Implementation and feasibility of inverse-ratio Airway Pressure Release Ventilation (APRV): Switching from Conventional Ventilation to APRV in Two French ICUs.

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Research

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Abstract

Background:

To evaluate the switching of patients mechanically ventilated on Pressure Support or Volume Control to inverse-ratio Airway Pressure Release Ventilation (APRV) during the COVID-19 pandemic.

Methods:

We performed a single-center retrospective observational analysis in two ICUs in a tertiary referral university teaching hospital in France. Were included patients with Covid-19 pneumonia requiring invasive ventilation with a PaO2:FiO2 ratio lower than 200 mmHg who performed a 6-hour trial of inverse-ratio APRV.

Results:

Seventeen consecutive patients who completed a 6-hour APRV trial in April 2020 were included. Three patients who were unable to be maintained on APRV due to an immediate fall in SpO2 were not included. In 12/17 patients (71%), the increase in PaO2:FiO2 ratio was greater than 20%. Mean (± standard deviation) PaO2:FiO2 ratio increased from 126 (± 28) mmHg to 178 (± 53) mmHg after 6 hours of APRV (p<0.001). Two patients presented a decrease in PaO2:FiO2 ratio after 6 hours of APRV. There was no appearance of significant hemodynamic impairment during APRV and an eventual increase in PaCO2 during the first hour of APRV was managed by increasing the respiratory rate (i.e. shortening T-high) and/or increasing tidal volume (i.e. increasing T-low).

Conclusions:

Switching from Conventional Ventilation (Pressure Support or Volume Assist Control) to inverse-ratio APRV for a 6-hour period in two ICUs that were not previously familiar with this ventilation technique was well tolerated, and associated with a marked improvement in oxygenation. Further studies evaluating inverse-ratio APRV in acute respiratory failure are warranted.

Trial registration:

NCT04386369

Introduction

Covid-19 pneumonia can lead to severe respiratory failure and ARDS requiring invasive ventilation. The cornerstone of management of severe ARDS is invasive lung protective ventilation. Airway Pressure Release Ventilation (APRV) was proposed as a ventilation mode in a recent single-center study which randomized patients to either APRV or Volume Control ventilation with a reduction in ventilation days observed in the APRV group\(^1\). When applied pre-emptively, APRV has the potential to prevent development
of ARDS\(^2\). Inverse-ratio APRV is characterized by a prolonged inspiratory time and a short expiratory time. We report the experience of switching patients from conventional ventilation (Volume Assist Control or Pressure Support) to inverse-ratio APRV during the Covid-19 pandemic.

**Methods**

Data were retrospectively collected from March to May 2020, in two ICUs of the Nancy University Hospital during the Covid-19 pandemic in France. When the ventilator permitted APRV, patients were started on inverse-ratio APRV in instances of a P/F ratio < 200 (DrägerEvita Infinity V500®, Puritan Bennett™ 840, Mindray™ SV300, Maquet™ Servo-i). Three ICU physicians were trained in initiating and managing the ventilator settings and the strategy consisted of a 6-hour APRV trial. Prior to APRV, the ventilators were set at the discretion of the attending physician (Volume Assist Control or Pressure Support). A daily neuromuscular blockers weaning trial was performed every day. No recruitment manoeuvres were performed. After 6 hours of APRV, patients were either returned to conventional ventilation or remained on APRV if the attending physician was familiar with APRV and deemed APRV beneficial for the patient.

The Primary Outcome was the proportion of patients improving PaO2/FiO2 ratio at 6 hours of APRV. Improvement was defined as the increase of at least 20% of the PaO2/FiO2 ratio. Secondary outcomes were hemodynamic and respiratory parameters.

Initial APRV settings were: P-high 28 cmH2O, T-High 3.5 seconds, P-Low 5 cmH2O and T-Low 0.5 seconds. Automatic Tube Compensation (ATC) was enabled on the DrägerEvita Infinity V500® ventilators and the inspiratory slope was set at 0. T-low was then adjusted to obtain a sufficient tidal volume. The expiratory flow curve was observed to ensure that the expiratory flow never reaches zero and stops at around 50–75% of the peak expiratory flow. Within the first hour of APRV, blood gases were measured to detect an eventual increase in PaCO2 and, if necessary, to increase the respiratory rate (i.e. decrease T-high). There was no concomitant initiation of adjuvant ARDS therapies (neuromuscular blockade, prone positioning, recruitment manoeuvres or nitrite oxide) at the time of APRV initiation. Blood gases, clinical and ventilator parameters were collected prior to APRV and after 6 hours of APRV. The study was approved by the Ethics Committee of Nancy’s Teaching Hospital and registered on ClinicalTrials.gov (NCT04386369).

**Results**

Seventeen consecutive patients were included from March to May 2020 (Flow-chart in Additional file 1). Three patients under VV-ECMO were not included as were 3 patients due to impossibility of starting APRV (excessive bronchial secretions and inability to obtain a sufficient tidal volume). Baseline characteristics are reported in Table 1. In 12/17 (71%) patients, the increase in PF ratio was greater than 20% and the mean (± standard deviation) PaO2:FiO2 ratio increased from 126 (± 28) mmHg to 178 (± 53) mmHg (p < 0.001) after 6 hours of APRV (Fig. 1). Two patients presented a decrease in PaO2:FiO2 ratio after 6 hours of APRV. No significant hemodynamic impairment appeared during APRV. The evolution of oxygenation and hemodynamic parameters (primary and secondary outcomes) during APRV is reported in Table 2.
Ventilation parameters prior to APRV are reported in Table 3. The evolution of APRV settings between APRV initiation and at 6 hours is reported in Table 4.
Table 1
Characteristics of the study population

| Demographic characteristics                                      | All patients (n = 17) |
|------------------------------------------------------------------|-----------------------|
| Age, years                                                      | 62 ± 11               |
| Male sex, n(%)                                                  | 14 (82)               |
| BMI                                                             | 33 ± 9                |
| Simplified Acute Physiological Score 2                          | 56 ± 16               |
| SOFA score at admission                                         | 6 ± 2                 |
| ICU mortality, n(%)                                             | 2 (11.8)              |
| Duration of ICU stay, days                                      | 29 [22–46]            |
| Duration of invasive ventilation during ICU stay, days          | 26 [19–31]            |
| Duration of mechanical ventilation in days prior to APRV, days  | 14 [8–19]             |
| Comorbidities, n (%)                                            |                       |
| Chronic kidney failure                                          | 1 (6)                 |
| Ischemic heart disease                                          | 3 (18)                |
| Hypertension                                                    | 9 (53)                |
| Diabetes                                                        | 5 (29)                |
| Chronic respiratory failure                                     | 1 (6)                 |
| Active cancer                                                   | 0 (0)                 |
| Interventions during the ICU stay, n (%)                        |                       |
| Neuromuscularblockers                                          | 17 (100)              |
| Prone positioning                                               | 15 (88)               |
| Corticosteroids                                                 | 8 (47)                |
| Renal replacement therapy, n(%)                                  | 4 (24)                |
| VV-ECMO, n(%)                                                   | 4 (24)                |

Data are presented as the mean ± standard deviation, the median [Q1-Q3] or number of patients with the percentage in parentheses, as appropriate.

Abbreviations:
BMI, Body Mass Index; SOFA score, Sequential Organ Failure Assessment score; APRV, airway pressure release ventilation; VV-ECMO, Veno-Venous Extracorporeal Membrane Oxygenation.
Table 2
Primary and secondary outcomes: evolution of oxygenation and hemodynamic parameters during APRV

| Respiratory and hemodynamic parameters | At baseline (n = 17) | At 6 hours of APRV (n = 17) | p-value |
|--------------------------------------|---------------------|-----------------------------|---------|
| **Arterial blood gas**               |                     |                             |         |
| PaO₂:FiO₂ (mmHg)                     | 126 ± 28            | 178 ± 53                    | < 0.001 |
| pH                                   | 7.40 ± 0.09         | 7.39 ± 0.08                 | 0.36    |
| PaCO₂ (mmHg)                         | 44 ± 9              | 44 ± 12                     | 0.95    |
| **Respiratory parameters**           |                     |                             |         |
| Minute ventilation (L/min)           | 13.0 ± 3.5          | 10.3 ± 3.3                  |         |
| Mean airway pressure (cmH₂O)         | 18.1 ± 3.1          | 21.8 ± 3.7                  | 0.002   |
| Total PEEP (cmH₂O)                   | 10.8 ± 2.5          | 13.9 ± 3.7 *                |         |
| Driving pressure (cmH₂O)             | 14.6 ± 2.6          | 13.5 ± 4.1 *                |         |
| Mean Tidal Volume (ml/kg of PBW)     | 7.0 ± 1.3           | 6.5 ± 1.7                   | 0.04    |
| **Hemodynamic parameters**           |                     |                             |         |
| Systolic arterial pressure (mmHg)    | 134 ± 28            | 121 ± 23                    | 0.10    |
| Diastolic arterial pressure (mmHg)   | 65 ± 11             | 63 ± 9                      | 0.57    |
| Mean arterial pressure (mmHg)        | 86 ± 16             | 82 ± 14                     | 0.57    |
| Heart rate (bpm)                     | 94 ± 21             | 92 ± 18                     | 0.92    |
| Lactate (mmol/l)                     | 1.5 ± 1.9           | 1.4 ± 0.6                   | 0.50    |
| Norepinephrine (µg/kg/min) **        | 0.07 ± 0.27         | 0.07 ± 0.16                 | 0.87    |
| **Concomitant therapy ***            |                     |                             |         |
| Nitric oxide                         | 1 (6)               | 1 (6)                       |         |

Data are presented as the mean ± standard deviation or the median [Q1-Q3], as appropriate.

Abbreviations: APRV, Airway Pressure Release Ventilation; PaO₂, Arterial Partial Pressure of Oxygen; PaCO₂, Arterial Partial Pressure of Carbon Dioxide.

* On APRV, data available for 10 patients under neuromuscular blockade. Driving pressure was calculated as the P-high minus total Positive End Expiratory Pressure. Total PEEP was measured during an end-expiratory occlusion at the end of T-low.

** Number of patients requiring norepinephrine: n = 4 at baseline and n = 6 after 6 hours of APRV

*** No concomitant therapy was started or withdrawn during the 6-hour APRV trial.
| Respiratory and hemodynamic parameters | At baseline (n = 17) | At 6 hours of APRV (n = 17) | p-value |
|----------------------------------------|---------------------|-----------------------------|---------|
| Prone positioning                      | 0                   | 0                           |         |
| Neuromuscular blockade                 | 9 (53)              | 9 (53)                      |         |
| Number of APRV parameters adjustments during the 6-hour period | | 1.2 ± 0.7 | |

Data are presented as the mean ± standard deviation or the median [Q1-Q3], as appropriate.

Abbreviations: APRV, Airway Pressure Release Ventilation; PaO2, Arterial Partial Pressure of Oxygen; PaCO2, Arterial Partial Pressure of Carbon Dioxide.

* On APRV, data available for 10 patients under neuromuscular blockade. Driving pressure was calculated as the P-high minus total Positive End Expiratory Pressure. Total PEEP was measured during an end-expiratory occlusion at the end of T-low.

**Number of patients requiring norepinephrine: n = 4 at baseline and n = 6 after 6 hours of APRV

***No concomitant therapy was started or withdrawn during the 6-hour APRV trial.
Table 3
Ventilation parameters prior to APRV

| Ventilator parameters prior to APRV | All patients (n = 17) |
|------------------------------------|----------------------|
| Volume Assist Control settings, n(%) | 12 (71) |
| Tidal volume (ml/kg of PBW)        | 6.7 ± 0.7 |
| Respiratory rate (cycle/minute)    | 28 ± 3 |
| Set PEEP (cmH\(\text{O}\))         | 11 ± 2 |

Ventilation monitoring during Volume Assist Control

|                         | All patients (n = 17) |
|-------------------------|----------------------|
| Minute ventilation (L/min) | 12 ± 3               |
| Plateau pressure (cmH\(\text{O}\)) | 26 ± 2               |
| Total PEEP (cmH\(\text{O}\)) | 11 ± 2               |
| Mean airway pressure (cmH\(\text{O}\)) | 18 ± 3               |
| Respiratory rate (cycle/minute) | 29 ± 5               |
| Respiratory static system compliance (mL/cmH\(\text{O}\)) | 32 ± 7               |
| Driving pressure (cmH\(\text{O}\)) | 15 ± 3               |
| Pressure Support settings, n(%) | 5 (29)                |
| Pressure above PEEP (cmH\(\text{O}\)) | 13 ± 4               |
| Set PEEP (cmH\(\text{O}\)) | 10 ± 3               |

Ventilation monitoring during Pressure Support

|                         | All patients (n = 17) |
|-------------------------|----------------------|
| Tidal volume expired (ml/kg of PBW) | 7.3 ± 2               |
| Minute ventilation (L/min) | 15 ± 4               |
| Mean airway pressure (cmH\(\text{O}\)) | 15 ± 4               |
| Respiratory rate (cycle/minute) | 30 ± 6               |

Data are presented as the mean ± standard deviation, or the number of patients with the percentage in parentheses (%), as appropriate.

Abbreviations: PBW, Predicted Body Weight; PEEP, Positive End Expiratory Pressure.

Driving pressure was calculated as the plateau pressure minus total positive end expiratory pressure.

Respiratory system compliance was calculated as tidal volume divided by driving pressure.
Table 4
APRV settings at initiation and after 6 hours of APRV.

| APRV parameters | On APRV initiation | After 6 hours of APRV |
|-----------------|---------------------|-----------------------|
| Ventilator settings |                    |                       |
| P-high (cmH2O)  | 26 ± 3              | 25 ± 5                |
| T-high (seconds) | 4 ± 1               | 3.7 ± 1.4             |
| P-low (cmH2O)   | 3 ± 2.4             | 3 ± 2.5               |
| T-low (seconds) | 0.55 ± 0.15         | 0.6 ± 0.2             |
| Ventilation monitoring |                |                       |
| Mean Tidal Volume (ml/kg of PBW) * | 6.3 ± 2.6       | 6.5 ± 1.7             |
| Total minute ventilation (L/min) ** | 9.7 ± 3.1        | 10.3 ± 3.3            |
| Respiratory rate (cycle/minute) * | 21 [16–37] | 22 [16–34]         |
| Total PEEP (cmH₂O) *** | 12.5 ± 2.2 | 13.9 ± 3.7          |
| Mean airway pressure (cmH₂O) ** | 23.5 ± 2.2 | 21.8 ± 3.7          |
| Driving pressure (cmH₂O) *** | 15 ± 2.4    | 13.5 ± 4.1          |

Data are presented as the mean ± standard deviation (SD) or as median [Q1-Q3], as appropriate.

Abbreviations: APRV, airway pressure release ventilation; PBW, Predicted Body Weight; PEEP, Positive End Expiratory Pressure; P-high, High airway pressure; T-high, time at high airway pressure; P-low, Low airway pressure; T-low, time at low airway pressure.

* Missing data for 2 patients
** Missing data for 1 patient
*** Data available for 10 patients under neuromuscular blockade. Driving pressure was calculated as the P-high minus total Positive End Expiratory Pressure. Total PEEP was measured during an end-expiratory occlusion at the end of T-low.

Discussion

These observations show a beneficial impact of APRV on oxygenation in patients with Covid-19 related acute respiratory failure. The increase in P/F ratio was observed after 6 hours of APRV after switching from Volume Control or Pressure Control modes.

Implementation of APRV in the ICU and APRV settings

In the two ICUs that implemented the inverse-ratio APRV, few physicians were familiar with the procedure. The strategy to initially set APRV in each patient for only 6 hours was dictated by the fact that during the
24-hour period in the ICU, the attending physician was not always familiar with APRV, especially at the beginning of the Covid-19 pandemic. Over the course of the pandemic, certain patients remained on APRV for longer than 6 hours when more physicians and nurses received basic training. This training was particularly focused on the management of T-low duration in order to achieve a tidal volume by observation of the Flow Curve. P-low was seldom set to 0 cmH2O due to concerns of alveolar pressure reaching P-low (in the case of inappropriately long T-low) and was set to 5 cmH2O as described by Zhou et al. Nurses were instructed to alert the physician if a drop in VT and/or minute ventilation was observed, with ventilator alarms being set accordingly. Individual APRV settings optimized after 6 hours of APRV are reported in Additional file 2.

**Inverse-ratio APRV and oxygenation**

The main finding of the present study is the increase in P/F ratio noted in most of the patients after a 6-hour APRV trial. The impact of such an improvement in oxygenation is significant as patients would otherwise require other adjuvant therapies, such as prone positioning, which can be cumbersome with a high patient volume during a pandemic. It is worth noting that Covid-19 pneumonia patients have been reported to have a high recruitment potential, thus possibly explaining this PaO2:FiO2 increase.

**APRV settings**

APRV can refer to two types of settings. One is more conventional, with a shorter inspiratory time (short T-high) and a longer expiratory time (long T-low), which can be compared to BiPAP. The other refers to inverse-ratio APRV in which the inspiratory time is longer (prolonged T-high) than the expiratory time (short T-low) and the expiratory phase lasts around 0.3 – 0.8 seconds with the aim of preventing alveolar pressure from reaching the set P-low and thus not allowing the lung to depressurize.

**Inverse-ratio APRV**

When setting APRV, we set T-low by observing the expiratory flow curve and ensuring that the expiratory flow is interrupted before reaching zero at 50-75% of the peak expiratory flow. Inverse-ratio APRV is a non-conventional ventilator mode in which tidal volume is delivered during a short decrease in pressure contrary to volume control or pressure support where VT is delivered during an increase in pressure from a set level of PEEP. Thus, in inverse-ratio APRV, the Functional Residual Capacity (FRC) is higher than in conventional ventilation. Spontaneous breathing remains possible if the patient is not paralyzed.

**Time Controlled Adaptive Ventilation**

Although we did not set APRV precisely with regards to the method of Time Controlled Adaptive Ventilation (TCAV), we tried to approach this technique as much as possible. TCAV is aimed at limiting Ventilator-Induced Lung Injury and has been proposed since 2005. In TCAV, expiration is interrupted before the expiratory flow reaches zero, at 75% of the slope of the expiratory flow curve, voluntarily creating an intrinsic PEEP and preventing cyclic alveolar opening and re-collapse. The beneficial
impact of TCAV was suggested by experimental and animal studies, by limiting atelectrauma and stabilizing the alveoli, thus reducing Ventilator-Induced Lung Injury $^{12,13}$.

In the ICU, the use of APRV/TCAV remains limited as reported by a recent meta-analysis of 5 studies including 330 patient $^{14}$. Moreover, much of the data stem from only a few expert centers with a strong experience in TCAV protocols. At present, the largest study randomizing patients to inverse-ratio APRV or conventional ventilation is a trial conducted by Zhou et al. with 71 patients in the APRV group $^1$.

**Limitations**

They are certain obvious limitations to this study. We retrospectively evaluated only a short period of APRV in our patients and while the improvement in oxygenation in some patients was significant after a few hours, the overall impact of APRV on patient outcome remains to be further assessed. As improvement in oxygenation does not always lead to improvement in survival, it has to be taken into account$^{15}$.

Some patients presented high VTs (up to 9 ml/kg of PBW), and even if lung compliance was less altered in some patients with COVID-19 pneumonia, the potentially harmful impact of high tidal volumes needs to be considered$^3$. This is a well-known concern when applying APRV, even when dedicated protocols are used $^{16}$. It is worth noting that our initial strategy of setting T-high at 3.5 sec resulted in low RRs often leading to hypercapnia and thus the need to increase the duration of T-low to obtain a higher VT and higher minute ventilation. Aiming for lower T-high (even as low as 1.8 sec) enabled us to obtain lower tidal volumes. Another concern are the oscillations in VTs observed in non-paralyzed patients with spontaneous breathing. However, in the acute phase, most of the patients were paralyzed limiting the variability in VTs.

**Perspectives**

Inverse-ratio APRV remains a ventilator mode that is not commonly accepted in the ICU community, with obvious limitations to its acceptance such as its counter-intuitive settings and the lack of randomized controlled studies. From our perspective, one of the challenges for future multi-center studies evaluating inverse-ratio APRV will be the standardization of APRV settings, particularly managing the T-low and its resulting tidal volumes. Even among practitioners using APRV there exists a lack of consensus on APRV settings$^{17}$.

**Conclusion**

In our severe ARDS Covid-19 patients, the use of inverse-ratio APRV was well tolerated and was associated with a marked improvement in oxygenation parameters. When APRV was maintained for at least 6 hours, the PF ratio increased by 20% or more in 11 out of 17 patients. Inverse-ratio APRV requires advanced ventilation skills, precise APRV parameter settings and careful monitoring of the ventilation
parameters. Further studies are needed to assess inverse-ratio APRV as a primary ventilator mode in the ICU setting.

**Declarations**

**Ethics approval and consent to participate**

The study received the approval of the local Ethics Committee.

**Consent for publication**

Not applicable.

**Availability of data and material**

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

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Each author equally contributed to the manuscript (conception, design of the work, interpretation of data). All authors read and approved the final manuscript.

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**Figures**

**Figure 1**

Evolution of the PaO2:FiO2 ratio in mmHg after 6 hours of APRV
Figure 1
Evolution of the PaO2:FiO2 ratio in mmHg after 6 hours of APRV

Evolution of the mean PaO2:FiO2 ratio after 6 hours of inverse-ratio APRV (n=17)

| Time Period                      | PaO2:FiO2 Ratio (mmHg ± Standard Deviation) |
|----------------------------------|---------------------------------------------|
| 4 Hours Before APRV              | 132 ± 30                                    |
| Before APRV Initiation           | 126 ± 28                                    |
| After 6 Hours of APRV            | 178 ± 53                                    |

p < 0.001

p = 0.34
Figure 1

Evolution of the PaO2:FiO2 ratio in mmHg after 6 hours of APRV

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