Monitoring respiratory mechanics by oscillometry in COVID-19 patients receiving non-invasive respiratory support

Chiara Torregiani1,*, Chiara Veneroni2, Paola Confalonieri1, Gloria Maria Citton1, Francesco Salton1, Mohamad Jaber1, Marco Confalonieri1, Raffaele Lorenzo Dellaca2

1 Department of Pulmonology, Azienda Sanitaria Universitaria Giuliano Isonitina, Trieste, Italy, 2 Department of Electronics, Information and Biomedical Engineering (DEIB), TechRes Lab, Politecnico di Milano University, Milan, Italy

*chiara.torregiani@asugi.sanita.fvg.it

Abstract

Background

Non-invasive ventilation (NIV) has been increasingly used in COVID-19 patients. The limited physiological monitoring and the unavailability of respiratory mechanic measures, usually obtainable during invasive ventilation, is a limitation of NIV for ARDS and COVID-19 patients management.

Objectives

This pilot study was aimed to evaluate the feasibility of non-invasively monitoring respiratory mechanics by oscillometry in COVID-19 patients with moderate-severe acute respiratory distress syndrome (ARDS) receiving NIV.

Method

15 COVID-19 patients affected by moderate-severe ARDS at the RICU (Respiratory Intensive Care Unit) of the University hospital of Cattinara, Trieste, Italy were recruited. Patients underwent oscillometry tests during short periods of spontaneous breathing between NIV sessions.

Results

Oscillometry proved to be feasible, reproducible and well-tolerated by patients. At admission, 8 of the 15 patients showed oscillometry parameters within the normal range which further slightly improved before discharge. At discharge, four patients had still abnormal respiratory mechanics, not exclusively linked to pre-existing respiratory comorbidities. Lung mechanics parameters were not correlated with oxygenation.

Conclusions

Our results suggest that lung mechanics provide complementary information for improving patients phenotyping and personalisation of treatments during NIV in COVID 19 patients.
especially in the presence of respiratory comorbidities where deterioration of lung mechanics may be less coupled with changes in oxygenation and more difficult to identify. Oscillometry may provide a valuable tool for monitoring lung mechanics in COVID-19 patients receiving NIV.

Introduction

Severe and critical respiratory failure characterised pandemic disease COVID-19 in about one-fifth of the cases [1] and stressed healthcare resources worldwide [2, 3]. In this context, non-invasive ventilation (NIV) modalities in severely de novo hypoxemic patients have spread inside and outside Intensive Care Units (ICU) [3, 4] to become first-line support. NIV reduced endotracheal intubations necessity and improved clinical outcomes [3, 5]. In pandemic COVID-19, NIV failure and the risks of delayed intubation have been debated [6, 7]. A recent review about COVID-19 non-invasive treatments underscored the lack of solid clinical predictors for non-invasive supports failure [8]. The decision to intubate can be based on an excessive work of breathing judged clinically [9], but often the intubation is a merely subjective decision of the physician in charge [6]. NIV failure is reported in case of decreased level of consciousness, exhaustion, refractory hypoxemia [10, 11], sepsis and hemodynamic instability [10] and it is related to clinical parameters of excessive work of breathing [6, 7]. In spontaneously breathing patients, objective measurement of respiratory effort, work of breathing and lung mechanics requires esophageal manometry. However, esophageal manometry is invasive, needs expertise, and produces discomfort for the patient with acute distress [6, 9], resulting not feasible in daily clinical practice.

The Forced Oscillation Technique (FOT), also known as Oscillometry [12], provides an effective, simple, and non-invasive approach for monitoring lung mechanics during spontaneous breathing at the bedside. A pressure oscillation is applied at the mouth, and the resulting flow is measured. The relationship between oscillatory pressure and flow provides the respiratory system’s resistance (Rrs) and reactance (Xrs) at the oscillation frequency. Depending on the oscillatory frequencies, different physiologic information can be obtained. Rrs tends to be largely frequency-independent in healthy adults in the range of 4–50 Hz and is mostly determined by the properties of the central airways [12]. An increased Rrs at lower frequencies (increased Rrs frequency dependence) indicates ventilation heterogeneity [12]. Rrs frequency dependence can be quantified by the differences between Rrs at two different frequencies, for example, Rrs at 5 Hz minus Rrs at 19 Hz. Xrs is determined by both respiratory system iner- tance (related to the pressure needed to accelerate the gas column) and compliance. In adults, Xrs at 5 Hz (X5) is commonly considered sensitive to changes in the lung periphery [12]. Reduced X5 are associated with lower respiratory system compliance, higher peripheral airway resistance or lower lung volume[13, 14]. Within breath changes in X5 is sensitive to dynamic airway compression and increased difference between inspiratory and expiratory X5 (ΔX5) identify the presence of tidal expiratory flow limitation [15].

Due to the poor predictability of COVID-19 patients clinical evolution and the risk of operators contamination during patients’ examination we decided to apply FOT to patients treated with NIV beginning during the first COVID 19 wave in the spring of 2020. This pilot study reports these data and the feasibility of monitoring longitudinal changes of respiratory mechanics by FOT in COVID-19 patients with ARDS at the NIV treatment was applied. We evaluated patients’ tolerance to the measurements, the reproducibility of the results, the
changes in lung mechanics with time and their relationship with the clinical characteristic of
the patients to probe the presence of valuable clinical information.

Materials and methods
We conducted an observational retrospective pilot study. The local Ethical Review Board
approved the study (Comitato Etico Unico Regionale Friuli Venezia Giulia, CEUR ID #3306)
and waived the informed consent due to the retrospective nature of the study. All the data col-
lected by the clinician who followed the patients were anonymised before data analysis as per
ethical review board requirement. The data were stored in a secure data system exchange pro-
vided by the regional IT provider Insiel.

Study subjects
The study was conducted at the RICU (Respiratory Intensive Care Unit) dedicated to COVID-
19 patients of the University Hospital of Cattinara, Trieste, Italy. FOT measurements were per-
formed between April and May 2020 and then after October 2020 until December 2020, when
the COVID unit was open and the FOT device available. Inclusion criteria were: i) laboratory-
confirmed Sars-Cov-2 infection by RT-PCR test from a nasopharyngeal swab, ii) moderate-
severe COVID-19 ARDS requiring non-invasive ventilation because of suboptimal saturation
(SpO2 < 94%) with high flow oxygen support, and iii) Glasgow Coma Scale (GCS) of 15.
Exclusion criteria were: i) sedative treatments, ii) anamnesis of cognitive impairment, iii) haem-
dynamic instability, and iv) age < 18-years. Participant selection followed a convenience
series based on the timely availability of the research team.

Patients’ management
At hospital admission, all the patients started treatment with prolonged low-dose methylpred-
nisolone [16]. Within the first 24 hours in RICU, arterial blood gas was measured during
HFNC support and the arterial oxygen partial pressure to fractional inspired oxygen ratio
(PaO2/FiO2) was calculated. The same day, the blood chemistry data lactate dehydrogenase
(LDH), D-dimer, lymphocyte count and creatinine were collected. Computed tomographic
pulmonary angiography (CTPA) was requested according to clinical judgment during hospita-
lisation to elucidate pulmonary embolism suspect. Patients were treated with NIV using oro-
nasal masks and NIV was maintained if tolerated and improved PaO2/FiO2 with reduction of
respiratory rate. Daily NIV with cyclic prone positioning was alternated to increasing periods
of HFNC until successful weaning.

FOT measurements
Respiratory mechanics were measured by oscillometry in a seated position using a multifact-
frequency signal comprising 5, 11, and 19 Hz (Resmon ProFULL, Restech Srl, Milan, Italy) dur-
ing continuous electrocardiographic and arterial oxygen saturation monitoring. Ten
spontaneous breaths were recorded, and the measurements were performed at least in tripli-
cate and following the current guidelines [12]. HFNC was immediately restored after a mea-
surement and kept between the repeated measurements for 3–5 min. Measurements were
repeated at least twice for each patient. Oscillatory measures were performed on patients start-
ing when periods of HFNC could be safely introduced between NIV sessions and the clinician
considered secure the temporary HFNC removal. Tests were performed at least once a week
and, when possible, twice a week with the last one taken at RICU discharge.
Data and statistical analysis

All the clinical and laboratory data were captured from the electronic medical record. When available, computed tomographic pulmonary angiography during RICU hospitalisation or subsequent perfusion scintigraphy data were also recorded. Patients with less than two FOT measurements or with the last FOT measured taken more than 24h before discharge from the unit were excluded. Resistance and reactance at 5 Hz ($R_5$ and $X_5$, respectively) were computed as an average of the three repeated measurements, discarding one outlier, if needed, to provide $R_5$ coefficient of variation ($R_5\_CV<10\%$, as per current guidelines [12]. Z-score of $R_5$ and $X_5$ were obtained considering their predicted normal ranges [17]. The difference between resistance at 5 Hz and 19 Hz ($R_5-R_{19}$) was computed to evaluate the frequency dependence of the resistance that is related to the heterogeneity of ventilation. Inspiratory and expiratory $R_5$ and $X_5$ were also calculated. The difference between inspiratory and expiratory $X_5$ ($\Delta X_5$) was computed to detect tidal expiratory flow limitation (EFL$_T$) [13]. Data were corrected for the impedance of the viral and bacterial filter used. A linear mixed-model was used to test changes in $R_5$ and $X_5$ with time, considering fixed effects for the intercept and time plus random effect for the intercept for each patient. Correlations between oscillometry parameters and laboratory data, initial $PaO_2/FiO_2$ values were tested by Spearman test. Data were analysed using Matlab R2020b (MathWorks, Natick, MA, USA), SigmaPlot v11 (Systat Software, Inc., San Jose, CA, USA), and R version 4.0.4 (R Foundation for Statistical Computing, Austria).

Results

A convenience series of 15 patients affected by COVID-19 critical pneumonia satisfying Berlin criteria for moderate-severe ARDS were enrolled. Ten patients were hospitalised between 08/04/2020 and 15/05/2020 during the first wave of COVID 19 and 5 patients at the beginning of the second wave between 28/10/2020 and 14/12/2020. Hospitalisation, anthropometric, clinical, laboratory and radiologic characteristics of the included patients are shown in Table 1. Clinical conditions that could impact respiratory function were the following. Three patients had a diagnosis of pulmonary embolism during hospitalisation (#2, #6, #10). One patient presented a previous diagnosis of respiratory comorbidity: patient #1 was affected by chronic obstructive pulmonary disease (COPD, 1). Another patient (#4) did not report pre-existing respiratory morbidities but had bronchospasms identified by auscultation during the first days of hospitalisation in RICU with no sign of heart failure and inhalation therapy was introduced. Only patient #1 was a smoker. Patients #8 and #9 were ex-smokers and quit smoking 40 and 20 years ago, respectively. All patients improved and were discharged to non-intensive medical wards.

A single FOT measurement took less than 1 minute to be performed. All patients well-tolerated the measurements, possibly showing modest and transient reduction of oxygen saturation ($SpO_2$) to 88–90% at the end of the tidal breathing with immediate restoration of the $SpO_2$ with nose clips removal and restart of HFNC oxygen delivery. No discomfort was reported by the attending physician. Triplicate measurements presented an $R_5\_CV<10\%$ in 55% of the cases. $R_5\_CV$ becomes <10% in the remaining cases after the exclusion of an outlier. Respiratory rate (22±9 breath/min at first measurement), tidal volume (0.88±0.44 L at first measurement), and minute ventilation (17±6 L/min at first measurement) during the measurements did not change in time.

Time intervals between measurement sessions were 3.7±1.6 (mean ± standard deviation) days. On average, $R_5$ significantly decreased (p<0.001) and $X_5$ increased (p<0.001) during hospitalisation (Fig 1), with only two patients (#6 and #10) showing a worsening of oscillometry data. Our patients presented different lung mechanical conditions. At the first
measurement, lung mechanics were abnormal in 8 out of 15 subjects. In particular, three patients presented increased \( R_5 \), five patients presented reduced \( X_5 \) and two patients presented both increased \( R_5 \) and reduced \( X_5 \) (Table 2). \( R_5 \) improved in all of them while \( X_5 \) worsen in two of them. Four patients had still abnormal oscillometry data at discharge: one patient presented increased \( R_5 \), three patients presented reduced \( X_5 \) and one patient presented both increased \( R_5 \) and reduced \( X_5 \) (Table 2). Two patients (#1 and #4) had higher \( R_5 - R_{19} \) and mean \( \Delta X_5 \) (Fig 2) than the other patients. At the first measurement and discharge, the oscillometric parameters did not correlate with initial \( \text{PaO}_2/\text{FiO}_2 \) and laboratory data.

**Discussion**

This pilot study aimed to test FOT feasibility in acute hypoxemic COVID 19 ARDS patients treated with non-invasive supports. To the best of our knowledge, this is the first report on the application of FOT to spontaneously breathing patients with COVID-19 acute respiratory

---

**Table 1. Patients data.**

| Patient | Age (y) | BMI (Kg/m\(^2\)) | Comorbidities | Smoking | Days at hospital [at RICU] | CTPA proven pulmonary embolism | \( \text{PaO}_2/\text{FiO}_2 \) (mmHg) [\text{FiO}_2\%] | CRP (mg/L) | D-dimer (mg/L) | LDH (units/L) | Lymphocytes (counts/\( \mu \)L) | Creatinine (mg/dL) |
|---------|---------|-----------------|---------------|---------|---------------------------|-------------------------------|-------------------------------|-----------|----------------|---------------|-----------------|-----------------|
| #1      | 68      | 28              | HT, COPD, pAF | Yes     | 55 [7]                    | -                             | 146 [50]                      | 132       | 0.38           | 117           | 420             | 0.71            |
| #2      | 67      | 28              | DM, HT        | No      | 37 [31]                   | Yes                           | 180 [85]                      | 37        | 0.55           | 327           | 620             | 0.67            |
| #3      | 79      | 28              | rD, DM, HT    | No      | 35 [16]                   | No                            | 164 [71]                      | 48        | 2.24           | 372           | 1750            | 1.19            |
| #4      | 53      | 33              | HT            | No      | 18 [8]                    | No                            | 192 [92]                      | 175       | 0.81           | 346           | 500             | 0.77            |
| #5      | 44      | 34              | HT            | No      | 29 [6]                    | -                             | 170 [60]                      | 61        | 0.20           | 385           | 670             | 0.73            |
| #6      | 82      | 25              | PAC, HT       | No      | 55 [12]                   | Yes                           | 167 [75]                      | 75        | 4.43           | 432           | 900             | 0.83            |
| #7      | 74      | 30              | HT            | No      | 9 [4]                     | No*                           | 162[60]                       | 328       | 0.9            | 401           | 690             | 0.84            |
| #8      | 76      | 30              | HT, pAF       | Former  | 41 [19]                   | No                            | 120[90]                       | 66        | 1.6            | 403           | 450             | 1.09            |
| #9      | 69      | 30              | -             | Former  | 44 [5]                    | No                            | 172[100]                      | 82.4      | 1.4            | 545           | 700             | 0.55            |
| #10     | 74      | 26              | BPH           | No      | 19 [10]                   | Yes                           | 170[80]                       | 328       | 9.8            | 593           | 890             | 0.59            |
| #11     | 43      | 30              | DM            | No      | 21 [5]                    | -                             | 115[100]                      | 36        | 0.36           | 341           | 1060            | 0.63            |
| #12     | 64      | 30              | DM            | No      | 20 [8]                    | No                            | 141[70]                       | 84        | 0.47           | 471           | 440             | 0.84            |
| #13     | 62      | 20              | -             | No      | 17 [8]                    | No                            | 62[90]                        | 86        | 0.93           | 236           | 560             | 0.89            |
| #14     | 55      | 31              | -             | No      | 15 [3]                    | No                            | 70[60]                        | 13        | 1.03           | 291           | 460             | 0.94            |
| #15     | 67      | 29              | HT            | No      | 12 [8]                    | No                            | 111[80]                       | 132       | 0.88           | 343           | 420             | 0.92            |

Median (IQR) 67 (58:74) 30 (28:30) 1 BPH 1 COPD 1 Smoker 2 Ex-smokers 21 (17:39) 8 (5:11) 3 Yes 162 (117:170) 82 (54:132) 9 No 9 No 9 NA

BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; pAF = permanent atrial fibrillation; HT = hypertension; DM = diabetes mellitus; rD = recent diverticulitis; PAC = prostatic adenocarcinoma; BPH = benign prostatic hyperplasia; Former smoker: stop at least 20 years ago; RICU = Respiratory Intensive Care Unit; CTPA = computed tomographic pulmonary angiography; \( \text{PaO}_2 \) = arterial oxygen partial pressure; \( \text{FiO}_2 \) = fractional inspired oxygen; CRP = C-reactive-protein; D-dimer. LDH = lactate dehydrogenase. All the laboratory data and \( \text{PaO}_2/\text{FiO}_2 \) were sampled at first days at RICU. Our laboratory normal values are CRP <5mg/L; D-dimer <0.5 mg/L; LDH < 250; Lymphocytes between 1000-4000/\( \mu \)L and Creatinine between 0.5–1.3 mg/dL. \( \text{PaO}_2/\text{FiO}_2 \) was measured during HFNC support.

* patient 7 underwent negative pulmonary scintigraphy 31 days after discharge. Data are presented as discrete values (yes/no/former) or median with interquartile range for continuous values.

https://doi.org/10.1371/journal.pone.0265202.t001
It was possible to perform FOT measurements in triplicate in all sessions for all patients and each test lasted less than one minute. Measurements were well tolerated and reproducible during the entire course of hospitalization.

Early reports about health personnel infected by COVID-19 [1] have addressed the risk of transmission during aerosol-generating procedures as a considerable burden and recommendations have been produced [18]. Coughing and heavy breathing increase the velocity and volume of air forced over the respiratory mucosa producing large amounts of respiratory particles [19]. Viral load during coughing atomises respiratory secretions more than tracheal intubation [20], exposing the healthcare personnel to the risk of viral droplets during physical examination. The possibility of applying FOT in this contest is of interest as it allows to monitor lung function in COVID 19 patients reducing the risk of viral droplets exposure. In fact, FOT only requires quiet breathing through a bacterial filter.

In our convenience sample, approximately half of the patients had normal $R_5$ and $X_5$ values while at RICU, showing that hypoxemia in COVID-19 is not only determined by airway obstruction or lung volume de-recruitment. Normal $X_5$ values are in line with previous studies reporting normal compliance in a minority of COVID 19 and non-COVID 19 ARDS patients [21–24].

Fig 1. $R_5$ and $X_5$ for all the patients vs days prior to RICU discharge. Closed symbols identify altered $R_5$ and $X_5$ values compared to normal reference (Zscore > 1.645).

[https://doi.org/10.1371/journal.pone.0265202.g001](https://doi.org/10.1371/journal.pone.0265202.g001)
and $\text{PaO}_2$/FiO$_2$ were not correlated in our patients and this is in line with previous studies reporting no correlations between oxygenation and lung compliance in intubated or non-invasively ventilated ARDS COVID 19 patients [23–25], but contrary to the data of Vandendunder et al. [26]. The lack of correlation between these variables also supports that in several patients oxygen requirement is mainly determined by other factors than reduced lung compliance and peripheral obstruction, such as, for example, ventilation perfusion mismatch or other factors related to pulmonary circulation. Recent literature reviews are clearing up the central role of thrombotic microangiopathy in the early phenotype of COVID 19 pneumonia that worsens the ventilation-perfusion ratio without especially weighting on lung compliance [27, 28].

FOT provides a quantitative and objective evaluation of lung mechanics that can be easily repeated at different time points, allowing monitoring changes in lung conditions. Therefore, the time course of the disease and the effects of treatments on lung mechanics can be evaluated. FOT data improved with time in most patients, even when the first measurement was within the normal range, showing a pattern more compatible with recovery from interstitial or very mild oedema into peripheral lung regions than those typical of extensive alveolar flooding [14, 29]. In our dataset, no patients failed NIV and the X$_5$ improvement we found is in line with the improvement in lung compliance reported in AHRF patients with NIV success [21].

Four patients with different underlying conditions had still abnormal oscillometry data at discharge. One patient was affected by chronic obstructive pulmonary disease (COPD, #1). Another one (#4), despite not reporting pre-existing respiratory morbidities, had bronchospasms as identified by auscultation. In these two patients, oscillatory mechanics were consistent with the presence of an obstructive pattern shown by increased R$_5$ values. They also showed the highest $R_5$-$R_{19}$ (the range of normality for this parameter is not reported in the literature) and $\Delta X_5$ values. $\Delta X_5$ values, despite not reaching the threshold for fully developed EFL$_T$, suggests that some airways developed choke points during expiration. This quantitative information provided by FOT data can help tailor bronchodilator therapy and follow the

### Table 2. Z-score of oscillometry measurements.

| Patient | First measurement | | Last measurement | |
|---------|-------------------|---|-------------------|---|
|         | $R_5$ z-score | $X_5$ z-score | $R_5$ z-score | $X_5$ z-score |
| #1      | 3.06   | 4.95   | 2.09   | 2.68   |
| #2      | 1.94   | 1.52   | 0.06   | -0.48  |
| #3      | 0.44   | -0.51  | -1.59  | -2.16  |
| #4      | 0.90   | 2.76   | 0.92   | 2.91   |
| #5      | -1.53  | -1.13  | -2.06  | -1.90  |
| #6      | 0.42   | 2.29   | 1.52   | 3.67   |
| #7      | 0.08   | -0.47  | -0.79  | -0.99  |
| #8      | -1.14  | -0.42  | -1.56  | 0.04   |
| #9      | 2.62   | 2.80   | 0.48   | 1.61   |
| #10     | 0.57   | 2.07   | 0.92   | 3.48   |
| #11     | 0.39   | 2.97   | 0.79   | 1.64   |
| #12     | 0.96   | 2.38   | -0.79  | 0.68   |
| #13     | 1.75   | 0.88   | 0.75   | 0.20   |
| #14     | 1.69   | 0.61   | 1.66   | 0.84   |
| #15     | 0.66   | 1.43   | 0.74   | 0.46   |
| Median (IQR) | 0.66 (0.40;1.72) | 1.52 (0.09;2.57) | 0.74 (-0.78;0.92) | 0.68 (-0.22;2.16) |

Z-scores $> 1.645$ indicate increased $R_5$ or decreased $X_5$ values compared to normal reference values as reported by [17].

https://doi.org/10.1371/journal.pone.0265202.t002

$X_5$ and $\text{PaO}_2$/FiO$_2$ were not correlated in our patients and this is in line with previous studies reporting no correlations between oxygenation and lung compliance in intubated or non-invasively ventilated ARDS COVID 19 patients [23–25], but contrary to the data of Vandendunder et al. [26]. The lack of correlation between these variables also supports that in several patients oxygen requirement is mainly determined by other factors than reduced lung compliance and peripheral obstruction, such as, for example, ventilation perfusion mismatch or other factors related to pulmonary circulation. Recent literature reviews are clearing up the central role of thrombotic microangiopathy in the early phenotype of COVID 19 pneumonia that worsens the ventilation-perfusion ratio without especially weighting on lung compliance [27, 28].

FOT provides a quantitative and objective evaluation of lung mechanics that can be easily repeated at different time points, allowing monitoring changes in lung conditions. Therefore, the time course of the disease and the effects of treatments on lung mechanics can be evaluated. FOT data improved with time in most patients, even when the first measurement was within the normal range, showing a pattern more compatible with recovery from interstitial or very mild oedema into peripheral lung regions than those typical of extensive alveolar flooding [14, 29]. In our dataset, no patients failed NIV and the X$_5$ improvement we found is in line with the improvement in lung compliance reported in AHRF patients with NIV success [21].

Four patients with different underlying conditions had still abnormal oscillometry data at discharge. One patient was affected by chronic obstructive pulmonary disease (COPD, #1). Another one (#4), despite not reporting pre-existing respiratory morbidities, had bronchospasms as identified by auscultation. In these two patients, oscillatory mechanics were consistent with the presence of an obstructive pattern shown by increased R$_5$ values. They also showed the highest $R_5$-$R_{19}$ (the range of normality for this parameter is not reported in the literature) and $\Delta X_5$ values. $\Delta X_5$ values, despite not reaching the threshold for fully developed EFL$_T$, suggests that some airways developed choke points during expiration. This quantitative information provided by FOT data can help tailor bronchodilator therapy and follow the
clinical course of obstructed ventilated COVID-19 while reducing the biological hazard of physical examination.

The other two patients with abnormal FOT data at discharge (patient #6 and #10) did not show signs of obstruction nor EFLT (normal R5 and ΔX5 close to 0), but were the only patients whose X5 worsened with time while at the RICU. These patients showed the worst initial D-dimer and evidence of pulmonary embolism at CTPA during hospitalisation in RICU. In these two patients, the abnormal oscillometry data may also be related to the pulmonary embolism that can lead to constriction of airways adjacent to the embolised lung segment and/or pulmonary edema, as previously reported [30]. If X5 worsening can predict acute or chronic worsening of clinical conditions remains to be evaluated. This could be valuable information since COVID 19 severe pneumonia needing invasive ventilation is characterized by a reduction in aerated lung surface with a progressive reduction in the compliance of the respiratory system [23, 24, 26], greater increase in the lung weight mainly due consolidated lung regions, and non-perfused areas that become predominant compared to COVID 19 severe pneumonia manageable with non-invasive support [31]. The majority of our patients had normal/near normal reactance, their gas exchange improved with time and they were discharged to medical ward. If oscillatory lung mechanics worsens in patients with less favorable progression leading to the need of mechanical ventilation requires future studies. Also, since about one-third of

Fig 2. R5—R19 and ΔX5 for all the patients vs days prior to RICU discharge. Dashed line identifies the threshold for fully developed EFLT. No reference values are available in literature for R5-R19.

https://doi.org/10.1371/journal.pone.0265202.g002
severe respiratory COVID 19 undergo long-lasting fibrotic-like changes in the lung [32] it will be interesting to evaluate if X5 worsening could predict fibrotic-like deterioration of lung parenchyma.

Our data suggest that longitudinal assessment of respiratory mechanics by oscillometry is feasible, produces reproducible results in patients receiving NIV and provides information on lung condition that may help physicians to evaluate disease progression, titrate and follow response to treatments. Future studies, including more patients with different clinical conditions, should further address this last concept.

Our study has limitations. Firstly, we studied a convenience series of patients and this can result in a selection bias. We included a small number of patients with heterogeneous clinical conditions. However, the heterogeneity and the high BMI of our subjects reflects a real-life hospitalised population in the COVID 19 ward. Moreover, as all patients in our convenience series improved and were discharged to medical wards we have no data to evaluate whether changes in lung mechanics may be predictive of NIV failure or mid-to-long term respiratory outcomes. Future studies should address this point.

In conclusion, our data showed that FOT is well tolerated by hypoxemic COVID-19 ARDS patients receiving NIV, suitable for being included in clinical management of such patients and provides reproducible data. Our data confirm that the COVID-19 ARDS hypoxemia is associated with heterogeneous mechanical lung conditions and longitudinal assessment of respiratory mechanics by oscillometry may constitute an additional tool to improve tailoring of treatments in settings where lung function data is unavailable. This may be especially valuable in the patients with respiratory comorbidities, congestive harth failure [33] or other conditions affecting lung mechanics. Further studies should be addressed to assess the clinical value of oscillometry in patients with ARDS due to COVID-19 receiving NIV.

Acknowledgments

We would like to thank all the colleagues who made most of the measurements during that tough days: Francesco Aretusi, Giacomo Centomo, Anna Mocellin, Francesca Bravin, Paolo Ghisleri, Maria Andolfatto, Brigitta Perencin, Davide Maione, Eva del Mestre, Johnny Ma, Roberto Palmisano, Valentina Samola, Giuseppe Cacciatore. We gratefully acknowledge Mar Janna Dahl of the University of Utah for revising the manuscript.

Author Contributions

Conceptualization: Chiara Torregiani, Chiara Veneroni, Marco Confalonier, Raffaele Lorenzo Dellaca’.

Data curation: Chiara Torregiani, Paola Confalonieri, Gloria Maria Citton, Francesco Salton, Mohamad Jaber.

Formal analysis: Chiara Torregiani, Chiara Veneroni.

Investigation: Raffaele Lorenzo Dellaca’.

Methodology: Chiara Veneroni.

Supervision: Marco Confalonier, Raffaele Lorenzo Dellaca’.

Writing – original draft: Chiara Torregiani, Raffaele Lorenzo Dellaca’.

Writing – review & editing: Chiara Veneroni, Paola Confalonieri, Gloria Maria Citton, Francesco Salton, Mohamad Jaber, Marco Confalonieri.
References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA—Journal of the American Medical Association. American Medical Association; 2020. pp. 1239–1242. https://doi.org/10.1001/jama.2020.2648 PMID: 32091533

2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382: 1708–1720. https://doi.org/10.1056/NEJMc2002032 PMID: 32109013

3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA—J Am Med Assoc. 2020; 323: 1574–1581. https://doi.org/10.1001/jama.2020.5394 PMID: 32250385

4. Bellani G, Grasselli G, Cecconi M, Antonelli L, Borelli M, De Giacomi F, et al. Noninvasive ventilatory support of patients with covid-19 outside the intensive care units (ward-covid). Ann Am Thorac Soc. 2021; 18: 1020–1026. https://doi.org/10.1513/AnnalsATS.202008-1080OC PMID: 3395553

5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076

6. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Annals of Intensive Care. Springer; 2020. https://doi.org/10.1186/s13613-020-00692-6 PMID: 32519064

7. Tobin MJ, Jubran A, Laghi F. Noninvasive strategies in COVID-19: Epistemology, randomised trials, guidelines, physiology. European Respiratory Journal. European Respiratory Society; 2021. https://doi.org/10.1183/13993003.00753–2019

8. Radovanovic D, Coppola S, Franceschi E, Gervasoni F, Duscie O, Chiumello DA, et al. Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: A rapid review. Journal of Critical Care. W.B. Saunders; 2021. pp. 1–8. https://doi.org/10.1016/j.jccr.2021.05.007 PMID: 34052780

9. Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clinics in Chest Medicine. W.B. Saunders; 2019. pp. 243–257. https://doi.org/10.1016/j.ccm.2019.02.012 PMID: 31078207

10. Antonelli M, Conti G, Moro M, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxic respiratory failure: A multicenter study. Intensive Care Med. 2001; 27: 1718–1728. https://doi.org/10.1007/s00134-001-1114-4 PMID: 11810114

11. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxic patients. Intensive Care Med. 2017; 43: 192–199. https://doi.org/10.1007/s00134-016-4601-3 PMID: 27812731

12. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellaca RL, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020; 55. https://doi.org/10.1183/13993003.00753–2019

13. Dellaca RL, Rotger M, Aliverti A, Navajas D, Pedotti A, Faire R. Noninvasive detection of expiratory flow limitation in COPD patients during nasal CPAP. Eur Respir J. 2006; 27: 983–91. https://doi.org/10.1183/09031936.06.00080005 PMID: 16446315

14. Dellaca RL, Andersson Olerud M, Zannin E, Kostic P, Pompillo PP, Hedenstierna G, et al. Lung recruitment assessed by total respiratory system input reactance. Intensive Care Med. 2009; 35: 2164–72. https://doi.org/10.1007/s00134-009-1673-3 PMID: 19789855

15. Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklemz PT, et al. Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J. 2004; 23: 232–240. https://doi.org/10.1183/09031936.04.0046804 PMID: 14979497

16. Salton F, Confalonieri P, Umberto Meduri G, Santus P, Harari S, Scala R, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. Open Forum Infect Dis. 2020; 7. https://doi.org/10.1093/ofid/foaa421 PMID: 33072814

17. Oostveen E, Boda K, Van Der Grinten CPM, James AL, Young S, Nieland H, et al. Respiratory impedance in healthy subjects: Baseline values and bronchodilator response. Eur Respir J. 2013; 42: 1513–1523. https://doi.org/10.1183/09031936.0126212 PMID: 23598554

18. Alhazzani W, Møller MH, Araki YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine. 2020. https://doi.org/10.1007/s00134-020-06022-5 PMID: 32222812
19. Klompas M, Baker M, Rhee C. What Is an Aerosol-Generating Procedure? JAMA Surg. 2021; 156: 113–114. https://doi.org/10.1001/jamasurg.2020.6643 PMID: 33320188

20. Brown J, Gregson FKA, Shrimpton A, Cook TM, Bzdek BR, Reid JP, et al. A quantitative evaluation of aerosol generation during tracheal intubation and extubation. Anaesthesia. 2021; 76: 174–181. https://doi.org/10.1111/anae.15292 PMID: 33022093

21. Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, et al. Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in de novo respiratory failure: A pilot study. Am J Respir Crit Care Med. 2020; 202: 558–567. https://doi.org/10.1164/rcrm.201912-2512OC PMID: 3235004

22. Grasso S, Mirabella L, Murgolo F, Di Mussi R, Pisani L, Dalfino L, et al. Effects of Positive End-Expiratory Pressure in “High Compliance” Severe Acute Respiratory Syndrome Coronavirus 2 Acute Respiratory Distress Syndrome. Crit Care Med. 2020;Publish Ah: 1–5. https://doi.org/10.1097/CCM.0000000000004084 PMID: 31833982

23. Grasselli G, Tonetti T, Pratti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020; 8: 1201–1208. https://doi.org/10.1016/S2213-2600(20)30370-2 PMID: 32861276

24. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernández M, Gea A, Arruti E, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020; 46: 2200–2211. https://doi.org/10.1007/s00134-020-06192-2 PMID: 32728965

25. Tonelli R, Busani S, Tabbì L, Fantini R, Castaniere I, Biagioni E, et al. Inspiratory Effort and Lung Mechanics in Spontaneously Breathing Patients with Acute Respiratory Failure due to COVID-19: A Matched Control Study. Am J Respir Crit Care Med. 2021; 204: 725–728. https://doi.org/10.1164/rccm.202104-1029LE PMID: 34214009

26. Vandenbunder B, Ehrmann S, Piagnerelli M, Sauneuf B, Serck N, Sourmagne T, et al. Static compliance of the respiratory system in COVID-19 related ARDS: an international multicenter study. Crit Care. 2021;25. https://doi.org/10.1186/s13054-021-03460-5 PMID: 33430915

27. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021; 9: 622–642. https://doi.org/10.1016/S2213-2600(21)00218-6 PMID: 33965003

28. Tonelli R, Marchioni A, Tabbì L, Fantini R, Busani S, Castaniere I, et al. Spontaneous Breathing and Evolving Phenotypes of Lung Damage in Patients with COVID-19: Review of Current Evidence and Forecast of a New Scenario. J Clin Med. 2021; 10: 1–12. https://doi.org/10.3390/jcm10050975 PMID: 33801368

29. Pellegrino R, Pompiolo P, Quaranta M, Aliverti A, Kayser B, Miserocchi G, et al. Airway responses to methacholine and exercise at high altitude in healthy lowlanders. J Appl Physiol. 2010; 108: 256–265. https://doi.org/10.1152/japplphysiol.00677.2009 PMID: 19940099

30. Elliott CG. Pulmonary physiology during pulmonary embolism. Chest. 1992; 101: 163S–171S. https://doi.org/10.1378/chest.101.4_supplement.163s PMID: 1555481

31. Ball L, Robba C, Herrmann J, Gerard SE, Xin Y, Mandelli M, et al. Lung distribution of gas and blood volume in critically ill COVID-19 patients: a quantitative dual-energy computed tomography study. Crit Care. 2021; 25: 1–12. https://doi.org/10.1186/s13054-020-03448-7 PMID: 33398077

32. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month follow-up chest CT findings after severe COVID-19 pneumonia. Radiology. 2021; 299: E177–E186. https://doi.org/10.1148/radiol.2021203153 PMID: 33497317

33. Witte KKA, Morice A, Clark AL, Cleland JGF. Airway resistance in chronic heart failure measured by impulse oscillometry. J Card Fail. 2002; 8: 225–231. https://doi.org/10.1054/jcfa.2002.126916 PMID: 12397570