Perpetual and Virtual Patients for Cardiorespiratory Physiological Studies

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Abstract

Keywords

- ▶ children
- ▶ intensive care
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- ▶ cardiorespiratory physiology
- ▶ simulation
- ▶ databases

As a result of innovations in informatics over the last decades, physiologic models elaborated in the second half of the 20th century could be transformed into specific virtual patients called computational models. These models, developed initially for teaching purposes, are of great potential interest in responding to current concerns about improving patient care and safety. However, even if there are obvious advantages to using computational models in cardiorespiratory management, major concerns persist as to their reliability and their ability to recreate real patient physiologic evolution over time. Once developed, these models require complex validation and configuration phases prior to implementation in daily practice. This article focuses on the development of computational models, and reviews the methodologies to clinically validate the models including specific patient databases (perpetual patients) and the use in clinical practice including very high fidelity simulation.

Introduction

There is currently an emphasis in health care on developing tools to improve both patient care and safety,^{1–6} by standardizing management and enhancing the continuing education of clinicians. At the same time, advances in informatics over recent decades have allowed for the development of technical devices designed for teaching and clinical care, especially during critical illness.^{7–9} Among these technical devices are software designed to simulate aspects (or even the entirety, in the most sophisticated versions) of human behavior: the so-called virtual patient (VP).

In the realm of cardiorespiratory physiology, the components of medical practice that include providing care to patients, increasing competency through medical education at the bedside, and developing knowledge through clinical research are closely linked. Because of these links, the mathematical models of cardiorespiratory physiology elaborated some years ago mainly for teaching purposes now serve as a template for the elaboration of more complex computerized devices used for clinical care and teaching.^{7,8,10–15}

Several physiologic models have been applied to the development of VPs which could be of great interest to daily practice, both for trainees and patients.^{7,8,10–15} The major factor limiting their widespread utilization is the lack of

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validation with respect to their robustness, reliability, and accuracy, when compared with real patients, both in a steady state and as they evolve during their intensive care unit course.^{10–18}

The purpose of this article is to define a VP for use in cardiorespiratory simulation and describe interactions with physiological modeling leading to the conception of computational models.¹⁹ We aim to review the literature on the development of such VPs, proposing a step-by-step methodology for their validation and to study their actual contribution to studies of cardiorespiratory physiology.^{20–22} We also emphasize the role of high-quality clinical databases for validation of computational models and the new concept of the perpetual patient (PP).

Virtual Patient and Computational Model: Definition and Positive Aspects

Widely inspired by nonmedical industries' use of virtual simulation,² the use of simulation-based medical education or virtual simulation has become widespread in health care over the past decades.^{2,5,23,24} The first objective of simulation-based training is to improve patient care and safety,^{2–5} providing a secure environment where students are able to learn, experiment, and acquire procedural skills without compromising the health of the patient. It has also become a way to enhance medical students' clinical exposure,^{2–5,20,25,26} which may be compromised due to decreasing teaching and learning opportunities.^{2,26} Several types of educational technologies, described in the medical and education literature, are considered to comprise virtual simulation, even if they differ from each other in terms of realism, complexity, financial and human cost, or interface.^{4,5,20,21,24,26} The focus of this work is on VP, defined as^{4,19,20,27,28} “interactive computer simulation of real-life clinical scenarios for the purpose of health care and medical training, education or assessment.” According to the VP definition of Ellaway et al,^{4,19,20,27,28} a VP attempts to recreate patients and their environment through a computer interface,⁵ with which students can interact to resolve clinical situations, physiological interrogations, or technical issues.⁵

There are many advantages^{4,19,20,25–33} to using VPs in medical training. Even though VPs do not replace the need for direct interactions with real patients, VPs have been proven to enhance clinical skills and to improve knowledge acquisition,^{3,4,27} as reported in several systematic reviews and meta-analysis.^{3,4,27} This positive effect is mainly due to the contextualization of prior theoretical knowledge while increasing one kind of medical exposure, following “the more you see, the more you know” medical teaching principle.²⁶ However, other positive elements appear to enhance the benefit of VPs on medical training. Initially, the medical education literature emphasized the ability of VPs to provide a secure and safe environment for students, where they can learn from their mistakes with the possibility of unlimited repetitive practice until skills are totally achieved, while receiving continuous feedback without fear of judgment by their supervisors.^{25,32,33} As well, VPs can be customized to tailor instructions to a student's needs,^{24,32,33} providing

numerous possibilities for scenarios depending on teaching objectives. Finally, the widespread availability of computers offers easy access to VPs, regardless of the student's location, availability of infrastructure, or faculty.

In the field of cardiorespiratory physiology, VPs must be enhanced with physiologic modeling, to increase their interactivity and reliability.¹⁹ This association between software and physiological modeling is called a *computational model*, defined as “a mathematical model implemented in a computer system [...]”.¹⁹

The purpose of physiological modeling is to recreate physiological processes and interactions of systems within the human body.^{10,15,16} These models, replicating human physiology using mathematical equations, are of great interest for both education and research.^{10,15,16} With these two objectives in mind, numerous physiologists, physicians, or mathematicians elaborated models of cardiopulmonary physiology during the second half of the 20th century.^{8,10,13,14} Since knowledge of cardiorespiratory physiology was already well advanced, these models remain reliable.^{8,11} In recent decades, the access to physiological models has widened, due to the advances in informatics and the development of computational models based on preexisting mathematical physiologic representations,^{7,8,10–14} as reviewed in 2013 by Flechelles et al.⁸

As previously described with other VPs, the interest in computational models for teaching is obvious, as they provide trainees with a high accessible, easy to use, almost limitless physiological “playground.”⁷ But they also remain useful for research purposes and optimization of therapies.⁷

Computational models help clinicians and physiologists to understand some unknown physiological phenomenon, as they make it possible to study a system in more detail than while performing experimental and animal studies.^{10,11,14} Furthermore, some could argue that a validated physiological model is probably a much more reliable representation of human physiology than animal models.

Second, physiological models provide an alternative to in vivo studies which are precluded by ethical concerns,¹¹ patient accessibility, or financial limitations. Other aspects of computational modeling with potential benefit, both clinical and for research, include the potential inclusion of time function (ability of models to predict a patient's evolution in hours), pathophysiological states (possibility to program several diseases that will interfere with VP evolution), human functions (rest, exercise, etc....), environmental parameters (local temperature, atmospheric pressure, altitude, etc....), or even therapeutic and pharmacological agents (ability to evolve depending on applied treatment).

Virtual Patient and Computational Model's Limitations for a Widespread Utilization

Unfortunately, despite all these positive characteristics, widespread use of VPs is hindered by some major limitations,²¹ which seem even more pronounced when studying computational modeling. In a survey published in 2007, Huang et al³⁴ reported that only 24% of North American

medical schools made use of VPs in their medical curricula. The first concern is cost, as developing VP can be an expensive venture^{25,29} and the second is time constraints. It has taken 50 years for physiological modeling to evolve from the first mathematical models to the computer interface, indicative of the vast time and resources (financial, technical, and human) needed to develop such powerful tools.^{7,14} To cope with these limitations, some teams have decided to collaborate to rationalize costs and also mutually benefit from sharing competencies and knowledge.^{19,29} The increasing description of VPs and computational models during the past 20 years⁸ suggests that the previously described limitations to development can be surmounted.

However, there are still major concerns as to the reliability and fidelity of VPs and computational models, especially in the cardiorespiratory domain, and these elements limit the skills that can be acquired with their use.^{15,18} The major remaining limitation facing both developers and users is the need to validate computational models and evaluate their reliability.^{8,15,18}

Validation of a Virtual Patient Simulating Cardiorespiratory Physiology

While there is no argument about the necessity of validation procedures to ensure the accuracy of models and their ability to predict a conventional patient's evolution, depending on the model's exploitation field,^{8,15,18} a gray area persists regarding the appropriate method.¹⁸ On the basis of a literature review of the subject, what follows is a recommended step-by-step validation process for VPs/computational models, testing both their reliability and robustness.

The first step consists of determining the validation targets, these physiologic variables being chosen depending on their clinical relevance, and the model's purposes and domain of exploitation.^{8,18} Second, control patients are selected, once again depending on the model's purposes and domain of exploitation.^{8,18} Then data extracted from the medical literature,^{8,35,36} previously recorded databases^{8,13} or prospectively,^{12,17,18} are entered as inputs in the models and the predicted variables are compared with those of controls (►Fig. 1).

The reliability of the model will be judged by three major criteria as defined previously by Summers et al^{16,18,37}: (1) qualitative, which means that the predicted output should evolve in the same way as the controls; (2) quantitative by steady state, which means that the values of predicted and control variables should be close to each other and predicted values should be stable over time if the patient's condition remains stable; (3) quantitative in dynamics, which means that predicted variables should evolve in the same way and in close relationship to controls under dynamic conditions.

If these criteria appear to be somewhat accepted in the medical literature, there is no standard concerning the statistical methods to be used.¹⁶ In the literature on this subject, several methods are proposed and deserved to be considered to test models' reliability, in terms of accuracy

Fig. 1 View of the validation process.

and precision.^{12,13,18} It is not surprising that authors have come to a false conclusion of good reliability of their model when using the correlation coefficient between simulated and real physiologic variables.⁸ If the calculation of the correlation coefficient is a requirement expressing the obvious relationship between the two compared variables, it is insufficient to certify the model's reliability, as it only tests the strength of the relationship and further analysis should be performed.^{38,39} However, to add weight to the calculation of the correlation coefficient, many have proposed the use of the coefficient of determination (R^2) and its adjustment.^{12,13,40,41} The coefficient of determination evaluates how well the predicted data generated by the model fit the control data and appears to be one of the most valuable methods used in the field of model validation. Although designed for the evaluation of the agreement between two different measurements of the same data,^{39,40} as performed while validating a new monitoring device, the Bland and Altman analysis is also favored by several teams.^{41,42} The agreement between the new and the reference devices, or in this case between the computational model's prevision and the already known physiologic variables, is evaluated, thanks to the expression of bias, estimated by the mean difference between the two series of variables and the standard deviation of the differences, limit of agreement, and percentage error (2 standard deviations/mean value).⁴³ However, validation of computational models using this type of analysis remains controversial,^{39,40} unlikely to be applicable for model validation in dynamic states and thus should be reserved for validation of a model in steady-state conditions.^{41,42}

Two other methods show great promise. The first is the evaluation of performance as described by Varvel et al,^{18,44,45} in the field of pharmacological modeling. In this method, assessment of reliability depends on the measure of (1) the performance error (PE % = difference between measure and predicted value, [(Measure – Predicted)/Predicted] × 100); (2) the bias, inaccuracy, and precision, evaluated by the determination of the median

performance error (MDPE % = median PE over all data points) and the median absolute performance error (MADPE). This latter variable, used to assess model performance especially in meteorology prediction modeling, consists of the measurement of the root-mean square error and the mean absolute error.¹³ None of these statistical analyses are completely optimal and caution is urged to avoid misleading results and overfitting.

In case of inaccuracy, the model's equations have to be modified following a four-time procedure (→ **Fig. 1**), developing on the same pattern as the plan-do-study-act of the Deming's wheel. In this situation, the steps would be configure-simulate-compare-reprogram, and this procedure should be repeated until the model is considered reliable. Furthermore, in cardiorespiratory modeling, the models, especially when designed for the intensive care setting, must be tested and validated, following the same process, under several pathophysiologic states. For example, in the case of a VP simulating cardiorespiratory states of both spontaneous breathing and mechanical ventilation, tests should be under various hemodynamic and respiratory conditions, including whether the patients are mechanically ventilated and/or receiving vasoactive therapy.⁸

Once this configuration phase is completed, robustness of the model is evaluated.^{8,15} Robustness can be defined as "the ability of a system to resist change without adapting its initial stable configuration."⁴⁶ In other words, robustness is the ability of the model to predict accurate output in the presence of several assumptions within the model's algorithm and inputs or within the patient's physiological status.¹⁵ Robustness evaluation appears to be a matter of quantity and time. To ensure a model's robustness, its prediction must remain stable within the same situation in numerous patients and within the same patient over time.

The more complex the model's exploitation domain is, the more elaborate should be the controls. Initially, validation procedures can be performed only with comparison to a knowledge-driven physiologic outcome; subsequently, researchers and programmers have to upgrade their validation procedure while improving their model's algorithm.⁸ In the cardiorespiratory field, validation procedure have to involve real patients, whose situation worsens as the model improves.^{8,10} While the initial steps in validation can be performed using patients as described in the literature, the validation procedure is not complete until numerous real patients are tested both under static and dynamic conditions,^{10,18,37} whether prospectively or retrospectively. Finally, the validation of both a model's reliability and robustness requires many patients and much regarding their course. Furthermore, to avoid, as much as possible, overfitting phenomena, it could be of great help to apply a cross-sectional-based approach, using part of the data for training the model and the other, smaller part, to evaluate the predictive ability of the model.⁴⁷⁻⁴⁹ Managing such a complex procedure implying large recruitment volumes and a repeated back and forth process appears quite complicated, as witnessed by the dearth of published studies of this approach. However, a key solution for this problem may be the advent of high-quality electronic databases.

Electronic Databases, the New Concept of the Perpetual Patient for Validation of Virtual Patients

Over the past few decades, intensive care medicine has evolved, stimulated by technological innovations.⁵⁰ Intensive care units contain abundant high-performance bedside medical systems, such as cardiorespiratory monitors, pulse oximeters, mechanical ventilators, or infusion pumps, whose purpose is to provide physicians with data concerning the patients' physiologic status, pharmacological treatment, or therapeutic procedures.⁵⁰⁻⁵⁵ By combining this electronic data with clinical evaluation and biological and radiological exams, the bedside physician is able to elaborate a therapeutic plan.^{53,56} Unfortunately, it became clear that much of this patient data had not been stored, even though the scientific community could benefit from their collection and analysis, including biosignals.^{51,57-59} Eventually, the concept of biosignal databases was born.^{60,61} However, it was not until 1990-2000 that the improvement of informatics permitted the building of large databases.^{50-54,56-59,62-65} Since then, many biosignal databases from intensive care unit patients have been built. Early databases mainly focused on electrocardiographic signals,^{52,62} subsequently becoming augmented by other biosignals, such as plethysmography waves, arterial pressure curves, etc....^{57-59,63-66} However, although useful for the understanding of some physiological phenomena, these databases did not provide enough information for broader research and clinical applications. It became obvious that biosignal databases were meant to be linked with clinical, paraclinical, and therapeutic data for research purposes in the intensive care unit.^{50,53,54,58,59,66-69} It is now possible, thanks to technical, electronic, and informatics innovations, to collect continuously virtually every parameter from almost every surveillance and therapeutic system available at the bedside,^{52,54,55,58-60,63,64,66,68} and computerized systems in intensive care units interface with patients' electronic medical records and other hospital electronic systems from radiology, pharmacy, or laboratories (→ **Fig. 2**). The gathered data are then stored and organized in large-scale high-quality databases that can be queried and enabled at will.⁷⁰⁻⁷⁴ Depending on the rhythm of the data gathering and the amount of data, it becomes possible to retrace the entire intensive care stay of a patient as closely as if the patient was still in the unit.⁷⁴ This *Ad vitam æternam* "reusable" patient constitutes what we call the perpetual patient. In our opinion,⁷⁴ the first purpose of the PP is to serve as a control patient for the validation of computational models (→ **Fig. 3**) as they have an already established long-term and reliable course.

Future Developments Using Virtual and Perpetual Patients in Intensive Care Units

Once validated, these computational models will become essential tools for new era doctors as they offer solutions to teaching, research, and therapeutic issues.

Developing VPs and computational models will reinforce the educational properties of physiological modeling. It is

Fig. 2 Gathering data in electronic database.

Fig. 3 Validation progress of a computational model. T0, initial time, TX, time of the therapeutic action.

time to make available to caregivers education platforms, similar to those of flight simulators. Linking these models with simulation manikins will enhance the ability of high fidelity simulation to recreate real patients' reactions and care environment, leading to the new concept of very high fidelity simulation.

VPs and PPs are of great applicability to the field of cardiopulmonary physiology research as they provide almost

a limitless interface to test and verify hypotheses. In the future, it is likely that, prior to conducting a trial or experimental test in the field of cardiopulmonary physiology, investigators might have to initially validate their hypothesis with computational models and/or PPs.^{10,37}

Finally, based on the same principle of testing hypotheses, physicians will be able to evaluate the efficiency of their therapeutic plan prior to applying to their patient.

Furthermore, VPs and PPs will serve to develop and calibrate computer-assisted protocols, reducing inter-caregiver variability and helping physicians to track anomalies in their patients' condition with the ultimate goal of improving patient care, especially in the intensive care unit.^{6,75,76}

Conclusion

VP/computational models are systems of great interest for both education and patient care applications in the fields of cardiorespiratory physiology and mechanical ventilation. Thanks to recent progress in informatics, mathematical models elaborated many decades ago by a small group of physiologists are now available as software accessible by almost everyone on personal computers. While their potential value to medical education is without question, there is still work to do to validate their robustness, reliability, and accuracy, when compared with the course over time of real patients in the intensive care unit, and then promote more widespread utilization in cardiorespiratory care and research.

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