratio between inspired CO_2 in the first 100 mL of inspired volume to the total inspired CO_2 grouped by all baselines and NHF treatments is presented in Figure 4D. NHF resulted in a significantly higher ratio during NHF treatment relative to baseline ventilation (0.84 (SD 0.10) vs. 0.75 (SD 0.12); $p < 0.01$, paired t-test). Change of tidal volume, respiratory rate, minute ventilation as well as SpO_2 and tissue CO_2 throughout the study are presented in Table 3.

DISCUSSION

In the first part of the study, dead-space clearance by NHF therapy was analyzed in 10 healthy volunteers by the use of ^{81m}Kr-gas, a radioactive tracer gas and a gamma camera. The major findings in this investigation are the NHF-dependent reduction of radioactive tracer-gas clearance half-times in the upper airways with very fast removal of the tracer gas from the nasal cavities (half-times < 0.5 s at an NHF rate of 45 L/min) that confirmed the authors' model study (18). Further in various volunteers significant ^{81m}Kr-gas clearance was detected in deeper compartments below the soft palate, which could be investigated only *in vivo*. Rates of NHF in the range of 15 to 45 L/min were used, which were also used previously (18) and which is common in clinical settings for adults. NHF rates up to 60 L/min were used in patients with acute respiratory failure (28), but cannot be well tolerated by some naïve healthy participants that were found during the preparation of the experiments. In the second part of the study, tracheal O_2 and CO_2 breathing profiles in three tracheotomized patients revealed an NHF-dependent increase of inspired O_2 and a decrease of inspired CO_2, which confirmed a reduction of re-breathing and supported a hypothesis that NHF reduces dead space.

The ^{81m}Kr-gas imaging has demonstrated very fast clearance of the tracer gas after the application of high flow through the nasal cannula. The clearance half-times were shorter in the anterior than in the posterior ROIs, demonstrating the direction of clearance, and they were inversely correlated with NHF. Most of the clearance took place in the nasal ROIs with half-times under 1.0 s (Figures 1B and 2A).

The clearance study was conducted during breath-holding. The effects of respiration on clearance were excluded in this research to avoid the effect of breathing and due to the technical restrictions. In several experiments there was no ^{81m}Kr-gas clearance below the soft palate (see also Figure 2B). This could be induced voluntarily, since it has been shown that subjects can close their soft palate unintentionally during the breath-holding, but the mechanism of this reflex is not fully understood (10).

Clearance of ^{81m}Kr-gas in the lower parts of conducting airways may be of lesser relevance due to very long half-times, as revealed; however, the fact that NHF can produce some clearance even in those deep compartments may suggest a potential increase of the NHF clearance efficiency with a presence of long end-expiratory pauses or opening of the mouth. In other words, clearance of the upper airways by NHF may not be limited by the volume of the nasal cavities.

The results of clearance from nasal cavities are very similar to experiments conducted in upper airway models (18). Faster clearance in the model study can be explained by the lack of restrictions in the reconstructed upper airways compared to those of the real human anatomy. Similar to the model experiments used during the current study, the clearance rate was assessed in the same two adjoining nasal ROIs and also showed a linear relationship with NHF. It is nearly doubled (from 40.6 (SD 12.3) to 72.9 (SD 21.3) mL/s) with an increase of NHF from a rate of 15 to 45 L/min.

Clearance of tracer gas in the upper airways was further confirmed in tracheal CO_2 and O_2 breathing profiles of three tracheotomized patients. The tracheal inhalation profiles plotted for one patient (see Figures 3A and 3B) show that an NHF rate of 45 L/min reduces the inspired CO_2 and increases the inspired O_2 compared to baseline. Profiles of inspired tracheal CO_2 and O_2 demonstrate that the maximum difference between the gases is positioned between the first 50 mL and 100 mL of the inspired volume. NHF resulted in a flow-related reduction of CO_2 re-breathing (Figure 4A) and an increase of O_2 in the inspired gas (Figure 4B) with a negative correlation ($cc = -0.767$; $n = 9$, $p < 0.05$), as further analyzed in Figures 4C and 4D.

At the end of expiration, conducting airways are filled with gas that typically contains approximately 5% of CO_2 and 16% of O_2 and at the beginning of inspiration the expired gas is re-inspired back into the lungs. NHF delivers fresh air into the upper airways through a pair of non-sealed cannulas, purging the expired gas outside the nasal cavity. There is very little CO_2 in ambient air (0.04%) and consequently CO_2 can be compared in a total inspired volume between the baseline and NHF. Inspired O_2 is greatly dependent on inspired tidal volume and in order to accurately measure a relatively small change of O_2, only a re-breathing portion has to be measured in the inspired volume. The authors chose the first 100 mL to measure a change of inspired CO_2 during NHF application. A smaller difference between the recorded decrease of inspired tracheal CO_2 and the increase of inspired tracheal O_2 can be explained by a calculation of inspired O_2 in the first 100 mL of inspired gas and the fact that gas was sampled from the trachea into the gas analyzer, prolonging the response time. Inspired CO_2 is presented in Figures 3A and 4A as a total rather than as the first 100 mL per breath, as with O_2, because of high clinical relevance.

The ratio of CO_2 in the first 100 mL of inspired air to the total inspired CO_2, as shown in Figure 4D, resulted in a significantly higher ratio during NHF relative to the baseline (ratio = 0.84 (SD 0.10) during NHF vs. 0.75 (SD 0.12) at baseline; $p < 0.01$, paired t-test). This can be explained by the clearance of expired gas in the upper airways that causes a reduction of the last portion of re-inspired CO_2 measured in the trachea, thereby enhancing the ratio. Therefore, when applying NHF, re-inspired CO_2 primarily results from the first 100 mL of the inspired air, making the difference between the volumes of inspired CO_2 smaller and shifting the ratio closer to 1.00. It can also be illustrated in Figure 3A, which shows most of CO_2 during NHF is measured within the first 100 mL and consequently increasing the ratio of CO_2 measured in 100 mL to CO_2 measured in the total inspired gas volume. The method of the ratio calculation can be recommended for future studies as it is informative and may be used without calibration of inspired volume.

Data on ventilation during the study (Table 3) shows a rather small amount of tidal volume measured with RIP in all three patients. RIP was calibrated with a pneumotachograph before and after the experiment and showed very small drift between calibrations, confirming the

298 robustness of the data. Nevertheless, tidal volumes smaller than 250 to 300 mL with normal
299 respiratory rate may suggest some inaccuracy of the method, which could affect volumes of
300 calculated inspired O_2 and CO_2 and lead to an underestimation of the parameters. It is
301 interesting to note that in two experiments minute ventilation was markedly reduced during
302 NHF while the respiratory rate was within normal values (range 10.6 to 15.0 min^{-1}) and there
303 was no change in blood gases. Reduction of minute ventilation through a decrease of tidal
304 volume may indicate a reduction in the work of breathing without a change in blood gases,
305 which could remain clinically undetected because tidal volume is not measured routinely
306 during NHF therapy. Variability in the ventilation parameters shows that the effect of NHF on
307 ventilation in patients has to be investigated in the homogenous groups. The presence of a
308 probe in the trachea may also affect the breathing pattern and is preferably to be excluded
309 in such studies.
310
311 **Physiological and clinical implications**
312 A decrease of re-breathing of CO_2 by approximately 1 mL to 3 mL per breath calculated from
313 the inspired volume with an end-tidal concentration of 5% and a similar increase of inspired
314 O_2 correspond to a reduction of dead space by 20 to 60 mL following a rise of the NHF rate
315 from 15 to 45 L/min. This indicates an agreement of data between the scintigraphy part of
316 the study in volunteers and the measurements of inspired gases in the tracheotomized
317 patients. The scintigraphy during breath-holding showed the tracer-gas clearance at
318 different levels of conducting airways in relation to NHF rates and time. Measurement of CO_2
319 and O_2 in the trachea during respiration confirmed the NHF-dependent decrease of re-
320 breathing of expired air, which is eventually a reduction of dead space.
321
322 The reduction of dead space by NHF may increase alveolar volume if tidal volume remains
323 the same. It may also slow down the respiratory rate or reduce tidal volume and minute
324 ventilation, as has been observed in this study and also as previously reported in healthy
325 subjects during sleep (19). Reduction of the respiratory rate is the most frequently described
326 respiratory parameter associated with NHF therapy in adults and children (1, 16, 26) and it is
327 also reported to be a simple and informative predictor of potentially serious clinical events
328 (3). It might be speculated that the reduction of respiratory rate by NHF can be more
329 substantial in patients with an increased respiratory rate. In this study the authors observed

very small reduction of the respiratory rate, which was within normal limits, but the small sample size and the study design did not allow for any definitive conclusion. Reduction of dead space may also affect gas exchange: a reduction of arterial CO_2 (1)ʹ(20) and an increase of oxygenation (7, 20) by NHF were shown, although these effects were not evident in this study, probably, because the NHF application times (10 min) were too short.

The ratio of dead space to tidal volume increases during shallow breathing or when the total physiological dead space is raised due to an increase of alveolar dead space in conditions like emphysema, pulmonary embolism or ARDS (9, 13); this requires an increase of breathing frequency to maintain the same level of alveolar ventilation. For the above-mentioned conditions a small reduction of dead space would lead to a significant improvement in gas exchange resulting in the reduction of minute ventilation, which would normalize blood gas parameters or both.

Physiological effects and clinical outcomes related to the reduction of dead space during NHF may also be affected by the generated positive airway pressure that can modify breathing patterns and change the efficiency of the dead space clearance. Based on the data from the scintigraphy it is also likely that the efficiency of dead-space clearance can potentially be increased with the reduction of respiratory rate.

Patients with obstructive and restrictive respiratory disease, as well as stable patients and those in respiratory distress or undergoing respiratory failure, are expected to respond differently to the reduction of dead space by NHF. Nevertheless, an improvement of gas exchange resulting in a reduction of minute ventilation and/or the normalizing of blood gases can be anticipated during NHF therapy.

Strengths and limitations

There are two key strengths in this current study. The first is the evaluation of dead-space clearance without a breathing component, which is also a limitation and is outlined below. The level of clearance is most efficient in the nasal cavities but may extend below the soft palate; however, this has to be interpreted with caution. The data adds weight to the argument that the respiratory support effects of NHF treatment are dependent not only on

the NHF rate but also on time; the longer the time during which NHF produces clearance at the end of expiration, the more significant clearance can be expected. The second key strength of the study is that the reduction of re-breathing by NHF was shown via a change of actual gas composition in the inspired air. A correlation between the change of inspired volumes of CO_2 and O_2 confirms the validity of the measurements. Elimination of CO_2 is of primary interest, as a fraction of removed CO_2 from the expired gas is relatively higher than the added fraction of O_2 and it is clinically relevant in hypercapnic patients. A role of additional O_2 as a result of dead-space clearance in normo- and hypoxemic patients is yet to be determined.

There are limitations to this study, however. The main drawback is that only static clearance rates in the absence of breathing were quantified in the scintigraphy part. There were three reasons to justify the design. First, ^{81m}Kr-gas has a short lifetime (13 s) and it is a technical restriction to visualize a fast-decaying radioactive tracer gas. Second, tidal breathing would not allow studying the maximum clearance that can be potentially achieved by NHF. Excluded in this study were investigations into the NHF clearance effects during a range of tidal volumes, breathing patterns, opening the mouth, position of the soft palate, vocal cords and the effects of changing the nasal prong size and position; these factors need to be addressed separately in future study designs. Had the authors endeavored to include some of these elements in the current study, they would have had to complicate the protocol significantly and increase the number of patients in the group substantially, who would also have needed to be homogeneous to allow adequate quantifications of individual responses. The study of three tracheotomized patients was sufficient to demonstrate the NHF-dependent reduction of re-breathing as a physical process – although a large sample size in a controlled trial would be required for the analysis of the above-mentioned parameters, physiological responses or clinical outcomes of NHF therapy, which need to be studied separately. It is unlikely that an increase of a sample size in the study without a change of the design would lead to a valid conclusion on the physiological and clinical effects of NHF therapy as the effects will greatly depend on the baseline parameters and duration of the therapy. Frequent change of NHF rates during a relatively short time is not a desirable study design for assessment of awake, spontaneously-breathing patients where an individual voluntary response may affect the results. Also, a maximum NHF rate of 45 L/min was used

394 in this study in order to repeat the same three flows investigated in a model study (18) and
395 to limit the maximum radioactive daily exposure for the volunteers. In tracheotomized
396 patients there was a risk of non-completion of the protocol should another NHF rate be
397 added. Apart from the above, the authors could not exclude the fact that some patients
398 would not tolerate higher NHF unless they are in respiratory distress.
399
400 In summary, this study has shown effective clearance of the tracer gas by NHF in the upper
401 airways. The clearance is directly related to the NHF rate and time, demonstrating that
402 expired air can be cleared even below the soft palate. The clearance of dead space leads to a
403 reduction in re-breathing of expired air. It may reduce the volume of dead space and
404 increase the alveolar volume, which can result in improvement of alveolar ventilation and
405 gas exchange during NHF therapy.
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407
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411
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419
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423
424 **AUTHOR CONTRIBUTIONS**
425 WM, SF, UD, PB, OE, OS, ST and GN – conception and design of research;

426 WM, GC, SF, UD, KJF, GM and ST – performed experiments;

427 WM, GC, SF, UD, OS and ST – analyzed data;

428 WM, SF, UD, ST and GN – interpreted results of experiments;

429 WM, SF, ST and GN – drafted manuscript;

430 WM, SF, OS, ST and GN – edited and revised manuscript;

431 WM, GC, SF, UD, KJF, PB, GM, OE, OS, ST and GN – approved final version of manuscript.

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525 **Tables**

526
527

	Mean (SD)
Male/Female	7/3
NS/S/XS	7/0/3
Age, Years	55 (14)
Height, cm	175 (10)
Weight, kg	74 (12)
BMI, kg/m^2	24 (6)
V_{DA}, mL	152 (19)
V_N, mL	42 (6)

528

529 Table 1: Anthropometric data of 10 healthy volunteers participating in the study. NS – non-
530 smokers, S – smokers, XS – ex-smokers, V_{DA} – anatomical dead-space volume based on
531 height (Hart MC, et al., *J. Appl. Physiol.* 1963; 18(3):519-522), V_N – nasal volume
532 corresponding to Nasal1 and Nasal2 ROIs derived from individual MRI scans.

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	Half time $T_{1/2}$, s Mean (SD)		
ROI	NHF 15 L/min	NHF 30 L/min	NHF 45 L/min
Nasal1	0.70 (0.26)	0.53 (0.17)	0.39 (0.11)
Nasal2	0.91 (0.34)*	0.69 (0.24)*	0.48 (0.11)*
Pharynx	7.80 (2.96)	6.19 (3.82)	4.43 (2.92)
Trachea	23.73 (6.63)	14.30 (13.43)	10.53 (9.85)

537

538 Table 2: Half-times $T_{1/2}$ of ^{81m}Kr-gas clearance (mean, standard deviation (SD)) in the anterior
539 (Nasal1), posterior (Nasal 2) part of nasal cavity, in the pharynx and trachea region of
540 interests (ROI) of healthy volunteers during 15, 30 and 45 L/min of nasal high flow (NHF). In
541 all compartments half-times correlated with NHF (Nasal1: cc = -0.55, $p < 0.01$; Nasal2: cc = -
542 0.57, $p < 0.01$; pharynx: cc = -0.41, $p < 0.01$; trachea: cc = -0.51, $p < 0.01$; *: $p < 0.05$ Nasal2 vs.
543 Nasal1, paired t-test).

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545

Patient A ○	Baseline	NHF 15 L/min	Baseline	NHF 30 L/min	Baseline	NHF 45 L/min
Tidal volume (mL)	332.0	282.6	348.7	300.4	331.5	191.7
Respiratory rate (min^{-1})	10.9	12.2	12.3	10.6	12.3	10.8
Minute ventilation (L/min)	3.6	3.4	4.3	3.2	4.1	2.1
SpO2 (%)	96.1	96.4	96.8	96.6	96.9	97.1
Tissue CO_2 (mmHg)	32.0	31.8	31.3	31.2	30.7	30.6

Patient B ●	Baseline	NHF 15 L/min	Baseline	NHF 30 L/min	Baseline	NHF 45 L/min
Tidal volume (mL)	366.7	289.7	438.5	364.3	334.6	332.3
Respiratory rate (min^{-1})	12.9	14.3	12.2	12.4	15.0	14.8
Minute ventilation (L/min)	4.7	4.1	5.4	4.5	5.0	4.9
SpO2 (%)	92.6	92.2	92.9	92.8	93.5	94.6
Tissue CO_2 (mmHg)	48.2	49.1	48.0	48.7	48.7	48.3

Patient C □	Baseline	NHF 15 L/min	Baseline	NHF 30 L/min	Baseline	NHF 45 L/min
Tidal volume (mL)	290.1	264.1	333.0	255.6	391.1	247.6
Respiratory rate (min^{-1})	14.1	13.2	12.2	12.1	14.0	12.3
Minute ventilation (L/min)	4.1	3.5	4.1	3.1	5.5	3.0
SpO2 (%)	96.6	96.5	97.4	97.6	97.0	97.0
Tissue CO_2 (mmHg)	39.2	38.5	41.2	40.0	38.3	37.8

Table 3: Change of ventilation parameters, peripheral capillary oxygen saturation (SpO2) and tissue CO_2 in three patients participating in the study by NHF 15, 30 and 45 L/min during measurement of tracheal gases. All patients had normal respiratory rate and relatively small tidal volume assessed with calibrated respiratory inductance plethysmography.

554

555 **Figure captions**

556

557 Figure 1: Lateral gamma camera image of nasal ^{81m}Kr-gas inhalation overlaid on the coronal
558 MRI image of a volunteer during breath holding. A) Definition of anterior (Nasal1), posterior
559 (Nasal2), pharyngeal, tracheal and lung ROIs. B) Visualization of ^{81m}Kr-gas distribution 500 ms
560 after the application of NHF at a rate of 45 L/min (right) in comparison to the control (left)
561 shows fast clearance of the tracer gas in the upper airways. The control measurement
562 without cannula flow shows stable ^{81m}Kr-gas concentration.

563

564

565 Figure 2: ^{81m}Kr-gas clearance half-times of the anterior (Nasal1) and posterior (Nasal2) nasal
566 cavity (A) and in the pharyngeal and tracheal space (B) during NHF rates of 15, 30 and 45
567 L/min. This figure demonstrates flow-dependent clearance (Nasal1 vs. NHF: cc = -0.55, $p <$
568 0.01; Nasal2 vs. NHF: cc = -0.57, $p < 0.01$) that was always faster in the Nasal1 ROI than in the
569 Nasal2 ROI, which shows a direction of clearance. Data are mean +/- SD; *: $p < 0.05$, paired t-
570 test.

571

572

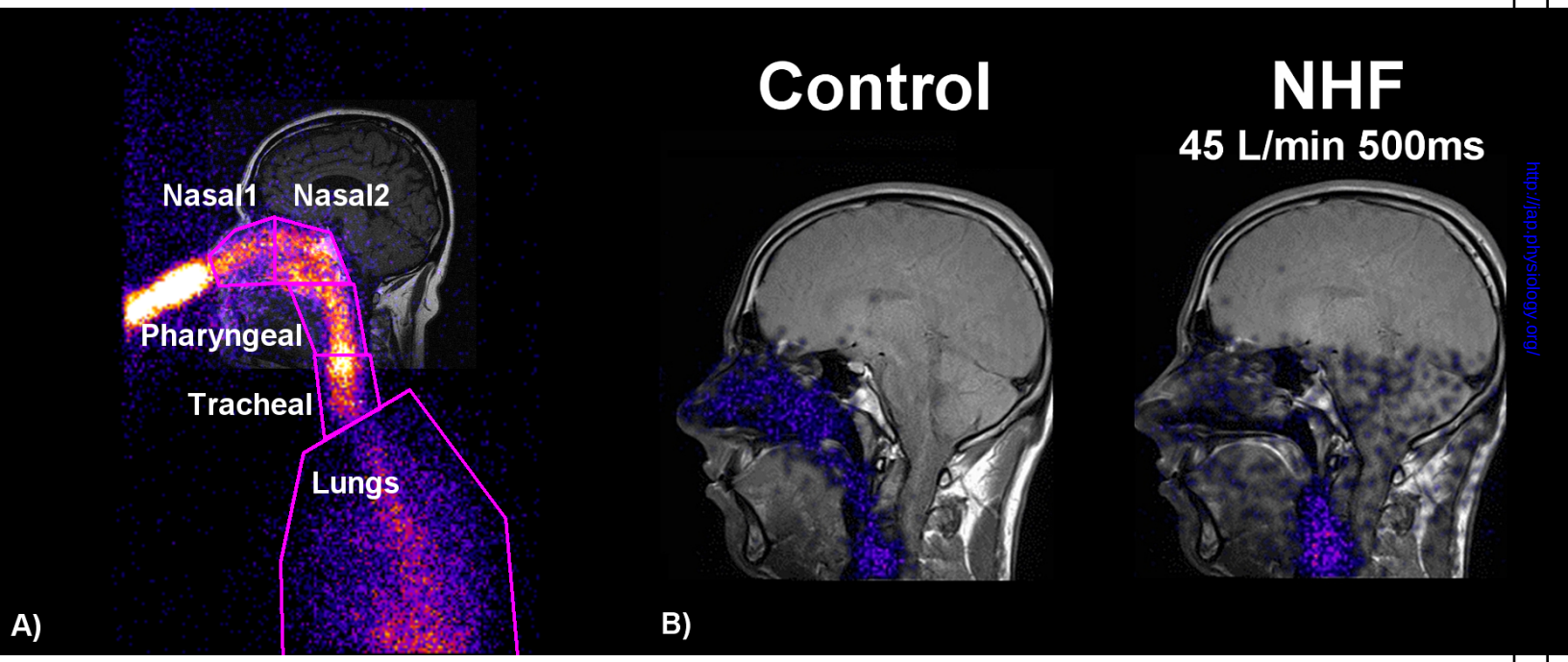
573 Figure 3: A) Tracheal CO_2 concentration plotted against inspired volume of a single breath of
574 a tracheotomized patient demonstrates a decrease of CO_2 re-breathing during an NHF rate
575 of 45 L/min. B) Tracheal O_2 concentration plotted against inspired volume illustrates an
576 increase of O_2 in the inspired gas during NHF. Both curves of inspired CO_2 and O_2
577 demonstrate maximum differences in the concentration of the gases within the first 0.1 L
578 (100 mL) of inspired volume.

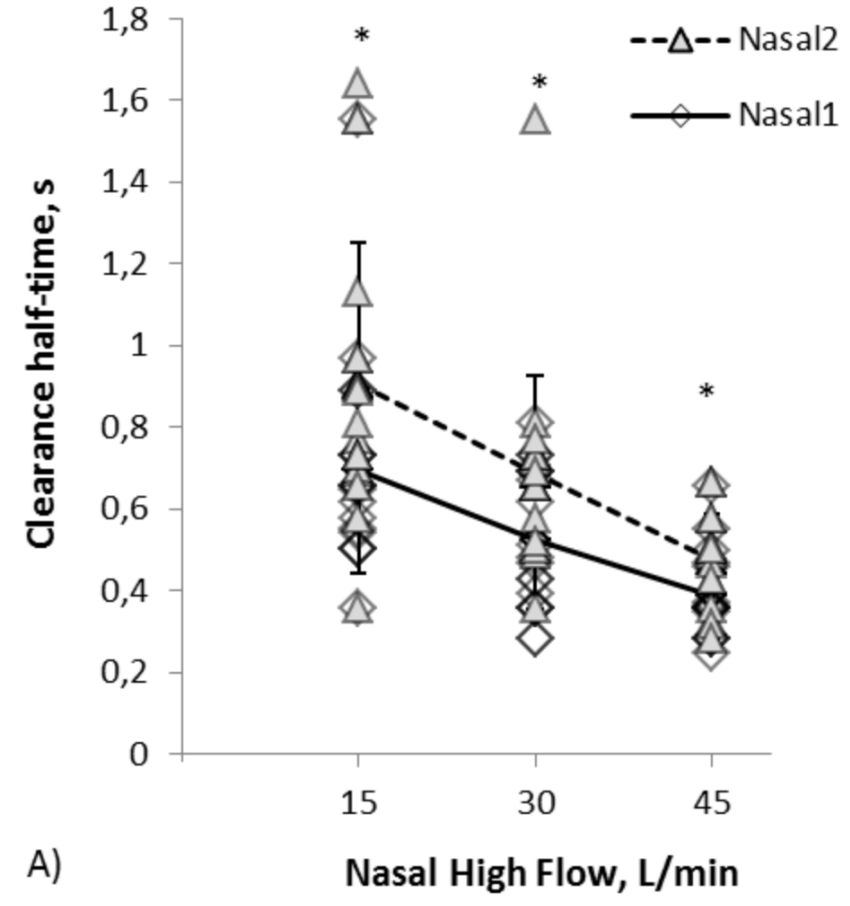
579

580

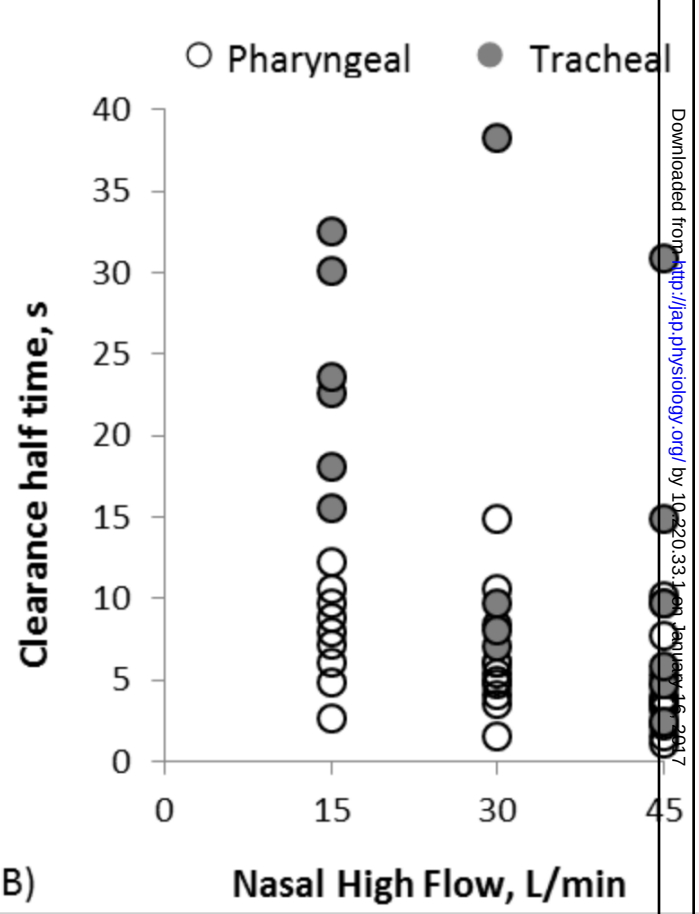
581 Figure 4: Effect of NHF rates at 15, 30 and 45 L/min on the total inspired tracheal CO_2 (A) and
582 inspired O_2 (B) in the first 100 mL of inspired volume in three patients who are individually
583 represented in the graphs, where the three symbols represent the three NHF rates applied.
584 The data in this figure is presented as means calculated from 2-minute intervals. An increase
585 of NHF from 15 to 45 L/min led to a flow-dependent reduction of inspired CO_2 and a rise of

586 inspired O_2. C) Relation between change (Δ) of total inspired O_2 vs. CO_2 in the first 100 mL
587 per breath with linear regression (r^2 = 0.59) and 95% confidence intervals. This figure
588 demonstrates that there is a significant correlation between the reduction of CO_2 and the
589 increase of O_2 by means of NHF therapy (cc = -0.767, p = 0.016). D) Ratio of inspired CO_2 in
590 the first 100 mL of tidal volume to the total inspired CO_2 per breath during baseline
591 ventilation and during NHF (15, 30 and 45 L/min; ratio = 0.84 (SD 0.10) vs. 0.75 (SD 0.12) for
592 baseline measurements; $p < 0.01$).
593
594


Nasal1
Nasal2
Pharyngeal
Tracheal
Lungs
A)
Control
NHF
45 L/min 500ms
B)
http://jap.physiology.org/



A)



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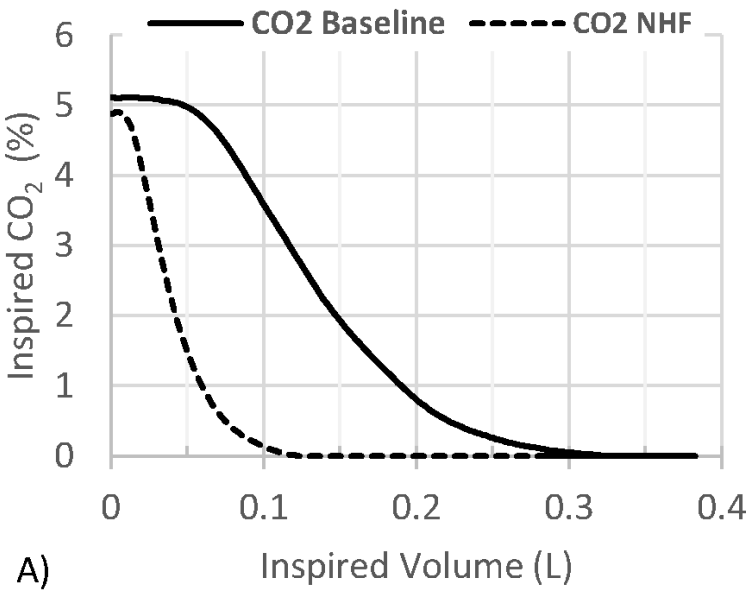
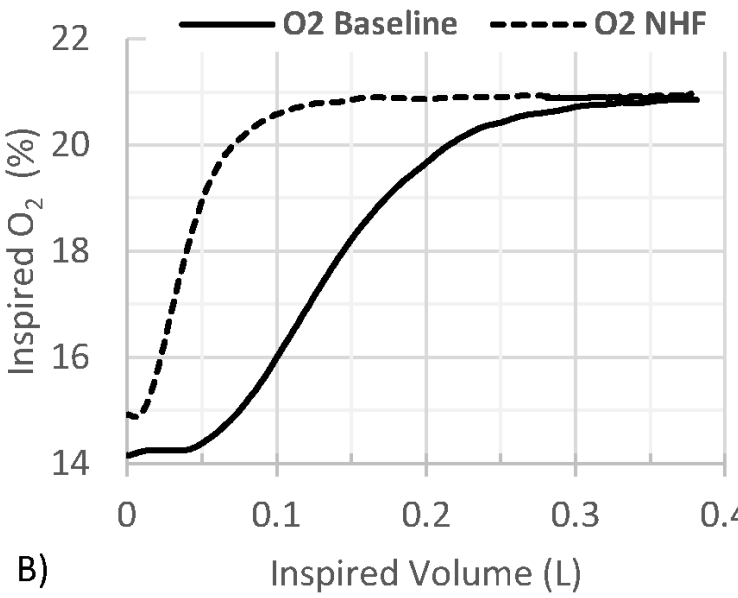


A)



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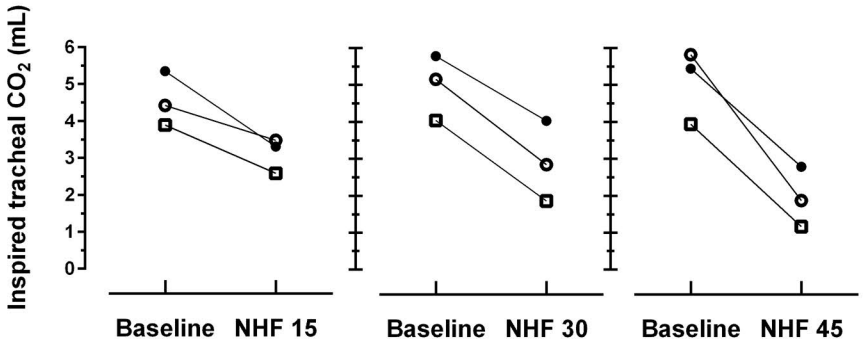
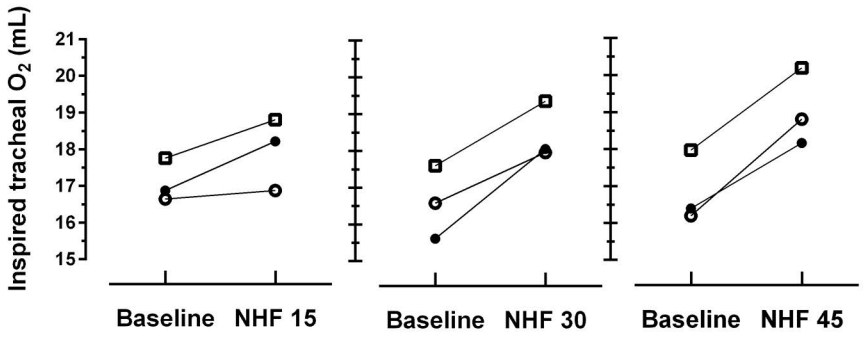
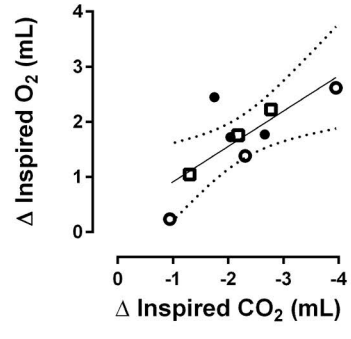

Inspired tracheal CO_2 (mL)
0
1
2
3
4
5
6
Baseline
NHF 15
Baseline
NHF 30
Baseline
NHF 45

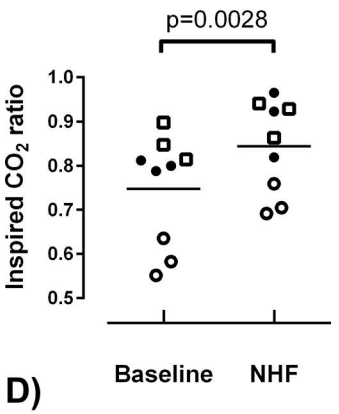
A)


Inspired tracheal O_2 (mL)
15
16
17
18
19
20
21
Baseline
NHF 15
Baseline
NHF 30
Baseline
NHF 45

B)


Δ Inspired O_2 (mL)
0
1
2
3
4
0
-1
-2
-3
-4
Δ Inspired CO_2 (mL)

C)


p=0.0028
Inspired CO_2 ratio
0.5
0.6
0.7
0.8
0.9
1.0
Baseline
NHF

D)