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Tidal Volume Estimation during Helmet Noninvasive Ventilation: an Experimental Feasibility Study

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We performed a bench (BS) and human (HS) study to test the hypothesis that estimation of tidal volume (V_T) during noninvasive helmet pressure support ventilation (nHPSV) would be possible using a turbine driven ventilator (TDV) coupled with an intentional leak single-limb vented circuit. During the BS a mannequin was connected to a lung simulator (LS) and at different conditions of respiratory mechanics, positive end expiratory pressure (PEEP) levels and leaks (30, 50 and 80 L/min). All differences were within the 95% limits of agreement (LoA) in all conditions in the Bland-Altman plot. The overall bias (difference between V_T measured by TDV and LS) was 35 ml (95% LoA 10 to 57 ml), 15 ml (95% LoA -40 to 70 ml), 141 ml (95% LoA 109 to 173 ml) in the normal, restrictive and obstructive conditions. The bias at different leaks flow in normal condition was 29 ml (95% LoA 19 to 38 ml). In the HS four healthy volunteers using nHPSV had a pneumotachograph (P) inserted through a mouthpiece to measure subject's V_T . The bias showed a scarce clinical relevance. In conclusions, V_T estimation seems to be feasible and accurate in all conditions but the obstructive one. Additional leaks seem not to affect V_T reliability.

Noninvasive ventilation (NIV) is widely used worldwide to support ventilation and oxygenation in patients with respiratory failure¹. The helmet is an interface that may increase comfort, reduce skin breakdown, and increase success rate during noninvasive helmet pressure support ventilation (nHPSV) compared to face mask¹⁻⁷.

Measurement of tidal volume (V_T) still remains an unresolved issue during nHPSV due to the mechanical properties of the helmet^{4,6,8-10}. The availability to assess V_T during nHPSV might be of importance because it was previously found that high V_T during noninvasive ventilation (NIV) in hypoxemic patients may increase lung injury¹¹⁻¹³. Nevertheless, no study has shown the possibility to assess V_T during nHPSV.

Intentional leak single-limb vented circuit configuration allows during face mask or nasal ventilation to make an estimation of the delivered V_T in all bi-level ventilators as well as in some intensive care unit (ICU) ventilators mainly dedicated for NIV use¹⁴⁻¹⁶.

We hypothesized that a turbine driven ventilator (TDV) coupled with intentional leak single-limb vented circuit and whose leak location is set at the helmet expiratory port would allow to estimate patient's V_T during nHPSV^{15,16}. The aim of the present study was to test this hypothesis on a bench and healthy volunteer study.

Methods

The Ethics Committee approved the study protocol (Comitato Etico Palermo 1 – Approval number 07/2018). All experiments were performed in accordance with relevant guidelines and regulations. The study was performed at the Simulation Lab of the Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), Section of Anesthesia, Analgesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, University of Palermo, Italy.

Materials and settings. *Bench study.* A modified mannequin head (LaerdalMedical AS, Stavanger, Norway) was connected to a lung simulator (LS) (ASL 5000; Ingmar Medical, Pittsburgh, PA, USA). The ASL 5000 is a digital controlled real-time breathing lung simulator, which allows creating various types of spontaneous breathing pattern and different conditions of respiratory mechanics (e.g. normal, restrictive or obstructive

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Turbine driven ventilator in intentional leak vented configuration

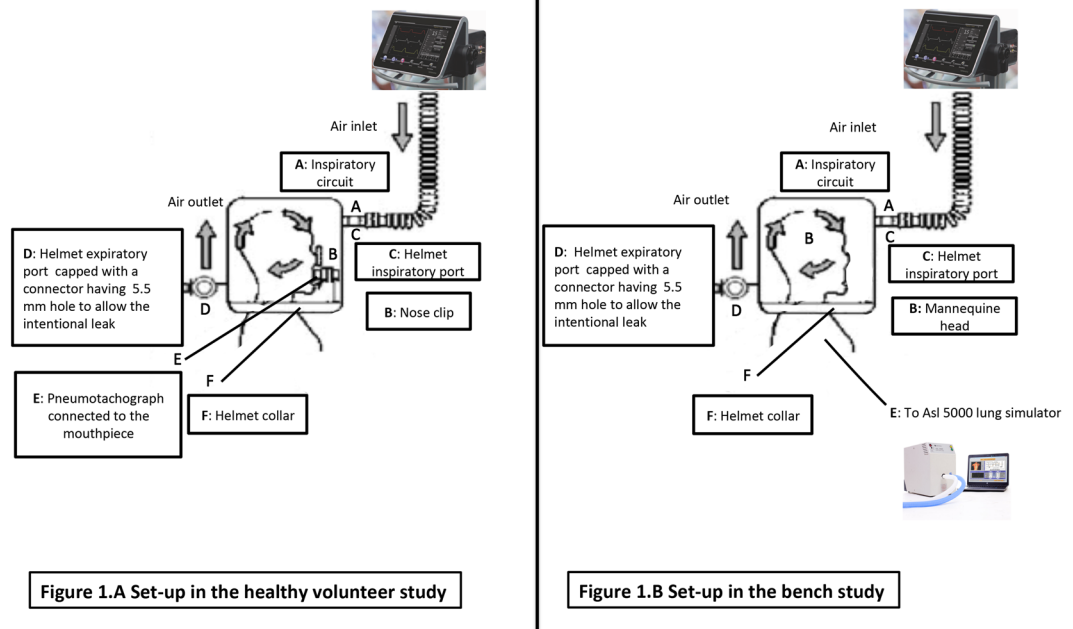


Figure 1. Schematic representation of the experimental set up in the healthy volunteer (A) and in the bench study (B). Authors' own figure.

condition). Its functioning is based on a direct-drive screw-driven piston, which moves inside a cylinder according to the equation of motion of an active respiratory mechanics system¹⁷. Its settings during the bench study, using a single-compartment model, was as follows:

(1) Normal condition: resistance 4 cmH₂O/L/s, compliance 60 mL/cmH₂O, inspiratory muscle pressure (P_{mus}) -5 cmH₂O (semisinusoidal waveform with rise time of 25%, inspiratory hold of 5%, release time of 25%) and LS respiratory rate set at 15 breaths/min;

(2) Obstructive condition: resistance 15 cmH₂O/L/s, compliance 80 mL/cmH₂O, P_{mus} -12 cmH₂O (semisinusoidal waveform with rise time of 20%, inspiratory hold of 5%, release time of 30%) and LS respiratory rate set at 25 breaths/min;

(2) Restrictive condition: resistance 7.5 cmH₂O/L/s, compliance 30 mL/cmH₂O, P_{mus} -12 cmH₂O (semisinusoidal waveform with rise time of 25%, inspiratory hold of 5%, and release time of 25%), and LS respiratory rate set at 30 breaths/min.

The mannequin head was connected to the LS through the mannequin's trachea after having positioned and secured a helmet (Castar, Next Intesurgical, size small, Mirandola, Italy)¹⁸. The helmet inspiratory port was connected to the TDV (Bellavista 100 ICU, Buches, Switzerland) via a single-limb circuit while the expiratory port was closed with a cap having a 5.5 mm hole to allow the intentional leak. This configuration was not provided with any type of inspiratory or expiratory valves and carbon dioxide flushes, as a function of mask pressure through an intentional leak port set in the circuit or in the interface itself. Neither inspiratory nor expiratory V_T is measured but they are estimated taking into account the leak according to a mathematical leak model as a function of mask pressure. This mathematical model is used to make an estimation the instantaneous leak and flow which are subtracted from the total flow output of the ventilator (which is the only measured flow) to calculate V_T¹⁹. Figure 1 shows the set-up.

During nHPSV, the ventilator was set at the fastest pressure rise time, cycling-off flow threshold of 25% in the normal and restrictive condition and 40% in the obstructive one. Inspiratory flow trigger initially set at 2 L/min was then always tuned at the lowest value not determining auto-triggering²⁰. Inspiratory pressure above positive end expiratory pressure (PEEP) was set to reach a V_T of about 300/500 ml in all conditions and did not change throughout each condition. Each condition was simulated at PEEP of 5, 8, 10 cmH₂O. PEEP 12 cmH₂O was only used in the restrictive condition. During nHPSV leaks were avoided by accurately fit the helmet to the mannequin's neck. During normal condition at PEEP 8 cmH₂O and inspiratory pressure (above PEEP) 0 cmH₂O we also tested the reliability of V_T estimation at different leak flows (30, 50 and 80 L/min) using a calibrated hole. During normal condition at PEEP 8 cmH₂O we also tested the reliability of V_T estimation at different leak flows (30, 50 and 80 L/min) using a calibrated hole.

Healthy volunteers study. After approval from our Institutional Ethics Committee (Comitato Etico Palermo 1 – approval N° 07/2018) and after obtaining written informed consent, four healthy volunteers, 1 female, 3

Simulated Condition	(TDV-LS) PEEP 5 cmH ₂ O	(TDV-LS) PEEP 8 cmH ₂ O	(TDV-LS) PEEP 10 cmH ₂ O	(TDV-LS) PEEP 12 cmH ₂ O	P value
Normal	51 (3) ^{o+}	31.1(3.5) ^{*+}	21.8 (2) ^{*o}		<0.001
Restrictive	61 (3) ^{o+§}	10,4 (1.3) ^{*+§}	1,1 (1.6) ^{*o§}	-11,9 (1.9) ^{*o+}	<0.001
Obstructive	164 (2) ^{o+}	132,5 (1.6) ^{*+}	127,3(3.1) ^{*o}		<0.001

Table 1. Differences in tidal volumes (V_T) measured by turbine driven ventilator and lung simulator at different levels of PEEP in the bench study. Data are expressed in ml and reported as mean (\pm SD). PEEP: positive end expiratory pressure; TDV: turbine driven ventilator; LS: lung simulator; (TDV-LS): difference between V_T measurements by turbine driven ventilator and lung simulator. *Different from 5; ^odifferent from 8, ⁺different from 10, [§]different from 12.

male, mean age 33 ± 4 years, mean body weight 70 ± 15 kg were ventilated in nHPSV (PSV 8 cmH₂O and PEEP 8 cmH₂O) via a helmet (Castar, Next Intesurgical, size small or medium, Mirandola, Italy), using the same TDV configuration used in the bench study. All experiments were performed in accordance with relevant guidelines and regulations. A mouthpiece was inserted in the volunteer's mouth and connected to pneumotachograph (P) (V_T mobile FLUKE, Germany) to measure subject's airflow and V_T . A nose clip was positioned on volunteer's nostrils to avoid leaks from the nose. The set-up is showed in Fig. 1. All the healthy volunteers were trained, using a metronome, to maintain an imposed respiratory rate of about 12/15 breaths per minute²⁰. During nHPSV, ventilator was set at the fastest pressure rise time and at cycling-off flow threshold of 25%. Inspiratory flow trigger was set at the lowest value not determining autotriggering starting from 2 L/min. During nHPSV, leaks were accurately avoided choosing the right helmet size and by appropriately fitting the helmet to the volunteer's neck.

Measurements. *Bench study.* Data were collected by the TDV and by LS software. Airflow (V), the airway pressure (Paw), PEEP as well as the V_T and respiratory rate delivered to mannequin were collected over 3 minutes. Differences in V_T between TDV and LS were compared during the last 20 breaths of each trial to ensure the stability of the system across settings modification (e.g. increasing leak, mechanical pattern and pressure level)¹⁶. During the test at different leak flows, each measurement was performed after 1 minutes after the institution of the new leak to let the TDV to adapt to the new setting. Autotriggering was determined as a mechanical insufflation in absence of inspiratory effort on the LS¹⁷.

Healthy volunteers. Each experimental condition was maintained for 3 minutes, to ensure the stability of the system across the modification of settings (e.g. increasing leak, respiratory pattern)¹⁶. Paw , PEEP obtained from the TDV and V_T and respiratory rate of both TDV software and pneumotachograph (P) were collected. V_T measured by TDV and P were compared during the last 20 breaths of each trial.

Statistical analysis. Normality of data distribution was checked graphically and by D'Agostino-Pearson test. Data are expressed as mean \pm standard deviation (SD) or as median and interquartile range (IQR) when appropriate. Bland-Altman graphs were used to plot differences between the V_T from the TDV and LS against the average of the two measurements.

Bland-Altman plot is the standard graphical statistical method to evaluate the agreement between quantitative measurements from two different devices, assays or raters. Bland-Altman plots reported the bias (defined as the average of the differences between measurements) and 95% limit of agreements (LoA), namely ± 1.96 SD of the bias²¹. We assumed as clinically relevant a difference of $>15\%$ of the LS.

Differences between V_T (TDV-LS) at different PEEP levels or leaks were compared using ANOVA for repeated measures and Student-Newman-Keus test was used for all pairwise comparisons. Paired sampled t-test was used to compare V_T measured by V and P in the healthy volunteers. P values < 0.05 were considered statistically significant. We used Prism 7 (GraphPad software; San Diego, CA) and Microsoft Excel (version 2013; Microsoft corporation, Redmond, CA).

Results

Bench study. *Normal, restrictive, obstructive condition.* The level of nHPSV to reach the default V_T was 8, 10 and 12 cmH₂O respectively in the normal, restrictive and obstructive condition.

Differences in V_T between TDV and LS at different levels of PEEP and pairwise comparisons are shown in Table 1. All plotted differences were within the 95% LoA in all conditions. The overall bias was 35 ml (95% LoA 10 to 57 ml), 15 ml (95% LoA -40 to 70 ml), 141 ml, (95% LoA 109 to 173 ml) respectively in the normal restrictive and obstructive conditions (Figs. 2–4). In the normal condition, the bias reached the least clinical relevance at PEEP 10 cmH₂O (Fig. 2) while in the restrictive one at PEEP 10 and 12 cmH₂O (Fig. 3). In the obstructive condition, the bias increased at PEEP 5 cmH₂O (Fig. 4). Autotriggering was never detected. Tables S1–S3 in the supplementary file 1 reported average V_T at different PEEP levels in the different simulated conditions.

Leaks simulation. Data on the difference in V_T between TDV and LS at different levels of leak flow are shown in Table 2. The only significant differences were found between 80 L/min vs. 30 L/min and 80 L/min vs. 50 L/min. The overall bias was 29 ml (95% LoA 19 to 38 ml) (Fig. 5). Table S4 in the supplementary file 1 reported average V_T at different levels of leak flow.

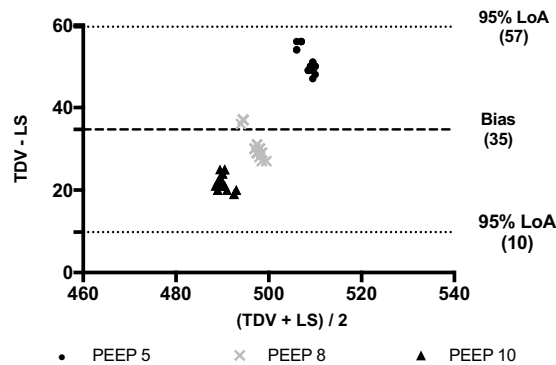


Figure 2. Bland-Altman plot of the differences between tidal volumes measured by the turbine driven ventilator and the lung simulator in the normal condition. Data are reported in ml. PEEP: Positive end expiratory pressure (values are expressed in cmH_2O). TDV: Tidal volume (V_T) measured by turbine driven ventilator; LS: Tidal volume (V_T) measured by lung simulator. Average (x-axis): average of the two measurements; TDV - LS (y-axis): difference between measurements. Bias: Average of the differences between measurements. 95% LoA: Limits of agreement (± 1.96 standard deviation - SD - of the bias). All plotted differences are within the 95% LoA. In this plot, the overall bias is 35 ml, and 95% LoA are from 10 to 57 ml. It reaches the least clinical relevance at PEEP 10 cmH_2O .

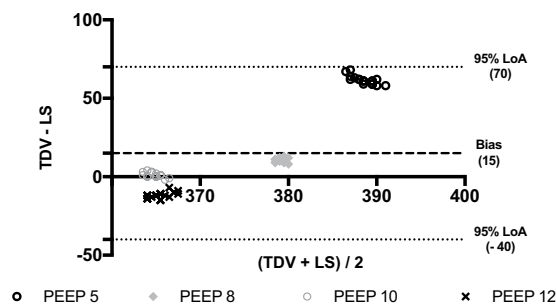


Figure 3. Bland-Altman plot of the differences between tidal volumes measured by the turbine driven ventilator and the lung simulator in the restrictive condition. Data are reported in ml. PEEP: Positive end expiratory pressure (values are expressed in cmH_2O). TDV: Tidal volume (V_T) measured by turbine driven ventilator; LS: Tidal volume (V_T) measured by lung simulator. Average (x-axis): average of the two measurements; TDV - LS (y-axis): difference between measurements. Bias: Average of the differences between measurements. 95% LoA: Limits of agreement (± 1.96 standard deviation - SD - of the bias). In this plot, the overall bias is 15 ml, and 95% LoA are from -40 to 70 ml. All plotted differences are within the 95% LoA. The bias reaches the least clinical relevance at PEEP 10 and 12. It significantly increased at PEEP 5 cmH_2O .

Autotriggering was never detected in any experimental records but at the beginning of the new leak condition before the complete TDV compensation (e.g. switching leak from 30 to 50 L/min).

Healthy volunteers study. Table 3 shows V_T measured by the TDV and the P for the four health volunteers. Mean difference between V_T measured by TDV and P was 45 ml (± 32) for volunteer 1, 11 ml (± 38) for volunteer 2, -35 ml (± 37) for volunteer 3 and 58 ml (± 40) for volunteer 4. Figure S1 in the supplementary material shows the distribution of V_T measured by TDV and P for each volunteer.

Discussion

The main findings of the bench study are: (1) No clinically relevant differences were found in V_T between TDV and LS in normal and restrictive conditions at all simulated level of PEEP; (2) The difference between TDV and LS remained stable across the different tested leak flows; (3) There was a large, clinically relevant, difference in V_T in the obstructive condition between TDV and the LS.

To the best of our knowledge this is the first study able to demonstrate the possibility of estimate V_T during helmet ventilation. The same circuit configuration was tested in a previous study, which used nHPSV in single-circuit vented intentional leak configuration to measure carbon dioxide (CO_2) rebreathing¹⁵. Interestingly, although V_T was not measured by the ventilator software in this study, this kind of circuit configuration should theoretically allow to estimate V_T as during non invasive intentional leak mask ventilation¹⁶. This estimation has been demonstrated to be pretty reliable in different condition of respiratory mechanics and linear non intentional leaks¹⁶.

Our bench study was carried out with a TDV with an intentional leak vented single-limb circuit because direct measurement of V_T was not possible due to the intrinsic mechanical features of the helmet, namely its large

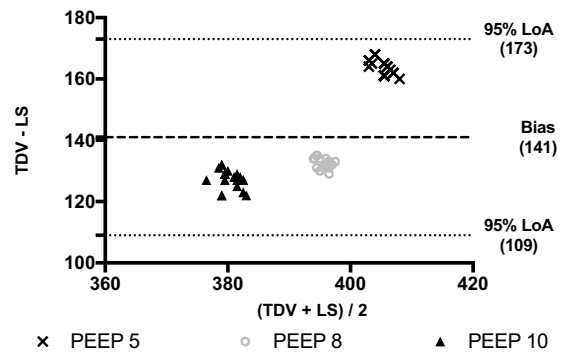


Figure 4. Bland-Altman plot of the differences between tidal volume measured by the turbine driven ventilator and the lung simulator in the obstructive condition. Data are reported in ml. PEEP: Positive end expiratory pressure (values are expressed in cmH_2O). TDV: tidal volume (V_T) measured by turbine driven ventilator; LS: Tidal volume (V_T) measured by lung simulator. Average (x-axis): average of the two measurements; TDV - LS (y-axis): difference between measurements. Bias: Average of the differences between measurements. 95% LoA: Limits of agreement (± 1.96 standard deviation - SD - of the bias). In this plot, the overall bias is 141 ml, and 95% LoA are from 109 to 173 ml. Although all plotted differences are within the 95% LoA, a large clinical relevance bias is found at all tested PEEP levels.

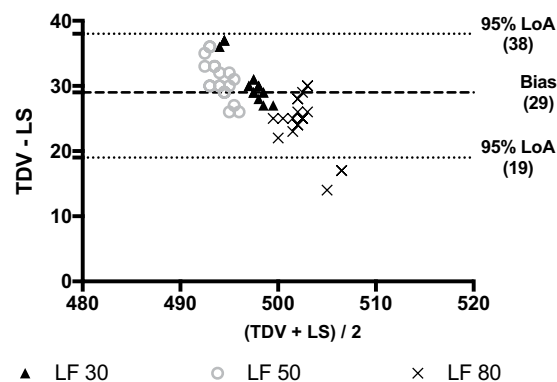


Figure 5. Bland-Altman plot of the differences between tidal volume measured by the turbine driven ventilator and the lung simulator at PEEP 8 cmH_2O and different levels of leak flow. Data are reported in ml. LF: leak flow (values are expressed in liter per minute); TDV: Tidal volume (V_T) measured by turbine driven ventilator; LS: Tidal volume (V_T) measured by lung simulator. Average (x-axis): average of the two measurements; TDV - LS (y-axis): difference between measurements. Bias: Average of the differences between measurements. 95% LoA: Limits of agreement (± 1.96 standard deviation - SD - of the bias). In this plot, the overall bias is 29 ml, and 95% LoA are from 19 to 38 ml. The difference between V_T measured by the TDV and the LS remains of no clinical relevance among all simulated leak flows.

Simulated Condition	(TDV-LS) LF 30 L/min	(TDV-LS) LF 50 L/min	(TDV-LS) LF 80 L/min	P value
Normal	31(4) ⁺	31(3) ⁺	24(4) ^{*o}	<0.001

Table 2. Differences in tidal volumes (V_T) measured by turbine driven ventilator and lung simulator at different levels of leak flow. Data are expressed in ml and reported as mean (\pm SD). LF: leak flow (expressed in liters per minute); TDV: turbine driven ventilator; LS: lung simulator; (TDV-LS): difference between V_T measurements by turbine driven ventilator and lung simulator. *Different from 30; ^oDifferent from 50; ⁺Different from 80.

internal volume¹⁵. Besides, a TDV with an intentional leak vented single-limb circuit better compensate for air leaks up to its leak compensation capability^{16,22}.

The helmet is an interface that may increase comfort, reduce skin breakdown, and increase success rate during nHPSV compared to face mask¹⁻⁷. The TDV was coupled to a new commercially available helmet. This new helmet is featured by an annular extendable ring placed under an inflatable large cushion that secures the interface without the need for armpit support²³. This helmet has been found to reduce to a large extent its upward displacement during the ventilator support thus improving patient-ventilator interaction²³.

Our results found a very good agreement between differences in V_T estimated by the TDV and that measured by the LS in the normal and restrictive condition using the Bland Altman plot. Although the difference between

Volunteer N°	TDV V_T (ml)	P V_T (ml)	P value
1	651 (62.5)	606 (52.8)	<0.001
2	795 (49.1)	784 (38.5)	0.22
3	911 (89.3)	945 (67.1)	0.03
4	697 (74.2)	693 (97.2)	<0.001

Table 3. Tidal volumes (V_T) measured by turbine driven ventilator and pneumotachograph in the human study. All measurements were done at PEEP and nHPSV of 8 cmH₂O. Data are expressed in ml and reported as mean \pm SD; PEEP: positive end expiratory pressure; TDV: V_T measured by turbine driven ventilator; P: V_T measured by pneumotachograph.

V_T measured by the LS and the TDV was statistically different among the groups at the different PEEP levels, this difference was of poor clinical relevance. Of note, Lyazidi *et al.* found that when setting a V_T of 6 ml/kg of predicted body weight, a difference of 1–2 ml/kg with the actually delivered V_T would be commonly found²⁴.

We found, both in the normal and in restrictive condition, that the higher the PEEP the less the difference between the V_T measured by the TDV and the LS. This result is very appealing being the restrictive lung one the most common application of helmet ventilation^{4,25}. Conversely, in the obstructive condition we found, although still in the 95% LoA, a clinically relevant discrepancy between the two V_T with an overestimation showed by the TDV. Interestingly, as opposite to our findings, Lujan *et al.* found that built-in software was underestimating the V_T in two of the tested ventilators¹⁶. This may suggest that different built-in software may behave differently in presence of an obstructive pattern. One can also speculate that underestimation might be linked to the reassessment of the zero flow value by the TDV in presence of air trapping. However, we can also hypothesize that during the bench study in this condition, the simulated patient's high resistances could have generated small non intentional leaks. While the ventilator software was not affected by the presence of the leak because it was able to compensate it, the monitoring system of the ASL 5000 did so reading smaller V_T .

Autotriggering was never detected in any trial. This result supports previous finding of the TDV capability in intentional leak vented configuration to better compensate for leaks when a flow trigger is used²². Autotriggering could also not be found due to the use of the new helmet, which presents less upward displacement during nHPSV. Only when simulated a new leak flow, few auto-triggered breaths were detected due to the need of the ventilator to compensate the loss in air flow.

Non intentional leaks are the most frequent drawback during NIV²⁶. We evaluated the reliability of V_T estimation increasing the values of the intentional leak flows to 30, 50 and 80 L/min during nHPSV in the normal simulated condition at PEEP of 8 cmH₂O. This range was selected because it includes the minimal value to avoid rebreathing even in absence of the inspiratory support⁷. Again, the difference in V_T at different leak flows was clinically negligible.

Software may underestimate both leaks and V_T with the greater the leak, the greater the difference between the estimated and actual V_T ²⁷. However, the ventilator software we used was provided with an algorithm that improves accuracy compensating for the difference between the estimated leak measured at the distal and proximal sides of the circuit¹⁶. The interesting clinical message is that being leaks a possible drawback of helmet ventilation this way of estimating V_T could theoretically assure V_T estimation even in presence of additional leaks.

The main findings of the healthy volunteer study are that although the differences in V_T were significantly different in all the volunteers but the second one, this difference was of scarce clinical relevance. During the human study, we used the same set-up that we previously described in other study¹⁵. We applied PEEP at 8 cmH₂O because it is one of the most common value used in the clinical setting^{18,28,29}.

Estimation of V_T has been the only mode of measuring V_T in TDV in intentional leaks single-limb vented configuration since the introduction of these ventilators at the beginning of the 90^{16,27}. The built-in software of these TDV should be able to accurately estimate V_T , even in presence of increased non-intentional leaks. Of note, using pressure controlled modes with compressed air driven intensive care unit (ICU) ventilator, the higher the non intentional leak the lower the expiratory V_T ^{22,30}. In addition, by using an helmet, which has a larger internal volume, the displayed V_T , when using a non vented configuration with a high pressure driven ICU ventilator is significantly higher than actual delivered V_T ⁵.

We can speculate that, using a TDV in this configuration, it would be possible to ventilate hypoxemic patients⁴ via an helmet by knowing that delivered V_T ¹¹ is pretty closed to what the patients is really breathing in.

The present study has several limitations. Firstly, this is a bench and human volunteers study. Therefore, these results need to be confirmed clinically. However, direct comparison of real measurements and its estimation at standardized condition of respiratory mechanics and respiratory rate in the same patient seems impossible for both practical and ethical reasons. Moreover, it should be noted that volunteers had healthy lungs. Second, we measured V_T under ambient temperature and pressure and dry gas conditions (ATPD). However, the V_T in the patient's lungs is at body temperature and pressure, and saturated with water vapor (BTPS). The conversion from ATPD to BTPS would increase V_T by about 10.4% for TDVs at 20 °C and at the vapor pressure of H₂O 17.5 mmHg¹⁶. We could speculate that the small gap we found between TDV and LS would be potentially further reduced by converting ATPD in BTPS. Third, we used to simulate an increase in leaks an increase in linear non intentional leak³¹. As previously demonstrated by Sogo *et al.*, the presence of unintentional random leaks may lead to an error in the measurement of V_T provided by the ventilator software³¹. In addition, we did not measure the pressurization time at the different simulated leaks. It is possible that by increasing the amount of the leak (intentional or non intentional) we approached the compensating capability of the TDV thus increasing the time necessary to achieve the preset level of pressure support⁵. Fourth, we did not measure CO₂ rebreathing in the

human study. However, we previously demonstrated that the same setting of the present study improved CO₂ rebreathing compared to a non-vented circuit configuration using an air compressed ICU ventilator¹⁵. Lastly, due to different algorithms used to estimate V_T in the built-in software of TDV, we cannot be sure that our data can be extrapolated to other TDVs in vented configuration^{16,27}.

In conclusion, this feasibility bench and human study demonstrated that V_T estimation during nHPSV seems to be feasible and accurate in all the conditions except the simulated obstructive condition. Additional leaks seem not to affect V_T reliability. Further studies are required to identify the magnitude of discrepancy between the proposed method and gold standard in bench and clinical setting.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Received: 22 July 2019; Accepted: 29 October 2019;

Published online: 21 November 2019

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Acknowledgements

We would like to thank Salvatore Arancio (Laerdal Italia) for his help in study materials.

Author contributions

A.C. and C.G. conceived the content of this manuscript and designed the study. A.C., P.N., G.A., G.M., I.S., M.I., A.B., E.G., C.P. and C.G. helped in data collection. A.C., P.N., G.A., G.M., I.S., M.I., A.B., E.G., C.P. and C.G. helped in data analysis and interpretation. AC, GA, CG drafted the manuscript. P.N., G.A. did a critical revision of the manuscript for important intellectual content. All authors provided final approval of the version submitted for publication.

Competing interests

Prof. Paolo Navalesi received research grants and/or equipment from Maquet Critical Care and Intersurgical SPA, royalties from Intersurgical SPA for Helmet Next invention, lecturing fees from Maquet, Philips, Resmed, Novartis. Prof. Cesare Gregoretti received fees for lectures or consultancies from Philips, Resmed, Vivisol, OrionPharma, Origin. All other authors declare to have no competing interests.

Additional information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41598-019-54020-5>.

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