Supplemental methods

*Fundamental equations*

Core computations performed in this work are the conversions from partial pressure (of \(O_2\) and \(CO_2\)) to contents, and vice versa.

- **Oxygen:**

  As the computations lead to a value of \(O_2\) content in the left atrium, to calculate the associated value of partial pressure (\(PO_2\)) and hemoglobin saturation (\(SO_2\)) an iteration is required:

  1. \(PO_2\) is increased iteratively by 0.1 mmHg and, for each value, the corresponding \(SO_2\) is calculated with Zander’s formula (2).

  2. Oxygen content is calculated as:

\[
Content_{O_2} = 1.39 \cdot [Hb]\cdot SO_2 + 0.00304 \cdot PO_2
\]

  3. The iteration is stopped when the oxygen content reached the target content.
• CO₂:

For pressure to content and content to pressure calculations we used Douglas formula (1).

• pH and Base Excess:

When BE was unknown and pH known, Zander’s formula (2) has been used. When pH was unknown and BE known an iteration was used:

1. A dummy pH of 6 is used and the BE is calculated with Zander’s formula.
2. pH is increased in 0.0001 steps until the calculated BE equals the target BE.

For further details, please consult the full code of the algorithm.

**Calculation of mixed venous PO₂ (PvCO₂)**

As PvCO₂ was not available, the value has been calculated hypothesizing a metabolic respiratory quotient (R) of 0.85.

• From cardiac output (CO) R and arterial O₂ content, the oxygen consumption (VO₂) can be calculated;
• From VO₂ and R, the carbon dioxide production can be calculated (VCO₂);
• From CO, VCO₂ and the arterial content of CO₂ the venous content of CO₂ can be calculated;
• Knowing mixed venous saturation and mixed venous PO₂, mixed venous pH can be calculated; (iterative approach on Zander’s equation);
• From mixed venous pH and mixed venous CO₂ content, PvO₂ can be calculated.
VentriQlar

VentriQlar code is fully available on www.github.com/mattiabusana/VentriQlar. Here we provide details regarding specific problems and assumptions.

- Right at the beginning of the computations, it is important to find the extremes of the $V_A/Q$ distribution which lead only to possible results ($V_A/Q > 0$). To do this, especially for the lower end of the distribution, a very dense space of possible $R$ values is checked (from 0.001 to 2 in 0.001 steps). As soon as FNDVAQ delivers a positive $V_A/Q$ compartment, this is considered the lower end of the distribution. With our simulations, this was always in the $10^{-2}$ order of magnitude.

- The various iterations within the program stop once the “gradient” between the actual value and the iteration fall below a certain tolerance threshold. The gradient was calculated as:

$$G = \frac{|\text{target} - \text{iteration}|}{\text{target}}$$

The tolerance was different in the various parts of the program and it was set to achieve a reasonable compromise between accuracy and possibility to find solutions. A too strict tolerance leads to no solutions, while a too liberal one leads to unreliable results. Please consult the code for a detailed view on the different thresholds used. In general, they varied between 1% and 25%.

- The space of possible choices of the 5 distribution parameter was very dense:
  - $Q_{\text{mean}1}$ and $Q_{\text{mean}2}$: from the minimum to the maximum $V_A/Q$, with 5000 values log spaced.
  - $Q_1$, $Q_2$, $D$, $Q_2$: from 0.3 to 2, with linear steps of 0.005.
  - $Q_1/Q_2$ ratio: from 0 to 1, with linear steps of 0.005.

- The anatomic dead space was calculated as 2.20 ml for each kg of Predicted Body Weight (airways) and adding the filter (27 ml) and the $\text{EtCO}_2$ adapter (5 ml) (3). As volumetric
capnography (and consequently the measurement of alveolar ventilation) was not available on our subjects, this estimated value of anatomic dead space was used to restrict the possible solutions to values with minute ventilation within 10% of the real. This is needed to “filter” solutions that would lead to extremely low values of alveolar ventilation (i.e., when $Q_{\text{mean}1}$ and $Q_{\text{mean}2}$ are both < 0.5).

**Supplemental results**

**Model testing**

Testing of Vent$_{\text{r,Q}}$ performance on a set of physiological data has been performed. The parameters used were:

- $Q_{\text{T}}$: 5 l/min
- $\text{FiO}_2$: 0.21
- Shunt: 0.5%
- Hemoglobin concentration: 14 g/dl
- BE: 0 mEq/l
- $\text{PvO}_2$: 40 mmHg
- $\text{PvCO}_2$: 45 mmHg

**Target values:**

- $\text{PaO}_2$: 90 mmHg
- $\text{PaCO}_2$: 40 mmHg

Figure 2 in the main manuscript represents the recovered $V_a/Q$ distribution with the smallest Euclidean distance from the target. Here we report the whole solution space. 1804/$10^6$ solutions were within 10% of both $\text{PaO}_2$ and $\text{PaCO}_2$ and $R \leq 1$. The total time required for the output was 21.6 minutes.
Compartment composition calculation required on average 742 ms and a single random solution output required on average 895 µs.

Figure E1: distribution of $Q_{\text{mean1}}$ and $Q_{\text{mean2}}$ recovered for the whole valid solution space in the ideal healthy subject.
Subject prediction

Figure E2: Distribution of $Q_{\text{mean}1}$ and $Q_{\text{mean}2}$ recovered for the whole valid solution space for each COVID-19 subject.
Figure E3: solution space for subject 1. None of the solutions fell within the range we considered acceptable.
Figure E4: Solution space for the 4 COVID-19, critically-ill subjects when the simulation was performed increasing the shunt to the 120% of the non-aerated tissue fraction. As shown, compared to the plots reported in the main manuscript (where the computations were done assuming a shunt equal to the 100% of the non-aerated tissue fraction), VentriQlar found many more solutions which were also, on average, closer to the target. This may suggest that the magnitude of shunt in these patients may be even higher than the already overestimated 120%. Note that the scale on the axis is not necessarily the same as in the analogous Figure on the main manuscript in order to display all the solutions.
Bibliography

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3. Radford EP, Jr. Ventilation standards for use in artificial respiration. *J Appl Physiol* 7: 451-460, 1955.