

Evaluation of the SIMULRESP: a simulation software of child and teenager cardiorespiratory physiology

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Abstract

BACKGROUND: Mathematical models based on the physiology when programmed as a software can be used to teach cardiorespiratory physiology and to forecast the effect of various ventilatory support strategies. We developed a cardiorespiratory simulator for children called “SimulResp”. The purpose of this study was to evaluate the quality of SimulResp. **METHODS:** SimulResp quality was evaluated on accuracy, robustness, repeatability and reproducibility. Blood gas values (pH, PaCO₂, PaO₂ and SaO₂) were simulated for several subjects with different characteristics and in different situations and compared to expected values available as reference. The correlation between reference and simulated data was evaluated by the coefficient of determination and Intraclass correlation coefficient. The agreement was evaluated with the Bland & Altman analysis. **RESULTS:** SimulResp produced healthy child physiological values within normal range (pH 7.40 +/- 0.5; PaCO₂ 40 +/- 5 mmHg, PaO₂ 90 +/- 10 mmHg; SaO₂ 97% +/- 3%) starting from a weight of 25 to 35 kg, regardless of ventilator support. SimulResp failed to simulate accurate values for subjects under 25 kg and/or affected with pulmonary disease and mechanically ventilated. Based on the repeatability was considered as excellent and the reproducibility as mild to good. SimulResp’s prediction remains stable within time. **CONCLUSIONS:** The cardiorespiratory simulator SimulResp requires further development before future integration into a clinical decision support system.

Original article

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Evaluation of the SIMULRESP

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Author Contributions

D.B and O.F. performed the SIMULRESP evaluation procedures. P.J. conceived the SIMULRESP and designed the study. M.S. and D.B. performed statistical analysis with consulting of a local statistician. All authors gave input into the SIMULRESP evaluation and contributed to writing the paper.

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Abstract

BACKGROUND: Mathematical models based on the physiology when programmed as a software can be used to teach cardiorespiratory physiology and to forecast the effect of various ventilatory support strategies. We developed a cardiorespiratory simulator for children called “SimulResp”. The purpose of this study was to evaluate the quality of SimulResp. **METHODS:** SimulResp quality was evaluated on accuracy, robustness, repeatability and reproducibility. Blood gas values (pH, PaCO₂, PaO₂ and SaO₂) were simulated for several subjects with different characteristics and in different situations and compared to expected values available

as reference. The correlation between reference and simulated data was evaluated by the coefficient of determination and Intraclass correlation coefficient. The agreement was evaluated with the Bland & Altman analysis. RESULTS: SimulResp produced healthy child physiological values within normal range (pH 7.40 +/- 0.5; PaCO₂ 40 +/- 5 mmHg, PaO₂ 90 +/- 10 mmHg; SaO₂ 97% +/- 3%) starting from a weight of 25 to 35 kg, regardless of ventilator support. SimulResp failed to simulate accurate values for subjects under 25 kg and/or affected with pulmonary disease and mechanically ventilated. Based on the repeatability was considered as excellent and the reproducibility as mild to good. SimulResp's prediction remains stable within time. CONCLUSIONS: The cardiorespiratory simulator SimulResp requires further development before future integration into a clinical decision support system.

Key words: *Computational model, clinical decision support systems, pediatrics, intensive care, respiratory physiological concepts, mechanical ventilation.*

Quick look

Current Knowledge

Physiology based mathematical models could be used to teach cardiorespiratory physiology and ventilation or determine optimal ventilation management.

SimulResp has been developed for modelling the children cardiorespiratory system, as none has been designed for this purpose so far.

What This Paper Contributes To Our Knowledge

SimulResp is able to produce blood gas values within the normal range when predicting blood gas values of healthy child over 8 years old spontaneously breathing or under mechanical ventilation.

Inconsistencies remain regarding prediction of blood gas values of healthy child under 8 years old or ventilated for pulmonary issues regardless of age.

Introduction

Mathematical models based on the physiology, namely, physiological models, have a crucial role in understanding the underlying mechanisms. When programmed as a software with a graphical user interface, these so-called computational models, or virtual patients, could be used to teach cardiorespiratory physiology and ventilation, determine optimal ventilation management as well as forecast the effect of various ventilatory support strategies (1–3). Furthermore, due to its virtual nature, prediction over a large amount of time can be summarized in a few minutes, making the assessment of the model more convenient than a real time assessment. Currently, there is no validated virtual patient specifically designed for modelling children cardiorespiratory system. Thus, our research team developed a cardiorespiratory simulator for children called “SimulResp” (figure 1) (2,4). SimulResp provides cardiorespiratory parameters, such as blood gases values, while simulating spontaneous and artificial ventilation situations for patients of various ages and weights with several pathological conditions. This simulator is based on physiological principles. Before a widespread use in respiratory status forecasting, this simulator must be validated (5). According to Summers et al. (6,7), the quality of a physiologic model is evaluated by three specific criteria: 1) qualitatively, which relates to the model's ability to provide directionally appropriate predictions; 2) quantitatively in steady states and 3) in dynamics, which is the ability of the model to provide accurate predictions in steady state situations as well as dynamic transitions. The purpose of this study was to evaluate the quality of SimulResp according to these criteria in a pediatric critical care population.

Methods

This study consisted in a prospective evaluation of the pediatric simulator SimulResp. This study was approved by the institutional review board of Sainte Justine Hospital (number 2016-1121) and waived the need of an explicit consent.

The simulator

SimulResp is a model of cardio-respiratory physiology based on CJ Dickinson’s model (8). The CJ Dickinson’s model (8) is a respiratory model based on three compartments : the capillary compartment where gas exchange takes place, the dead-space and the left-to-right shunt. SimulResp and the CJ Dickinson’s model (8) were both previously presented with more details (2,4) and we provide more details on the model’s algorithm as supplemental file (supplemental file 1). The initial model implementation in FORTRAN was translated to C++ and a visual interface was added. Simulresp uses a dynamic link library to perform different tasks in harmony.

Study protocol

To perform the study, we used the SimulResp versions 2015.10.11.01 (2015 version) and 2012.06.09.01 (2012 version). The two versions were considered equivalent as the formula within the software remained unchanged, only the design of the interface changed. All tests were performed by OF or DB. OF ran the SimulResp 2012 version, under windows 7 (Microsoft, Albuquerque, NM), on a 2011 computer SONY VAIO (Sony, Minato, Japan) equipped with a Intel Core i3 processor (Intel, Santa Clara, CA) and DB ran the 2015 version, under window 8.1, on a 2016 computer ASUS X541UV (Asus, New Taipei, Taiwan) equipped with a 2.50 GHz dual core Intel Core i7-6500U processor. Blood gas values: pH, arterial partial pressure in CO_2 (PaCO_2), arterial partial pressure in O_2 (PaO_2) and arterial oxygen saturation in O_2 (SaO_2) were simulated at different time points for several types of subjects with different characteristics. For each combination, the following subjects’ characteristics were specified: age, weight, height, type of patient, and ventilation mode (spontaneous (SV) or mechanical (MV) ventilation). The characteristics were systematically entered in the same order: age, weight, height, type of patient, gender, ventilation mode. “Personalized” type of patient was selected when mechanical ventilation was chosen, in order to enter the ventilation parameters: inspired oxygen fraction (FiO_2), positive end expiratory pressure (PEEP), respiratory rate (RR) and tidal volume (Vt). By default, the gender was set to male and switched to female as needed. When available hemoglobin value was entered or considered as normal when missing. Each simulation was repeated three times to address potential input error and in case of a mismatch, a fourth simulation was performed to verify or eventually replace the outlier.

A preliminary study was conducted to assess for several assumptions of the SimulResp configuration: the range of age within which SimulResp was supposed to be accurate and its ability to remain stable even when the simulation speed was modified, from 2 to 4000 times. Blood gas values (pH, PaCO_2 , PaO_2 and SaO_2) were simulated for several fictive healthy subjects with different characteristics: gender (M, F) and age (1, 2, 4, 6, 8, 10, 12, 14, 16, 18 years old), with a 50th percentile weight and height at different simulation speeds (from 1 to 4000) and were collected after a virtual patient clinical evolution (VPCE) of 30 minutes.

First phase of the study

The first phase intends to assess the accuracy, the robustness, the repeatability and the reproducibility of SimulResp when simulating blood gas values of healthy fictive subjects. The first phase of the study consisted in assessing SimulResp’s predictions with simulated healthy subjects. Based on the results of the preliminary study, the tests were restricted to subjects from 8 to 18 years old (8, 10, 12, 14, 16, 18 years), with different characteristics; gender (M, F) and weight (10th, 50th and 90th percentile). Blood gas values were collected 3 times for each patient at a VPCE of 30 minutes, 3 and 24 hours, with a simulation speed of respectively 64, 258 and 1048. This study was conducted for both spontaneously breathing and mechanically ventilated subjects. For mechanically ventilated subjects, the following ventilation parameters were set: FiO_2 21%, PEEP 3 cmH_2O , Vt 7.5mL/kg, normal RR for age (9)

Second phase of the study

The second phase intends to evaluate the quality of SimulResp when simulating blood gas values for real healthy or ill subjects in specific situations. We replicated, previously described in scientific literature, blood gas values in SimulResp. We used data from healthy men during physical activity (10) and immersed prone at 4.7 absolute atmosphere (ATA) (11), to evaluate SimulResp’s in spontaneously breathing subjects and data from a previously published study performed with ventilated pediatric intensive care subjects to evaluate

SimulResp’s predictions in mechanically ventilated subjects (12).

Endpoints

SimulResp quality was evaluated on accuracy, robustness, repeatability and reproducibility. Accuracy was evaluated by the ability of SimulResp to produce physiological values of a healthy child within the normal range (pH 7.40 +/- 0.5; PaCO₂ 40 +/- 5 mmHg, PaO₂ 90 +/- 10 mmHg; SaO₂ 97% +/- 3%) when simulated fictive subjects and reference values when replicated clinical situations. Robustness, defined as the ability of the SimulResp prediction to remain stable within time when the conditions remained stable, was evaluated by comparing the blood gas values of each fictive patient at a VPCE of 30 minutes, 3 and 24 hours. Repeatability, defined as the ability of the SimulResp prediction to remain equal when the simulation is repeated within the same conditions (the same method, in the same operator with the same equipment within short intervals of time), was evaluated by comparing each blood gas values of each simulation for the same patient at a VPCE of 24 hours. Reproducibility, defined as the ability of the SimulResp prediction to remain equal when the simulation is repeated for the same patient but within different conditions (the same method but by a different operator and equipment) was evaluated by comparing simulation ran by OF and DB for the same patient at a VPCE of 24 hours.

Statistical analysis

Variables were expressed as mean +/- standard deviation or median [Interquartile range (IQR)] for continuous variables, according to their distribution (Shapiro Wilk test) and number (percentage) for categorical variables. Data were analysed with both subjective and objective approaches (13). Subjective approach consisted in a graphic display of blood gas evolution depending on age and/or time compression. The objective approach consisted in a comparison of references and SimulResp values using dependent tests as appropriate. Quantitative variables were expressed as median [interquartile range] or mean +/- standard deviation, according to the distribution of the variable. Comparison between quantitative variables were performed with Wilcoxon’s signed rank tests or paired T test as appropriate. The correlation between reference and simulated data was evaluated by the coefficient of determination (R²). Intraclass correlation coefficients (ICC) and 95% confidence intervals and F test results were calculated with the R statistical packages “irr” (14) based on a single or average measurement, agreement, two-way mixed effect model (15), as appropriate. Based on statistical inference and literature (14), we considered the values of ICC to be the determinant of the level of reliability. Values under 0.5 indicated poor reliability, values between 0.5 and 0.75 indicated moderate reliability, values between 0.75 and 0.9 indicated good reliability, and values greater than 0.90 indicated excellent reliability. The agreement between SimulResp and reference data were evaluated with the Bland & Altman analysis. Bias, limits of agreement and percentage of error were calculated with the R statistical package “BlandAltman” (16,17). A p value of 0.05 was considered statistically significant. Statistical analyses were performed using open access R software (3.5.1, 2018-07-02, <http://cran.r-project.org/>).

Results

First phase

Accuracy

Preliminary results are depicted in figure 2 and supplemental file 2. These graphics display blood gas evolution depending on age and simulation’s speed. Figure 2 shows that SimulResp failed to predict healthy child physiological values when patient was under 8 years old. Figure 2 and Supplemental file 2 shows that Simulresp’s predictions tended to be within normal range when simulation’s speed was over 1000, regardless of age, which question the ability of SimulResp of being accurate when speed is too high. SimulResp’s prediction of fictive healthy child blood gas values according to weight and gender is depicted in figure 3. This graphic representation shows that SimulResp produced healthy child physiological values within normal range starting from a weight of 25 to 35 kg depending of the parameters studied and the length of the simulation. The same findings were observed regarding SimulResp’s prediction of fictive ventilated subjects (Supplemental file 3).

Repeatability, reproducibility and robustness

Based on the performed analysis, the repeatability was considered as excellent (Table 1) and the reproducibility as moderate to good (Table 1), with observed inconsistencies with pathological values (Supplemental file 4). The robustness analysis is depicted in Table 1. These results showed that SimulResp's prediction remains stable within time with good correlation between measures and with non-clinically significant differences.

Second phase

Regarding SimulResp's prediction accuracy in specific situations, supplemental file 5 depicted PaO_2 and PaCO_2 evolution depending on the intensity of workout. Mean differences between predicted and true blood gas were small and correlations were good. Simulated curves in PaCO_2 and PaO_2 got the same shape than true results. The gap between predicted and true values was small (Table 2). When considering diving situations, significant discrepancies between predicted and true values were observed (Table 2). The gap between predicted and true values was 5.9% for PaCO_2 and 2.1% for PaO_2 . Comparison between predicted and true data of children under ventilatory support were presented in Table 3. These results showed disagreement between predicted and true values as well as poor correlation.

Discussion

This study showed the reliability of Simulresp when predicting blood gas values of healthy child over 8 years old, confirming O. Flechelles et al. data (2,4). The inconsistencies of Simulresp's prediction regarding under 8 years old and/or ventilator supported subjects might be due to the fact that 1977 CJ Dickinson's model didn't considered physiologic and physio-pathologic specificities of these conditions (8). Children respiratory system differs from that of the adult, anatomically and mechanically, mainly during the first 6 to 8 years. Less than 20% of "adult" cells are present at birth. In the first years of life, lung growth occurs by adding or creating new alveoli (18). This alveolarization is accompanied by an increase in the capacity of the lung to perform gas exchanges (18). Alveolarization is considered complete around the age of 6 to 8 years. Thereafter, the alveolar surface will grow due to the growth of the child. This growth of the alveolar surface is related to lung growth but is not associated with an increase in the number of alveoli (18). In addition, from birth to the age of 2 to 3 years, the shape of the rib cage will evolve from a circular shape to a more oval or rectangular shape (19). This shape causes a lower mechanical efficiency of the thoracic cavity compared to adults (20), especially since it is associated with a flattened less efficient diaphragm. Besides, the discrepancies between a high compliance rib cage and a low compliance lung will altered the residual functional capacity. Thus, the child must develop several dynamic compensation mechanisms to maintain its reserves in oxygen and avoid atelectasis. Mechanical ventilation substitutes positive pressure insufflation by an external machine induced to negative pressure insufflation by diaphragmatic contraction. The installation of a ventilatory support requires four elements: a suitable interface between the respirator and the patient, an energy source that operates the machine, an insufflation whose magnitude and rhythm will be regulated or controlled and a system to monitor the performance of the respirator and the condition of the patient. These four elements are associated with mechanic, physic and physiologic constraints that can be difficult to predict, record or standardize in the form of mathematical equations. In addition, if these four elements are mandatory, they are not sufficient to ensure the effectiveness of the respiratory support and other elements such as the adaptation of the parameters, the synchrony between the patient and the machine, the need for sedation or the type of respirator are to be considered and added as constraints and limits to the success of the modeling.

The goal of validation is giving confidence to users on simulator results because the future use of a simulator depends on it. The quality assessment procedures of a simulator are essential to ensure its validity and usability (5). The validity of a simulator will depend directly on the objective for which it was developed (2,13,21,22). Targets, safety ranges, gap between simulated values and expected values can differ depending on simulator goals. For example, when the simulator is used for teaching, an inaccurate output can likely be tolerated if the evolution or prediction approaches a physiologically normal value, and both repeatability and reproducibility are satisfactory. On the other hand, use in care cannot be conceived with a simulator

that would not be accurate.

Several cardio-respiratory simulators are described in the literature (2,22,23), but there are few descriptions of the validation process. Most of the publications on the subject focus on the description of the simulator's performance rather than on the actual technical report of the process applied to guarantee the quality of the simulator and its prediction (24). Some teams took the trouble to evaluate the performance of their simulator by comparing the simulated data with data observed in real patients in mechanical ventilation (25,26). However, the content of these articles remains focused on the description of the purpose of the simulator and how it is developed. The idea of carrying out and presenting a complete validation process, aimed at judging the ability of the simulator to provide a fair and reliable prediction in time and situations, only rarely seems to be part of the research protocol (5,13,27).

The strength of this work lies in the large number of tests performed. In addition, we evaluated each quality component of the simulator: accuracy, repeatability, reproducibility and robustness. We have thus been able to highlight the limitations of the simulator, particularly as regards the prediction of the patient under 8 years of age, the patient who is ill and the patient in mechanical ventilation. This work has major limitations. The use of graphical representations to judge the accuracy of the simulator, although described in the literature (5,13) may seem trivial and in all cases particularly subjective and unreliable. In addition, the question arises as to the choice of statistical tests carried out. While it is certain that the measurement of Pearson or Spearman correlation coefficients is insufficient to judge the accuracy and concordance between simulated and reference values, the relevance of the other statistical methods applied remains equally questionable (15,28). Nonetheless, the performed tests were based on previously described simulator evaluations (25,29). Finally, the question of external applicability arises. The results we obtained apply only to SimulResp and cannot be extrapolated to other simulators, even if they were developed using the Dickinson model.

This work allowed us to better define the next steps in the development of SimulResp. In this actual form, SimulResp is limited by the limits of the model it is built on. For this reason, we are currently working on the content of the algorithm in order to improve SimulResp. we need to study and modified the formula within the model in order to make it accurate when simulating blood gas value of under 8 years old patients. To do so, we have gathered a high-resolution database (30,31), on which we intend to apply several machine learning approaches (32,33). Besides, we have begun to develop the method that will allow us to calibrate the simulator to be reliable in several respiratory physio-pathological situations (normal compliance (> 2 ml/cmH₂O/kg), abnormal compliance, increased resistance) and hemodynamic (shock states) in both spontaneous and invasive ventilation (2,30). SimulResp, once completely validated, will be integrated in future clinical decision support systems and will collect data from real patient and then simulate breathing pattern with accelerated time. Resulting simulated blood gases will be presented to physician whom could test different ventilator settings to determine the best one and adjust the patient's therapy in an individualized but still protocolized care.

Conclusion

Medical simulators are used in many fields, to enhance safety issues. SimulResp is a cardiorespiratory simulator that requires further development and validation of the model before future integration into a clinical decision support system to help caregivers prescribe respiratory assistance.

Reference

1. Sward KA, Newth CJL, Khemani RG, Page K, Meert KL, Carcillo JA, et al. Potential Acceptability of a Pediatric Ventilator Management Computer Protocol. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc.* 2017;18(11):1027-34.
2. Flechelles O, Ho A, Hernert P, Emeriaud G, Zaglam N, Cheriet F, Jouvet P. Simulations for Mechanical Ventilation in Children: Review and Future Prospects. *Crit Care Res Pract.* 2013;2013:1-8.
3. Morozoff E, Smyth JA, Saif M. Applying Computer Models to Realize Closed-Loop Neonatal Oxygen Therapy. *Anesth Analg.* 2017;124(1):95-103.

4. Flechelles O, Hernert P, Cheriet F, Zaglam N, Emeriaud G, Jouvet P. 999 Validation of Pediatric Cardiorespiratory Simulator: Simulresp. *Arch Dis Child*. 2012;97(Suppl 2):A286-7.
5. Das A, Gao Z, Menon PP, Hardman JG, Bates DG. A systems engineering approach to validation of a pulmonary physiology simulator for clinical applications. *J R Soc Interface*. 2010;8(54):44-55.
6. Summers RL. Computer Simulation Studies and the Scientific Method. *J Appl Anim Welf Sci*. 1998;1(2):119-31.
7. Summers RL, Ward KR, Witten T, Convertino VA, Ryan KL, Coleman TG, Hester R. Validation of a computational platform for the analysis of the physiologic mechanisms of a human experimental model of hemorrhage. *Resuscitation*. 2009;80(12):1405-10.
8. Dickinson CJ. A computer model of human respiration : ventilation, blood gas transport and exchange, hydrogen ion regulation. Lancaster: M.T.P. press; 1977.
9. Chatburn RL, Mireles-Cabodevila E. Handbook of respiratory care. Sudbury, MA: Jones & Bartlett Learning; 2011.
10. Aguilaniu B, Flore P, Maitre J, Ochier J, Lacour JR, Perrault H. Early onset of pulmonary gas exchange disturbance during progressive exercise in healthy active men. *J Appl Physiol*. 2002;92(5):1879-84.
11. Cherry AD, Forkner IF, Frederick HJ, Natoli MJ, Schinazi EA, Longphre JP, et al. Predictors of increased Pa CO₂ during immersed prone exercise at 4.7 ATA. *J Appl Physiol*. 2009;106(1):316-25.
12. Baudin F, Bourgoin P, Brossier D, Essouri S, Emeriaud G, Wysocki M, Jouvet P. Noninvasive Estimation of Arterial CO₂ From End-Tidal CO₂ in Mechanically Ventilated Children: The GRAeDIENT Pilot Study. *Pediatr Crit Care Med*. 2016;17(12):1117-23.
13. Sargent RG. Verification and validation of simulation models. In: *Proceedings of the 2010 Winter Simulation Conference*. Baltimore, MD, USA: IEEE; 2010:166-83.
14. Gamer M, Lemon J, Singh IFP. irr: Various Coefficients of Interrater Reliability and Agreement [Internet]. 2019 [28 apr 2019]. Available at: <https://CRAN.Rproject.org/package=irr>
15. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med*. 2016;15(2):155-63.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-10.
17. Michael Sauthier and David Brossier. BlandAltman: Bland-Altman Analysis and Plot [Internet]. 2018. Available at: <http://github.com/sauthiem/BlandAltman>
18. Balinotti JE, Tiller CJ, Llapur CJ, Jones MH, Kimmel RN, Coates CE, et al. Growth of the lung parenchyma early in life. *Am J Respir Crit Care Med*. 2009;179(2):134-7.
19. Openshaw P, Edwards S, Helms P. Changes in rib cage geometry during childhood. *Thorax*. 1984;39(8):624-7.
20. Gaultier C. Respiratory muscle function in infants. *Eur Respir J*. 1995;8(1):150-3.
21. Keegan R, Henderson T, Brown G. Use of the virtual ventilator, a screen-based computer simulation, to teach the principles of mechanical ventilation. *J Vet Med Educ*. 2009;36(4):436-43.
22. Rutledge GW. VentSim: a simulation model of cardiopulmonary physiology. In: *Proceedings of the Annual Symposium on Computer Application in Medical Care*. American Medical Informatics Association; 1994: 878.

23. Lino JA, Gomes GC, Sousa ND, Carvalho AK, Diniz ME, Viana Junior AB, Holanda MA. A Critical Review of Mechanical Ventilation Virtual Simulators: Is It Time to Use Them? *JMIR Med Educ.* 2016;2(1):e8.
24. Reynolds A, Bard Ermentrout G, Clermont G. A mathematical model of pulmonary gas exchange under inflammatory stress. *J Theor Biol.* 2010;264(2):161-73.
25. Karbing DS, Allerod C, Thorgaard P, Carius A-M, Frilev L, Andreassen S, et al. Prospective evaluation of a decision support system for setting inspired oxygen in intensive care patients. *J Crit Care.* 2010;25(3):367-74.
26. McCahon RA, Columb MO, Mahajan RP, Hardman JG. Validation and application of a high-fidelity, computational model of acute respiratory distress syndrome to the examination of the indices of oxygenation at constant lung-state. *Br J Anaesth.* 2008;101(3):358-65.
27. Pace DK. Modeling and Simulation Verification and Validation Challenges. *Johns Hopkins apl Tech Dig.* 2004;25(2):10.
28. O'Connor DP, Mahar MT, Laughlin MS, Jackson AS. The Bland-Altman Method Should Not Be Used in Regression Cross-Validation Studies. *Res Q Exerc Sport.* 2011;82(4):610-6.
29. Wang A, Mahfouf M, Mills GH, Panoutsos G, Linkens DA, Goode K, et al. Intelligent model-based advisory system for the management of ventilated intensive care patients: Hybrid blood gas patient model. *Comput Methods Programs Biomed.* 2010;99(2):195-207.
30. Brossier D, Sauthier M, Alacoque X, Masse B, Eltaani R, Guillois B, Jouvét P. Perpetual and Virtual Patients for Cardiorespiratory Physiological Studies. *J Pediatr Intensive Care.* 2016;5(03):122-8.
31. Brossier D, El Taani R, Sauthier M, Roumeliotis N, Emeriaud G, Jouvét P. Creating a High-Frequency Electronic Database in the PICU: The Perpetual Patient. *Pediatr Crit Care Med.* 2018;19(4):e189-98.
32. Gutierrez G. Artificial Intelligence in the Intensive Care Unit. *Crit Care.* 2020;24(1):101.
33. Mesko B, Gorog M. A short guide for medical professionals in the era of artificial intelligence. *Npj Digit Med.* 2020;3(1):126.

Tables:

Table 1: *Evaluation of repeatability, reproducibility and robustness*

Data are expressed in median [IQR]

SaO₂: Arterial saturation, PaCO₂: Partial arterial pressure of carbon dioxide, PaO₂: Partial arterial pressure of oxygen. ICC: Intraclass correlation coefficient

Table 2: *Comparison between predictive and true values during workout and diving, data extracted from (10) and (11).*

Data are expressed in mean +/- standard deviation

PaO₂: Partial arterial pressure of oxygen, PaCO₂: Partial arterial pressure of carbon dioxide

Table 3: *Comparison between predictive and true values in patients with ventilatory support, data extracted from (12).*

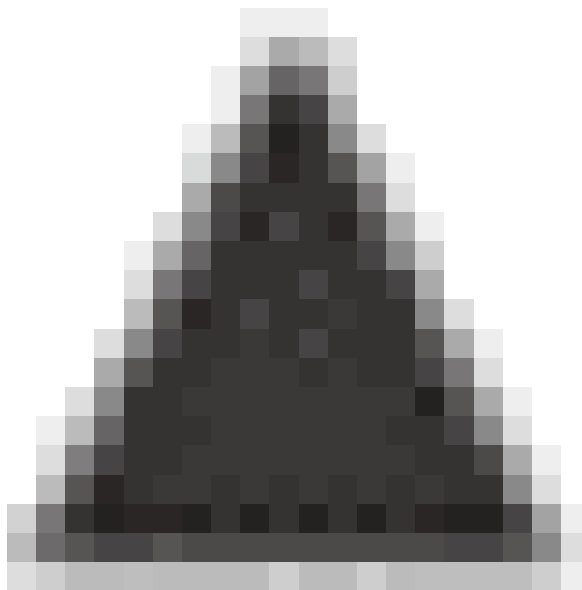
Data are expressed in median [IQR]

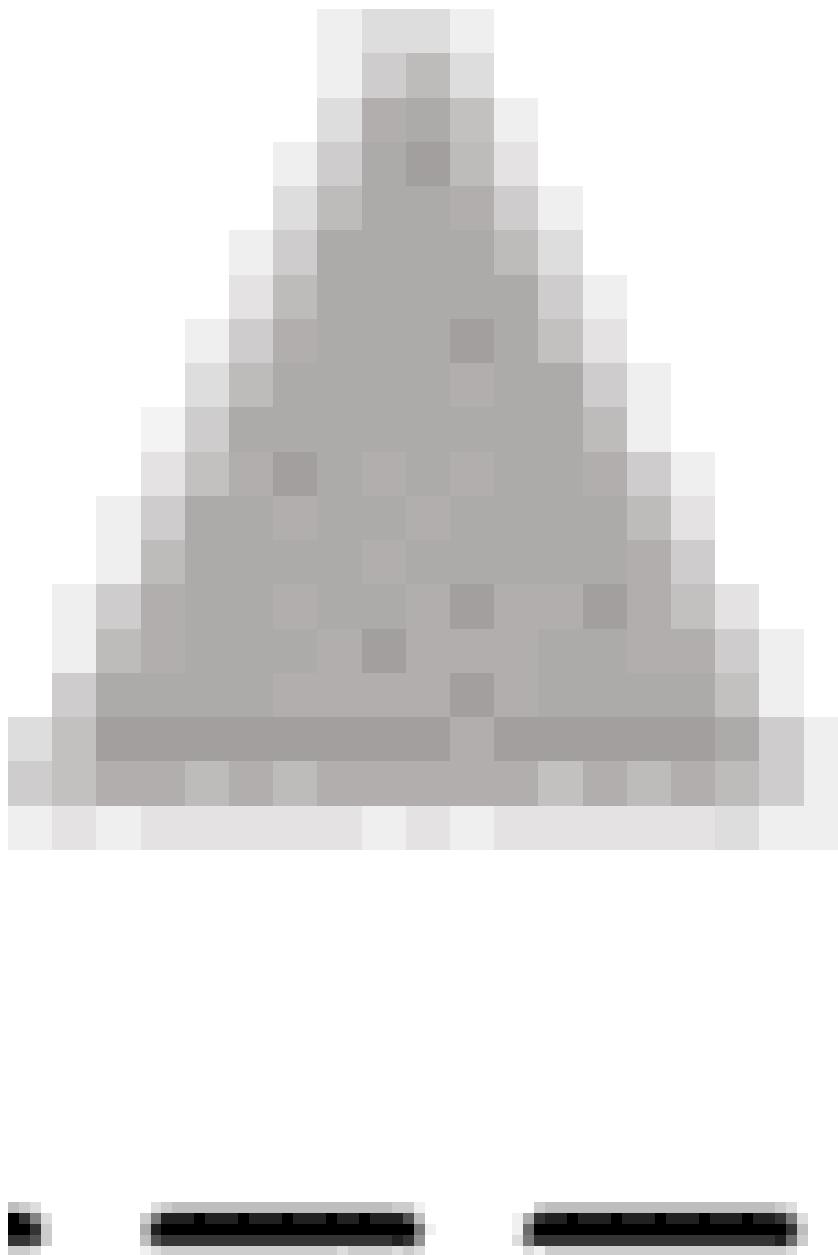
PaO₂: Partial arterial pressure of oxygen, PaCO₂: Partial arterial pressure of carbon dioxide

Figures:

Figure 1: Simulresp graphic interface

Figure 2: graphic representation of Simulresp's prediction in healthy fictive subjects, depending on patients' age.

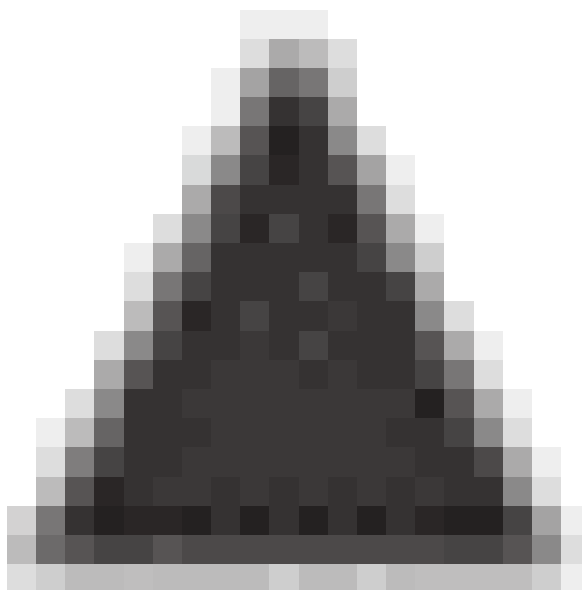


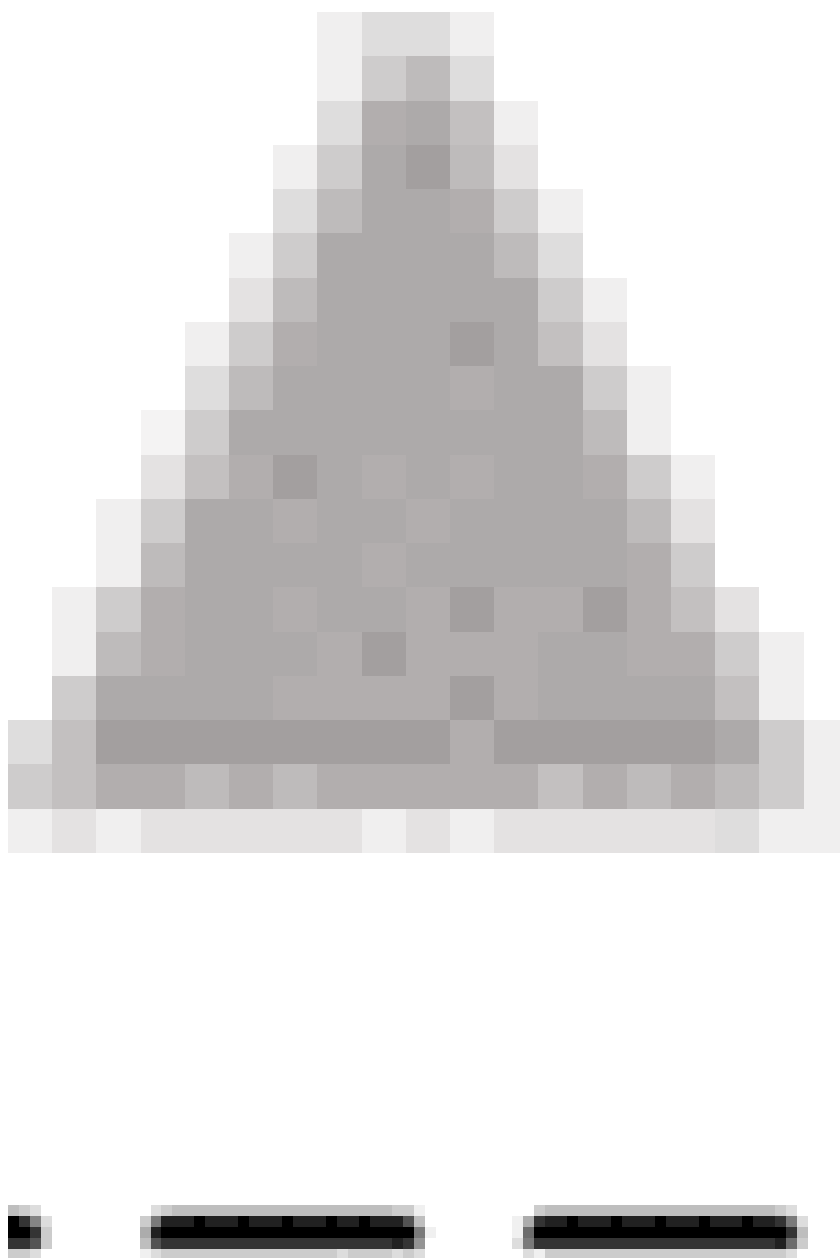


Each point is characterized by the simulation speed (from 1 to 4000). Panel a: pH ; panel b: arterial satura-

tion of oxygen (SaO_2) ; panel c: Partial arterial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2).lower and upper limits of normal values.

Figure 3:graphic representation of Simulresp's prediction in healthy fictive subjects, depending on patients' weight and gender, in spontaneous ventilation.





Panel a : pH ; panel b: arterial saturation of oxygen (SaO₂) ; panel c: Partial arterial pressure of oxygen

(PaO₂) and carbon dioxide (PaCO₂). lower and upper limits of normal values. Black curve: virtual patient clinical evolution (VPCE) of 30 minutes. Dark grey: VPCE of 3 hours. Light grey: VPCE of 24 hours.

Supplemental file:

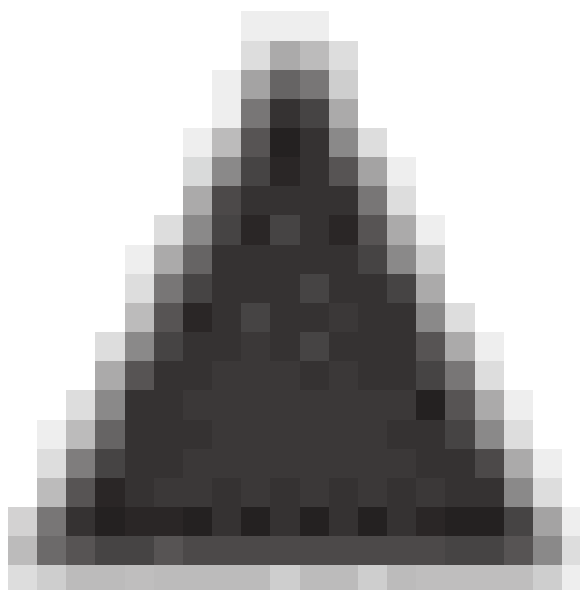
Supplemental file 1: Details on the model's algorithm

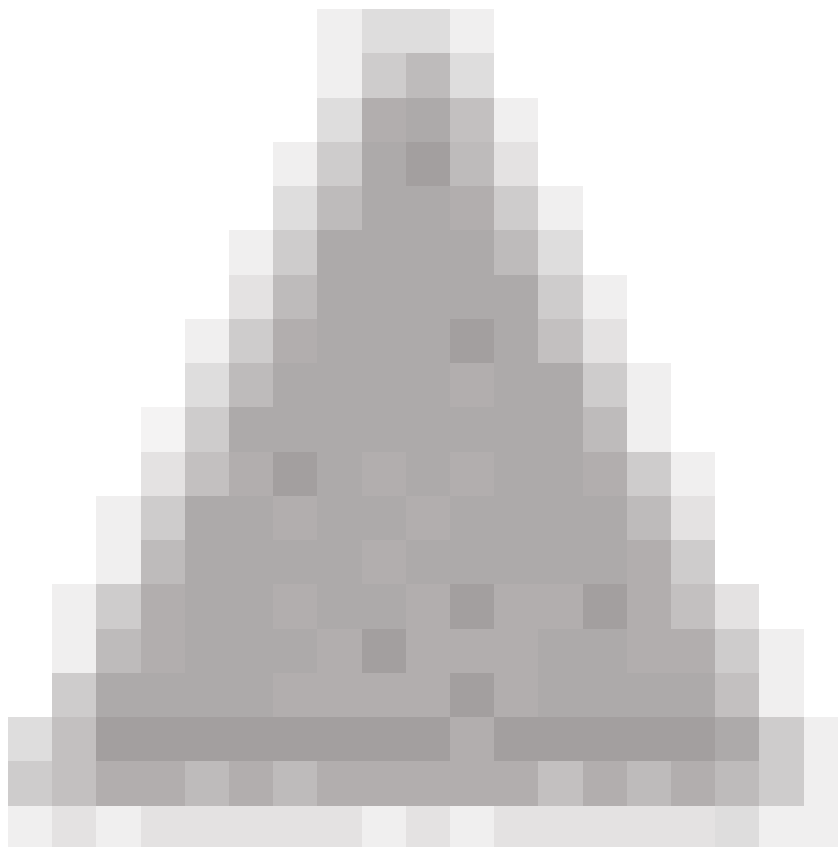
Supplemental file 2: graphic representation of Simulresp's prediction in healthy fictive patients, depending on patients age and gender

Each curve is characterized by the simulation speed (from 1 to 4000). black curve corresponds to real time (1) simulation.

a. pH.

b. arterial saturation of oxygen (SaO₂)





c. Partial arterial pressure of oxygen (PaO₂) and carbon dioxide (PaCO₂)

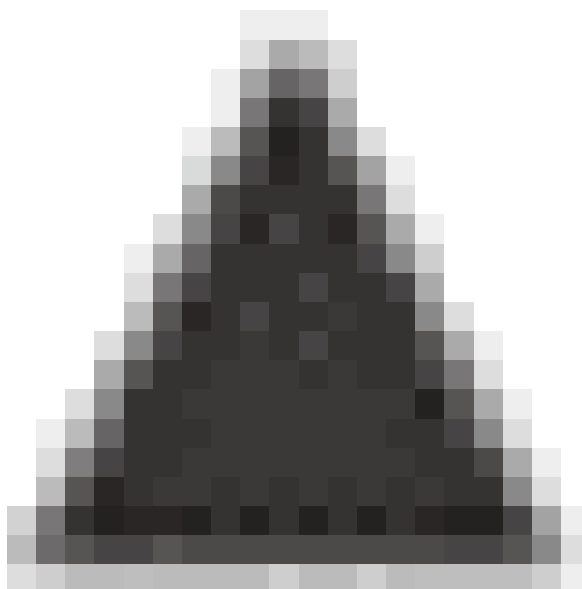


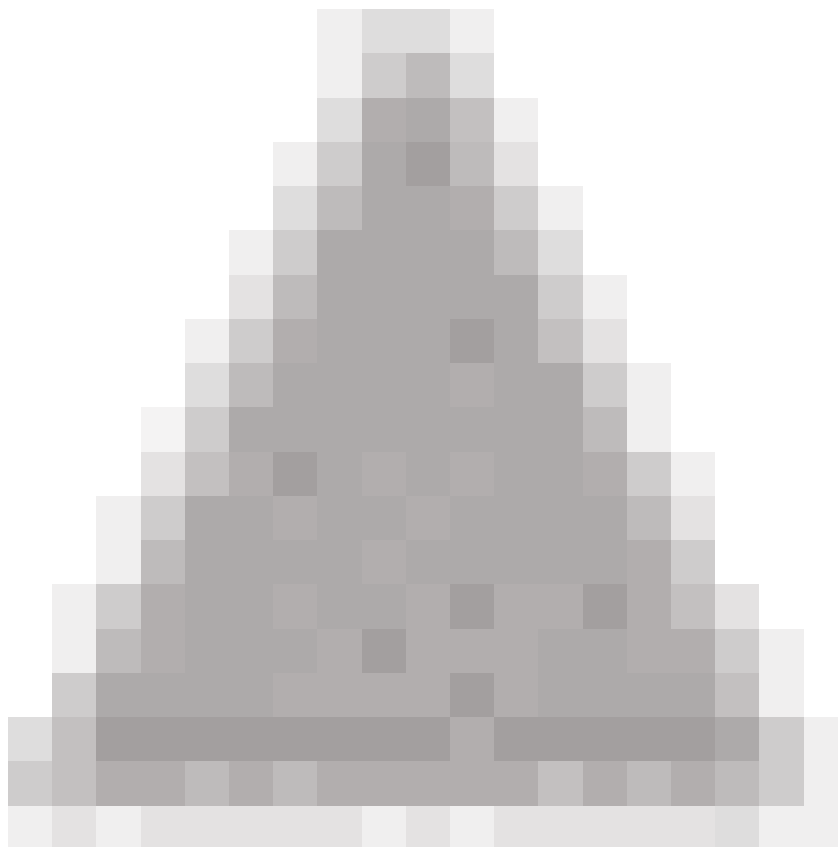
lower and upper limits of normal values

Supplemental file 3: graphic representation of Simulresp's prediction in ventilatory supported fictive patients, depending on patients' weight and gender.

a. pH.

b. arterial saturation of oxygen (SaO₂)





c. Partial arterial pressure of oxygen (PaO₂) and carbon dioxide (PaCO₂)



lower and upper limits of normal values.

Black curve: virtual patient clinical evolution (VPCE) of 30 minutes. Dark grey: VPCE of 3 hours. Light grey: VPCE of 24 hours.

Supplemental file 4: Evaluation of reproducibility

Method A: investigator 1's measurements (OF). Method B: investigator 2's measurements (DB)

Supplemental file 5: Comparison between predictive and true values during workout, data extracted from (10).

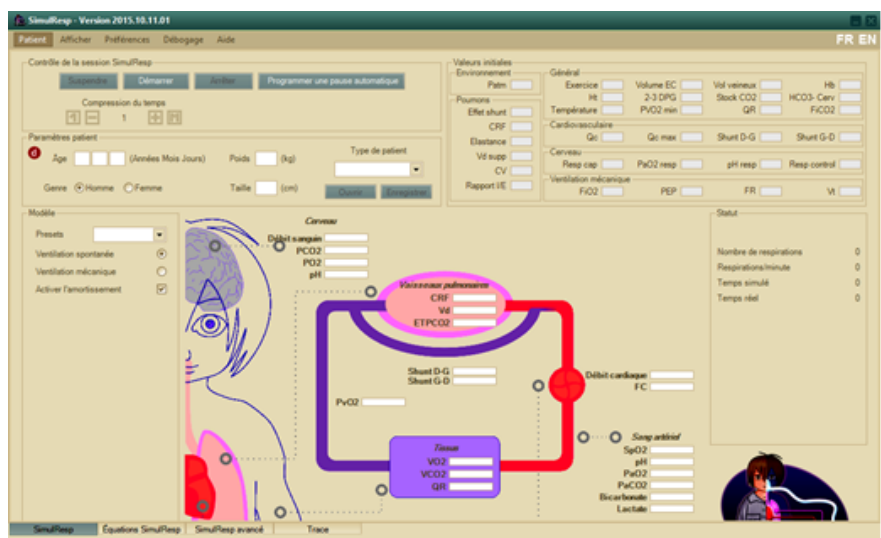


Figure 1: Simulresp graphic interface

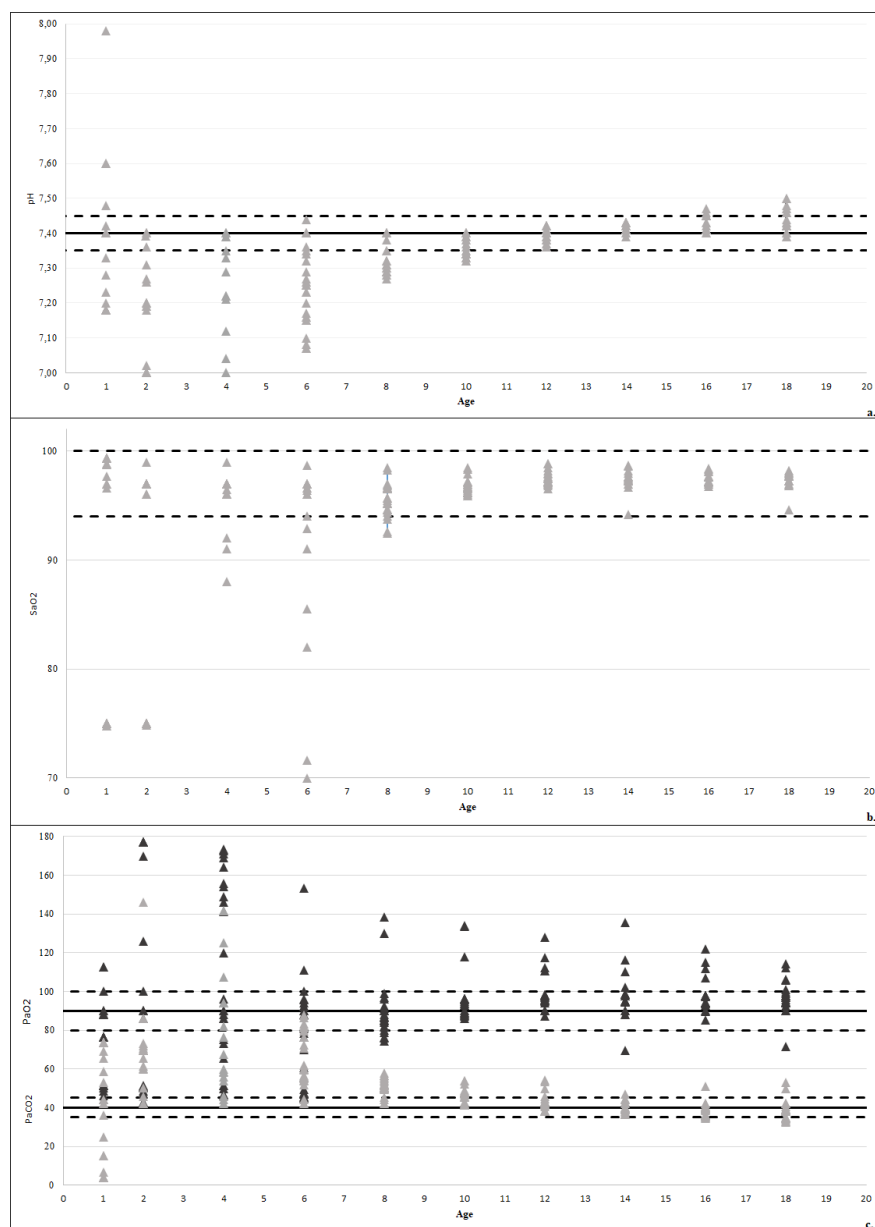


Figure 2: graphic representation of Simulresp's prediction in healthy fictive subjects, depending on patients' age

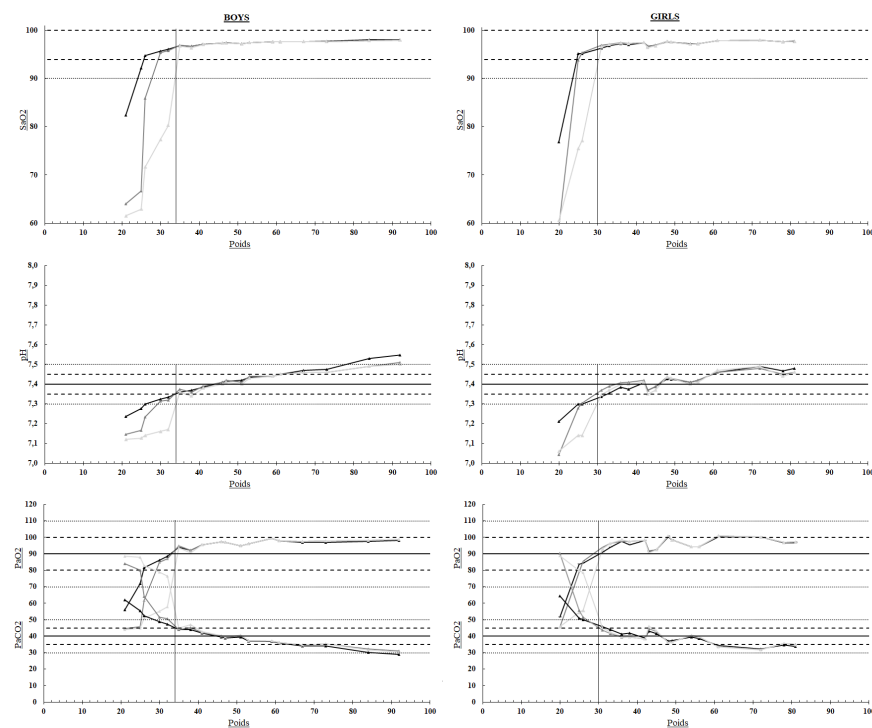


Figure 3: graphic representation of Simulresp's prediction in healthy fictive subjects, depending on patients' weight and gender, in spontaneous ventilation

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Table 2.docx available at <https://authorea.com/users/303353/articles/568607-evaluation-of-the-simulresp-a-simulation-software-of-child-and-teenager-cardiorespiratory-physiology>

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Table 3.docx available at <https://authorea.com/users/303353/articles/568607-evaluation-of-the-simulresp-a-simulation-software-of-child-and-teenager-cardiorespiratory-physiology>