UNIVERSITE DE MONTREAL

Elaboration et validation d'une base de données haute résolution destinée à la calibration d'un patient virtuel utilisable pour l'enseignement et la prise en charge personnalisée des patients en réanimation pédiatrique

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Thèse présentée en vue de l'obtention du grade de Philosophiae doctor (Ph.D.)

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RESUME EN FRANÇAIS

La complexité des patients de réanimation justifie le recours à des systèmes d'aide à la décision thérapeutique. Ces systèmes rassemblent des protocoles automatisés de prise en charge permettant le respect des recommandations et des simulateurs physiologiques ou patients virtuels, utilisables pour personnaliser de façon sécuritaire les prises en charge. Ces dispositifs fonctionnant à partir d'algorithmes et d'équations mathématiques ne peuvent être développés qu'à partir d'un grand nombre de données de patients. Le principal objectif de cette thèse était la mise en place d'une base de données haute résolution automatiquement collectée de patients de réanimation pédiatrique dont le but sera de servir au développement et à la validation d'un simulateur physiologique : SimulResp©. Ce travail présente l'ensemble du processus de mise en place de la base de données, du concept jusqu'à son utilisation.

Mots clés : Base de données ; Réanimation ; Système d'aide à la décision ; pédiatrie ; modèle informatique ; big data

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RÉSUMÉ EN ANGLAIS

Development and validation of a high-resolution database for the calibration of a virtual patient usable for the teaching and the management of patients in pediatric intensive care.

The complexity of the patients in the intensive care unit requires the use of clinical decision support systems. These systems bring together automated management protocols that enable adherence to guidelines and virtual physiological or patient simulators that can be used to safely customize management. These devices operating from algorithms and mathematical equations can only be developed from a large number of patients' data. The main objective of the work was the elaboration of a high resolution database automatically collected from critically ill children. This database will be used to develop and validate a physiological simulator called SimulResp© . This manuscript presents the whole process of setting up the database from concept to use.

Key words: Database; Intensive care unit; clinical decision support system; children; computational model; big data

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TABLE DES MATIERES

ABRÉVIATIONS

ANZICS - Australian and New Zealand Intensive Care Society

BPCO – Broncho-Pneumopathie Chronique Obstructive

Brain IT – Brain monitoring with Information Technology

CCI – Coefficient de Corrélation Intra-classe

CDSS – Clinical Decision Support System (Article 2)

CRF – Capacité Résiduelle fonctionnelle

CVP – Central Veinous Pressure (Article 4)

DB – Database (Article 4)

DBP – Diastolic Blood Pressure

DoCDat – Directory of Clinical Audit Databases (Article 3)

DQC – Data Quality Collaborative (Article 3)

EAV – Entity – Attribute – Value (Article 3)

EMR – Electronic Medical Record (Article 2)

EV – Expiratory tidal Volume (Article 4)

FiO2 – Fraction Inspirée en Oxygène

FR – Fréquence Respiratoire

GB – GigaByte (Article 2)

GO – GigaOctet

HL7 – Health Language 7 (Article 2)

HR – Heart Rate (Article 4)

HRD – High Resolution Database (Article 3)

HRDB – High Resolution Database (Article 4)

ICC – Intraclass Coefficient Correlation (Article 4)

ICCA – Intellispace Critical Care and Anesthesia (Article 2)

ICU – Intensive Care Unit (Article 2)

IQR – Interquartile Range (Article 2)

IT - Information Technology (Article 2)

MADPE – Mean Absolute Performance Error (Article 1)

MBP – Mean Blood Pressure (Article 4)

MDPE – Mean Performance Error (Article 1)

MIMIC – Multiparameter Intelligent Monitoring in Intensive Care (Article 2)

MV – Minute Ventilation (Article 4)

PaO2 – Pression artérielle en Oxygène

PaCO2 – Pression artérielle en Dioxyde de Carbone

PE – Performance Error (Article 1)

PELOD – Pediatric Logistic Organ Dysfunction (Article 2)

PEP – Pression Expiratoire Positive

PEEP – Positive End Expiratory Pressure (Article 4)

PIP – Pression Inspiratoire Positive / Positive Inspiratory Pressure (Article 4)

PP – Perpetual Patient (Article 1)

R&D – Research and Development

RR – Respiratory Rate (Article 4)

SDRA – Syndrome de Détresse Respiratoire Aigu

SaO2 – Saturation artérielle en oxygène

SBP – Systolic Blood Pressure

SpO2 – Saturation pulsée en oxygène (Article 4)

SQL - Structured Query Language

VC – Volume Courant

VP – Virtual Patient (Article 1)

VPS – Virtual Pediatric System (Article 2)

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INTRODUCTION

La capacité du cerveau humain à intégrer et traiter de nouvelles informations simultanément est limitée (1–3). Cette limite est grandement influencée par le contexte dans lequel le sujet reçoit ces informations (2,4). Ainsi, dans le domaine de la réanimation et des soins intensifs, un milieu stressant, dans lequel le praticien est soumis à de nombreuses sollicitations simultanées et doit prendre des décisions impliquant la survie de patients parfois sans discontinuer pendant 24h, le contraste entre les capacités cérébrales et la quantité de données à analyser peut expliquer en partie la variabilité des pratiques (5,6) et les erreurs médicales (3). Pour assurer une prise en charge optimale, le réanimateur doit prendre en considération un grand nombre de paramètres liés les uns aux autres et variables dans le temps. Il doit aussi être en mesure d'anticiper et de prévoir leur évolution au rythme de ses interventions médicales**.** Dans ce contexte peu favorable à l'intégration des informations, il est probable que le praticien ne prenne pas en compte toutes les données essentielles au bon déroulement de la prise en charge du patient (1,2). Le milieu médical n'est pas unique, il existe de nombreuses professions à risque qui expérimentent la même problématique. Dans le domaine de l'aéronautique notamment, il est depuis longtemps reconnu que la défaillance humaine est souvent à l'origine des accidents (7–10). Dans ce contexte, il est établi que l'utilisation de protocoles automatisés (pilotes automatiques) ainsi que l'entraînement par la simulation ont permis de réduire considérablement leur survenue (7–10). Forts de cette expérience en aéronautique, plusieurs équipes médicales ont considéré que le développement d'outils d'aide à la décision et à l'enseignement par la simulation étaient pertinents pour assister les professionnels et optimiser la prise en charge des patients de réanimation (3,6,11–22).

A. Systèmes d'aide à la décision médicale et protocoles automatisés

Les systèmes d'aide à la décision consistent en l'intégration des connaissances médicales dans un logiciel. Le logiciel recueille des données (données cliniques, paramètres de ventilation, données gazométriques, par exemple) et les analyse (15,23–25). Ensuite, sa conduite va varier en fonction de l'objectif pour lequel l'outil a été développé. Ainsi on distingue 2 niveaux d'utilisation des systèmes d'aide à la décision médicale dans le domaine de la réanimation et des soins intensifs :

1- l'assistance diagnostique et le dépistage des situations pathologiques d'une part (17,21,24) ; à partir de la synthèse de plusieurs données fournies par les dispositifs connectés au patient, l'outil d'assistance diagnostique ou de dépistage va alerter le clinicien d'une situation d'une particulière gravité justifiant la mise en place d'un traitement ou d'une surveillance spécifique.

2- l'assistance à la prise en charge à proprement parlé d'autre part (15,17,20) ; ici, soit le logiciel émet des recommandations thérapeutiques au clinicien qui valide ou non ces propositions, le système est alors appelé « en boucle ouverte », soit il modifie directement la prise en charge du patient sans la validation du clinicien, on parle alors de « boucle fermée » ou de protocoles automatisés (Fig. 1).

A l'heure actuelle, plusieurs de ces systèmes d'aide à la décision sont disponibles pour le dépistage et/ou l'assistance thérapeutique dans le cas de troubles hémodynamiques (18), septiques, respiratoires (12–15,19,20,23,26–30) ou encore neurologiques (24).

En réanimation pédiatrique, c'est vraisemblablement dans le domaine de l'assistance respiratoire que le recours à des systèmes d'aide à la décision de prise en charge semble le plus pertinent. La défaillance respiratoire représente l'un des principaux motifs d'admission en réanimation pédiatrique (31). Depuis de nombreuses années, à côté de l'amélioration des respirateurs, l'utilisation de protocoles de prise en charge est en grande partie à l'origine des

progrès faits en matière d'assistance respiratoire chez l'adulte et l'enfant. Cependant leur impact au quotidien et la compliance des cliniciens restent trop faibles (de l'ordre de 30 à 40% selon les études) (5). Ainsi, le recours à des systèmes d'aide à la décision permettrait une meilleure adhésion aux recommandations internationales et ainsi d'améliorer le devenir des patients et de réduire les complications et les durées de ventilation mécanique (3,15,20,23,30).

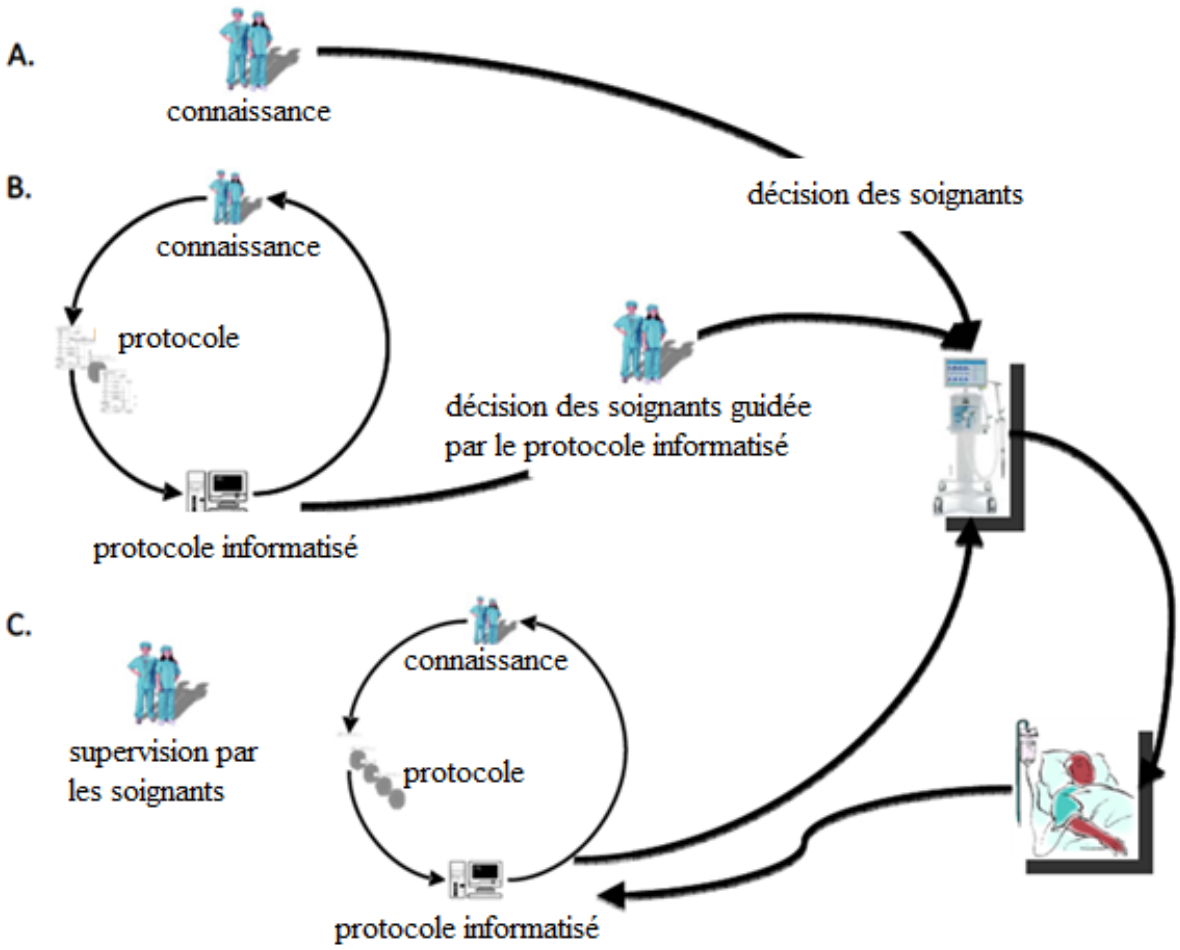

Fig. 1: Représentation des différents processus de décision, d'après Jouvet et al. (13)

A. Prise en charge actuelle guidée par les soignants, B. Protocole informatisé en boucle ouverte, C. Protocole informatisé en boucle fermée.

Le développement et l'implémentation en médecine de systèmes d'aide à la décision nécessitent une démarche rigoureuse (17). Jusqu'à présent les systèmes étaient développés au sein des secteurs R&D des industries et validés par l'inclusion de quelques patients dans une étude clinique prospective avant commercialisation (12,14). Cependant, la complexification de

ces systèmes et la nécessité d'avoir une meilleure approche en termes de sécurité pose la question du processus d'autorisation à la commercialisation (17). Dans ce contexte, l'idée de tester les performances et la sécurité de ces systèmes sur des simulateurs physiologiques s'impose.

B. Simulation et modélisation physiologique

1. Principes

La simulation ou modélisation physiologique a pour objectif de reconstituer le fonctionnement du corps humain et les interactions entre les différents systèmes qui le composent (32–36). Par l'intermédiaire d'équations mathématiques, il est possible de programmer un modèle capable de recréer la physiologie humaine et de la rendre ainsi accessible à l'étude (32–36). Du fait des progrès informatiques, ces simulateurs ont pu être agrémentés d'interfaces virtuelles facilitant leur utilisation (37).

2. Modélisation respiratoire

a) Généralités

Un simulateur cardio-respiratoire est spécifiquement conçu pour modéliser la physiologie et la physiopathologie cardio-respiratoire. En pratique courante, on en distingue essentiellement 4 utilisations principales :

- l'enseignement de la physiologie cardio-respiratoire et de la ventilation
- l'évaluation des performances des respirateurs utilisés en service de réanimation
- l'édition de recommandations sur la prise en charge cardio-respiratoire
- l'élaboration et calibration d'outils d'aide à la décision thérapeutique.

Dans le domaine de l'aide à la décision en ventilation mécanique, il est possible d'étudier la prédiction faite par le simulateur physiologique en réponse à des modifications des paramètres ventilatoires dans certaines conditions définies préalablement (Fig. 2).

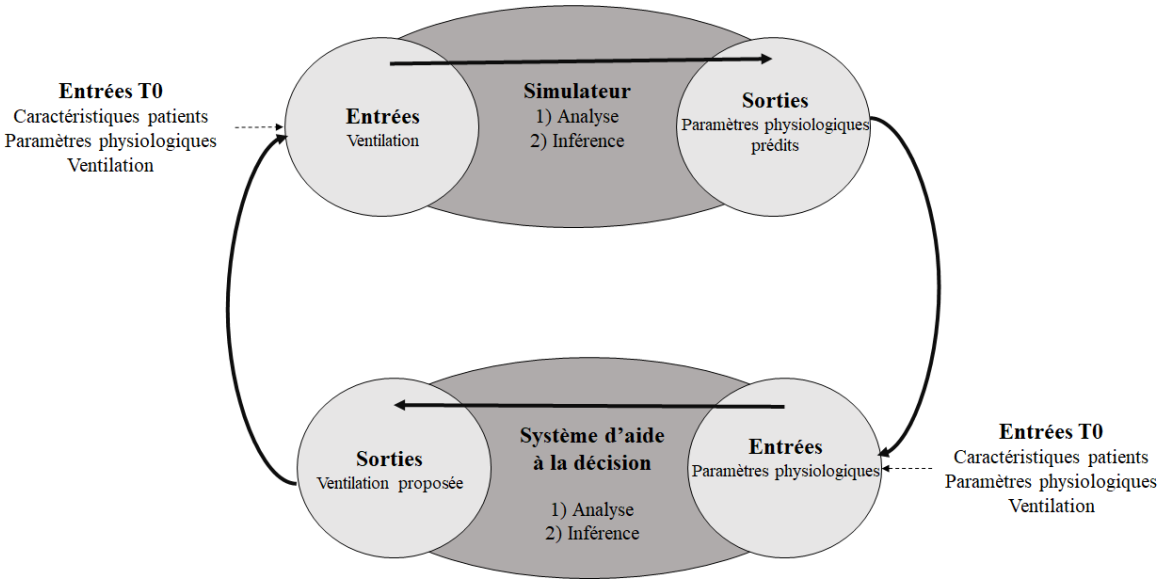

Fig. 2 : Schéma de processus de développement et validation du système d'aide à la décision thérapeutique à partir d'un simulateur cardio-respiratoire

La figure 2 schématise le processus de développement et de validation de systèmes d'aide à la décision à partir d'un simulateur physiologique. Au départ, les caractéristiques d'un patient ainsi que ses paramètres de ventilation vont être implémentés dans le cycle soit au niveau du simulateur, soit au niveau du système d'aide à la décision. Si l'entrée est au niveau du simulateur, celui-ci va prédire une évolution physiologique qui va dépendre d'une part, des informations implémentées à l'entrée du cycle et d'autre part, des formules mathématiques sur lesquelles il s'appuie pour réaliser sa prédiction. Si l'entrée est au niveau du système d'aide à la décision, celui-ci va proposer au soignant une conduite thérapeutique visant à normaliser la situation du patient. Cette conduite thérapeutique va dépendre comme précédemment des informations implémentées à l'entrée mais aussi des protocoles de soins à partir desquels le système d'aide a été développé. La sortie de l'un correspond à l'entrée de l'autre et inversement. L'association des 2 dispositifs permets de s'assurer, dès lors que l'un a été validé préalablement (classiquement le simulateur) de la fiabilité de l'autre (13,38). Initialement, la création des simulateurs a été motivée par le besoin de compréhension des mécanismes physiologiques et la transmission des connaissances dans ce domaine, ainsi de nombreux simulateurs sont dédiés à la pédagogie (39,40). Par la suite, certains simulateurs sont devenus aptes à produire des valeurs

de gaz du sang, permettant d'une part de proposer un enseignement plus complet de la physiologie et de la ventilation (37,41) et d'autre part d'assister le clinicien au lit du malade en fournissant une prédiction plus ou moins fiable de l'évolution de l'hématose du patient en fonction de son état physiopathologique mais aussi des modifications thérapeutiques réalisées (42). Ces simulateurs ont, pour la plupart, été testés et validés chez des patients sains mais peuvent aussi simuler certaines maladies (43,44). Selon le type de simulateurs, ils reposent classiquement sur une modélisation à 3 compartiments (zone d'échange, espace-mort, shunt) (39) mais parfois plus (45–47). Sous l'impulsion des progrès informatiques, de la complexification des prises en charge et des intérêts médico-économiques, ces programmes utilisés sur des supports rudimentaires pour l'enseignement (36,37,41) puis l'assistance ventilatoire (42,48–51) sont devenus de véritables dispositifs médicaux et objets marketing (40,52). Plus récemment, les simulateurs hybrides associant deux ou plusieurs modèles interagissant les uns avec les autres sont apparus. Le plus souvent l'association combine une composante numérique avec une composante mécanique (53). Ces dispositifs hybrides semblent en mesure de reproduire la mécanique ventilatoire de plusieurs types de patients et notamment des nouveau-nés (44).

b) Le modèle de Dickinson

Le modèle de CJ Dickinson (54) a comme avantage d'avoir son code source dans le domaine publique. C'est un modèle respiratoire à 3 compartiments : capillaires, espace mort et shunt droit-gauche. Les poumons sont modélisés afin d'inclure l'espace mort anatomique et physiologique, ainsi que le rapport ventilation-perfusion (alvéoles ventilées ou non et perfusées ou non).

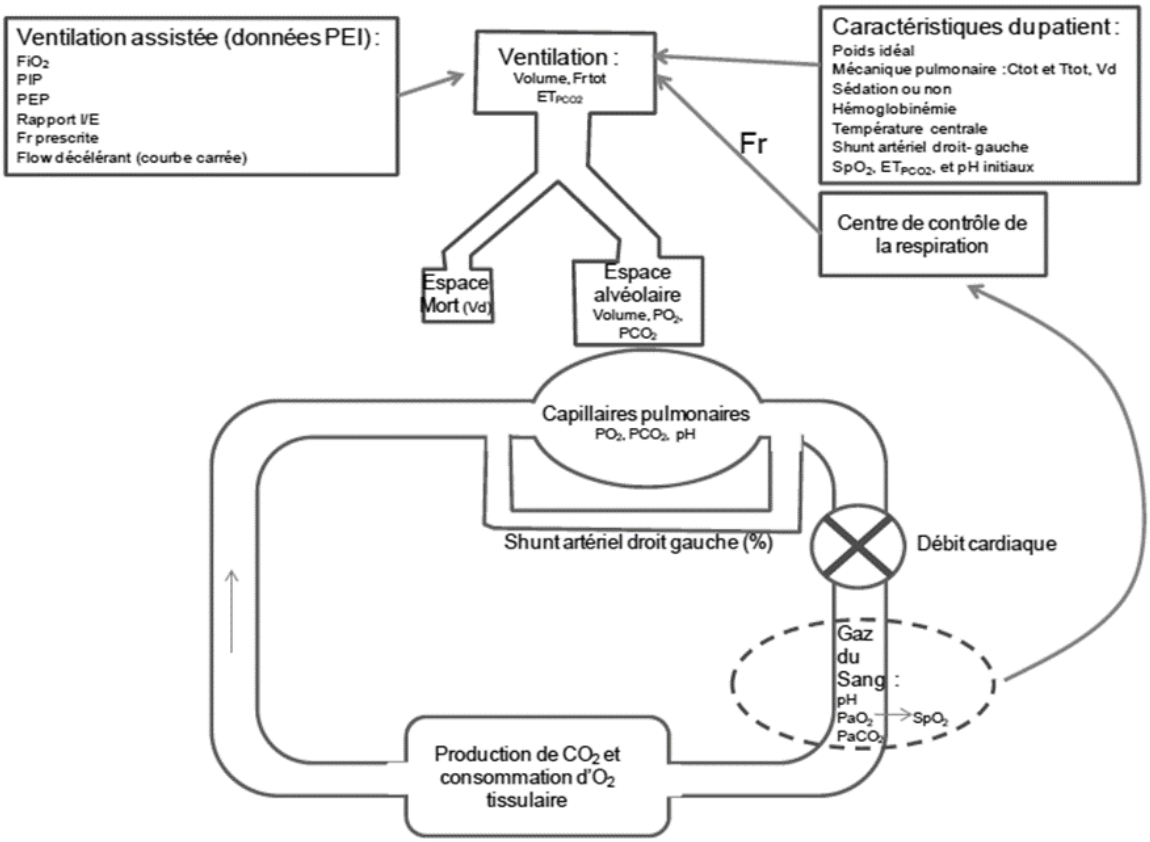

Fig. 3 : Modèle cardio-respiratoire multi-compartimental de Dickinson

Le flux sanguin pulmonaire est modélisé en 2 compartiments : un compartiment avec shunt et un compartiment sans shunt. Le sang passe au niveau de l'alvéole sous forme de volume par unité de temps. Chaque unité de volume sanguin passe par une modélisation du transfert de gaz à travers la paroi alvéolo-capillaire de telle sorte qu'une simulation du processus d'équilibre des gaz alvéolaires est obtenue. Les échanges gazeux sont corrigés pour la pression expiratoire positive, le débit cardiaque et le pH. La production de dioxyde de carbone et l'extraction d'oxygène proportionnelles à l'âge de l'enfant simulent le métabolisme tissulaire.

c) Logiciel

A partir de ce modèle mathématique, notre équipe de recherche a programmé et développé le simulateur cardio-respiratoire : SimulResp© (13,39,55). Ce simulateur a vocation à reproduire la physiologie respiratoire d'un patient de plus de 8 ans, sain ou dans certaines

situations pathologiques (syndrome de défaillance respiratoire aiguë (SDRA), asthme, BPCO, hémodynamique instable) (13,39,55) (Fig. 4) .

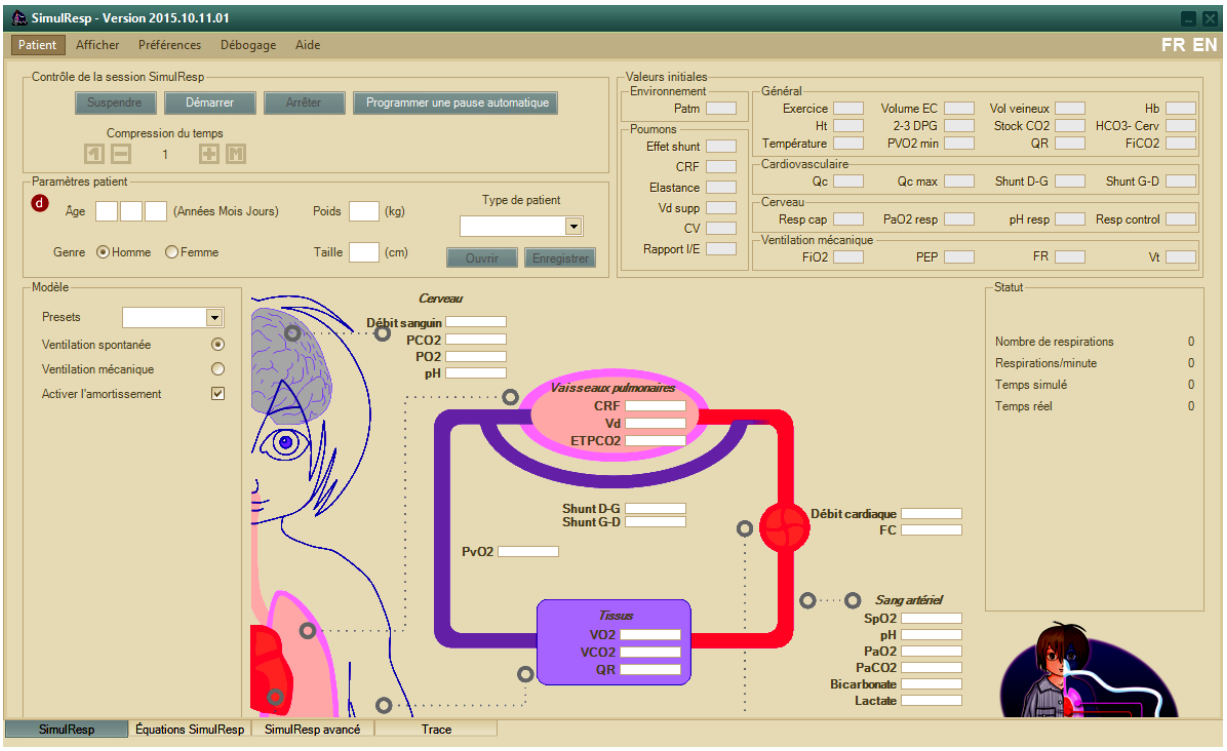

Fig. 4 : Aspect graphique de l'interface du simulateur

d) Limites

Si les premières étapes de validation ont mis en évidence une bonne reproductibilité et robustesse du simulateur en situation de ventilation spontanée (55), des incertitudes persistent en ce qui concerne la justesse de ses prévisions, notamment dans le domaine de la ventilation mécanique. Ainsi, avant de pouvoir utiliser le simulateur SimulResp© pour développer, tester et appliquer des protocoles automatisés de prise en charge, il est nécessaire de s'assurer de sa fiabilité.

e) Evaluation de la qualité.

L'évaluation des capacités et de la fiabilité d'un modèle physiologique fait appel à plusieurs concepts (56–58).

- L'exactitude (« accuracy ») qui rassemble à la fois les termes de justesse (« trueness ») et de fidélité (« precision »). La justesse s'exprime par le biais et correspond à l'accord entre la valeur moyenne des résultats d'un essai, ici la prédiction du simulateur, et la valeur de référence. La fidélité correspond à l'étroitesse d'accord entre les résultats des essais et correspondrait à la dispersion des résultats de l'essai réalisé dans des conditions définies.
- La répétabilité correspond à l'étude de la fidélité pour des résultats obtenus dans des conditions de mesure identiques, c'est-à-dire avec la même méthode ou le même simulateur avec le même équipement, dans le même lieu, par le même opérateur, dans le même intervalle de temps.
- La reproductibilité correspond à l'étude de la fidélité pour des résultats obtenus dans des conditions de mesure identiques, c'est-à-dire avec la même méthode ou le même simulateur mais avec un équipement, un lieu et un opérateur différents.
- La robustesse qui correspond à la capacité du simulateur à rester stable et fiable dans le temps et les conditions.

PROBLEMATIQUE DU TRAVAIL

La complexité des malades hospitalisés en réanimation et la nécessité d'intégrer un nombre croissant de données cliniques, paracliniques et thérapeutiques surpassant l'esprit humain, justifient le recours des réanimateurs à des outils d'aide à la décision thérapeutique ou diagnostique pour garantir aux patients une prise en charge optimale (17)**.** Afin d'assurer une sécurité d'utilisation de ces outils d'aide à la décision, il est apparu préférable de les tester et d'encadrer leur déploiement à l'aide de simulateurs physiologiques. En plus de servir à la programmation d'outils d'aide à la décision, ces simulateurs physiologiques ont la possibilité d'être utilisés à des fins d'enseignement.

Le développement et l'évaluation de ces simulateurs physiologiques et des outils d'aide à la décision nécessitent l'acquisition d'une quantité importante de données cliniques, paracliniques et thérapeutiques (16,59). Pour être utiles dans le contexte des soins intensifs et de la réanimation, ces données doivent être recueillies à haute fréquence, fiables, validées et interrogeables. A partir de ces données, il est alors possible de développer puis de tester des algorithmes diagnostiques et thérapeutiques, plus ou moins autonomes (16,59,60).

C'est ainsi que dans le cadre notre travail de développement et de validation du simulateur cardio-respiratoire SIMULRESP©, nous en sommes venus à la création du concept de PATIENT PERPETUEL. Ce concept sera illustré tout le long du manuscrit et est défini comme un patient dont on peut reprendre à l'infini le déroulé du séjour en soins intensifs du fait de la grande quantité de données organisables dans le temps qui a été recueillie pendant son séjour.

OBJECTIFS DE LA THESE

L'objectif principal de cette thèse de science était la mise en place d'une base de données haute résolution automatiquement collectée de patients de réanimation pédiatrique.

Les objectifs secondaires étaient :

- l'évaluation de la base de données,
- la validation de la base de données,
- la réalisation d'un portrait des capacités et des limites actuelles du simulateur cardio-respiratoire SIMULRESP© ,
- le développement du processus de validation et de calibration du simulateur cardio-respiratoire SIMULRESP© .

DEMARCHE SCIENTIFIQUE ET CONDUITE DE LA THESE

Cette thèse repose sur 5 travaux principaux réalisés entre 2016 et 2019 qui ont pour fil conducteur le concept de patient perpétuel et son utilisation pour calibrer et valider le simulateur cardio-respiratoire SIMULRESP© :

1) **D. Brossier**, M. Sauthier, X. Alacoque, B. Masse, R. Eltaani, B. Guillois, P. Jouvet. **Perpetual and virtual patients for cardio-respiratory physiological studies.** Ce premier article a été publié dans *journal of pediatric intensive care* en 2016. Cette revue de la littérature permet d'introduire dans la thèse le concept de patient virtuel, concept étroitement associé à celui de simulateur et pouvant être dans ce contexte de simulation physiologique cardio-respiratoire considéré comme synonyme. Cette revue de la littérature avait pour objectif de définir ce qu'est un patient virtuel, notamment dans le domaine des études physiologiques cardio-respiratoires et de déterminer la méthode de validation de ces patients virtuels. Cette article marque la naissance du concept de patient perpétuel (38).
2) **D. Brossier**, R. El Taani, M. Sauthier, N. Roumeliotis, G. Emeriaud, P. Jouvet. **Creating a high frequency electronic database in the pediatric intensive care unit: The perpetual patient.** Ce deuxième article a été publié en 2018 dans *Pediatric critical care medicine (IF 3.092, Rang B)*. L'objectif de cet article était de décrire le procédé de collecte de données au lit du malade et l'organisation de ces données dans une base de données de recherche. Cet article est une illustration du concept de patient perpétuel (31).
3) **D. Brossier**, M. Sauthier, A. Mathieu, I. Goyer, G. Emeriaud, P. Jouvet. **Qualitative subjective assessment of a high-resolution database in a pediatric intensive care unit – Elaborating the perpetual patient's ID card.** Ce troisième article a été publié en 2019 dans *journal of evaluation in clinical*

pratice (IF 1.536, Rang C). Cette publication avait comme principal objectif de présenter une évaluation de la base de données réalisée par ses concepteurs et premiers utilisateurs. Cette évaluation a permis de présenter une description plus précise de la base, de ses possibilités et limites, selon les recommandations du Data Quality Collaborative (DQC) (61–64).

4) A. Mathieu, M. Sauthier, P. Jouvet, G. Emeriaud, **D. Brossier. Validation process of a high-resolution database in a pediatric intensive care unit – Describing the perpetual patient's validation.** Ce travail soumis en 2019 au J*ournal of the American Medical Informatics Association (IF 4.292, Rang A)* avait pour objectif de valider le processus de collecte de données et d'évaluer la fiabilité des données incluses dans la base. C'est un travail qui a été réalisée par Audrey Mathieu, une étudiante à la maitrise de science biomédicale sous ma supervision (65).

5) Le dernier travail avait comme objectif d'évaluer les capacités et les limites du simulateur cardio-respiratoire SimulResp©. Ce travail s'intègre dans le cadre du processus de calibration et validation de SimulResp© (55). Il permet de préciser l'état actuel du SimulResp© et ainsi guider les démarches de recalibration de ce dernier. Ce travail devrait conduire à la rédaction de l'article suivant : **D. Brossier,** O. Flechelles, M. Sauthier, G. Emeriaud, F. Cheriet, B. Guillois, P. Jouvet**. Evaluation of SimulResp©: a simulation software of child and teenager cardiorespiratory physiology.**

A ces travaux s'ajoutent 4 publications annexes :

- Annexe A : S. Ghazal, M. Sauthier, **D. Brossier**, W. Bouachir, R Noumeir, P Jouvet. Using machine-learning models to predict oxygen saturation following ventilator

support adjustment in critically ill children: a single center pilot study. PLoS One. 2019;14(2):e0198921. (66)

- Annexe B : P. Bourgoin, F. Baudin, **D. Brossier**, G. Emeriaud, M. Wysocki, P. Jouvet. Assessment of Bohr and Enghoff Dead Space Equations in Mechanically Ventilated Children. Respir Care. 2017;62(4):468-474. (67)
- Annexe C: F. Baudin, P. Bourgoin, **D. Brossier**, S. Essouri, G. Emeriaud, M. Wysocki, P. Jouvet. Noninvasive estimation of arterial CO2 from end-tidal CO2 in mechanically ventilated children: The GRAeDIENT pilot study. Pediatr Crit Care Med. 2016;17(12):1117-1123. (68)
- Annexe E: S. Fartoumi, G. Emeriaud, N. Roumeliotis, **D. Brossier**, M. Sawan, G. Emeriaud. Clinical decision support system for traumatic brain injury management. J Pediatr Intensive Care. 2016;5:101-107. (24)

ARTICLE I: PERPETUAL AND VIRTUAL PATIENTS FOR CARDIORESPIRATORY PHYSIOLOGICAL STUDIES

A. Présentation

Cet article est le point de départ du travail de thèse, il est paru dans un numéro spécial du Journal of Pediatric Intensive Care portant sur les bases de données et les systèmes informatiques en soins intensifs pédiatriques. Il va permettre d'introduire plusieurs concepts complémentaires de ceux déjà présentés dans l'introduction de la thèse.

Cet article a été rédigé après revue de la littérature sur les thèmes patient virtuel (virtual patients), modèles informatiques ou numériques (computational model), modélisation physiologique (physiological modeling) et base de données (databases) avec une analyse centrée sur les études cardio-respiratoires et l'application dans ce domaine.

La rédaction de cet article a impliqué un travail de coordination d'une équipe multidisciplinaire composée de spécialistes en soins critiques pédiatriques, en simulation, en modélisation physiologique, en informatique, en base de données, en méthodologie et en statistiques au Canada et en France.

B. Article

Review Article

Perpetual and Virtual Patients for Cardiorespiratory Physiological Studies

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J Pediatr Intensive Care

Abstract

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.

Keywords
- children
- intensive care
- modeling
- cardiorespiratory physiology
- simulation
- databases

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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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 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 "interactive computer simulation of real-life clinical scenarios for the purpose of health care and medical training, education or assessment." (4,19,20,27,28) 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 al (34) 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 years (8) 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).

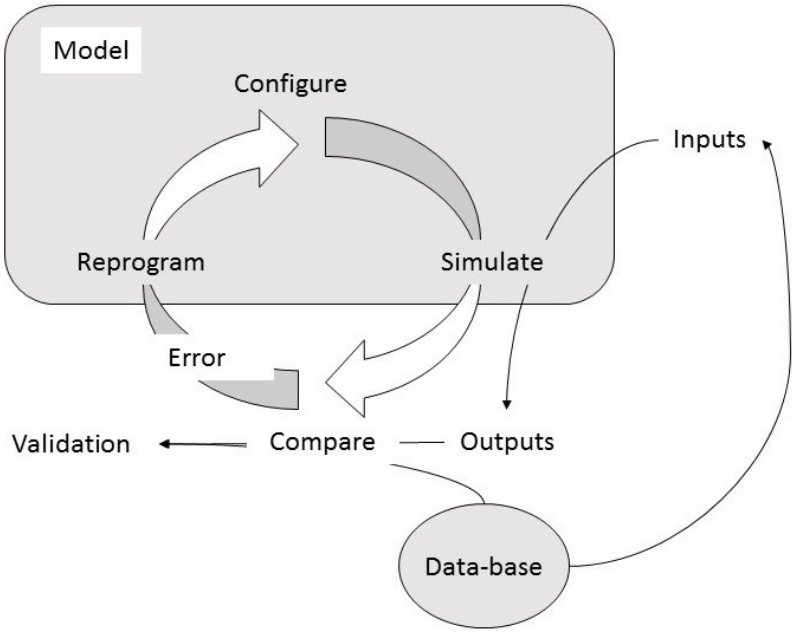

Fig. 1 : View of the validation process.

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 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 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] x 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 (PP). 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.

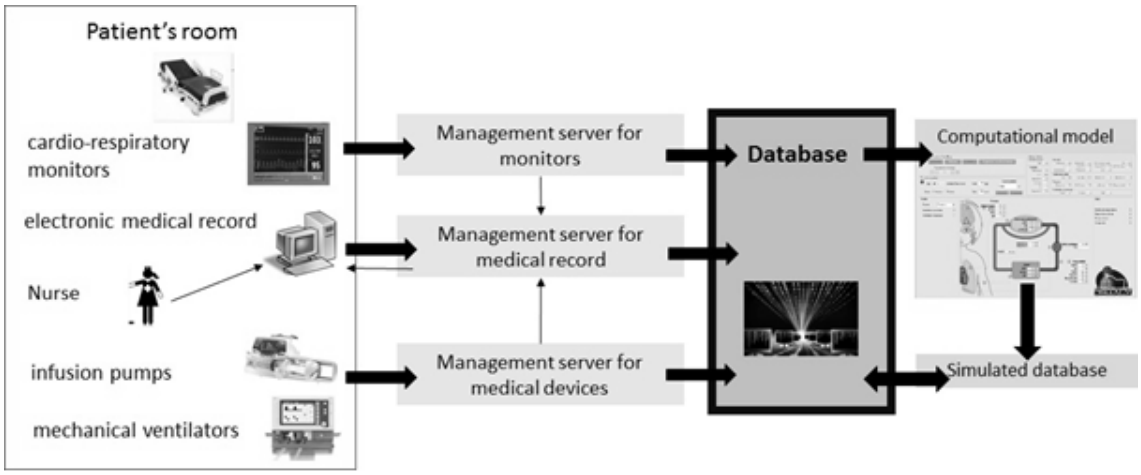

Fig. 2: Gathering data in electronic database.

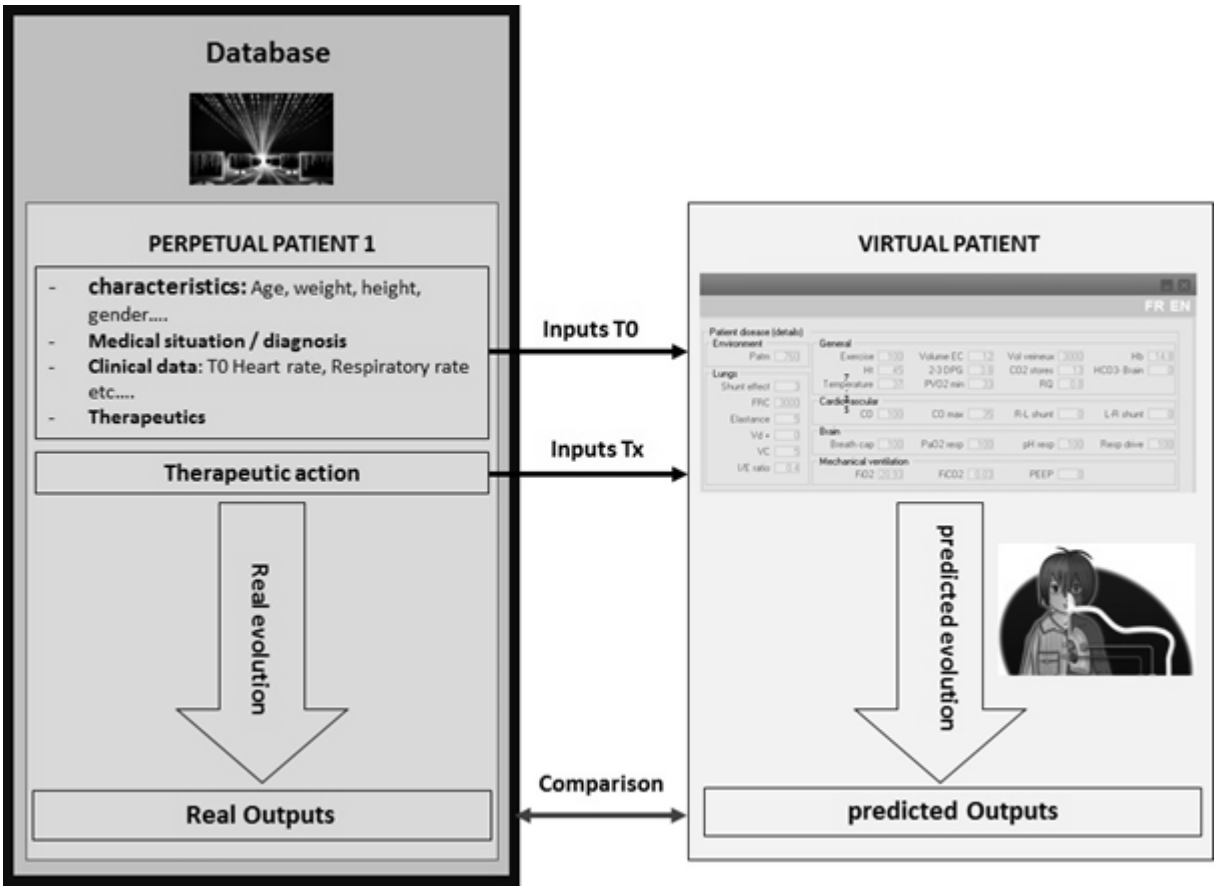

Fig. 3: Validation progress of a computational model.
T0, initial time, TX, time of the therapeutic action.

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 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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C. Discussion

Cet article doit être considéré comme une introduction au travail de thèse. Ce premier travail nous a permis de clarifier les étapes à franchir pour amener SimulResp© à un niveau de validité compatible avec une utilisation dans les soins.

L'introduction du concept de **patient perpétuel** (130) est l'élément essentiel de cet article. Nous avons créé et défini le patient perpétuel comme un patient dont on peut reprendre à l'infini le déroulé du séjour en soins intensifs du fait de la grande quantité de données organisables dans le temps qui a été recueillie pendant son séjour. Ce séjour peut être « ré-étudié » de multiples fois alors que le patient n'est plus hospitalisé. R. Wetzel agrémentera cette définition en précisant que le patient perpétuel correspond à un ensemble de données restant pour toujours disponibles pour la recherche, l'innovation thérapeutique et l'enseignement et représente une alternative aux essais cliniques classiques (131) (Annexe E).

Le second concept que cet article permet d'introduire est celui de **patient virtuel**. Dans le cadre de ce travail, les termes patient virtuel, simulateur cardio-respiratoire et modèle informatique ou physiologique peuvent être considérés comme équivalents. Un simulateur cardio-respiratoire, développé à partir d'algorithmes et des formules mathématiques devient un patient virtuel dès lors qu'il est accessible par l'intermédiaire d'une interface informatique (Fig. 5).

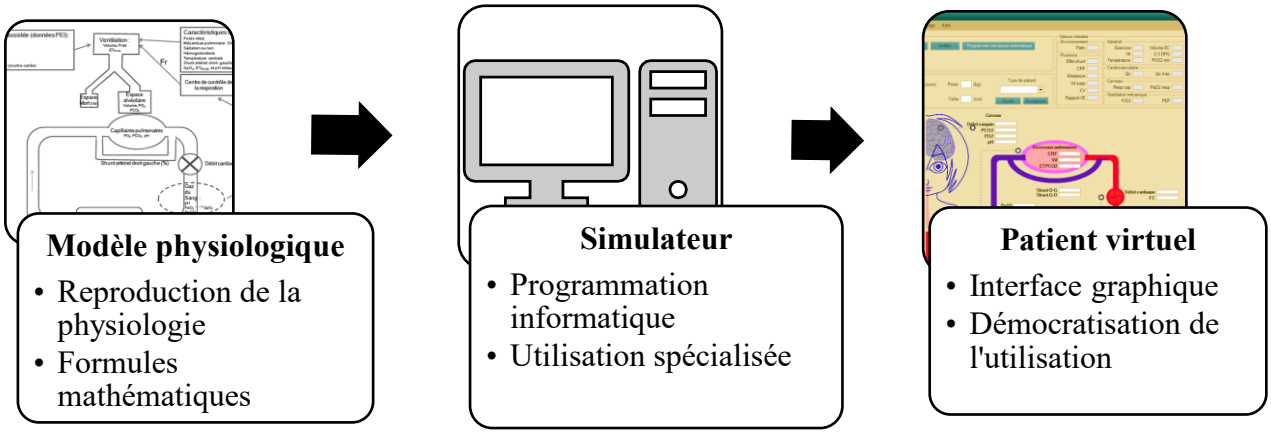

Fig. 5 : Du modèle physiologique au patient virtuel. L'exemple de SimulResp©

S'il est possible d'assimiler le terme de patient virtuel avec celui de simulateur, il est important de le différencier du terme de patient perpétuel (Tableau 1).

Tableau 1 : Différenciations entre patient perpétuel et patient virtuel

	Patient perpétuel	**Patient virtuel**
Origines	Concept créé en 2014 par Philippe Jouvet et David Brossier (38)	Première mention en 1991 par George Sherouse et Edward Chaney (132)
Définition	Patient dont le déroulé du séjour peut être repris à l'infini (31,38,131)	Logiciel qui simule une histoire de cas, une situation clinique ou physiologique (39,80)
Concept	1) Le patient perpétuel est constitué à partir d'un patient réel. 2) Les données du patient réel ont été enregistrées à haute fréquence dans une base de données haute résolution durant son séjour en réanimation. 3) Après la sortie du patient réel, les données restent disponibles. Elles sont organisables dans le temps et analysables à l'infini.	1) le patient virtuel reconstitue à l'aide d'une interface informatique une situation clinique ou physiologique, réelle ou non. 2) Du fait de cette interface informatique, il rend cette situation accessible à un utilisateur 3) Le patient virtuel est réutilisable à volonté mais son utilisation reste circonscrite à la programmation initiale du logiciel.
Objectif	1) Utilisation en recherche clinique. 2) Développement et évaluation de patients virtuels et d'outils d'aide à la décision clinique.	1) Utilisation pédagogique dans le cadre d'une formation axée sur les cas. 2) Utilisation en clinique. Il sert « d'assistant » au clinicien qui va pouvoir tester et évaluer l'efficacité de ses prises en charge avant de les appliquer sur les patients.
Interactions	Le patient perpétuel va pouvoir être utilisé pour constituer ou évaluer un ou des patients virtuels. Le patient virtuel va permettre d'assister le clinicien sur sa prise en charge du malade réel et donc, indirectement, influencer les données constituant le patient perpétuel.	

L'autre point important de ce travail repose sur les considérations méthodologiques. Que ce soit dans le cadre de la validation du patient virtuel ou bien des données collectées dans la base de données, cette question des analyses statistiques à réaliser pour tester la justesse et la fiabilité des données recueillies ou simulées s'est posée tout au long du travail de thèse et se pose encore dans la littérature (95–97,133–136). Il y a tout de même plusieurs points à considérer qui seront repris et/ou complétés dans les autres travaux constituant cette thèse :

- les statistiques comparatives de base ainsi que le calcul d'un coefficient de corrélation simple ne sont pas suffisants pour garantir la concordance entre données simulées et données réelles ou bien données enregistrées et données réelles (95,137) ;
- la méthode de Bland & Altman n'a pas été développée pour ce type de comparaisons et d'analyses. De ce fait, son utilisation dans ce contexte, bien que répandue (135), reste controversée (96,97,134).

Enfin, le dernier élément marquant est la nécessité de considérer l'utilisation d'un nombre important de données en provenance d'un nombre important de patients et donc le recours à une base de données haute résolution collectée sur de nombreuses années et/ou dans de nombreux centres. La figure 6 (Fig. 6) présente l'intégration de la base de donnée dans le processus de développement de patients virtuels et de systèmes d'aide à la décision. Tout d'abord, à partir des données de la base de données, il va être possible de développer et de tester des équations mathématiques permettant de modéliser la physiologie (24,66,67). Ces équations vont pouvoir secondairement être implémentées dans le simulateur cardio-respiratoire pour d'une part augmenter sa fiabilité et d'autre part élargir ses possibilités de prédiction. Cette procédure évoquée dans l'article 1 (38) sera reprise et détaillée ultérieurement dans la discussion du travail 5. Par ailleurs, la mise en commun des données issues de patients présentant des similitudes physiopathologiques va permettre, après analyse des données physiologiques, biologiques, thérapeutiques ou de devenir incluses dans la base, le

développement d'algorithmes diagnostiques ou de prise en charges qui vont pouvoir être implémentés dans les dispositifs d'aide à la décision (16,138–140).

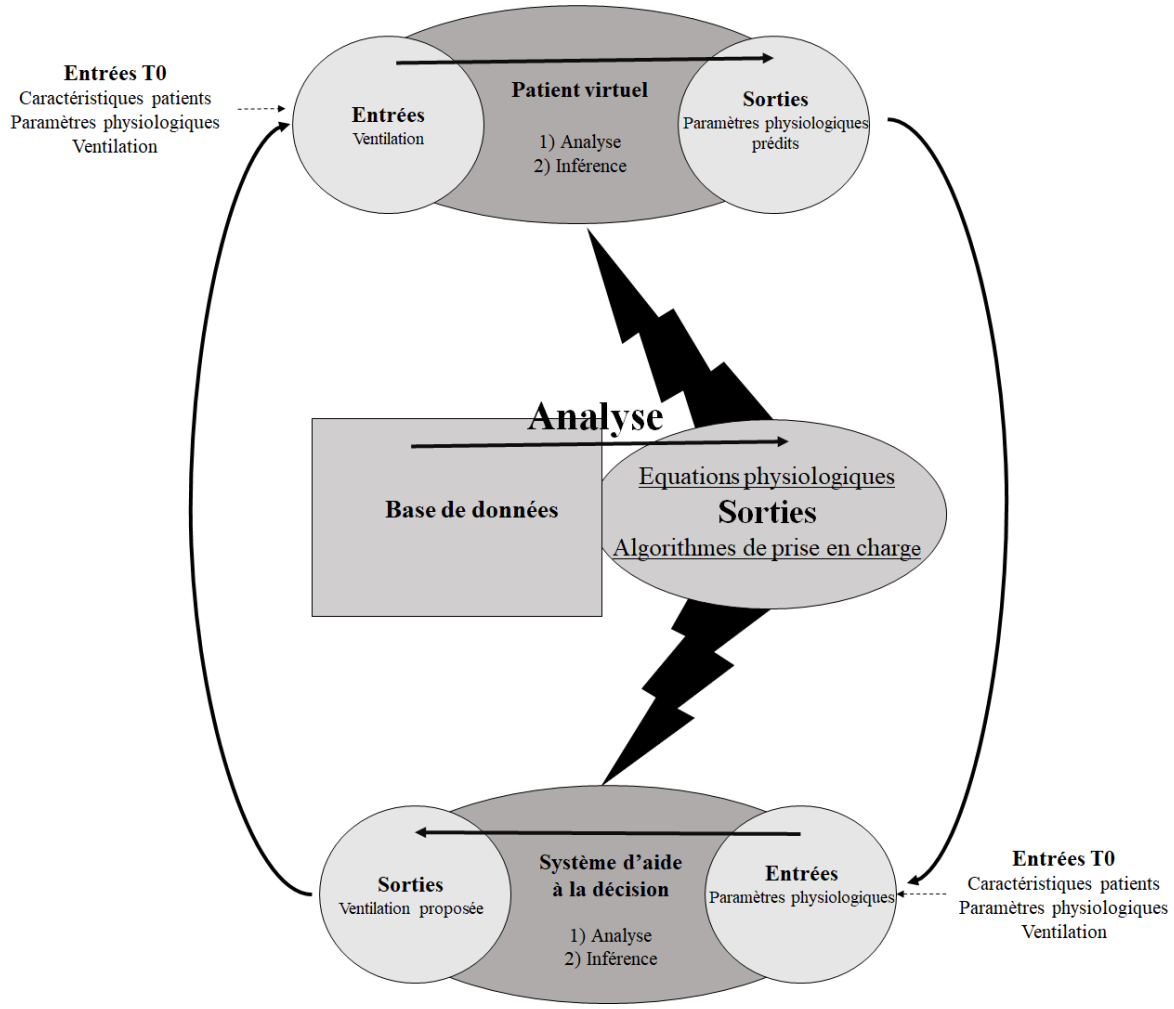

Fig. 6: Importance de la base de données dans le processus de développement de patients virtuels et d'outils d'aide à la décision.

La faiblesse de cet article réside dans le caractère insuffisamment systématique de la revue de la littérature à partir de laquelle il a été écrit. Cet article reprend de nombreux concepts pédagogiques, scientifiques ou encore méthodologiques et il est apparu difficile d'être exhaustif en dépit d'une bibliographie conséquente. Par ailleurs, l'implication limitée des méthodologistes à ce moment du travail a probablement contribué à limiter l'exhaustivité et la pertinence de la section « validation of a virtual patient simulating cardiorespiratory

physiology ». Ainsi, par exemple, à ce moment du travail, nous n'avions aucunement considéré la place du coefficient de corrélation intra-classe (133).

ARTICLE II: CREATING A HIGH-FREQUENCY ELECTRONIC DATABASE IN THE PICU: THE PERPETUAL PATIENT

A. Présentation

Une base de données informatisée se définit comme un ensemble de données organisé en fonction d'un objectif préalablement défini (118,141,142) et stocké sur un support accessible par ordinateur.

Si l'on souhaite exploiter la base dans le cadre d'une activité de recherche, il est important de s'assurer **:**

- que celle-ci est interrogeable, c'est à dire organisée et accessible (142) ;
- que la réponse fournie est exploitable, c'est à dire représentative du sujet étudié, uniforme et idéalement, dans un souci de coopération scientifique, partageable de façon compréhensible indépendamment du lieu de recueil des données (143).

Une base de données collectée automatiquement à haute fréquence est souvent de type relationnel, c'est-à-dire qu'elle associe plusieurs tables liées les unes aux autres (118,141,142). La classification des données et les interactions entre les tables vont dépendre directement de l'objet étudié et des données collectées. Les règles de programmation vont permettre d'uniformiser, d'organiser, et de stocker les données de manière à rendre chaque donnée unique, tout en liant entre elles toutes les données d'un même patient (118,141,142,144)**.** A cela s'ajoutent des procédures de nettoyage et de suppression des données inutiles dans le but de limiter la surcharge et le ralentissement de la base. La programmation de ce type de base de données est souvent réalisée en langage SQL (Structured Query Langage). Le langage SQL comporte plusieurs composantes qui vont permettre la manipulation, l'organisation et le contrôle des données tout en facilitant la réalisation de requêtes. Le système de gestion de la base de données permet la programmation et l'utilisation de la base, mais garantit aussi l'intégrité et la sécurité de celle-ci, en respectant les propriétés ACID (atomicité, cohérence,

isolation et durabilité). Ces propriétés font en sorte, notamment, que chaque transaction réussit complètement ou échoue complètement ; aucune transaction ne peut être partiellement complétée (145). Le système de gestion choisi dans le cadre d'une base de données de grande taille est un système sur serveur. Ce type de dispositif va permettre la gestion, l'organisation et le stockage d'une grande quantité de données tout en autorisant simultanément l'accès à plusieurs utilisateurs (142,144)**.**

B. Article

Creating a High-Frequency Electronic Database in the PICU: The Perpetual Patient

David Brossier, MD, MSc[1,2,3]; Redha El Taani, MSc[2,4]; Michael Sauthier, MD[1,2]; Nadia Roumeliotis, MD, MSc[1,2]; Guillaume Emeriaud, MD, PhD[1,2]; Philippe Jouvet, MD, PhD[1,2]

Objective: Our objective was to construct a prospective high-quality and high-frequency database combining patient therapeutics and clinical variables in real time, automatically fed by the information system and network architecture available through fully electronic charting in our PICU. The purpose of this article is to describe the data acquisition process from bedside to the research electronic database.
Design: Descriptive report and analysis of a prospective database.
Setting: A 24-bed PICU, medical ICU, surgical ICU, and cardiac ICU in a tertiary care free-standing maternal child health center in Canada.
Patients: All patients less than 18 years old were included at admission to the PICU.
Interventions: None.
Measurements and Main Results: Between May 21, 2015, and December 31, 2016, 1,386 consecutive PICU stays from 1,194 patients were recorded in the database. Data were prospectively collected from admission to discharge, every 5 seconds from monitors and every 30 seconds from mechanical ventilators and infusion pumps. These data were linked to the patient's electronic medical record. The database total volume was 241 GB. The patients' median age was 2.0 years (interquartile range, 0.0–9.0). Data were available for all mechanically ventilated patients (n = 511; recorded duration, 77,678 hr), and respiratory failure was the most frequent reason for admission (n = 360). The complete pharmacologic profile was synched to database for all PICU stays. Following this implementation, a validation phase is in process and several research projects are ongoing using this high-fidelity database.
Conclusions: Using the existing bedside information system and network architecture of our PICU, we implemented an ongoing high-fidelity prospectively collected electronic database, preventing the continuous loss of scientific information. This offers the opportunity to develop research on clinical decision support systems and computational models of cardiorespiratory physiology for example. (*Pediatr Crit Care Med* 2018; XX:00–00)
Key Words: critical care; databases, decision support systems; electronic health records; health level 7

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Drs. Brossier, El Taani, Sauthier, and Jouvet built the database. All authors gave input into the database development process and contributed to writing the article.
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Stimulated by massive technologic innovation, ICUs currently contain abundant high-performance bedside medical systems, such as cardiorespiratory monitors, pulse oximeters, mechanical ventilators, and infusion pumps (1–5). These systems provide physicians with clinical data, such as physiologic signals, pharmacotherapy, or therapeutic procedures, in order to establish the patient's therapeutic care plan (5, 6). Simultaneously, it became obvious to the scientific community that elaborating data gathering procedures was crucial, as a wide amount of data was lost rather than used to improve clinical research efficiency and data analysis (1–7). This data

INTRODUCTION

Stimulated by massive technologic innovation, ICUs currently contain abundant high-performance bedside medical systems, such as cardiorespiratory monitors, pulse oximeters, mechanical ventilators, and infusion pumps (1–5). These systems provide physicians with clinical data, such as physiologic signals, pharmacotherapy, or therapeutic procedures, in order to establish the patient's therapeutic care plan (5, 6). Simultaneously, it became obvious to the scientific community that elaborating data gathering procedures was crucial, as a wide amount of data was lost rather than used to improve clinical research efficiency and data analysis (1-7). This data collection gives rise to the concept of biomedical signal databases. Subsequently, electronic medical devices surrounding critically ill patients expanded and theses biomedical signals can now be timely linked to clinical, radiologic, laboratory, and pharmaceutical data (8–16). At the same time, several researchers have developed virtual patients, or computational models, attempting to recreate a real patient's clinical course under several medical situations, particularly during mechanical ventilation and hemodynamic support (17, 18). Based on these models, ICU teams have conceived computerized clinical decision support systems (CDSSs) aiming to assist caregivers in the management of critically ill patients (19–21). In order to develop and validate both virtual patient and CDSS in critical care, databases that combine biomedical signals, therapeutics, and the clinical outcome following these treatments are necessary (13, 14, 17, 22). To be used in pediatric critical care, such database should include patients under 18 years old, be exhaustive including mechanical ventilation, hemodynamic support, clinical and therapeutics data, and collect data at a high frequency to capture changes in patient physiology. To our knowledge, none of the databases currently described in the literature meet these criteria in pediatric critical care (1, 7, 9, 10, 15, 23–27). Thus, our objective was to build such a database, combining patient therapeutics and clinical variables in time, using the information system and network architecture available through fully electronic

charting in the PICU of a university hospital. The purpose of this article is to describe the data acquisition process from bedside to a research electronic database.

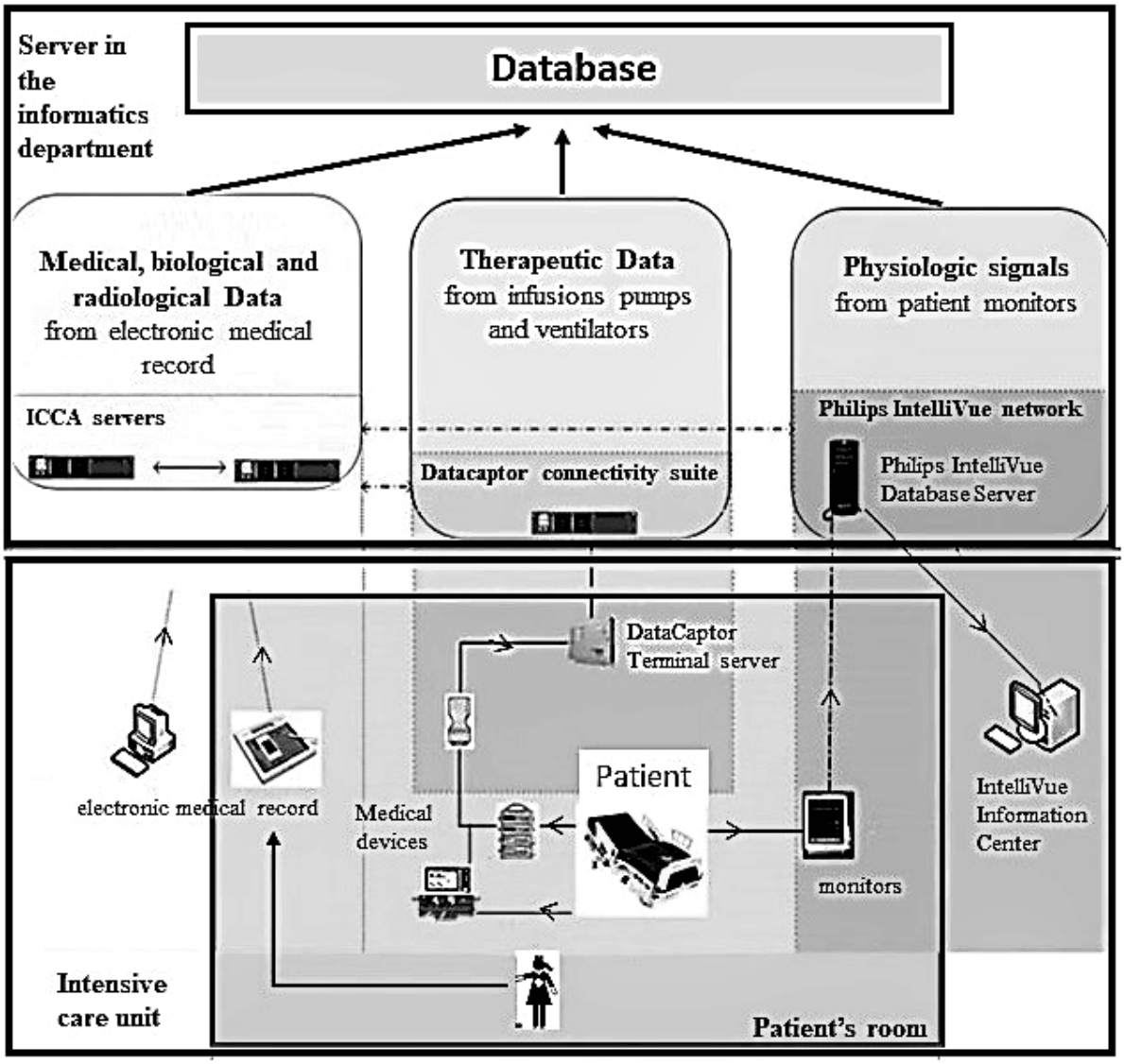
METHODS

This article describes the collection of a prospective database gathered in the PICU of Sainte Justine Hospital, a 24-bed PICU, medical ICU, surgical ICU, and cardiac ICU in a free-standing tertiary maternal child health center in Montreal, Canada. A fully electronic ICU-specific medical record (IntelliSpace Critical Care and Anesthesia [ICCA]; Koninklijke Philips Electronics, Amsterdam, The Netherlands) was implemented in the PICU in January 2013. We included all patients under 18 years old admitted to the PICU since May 21, 2015. From admission to discharge, all patients' demographic, physiologic, medical, and therapeutic data were prospectively collected.

Data Acquisition

Four types of data are collected in our database from medical devices available at the bedside (**Supplemental Fig. 1**): 1) physiologic signals or biomedical signals from patient monitors (i.e., heart rate, blood pressure, saturation); 2) respiratory and ventilator variables from the ventilator (e.g., Fio2, positive end-expiratory pressure, respiratory rate); 3) pharmacotherapy from the infusion pumps (e.g., drug name, dose, timing of drug administration); and 4) patient demographics and information from the electronic medical record (age, sex, weight, diagnosis, laboratory results). Patient monitors are IntelliVue MP60, MP70, and MX800 (Koninklijke Philips Electronics, the Netherlands). These monitors are designed for surveillance purposes; monitoring physiologic cardiorespiratory waveforms and values such as the electrocardiogram, invasive or noninvasive blood pressure, oxygen saturation, respiratory rate, and end-tidal Co2. The monitors' biomedical signals from each patient admitted to the unit are continuously transmitted in health level 7 (HL7), across the IntelliVue medical network to the IntelliVue Database Server (Koninklijke Philips Electronics, the Netherlands). The signals are then sent

to the corresponding patients' electronic medical record (ICCA; Koninklijke Philips Electronics), and the value is recorded. The nurse verifies the data every 5–60 minutes and modifies it if the data do not correspond to the subject (i.e. artefacts). The same signal is transmitted simultaneously to the research database every 5 seconds. Prior to being implemented in the research database, the signal, coded in HL7, must be translated into ordinary medical data, using the free software HL7 listener "Mirth Connect Server 3.1.0.7420" from Mirth (Quality Systems Inc., Irvine, CA) (**Supplemental Fig. 1)**.



Supplemental Fig 1: Global architecture

Data collected into the research database include the patient's specific identification number; all values and units of measure described above, and times these values occurred (**Fig. 1**).

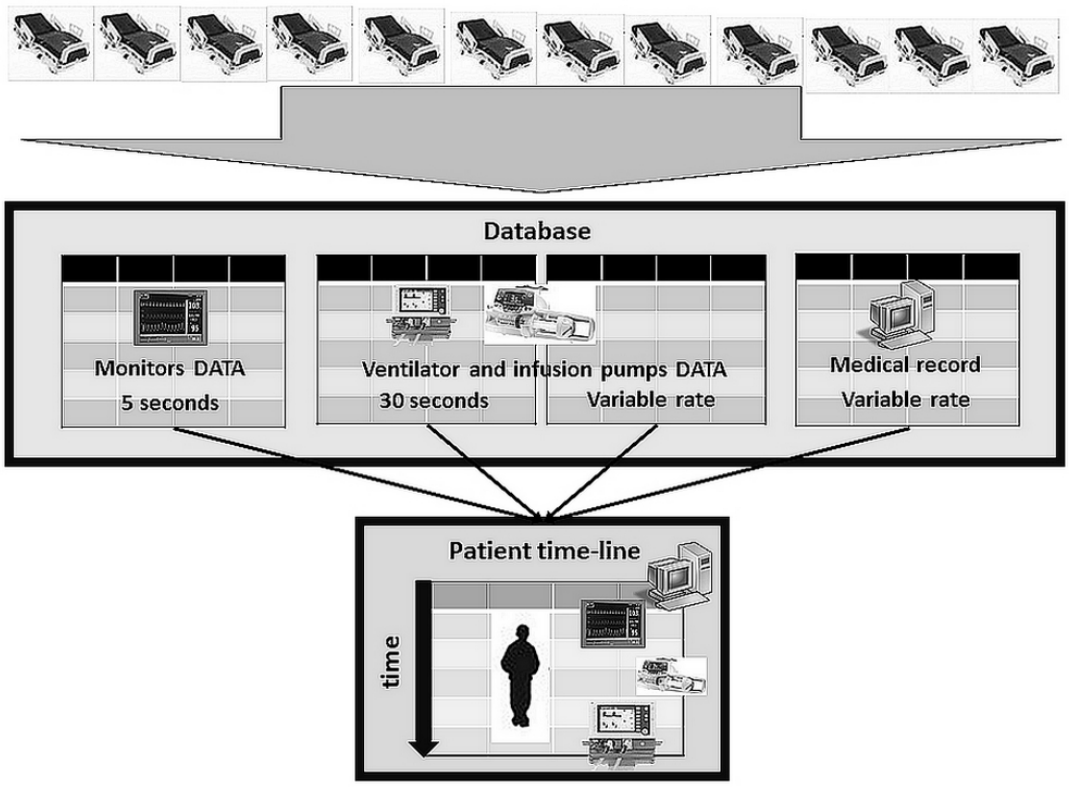


Fig 1. Data gathering process

In order to spare data storage space, a programmed cleaning process runs hourly to erase useless nonmedical entries automatically generated by the Mirth Connect Server 3.1.0.7420 while translating the HL7 signal. The ventilators used in the unit and connected to the server are Servo I (Maquet, Rastatt, Germany), and the infusion pumps are Infusomat (B. Braun Medical, Melsungen, Germany). The ventilator settings and the physiologic measurements available on the ventilator are transmitted to the Datacaptor connectivity suite (Capsule Technologie, Andover, MA) through the Datacaptor terminal server (Capsule Technologie) to the patient's electronic medical record ICCA (Koninklijke Philips Electronics). For research purposes, these data are captured from the Datacaptor terminal server (Capsule Technologie) using periodic-programmed Structured Query Language requests and stored every 30 seconds in a specific table in the research database based on Microsoft Server 2008 (Microsoft, Redmond, WA). The type of medication and its concentration and infusion flow rate are transmitted to the electronic medical record ICCA (Koninklijke Philips Electronics) and the research database using the

same process as described for ventilators. The medication data are gathered in two separate tables depending on the type of medication administration, either continuous or intermittent (IV push medication). The infusions data are stored every 30 seconds, whereas IV push medications are stored by nurses in the electronic medical record at the time of administration. The research database is also linked to the electronic medical record ICCA (Koninklijke Philips Electronics), in order to retrieve medical data, including, push and oral medication, diagnosis, and laboratory test results.

Database Organization and Data Extraction

Prior to being stored, all data are coded and organized in three tables (Fig. 1). To facilitate database use and query, research valuable data are extracted from the tables and summarized into a single time-organized table. Depending on the research purposes, data can be extracted and organized in a single patient timeline. This ad vitam æternam reusable full set of data variables constitutes what we define as the perpetual patient (17).

Practical Considerations

The servers dedicated to the database are physically located in the informatics department of the Sainte Justine Hospital with restricted access to guarantee data security. The database and the workstation maintenance are overseen by the applied clinical research unit of the hospital.

Ethics

The study and the database construction were approved by the institutional review board of Sainte Justine Hospital (number 4061) with a waiver of consent but an opt-out option. The exploitation of the database is regulated by a database policy validated by the institutional review board, and no patient identifiers (name, health insurance number) are stored in the database.

Trouble Shooting

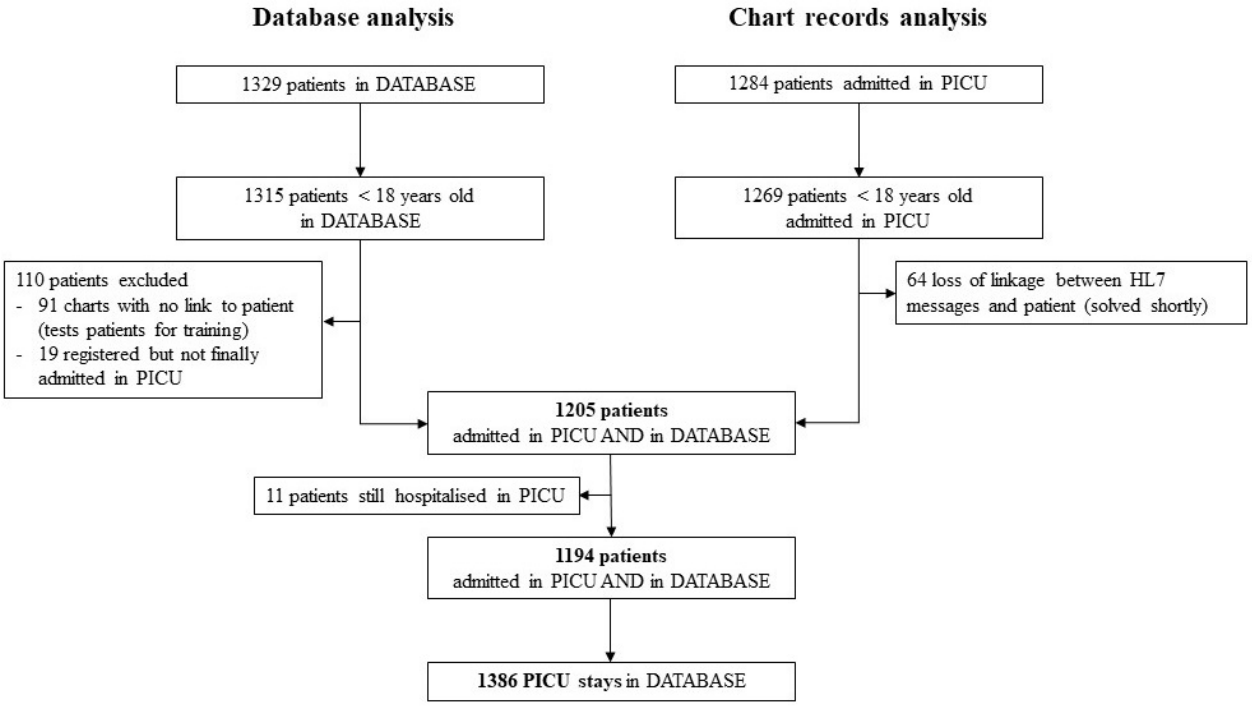
To limit the inconvenience on daily medical practice, each step of the process had to be closely checked and prepared, justifying the involvement of caregivers' staff, IT specialist, and manufacturer. Despite this preparation phase, we dealt with technical issues, including synchronization among therapeutic and surveillance devices during the first 3 months of the project. Other than cost and storage capacity, a major setback was the interference between concurrent data collection and data input into medical chart. This could have potentially compromised patient care in the unit, as the database system and the patients' electronic medical record (ICCA; Koninklijke Philips Electronics) run through the same network. This interference was limited to a slight slowdown of the medical record system and an impairment of the blood test results retrieving process into the medical record. We do not believe that there was any consequence on patient care and safety, as access to the laboratory server was not altered. This issue was solved in the 3 first months.

Validation Procedures

Once the data gathering process was running properly, the validation procedure was performed to control the accuracy of the data and to ensure the appropriateness of the gathering process. The objective validation procedure is to settle data accuracy and synchronization. It combined several phases performed at the bedside, including video recording. The validation phases are currently being conducted prospectively within the PICU. During this time, patients' data collected in the database are compared to data simultaneously displayed on monitoring and therapeutic devices available at bedside.

RESULTS

Between May 21, 2015, and December 31, 2016, 1,386 PICU stays were recorded in the research database from 1,194 patients (**Supplemental Fig. 2)**



Supplemental Fig. 2: Flowchart

The research database contained one table of 135,224,902 entries (five data sets/entry, a dataset is composed of the storage time, the data description, and its point estimate) from the physiologic signal monitors with an average of 487,820 physiologic data sets/PICU stay and two tables of 408,131,514 and 16,131,718 entries (one dataset/ entry) from the ventilators and infusion pumps for a total volume of 241 GB (approximately 150 GB/yr). Patients' characteristics at admission to the PICU are depicted in Table 1. PICU stays were divided into 870 medical (63%), 463 non-trauma surgical (33%), and 53 trauma (4%) admissions. A wide spectrum of diagnoses was represented (**Table 1**).

Table1: Demographic data and disease categories of stays included in the database

Demographic data	**n PICU stays = 1,386**
Age (years), median [IQR]	2.0 [0.0 – 9.0]
Weight (Kg), median [IQR]	12.7 [6.2 – 27.0]
Length of stay (hours), median [IQR]	51.0 [26.0 – 103.0]
Dead, n (%)	52 (3.8%)
Main diagnostic category at admission, n (%)	
Pulmonary	360 (26.0%)
Post-surgical care	261 (18.8%)
Post-cardiac surgery care	202 (14.6%)
Neurologic	150 (10.8%)
Cardiac	107 (7.7%)
Infectious	58 (4.2%)
Traumatic / Burn	53 (3.8%)
Intoxication	49 (3.5%)
Otorhinolaryngology	39 (2.8%)
Metabolic / hydroelectrolytic	34 (2.5%)
Hematologic / non cerebral tumor	28 (2.0%)
Renal and liver grafts	21 (1.5%)
Liver and gastrointestinal causes	14 (1.0%)
Renal	10 (0.7%)

IQR: Interquartile Range

The research database gathered abundant physiologic, respiratory, therapeutic, and clinical information (**Supplemental Table 1**). In particular, ventilation data were automatically collected for every ventilated patient to a maximum of 25 ventilator-setting items and 22 ventilator-related surveillance items every 30 seconds, depending on the type and mode of ventilatory support (**Table 2**). With regard to medication, we successfully collected data on infusion medications, their concentration, and rate for all admissions (**Supplemental Table 1**). The data collection permitted the reconstruction of included patient's entire critical care admission course: patient timeline (**Fig. 2**).

Supplemental Table 1: Example of therapeutic information collected at the same time as the physiologic parameters

Therapeutic Data	**n patients = 1,194**
Ventilator support	
High Flow oxygen, n (%)	336 (28.1%)
Recorded duration (hr)	30477
Noninvasive ventilation, n (%)	295 (24.7%)
Recorded duration (hr)	29140
Invasive ventilation, n (%)	511 (42.8%)
Recorded duration (hr)	77678
Inotropic and vasoactive medication order[1]	
Epinephrine, n (%)	303 (25.4%)
Dobutamine, n (%)	22 (1.8%)
Milrinone, n (%)	195 (16.3%)
Levosimendan, n (%)	9 (0.8%)
Dopamine, n (%)	92 (7.7%)
Norepinephrine, n (%)	98 (8.2%)
Isoproterenol, n (%)	19 (1.6%)
Sedative and analgesic treatment order (continuous and discontinuous)[1]	
Midazolam, n (%)	375 (31.4%)
Lorazepam, n (%)	410 (34.3%)
Dexmedetomidine, n (%)	273 (22.9%)
Propofol, n (%)	195 (16.3%)
Ketamine, n (%)	439 (36.8%)
Morphine, n (%)	777 (65.1%)
Hydromorphone, n (%)	111 (9.3%)
Fentanyl, n (%)	578 (48.4%)
Sufentanil, n (%)	10 (0.8%)
Remifentanil, n (%)	4 (0.3%)

1. Ordered treatment, not necessarily administered

The preliminary data on validation of the database demonstrated an accurate capture of monitoring signals (28). Following this validation phase, we ensured that the data time stamp was always the same (i.e., data server time). However, we have huge amount of data on infusion pumps and ventilator variables and therefore the validation process is still ongoing. This database is currently used in several concomitant research studies including the development and validation of the automated pediatric logistic organ dysfunction (PELOD) 2 score (29), real-time diagnosis of cerebral status following traumatic brain injury (30), automatic real-time hypoxemia in pediatric acute respiratory distress syndrome monitoring (31), and detection of ventilator-associated events (32), for example.

Table 2: Major items in the database

Class of Data	Description	Acquisition Frequency
Physiologic	Respiratory data	
	- From monitors (pulse oximetry, respiratory rate, end-tidal Co_2)	Every 5 s
	- From respirators (measured variables minute ventilation, tidal volume, airway pressure, etc.)	Every 30 s
	- From medical record (nurse-verified vital signs)	By request/hourly
	Hemodynamic data	
	- From monitors (heart rate, arterial pressure, venous pressure, atrial pressure, pulse, etc.)	Every 5 s
	- Pulse contour cardiac output (Pulsion medical systems, Germany) technology data	
	- From medical record (nurse-verified vital signs, diuresis, chest drains, etc.)	By request/hourly
	Neurologic data	
	- From monitors (intracranial pressure, cerebral perfusion pressure, partial pressure of brain tissue O_2)	Every 5 s
	- From medical record (nurse-verified vital signs, Glasgow score, pupil, etc.)	By request/hourly
	Other data	
	- From monitors (temperature, etc.)	Every 5 s
	- From medical record (nurse-verified vital signs, pain evaluation, temperature, etc.)	By request/hourly
Supportive care	Respiratory support	
	- From respirators (ventilatory settings: respiratory rate, tidal volume, expiratory and inspiratory pressure, etc.)	Every 30 s
	- From medical record (inhalotherapist-verified settings)	By request/hourly
	Other support	
	- From medical record (nurse-verified settings, dialysis, extracorporeal circulation, etc.)	By request/hourly
Therapeutic data	Continuous infusion	
	- From infusion pumps (INN, concentration, infusion rate)	Every 30 s
	Discontinuous infusion	
	- From infusion pumps (INN, concentration, infusion rate)	At acquisition
	Intermittent medication	
	- From medical record (nurse-verified administration, INN, dose)	By request/at acquisition
Other medical data	Descriptive data	
	- From medical record (age, date of admission and discharge, admission and discharge condition, etc.)	By request/at acquisition
	Clinical data	
	- From medical record (diagnosis, medical history, intervention, catheters, tubes, etc.)	By request/at acquisition
	Laboratory tests	
	- From medical record (blood, urinary, microbiology tests, etc.)	By request/at acquisition

INN = international nonproprietary names.

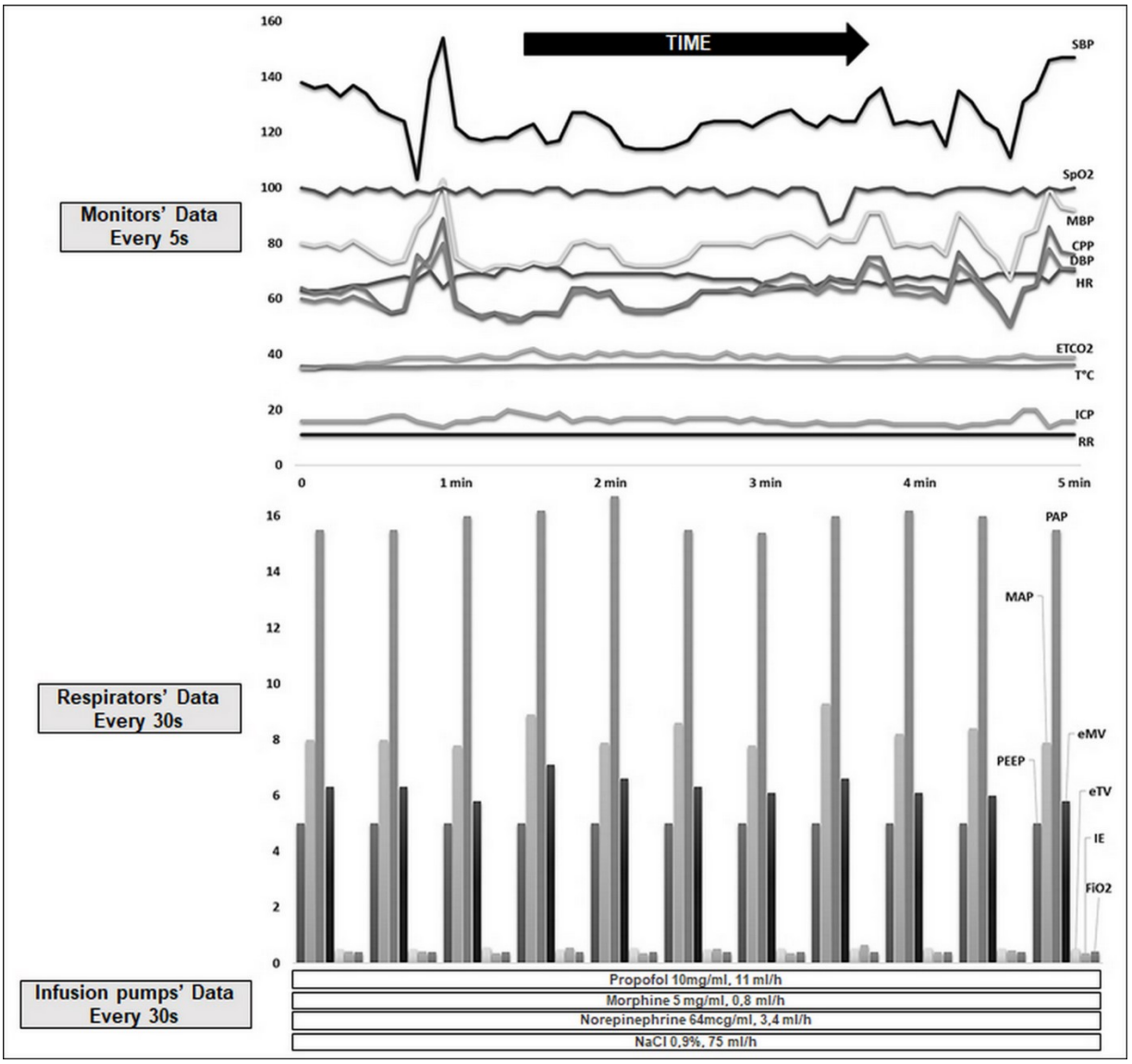


Fig. 2: Patient timeline

DISCUSSION

Using the bedside information systems and network architecture already available in the PICU of Sainte Justine Hospital, we successfully prospectively collected a large amount of high-frequency and time-organized clinical data into a comprehensive database. Our research database responds to the successful characteristics by Pryor et al (33), which are multidisciplinary team, stable funding, focused goals, data collection, design tied to a particular database focus and function, and relevant leadership. Informatics improvements and the expansion of electronic medical records have empowered data gathering process at the bedside.

Currently, several systems of data gathering are described in the literature (2), both in critical care (8, 10, 15, 25–27) and in other medical fields (4, 12, 34, 35), but few with such a high rate of storage and high amount of data (9, 25–27).

Table 3: PICU databases and physiologic acquisition systems

Name Characteristics	Medical Information Mart for Intensive Care	Pediatric Intensive Care Audit Network	Complex System Lab	VPS	Tracking, Trajectory, and Triggering Tool System	Sainte Justine PICU Database
Year of implementation	2001 (1996)	2001	2003	2005 (1997)	2013	2015
Country	United States	United Kingdom and Ireland republic	United States	United States and Canada	United States	Canada
No. of participating centers	1	34	1	135	1	1
Type of ICU	Neonate ICU	Pediatric (including cardiac) Transport teams	Pediatric (including cardiac)	Pediatric (VPS PICU) Cardiac (VPS cardiac) Neonate (VPS neonatal ICU)	Pediatric Cardiac	Pediatric (including cardiac)
Type of patients	0–1 mo	0–16 yr old > 16 yr old	0–18 yr old	0–18 yr old	0–18 yr old	0–18 yr old
No. of patients	From 2001 to 2008 7,870	From 2013 to 2015 61,146	170	Ongoing acquisition > 1,300,000	Ongoing acquisition Unknown > 10,000,000 hr	Ongoing acquisition 1,194
Type of data	Demographic Physiologic Therapeutic Laboratory test Imaging reports Interventions	Demographics Clinical Interventions Severity scores	Mainly physiologic	Demographics Diagnosis Interventions Severity scores	Physiologic Respiratory Demographics Diagnosis	Physiologic Supportive care Therapeutic Demographics Diagnosis/ clinical Interventions
Acquisition length	From admission to discharge					
Acquisition frequencies	High frequency (0.0003 Hz)	Low frequency	Very high frequency (1–500 Hz)	Low frequency	Very high frequency (0.2 Hz)	Very high frequency (0.03–0.2 Hz)
Database purposes	To support epidemiologic, physiologic, and biosignal analysis research and industrial innovation To improve quality of pediatric critical care	To compare outcomes and activities between PICU	To support biosignal analysis research	To compare outcomes and activities between PICU To improve quality of pediatric critical care	To support epidemiologic and physiologic research and industrial innovation To improve quality of pediatric critical care	To support epidemiologic and physiologic research and industrial innovation To improve quality of pediatric critical care

VPS = virtual pediatric systems.

The database's "gold standard" is undoubtedly the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) database implemented in the ICUs of the Boston's Beth Israel Hospital in 1996 (32). This database have evolved and flourished throughout the past 20 years (1, 7, 36–38) from its first version in the late 90s to its current third version, described in 2016 (15). In its latest version (MIMIC III), freely available after the researcher completed a recognized course in protecting human research participants and signed a data use agreement, the MIMIC database gathered data from 38,597 patients above 16 years old admitted to the ICU between 2001 and 2012, and from 7,870 neonates admitted from 2001 to 2008. The MIMIC database addresses many questions surrounding not only data gathering but also data sharing (36, 37) in the field of critical care. The MIMIC database, however, as numerous other high- and low-rate storage databases (2, 10, 15, 38, 39), has failed to include pediatric patients from 28 days old to 16 years old. Indeed, only a few databases described in the past 10 years include all types of admissions in PICU with this high-rate data collection (**Table 3**) and, to our knowledge, none of them integrate the variety of data we describe (**Tables 2 and 3**). The currently available database described in the literature more exhaustive than ours in terms of demographic and medical data is the Virtual Pediatric System (VPS), LLC, an online pediatric critical care network implemented in 2005 and accessible online since 2009. It was built in 2005 on the previously described Virtual PICU (implemented in 1997) (40) along with the partnership of the National Outcomes Center, the National Association of Children's Hospitals and Related Institutions, and the Children's Hospital Los Angeles. The VPS database is a prospective observational cohort of more than one million consecutive admissions from 135 PICUs around the United States and Canada. Its main objective was to develop a web-based database with prospective data collection, aiming to provide information on PICU practices and patients outcomes (41), with no or few biomedical signals, ventilator settings, or medication data. With regard to biomedical signals and high rate data acquisition, the previously available database

gathering system in PICU was described in 2003 by Goldstein et al (9) and implemented at Doernbecher Children's Hospital, Oregon Health and Science University. In their publication, Goldstein et al (9) described about 170 pediatric patients where the main admission diagnosis was brain injury. The database by Goldstein et al (9) was mainly a physiologic signal and waveform database with a high-frequency recording rate (from 1 to 500 vs 0.2 to 0.03 Hz). Finally, the only database presently comparable to ours is the trending, tracking, and triggering system (T3) (Etiometry, Boston, MA) (25–27). T3 is a Food and Drug Administration–approved system, implemented in the PICU and cardiac PICU of the Boston Children's Hospital (United States) in 2013 and the Hospital for Sick Children (Canada, 2015) which authorizes collection, storage, and display of organized data at the bedside in near-real time, providing physicians with crucial clinical information and a research database. The T3 system is based on the same architecture as ours, the IntelliVue medical network, and collects physiologic data from monitors and respiratory settings from respirators at a 5-second frequency (25). Other clinical, laboratory, and demographic data are manually collected from patients' chart without collection on medication and other therapeutics. Depending on database purposes, collected data and recording rates will vary. When studying physiologic signals and variability, a high recording and acquisition rate is necessary, in contrast to epidemiologic studies where the number of variables matters most (33). Technologic improvement has progressively challenged researchers to deal with both storage and cost problems (14). Data storage capacity has increased throughout the years, for a limited incremental cost increase (14). The future scope of research with high-frequency database is undeniable. The main purpose of this database is to provide our research group with a large, high-quality, multimodal dataset. In the future, the dataset will help us develop, validate, and model virtual patients in cardiorespiratory physiology (17, 18) as well as CDSS's and data-driven learning systems (42) prior to applying them in PICU daily practice (19, 20, 25, 27, 43, 44). It has already served to construct physiologic

predictive models that will soon be published and might serve for future epidemiologic studies, registry-based randomized controlled trial (24). Indeed, this type of database will simplify screening of patients and data of interest, and complete case report forms automatically, thus saving time and cost while insuring completeness (24, 39). Combining data from biomedical signals, ventilatory support and timed IV medication might be of great interest to conduct physiology studies, ventilator to patient interactions, or pharmacodynamics studies. Furthermore, due to the large amount of collected data, these databases, once linked to specific software, could be useful for data mining; a knowledge discovery process while exploring the database (22). By providing diagnostic and therapeutic tools while improving research efficiency and cost, this database could potentially enhance patient care and safety. Our database has several limitations. First, data reliability is critical in this kind of data storage. High-frequency database validation procedures are not well established in literature. Despite the ability to compare database samples to patient medical records (45), a data extraction system to validate the reliability of data gathering over time is still necessary. Data gathering and organization are crucial, as important clinical information can be lost from ICU monitoring devices (2, 39). Validation procedures were often not included or insufficiently considered in numerous databases' description (9, 24, 46). To ensure data reliability, accuracy, and synchronization to future users of the database, we are currently completing the validation procedures. Based on other high-quality database validation procedures available in literature (10, 45, 47, 48), we have elaborated a human resource prospective validation procedure. We are using videotaped data displayed at the bedside, and comparing it to simultaneously collected data stored in our database. This validation procedure includes several phases aiming to validate the four types of data acquisition and should be completed shortly. Second, as noted on the flowchart (**Supplemental Fig. 2**), the data of 64 patients (5%) are not accessible. This loss of patients is assumed to be at random but could lead to selection bias in future studies. Those

patients were recorded in the database, but due to a loss of linkage between some of the HL7 messages and the corresponding patient number when encoded in the database, those patients are not retrieved by general query, as they were not properly coded. To address this, we are currently conceiving a retrieving software, able to relink HL7 messages to the corresponding patients. Third, the database can only be queried by a restricted number of personnel familiar with it conception and design. Based on the MIMIC published experience, the next step would be the creation of an interactive and user-friendly data query tool, helping researchers and clinicians with limited computer abilities to use and explore the research database. Fourth, despite our high-frequency data acquisition, studies on physiologic variability may still be limited and require even higher data acquisition frequency. Finally, this database, as many other ones, is single center limiting its generalizability. However, after standardization of the data (49, 50) and subsequent knowledge translation, we expect this data gathering process to be active in other PICUs with similar networks for further data expansion. Long-term, this research database is a valuable tool with the potential for data mining synchronized into a unique multicenter critical care database (24).

CONCLUSION

Using the bedside information systems and network architecture already available in the PICU of Sainte Justine Hospital, we successfully collected a large electronic clinical database that is time organized and reusable, developing the new concept of the perpetual patient. The main objective of this database will be to validate computational models and CDSSs. Although there are several steps to perform before this research database becomes a valid worldwide user-friendly research tool, we hope this database may be of great interest in the field of pediatric intensive care research.

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C. Discussion

La force de ce travail réside dans le fait d'avoir rendu accessible à la communauté médicale un processus de collecte de données applicable au lit du malade à partir de l'architecture informatique déjà implémentée dans un service de réanimation. En proposant une description complète et détaillée du processus de collecte, nous le rendons évaluable, critiquable mais aussi reproductible.

Ce travail soulève la question suivante : est-ce que constituer une base de données relève de la recherche ? Cette question entendue à quelques reprises durant la réalisation de ce PhD, a été posée par R. Wetzel, créateur de la base VPS (158), en ces termes : « *this article is not research in the classical sense […]. One then may ask : what use is it ? »* (131).

Tout en posant la question dans son éditorial « First get the data, then do the science » qui introduit notre article, R. Wetzel apporte la réponse (annexe E) :

« *This article is not research in the classical sense that it presents new information that will directly guide care.[…] The meticulous description of a prospective, premeditated, nontrivial system to capture data for multiple purposes from the care process, without impeding care, is the value of this article.[…] Prospectively collected pediatric critical care data have been useful for hypothesis testing, quality improvement, and better understanding our care process.[…]. The automated collection of these clinical data, melded with further clinical data, will have an even greater impact on our understanding of critical illness in children* ».

Si la constitution d'une base de données haute résolution automatiquement collectée n'est pas de la recherche au sens classique du terme, elle doit être considérée comme telle car elle en stimule la réalisation (131). En effet, il existe aujourd'hui de nombreux exemples d'études et de publications qui n'auraient pu être réalisées sans la collecte préalable d'une base de données haute qualité (66,127,149–151,165–170).

En juin 2019, après 4 ans d'exploitation, la base de données de soins intensifs du CHU Sainte Justine contenait les données de 3303 patients pour 4207 admissions, pour un total de 606031 heures d'enregistrement et 2284 GO de données. L'évolution de la base a permis d'augmenter le rythme de recueil des données à toutes les secondes et aussi de sauvegarder l'intégralité des signaux physiologiques. Actuellement, le volume de données de la base est pris à 65% par les courbes et signaux physiologiques, 31% par des données numériques de monitorage physiologique recueillies à chaque seconde, 4% par des données recueillies toutes les 30 secondes depuis les respirateurs, les pousses seringues et les moniteurs. Les alarmes sont aussi enregistrées mais représentent un volume de données encore négligeable de l'ordre de 0.05%. A ces volumes s'ajoutent ceux pris par les index, qui correspondent à des listes structurées de données facilitant la recherche d'informations dans la base.

Ce travail présente plusieurs faiblesses. Tout d'abord, l'applicabilité externe de notre méthode de collecte est limitée. Bien que très détaillée dans l'article, cette méthode de collecte requiert tout de même l'implication locale d'une équipe multidisciplinaire conséquente comprenant notamment des personnes compétentes dans le domaine de l'informatique médicale et de la gestion de base de données. Par ailleurs, elle suppose l'implémentation préalable dans le service concerné d'un dossier patient informatisé, ce qui n'est pas encore un standard de pratique en Europe. En effet, la principale faiblesse de ce processus de collecte réside dans sa dépendance au dossier patient informatisé tant sur l'utilisation de l'architecture informatique et réseau que sur le lien avec la base de données interne du dossier patient.

L'absence de validation du processus de collecte et des données collectées représentait au moment de la publication de l'article une autre faiblesse. Toutefois, des étapes de validations en cours de réalisation y avaient été mentionnées. Ses étapes ont été secondairement réalisées et seront détaillées dans les articles 3 et 4 (64,65).

Enfin, l'absence d'issues cliniques dans les résultats de l'article a été considérée par certains reviewers comme une insuffisance du travail. Toutefois, les objectifs de cet article relevaient plus du domaine technique que clinique et l'intégration de plus de données cliniques, que celles déjà présentées, aurait possiblement eu comme conséquence de diluer le message sans ajouter de valeur au propos.

ARTICLE III : QUALITATIVE SUBJECTIVE ASSESSMENT OF A HIGH RESOLUTION DATABASE IN A PEDIATRIC INTENSIVE CARE UNIT – ELABORATING THE PERPETUAL PATIENT'S ID CARD

A. Présentation

Avant de pouvoir utiliser la base de données à des fins de recherche, il est nécessaire d'étudier et d'évaluer sa qualité. L'évaluation de la qualité d'une base de données va se faire à plusieurs niveaux (62,63,160,162,171–173). Il est raisonnable de schématiquement représenter ces différents niveaux de la façon suivante (Fig. 7 : Etapes d'évaluation de la qualité d'une base de données

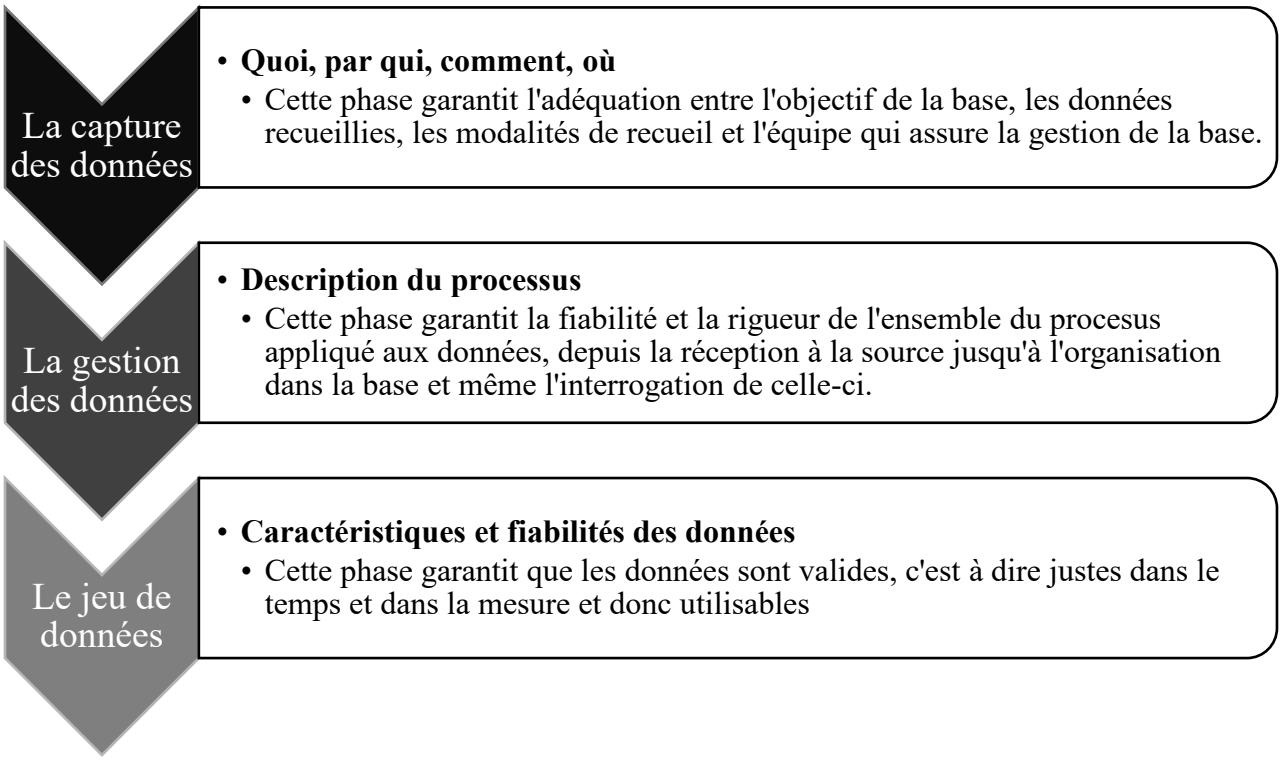

Fig. 7 : Etapes d'évaluation de la qualité d'une base de données

Ce premier travail de validation ne cherchait pas à évaluer la validité et la fiabilité des données mais à évaluer la qualité de la base de données dans son ensemble et fournir à des futurs utilisateurs une description de ses caractéristiques.

Pour réaliser ce travail, nous nous sommes basés sur la méthodologie décrite par Stow et al. (116) dans leur publication de 2006 dont l'objectif était de présenter et d'évaluer la qualité

de la « ANZICS Adult Patient Database », base de données de patients adultes de la société de soins intensifs d'Australie et de Nouvelle-Zélande. Nous avons donc choisi d'utiliser les recommandations éditées en 2003 par le Directory of Clinical Audit Databases (DoCDat) (162) dont l'un des objectifs était de standardiser une méthode d'évaluation de la qualité des bases de données, permettant par la suite de comparer les bases de données entre elles (116,174). Toutefois, la simple description de notre base de données à partir des critères définis par le DoCDat nous a semblé insuffisante. Nous avons donc eu recours au modèle proposé en 2015 par Kahn et al.(62) pour retranscrire avec des critères plus robustes et de façon plus objective l'évaluation de la qualité de notre base de données.

B. Article

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BRIEF REPORT

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Qualitative subjective assessment of a high-resolution database in a paediatric intensive care unit—Elaborating the perpetual patient's ID card

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Abstract

Objective: The main purpose of our study was to subjectively assess the quality of a paediatric intensive care unit (PICU) database according to the Directory of Clinical Databases (DoCDat) criteria.

Design and setting: A survey was conducted between April 1 and June 15, 2018, among the Sainte Justine PICU research group.

Population: Every member of this group whose research activity required the use of the database and/or who was involved in the development/validation of the database.

Interventions: None.

Measurements and main results: All 10 research team members (one Information Technology specialist, one junior medical student, and eight clinician researchers) who used the high-resolution database fulfilled the survey (100% response rate). The median quality level of the Sainte Justine PICU database across all the 10 criteria was 3 (2-4), rated on a 1 (worst) to 4 (best) numeric scale. When compared with previously assessed databases through the DoCDat criteria, we found that the Sainte Justine PICU database performance was similar.

Conclusions: The PICU high-resolution database appeared of good quality when subjectively assessed by the DoCDat criteria. Further validation procedures are mandatory. We suggest that data quality assessment and validation procedures should be reported when creating a new database.

KEYWORDS

database, DoCDat, quality assessment

1 | INTRODUCTION

Over the last two decades, numerous health care electronic databases were created, especially in intensive care units (ICUs).[1-3] Among these databases, high-frequency electronic databases (data collection rate > 1 per min) were developed using the existing bedside information systems and hospital network architecture to automatically collect and store the data.[1,3,4] Our team recently published the descriptive report

This study was performed at the CHU Sainte Justine, Montreal, Canada.

INTRODUCTION

Over the last two decades, numerous health care electronic databases were created, especially in intensive care units (ICUs) (1-3). Among these databases, high frequency electronic databases (data collection rate > 1 per min) were developed using the existing bedside information systems and hospital network architecture to automatically collect and store the data (1, 3, 4). Our team recently published the descriptive report and analysis of a prospective automatically collected database in the pediatric ICU (PICU) i.e. PICU high resolution database (HRD) (1). Given the tremendous amount of data that are automatically collected, it is crucial that database quality is validated based on standardized and well-defined criteria before using the data for research purposes (5, 6). In 2003, the Directory of Clinical Databases (DoCDat) published guidelines to standardize the quality assessment of databases and stored data (7). These criteria assess database quality regarding three main categories: the ability of the database to represent the population that it intends to describe, the completeness of the collected data and the accuracy of the data gathered (2, 7). Several years later, the Data Quality Collaborative (DQC) edited data quality reporting guidelines (6, 8). These guidelines were elaborated in the context of electronic medical records (EMR) based database and research. The reports are recommended to be organized in four sections: data capture description, data processing descriptions, data elements characterization and analysis-specific data elements characterization. The main purpose of our study was to subjectively assess the quality of a PICU HRD according to the DoCDat criteria. The secondary objective was to compare the quality assessment results to the median levels of performance of previously assessed databases. As a third objective, the assessment results of this study helped the HRD designers completing the DQC report table and thus providing a more comprehensive description of this database.

METHODS

A survey was conducted between April 1st and June 15th 2018, among the Sainte-Justine PICU research group. This study was approved by the Sainte-Justine University hospital ethical Committee (number 2016-1210, 4061) as part of the Sainte-Justine PICU database validation process.

All individuals who developed or used the Sainte-Justine PICU HRD were included and completed a two-part survey. The first part was a qualitative subjective assessment of the database using the DoCDat criteria (**fig 1**) (2, 7). The 10 criteria were rated on a 1 (worst) to 4 (best) numeric scale (**fig 1**). The second part of the survey consisted in a subjective assessment of the appropriateness of each DoCDat criterion with a 5-level Likert scale regarding assessment of high frequency electronic databases. The answers were anonymized before analysis.

The survey results regarding performance level of our database were compared to the available median levels of performance of all previously assessed databases for each DoCDat criteria, as previously described by Stow et al.(2) (**fig 1**). To perform this comparison, we used the median levels of performance provided in 2006 by Stow et al. (2). The databases included in this article (2) followed the DoCDat clinical databases inclusion criteria defined by Black et al (7). These criteria were as follow: gathered in the United Kingdom; providing individual level information on health care recipients; a scope defined by a common condition, intervention or facility at inclusion in the database; data from more than one health care provider. The main areas of the DoCDat included databases were general, cancer, surgical, congenital anomalies and traumatic and intensive care (9).

Continuous variables were expressed as medians (1st and 3rd quartiles).

Based on the survey results and on the previous description of the database gathering process (1), DQC data quality report was edited by the Sainte-Justine PICU HRD designers.

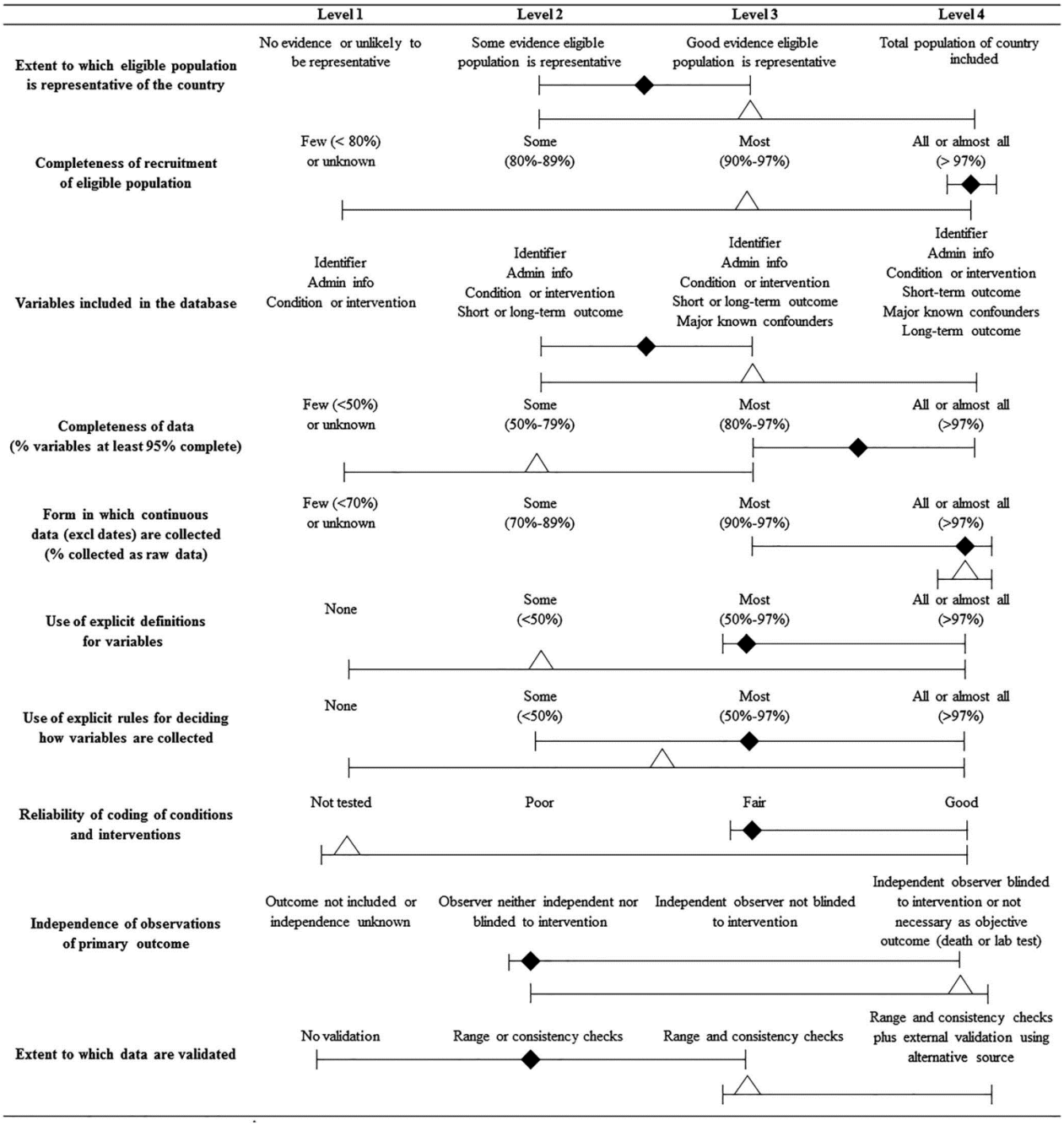

Fig. 1: Assessment of the Hospital Sainte Justine PICU database according to the Directory of Clinical Databases (DoCDat) criteria (adapted from Black and Payne (7))

Data are expressed as median (1st and 3rd quartiles).

◆ Survey results regarding performance level of the Sainte Justine PICU database.

△ Available median levels of performance of all previously assessed databases

RESULTS

All ten-research team members (100% response rate) who used the high-resolution database fulfilled the survey (one Information Technology (IT) specialist, one junior medical student and eight clinician researchers including two MD PhDs and five MD PhD candidates). Six were involved in the database design and four were database users only.

The median quality level across all of the 10 criteria was 3 [IQR: 2 - 4]. When compared with the median levels of previously reported database quality performance (2), the Sainte Justine PICU database seemed to perform better regarding 5 criteria, performed as well for 1, and worse for 4 (**fig 1**). The 10 criteria were considered appropriate by the responders regarding the assessment of a PICU HRD (**fig 2**).

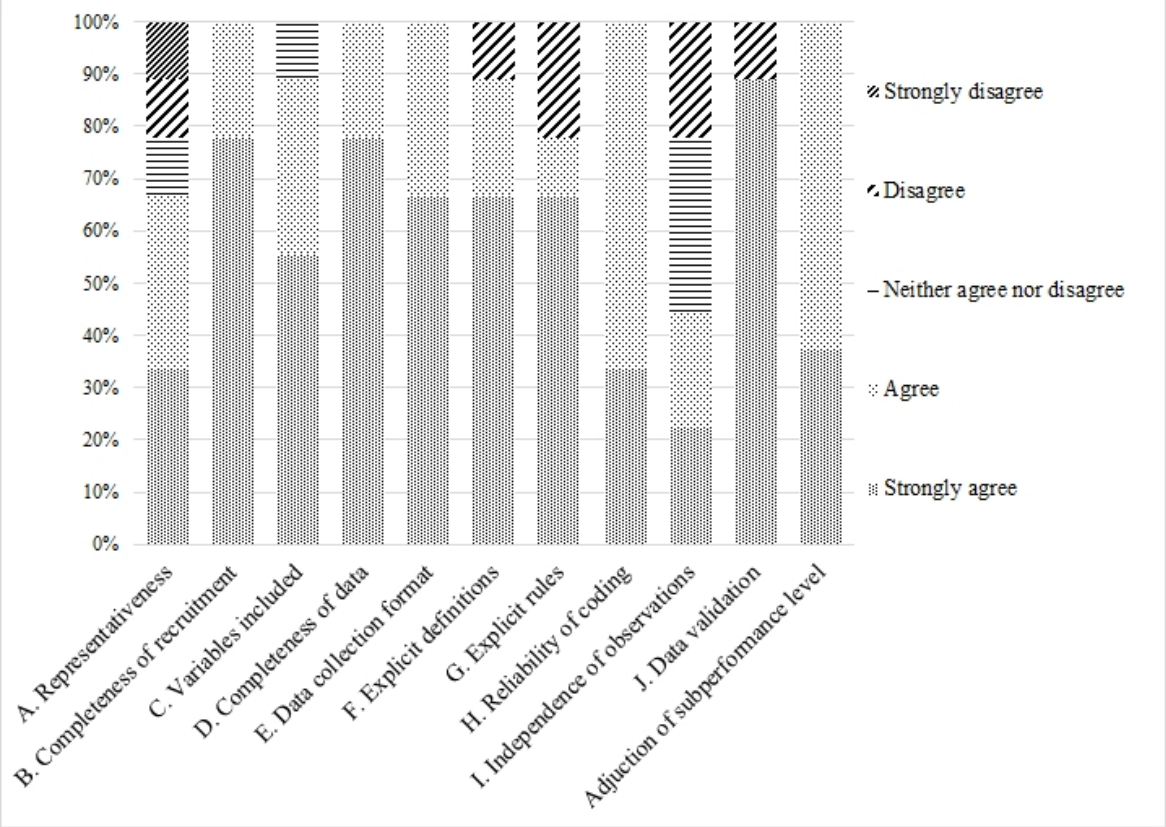

Fig. 2: Assessment of the appropriateness of the Directory of Clinical Databases criteria

The DQC data quality report was partially fulfilled (table 1) based on the database description (1) and survey results. Details on data validation rules (item 10, section data processing) and

data elements characterization were incomplete as the validation process is ongoing (10). Analysis and specific data quality documentation were not reported as not routinely performed.

Table 1 : Data quality documentation and reporting based (adapted on (6))

HSJ HRD : Hospital Sainte Justine High Resolution Database, EMR : Electronic Medical Record, HL7 : Health Language 7, PICU : Pediatric Intensive Care Unit, CDSS : Clinical Decision Support System, SQL : Structured Query Language, EAV : entity-attribute-value. NA: Not applicable.

Data capture	
1. Original data source	
1) Data Origin	Biomedical data collected in the HSJ HRD are collected from devices available at beside. Biomedical data from the devices come from two temporary servers: one storing the monitors data including 1 Hz data and raw signal (62-500 Hz) and the second from the other biomedical devices (infusion pumps, ventilator and other devices) between 0.2 and 0.03 Hz. No transformation occurs at this stage. The HSJ HRD is linked with the EMR database. Demographic, clinical, laboratory and treatment data come from the EMR without any transformation. In the EMR, data are collected from their original source: ADT [admission-discharge-transfer], medical and nursing notes and pharmacy.
2) Data capture method	High Frequency Automatic Collection is performed through HL7 protocol, SQL queries and direct entry from the caregivers
3) Original collection purpose	PICU / Research purpose, CDSS elaboration
2. Data steward information	
4) Data steward	Public University Hospital: Sainte Justine Hospital PICU Research Group.
5) Data set structure	Data are store in a SQL database. Biomedical data are stored on a flexible EAV structure with values being separated in numerical and textual data. A local ontology has been built on the keys from the different devices. Raw signals are stored by 5 seconds blocs of consecutive y-coordinates. In the EMR, most of the fields filled by clinicians are drop-down menus and presuggested lists, except for daily notes that are free text.

6) Data set definitions	The ontology used with the EAV has a description for each key. For example, a key could be “pulse rate - arterial line” and would be stored in a specific row along with the patient identifier, the datetime and up to two modifiers.
Data processing / Data provenance	
7) Data extraction specifications	Except for backup, there is no automatic extraction. All extractions are personalized. A graphical user interface to extract the data is currently tested.
8) Mappings from original to standardized values	Two small modifications are performed at the insertion: - The time zone is added to every datetime - Patient identification is verified with the bed identifier and the datetime of each data.
9) Data management organization	No alteration of the data is performed in the database. Some frequently grouped data (e.g. blood gases) are preidentified in a separate table. Other modifications are only performed after the data extraction. We stored frequent queries (SQL views) for patient lists or severity scores.
10) Data processing validation routines	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS
11) Audit trail	As no modification is performed on data, each user of the database is responsible for doing its own track change.
Data elements characterization	
12) Data format	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS Exact numerical values are stored.
13) Single element data descriptive statistics	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS
14) Temporal constraints	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS
15) Consistency	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS
Analysis-specific data quality documentation	
16) Data Cleansing/customization	Dataset comparison against raw data extracted from source. Sample validation. ONGOING PROCESS
Data quality checks of key variables:	
17) used for cohort identification	NA
18) used for outcome categorization	NA
19) used to classify exposure	NA
20) confounding variables	NA

DISCUSSION

A way of comparing available datasets, and reporting their quality would be of great interest. Several guidelines tend to guide data quality reporting. None has been especially elaborated to report data quality regarding high frequency electronic database (6, 11). Thus, we are left with using criteria developed for a former time (2, 7), for data collected in a lower volume and/or a lower velocity (6, 8). To perform this PICU HRD qualitative subjective assessment we choose to apply the DoCDat assessment method to a HRD derived from one ICU, in a new setting, different from any of the previous reports (2, 7). The DoCDat assessment method was historically created to compare national registries to each other (2, 7). Other methods have been proposed, such as the Hall et al. "checklist for investigators in database research" (12) and the Arts et al. "framework of procedures for the assurance of data quality in medical registries"(2, 13). The Hall et al. "checklist" provides more information to users but is complex, non-user friendly and seems inappropriate to compare databases quality performance between them as it's restricted to pharmacoepidemiology (12) . The Arts et al framework was elaborated to guide national multicenter registry builders at each steps of the data collection at the initiation of their registry. Very useful regarding registry creation, this framework appears inappropriate to described HRD in a reproductive and a more objective way (2, 13).

The quality assessment using DoCDat criteria of a PICU HRD combined to the EMR documented an overall good quality level. The eligible patient population was considered partially representative of the country but the recruitment was considered high. Indeed, this database includes data from every patient admitted in the largest PICU in Quebec but doesn't include data from the other PICUs in this province. The database is linked to the patients' PICU EMR so the collected variables included short-term outcomes until PICU discharge and some major confounders, but the database also gathered physiologic and biomedical signals. The completeness of the data collection was considered high and numerous data are collected as raw data directly from monitors, ventilators and infusion pumps. The use of explicit definitions

for variables, explicit rules for collection and the reliability of coding were considered as fair as most of the included data were directly collected from medical devices available at the bedside used in daily practice. This subjective qualitative assessment based on the DoCDat criteria appears of great interest. It depicts a global picture of the database to potential future users with information on the population studied, the data collected and data characteristics. However, given the actual DocDat criteria structure it is impossible to account for the type of clinical data gathered, thus sub criteria could be added to describe their nature. For example, each performance level could include a sub performance level 1 for not gathering any clinical data, 2 for gathering laboratory data only (hemoglobin, lactates, etc.), 3 for biometric data only (heart rate, blood pressure, etc.) and 4 for gathering both laboratory and clinical data. A database could then obtain a 2.2 or 3.4 level of quality performance on this criterion for example.

Besides, major biases must be considered as the people who designed and use the database performed the evaluation.

Based on the database description and this collaborative assessment, we could partially fulfill DQC data quality report. Thus, this report remains insufficient to guarantee the validity, the reproducibility, the reliability, the accuracy and the rightfulness of the dataset. Further independent data validation procedures should be performed (2, 6-8) and are currently ongoing on this specific database (10).

In our opinion, high frequency database creators around the world should gather to elaborate guidelines regarding high frequency automatically collected database quality assessment and dataset validation procedures to better understand the strengths and the weaknesses of the HRDs we are collecting.

CONCLUSION

Database quality assessment is rarely described. Nevertheless, data quality is crucial to ensure the scientific validity of conclusions drawn from that data analysis. We subjectively assessed

our previously reported PICU HRD with the DoCDat criteria and found that its quality was comparable to previously reported results.

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C. Discussion

Cette évaluation qualitative subjective est retranscrite en toute transparence et le plus objectivement possible à partir d'outils précédemment décrits. En appliquant les recommandations de Kahn et al. (62) pour retranscrire les résultats de l'enquête, nous avons tenté de faire référence à des critères plus solides d'évaluation de la qualité et de fournir un représentation plus objective de la base de données dans son ensemble (62). Ce rapport est basé sur deux des principales recommandations publiées dans le domaine de l'évaluation de la qualité des bases de données (62,162). Ces deux équipes ont publié de nombreux travaux afin d'exhorter les équipes de recherche médicale à tenir compte de la nécessité d'évaluer la qualité de leur données (61,63,125,171,174). Toutefois, dans le domaine des mégadonnées et des bases de données à haute résolution, nous sommes obligés de réaliser que très peu d'équipes considèrent la nécessité, sinon d'effectuer, au moins de décrire précisément ces procédures de validation (136,147,151). La force de ce travail est qu'il établit un précédent en termes de procédure de validation des bases de données haute résolution et offre la possibilité aux autres équipes de reproduire la démarche. Il favorise ainsi la comparaison des bases de données les unes avec les autres et une plus grande transparence sur les différents processus impliqués dans la collecte de certaines bases de données de même type (121,147). D'autres recommandations et méthodes d'évaluation de la qualité des données existent et, même si nous ne les avons pas retenues pour notre publication, certaines restent importantes à considérer dans notre démarche de validation (172,173). C'est le cas notamment du « framework of procedures for the assurance of data quality in medical registries» proposé par Arts et al.(173) qui a été élaboré après revue quasi-systématique de la littérature traitant de la qualité des données. Bien qu'il ait déjà été utilisé dans le domaine des soins intensifs (116), il ne nous a pas semblé répondre à nos considérations spécifiques en lien avec la haute fréquence de collection. Toutefois, l'analyse de

la littérature présentée dans cet article a permis de mieux définir le terme de « data quality » : « *the totality of features and characteristics of a data set, that bear on its ability to satisfy the needs that result from the intended use of the data* ». De plus, il a précisé quelles caractéristiques des données enregistrées étaient essentielles pour que celles-ci soient considérées comme valides et utilisables. Les attributs principaux étant l'exactitude (« accuracy ») et l'exhaustivité du recueil (« completeness »). Le premier terme étant défini comme la conformité entre la donnée enregistrée et la réalité, le second comme le fait que les données jugées pertinentes qui pouvaient être recueillies l'avaient été. Enfin, le dernier point essentiel souligné par cet article est la description du type d'erreurs altérant la qualité et donc la fiabilité du jeu de données. Il existe plusieurs façons de caractériser les erreurs, mais dans le cadre de notre travail de validation d'une base de données haute résolution nous retiendrons 2 principaux types d'erreurs : l'erreur systématique (se reproduit à chaque entrée dans la base de la variable considérée) et l'erreur aléatoire (survient de façon inopinée) (173,176).

Plusieurs faiblesses sont à considérer dans ce travail. Tout d'abord, en l'absence d'outil applicable aux bases de données hautes résolutions, il a été nécessaire d'avoir recours à des critères développés à une autre époque pour évaluer et comparer des bases de données au contenu différent et recueillies à un autre rythme (116,162). Par ailleurs, bien que comparées avec les mêmes outils, les bases de données ne l'ont pas été par les mêmes évaluateurs ni de la même manière. En effet, la DoCDat est un organisme qui a pu évaluer les bases de données au Royaume Unis de façon indépendante (162,174). A contrario, les évaluateurs de notre base de données étaient tous membres de l'équipe, voire même impliqués dans la conception de celle-ci. Ainsi, il est important de considérer, comme le souligne l'équipe de Stow et al. dans son étude de la base de données ANZICS, que notre évaluation est biaisée et possiblement trop optimiste (116) et en aucun cas suffisante pour garantir l'exactitude des données et

l’exhaustivité du recueil. A ce stade du travail, il est nécessaire de considérer une étape complémentaire visant à évaluer la qualité des données incluses dans la base.

ARTICLE IV: VALIDATION PROCESS OF A HIGH RESOLUTION DATABASE IN A PEDIATRIC INTENSIVE CARE UNIT – DESCRIBING THE PERPETUAL PATIENT'S VALIDATION

A. Présentation

Dans le cadre de l'évaluation de la qualité des données, il faut détailler 2 phases (173,177) :

1. La phase d'assurance de qualité ou d'assurance qualité (« Quality assurance ») qui correspond à l'ensemble des dispositifs mis en place en amont du recueil de données pour garantir sa fiabilité, son exhaustivité et son adéquation avec les objectifs de la base.
2. La phase de contrôle dont l'objectif est de dépister et corriger les éventuelles erreurs. Cette phase intervient soit de façon concomitante à la collecte de données soit après celle-ci.

La description et l'évaluation des processus impliqués dans la constitution de la base et présentés dans les 2 précédents articles relèvent de la phase d'assurance qualité. Afin de garantir aux utilisateurs de la base, ainsi qu'aux lecteurs des publications scientifiques qui en découlent, de la validité des données, nous avons réalisé un travail de contrôle des données (136). Nos hypothèses étaient que :

- toutes les données (100%) jugées pertinentes qui pouvaient être recueillies l'avaient été, répondant au critère d'exhaustivité.
- les valeurs des données enregistrées et les métadonnées (heures, identifiants) correspondantes, comparées aux valeurs des données réelles, étaient exactes et concordantes, répondant aux critères d'exactitude.

Plusieurs méthodes et exemples de processus de validation de données médicales sont décrits, notamment dans le cadre des données issues de dossiers médicaux informatisés, utilisées en recherche (136,160). Nous avons choisi, pour réaliser ce travail de contrôle de données, d'utiliser une méthode par validation externe (136,178). L'idée était de contrôler humainement et manuellement, à partir de chaque source de données et à différents moments, plusieurs échantillons de données considérés comme représentatifs de l'ensemble de la base (135,160).

Ainsi, nous avons étudié l'exhaustivité du recueil, l'exactitude et la cohérence des données ainsi que la robustesse du processus, c'est à dire sa capacité à rester fiable et stable dans le temps.

B. Article

Original article

Validation Process of a High-Resolution Database in a Pediatric Intensive Care Unit – Describing the Perpetual Patient's Validation

Running Head: Validation of a High-resolution Database

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Author Contributions

D.B, M.S. and P.J. built the database. A.M. performed data validation procedures. M.S. and D.B. performed statistical analysis. All authors gave input into the database development process and contributed to writing the paper.

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Abstract:

Objective: High data quality is essential to ensure the validity of clinical and research inferences based on it. However, these data quality assessments are often missing even though these data are used in daily practice and research. Our objective was to evaluate the data quality of our high-resolution electronic database (HRDB) implemented in our pediatric intensive care unit (PICU).

Design: A prospective validation study of a HRDB**.**

Setting: A 32-bed pediatric medical, surgical and cardiac PICU in a tertiary care freestanding maternal-child health center in Canada.

Population: All patients admitted to the PICU with at least one vital sign monitored using a cardiorespiratory monitor connected to the central monitoring station.

Interventions: None

Measurements and Main Results: Between June 2017 and August 2018, data from 295 patient days were recorded from medical devices and 4,645 data points were video recorded and compared to the corresponding data collected in the HRDB. Statistical analysis showed an excellent overall correlation (R^2=1), accuracy (100%), agreement (bias=0, limits of agreement=0), completeness (2% missing data) and reliability (ICC=1) between recorded and collected data within clinically significant pre-defined limits of agreement. Divergent points could all be explained.

Conclusions: This prospective validation of a representative sample showed an excellent overall data quality.

Key words: Pediatrics; Critical care; Database; Electronic Health Record; Big data

INTRODUCTION

Over the past two decades, technological and computer advances were used extensively to modernize medicine and assist medical teams in daily practice, as shown by the widespread use of electronic medical records (EMR) or connected biomedical devices. While the dedicated purpose in health care services is patient management, these systems have been perceived by many scientists as a way of improving clinical research efficiency and data analysis (1–4). As a result, many medical databases (DB) have been built since the beginning of the twenty-first century (4–6). To optimize our research quality in our different fields of expertise such as respiratory physiology and the development of clinical decision support systems (CDSS) (7), we implemented in 2015 an automated electronic data gathering process in our pediatric intensive care unit (PICU) (8). This DB was designed to develop and validate virtual or synthetic patients for cardiorespiratory physiology as well as for CDSS and data-driven learning systems (8). However, a validation step of the collected data is necessary before considering this DB suitable for research purposes (9–11). Indeed, the value of research findings depends on data quality (12,13). Several guidelines or frameworks were elaborated to evaluate and report the quality of DBs and national registries and to guide designers of DBs at each step of the data collection (12,14,15). These documents highlighted the need to evaluate data quality, to compare dataset quality performance between them and raised the question of data validity that every scientist or clinician, as data users, deal with whether in day-to-day clinical care decision-making or in medical research (16,17). However, none of these guidelines provide a detailed validation process that is entirely suitable for high resolution electronic DB (HRDB), defined as a database that collects more than one data point per minute per variable and per patient. Besides, to our knowledge, none of the HRDB published a detailed validation procedure and evaluation of the quality of the data (18–20). This article constitutes the final part of the validation process of our HRDB (8,11). The purpose of this study was to assess the quality of

the data include in our HRDB and to provide a generalizable validation method for all HRDB.

METHODS

This study was a prospective data quality assessment conducted in the PICU of Sainte-Justine hospital (Montreal, Canada), a pediatric 32-bed medical, surgical and cardiac ICU in a free-standing tertiary maternal-child health center. The study was performed between June 2017 and August 2018.

Population: Eligible patients were those admitted to the PICU with at least one vital sign monitored using a cardiorespiratory monitor connected to the central monitoring station. Patients were excluded if the presence of one study observer in the patient room was considered incompatible or inappropriate by the physician or the nurse in charge.

Standard management: As previously reported (8), as a standard of practice in our PICU, all physiological, therapeutic and clinical data from medical devices available at the bedside of all children admitted in the PICU were continuously collected in an organized HRDB linked to the EMR from admission to discharge of the PICU (8). Biomedical signals from the monitors were sampled and recorded every seconds while data from ventilators and infusion pumps were recorded every 30 seconds. The full details of the HRDB structure were previously reported (8).

Study protocol: The study was divided in three periods of 14, 16 and 17 days respectively (convenient samples): the first was dedicated to data from the monitors, the second to the data from the ventilators and the third to the infusion pumps. During the first period, data were collected on devices that displayed the monitored data outside of the patient's room, whereas both second and third period took place at the bedside. On every study day, a sample of 20% of the children hospitalized in the PICU that meet the inclusion criteria was randomly selected. One patient could have been included more than once. A videotape of the data displayed on the medical devices (monitors, ventilators and infusion pumps) and available at the bedside, such

as heart rate or positive inspiratory pressure (Figure 1) was recorded.

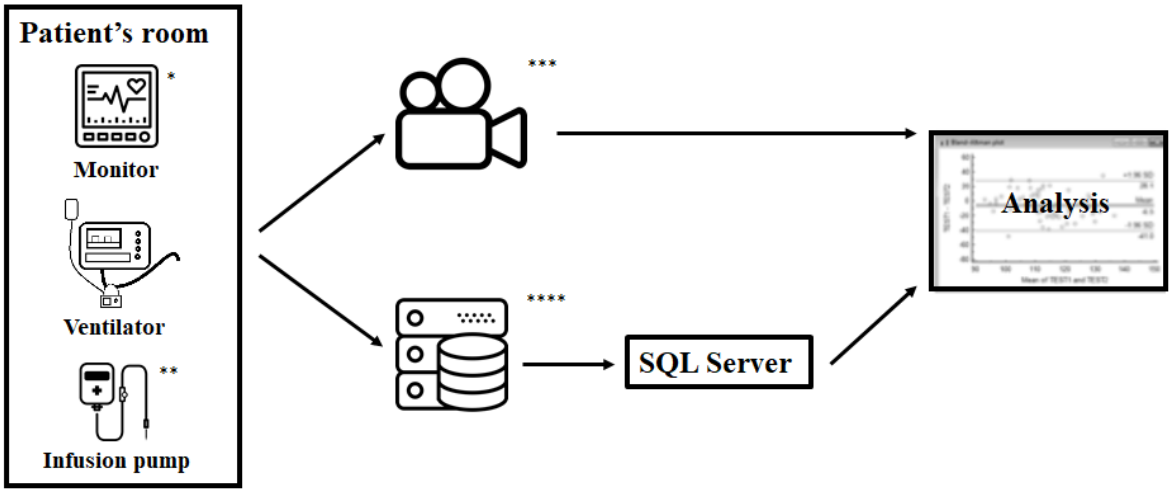


Figure 1: Data validation process

* Icons made by monkik from www.flaticon.com, ** Icons made by Freepik from www.flaticon.com, *** Icons made by Chris Veigt from www.flaticon.com, **** Icons made by Smashicons from www.flaticon.com.

Each day, a time synchronization process with the automatically calibrated clocks of the hospital and the video recorder was made. Each monitor (IntelliVue MP60, MP70 and MX800, Koninklijke Philips Electronics, Amsterdam, the Netherlands) was video recorded for 30 seconds, each ventilator (Servo-I©, Maquet, Getinge, Sweden) for 90 seconds and each infusion pump (Infusomat©, B. Braun Medical Inc, Bethlehem, Pennsylvania, U.S.) was simply photographed. Since ventilator data are recorded every 30 seconds in the HRDB, 90 seconds was enough to get at least two consecutive records in the HRDB. Because the infusion pumps parameters are only set, and not measured, static pictures were considered enough. The data displayed on the devices were then manually extracted into a spreadsheet from the pictures or at every second from the videotape. Data were periodically screened for aberrant values. These data, collected by one independent observer (AM) who was not implicated in patients' care, were considered as the reference data. Three types of data from medical devices were collected (Figure 1): 1) Physiologic signals from patient monitors (heart rate, oxygen saturation and systolic, diastolic and mean blood pressure) 2) Respiratory and ventilator parameters from the ventilator (positive end-expiratory pressure, peak inspiratory pressure, respiratory rate,

respiratory minute volume) 3) Pharmacotherapy from the infusion pumps (ex: drug names and infusion rate). The corresponding HRDB data were extracted using structured query language (SQL) and used for comparison (Figure 1).

Endpoints: The primary endpoints were the absolute value of the selected variables (heart rate (HR) and pulse oximetry (SpO_2)) recorded from the monitors. The secondary endpoints were:

- The absolute value of the selected variables recorded from the monitors when available: invasive arterial blood pressure (systolic (SBP), diastolic (DBP) and mean blood pressure (MBP)) and central venous pressure (CVP)
- The absolute value of the selected variables recorded from the ventilators: positive end-expiratory pressure (PEEP), positive inspiratory pressure (PIP), respiratory rate (RR), minute ventilation (MV), expiratory tidal volume (EV)
- The infusion rate
- The infused drugs' name
- The recording time of the data
- The missing data or the completeness of the dataset.

Statistical analysis and features' definition: Reference data were compared to the experimental data simultaneously collected in the PICU HRDB at a specific time point for each patient. Variables were expressed as mean ± standard deviation or median [minimal – maximal value] for continuous variables, depending on whether they followed a normal distribution (Shapiro-Wilk normality test) and number (percentage) for categorical variables. Comparisons between experimental and reference data were made by dependent tests as appropriate.

Under the concept of quality lies several features that tends to delineate the degree to which the HRDB is a true representation of the reality of the PICU's data (14,21)

- The accuracy is defined as the closeness of agreement between the experimental and the reference data. Accuracy refers to both trueness and precision. Trueness is expressed in

terms of bias and corresponds to the difference between experimental and reference value. Precision relates to the distribution of the experimental values. The agreement between experimental and reference data were evaluated for each parameter measuring the absolute agreement, the mean difference (22) and using the Bland & Altman analysis. Bias and limits of agreement were calculated with the R statistical package "BlandAltman" (23) based on both the original method (the difference of the two paired measurements was plotted against the mean of the two) and the modified one (the difference of the two paired measurements was plotted against the value of the reference data) of the Bland Altman analysis (24,25). In theory, the data should not be modified between the measure (monitor) and the storage (database) and the accuracy should be perfect. However, rounding process could slightly impact accuracy evaluation. Moreover, accuracy implies more than just the data itself: metadata, such as timestamps and patient identifiers, could also impact accuracy in case of asynchrony for example. Acceptable limits of agreement were *a priori* defined as ±5% of the mean of the reference.

- The correlation, defined as the association between reference and experimental data, was evaluated by the determination coefficient (R^2).
- The reliability, defined as the degree to which measurements can be reproduced, echoes both agreement and correlation between experimental and reference data. It was evaluated by intraclass correlation coefficients (ICC) for each parameter. ICCs estimates, 95% confidence intervals and F test results were calculated with the R statistical packages "irr"(26) and "psych" (22) using a single measurement, agreement, two-way mixed effect model (27).
- The completeness is related to the amount and the nature of the missing data and is defined as the extent to which the data that should have been included were indeed

included. To evaluate the completeness, the data of infusion pumps within the HRDB were compared to the corresponding data in the EMR. We compared for each selected patient, throughout the day, the data recorded in the HRDB to those recorded in the EMR for each infusion. Additionally, we selected 14 daily-used PICU drugs and their respective standardized concentration (sedative, analgesic and vasoactive drugs) and compared the correlation between the HRDB and the EMR within the study period (from August 31, 2017, to August 1, 2018).

All analyses were performed after the exclusion of the paired measurements when one of the experimental or reference data was missing. Thus, we intended to differentiate inaccurate data from missing data. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using open access R software (version 3.5.1, 2018-07-02, http://cran.r-project.org/).

Ethics: The study was approved by the institutional review board of Sainte-Justine Hospital (reference number 2016-1210, 4061). The exploitation of the HRDB is regulated by a DB policy validated by the institutional review board and no protected health information were stored in the HRDB nor in the video recordings. No patients or caregivers were recorded in the videos.

RESULT

Between June 1, 2017, and August 30, 2018, 1378 patients were admitted to the PICU and 100% were included in the HRDB. During the effective 47 days of study, 81 patients were hospitalized in PICU and 81 (100 %) were included in the HRDB. Data from 70 patients (86 %), 295 patients' days, were recorded from medical devices (Table 1) and 4645 data points were video recorded and compared to the corresponding data collected in the HRDB (Table 2).

Monitor data validity: Statistical analysis showed an overall excellent correlation, agreement and reliability, as shown in Table 2. ICCs were considered as excellent for all the tested variables (Table 2). Bland-Altman analysis showed an excellent accuracy and precision

between recorded and collected data within clinically significant pre-defined limits of agreement (Supplemental Digital Content 1). A single heart rate measurement in the experimental data (0.03 %) was considered as clinically different from the reference data (Figure 2,3). We documented 74 data points (2 %) that were missing, as detailed in Table 2.

Table 1: Patients' characteristics

Characteristics of all patients included (n=70)	
Age (years), median [min-max]	3 [0.0- 20]
Weight (kg), median [min-max]	11.2 [2.1-81.8]
PELOD2, median [min-max]	6 [0-24]
Main diagnostic category at admission, n (%)	
Post-surgical care	12 (17.1%)
Post-cardiac surgery care	7 (10.0%)
Cardiac	14 (20.0%)
Pulmonary	10 (14.3%)
Neurologic	7 (10.0%)
Infectious	6 (8.6%)
Accidents (Traumatism/Burn/Intoxication)	5 (7.2%)
Others	9 (12.9%)

Characteristics of the data studied (n=4645)		
	n (%)	**Total recording time (s)**
Monitors' data	3703 (79.7%)	
Heart rate (bpm)	1104 (23.8%)	10202
Respiratory rate (bpm)	1079 (23.2%)	10281
Pulse oxymetry (%)	975 (21.0%)	9907
Pulse (bpm)	316 (6.8%)	2839
Expiratory tidal CO_2 (mmHg)	12 (0.3%)	131
Systolic blood pressure (mmHg)	54 (1.2%)	529
Diastolic blood pressure (mmHg)	54 (1.2%)	529
Mean blood pressure (mmHg)	66 (1.4%)	527
Central Venous pressure (mmHg)	43 (0.9%)	224
Ventilators' data	670 (14.4%)	
Positive end expiratory pressure (cmH_2O)	134 (2.9%)	4230
Positive inspiratory pressure (cmH_2O)	134 (2.9%)	4230
Measured respiratory rate (bpm)	134 (2.9%)	4230
Measured expiratory Tidal Volume (ml)	134 (2.9%)	4230
Minute ventilation (L/min)	134 (2.9%)	4230
Infusion pumps		
Flow (ml/h)	272 (5.9%)	272

Others: Metabolic, electrolyte disturbance, hematologic, non-cerebral tumor, liver and digestive causes.

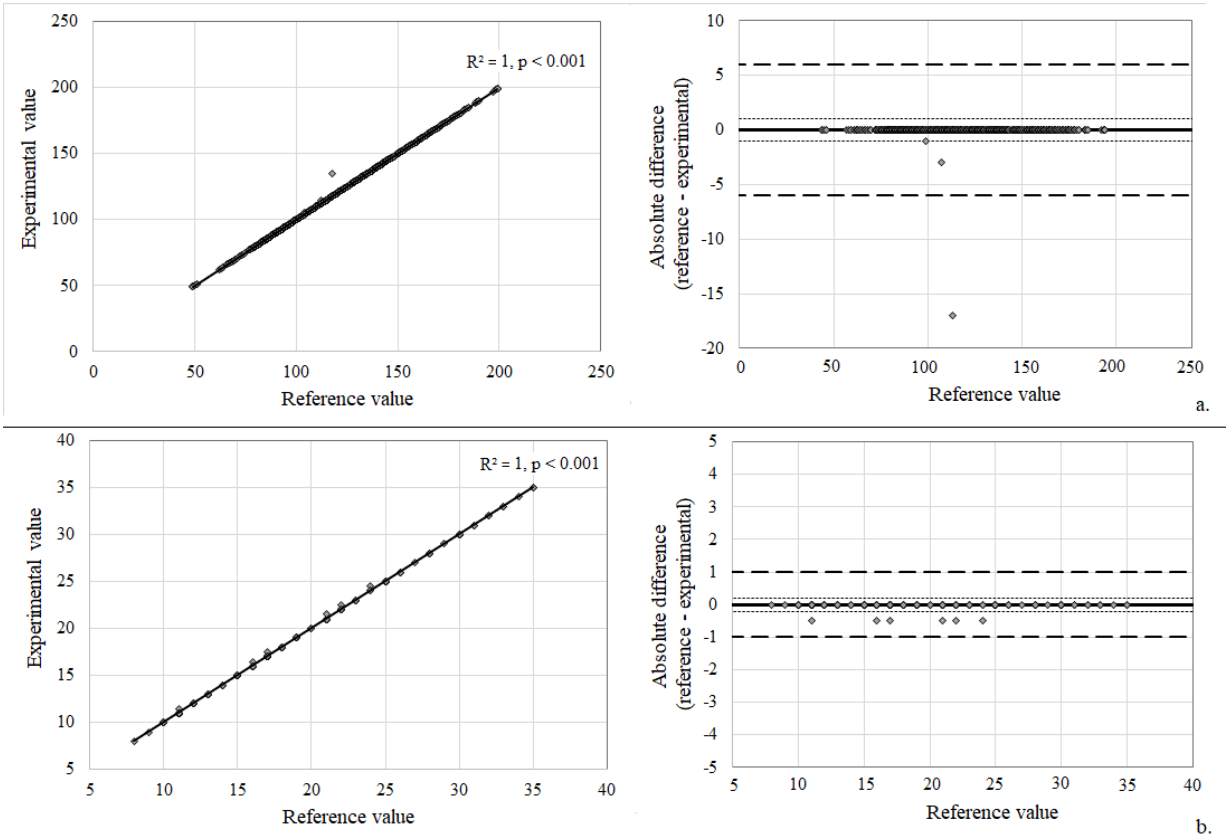


Figure 2: Correlation and Bland-Altman plot

a. Heart rate. Average bias of -0.02 bpm (95% Confident Interval +/- 0.03) and ····· limits of agreement (Average bias +/- 1.96 standard deviation) -1.05;1.01 (95% Confident Interval +/- 0.05). ·— — Acceptable limits of agreement -5;+5 bpm.

b. Positive inspiratory pressure. Average bias of -0.02 cmH20 (95% Confident Interval +/- 0.02) and ····· limits of agreement (Average bias +/- 1.96 standard deviation) -0.23;0.18 (95% Confident Interval +/- 0.03). ·— — Acceptable limits of agreement -1;+1 cmH2O.

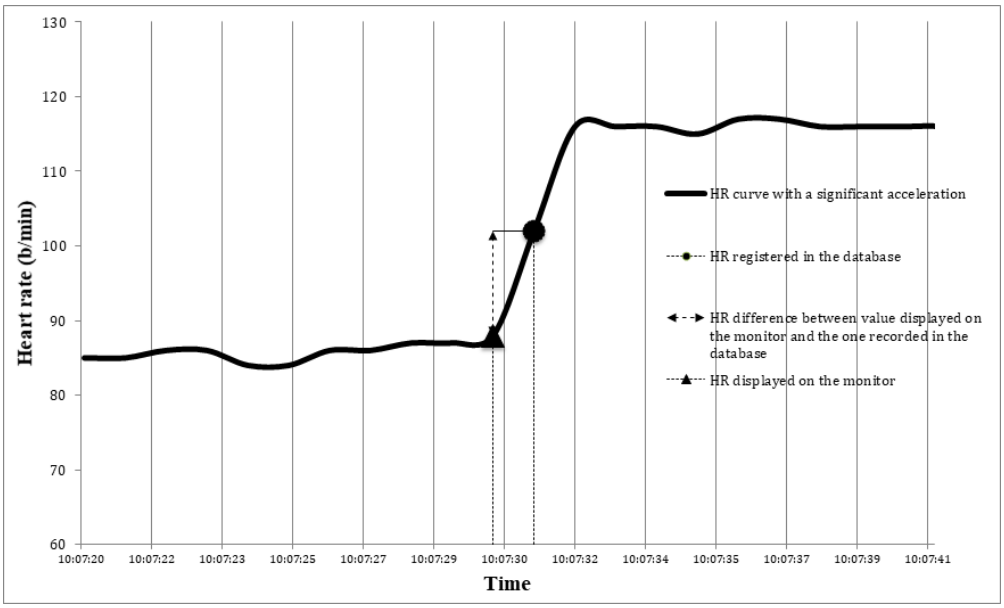


Figure 3: Schematic representation of a heart rate curve with a significant acceleration

HR: Heart Rate

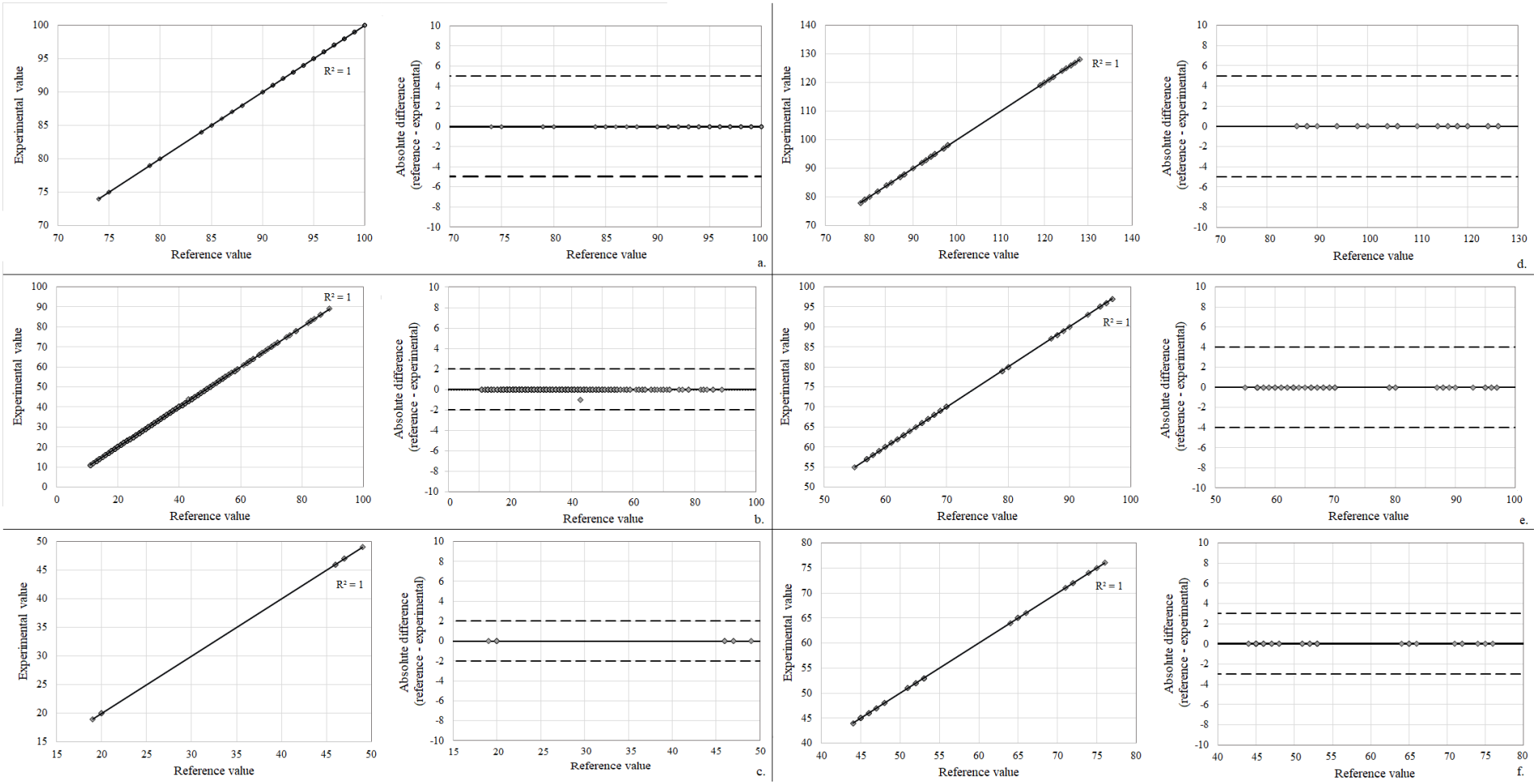
Table 2: Comparison between reference data and database data

	Reference	Database		Mean difference	Agreement	p	R^{2*}	ICC** (CI95%)
	Median [min-max]	Missing data	Median [min-max]					
Monitors' data		74 (2%)						
Heart rate (bpm)	117 [49-199]	25 (2%)	117 [49-199]	-0.019	99.7%	0.18	1	1 (1-1)
Respiratory rate (bpm)	28 [11-89]	8 (1%)	28 [11-89]	-0.001	99.9%	1	1	1 (1-1)
Pulse oxymetry (%)	100 [74-100]	10 (1%)	100 [74-100]	0	100.0%	NA	1	1 (1-1)
Pulse (bpm)	120 [35-173]	12 (4%)	120 [35-173]	0	100.0%	NA	1	1 (1-1)
Expiratory tidal CO2 (mmHg)	33 [19-49]	1 (1%)	33 [19-49]	0	100.0%	NA	1	1 (1-1)
Systolic blood pressure (mmHg)	92.5 [78-128]	6 (11%)	94 [78-128]	0	100.0%	NA	1	1 (1-1)
Diastolic blood pressure (mmHg)	51 [44-76]	6 (11%)	51 [44-76]	0	100.0%	NA	1	1 (1-1)
Mean blood pressure (mmHg)	66 [55-97]	6 (9%)	66.5 [55-97]	0	100.0%	NA	1	1 (1-1)
Central venous pressure (mmHg)	9 [6-25]	0	9 [6-25]	0	100.0%	NA	1	1 (1-1)
Ventilators' data		0						
Positive end expiratory pressure (cmH_2O)	7 [5-13]	0	7 [5-13]	0	100%	NA	1	1 (1-1)
Positive inspiratory pressure (cmH_2O)	18 [8-35]	0	18 [8-35]	-0.022	95.5%	0.02	1	1 (1-1)
Respiratory rate (rpm)	34 [11-56]	0	34 [11-56]	0.008	94%	0.53	1	1 (1-1)
Expiratory tidal volume (ml)	25 [5.50-600]	0	25 [5.50-600]	-0.015	97%	0.07	1	1 (1-1)
Minute ventilation (L/min)	1 [0.4-7]	0	1 [0.4-7]	0	100%	NA	1	1 (1-1)
Infusion pumps								
Rate of infusion (ml/h)	1.3 [0-100]	23 (9%)	1.3 [0-100]	0	100%	NA	1	1 (1-1)

*All *p*-values were < 0.001

** All p-values were = 0

CI95%: 95% confident interval



Supplemental Digital Content 1: Correlation and Bland and Altman analysis for monitors' data

a. Pulse oximetry. b. Respiratory rate. c. End tidal CO2. d. Systolic arterial pressure. e. Mean arterial pressure. f. Diastolic arterial pressure

- — — Acceptable limits of agreement (±5% of the mean of the reference)

Ventilators' data validity: Statistical analysis showed an excellent overall correlation, agreement and reliability (Table 2, Supplemental Digital Content 2). A small, but statistically significant difference was found for the positive inspiratory pressure (mean difference of -0.022 cmH_2O, p-value 0.02). This difference was observed only for a minority of the data (95.5% of all values were equal). Agreement remained over 90% with an excellent correlation between reference and experimental data. ICCs were considered as excellent for all the tested variables (Table 2). Bland-Altman analysis showed excellent accuracy and precision (Supplemental Digital Content 2). No data were missing (table 2).

Infusion pumps data validity: The comparison with the data displayed on the infusion pumps showed an overall excellent correlation, agreement and reliability (Table 2) with Bland-Altman analysis showing an excellent accuracy and precision between recorded and collected data for all the tested variables (Supplemental Digital Content 2). ICCs were considered as excellent for all the tested variables (Table 2). Twenty-three infusions (9 %) were not retrieved in the HRDB (Table 2). Nine episodes were related to six patients without any pharmacological data collected in the HRDB and 14 episodes were related to pump dysfunction. Other minor discrepancies were noticed between HRDB and EMR (Table 3). Correlation between HRDB and EMR regarding drugs of interests over the study period were depicted in figure 4.

Timestamps: A delay was observed between time synchronized videotapes and collected data from the monitors and the ventilators. This delay was less than 28 seconds and remained stable among patients. Besides, regarding infusion pumps data, we discovered that the data were not collected in the HRDB every 30 seconds as expected, but at different time interval between 10 and 40 seconds or when a modification was done. No delays were observed between the source and the HRDB.

Table 3: Descriptive summary of discrepancies between the database and the electronic medical record

Types of discrepancies	Number of episodes	Consequences on the DTB
Failure to connect the pump to the network	14	LOSS OF DATA
Transient pump disconnection	2	
Drug name inadequacy between HRDB and EMR	2	INACURACY
Drug started earlier in the HRDB than in the EMR	6	COMPLETENESS IMPROVEMENT
Drug stopped later in the HRDB than in the EMR	5	
Prescription not registered in the EMR	2	

HRDB: High Resolution DataBase; EMR: Electronic Medical Record

	EMR	HRDB
Dexmedetomidine 4µg/ml	182	183
Dexmedetomidine 2µg/ml	254	263
Midazolam 5mg/ml	67	93
Midazolam 1mg/ml	17	17
Propofol 10mg/ml	94	154
Morphine 1mg/ml	144	143
Morphine 5mg/ml	8	13
Hydromorphone 0.5 mg/ml	14	39
Hydromorphone 5 mg/ml	3	3
Fentanyl 50µg/ml	19	34
Fentanyl 10µg/ml	4	4
Milrinone 50µg/ml	1	3
Milrinone 100µg/ml	15	19
Milrinone 200µg/ml	78	91
Milrinone 500µg/ml	29	34
Epinephrine 10µg/ml	35	57
Epinephrine 25µg/ml	86	102
Epinephrine 50µg/ml	33	48
Dobutamine 750µg/ml	7	15
Dobutamine 1500µg/ml	5	8
Dobutamine 3000µg/ml	1	1
Dopamine 800 µg/ml	13	20
Dopamine 1600 µg/ml	1	4
Dopamine 3200µg/ml	2	4
Norepinephrine 16 µg/ml	16	43
Norepinephrine 32 µg/ml	35	45
Norepinephrine 64 µg/ml	64	76
Nicardipine 100 µg/ml	0	2
Nicardipine 200 µg/ml	59	56
Nitroprussiate 100µg/ml	0	2
Nitroprussiate 200µg/ml	10	16
Nitroprussiate 400µg/ml	5	7
Nitroprussiate 1000µg/ml	4	9
Heparin 100 Ui/ml	117	104

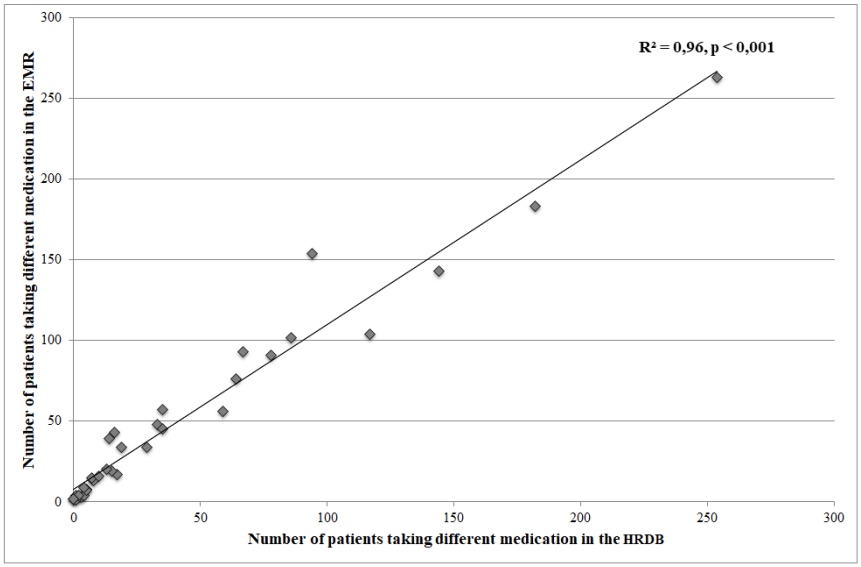
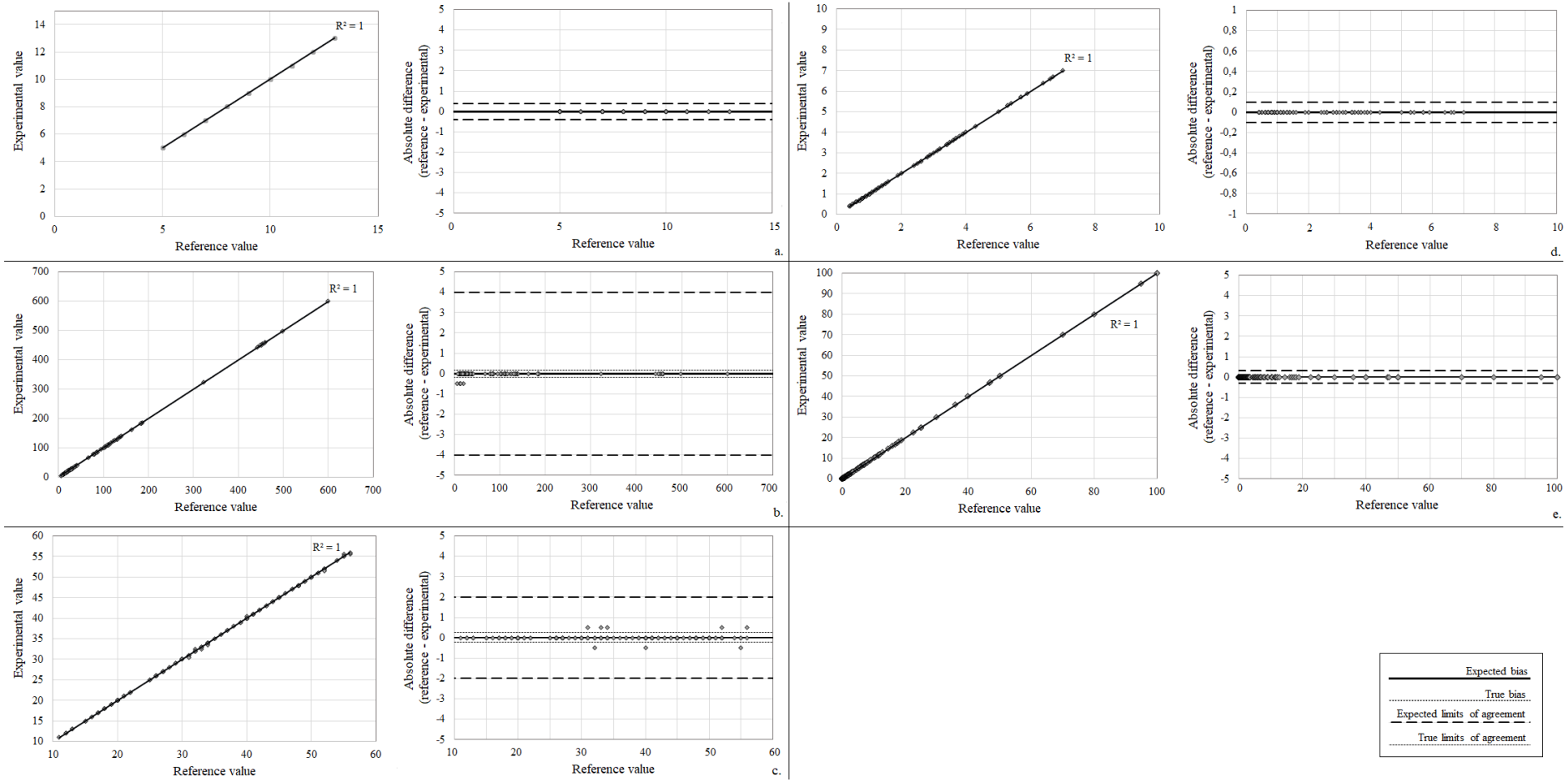


Figure 4: Correlation between EMR and HRDB

EMR: Electronic Medical Record, HRDB: High Resolution Electronic DataBase



Supplemental Digital Content 2: Correlation and Bland and Altman analysis for ventilators' data and for infusion pumps' data

a. Positive end expiratory pressure. b. Expiratory volume. c. Respiratory rate. d. Minute Ventilation. e. Rate of infusion

DISCUSSION

Whether in day-to-day clinical care decision-making or in medical research, the need to evaluate data quality is essential to ensure the reliability of DB (9,21,28,29). To our knowledge, this is the first study to validate PICU data contained in a specific HRDB (20,30). This article is indissociable from our two previously reports (8,11). The first report described the gathering process of our HRDB (8) and the second gave a comprehensive description of the HRDB's architecture and process (11), this articles constitute the quality assurance of the HRDB (14,31). This third article completes this set. It contributes to the quality assurance phase and to the quality control phase of the HRDB (14,31).

As there were no guidelines specifically designed to guarantee the quality of high-resolution data (9,14), we elaborated the first complete validation procedure. Our validation procedure was inspired by previously published experiences (9,10,30,32–34) and guidelines (13–15,28,35) regarding data quality assessment in the field of medical DB collected at a lower rate or in a restricted area. To evaluate the quality of the data, we chose to perform an external validation procedure. We compared our extracted results with the information displayed on the monitor or the biomedical device (21). Our study showed an excellent overall accuracy, completeness and reliability of our HRDB when compared to displayed data at the bedside at the same time.

Regarding the accuracy of the dataset, we noticed only one clinically significant different heart rate value. This error was due to a rapid acceleration of the heart rate (Figure 2). In the video, the heart rate increase from 118 beats/minute to 154 beats/minute and the HRDB recorded one single value at 135 beats/minute during the transition. This suggests that monitors processed those data and only refreshed the display at a specific interval (probably between one and two seconds) and did not show intermediate data. Then, the HRDB recorded an intermediate value, which explains the importance of the difference between the reference value and the

experimental value. Differences between the HRDB's data and the reference data were observed regarding PIP. Even statistically significant, disagreements were not clinically significant (the maximal difference was 0.5 cmH_20 and concerned only 4.5% of all the collected PIP, the remaining 95.5% values were strictly equal) as shown by a mean difference of -0.022 cmH_2O. Only integers are displayed on the ventilator screen and the data processing algorithm of the raw values measured by the ventilator is unpublished. Thus, we suspect that these very minor differences may be due to rounding process.

Regarding the completeness of the dataset, 2% of the data were missing. Even less than previously reported (9,14,30), this number of missing data didn't meet our expectations for this HRDB, as we planned for a 0% missing data. This loss of data was mainly caused by a systematic error in the data processing. Indeed, we discovered that the original HRDB structure could only record nine parameters simultaneously. Then, when more than nine parameters were sent, the additional data were not registered. Once this issue was identified, we modified our database for an entity-attribute-value structure where each data point is stored as an independent row (36,37).

Regarding infusion pumps and pharmacological data, the discrepancies between the experimental and the reference data or the EMR appeared associated with variability in care more than with a gathering process failure. Regarding the 23-missing data from infusion pumps, we proved that the corresponding infusion pumps were disconnected from the network, thus the data were not sent to the HRDB. This disconnection of the infusion pumps explained these discrepancies between the EMR and the experimental data, with all the pharmacological data missing in six patients. In addition, the large majority of inconsistencies between the EMR and the experimental data were due to a time difference from the beginning or the end of the drug. In the EMR, a drug needs to be ordered before the drug rate could be registered, while in the HRDB, the rate starts to be registered directly when the pump is connected to the network.

Furthermore, medications were not registered in the patient EMR, probably because the physician did not order it. However, nursing notes confirmed that the drug was given. In these situations, the HRDB could be considered as more accurate than the EMR. On two occasions, the name of the fluid was different between EMR and HRDB. However, the name recorded on the pump and the one in the HRDB was the same, suggesting the infusion pump drug name was not modified when the medication was replaced. Finally, it happened twice that no data were recorded over a period when they should be. These intervals happened just before the patient was moved to another room and the procedure is to disconnect the pumps before moving the patient. Although these four situations altered the HRDB accuracy, they were not due to a HRDB limitation. Last, timestamp asynchronies were due to a server setting that was corrected after this study.

This study's main limit lies in the lack of validation of the complete dataset (10,14,30). We have considered several procedures to apply either during or after the gathering of the HRDB. Given the gigantic data gathering rate (about 10,000 data points per minute), it is humanly impossible to both gather and validate the data simultaneously while collecting the DB or even validate the entire database retrospectively. Thus, we decided to perform a point-by-point data analysis on a randomly chosen patients sample considered as representative of the HRDB (30). Besides, some could argue, and they would be right, that we were not able to correct abnormal values or undisplayed data. But, as this dataset is supposed to reproduce the patient's entire course in PICU, abnormal values and undisplayed data should be considered as part of the patient's course as much as a true value (19). Furthermore, this is a study in one institution with an excellent understanding of the value of data quality. Even if the methodology is transferable to other data, this study only validates this particular data in this particular HRDB and its results shouldn't be generalized to other clinically collected data. Finally, even limited as most of the analyzed data were electronically captured, we must consider the possibility of a Hawthorne

effect. The observational methodology might have modified the quality of the data being entered in the EMR by the bedside personnel.

CONCLUSION

This study showed an excellent overall quality of the data include in the HRDB of our PICU while performing validation procedures on a representative sample. We considered that this study provides an assurance for future HRDB users of the data quality, especially regarding monitor and respirator data. By reporting and detailing this data quality validation process, the process becomes reproducible by any research team and sets a reference for future validation studies of similar datasets.

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C. Discussion

Il a déjà été mentionné que bien qu'il existe aujourd'hui plusieurs bases de données haute résolution dans le domaine des soins intensifs, adultes et pédiatriques (121,147), nous n'avons pas été en mesure de trouver une description détaillée d'un processus d'évaluation de qualité des données. De plus, les mentions qui en sont faites dans les articles décrivant ou utilisant ces bases sont très succinctes (147,151,153). C'est pourquoi l'idée de consacrer une étude à la phase de validation de notre base de données peut être considérée comme novatrice et par sa simple existence faire la force de ce travail. Une fois de plus, notre travail établit un précédent en termes de procédure de validation, cette fois ci des données collectées à haute fréquence. Il offre la possibilité aux autres équipes de reproduire la démarche tout en poussant la communauté médicale et scientifique à se questionner sur la qualité des données qu'elle emploit quotidiennement dans les soins ou la recherche.

L'autre force de ce travail semble résider dans la méthode d'étude des données et les analyses statistiques proposées qui apparaissent adaptées aux objectifs. D'une part, nous avons méticuleusement étudié les données incluses dans la base. Bien que restreintes à un petit groupe de patients, les étapes d'évaluation de qualité appliquées aux 3 types de données (signaux physiologiques, paramètres ventilatoires et données pharmacologiques) recueillies dans notre base ont permis de montrer que les mécanismes et les modalités de collecte de données cliniques en vigueur dans notre service au lit du malade étaient vraisemblablement fiables. Elles répondaient aux exigences d'exhaustivité et de justesse, tout du moins en ce qui concerne les données recueillies avec la plus haute fréquence et donc les moins « vérifiables » lors de la réalisation d'études cliniques. D'autre part, nous nous sommes astreints à rechercher et expliquer les éventuelles erreurs de collecte et corriger dès que possible leur source. Nous avons observé que le contenu de la base allait être influencé positivement ou négativement selon le type d'erreur. Ainsi, le risque est de produire des conclusions erronées, positivement ou

négativement, en cas d'études conduites à partir de données de qualité insuffisante. Toutefois, il a été évoqué par l'un des reviewers de l'article que les inquiétudes devaient être tempérées car les éventuels écarts observés entre la réalité et la base de données étaient vraisemblablement peu susceptibles d'influencer la pertinence clinique des données. De plus, il semble important de différencier les erreurs liées à un mauvais recueil de données justes, des erreurs liées au bon recueil de données erronées. La première erreur doit être considérée comme un manque de fiabilité du processus de collecte et donc une altération de la qualité des données, la seconde comme un aléa de la surveillance ou de la prise en charge qui représente la réalité du quotidien des soins intensifs mais qui ne remet pas en compte la qualité de la base de données (188,189). On peut d'ailleurs considérer que ne pas prendre en compte ces « vraies fausses informations » est une perte car elles ont autant de valeur à être étudiées que les « vraies vraies informations » (189). Cela soulève la question de l'objectif de la base et de la nécessité de prévoir un temps de retraitement des données avant toute étude clinique.

L'une des originalités de notre article est l'utilisation adaptée au contexte de la méthode de Bland & Altman (134). En effet, dans ce contexte, nous disposons d'une valeur vraie et non d'une mesure de cette valeur effectuée par un outil de monitorage considéré comme un « gold standard » (95,100,137). Ainsi, il est apparu pertinent de rapporter la différence entre les 2 valeurs (expérimentale et référence) pas uniquement à la moyenne des deux mais aussi à la valeur réelle utilisée comme référence. Dans cette étude, nous n'avons pas constaté de différence entre les 2 méthodes, vraisemblablement du fait de l'absence de différence entre les données. Toutefois, cette considération semble pertinente et sera à prendre en compte dans la suite des travaux sur le simulateur. Nous avons décidé de ne pas présenter les résultats des pourcentages d'erreur. Dans cette situation, le pourcentage d'erreur correspond à un pourcentage d'erreur des limites d'agrément qui s'évalue à partir de la mesure de la précision des 2 méthodes comparées. Cette précision est dépendante de la moyenne de la population et

de l'étendue des valeurs (100,190,191). Ainsi, plus l'étendue des valeurs est importante plus le pourcentage d'erreur risque d'être important. Les pourcentages d'erreur étaient relativement élevés et variables allant de 10% pour la SpO2 à 672% pour les débits de perfusion. Ici, c'est la précision qui est remise en question, logiquement, du fait de l'étendue des valeurs dans le contexte de l'enregistrement de données physiologiques et thérapeutiques diverses chez des patients hétéroclites en termes d'âge, de gabarit et de motif d'hospitalisation.

Ce travail présente tout de même plusieurs faiblesses. Tout d'abord, une nouvelle fois, de par son caractère monocentrique, la question de l'applicabilité externe de cette étude se pose. Ainsi, si la méthode est applicable dans une autre institution disposant d'un dispositif similaire, les résultats de cette étude ne doivent pas être transposés à d'autres bases de données haute résolution, même si celles-ci semblent avoir été collectées de la même manière.

Ensuite, la taille de l'échantillon est questionnable. En effet, il n'a pas été possible préalablement à l'étude de calculer la taille de l'échantillon adéquate qui une fois validé garantirait la validité des données du reste de la base. Pour déterminer le nombre de sujets, nous nous sommes appuyés sur les travaux du « brain monitoring with Information Technology (BrainIT) collaborative network » (135,160,192,193). Ainsi, nous avons retenu d'une revalidation de 20% des données inclues dans la base avec une sélection aléatoire de ces 20%. Cependant, nous avons dû adapter cette méthode appliquée rétrospectivement sur une base de données restreinte à un type précis de patients et collectée dans plusieurs centres à notre base de données intégrant tous les patients admis en soins intensifs pédiatriques dans un centre ne disposant que d'un investigateur réalisant son étude prospectivement. Ainsi, de 20% des données inclues dans la base, nous avons restreint à 20% des patients présents dans le service chaque jour où l'étude était réalisable. Ainsi, à titre de comparaison, nous avons étudié 4645 données provenant de 70 des 81 patients hospitalisés sur la durée de 47 jours d'étude alors que

le BrainIT collaborative network a étudié 19461 données sur une durée d'étude de 2 ans et un nombre non précisé de patients parmi les 200 patients inclus dans la base de données.

Enfin, la dernière faiblesse de ce travail concerne sa représentativité des séjours inclus dans la base de données. En effet, les valeurs physiologiques observées dans cette étude apparaissent proches de la normale ce qui est surprenant considérant le type de patients concernés. Il est probable que le critère d'exclusion visant à exclure de l'étude tout patient dont l'état clinique ou la situation rendaient la présence de l'investigateur impossible ou inappropriée a conduit à un biais de sélection ayant altéré la représentativité de l'échantillon. Toutefois, même si les résultats ne sont pas physiopathologiquement représentatifs des séjours inclus dans la base de données, du fait de la sélection aléatoire des patients étudiés, ils restent tout de même représentatifs de la méthode de recueil et donc rassurants quant à la fiabilité de celle-ci.

Sans valider l'intégralité du contenu de la base de données, cette procédure d'évaluation et de validation des données de par sa rigueur méthodologique a permis de valider globalement la méthodologie de recueil ainsi que partiellement l'exactitude des données. Si ces conclusions sont logiques et attendues, considérant le fait que notre système de collecte de données a été élaboré à partir de l'architecture électronique et informatique disponible au lit du malade et utilisée quotidiennement pour les soins (31), elles n'en restent pas moins intéressantes et indispensables avant de concevoir une utilisation des données en recherche complexe en « big data » (194).

EVALUTION DE SIMULRESP, LE SIMULATEUR DE PHYSIOLOGIE CARDIO-RESPIRATOIRE DEDIE AUX ENFANTS ET AUX ADOLESCENTS

A. Présentation

Afin de pouvoir initier le processus de calibration et de validation de SimulResp© et donc de satisfaire à l'objectif premier de la base de données, il a été nécessaire d'évaluer l'état actuel de SimulResp©, ses capacités de prédiction, ses caractéristiques et ses limites de fonctionnement. Pour ce faire, nous avons appliqué les principes de Summers et al. (77,94) en matière de validation des modèles physiologiques. La fiabilité d'un simulateur physiologique va être évaluée selon 3 critères :

- *qualitatif* : capacité du modèle à faire des prédictions qui évoluent dans le sens du contrôle,
- *quantitatif en état stable* : capacité du modèle à maintenir des prédictions stables quand les conditions restent stables,
- *quantitatif en dynamique* : capacité du modèle à adapter ses prédictions quand les conditions évoluent et changent.

L'objectif de ce travail était d'évaluer la qualité de SimulResp© selon sa capacité à satisfaire à ces critères.

En nous basant sur les travaux déjà réalisés (39,55), nous avons émis l'hypothèse que SimulResp© était apte à produire une prédiction exacte des valeurs du gaz du sang chez le patient sain de plus de 8 ans en ventilation spontané. Nous avons aussi évalué SimulResp© chez le patient sain de moins de 8 ans en ventilation spontanée et de plus de 8 ans en ventilation mécanique.

B. Généralités sur la méthode de travail

Nous avons réalisé une évaluation prospective de SimulResp© à partir des versions 2015.10.11.01 (version 2015) et 2012.06.09.01 (version 2012). Ces 2 versions étaient considérées équivalentes car les formules contenues dans le logiciel n'avaient pas été modifiées. Ce travail a reçu l'avis favorable des comités d'éthique du CHU Sainte Justine de Montréal et du CHU de Caen.

1. Conditions de réalisations des tests

Les tests ont été réalisés par 2 investigateurs à 2 périodes différentes. Olivier Fleschelles avait réalisé en 2013 des tests sur la version 2012, à partir d'un ordinateur SONY VAIO© de 2011 équipé d'un processeur Intel Core i3. J'ai moi-même effectué des tests sur la version 2015 à partir d'un ordinateur ASUS X541UV© de 2016 équipé d'un processeur Intel Core i7-6500U.

2. Modalités de réalisation des tests

Des résultats de gaz de sang (pH, PaCO2, PaO2 and SaO2) ont été simulés à plusieurs moments pour différents patients avec des caractéristiques spécifiques. A chaque simulation, les caractéristiques suivantes étaient entrées dans le logiciel manuellement : Age, poids, taille, type de patient (normal ou personnalisé) et le mode de ventilation (spontanée ou mécanique). L'ordre d'entrée des données était systématiquement le même. Par défaut, le genre était réglé sur masculin et modifié en féminin au besoin. Le type personnalisé était sélectionné lorsque les tests étaient réalisés en ventilation mécanique pour permettre de rentrer les paramètres de ventilation : la fraction inspirée d'oxygène (FiO2), la pression positive expiratoire (PEP), la fréquence respiratoire du respirateur (FR) et le volume courant (VC). Par ailleurs, de par son support informatique, le SimulResp© bénéficie d'une option qui permet de réduire la durée de simulation. Ainsi une période d'évolution d'un patient de plusieurs heures peut être compressée et résumée en quelques minutes (1 à 4000). La compression de temps a pu varier d'un test à

l'autre en fonction notamment de la durée de simulation souhaitée (quelques minutes ou plusieurs heures) et a, elle aussi, fait l'objet d'une évaluation.

Les tests ont été réalisés à partir de patients fictifs sains, en ventilation spontanée ou mécanique ou bien de patients réels sains ou malades, en ventilation spontanée ou mécanique, dont les données étaient extraites de la littérature ou d'études précédemment réalisées.

3. Analyses statistiques

Les variables ont été exprimées, pour les variables continues, en moyenne +/- déviation standard ou médiane [écart interquartiles], selon leur distribution évaluée par le test de Shapiro-Wilk.

La réponse de SimulResp© aux critères de Summers (77,94) et donc la qualité du SimulResp© a été jugée sur plusieurs concepts précédemment détaillés et dont certains ont été appliqués lors de l'évaluation de la base de données (56–58) : l'exactitude, la répétabilité, la reproductibilité et la robustesse.

Les données ont été analysés par des approches objectives et/ou subjectives décrites dans la littérature (56,136,195). L'approche subjective consistait en une représentation graphique de la prédiction de SimulResp© en fonction du temps, de la vitesse de simulation et des caractéristiques du patient simulé. Cette représentation graphique permettait de visuellement évaluer l'aptitude de SimulResp© à réaliser ou maintenir une prédiction qui se situait dans les normes de valeur de gaz du sang (pH 7.4 +/- 0.5; PaCO2 40 +/- 5 mmHg, PaO2 90 +/- 10 mmHg; SpO2 97% +/- 3%) lorsqu'une simulation était réalisée à partir de patients sains, fictifs ou réels. L'approche objective consistait en la réalisation de tests statistiques, quand ceux-ci étaient pertinents et applicables aux données, tels que le test de t, le test des rangs de wilcoxon ou le test de Friedman pour les variables continues (selon leur distribution), le calcul du coefficient de détermination (R^2), du coefficient de corrélation intra-classe (ICC) et l'analyse de Bland & Altman. Nous avons considéré une p value de 0.05 comme statistiquement

significative. Les analyses statistiques ont été réalisées par moi-même, après consultation du comité technique et de l'unité de biostatistique du CHU de Caen, à partir du logiciel en libre accès R (3.5.1, 2018-07-02, http://cran.r-project.org/.

C. Tests et résultats correspondants

1. Evaluation de l'exactitude

a) Patient fictif de 0 à 18 ans.

Tout d'abord, nous avons cherché à évaluer la gamme d'âges pour laquelle SimulResp© était supposé être juste ainsi que son aptitude à rester fiable même lorsque le temps était compressé, de 2 à 4000 fois. Nous avons donc simulé les valeurs de gaz du sang (pH, PCO2, PO2 and SpO2) de différents patients fictifs supposés sains avec différentes caractéristiques d'âge (1, 2 ,4, 6, 8, 10, 12, 14, 16, 18 ans) et de genre avec un poids et une taille au 50^{e} percentile pour l'âge et à différentes vitesses de simulation allant de 1 à 4000. Les valeurs de gaz du sang étaient relevées après une durée d'évolution du patient fictif de 30 minutes.

La figure 8 (Fig. 8) présente la prédiction de SimulResp© en fonction de l'âge du patient. Chaque point représente le niveau de compression appliqué. Graphiquement, il est possible de constater que, quel que soit le niveau de compression, la prédiction de SimulResp© ne semble se concentrer dans les limites de normales prédéfinies qu'à partir de l'âge de 8 ans, voire même 10 ans. L'étendue des valeurs est importante avant l'âge de 8 ans quel que soit le paramètre considéré. La figure 9 (Fig. 9) est une représentation graphique différente qui reprend les mêmes éléments en distinguant garçons et filles, à partir de laquelle il est possible de tirer les mêmes conclusions en ce qui concerne l'incapacité de SimulResp© à réaliser une prédiction de pH, PaO2, PaCO2 ou SaO2 qui se situe dans les limites acceptables de la normale chez le patient sain de moins de 8 ans.

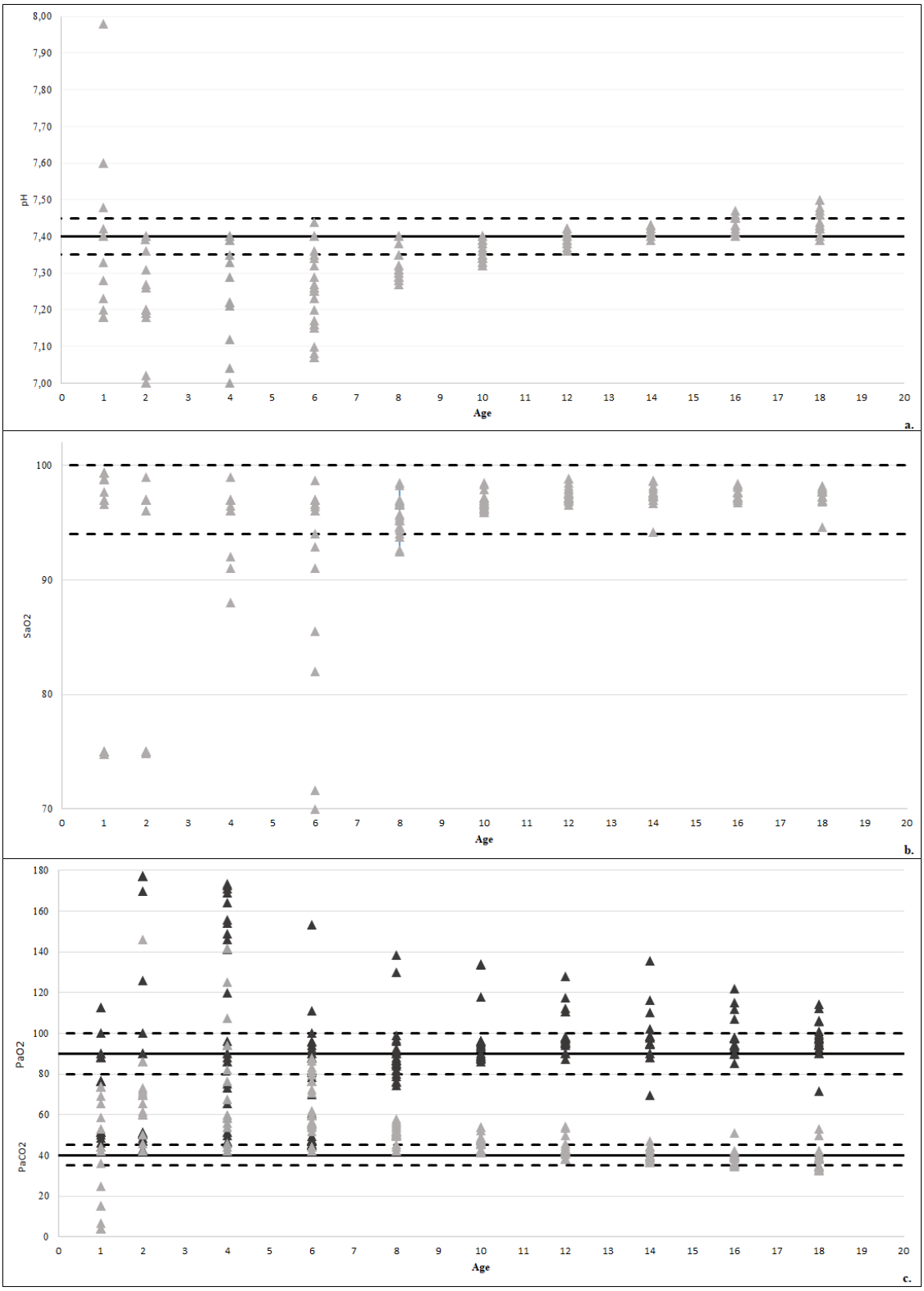

Fig. 8 : Représentation graphique de la prédiction de SimulResp© en fonction de l'âge.
Chaque point est caractérisé par un niveau de compression du temps de 1 à 4000 et l'âge du patient ayant servi pour réaliser le test.

a. pH. b. Saturation artérielle en oxygène (SaO2). c. Pressions artérielle en oxygène (PaO2 ▲) et en dioxyde de carbone (PaCO2 ▲). ‾ ‾ Limites supérieure et inférieure de la normale.

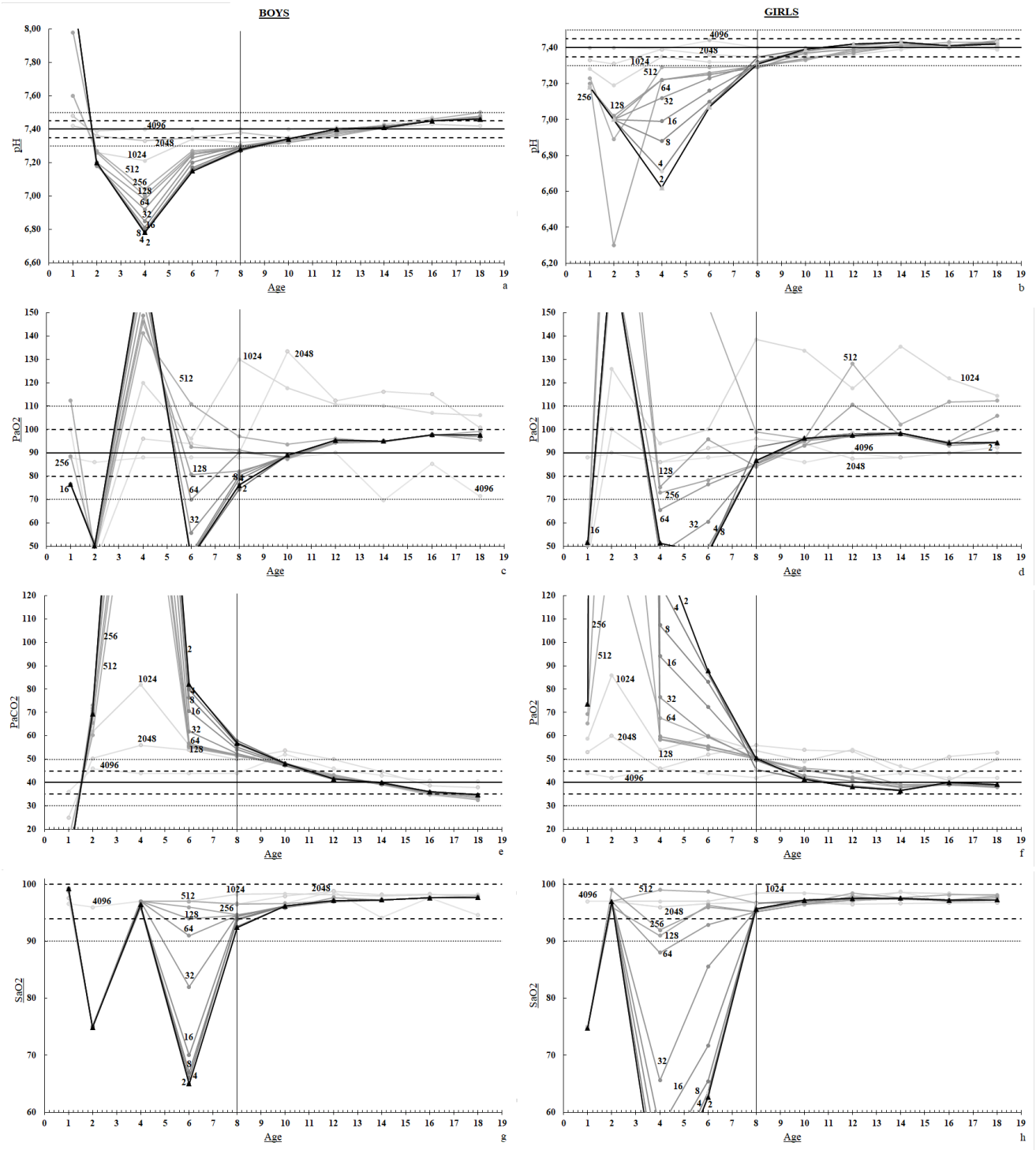

Fig. 9 : Représentation graphique de la prédiction de SimulResp© en fonction de l'âge et du genre.

Chaque courbe représente le niveau de compression sélectionné (1 à 4000) pour réaliser la simulation. La courbe noire représente l'évolution de la simulation en vitesse réelle.

a. pH garçon. b. pH fille. c.PaO2 garçon. d. PaO2 Fille. e. PaCO2 garçon. f. PaCO2 fille. g. SaO2 garçon. h. SaO2 filles

Les figures 10 (Fig. 10) et 11 (Fig.11) représentent l'évolution de la prédiction de SimulResp© en fonction de la compression de temps appliquée pour faire le test. On constate que quel que soit l'âge du patient et le paramètre simulé, plus la compression est importante plus la prédiction de SimulResp© se concentre dans les limites de la normale. La figure 11 (Fig.11) est une représentation graphique différente qui reprend les mêmes éléments en distinguant garçons et filles, à partir de laquelle il est possible de tirer les mêmes conclusions. La figure 11 (Fig.11) permet aussi d'appuyer avec une représentation différente, les conclusions tirées des figures 8 (Fig. 8) et 9 (Fig. 9).

En nous basant sur ces résultats, nous avons par la suite restreint nos tests à des patients de 8 à 18 ans (8, 10, 12, 14, 16, 18 ans) avec des caractéristiques différentes de genre, de poids et de taille (10ème, 50ème and 90ème percentile). Nous avons aussi adapté les vitesses de compression sélectionnées aux durées de simulation souhaitées. Ainsi, nous avons collecté des valeurs de gaz du sang à 3 reprises pour chaque patient à 30 minutes, 3 et 24 heures avec des compressions de temps de respectivement 64, 256 et 1024.

La figure 12 représente l'évolution de la prédiction de SimulResp© en fonction du poids et du genre du patient. Cette représentation graphique nous permet de constater que SimulResp© semble fiable pour produire une prédiction dans les limites de la normale à partir d'un poids variant de 25 à 35kg en fonction du paramètre étudié et de la durée de la simulation. Lorsque la prédiction porte sur les paramètres d'évaluation de l'oxygénation (PaO2 et SaO2), elle reste comprise dans les valeurs normales, quel que soit le poids, le genre et la durée de simulation. Cela n'est pas le cas lorsque la prédiction porte sur la PaCO2 ou pH. Dans ces 2 situations, le SimulResp© ne semble exacte que jusqu'à 60 kg.

Pour réaliser les tests sur patients fictifs en ventilation mécanique, nous avons réglé les paramètres de ventilation suivants : FiO2 21%, PEP 3 cmH_2O, VC 7.5mL/kg et valeur normal de FR pour l'âge (196).

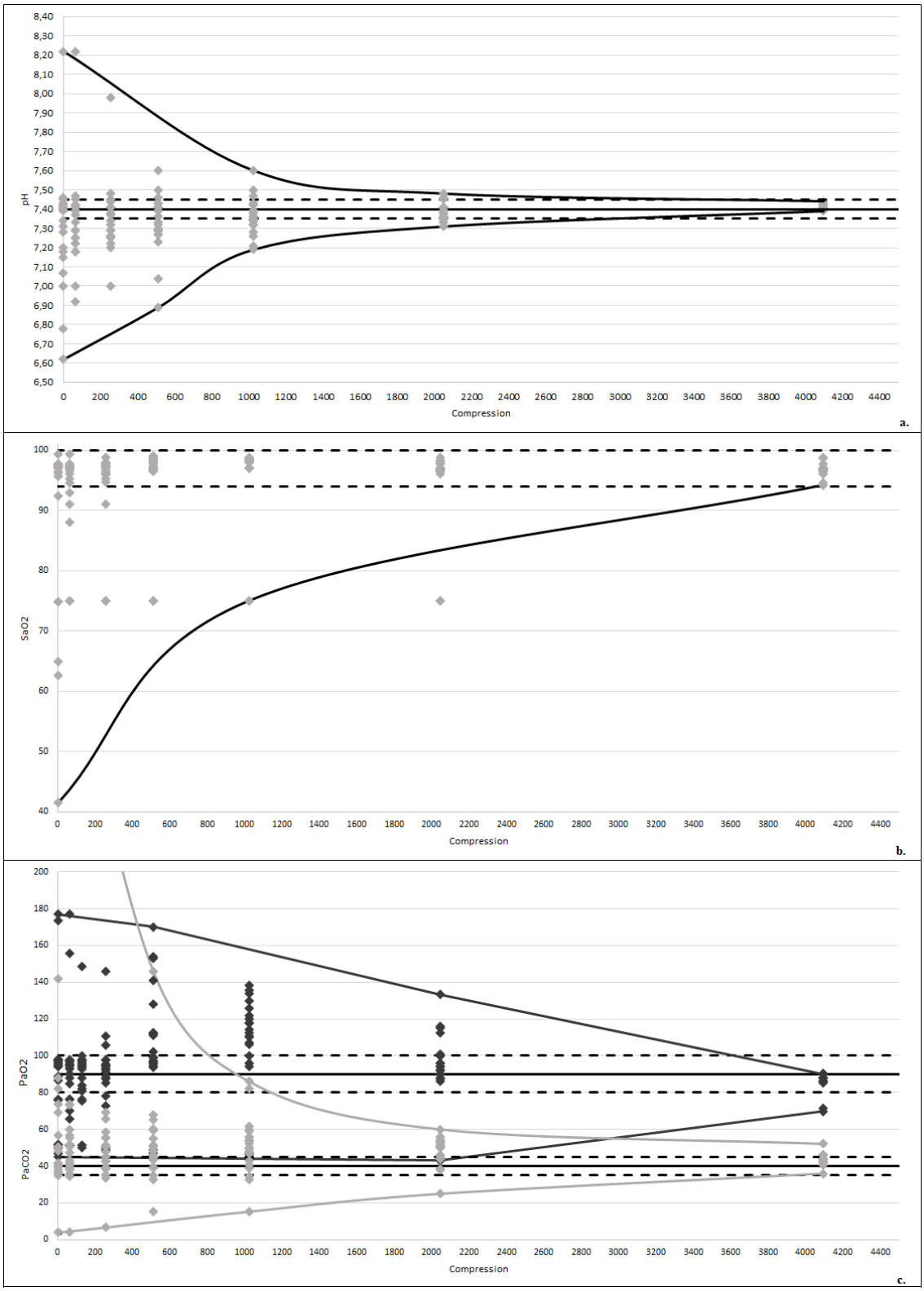

Fig. 10 : Représentation graphique de la prédiction de SimulResp© en fonction de la compression.

Chaque point est caractérisé par l'âge du patient et le niveau de compression du temps de 1 à 4000 ayant servi pour réaliser le test.

a. pH. b. Saturation artérielle en oxygène (SaO2). c. Pressions artérielle en oxygène (PaO2◆) et en dioxyde de carbone (PaCO2 ◆). ' — — Limites supérieure et inférieure de la normale.

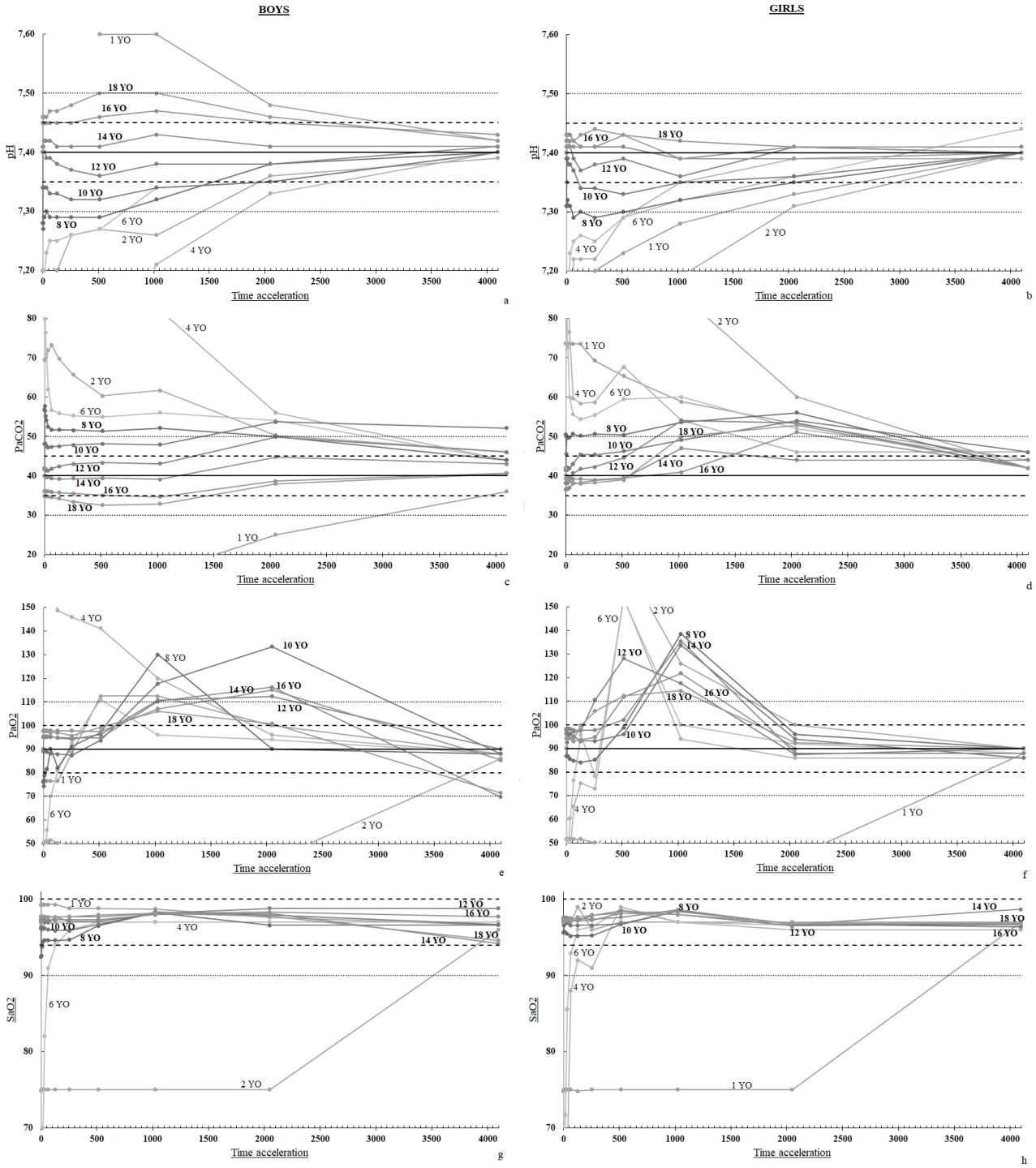

Fig.11 : Représentation graphique de la prédiction de SimulResp© en fonction la compression et du genre.

Chaque courbe représente l'âge du patient utilisé pour réaliser la simulation.

a. pH garçon. b. pH fille. c.PaO2 garçon. d. PaO2 Fille. e. PaCO2 garçon. f. PaCO2 fille. g. SaO2 garçon. h. SaO2 filles

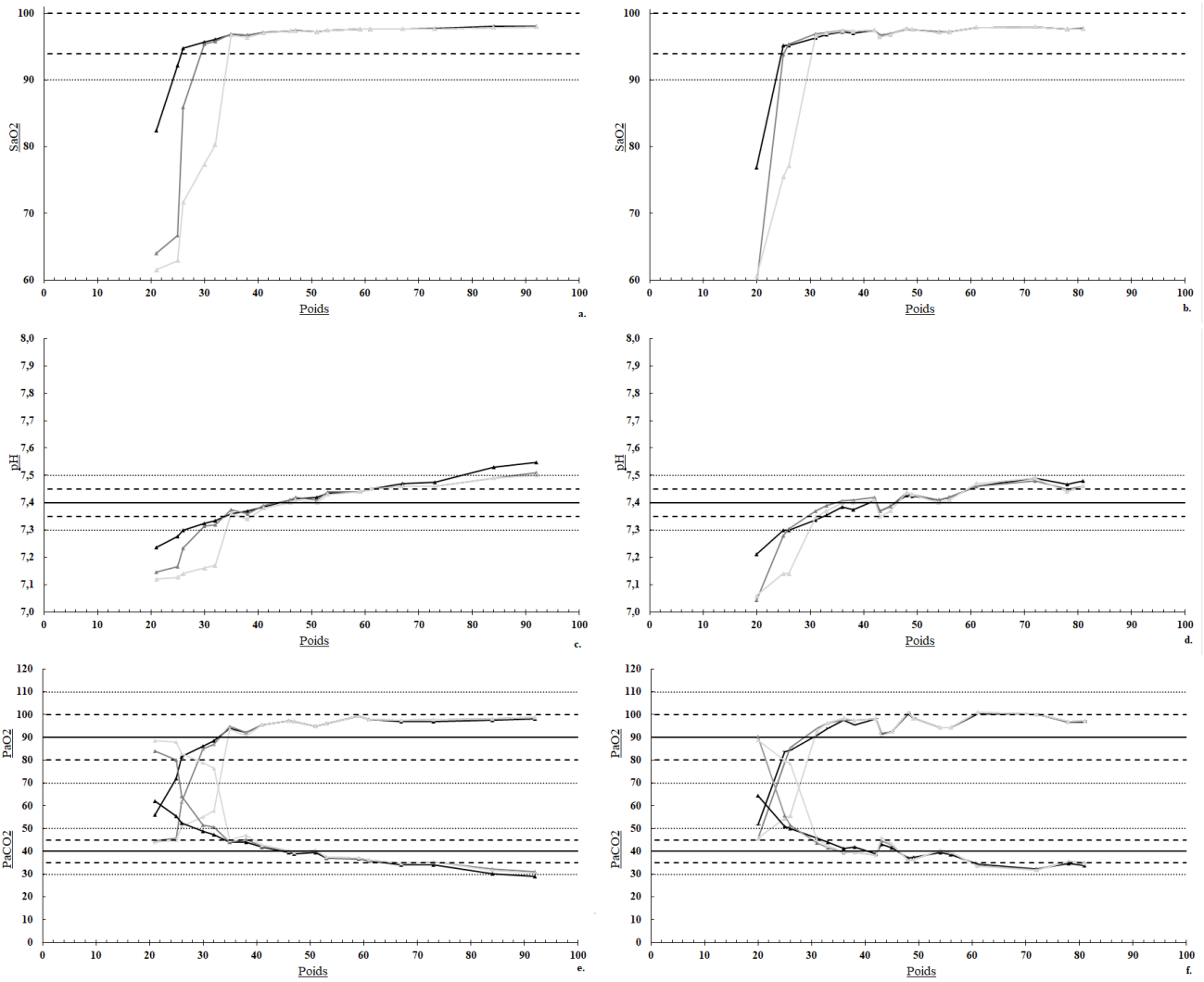

Fig. 12 : Représentation graphique de la prédiction de SimulResp© en fonction du poids et du genre en ventilation spontanée.

a. Saturation artérielle en oxygène (SaO2) garçons. b. SaO2 filles. c. pH garçons. d. pH filles. e. Pressions artérielles en oxygène (PaO2 ▲) et en dioxyde de carbone (PaCO2 ▲) garçons. f. PaO2 et PaCO2 fille.

Limites supérieure et inférieure de la normale. Courbe noire / : simulation de 30 minutes. Courbe gris foncée / : simulation de 3 heures. Courbe gris clair / : simulation de 24h

La figure 13 représente l'évolution de la prédiction de SimulResp© en fonction du poids et du genre du patient en ventilation mécanique. L'analyse de cette figure permet de faire les mêmes constatations que lors de l'analyse de la figure 12. SimulResp© semble fiable pour produire une prédiction dans les limites de la normale à partir d'un poids variant de 25 à 35kg en fonction du paramètre étudié et de la durée de la simulation. De plus, cette prédiction semble se maintenir dans les limites normales de PaO2 et de SaO2, quel que soit le poids, le genre et la durée de simulation, alors qu'elle sort des limites de la normale de PaCO2 et de pH pour des poids supérieurs à 70 kg.

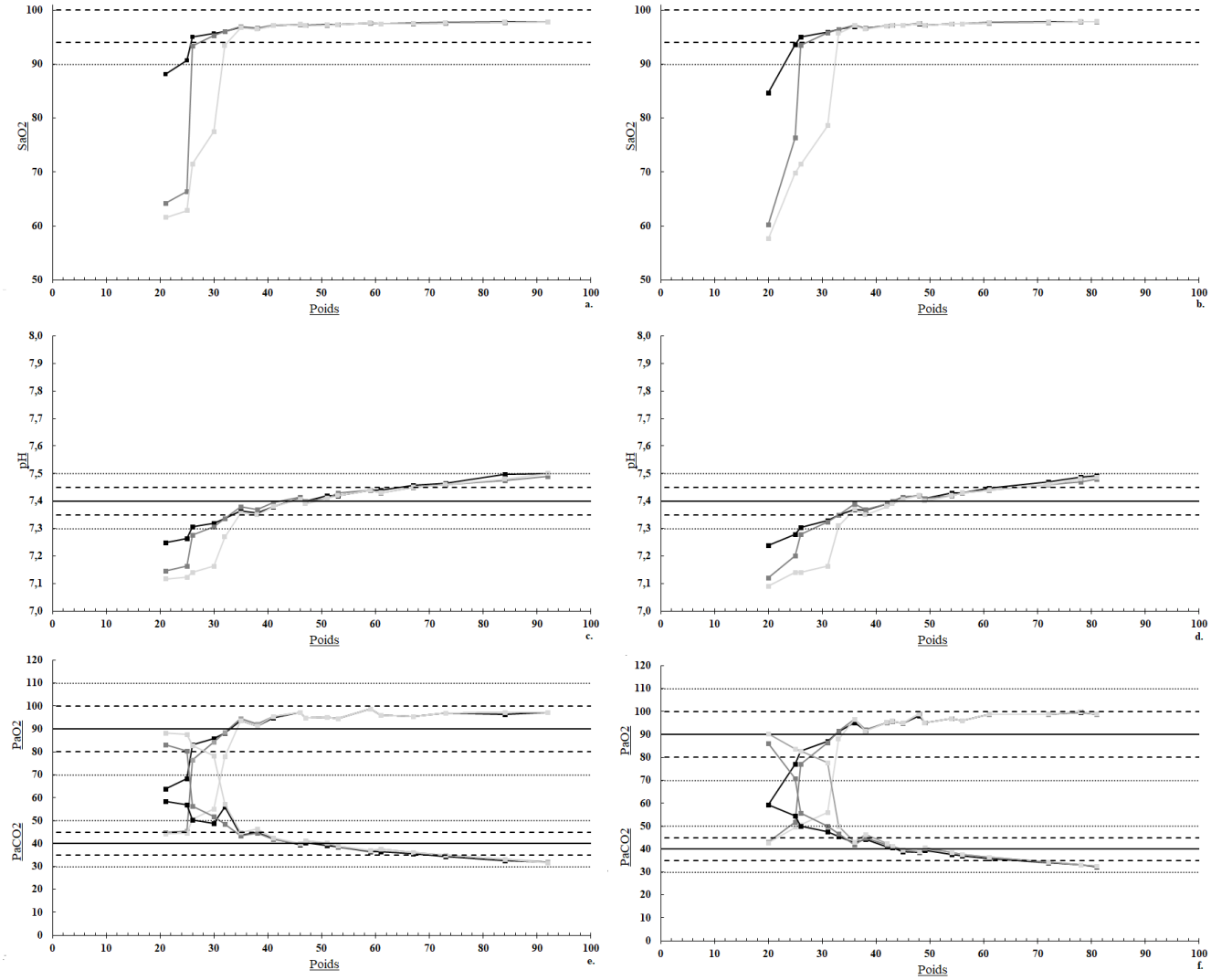

Fig. 13 : Représentation graphique de la prédiction de SimulResp© en fonction du poids et du genre en ventilation mécanique.

a. Saturation artérielle en oxygène (SaO2) garçons. b. SaO2 filles. c. pH garçons. d. pH filles. e. Pressions artérielles en oxygène (PaO2) et en dioxyde de carbone (PaCO2) garçons. f. PaO2 et PaCO2 fille.

Limites supérieure et inférieure de la normale. Courbe noire / : simulation de 30 minutes. Courbe gris foncée / : simulation de 3 heures. Courbe gris clair / : simulation de 24h

b) Evaluation chez le patient réel ventilation spontanée

Cette partie de l'évaluation a été réalisée par Olivier Flechelles en 2012. Les tests ont été réalisés à partir de données publiées dans la littérature provenant de sujets sains en ventilation spontanée lors d'exercice (197) ou en plongé (198). A partir des caractéristiques des sujets décrits dans la littérature, il a été possible de reproduire avec SimulResp© des situations physiologiques cardio-respiratoires. Les valeurs de gaz du sang prédites par SimulResp© ont pu être comparées à celles connues disponibles dans les articles correspondants.

Concernant l'évaluation en situation d'exercice, il a été considéré que la charge de travail maximale mesurée par la VO2max correspondait à 400% de la consommation d'énergie au repos. En partant de ce postulat, l'augmentation progressive de l'effort a été reproduite en commençant avec un effort léger (150% de la consommation d'énergie au repos) jusqu'à l'effort maximal (400% de la consommation d'énergie au repos). La figure 14 (Fig. 14) représente l'évolution de la PaO2 et de la PaCO2 en fonction de l'intensité de l'exercice. Les différences entre les valeurs réelles et simulées sont apparues faibles et non significatives (Tableau 2).

Tableau 2 : Comparaison entre les données simulées et les données réelles au cours de l'exercice chez l'homme sain.

	Simulation	**Mean ≠**	**p**	**r**	**p**
Sim-Exp PaCO2	37,8+/- 2,37 mmHg	-0.77	0.17	0.88	0.022
Sim-Exp pO2	91,8 +/- 3.67 mmHg	1.73	0.1	0.84	0.036

Résultats exprimés en moyenne +/- écart type. mean ≠, moyenne des différences absolues avec la reference. R: coefficient de correlation de Pearson. Valeurs de références issues de Aguilaniu et al.(197)

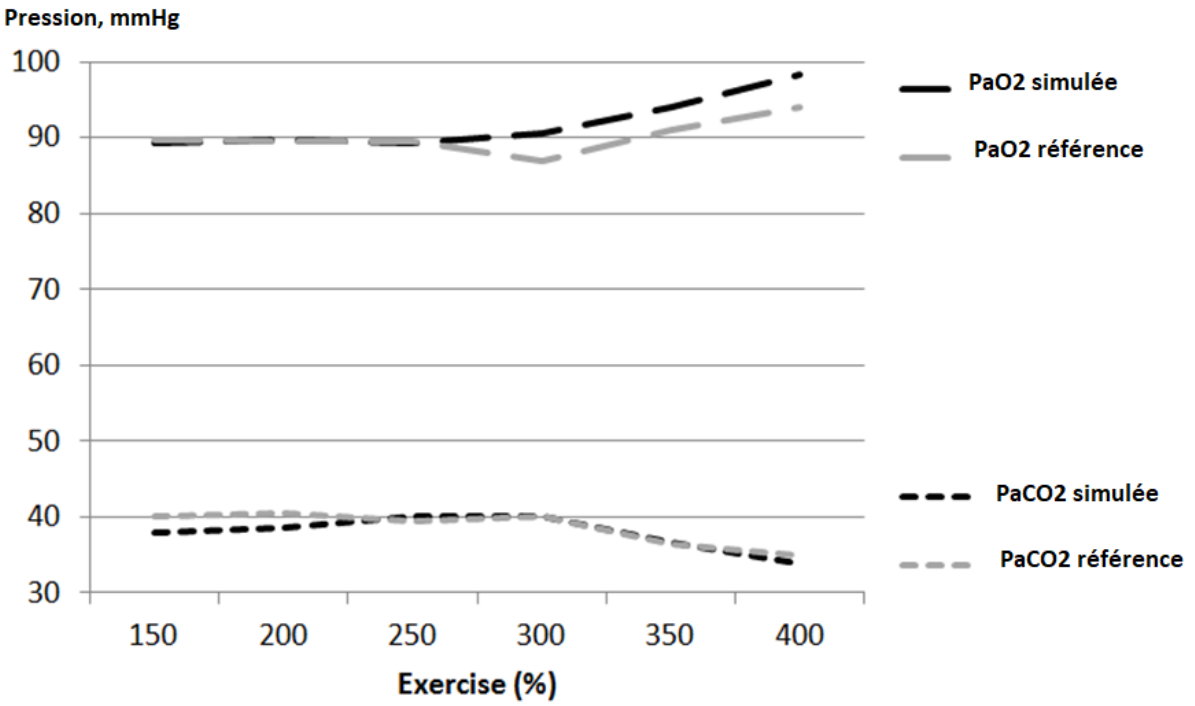

Fig. 14: Comparaison entre les données simulées et les données réelles au cours de l'exercice chez l'homme sain.
PaO2: Pression artérielle en O2. PaCO2 : Pression artérielle en Dioxyde de Carbone. Valeurs de référence issues de Aguilaniu et al.(197).

Concernant l'évaluation en plongée, la situation de sujets sains exposés à une pression équivalente à 4.7 atmosphères a été reproduite. La différence entre les valeurs simulées et les valeurs réelles étaient significativement différentes (Tableau 3).

Tableau 3: Comparaison entre les données simulées et les données réelles au cours d'une plongée à 4,7 atmosphères chez l'homme sain.

	Simulation	Mean ≠	p
Sim-Exp PaCO2	43.4 +/- 0,17 mmHg	-2.7	<.001
Sim-Exp PaO2	629.5 +/- 0.6 mmHg	13.3	<.001

Résultats exprimés en moyenne +/- écart type. mean ≠, moyenne des différences absolues avec la reference. R: coefficient de correlation de Pearson. Valeurs de référence issues de Cherry and al.(198)

c) Evaluation chez le patient réel en ventilation mécanique invasive

Pour réaliser ces tests, nous avons repris les caractéristiques physiques et les données de ventilation de vrais patients inclus dans l'étude GRAeDIENT (68) (Annexe C) pour réaliser plusieurs simulations avec SimulResp©. Les valeurs simulées de pH, PaO2 et PaCO2 ont ensuite été comparées avec celles réelles disponibles dans l'étude (Tableau 4). Les données présentées concernent les patients de plus et de moins de 8 ans. Afin d'inclure les patients de moins de 8 ans dans l'étude, nous avons modifié leurs caractéristiques morphologiques en leur réattribuant des caractéristiques équivalentes à leur percentile de poids et de taille pour un âge de 8 ans.

Tableau 4 : Comparaison entre les données simulés et les données réelles chez l'enfant en ventilation mécanique.

	Réelles n = 67	**Simulées n = 67**	**p**	**R^2**	**p**
pH	7,35 +/- 0,08	7,44 +/-0,1	< 0,0001	0,0002	0,9
PaCO2	43,5 [38,8 - 48,15]	38,2 [35,1 - 43,5]	0.004	0,0009	0,5
PaO2	111 [88,9 - 143,5]	298,2 [198,8 - 692,2]	< 0,0001	0,0199	0,8

Les résultats sont exprimés en moyenne +/- écart type ou médiane [écart interquartile]

2. Evaluation de la répétabilité

La répétabilité est définie comme la capacité de SimulResp© à maintenir une prédiction stable pour un même patient quand les conditions restent inchangées (même méthode, même opérateur, même équipement, intervalle de temps entre les tests court). Pour évaluer la répétabilité, nous avons comparé les valeurs de gaz du sang obtenues à chacun des 3 essais réalisés chez les patients fictifs pour une durée de simulation de 24h (Tableau 5).

Tableau 5 : Evaluation de la répétabilité

	T1	T2	T3	p	CCI	p
SaO2	97 [96,8 - 98]	97 [96 - 98]	97 [96 - 98]	0,8	1 [1 - 1]	< 0,0001
pH	7,40 [7,35 - 7,44]	7,4 [7,34 - 7,44]	7,4 [7,35 - 7,43]	0,2	0,99 [0,99 - 1]	< 0,0001
PaCO2	40 [36 - 46,3]	40 [36 - 46,3]	40 [36 - 46,3]	1	1 [1-1]	< 0,0001
PaO2	96 [91-98]	96 [90,8 - 98]	96 [90,8 - 98]	0,2	1 [1-1]	< 0,0001

Les résultats sont présentés en médiane [Intervalle interquartile]. CCI : Coefficient de corrélation Intra-classe.

Les données présentées dans le tableau 5 sont en faveur d'une excellente répétabilité de la prédiction de SimulResp©.

3. Evaluation de la reproductibilité

La reproductibilité est définie comme la capacité de SimulResp© à maintenir une prédiction stable pour un même patient malgré des conditions différentes (même méthode mais avec un opérateur et/ou un équipement différents). Pour évaluer la reproductibilité, nous avons comparé les résultats obtenus par les 2 opérateurs chez les patients fictifs pour une durée de simulation de 24h (Tableau 6).

Tableau 6 : Evaluation de la reproductibilité

	Investigateur 1	Investigateur 2	p	CCI	p
pH	7,40 [7,35 - 7,44]	7,41 [7,4 - 7,41]	0,3	0,76 [0,61 - 0,86]	< 0,0001
PaCO2	40,1 [36,2 - 46,3]	39,9 [39,1 - 41,8]	0,4	0,71 [0,54 -0,84]	< 0,0001
PaO2	96,2 [90,8 - 98,1]	95,3 [92,6 - 98,8]	0,7	0,58 [0,34 - 0,76]	< 0,0001

Les résultats sont présentés en médiane [Intervalle interquartile]. CCI : Coefficient de corrélation Intra-classe.

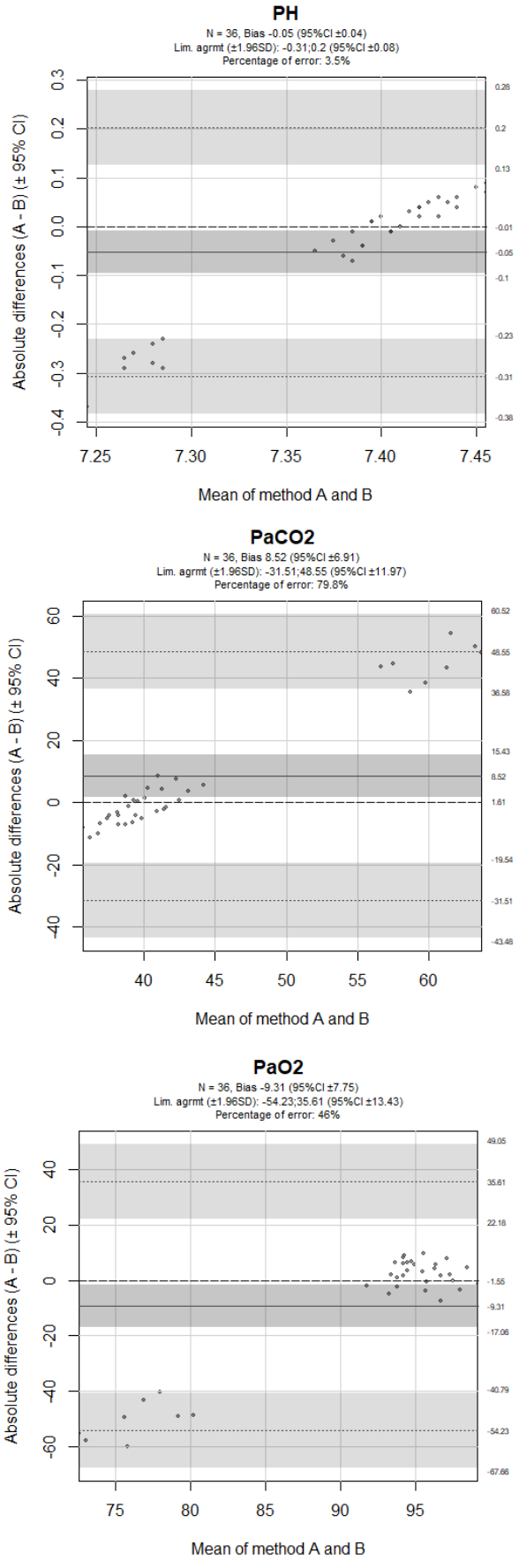

Fig. 15 : Evaluation de la reproductibilité.
Méthode A : Simulation générée par l'investigateur 1
Méthode B : Simulation générée par l'investigateur 2

Les résultats sont en faveur d'une reproductibilité modérée à bonne. Les représentations de Bland & Altman (Fig. 15), montrent que quel que soit le paramètre étudié, la reproductibilité s'altère lorsque les valeurs se situent en zone pathologique.

4. Evaluation de la robustesse

La robustesse définie comme la stabilité de la performance a été évaluée par la capacité de SimulResp© à maintenir une prédiction stable dans le temps quand les conditions restent inchangées. Pour évaluer la robustesse, nous avons comparé les valeurs de gaz du sang obtenues pour chaque patient fictif pour des durées de simulation de 30 minutes, 3 et 24h (Tableau 7) .

Tableau 7 : Evaluation de la stabilité de la prédiction dans le temps

	M30	H3	H24	p	CCI	p
SaO2	97 [96,8 - 98]	97 [97 - 98]	97 [96 - 98]	<0,01	0,86 [0,79 - 0,93]	< 0,0001
pH	7,41 [7,35 - 7,44]	7,41[7,37 - 7,44]	7,40 [7,35 - 7,44]	< 0,001	0,94 [0,89 - 0,97]	< 0,0001
PaCO2	39,5 [36,8 - 44,5]	40 [36 - 45]	40 [36 - 46,3]	0,0001	0,90 [0,80 - 0,95]	< 0,0001
PaO2	95,5 [91,8 - 98]	96 [92 - 98]	96 [91 - 98]	0,1	0,93 [0,87 - 0,96]	< 0,0001

Les résultats sont présentés en médiane [Intervalle interquartile]. CCI : Coefficient de corrélation Intra-classe.

Les différences entre les 3 temps sont statistiquement significatives, mais probablement peu cliniquement signifiantes comme le témoigne le témoigne l'évaluation des coefficients de corrélation intra-classe, en faveur d'une excellente robustesse du SimulResp© et l'analyse des figures 12 et 13.

D. Discussion

Cet article vient clore l'ensemble du travail de thèse visant à préparer le développement, la calibration et la validation du patient virtuel SimulResp©. Nous avons ainsi pu constater la qualité de SimulResp© en ce qui concerne la simulation de valeurs gazométriques chez le patient

sain de plus de 10 ans en ventilation spontanée, confirmant ainsi en partie les données de O. Flechelles et al. (39,55).

Les limites de SimulResp© en ce qui concerne la prédiction chez le moins de 8 ans et/ou en ventilation mécanique s'expliquent probablement par le fait que les algorithmes et formules contenues dans le simulateur adapté du modèle développé en 1977 par CJ Dickinson (54) ne tiennent pas compte des particularités physiologiques et physiopathologiques propres à ces 2 situations.

Physiologiquement le système respiratoire de l'enfant diffère de celui de l'adulte, anatomiquement et mécaniquement (199), essentiellement pendant les 6 à 8 premières années. Moins de 20% des alvéoles « adultes » sont présentes à la naissance. Dans les premières années de vie, la croissance pulmonaire se fait par ajout ou création de nouvelles alvéoles (200). Cette alvéolisation s'accompagne d'une augmentation de la capacité du poumon à réaliser des échanges gazeux (200). On considère que l'alvéolisation est complète vers l'âge de 6 à 8 ans. Par la suite, la surface alvéolaire va croître du fait de la croissance de l'enfant. Cette croissance de la surface alvéolaire est en lien avec la croissance pulmonaire mais n'est pas associée à une augmentation du nombre d'alvéoles (200,201). Par ailleurs, à ces phénomènes de maturation et de croissance pulmonaires, s'ajoutent les particularités anatomiques de la cage thoracique (202). Ainsi, de la naissance à l'âge de 2 – 3 ans, la forme de la cage thoracique va évoluer pour passer d'une forme circulaire à une forme plus ovalaire ou rectangulaire chez l'adulte (202). Cette forme particulière du thorax est à l'origine d'une moindre efficacité mécanique de la cage thoracique en comparaison à l'adulte (203,204), d'autant qu'elle s'associe à un aplatissement du diaphragme dont l'activité mécanique est elle aussi moins bonne. De plus, la compliance de la cage thoracique est élevée alors que celle du poumon est faible. Du fait de cette disparité de compliance, la capacité résiduelle fonctionnelle (CRF) est plus faible et le jeune enfant doit développer plusieurs mécanismes dynamiques de compensation pour maintenir ses réserves en

oxygène et éviter les phénomènes d'atélectasie. En raccourcissant son temps expiratoire, en utilisant l'activité post-inspiratoire du diaphragme et le rétrécissement actif de sa glotte, le nourrisson va freiner son débit expiratoire et générer une pression expiratoire positive intrinsèque maintenant son volume pulmonaire au-dessus de celui de la CRF (203–206). Enfin, à l'ensemble de ces mécanismes s'associent une différence de répartition des fibres musculaires, possiblement à l'origine d'une fatigabilité plus forte de l'enfant, des résistances des voies aériennes supérieures plus importantes, du fait notamment de leur faible diamètre et de leur immaturité (203,204,207) et une immaturité de la commande respiratoire.

La ventilation mécanique diffère physiologiquement de la ventilation spontanée car elle substitue à l'insufflation par dépression induite par la contraction diaphragmatique, une insufflation en pression positive réalisée par une machine externe (199). La mise en place d'un support ventilatoire nécessite 4 éléments :

- une interface adaptée entre le respirateur et le patient,
- une source d'énergie faisant fonctionner la machine,
- une insufflation dont l'importance et le rythme vont être régulés ou contrôlés,
- un système de surveillance des performances du respirateur et de l'état du patient.

Ces 4 considérations élémentaires sont associées à des contraintes mécaniques, physiques et physiologiques qui peuvent être difficiles à prévoir, enregistrer ou standardiser sous forme d'équations mathématiques. De plus, si ces 4 éléments sont nécessaires à la mise en place du support ventilatoire, ils ne sont pas suffisants pour assurer l'efficacité de celui-ci et d'autres éléments comme l'adaptation des paramètres du respirateur au gabarit du patient et sa maladie, la synchronie entre le patient et la machine, le besoin de sédation ou encore le type de respirateur sont à prendre en compte et s'ajoutent comme contraintes et limites à la réussite de la modélisation.

L'étape d'évaluation de la qualité de la prédiction d'un simulateur est essentielle pour assurer la validité de celui-ci et le rendre utilisable (34). La validité d'un simulateur et les exigences des utilisateurs vont dépendre directement de l'objectif pour lequel il a été développé (37,39,42,56). Ainsi, par exemple, il est probable qu'en cas d'utilisation pour l'enseignement une inexactitude puisse être tolérée dès lors que l'évolution ou la prédiction s'approche d'une valeur physiologiquement normale, et que la répétabilité et la reproductibilité sont toutes deux satisfaisantes. Alors qu'une utilisation dans les soins ne peut se concevoir avec un simulateur qui ne serait pas juste.

Plusieurs simulateurs cardio-respiratoires sont décrits dans la littérature (39,40,50,195), mais il n'y que peu de descriptions du processus de validation. La plus part des publications sur le sujet relèvent plus de la description de performance que du réel compte rendu technique du procédé appliqué pour garantir la qualité du simulateur et de sa prédiction (208,209). Quelques équipes ont pris la peine d'évaluer les performances de leur simulateur en comparant les données simulées à des données observées chez des patients réels en ventilation mécanique (47,75,195,210,211). Toutefois, le contenu de ces articles reste centré sur la description de l'objectif du simulateur et les modalités d'élaboration de celui-ci. L'idée de réaliser et de présenter un processus complet de validation, visant à juger de l'aptitude du simulateur à proposer une prédiction juste et fiable dans le temps et les situations, ne semble que rarement faire partie du protocole de recherche (34,212).

La force de ce travail réside dans le grand nombre de tests réalisés. En effet, nous avons multiplié les tests pour augmenter la puissance de nos résultats et limiter le risque de fausses données. Chaque simulation a été répétée 3 fois et en cas de valeur discordante, une quatrième simulation était réalisée pour la remplacer. De plus, nous avons essayé d'évaluer chaque composante de qualité du simulateur : exactitude, répétabilité, reproductibilité et robustesse. Nous avons ainsi pu mettre en lumière les limites du simulateur, notamment en ce qui concerne

la prédiction du patient de moins de 8 ans, le patient malade et le patient en ventilation mécanique.

Ce travail présente tout de même des limites majeures. Le recours à des représentations graphiques pour juger de l'exactitude du simulateur, bien que décrite dans la littérature (34,56,74,213) peut paraitre triviale et dans tous les cas, particulièrement subjective et peu fiable. De plus, la question se pose quant au choix des tests statistiques réalisés. Si il est certain que la mesure de coefficients de corrélation de Pearson ou Spearman est insuffisante pour juger de l'exactitude et de la concordance entre valeur simulée et valeur de référence, la pertinence des autres méthodes statistiques appliquées reste tout aussi questionnable (96,97,133). Enfin, une fois de plus dans ce travail de thèse, la question de l'applicabilité externe se pose. Les résultats que nous avons obtenus ne s'appliquent qu'au SimulResp© et ne peuvent en aucun cas être extrapolée à d'autres simulateurs, même si ceux-ci ont été élaborés à partir du modèle de Dickinson.

Ce travail nous a permis de mieux définir les prochaines étapes de développement de SimulResp© :

- calibration et validation en situation de ventilation spontanée chez le moins de 8 ans avec patients fictifs, puis avec patients réels sains et malades ;
- calibration et validation de la prédiction en ventilation mécanique, chez l'enfant de 0 à 18 ans, avec patients fictifs et avec patients réels sains et malades.

Nous espérons pouvoir réaliser ces étapes à partir de la base de données haute résolution (**Fig. 16**). Dans cette perspective, nous avons commencé à élaborer la méthode qui nous permettra de calibrer le simulateur pour que celui-ci soit fiable dans plusieurs situations physiopathologiques respiratoires (compliance normale (> 2 ml/cmH2O/kg), compliance anormale, résistances augmentées) et hémodynamiques (états de choc) en ventilation spontanée et invasive (**Fig. 16**).

Les patients chez lesquels des gaz du sang auront été prélevés, dans l'heure précédant et dans les 30 minutes à 3 heures suivant une modification des paramètres ventilatoires (47), et dont les données seront enregistrées dans la base de données vont être inclus dans l'étude. Les caractéristiques morphologiques et physiologiques de ces patients seront implémentées dans le simulateur depuis la base de données, idéalement de façon automatisée. Le simulateur génèrera alors une évolution cardio-respiratoire, dépendante de l'état initial du patient, des traitements administrés susceptibles d'influencer la ventilation et les échanges gazeux ainsi que des réglages de la ventilation. Cette prédiction sera comparée à celle connue chez le patient témoin disponible dans la base de données. L'analyse consistera en l'étude de l'exactitude entre les paramètres générés par le simulateur et ceux disponibles dans la base de données pour le patient correspondant. En l'absence de concordance, les équations du modèle seront modifiées afin d'assurer, par une boucle évaluation-amélioration, la maturation du système. Cette phase impliquera du personnel compétent en informatique et fera appel à des techniques d'apprentissage automatique (« machine learning ») (66,139,214–216). L'apprentissage automatique entre dans le champ de l'intelligence artificielle. Il a pour objectif de développer, à partir d'un jeu de données, un modèle permettant de relier certaines données d'intérêt les unes aux autres. Dans le cadre du développement d'un modèle physiologique cardio-respiratoire complexe, nous attendons de l'apprentissage automatique qu'il soit en mesure de déterminer un paramètre physiologique d'intérêt à partir de données physiologiques et thérapeutiques connues, par exemple, prédire l'évolution de la PaO2 en fonction des paramètres ventilatoire, de la maladie et des caractéristiques morphologiques du patient (66).

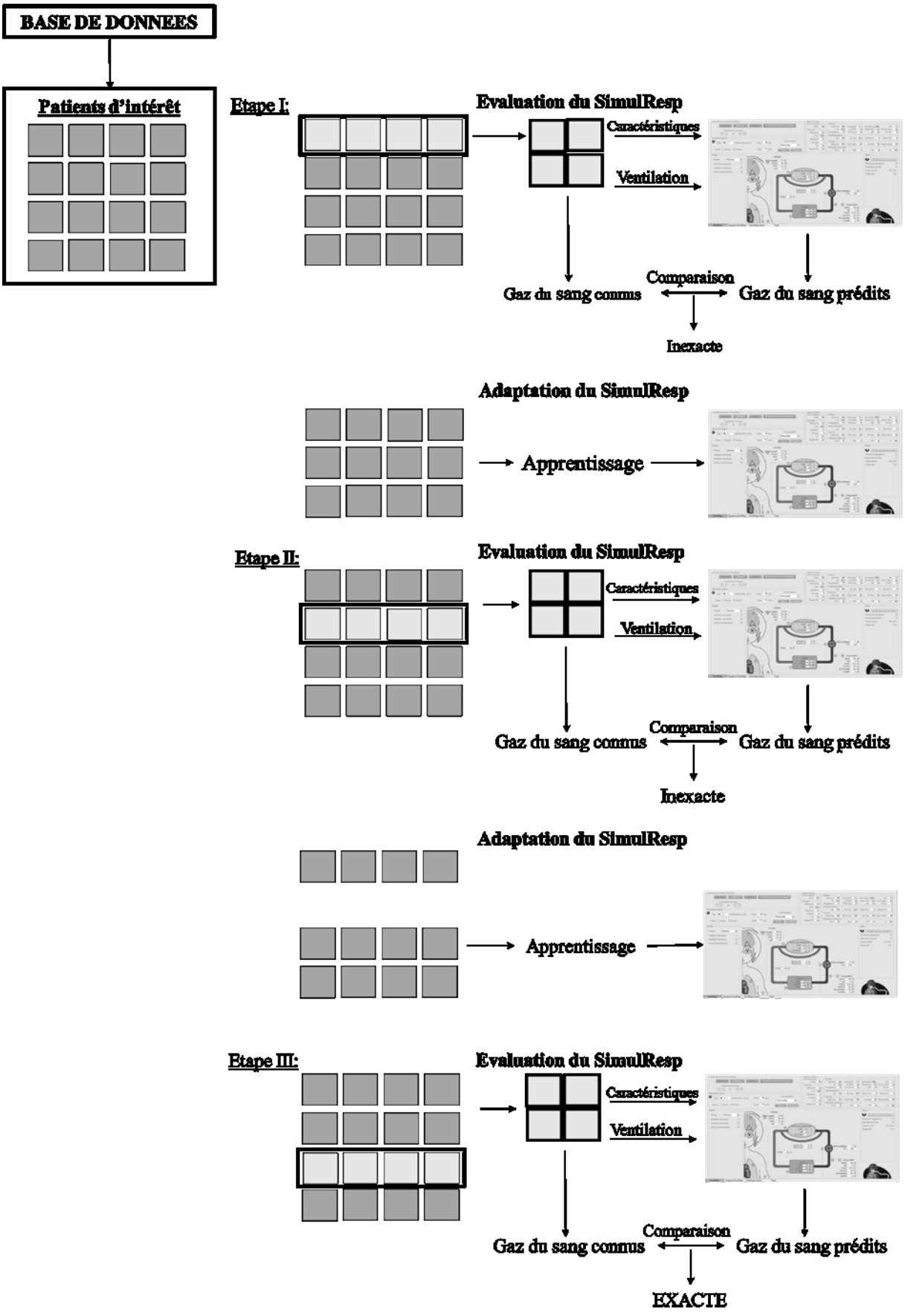

Fig. 16 : Déroulement de l'étude

Plusieurs méthodes d'apprentissage automatiques ont été proposées dans le domaine de l'analyse des données médicales. L'apprentissage en profondeur (« deep learning ») (217) ou l'utilisation d'arbres de décisions (218,219) semblent présenter le plus de pertinence dans ce contexte. Ces étapes seront réalisées dans le cadre d'une étude transversale ou cross-validation (**Fig. 16**) et requièrent l'utilisation d'une partie des données pour entrainer et optimiser le modèle et l'autre partie pour s'assurer de l'efficacité de celui-ci.

Afin de rendre ce travail le plus efficace possible, il apparaît important d'automatiser la plupart des processus comme l'implémentation et l'extraction des données dans le simulateur ou encore l'apprentissage automatique sur les jeux de données pour générer ou raffiner les équations du modèle (66,68,216,220,221). L'automatisation et l'adaptation du code informatique justifient la collaboration en recherche avec une équipe composée d'informaticiens et de mathématiciens.

DISCUSSION GENERALE

Ce travail de thèse rassemble l'ensemble des éléments nécessaires au développement, à la calibration et à la validation du patient virtuel SimulResp©. Ces éléments sont :

- la définition des concepts (31,38),
- la présentation des diverses considérations méthodologiques dans le cadre d'un travail de développement et de validation d'un patient virtuel (38),
- la collecte d'une base de données électronique haute résolution (31,130),
- la validation des données et des processus impliqués dans la collecte des données (65),
- la description de SimulResp© et de ses capacités actuelles (55).

A. La place des outils d'aide à la décision dans la médecine actuelle

La complexité des patients évolue parallèlement aux progrès de la médecine et réciproquement. Stimulée par le souhait de prendre en charge l'ensemble des maladies, même les plus graves, la médecine a évolué. Ainsi, les innovations médicales des dernières décennies ont permis de diagnostiquer et de prendre en charge de plus en plus de maladies graves et complexes. Dans le domaine de la réanimation et des soins intensifs pédiatriques, les patients aux lourds passés médicaux et aux situations physiopathologiques compliquées sont venus s'associer aux enfants sans antécédent, historiquement pris en charge en aigu pour une défaillance mono-système (222–224). Pour assister les praticiens dans la prise en charge de ces patients, de nombreuses recommandations et protocoles sont édités par les sociétés savantes et des groupes d'experts. Cependant, plusieurs obstacles empêchent l'application correcte de ceux-ci. Ces obstacles peuvent être associés aux praticiens, aux soins (5,6,225) mais aussi au patient lui-même. Dans ce contexte, plusieurs outils ont été ou sont en cours de développement,

pour assister les cliniciens au lit du malade. Ces outils vont servir d'une part à standardiser l'application des recommandations et d'autre part à personnaliser les prises en charge, en les adaptant aux particularités du malade et aux conséquences de celles-ci sur l'expression de la maladie. Ces outils sont appelés systèmes d'aide à la décision, ils vont notamment comprendre les protocoles automatisés (12,20) et les simulateurs physiologiques (39,40). L'élaboration de ces systèmes est complexe et les considérations qui entourent cela ont été présentées dans notre article 1. Le point essentiel réside dans la nécessité de recourir à un grand nombre de données patients, à la fois pour permettre leur développement mais aussi leur validation dans plusieurs situations cliniques.

B. La collecte des données à l'heure du dossier médical informatisé

La collecte des données patients semble être facilitée par l'avènement et l'expansion de l'utilisation des dossiers médicaux informatisés. Dans quelques années, le recours à un dossier médical informatisé en réanimation sera devenu un standard de soin et aucun service ne pourra prétendre faire une activité de réanimation de qualité sans lui. Au-delà des bénéfices de sécurisation, d'efficience des soins et de maximalisation financière, le dossier médical informatisé devient un outil majeur de l'optimisation de la recherche clinique (226). En rassemblant l'ensemble des données patients dans des serveurs interrogeables, le dossier médical informatisé accélère les procédures de recrutement des patients et de recueil de données en diminuant les coûts de recherche (226). Toutefois, dans le cadre du développement de systèmes d'aide à la décision, l'utilisation des seules données issues des dossiers médicaux informatisés est problématique. D'une part, l'emploi de certaines données contenues dans les dossiers médicaux informatisés pour une activité de recherche clinique questionne, notamment du fait d'un manque d'homogénéisation des termes médicaux (180). D'autre part, la fréquence de recueil de données apparaît peu compatible avec un travail de développement d'outils physiologiques d'aide à la décision. En effet, les données recueillies au sein du dossier médical

informatisé vont être recueillies soit à un rythme de l'ordre d'une dizaine de minutes à une heure, incompatible avec le développement et l'évaluation des compétences des algorithmes et du simulateur, soit, plus rarement, à un rythme de l'ordre de la seconde à la minute, incompatible avec la validation humaine des données. A cela s'ajoute les problématiques de requêtes spécifiques à chaque dossier patient informatisé ainsi que la problématique des coûts et de la propriété des données dans le cadre d'un entrepôt de données géré par les concepteurs du logiciel. C'est donc dans ce contexte qu'il nous a paru préférable de construire une base de données indépendamment du dossier patient informatisé mais restant lié à celui-ci pour l'exploitation des données contrôlables puis homogénéisables, recueillies à basse fréquence. C'est ce que présente notre article 2.

C. La validation des données dans le cadre d'une activité de recherche

A haute fréquence, le recueil de données dans un contexte aussi labile que les soins intensifs pose plusieurs questions concernant l'exhaustivité du recueil, l'exactitude et la synchronisation des données. Si à basse fréquence, dans le cadre d'une activité de soins, les données sont pratiquement toutes validables et validées au chevet par l'infirmière avant d'être intégrées dans la base, ce processus de validation systématique est impossible lorsque le recueil est réalisé à haute fréquence. Par ailleurs, il apparaît difficile à automatiser et l'intervention humaine est nécessaire. Le travail est ainsi fastidieux et limité.

La description la plus séduisante d'un processus de validation de données après intégration dans une base de données semble être celle de Barnes et al (160). Réalisée dans le cadre de la base de données internationale sur les traumatisés crâniens, cette procédure de validation est réalisée en 3 phases qui vont permettre de classer les données en 4 niveaux de fiabilité. La phase 1 est une phase locale de validation pré-intégration, c'est-à-dire dans le centre où les données sont recueillies, elle implique un contrôle humain, médical et paramédical avant

transfert des données dans la base de données locale. La phase 2, est une phase intermédiaire avant intégration dans la base de données commune. Elle est automatisée et consiste, dans le même temps, en une standardisation avec uniformisation des données et en un dépistage des données manquantes ou aberrantes. Cette phase 2 correspond aux 3 premiers niveaux de validation : Le niveau 1, correspond à une validation de la forme de la donnée, notamment en ce qui concerne le respect du temps. Le niveau 2 diffère en fonction du type de variables. Un contrôle de transcription est réalisé au niveau des variables non numériques alors que les données numériques sont analysées selon la méthode de Bland et Altman. Le niveau 3 contrôle la bonne conversion des unités. En cas de données manquantes une requête est adressée au centre d'origine des données. Ce processus est renouvelé jusqu'à la collecte de toutes les données manquantes. A cette requête est associée une sélection randomisée de 20% des données d'intérêt qui est comparée par un collaborateur local au dossier médical du patient, c'est la phase 3 qui correspond au niveau 4 de validation. A la fin de ce processus de validation, les données sont classées en validées ou non validées selon qu'elles aient ou non été soumises à la phase 3. Les données non validées sont utilisables pour formuler et tester des hypothèses alors que les données validées le sont pour réaliser des analyses à des fins de publication. Ce procédé de validation a été repris en 2008, par Shaw et al. (135) toujours dans le cadre du Brain IT. Dans cette deuxième description de validation de la base Brain IT, le coefficient de détermination R^2 ainsi que l'évaluation du taux d'erreur viennent s'ajouter à l'analyse de Bland et Altman. En analysant ces descriptions du processus de validation de la base Brain IT (135,160), on comprend pourquoi la phase de validation des bases de données collectées automatiquement à haute fréquence est souvent délaissée. A l'époque de la première publication (160), la base Brain IT ne comptait que 50 patients répartis dans 15 centres, ce qui est peu, comparé au plus de 800 patients inclus dans 1 centre à la même époque dans la base MIMIC II (115). En effet, un tel processus de validation ne semble que partiellement applicable à une base

de données haute résolution de grande ampleur. C'est pourquoi, dans cette situation, l'évaluation de la qualité d'un échantillon de données représentatif de la base permet de valider la qualité du concept de récolte de données appliqué. Ces étapes de validation de notre base de données sont présentées dans les articles 3 et 4. Ces articles sont uniques dans le contexte des bases de données haute résolution. La difficulté de validation d'une base de données électroniques automatiquement collectées est telle que la plupart des concepteurs semblent avoir occulté le problème en misant essentiellement sur la fiabilité des systèmes d'enregistrement et un contrôle humain à basse fréquence. Néanmoins, quel que soit le procédé de validation, il reste important lors de la réalisation d'études d'envisager une phase de revalidation préanalyse ou à défaut d'avoir conscience des limites possibles de fiabilité de tels ensembles de données et d'informer le lecteur de ces limites.

D. De la donnée au patient virtuel – boucler la boucle

Les 3 premiers articles de cette thèse sont venus assoir le concept de patient perpétuel (« perpetual patient »). Jamais encore utilisé dans la littérature scientifique jusqu'à notre première publication de 2016, ce concept défini comme un patient dont on peut reprendre à l'infini le déroulé du séjour du fait de la grande quantité de données organisables dans le temps qui ont été recueillies pendant son séjour a été repris par R Wetzell (131). Ces patients perpétuels vont servir de « patron » pour le développement des algorithmes et des formules assurant le juste fonctionnement du patient virtuel puis d'autres vont être utilisés pour tester la fiabilité de celui-ci, selon un processus de cross-validation (104,105).

PERSPECTIVES

Si la mise en place de notre base de données avait comme premier objectif le développement et la validation du patient virtuel SimulResp©, la valeur scientifique des données physiologiques et thérapeutiques qu'elle contient dépasse ce cadre. Cette base de données haute-résolution s'intègre dans le concept plus large de Big Data ou données massives (59). En plus des considérations méthodologiques informatiques nécessaires à la programmation précédemment décrites, l'utilisation optimale d'une telle base de données passe par le recours à des outils d'interrogation, de visualisation et d'analyse performants (217,227–230). Il existe aujourd'hui plusieurs outils informatiques et méthodologiques permettant l'analyse d'une grande quantité de données. Classiquement on distingue 4 types d'analyses (140,217) : les requêtes, les rapports, le traitement analytique en ligne et le « data mining ou fouille de données ». Chacun de ces types d'analyses impliquent des outils différents et spécialisés (108,124,227). Initialement réservés à des initiés étant donné leur caractère peu intuitif, ces outils se sont progressivement popularisés (157). En nous appuyant sur ces précédentes expériences, dans l'objectif d'optimiser l'utilisation de cette base de données dans le cadre d'une activité de recherche clinique, il semble nécessaire de développer des outils en facilitant l'accès et l'interrogation.

Par ailleurs, si les informations contenues dans une telle base locale ont une grande valeur, on imagine la pertinence d'étendre ce recueil à une plus large échelle. Si mutualiser des bases de données électroniques collectées automatiquement en haute résolution en une base de données unique conjointe multicentrique, voire multinationale, représente un grand intérêt, c'est un projet colossal qui soulève beaucoup de questions et de problématiques, notamment réglementaires, légales et financières. Toutes ces questions doivent se poser en amont avec des réponses au niveau local et au niveau global (108,116,124,160,185,192,193).

En ce qui concerne le simulateur SimulResp©, une fois validé, bien que son objectif premier soit une utilisation pour le développement et la calibration d'outils d'aide à la décision clinique, il a aussi vocation à être utilisé pour l'enseignement de la physiologie respiratoire et la ventilation mécanique. Dans le cadre de cette utilisation en pédagogie, à l'avenir, on peut envisager de l'associer et de l'implémenter dans un mannequin de simulation. En fonction des interventions réalisées par l'apprenant sur le mannequin, le simulateur réalise une prédiction faisant évoluer la situation simulée et la rendant ainsi plus vraisemblable. Dans le cadre de ce travail, nous avions défini cette boucle entre le simulateur et le mannequin comme la simulation « très haute » fidélité (38).

CONCLUSIONS

L'avenir des soins intensifs, en particulier pédiatriques, passe par le développement et l'utilisation de systèmes d'aide à la décision incluant des protocoles automatisés. Ces dispositifs auront comme avantage de permettre une meilleure adéquation entre les pratiques et les recommandations mais aussi par l'intermédiaire de simulateurs, notamment en ventilation mécanique, d'améliorer la personnalisation des prises en charge en réanimation, tout en assurant la sécurité des patients.

Dans ce contexte, la mise en place d'une base de données haute résolution associant des signaux bio-médicaux, à des données ventilatoires, cliniques et thérapeutiques semble essentielle. Après évaluation et validation de la qualité de la base et des données qui la constituent, celle-ci représente une source inépuisable et inestimable d'apprentissages et de découvertes permettant d'optimiser la recherche clinique.

L'utilisation optimale d'une base de données électronique automatiquement collectées à haute fréquence nécessite le recours à plusieurs outils méthodologiques avant, pendant et après la conception. Chacun de ces aspects est à considérer tout au long de la constitution et de l'exploitation de la base de données. Le médecin impliqué dans un tel projet ne peut raisonnablement pas connaître l'ensemble des détails de programmation et d'analyse de la base mais doit être en mesure de collaborer en équipe multidisciplinaire pour être certain d'exploiter les meilleures méthodes disponibles afin de tirer des connaissances et des réponses fiables à partir des données collectées.

Ce travail de thèse semble avoir satisfait tous ses objectifs, de la mise en place de la base de données haute résolution en soins intensifs pédiatriques à la réalisation d'un portrait de l'état actuel du simulateur cardio-respiratoire SimulResp©. L'ensemble des éléments semble réuni pour permettre la suite du processus de calibration et de validation de SimulResp© ainsi que le développement de nouveaux dispositifs d'aide à la décision.

A partir de la base de données, il sera possible de tester l'exactitude de la prédiction de SimulResp© dans plusieurs situations en ventilation spontanée comme invasive, en la comparant à l'évolution connue des patients inclus dans la base. En l'absence de concordance entre la prédiction et la réalité, les équations du modèle seront modifiées afin d'assurer par une boucle évaluation-amélioration la maturation du système.

Enfin, cette base de données représente un puit de connaissances qu'il sera possible d'étudier par l'intermédiaire des procédés d'apprentissage machine. Ces méthodes d'analyse des gros volumes de données devraient apporter de nombreuses réponses fiables sur des questionnements d'ordre physiologique mais aussi thérapeutique. A l'avenir, ces modalités de recherche pourraient être considérer à haut niveau de preuve dès lors qu'elle sont appliquées sur des données vérifiées, de qualité et idéalement recueillies à l'échelle internationale, proposant ainsi une alternative intéressante aux essais randomisés, lourds à mettre en place, particulièrement en pédiatrie.

COMMUNICATIONS ASSOCIEES

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ANNEXES

A. Using machine learning models to predict oxygen saturation following ventilator support adjustment in critically ill children: a single center pilot study.

PLOS ONE

RESEARCH ARTICLE

Using machine learning models to predict oxygen saturation following ventilator support adjustment in critically ill children: A single center pilot study

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Data Availability Statement: To reproduce our analysis the algorithm is available in the following public repository: https://github.com/sauthiem/SpO2-Prediction. For access to the dataset, please contact Mme Genevieve Cardinal at genevieve.cardinal@recherche-ste-justine.qc.ca, president of the Ethical Review Board of Ste-Justine Hospital. Our ERB request a protocol submission and an interinstitutional agreement.

Abstract

Background

In an intensive care units, experts in mechanical ventilation are not continuously at patient's bedside to adjust ventilation settings and to analyze the impact of these adjustments on gas exchange. The development of clinical decision support systems analyzing patients' data in real time offers an opportunity to fill this gap.

Objective

The objective of this study was to determine whether a machine learning predictive model could be trained on a set of clinical data and used to predict transcutaneous hemoglobin oxygen saturation 5 min ($_{5min}$ SpO_2) after a ventilator setting change.

Data sources

Data of mechanically ventilated children admitted between May 2015 and April 2017 were included and extracted from a high-resolution research database. More than 776,727 data rows were obtained from 610 patients, discretized into 3 class labels (< 84%, 85% to 91% and c92% to 100%).

Performance metrics of predictive models

Due to data imbalance, four different data balancing processes were applied. Then, two machine learning models (artificial neural network and Bootstrap aggregation of complex decision trees) were trained and tested on these four different balanced datasets. The best model predicted SpO_2 with area under the curves < 0.75.

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Competing interests: The authors have declared that no competing interests exist.

Conclusion

This single center pilot study using machine learning predictive model resulted in an algorithm with poor accuracy. The comparison of machine learning models showed that bagged complex trees was a promising approach. However, there is a need to improve these models before incorporating them into a clinical decision support systems. One potentially solution for improving predictive model, would be to increase the amount of data available to limit over-fitting that is potentially one of the cause for poor classification performances for 2 of the three class labels.

Introduction

In case of respiratory failure, mechanical ventilation supports the oxygen (O_2) diffusion into the lungs and the carbon dioxide (CO_2) body removal. As an expert in mechanical ventilation cannot reasonably be expected to be continuously present at the patient's bedside, specific medical devices aimed to help in ventilator settings adjustments may help to improve the quality of care [1]. Such devices are developed using algorithms either based on medical reasoning that adapt ventilator settings in real time based on patients' characteristics [2, 3] or based on physiologic models that simulate cardiorespiratory responses to mechanical ventilation settings modifications [4]. The first ones are not accurate enough to be used widely in clinical practice, especially in children, and the latter are not validated for this indication. Both algorithms do not learn from ever-growing sets of clinical research data that could potentially improve their performances. To overcome this drawback, another avenue is the development of algorithms using artificial intelligence to provide caregivers with support in their decision-making tasks.

Among the vital parameters, transcutaneous hemoglobin saturation oxygen (SpO_2) is monitored continuously at the bedside in intensive care and must be maintained in an adequate range to insure tissue oxygenation. In mechanically ventilated patients, when SpO_2 is low, either FiO_2 or ventilation pressures/volume are increased.

In this retrospective study, we assessed machine learning methods to predict the classification (normal, low or critically low) SpO_2 of mechanically ventilated children after a ventilator setting change using a high-resolution research database. Such a modelling will help caregivers for the prescription of ventilator settings i.e. the caregiver will use the model to predict the effect of a ventilator setting change on SpO_2 and will apply this ventilator modification if satisfied of the predicted SpO_2.

Materials and methods

This retrospective study was conducted at Sainte-Justine Hospital, Quebec, Canada and included the data collected prospectively between May 2015 and April 2017 of all the children, less than 18 years old, admitted to the Pediatric Intensive Care Unit (PICU) and were mechanically ventilated with an endotracheal tube. Patients' data were excluded if the patient was hemodynamically unstable defined as 2 or more vasoactive drugs delivered at the same time (ie., epinephrine, norepinephrine, dopamine or vasopressin) or with an uncorrected cyanotic heart disease defined by no $SpO_2 > 97\%$ during all PICU stay. All the respiratory data from included patients were extracted from the PICU research database [5], after study approval by the ethics review board (ERB) of Sainte-Justine hospital (ERB study number 2017 1480).

Prediction problem

The predictive SpO_2 class (prognostic class) was the SpO_2 5 minutes after a change of a ventilator setting. The delay of 5 min corresponded to the shortest period of time to reach a steady state after modification of a ventilator setting [6]. SpO_2 levels at 5min were classified into three categories (Table 1). The thresholds were selected according to clinical value: a $SpO_2 < 92\%$ is a target to increase oxygenation in mechanically ventilated children [7]. The critical level of 85% SpO_2 is used as an alarm of severe hypoxemia in intensive care [8]. The success criteria for prediction was the ability of the model to predict the SpO_2 category, 5min after a ventilator setting change *ie* delta in inspired fraction of Oxygen (ΔFiO_2), delta in tidal volume, pressure support or pressure controlled (ΔVt, ΔPS or ΔPC) or delta in Positive end expiratory pressure set ($\Delta PEEP$). The variables used in the model are detailed in Fig 1. These ventilator parameters were determined by an item generation-selection methods conducted by three physicians (PAJ, MS, DB). The resulting items are presented in Fig 1 within their sources, means of extraction and a schematic of the main components of the study.

Data preparation for model building

The data were extracted from a research database approved by the ethics committee of Sainte-Justine Hospital (database ERB number 2016–1210, 4061). The data extracted from the research database needed: (1) to remove erroneous data due to disconnection of the patient from the ventilator or the monitor, or due to transient interventions such as suctioning; (2) to remove the rows at which no ventilator setting variables was modified; (3) to adapt data format for classifier training. The methodology to format the data is described in S1 File. In summary, we first transformed the data from the linear format into a table, where the clinical variables are the column labels and the patient codes and storing times are the row labels. Since the readings for the various variables involved are not all set at the same frequency, the data for the different variables were aligned along the rows time-steps. Then, only the rows at which at least one of the setting variables is modified were preserved in the data file. The rows with change in "FiO_2 Setting" more than 0.2 were excluded, to remove increase of FiO_2 to 1 when suctioning. For each row, the target variable is added by binning the data of variable "SpO_2 in 5 min" into three classes (Table 1). The binning of the target variable data into three classes allows for better classification performance. For all time-steps, SpO_2 values were validated and kept in the database if heart rate (HR) from monitors in each row was within ± 10 bpm the HR from the pulse oximeter. All rows containing HR readings which do not respect this condition were removed.

The number of patients included was 610 mechanically ventilated children and the total number of rows according to SpO_2 classification is specified in Table 1. We randomly distributed the number of rows between the training and test databases, without considering the number of patients in each dataset.

Data balancing

The data analysis showed a severe imbalance with most SpO_2 at 5min above 92%. This is logical as caregivers want to maintain SpO_2 in normal range during child PICU stay. In such

Table 1. Definition of SpO_2 class labels.

SpO_2 classification	SpO_2 range (%)	Rows number (n)
1	< 84	17,112
2	85 to 91	29,869
3	92 to 100	729,746

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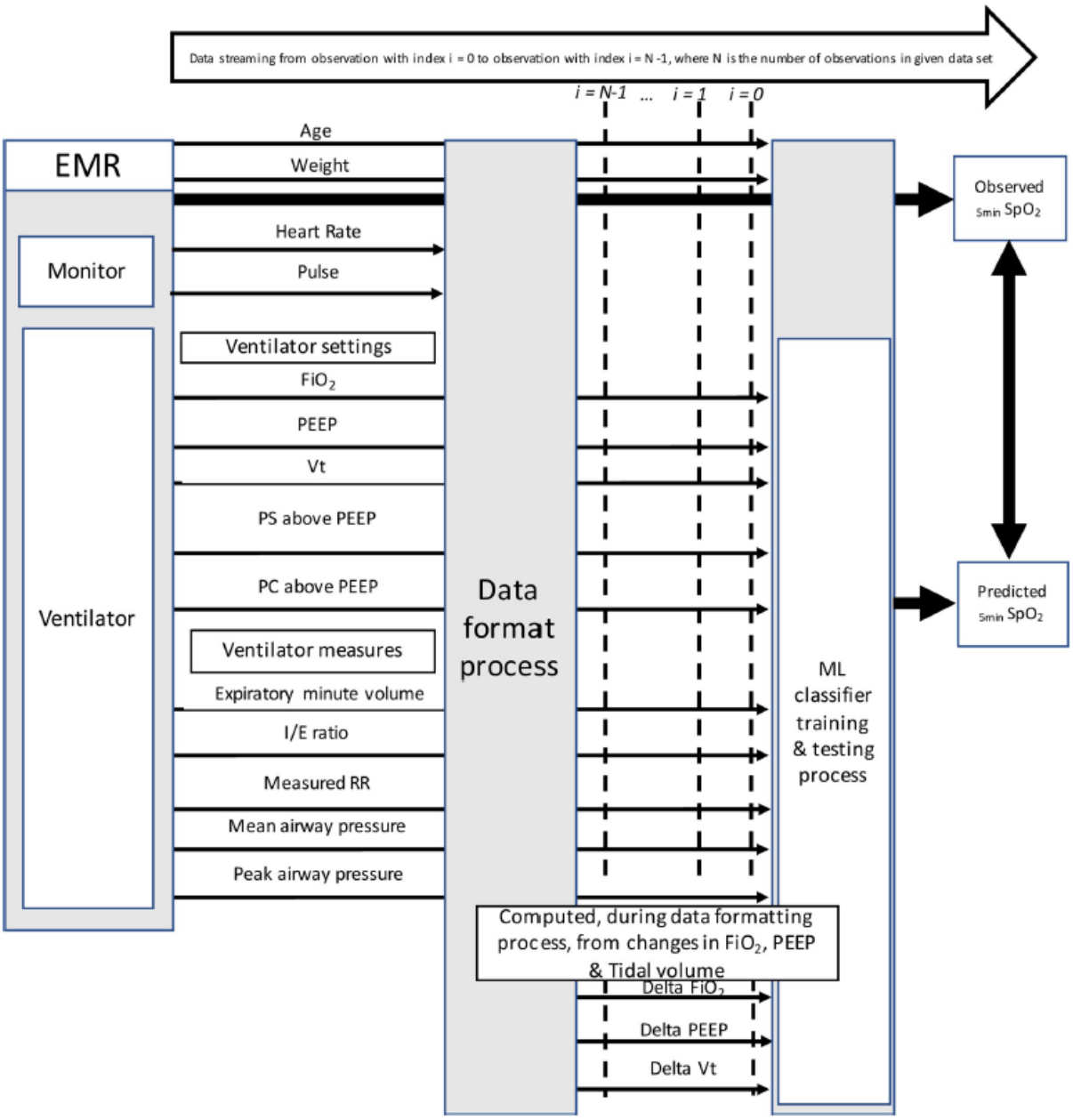

Fig 1. Schematic description of the items involved and analysis process. EMR: electronic Medical Record, FiO_2: inspired fraction of Oxygen, Vt: tidal volume, PEEP: Positive end expiratory pressure, PS above PEEP: pressure support level Above PEEP, PC above PEEP: pressure control level above PEEP, I:E Ratio: inspiratory time over expiratory time, Measured RR: respiratory rate measured by the ventilator. $_{5min}SpO_2$: SpO_2 observed 5 min after PEEP, FiO_2, tidal volume, PS above PEEP, PC above PEEP change, ML: machine learning. Heart and pulse rate were only used to validate the database SpO_2 value (see below and S1 File).

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condition, the classifier learns the majority class label (class 3) (Table 1) but doesn't learn the minority class labels (class 1 and 2) [9]. As, the data balancing process aims to allow the

Table 2. Descriptions of the four balancing procedures. The training/test split was done on the number of data samples.

DATASET 1	DATASET 2	DATASET 3	DATASET 4
Training set: 975,036 samples **Test set:** 193,528 samples **Class Balancing:** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (325,012).	**Training set**: 2,293,119 samples **Test set:** 201,926 samples **Class Balancing**: SMOTE applied to classes 1 & 2 to make their cardinalities equal to that of class 3 (764,373).	**Training set:** 487,464 samples **Test set:** 106,028 samples **Class Balancing:** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (162,488).	**Training set**: 1,462,503 samples **Test set:** 281,028 samples **Class Balancing** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (487,501).

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classifier to learn from all class equally, a combination of down-sampling and up-sampling techniques were included: to balance the three classes of the data involved, a down-sampling of the SpO_2 class 3 using TOMEK algorithm [10] and an over-sampling of SpO_2 class 1 and 2 using Synthetic Minority Oversampling Technique (SMOTE) [11] were performed.

The down-sampling process was made up of the following steps: (1) TOMEK algorithm was used to detect TOMEK links throughout the whole dataset, for all three classes, and removed them. TOMEK links are the links between any two observations considered nearest neighbors, but which belong to different classes [9], (2) points remainders removed are selected at random.

The creation of synthetic data points by SMOTE can be formulated as follows:

$$x_{syn} = x_i + (x_{knn} - x_i) \times \delta$$

In this equation, x_{syn} represents the synthetic data point. The variables x_i and x_{knn} are respectively the original instance, and the nearest neighbor data point which is randomly picked among the k nearest neighbors. The random number δ is generated in [0,1] to determine the position of the created synthetic data point along a straight line joining the original data point x_i and its chosen nearest neighbor x_{knn}.

To study which data balancing method provided the more accurate algorithm, four datasets were produced via four different balancing procedures, involving different combinations of data balancing techniques (Table 2).

Predicted SpO_2 model construct

To identify the best machine learning classification method, we tested two classification models: artificial neural network and bagged complex decision trees, on the four balanced training datasets.

Artificial Neural Network (ANN). Once the data has been pre-processed, a machine learning predictive model was trained on a sub-set of labeled training data. The model is then used to predict the target variable values on a testing subset where the class labels are hidden. We used Artificial Neural Networks (ANN) to make predictions of the SpO_2 variable, based on the values of the other variables of interest. Through the function approximation that the ANN performs, it is possible to make predictions of SpO_2 variable, based on the input data. The outputs are the probability for each of the 3 class where the sum of their probabilities is 1.

The ANN is learned from training data, using the backpropagation algorithm [12] and is tested on a test set made of the remaining rows of data to validate the generalization of the model. The learning algorithm runs through all the rows of data in the training data set and compares the predicted outputs with the target outputs found in the training data set. The

weights are adjusted via supervised learning, in a manner to minimize the error of predicted SpO_2 vs target SpO_2. The process is repeated until the error is minimized.

The ANN classifier was implemented through cycles of forward propagation followed by backward propagation through the network's layers. The backpropagation algorithm is used for performance optimization. For detailed information see S2 File.

Bootstrap aggregation of complex decision trees. Bootstrap aggregating (acronym: bagging) was proposed by L Breiman in 1994 to improve classification by combining classifications of randomly generated training sets [13]. Bagging allows for the creation of an aggregated predictor via the use of multiple training sub-sets taken from the same training set. Let ($\boldsymbol{T}^i$) denote the replicate training sub-sets bootstrapped from the training set $\boldsymbol{T}$. These replicate sub-sets each contain N observations, drawn at random and with replacement from $\boldsymbol{T}$. For each of these sub-sets of N observations, a prediction model, or classifier, is created. The computational model used for bagging was complex decision trees. This means that, for each bootstrapped sub-set of training data, a complex decision tree is trained and thus a classifier is created. If $i = 1, \ldots, n$, then n classifiers are created through the bagging process.

A decision tree is a flowchart computational model which can be used for both regression, as well as classification problems. Paths from the root of the tree to its various leaf nodes go through decision nodes in which decision rules are applied in a recursive manner, based on values of input variables. Each path represents an observation $(\boldsymbol{X}, y) = (x_1, x_2, x_3, \ldots, x_n, y)$, where the label assigned to the target y is given in the leaf node, at the end of the path *i.e.* classification [14].

The measure used to build sub-trees was the gini index (see infogain.doc for details). We tested the BACDT model using 30, 50 and 70 decision trees.

In the aim of maximizing the model's generalization capability during the training process, the Bagged Complex Trees' performance is tested via k-fold cross-validation. A value $k = 10$, which is common practice, was used in this study for both the complex decision trees and ANN. The training using k-fold cross-validation is carried out as described below:

The data-set is first divided into two parts; the training-set and the test-set. The training of the "Bagged" Complex Trees includes a k-fold cross-validation, which is performed as follows:

- Randomly partition the data-set into k equal-sized subsets (folds).
- For each of the k equal-sized subsets:
  - Train/fit the model on the elements contained in the other (k-1) subsets.
  - Test the model's accuracy on the given subset.
- Iterate over the k subsets, until each one has been used once for testing the model's performance during its training.
- The training validation score consists of the average score obtained by validating the model on all k subsets.

The mathworks Matlab R2016b Machine Learning toolbox was used for the creation of the ensemble of Bagged complex trees model. The ANN classifiers were implemented using the Scikit-Learn package within the Python programming language [http://scikit-learn.org].

Classifiers performances assessments

If the model outputted a predicted probability >0.9 for a given class, then the predicted class was considered positive. We evaluated the performances of the classifiers based on the metrics including ROC curves, average accuracy, precision (ratio of all correct classifications for class i to all instances labeled as class label i by the model), recall (ratio of the number of instances

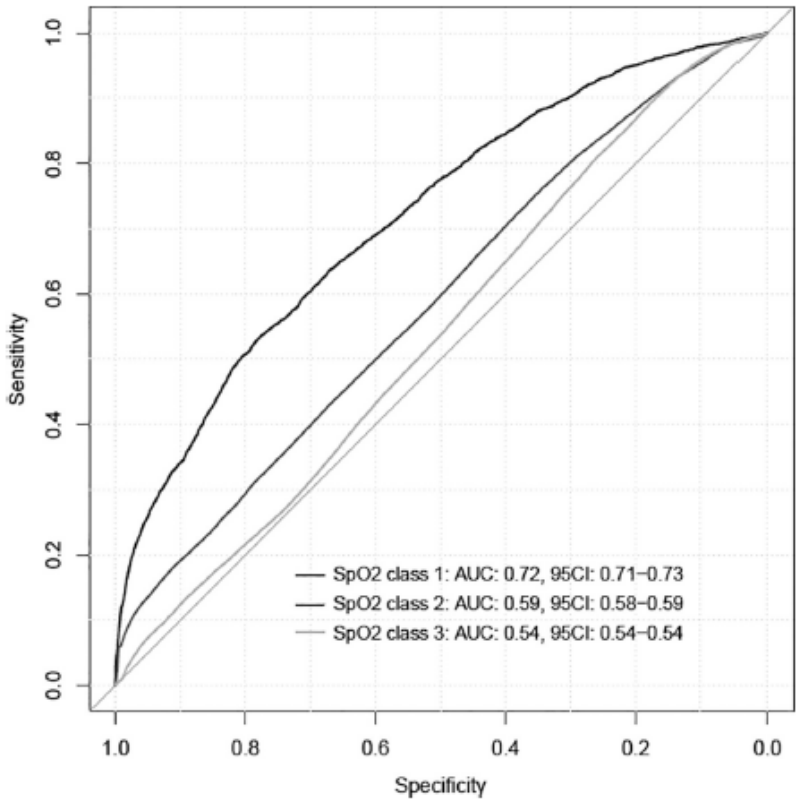

Fig 2. ROC curve for each SpO_2 prediction at 5 min following a ventilator setting change of the best predictive model (bootstrap aggregation of complex decision trees (BACDT) classifiers on Test Dataset 3). Class 1: $_{5\ min}SpO_2$ < 84%, class 2: $_{5\ min}SpO_2$ between 85% and 91%, class 3: $_{5\ min}SpO_2$ between 92% and 100%. AUC: area under the curve, 95IC: 95% confidence interval.

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classified in class label *i* to the number of true class *i* labels) and F score (single measure of classification performance of the model used), see S2 File for further details [15].

Results

The number of patients included was 610 mechanically ventilated children with a median duration of ventilation of 33hrs (1st quartile: 6.5hr and 3rd quartile: 116.9 hr), similar to a previous study [16]. In the 776,727 ventilator settings modifications (Table 1), 98% of the ventilator settings modifications were FiO_2 setting changes. The performances of the two machine learning classifiers to predict SpO_2 at 5 min after a ventilator setting change (*ie* FiO_2, PEEP, Vt/Pressure support or pressure controlled above PEEP) was developed on four different balanced training datasets and assessed on four different balanced test datasets (see Table 2). In Fig 2 and Table 3, we report the performances of these two classifiers. Using the classification performance metrics, the bagged trees classifier trained on dataset #3 has yielded the best classification performance on the test sets (Table 3) and was the predictive model retained. The ROC curves are shown in Fig 2 with area under the curves below 0.75 for all class.

Impact of hidden layers for ANN and number of complex trees for BACDT on performance

For the artificial neural network, the variation of the number of hidden layers and number of neurons per hidden layer did not seem to have a significant effect on the model's classification

Table 3. Performance of artificial neural networks (ANN) and bootstrap aggregation of complex decision trees (BACDT) classifiers for SpO_2 prediction at 5 min following a ventilator setting change, on test datasets (see Table 2). Avg/total: average accuracy of total classification values. In italics is the performance of the best predictive model obtained among the eight tested.

Balanced datasets	$_{5min}SpO_2$ class	ANN			BACDT		
		Precision	Recall	F-score	Precision	Recall	F-score
Dataset 1	1	0.12	0.70	0.21	0.80	0.76	0.78
	2	0.16	0.43	0.23	0.61	0.56	0.59
	3	0.96	0.67	0.79	0.97	0.98	0.97
	Avg/total	0.88	0.65	0.73	0.94	0.94	0.94
Dataset 2	1	0.09	0.72	0.16	0.77	0.72	0.74
	2	0.09	0.47	0.16	0.57	0.53	0.55
	3	0.98	0.70	0.81	0.98	0.99	0.98
	Avg/total	0.93	0.69	0.78	0.96	0.97	0.97
Dataset 3	1	0.16	0.68	0.25	**0.80**	**0.76**	**0.78**
	2	0.26	0.42	0.33	**0.67**	**0.62**	**0.65**
	3	0.92	0.60	0.72	**0.95**	**0.96**	**0.96**
	Avg/total	0.80	0.58	0.65	**0.91**	**0.91**	**0.91**
Dataset 4	1	0.09	0.69	0.16	0.80	0.74	0.77
	2	0.12	0.47	0.19	0.58	0.54	0.56
	3	0.97	0.68	0.80	0.98	0.98	0.98
	Avg/total	0.92	0.67	0.76	0.96	0.96	0.96

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performance (Table 4). As for the Bagged complex trees, the variation of the number of complex trees did not yield significant changes in classification performance (Table 5). The number of decision trees used in best BACDT model was 50.

Discussion

This single center pilot study using machine learning predictive model resulted in a predictive model with a poor accuracy (area under the ROC curves < 0.75). The comparison of machine learning models showed that bagged complex trees was the best approach. However, the model was of limited value for to predict SpO_2 below 92%.

In agreement with previous studies regarding bagging being a better method for medical data classification, tree Bagging fared better than the artificial neural network [13]. The gap in performance between the training and testing confusion matrices in the case of bagged trees model (data not shown) seems to indicate that, although the bagged trees model was capable of learning very well from the data, there's still room for improvement in the generalization.

Table 4. Absence of impact on performance of the increase of neurons and hidden layers for artificial neural network (ANN). Example of the performance assessed by the F score on the balanced test dataset 3 (see Table 2).

		ANN								
Error minimization algorithm		Stochastic Gradient-Descent (SGD)								
Activation function		Logistic Sigmoid								
Regularization		No								
Nb hidden layers (n)		1			2			3		
Neurons/hidden layer (n)		10	50	100	10	50	100	10	50	100
F-score	$_{5min}SpO_2$ class 1	0.25	0.25	0.25	0.25	0.25	0.25	0.22	0.22	0.19
	$_{5min}SpO_2$ class 2	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.32
	$_{5min}SpO_2$ class 3	0.72	0.72	0.72	0.72	0.72	0.72	0.69	0.69	0.69

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Table 5. Absence of impact on performance of the number of complex trees for bootstrap aggregation of complex decision trees (BACDT). Example of the performance assessed by the F score on the balanced test dataset 3 (see Table 2).

		BACDT	
		n = 30	n = 50
F-score	$_{5min}SpO_2$ class 1	0.78	0.78
	$_{5min}SpO_2$ class 2	0.65	0.65
	$_{5min}SpO_2$ class 3	0.96	0.96

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The SMOTE algorithm is designed in such a way that should theoretically not affect the generalization of the trained model. However, in cases of extreme data imbalance, as in this study, the over-sampling of minority class label is also likely to be extreme. This may render the data space of this class relatively dense with respect to the rest of the data made up of real data points. This may potentially explain the classification model's relatively poor generalization for $_{5min}SpO_2$ class "1" and "2". Also, since SMOTE generates synthetic data points by interpolating between existing minority class instances, it can increase the risk of over-fitting when classifying minority class labels, since it may duplicate minority class instances but this needs to be further investigated.

The strengths of this study include a large clinical database of mechanically ventilated children with more 776,727 rows. In a recent similar study in PICU, 200 patients were included with 1,150 rows [17]. However, the volume of data is clearly insufficient. To use such machine learning predictive models both for low SpO_2 class and for ventilator setting modification such as PEEP. The pediatric intensive care community needs to combine multicenter high resolution database to increase the datasets. In addition, children data could be pooled to neonatal and adult intensive care data, when possible, such as MIMIC III database in specific clinical analysis[18]. The other strength is the process used to transform the data into a usable format and to correct a variety of artifacts (see S1 File). In health care, there is a significant interest in using clinical databases including dynamic and patient-specific information to develop clinical decision support algorithms. The ubiquitous monitoring of critical care units' patients has generated a wealth of data that creates many opportunities in this domain. However, when developing algorithms, such as transport or finance, data are specifically collected for research purposes. This is not the case in healthcare where the primary objective of data collection systems is to document clinical activity, resulting in several issues to address in data collection, data validation and complex data analysis [19]. As detailed in S1 File, a significant amount of effort is needed, when data have been successfully archived and retrieved, to transform the data into a usable format for research.

This study has several limitations. First, the limited row number in low SpO_2 levels reduced the SpO_2 classification for machine learning predictive model to three clinically relevant classes. SpO_2 is a continuous variable and the use of three class is probably insufficient [20, 21]. Instead of the classification model, the next step could be to test regression models' performance. Second, SpO_2 was predicted at 5min after ventilator setting change, a clinically relevant delay. However, the delay between ventilator setting change and oxygenation steady state is not well defined and vary from 1 to 71 minutes according to the parameter set (FiO_2, PEEP or other parameters that change mean airway pressure) and clinical conditions studied [17, 22, 23]. This needs further research and probably more sophisticated clinical decision support systems using machine learning predictive models should consider these factors. Third, we excluded hemodynamic unstable patients using a treatment criteria ($\geq$ 2 vasoactive drugs infused) because this condition decreases pulse oximeter reliability [24, 25]. The validation

and electronic availability of reliable markers of hemodynamic instability in children such as plethysmographic variability indices could be helpful [26]. Finally, based on the classification approach taken, we didn't stratify the number of unique patients whose data were used for training versus testing, but only the number of instances for train versus test. The median duration of ventilation in our PICU is 33 hours, the medical conditions are numerous and the weaning phase where lung condition is almost the same among children represents 50% of the mechanical ventilation duration [16]. By random, the number of unique patient in the training and validation dataset is proportional to the whole population and reflects the whole PICU population studied. If we had determined a given number of patient per training and validation, we probably should also ned to dispatch the medical condition, the duration of ventilation, the underlying medical conditions. To address this problem, we included in the model variables that characterize the patient and lung severity at a given time including age, weight and mean airway pressure (see Fig 1).

Conclusion

This pilot study using machine learning predictive model resulted in an algorithm with poor accuracy. We have proposed a method to apply supervised machine learning algorithms to extract knowledge from large amounts of patient mechanical ventilation data. Our method aimed at predicting the behavior of SpO_2, based on ventilator setting changes made by the clinician and other clinical variables. To do that, we have exploited large amounts of data from a PICU research database and proposed a data formatting process which creates datasets that can be used for supervised training. The comparison of machine learning models showed the use of ensembles of bagged complex trees to be a promising approach. As for future work, various approaches and methods may be considered, in the aim of improving prediction of SpO_2 classification, or level prediction in the case of regression models. One potentially viable solution for improving predictive models would be to use a greater amount of data. Although this could not be considered a warrant for better classifier robustness, it will decrease the need of a data balancing process and may be a relatively simple approach to be considered in future work. This will require a multicenter pediatric intensive care high resolution databases. For the moment, the study presents a model that predicts SpO_2 using known setting changes made by the clinician, as well as the other clinical data that the clinicians involved in the study deemed relevant for SpO_2 prediction. However, it is hoped that this predictive model will be incorporated in a larger Clinical Decision Support System to assist PICU clinicians in making decisions about required setting changes, based on the range in which SpO_2 and other parameters ($PaCO_2$, hemodynamic status, . . .) are to be maintained.

Supporting information

S1 File. Data formatting process.
(DOCX)

S2 File. Performance tests used in the machine learning models to predict oxygen saturation following ventilator support adjustment in critically ill children.
(DOCX)

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B. Assessment of Bohr and Enghoff Dead Space Equations in Mechanically Ventilated Children.

Assessment of Bohr and Enghoff Dead Space Equations in Mechanically Ventilated Children

Pierre Bourgoin MD, Florent Baudin MD, David Brossier MD, Guillaume Emeriaud MD, Marc Wysocki MD, and Philippe Jouvet MD

BACKGROUND: Recent findings suggest that using alveolar P_{CO_2} (P_{ACO_2}) estimated by volumetric capnography in the Bohr equation instead of P_{aCO_2} (Enghoff modification) could be appropriate for the calculation of physiological dead space to tidal volume ratio ($V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$, respectively). We aimed to describe the relationship between these 2 measurements in mechanically ventilated children and their significance in cases of ARDS. METHODS: From June 2013 to December 2013, mechanically ventilated children with various respiratory conditions were included in this study. Demographic data, medical history, and ventilatory parameters were recorded. Volumetric capnography indices (NM3 monitor) were obtained over a period of 5 min preceding a blood sample. Bohr's and Enghoff's dead space, S2 and S3 slopes, and the S2/S3 ratio were calculated breath-by-breath using dedicated software (FlowTool). This study was approved by Ste-Justine research ethics review board. RESULTS: Thirty-four subjects were analyzed. Mean $V_D/V_{T\ Bohr}$ was 0.39 ± 0.12, and $V_D/V_{T\ Enghoff}$ was 0.47 ± 0.13 ($P = .02$). The difference between $V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$ was correlated with P_{aO_2}/F_{IO_2} and with S2/S3. In subjects without lung disease ($P_{aO_2}/F_{IO_2} \geq 300$), mean $V_D/V_{T\ Bohr}$ was 0.36 ± 0.11, and $V_D/V_{T\ Enghoff}$ was 0.39 ± 0.11 ($P = .056$). Two children with status asthmaticus had a major difference between $V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$ in the absence of a low P_{aO_2}/F_{IO_2}. CONCLUSIONS: This study suggests that $V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$ are not different when there is no hypoxemia ($P_{aO_2}/F_{IO_2} > 300$) except in the case of status asthmaticus. In subjects with a low P_{aO_2}/F_{IO_2}, the method to measure V_D/V_T must be reported, and results cannot be easily compared if the measurement methods are not the same. *Key words: respiratory physiological concepts; mechanical ventilation; pediatric ICU; ventilation-perfusion ratio; capnography; ARDS.* [Respir Care 2017;62(4):468–474. © 2017 Daedalus Enterprises]

Introduction

Lung physiologic dead space (V_D) is defined as the wasted tidal volume during respiration (ie, the volume remaining in the conducting airways [anatomical dead space] and in poorly perfused and non-perfused alveoli [alveolar dead space] that are not participating in gas exchange). Employing the law of mass conservation, Bohr proposed a formula using alveolar P_{CO_2} (P_{ACO_2}) to esti-

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mate physiologic dead space, expressed as a ratio of dead space volume (V_D) to tidal volume (V_T).[1] Later, Enghoff proposed a simplification of Bohr's formulae to calculate the physiologic dead space ratio at the bedside using arterial P_{CO_2} (P_{aCO_2}) instead of P_{ACO_2}.[1] Currently, physiologic dead space measurement is used by clinicians in the management of mechanical ventilation because CO_2 removal is inversely proportional to V_D/V_T, and V_D fluctuates considerably, depending upon the severity of lung disease.[2] The dead space on V_T (V_D/V_T) ratio informs caregivers as to the effect of therapeutic procedures such as prone positioning,[3] surfactant administration,[4] or lung recruitment maneuvers[5,6] and provides information useful in prognostication, depending on the severity of lung disease in adults and children.[7,8]

Recent findings suggest that using P_{ACO_2} estimated by volumetric capnography can be appropriate to calculate the Bohr physiological dead space/tidal volume ratio ($V_D/V_{T\,Bohr}$). P_{aCO_2} (Enghoff modification) can be used as well ($V_D/V_{T\,Enghoff}$). Especially in the case of lung injury, comparison of $V_D/V_{T\,Bohr}$ and $V_D/V_{T\,Enghoff}$ may have complementary physiological meaning, as recently suggested[9,10]: Bohr's equation estimates the true dead space (ie, high ventilation/perfusion [$\dot{V}/\dot{Q}$] units plus anatomical and mechanical dead space), whereas Enghoff's estimates not only the dead space but also the shunting and low $\dot{V}/\dot{Q}$ regions of the lungs (Fig. 1). We conducted a prospective observational study to compare Bohr's and Enghoff's measurements of V_D/V_T in mechanically ventilated children, and we hypothesized that a difference between these 2 measurements may be observed in cases of lung injury. If confirmed, a large difference between $V_D/V_{T\,Bohr}$ and $V_D/V_{T\,Enghoff}$ would indicate significant lung heterogeneity with regard to the degree of shunt and low $\dot{V}/\dot{Q}$ regions in the lungs.

QUICK LOOK

Current knowledge

Monitoring dead space ratio in critically ill patients is of prognostic value and may help to manage ventilator settings in patients with ARDS. Recent studies on the estimation of dead space using volumetric capnography validate a noninvasive estimation of alveolar CO_2 pressure (P_{ACO_2}) to calculate Bohr dead space, whereas most studies have used physiologic dead space (Enghoff dead space, replacing P_{ACO_2} with P_{aCO_2}).

What this paper contributes to our knowledge

Major variations existed between Bohr and Enghoff estimations of deadspace in cases of hypoxemic lung injury. The use of volumetric capnography explains these differences. The method of deadspace estimation should always be detailed to allow interpretation based on these findings.

Methods

Subjects

All patients admitted to the Pediatric ICU of Sainte-Justine Hospital (Montreal, Canada), <18 y old, mechanically ventilated with an endotracheal tube for ≥6 h were eligible for the study. They were included if they had an arterial line and a blood gas scheduled. Exclusion criteria were: gestational age <36 weeks, hemodynamic instability (fluid administration or increasing use of catecholamines in the last hour or serum lactate >2.2 mmol/L), high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, air leak around the endotracheal tube >20%, cyanotic heart disease, primary pulmonary hypertension, palliative care, pregnancy, research assistant unavailable for the study, and volumetric capnograph monitor unavailable. The study was approved by the Sainte-Justine Hospital institutional review board (approval 3622 [November 26, 2012]) without the need for parental or subject consent.

Study Protocol

Once the subject reached inclusion criteria without any exclusion criteria, the subject's head was positioned to avoid air leak if any was detected. Then an infrared mainstream CO_2 sensor (Capnostat, Philips Healthcare, Markham, Ontario, Canada) was placed between the T-piece and the endotracheal tube. The sensor was connected to an NM3 volumetric capnograph (Philips Healthcare, Markham, Ontario, Canada). We used the neonatal sensor for children <5 kg and the pediatric sensor above that weight. Volumetric capnography data were electronically recorded over the 5 min before blood gas analysis. Only one blood gas per subject was analyzed. Blood gas values were corrected for body temperature.

Data Collected

Demographic characteristics of the subject, diagnosis, ventilatory parameters, blood gas results, blood hemoglobin level, sedation scale, and clinical severity scores [PRISM (Pediatric RISk of Mortality), PELOD (PEdiatric Logistic Organ Dysfunction)] were documented in a case report form. Severity of lung injury was assessed using both P_{aO_2}/F_{IO_2} ratio and oxygenation index $F_{IO_2} \times$ mean airway pressure/P_{aO_2} (mm Hg). Lung injury severity was classified using P_{aO_2}/F_{IO_2} ratio thresholds according to the Berlin definition.[11]

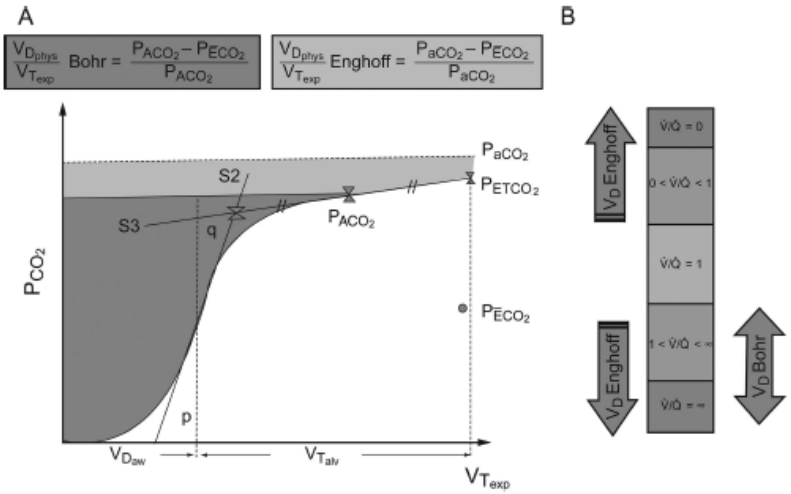

Fig. 1. A: Representation of a volumetric capnogram with a schematic approach for the measurement of dead space. Noninvasive estimation of dead space is related to Bohr's approach after estimation of alveolar P_{CO_2} (P_{ACO_2}), whereas Enghoff's method requires an invasive measurement of arterial P_{CO_2} (P_{aCO_2}). P_{ACO_2} is calculated as the middle point of a line joining the intersection of S2 and S3 slopes and end-tidal P_{CO_2} (P_{ETCO_2}). P_{ECO_2} is mixed expiratory P_{CO_2} that corresponds to the integration of the P_{CO_2} vs tidal volume curve. Airway dead space ($V_{D_{aw}}$) is calculated according Fowler's method (ie, the equality of area p and q). B: A representation of Riley's model of the lung with a superposition of Bohr and Enghoff dead space assessment formulas. In the bottom, the ventilation/perfusion ratio (V̇/Q̇) tends to infinity (dead space); in the top, V̇/Q̇ tends to zero and represents the amount of venous admixture or shunt. Enghoff's dead space (arrows on the left) is the addition of high V̇/Q̇ and low V̇/Q̇ units. It may be higher than Bohr's dead space (arrow on the right), which represents "pure dead space" (ie, high V̇/Q̇ units). Data from Reference 10.

Data were collected electronically from the volumetric capnograph and calculated via dedicated software (Flowtool Viewer 3.03, Philips Healthcare, Markham, Ontario, Canada). All recorded breaths were analyzed. Aberrant capnograms were manually deleted if V_T was <80% of the mean V_T or presented an aberrant aspect, such as a sharp increase in P_{CO_2} after phase 3 (named "phase 4"), or very different slopes of phase 2 or phase 3. Subjects were secondarily excluded if >30% of capnograms were aberrant. The following values are the average of values consecutively obtained during a period of 5 min preceding the blood sample: the slope of the phase 2 (S2) and phase 3 (S3) of the capnogram; P_{ACO_2} (alveolar partial pressure of CO_2 calculated at the midpoint of phase 3 starting from the S2-S3 intersection, ending at end-tidal carbon dioxide pressure); mixed partial pressure of CO_2 in the expired volume; $V_{D\ Bohr}$; $V_{D\ Enghoff}$; and the capnographic index, which is defined as the S3/S2 ratio. Airway dead space was automatically calculated (Fowler's method). See Figure 1 for details.

Statistical Analysis

Statistical analysis was performed using SPSS 19 (SPSS, Chicago, Illinois). Descriptive statistics are presented as mean ± SD. Comparisons of mean V_D/V_T values were performed using a *t* test for independent or paired samples. Analysis of variance and Bonferroni tests were used to compare 3 samples or more if variance homogeneity was achieved. The Pearson coefficient was used to describe correlation between 2 continuous variables with a linear correlation. $P < .05$ was considered as statistically significant.

Results

Subjects

Forty subjects were included in the study from December 2012 to June 2013. Subject characteristics and the distribution of P_{aO_2}/F_{IO_2} values are described in Table 1. Six subjects were secondarily excluded from analysis. All of them presented aberrant values of capnographic parameters. These findings were mostly associated with low V_T (<30 mL) (Fig. 2).

Dead Space Measurements and Relationship With Lung Injury Severity

Mean $V_D/V_{T\ Bohr}$ was 0.39 ± 0.12, and mean $V_D/V_{T\ Enghoff}$ was 0.47 ± 0.13 ($P = .02$). $V_D/V_{T\ Bohr}$ was correlated with P_{aO_2}/F_{IO_2} ($r = -0.35$, $P = .031$) and oxygenation index ($r = 0.44$, $P = .005$). Similar results were found for $V_D/V_{T\ Enghoff}$ with P_{aO_2}/F_{IO_2} ($r = -0.62$, $P < .001$) and

Table 1. Subject Characteristics

Characteristics	Values ($N = 34$)
Age, mean ± SD y	6.3 ± 5.6
Weight, mean ± SD kg	23 ± 20
Male/female sex, *n*	15/19
PELOD score, mean ± SD	8.7 ± 7.6
PRISM score, mean ± SD	9.8 ± 0.8
pH, mean ± SD	7.34 ± 0.34
P_{aO_2}, mean ± SD mm Hg	118 ± 18
Hb, mean ± SD g/L	98 ± 8
Reason for admission, *n*	
Cardiac postoperative care	6
Non-cardiac postoperative care	5
Medical	22
Trauma	1
Lung injury categories, *n*	
No ARDS ($P_{aO_2}/F_{IO_2} \geq 300$)	12
Mild ARDS ($200 \leq P_{aO_2}/F_{IO_2} \leq 300$)	11
Moderate ARDS ($100 \leq P_{aO_2}/F_{IO_2} \leq 200$)	11
Severe ARDS ($P_{aO_2}/F_{IO_2} < 100$)	0

PRISM = Pediatric RISk of Mortality
PELOD = PEdiatric Logistic Organ Dysfunction

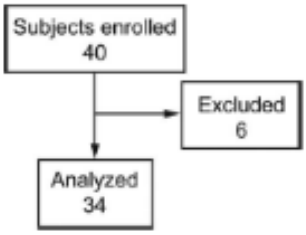

Fig. 2. Flow chart.

oxygenation index ($r = 0.65$, $P < .001$). Dead space assessment among different categories of severity of lung injury is represented in Figure 3. Analysis of variance showed significant $V_D/V_{T\ Enghoff}$ difference for each category of P_{aO_2}/F_{IO_2} ($P = .003$). However, no difference in $V_D/V_{T\ Bohr}$ was observed.

The percentage difference between $V_D/V_{T\ Enghoff}$ and $V_D/V_{T\ Bohr}$ $(V_D/V_{T\ Enghoff} - V_D/V_{T\ Bohr})/V_D/V_{T\ Enghoff}$ was 17 ± 16% (from −21 to +65%). Figure 4 represents the correlation between percentage difference and P_{aO_2}/F_{IO_2} ($r = -0.50$, $P = .003$). Subjects were divided into 3 quartiles of percentage difference: 0–5% (first quartile, $n = 8$), 5–25% (second and third quartiles, $n = 16$), and >25% (fourth quartile, $n = 11$). Table 2 shows the factors associated with percentage difference.

Discussion

Our study confirms that in mechanically ventilated children, dead space measurements using P_{ACO_2} from volumetric capnography ($V_{D\ Bohr}$) gave lower values compared with dead space measurements using P_{aCO_2} ($V_{D\ Enghoff}$). Major differences are found in subjects presenting the most severe lung injury. Furthermore, our results suggest that the shape of the capnogram itself (capnographic index) is predictive of major variations.

Based on the 3-compartment model of Riley, dead space represents the fraction of lung that is ventilated but unperfused ($\dot{V}/\dot{Q} = \infty$). However, Enghoff's equation, by using P_{aCO_2} instead of P_{ACO_2}, overestimates Riley's dead space (Fig. 1). Indeed, P_{aCO_2} differs from P_{ACO_2} in the case of right to left shunt or in subjects with high $\dot{V}/\dot{Q}$ heterogeneity and consequently high P3 slope.[12,13]

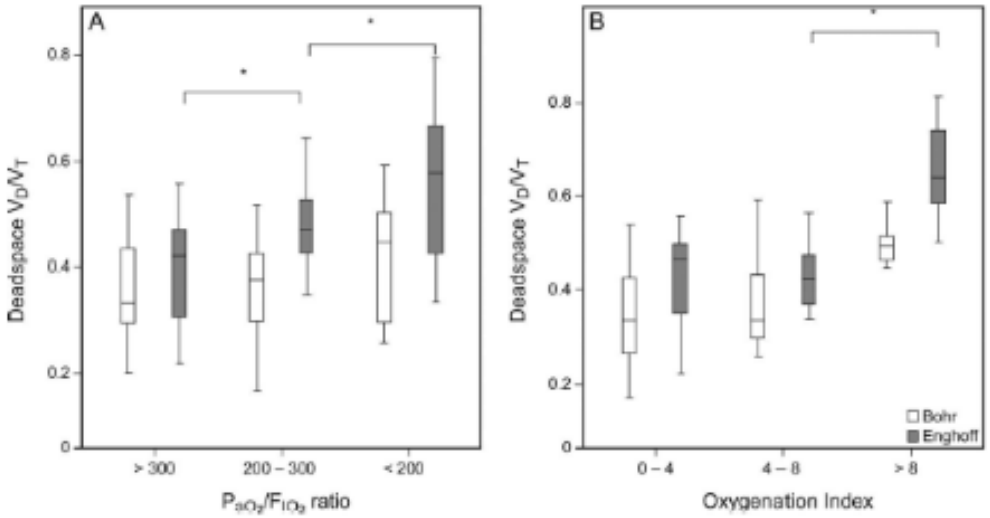

Fig. 3. V_D/V_T values according to different levels of lung injury severity. The asterisk shows interclass differences after analysis of variance (A: $P = .03$; B: $P = .014$).

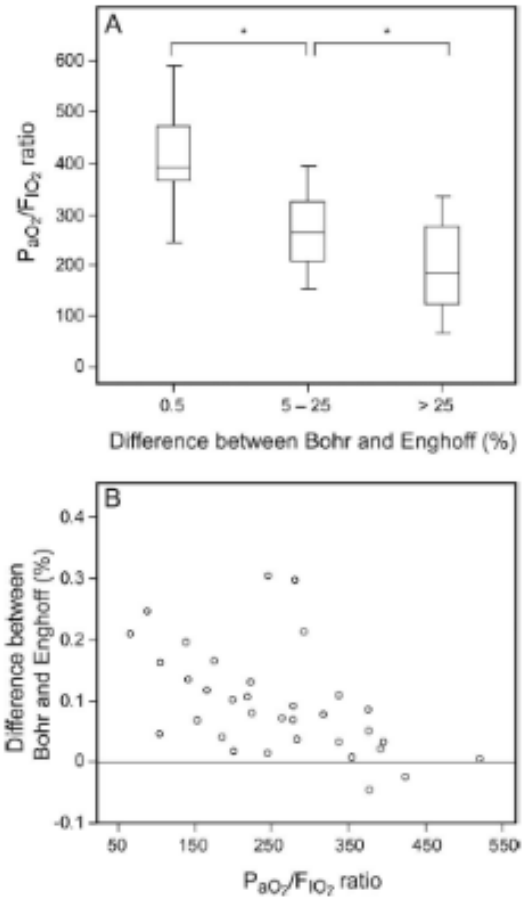

Fig. 4. A: P_{aCO_2}/F_{IO_2} values for 3 intervals of variations between Bohr's and Enghoff's calculation of dead space (percentage difference = $(V_D/V_{T\ Enghoff} - V_D/V_{T\ Bohr})/V_D/V_{T\ Enghoff}$). Asterisks indicate significant differences with $P = .003$ after analysis of variance/Bonferroni test. B: Representation of the correlation between P_{aCO_2}/F_{IO_2} and difference between Bohr and Enghoff.

Table 2. Factors Associated With an Increase in the Difference Between $V_{D\ Bohr}$ and $V_{D\ Enghoff}$ Measurement

Variables	r	P
P_{aO_2}/F_{IO_2}	−0.50	.003
Oxygenation index	0.233	.19
Capnographic index	0.479	.004
P2 slope	−0.279	.11
P3 slope	0.025	.89
$V_{D_{aw}}/V_T$	−0.249	.16

$V_{D_{aw}}$ = airway dead space

In our study, larger differences between Bohr's and Enghoff's dead space occurred as lung injury worsened. Such large differences between $V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$ have been observed for intrapulmonary shunt fraction >20–30% (using Berggren's formula for shunt calculation) in an animal model of ARDS.[14] This study confirmed data obtained from computerized models with similar levels of shunt,[15] whereas older studies suggested that only contexts of high right to left shunt (50%), unlikely to occur in most critically ill patients, resulted in increased V_D/V_T.[16] In Suarez-Sipmann et al[14] again, the use of known algorithms to correct the effect of shunt leads to a better correlation of $V_{D\ Bohr}$ and $V_{D\ Enghoff}$, but this correction failed to explain the entire difference.

Apart from intrapulmonary shunt, the coexistence of a large variety of alveoli with very high and very low $\dot{V}/\dot{Q}$ can explain higher P3 slopes, because each $\dot{V}/\dot{Q}$ is associated with a given expiratory time constant. Thus, high-$\dot{V}/\dot{Q}$ alveoli (that contain a low quantity of CO_2) generate the first part of the phase 3 slope, whereas low-$\dot{V}/\dot{Q}$ alveoli generate the last part of the phase 3 slope due to higher concentration of CO_2. In an animal model of acute lung injury, a good correlation was observed between P3 slope and $\dot{V}/\dot{Q}$ dispersion (assessed by the multiple inert gas elimination technique).[17] In the clinical setting, this dispersion of $\dot{V}/\dot{Q}$ values is best described by S2/S3, elsewhere named the capnographic index or KPI, and this has been reported in children with chronic obstructive disease (cystic fibrosis, bronchopulmonary dysplasia, or asthma).[18-20] Our study is the first to report the statistically significant association of the capnographic index and the difference between Bohr's and Enghoff's calculation of dead space in the critical care setting, and our results are comparable with those found in children with cystic fibrosis versus controls[18] (ie, patients with major variations of dead space measurement also present with a higher capnographic index). These results suggest that the interpretation of the appearance of the capnogram itself may be appropriate and may guide decisions in the management of patients with ARDS.

One limitation of our study is the absence of evaluation of pulmonary blood flow. Apart from shunt and dispersion of $\dot{V}/\dot{Q}$ values, increases in dead space could be due to decreased blood flow in the pulmonary artery.[15,21,22] Pulmonary blood flow is not measured routinely in children, but we excluded patients with hemodynamic instability and intracardiac right to left shunt, allowing us to assume that pulmonary blood flow was near normal ranges. Furthermore, other parameters that influence dead space in ARDS computerized models were not necessarily controlled for in our study: Hemoglobin and pH are 2 variables that influence the amount of dissolved CO_2 and thus the calculation of dead space.[20] However, pH and hemoglobin were within normal ranges in the pediatric ICU subjects included (Table 1).

Another limitation of our study may be the choice to consider the effect of temperature on CO_2 partial pressure measurement. Indeed, because exhaled gas measurements

reflect the in vivo alveolar P_{CO_2}, we chose to take into account corrected (for subject's temperature) values of P_{aCO_2}. This choice was suggested in previous studies.[23,24] However, the comparison of uncorrected versus corrected values of $V_D/V_{T\ Bohr}$ and $V_D/V_{T\ Enghoff}$ would be interesting to further analyze the impact of temperature on both measurements.

Apart from our main results, we identified subjects of special interest: those with high percentage difference in the absence of hypoxemia and those with low percentage difference and severe hypoxemia. Three subjects were isolated. One was a 6-month-old infant weighing 4 kg with dilated cardiomyopathy admitted after cardiac surgery having a P_{aO_2}/F_{IO_2} of 104 and an oxygenation index of 12. The percentage difference was only 6% despite severe hypoxemia. This subject had a V_T of 36 mL with an airway dead space equal to 18 mL that explained most of the V_D/V_T (0.66). This low difference was probably due to the proportional low influence of V/Q mismatch when compared with instrumental + anatomical dead space (ie, airway dead space). Two children were intubated for severe status asthmaticus resistant to β_2 agonists who displayed severe hyperinflation without any consolidation on chest radiograph. In these subjects, $V_D/V_{T\ Enghoff}$ values were high (0.51 and 0.53) with a high percentage difference (65 and 55%) and high P_{aO_2}/F_{IO_2} (245 and 280 mm Hg, respectively). In such subjects, a large variation between Bohr and Enghoff dead space measurements may be observed without much hypoxemia, suggesting that Enghoff dead space measurements (including a P_{aCO_2} measurement) are required to measure dead space accurately.

Conclusions

Our results suggest that Bohr and Enghoff dead space measurements are not similar in cases of hypoxemia (P_{aO_2}/F_{IO_2} <300) except in the case of status asthmaticus. Our study confirmed that Enghoff dead space measurements are usually higher than Bohr dead space measurements. The method used to measure V_D/V_T must be reported, and the availability of volumetric capnography to assess both $V_{D\ Bohr}$ and $V_{D\ Enghoff}$ may be more informative than dead space monitoring alone in the management of patients with ARDS.

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C. Noninvasive estimation of arterial CO2 from end-tidal CO2 in mechanically ventilated children: The GRAeDIENT pilot study

Noninvasive Estimation of Arterial Co_2 From End-Tidal Co_2 in Mechanically Ventilated Children: The GRAeDIENT Pilot Study*

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Objectives: The aim of our pilot study was to develop a model to better predict $Paco_2$ in mechanically ventilated children using noninvasive parameters including volumetric capnography.
Design: Prospective clinical pilot study.
Setting: Level III PICU.
Patients: Sixty-five mechanically ventilated children.
Interventions: None.
Materials and Methods: We conducted a prospective clinical pilot study that included all children admitted to the PICU (< 18 yr; weight, > 3 kg; mechanically ventilated, > 6 hr; with an arterial line). A predictive model for $Paco_2$ was developed using linear multivariable regression. Among the data collected in PICU patients, candidate predictors of $Paco_2$ were defined by a panel of experts and included end-tidal partial pressure of carbon dioxide, ventilation parameters, and data resulting from the analysis of volumetric capnogram recorded 5 minutes before an arterial blood gas. Children with tidal volume less than 30 mL were excluded because of technical limits.
Results: A total of 65 children (43 boys, 65%) (65 [21–150] mo old) were analyzed. By linear multivariable regression, the best model included the mean airway pressure, end-tidal partial pressure of carbon dioxide, Fio_2, and the capnographic index with an R^2 equal to 0.90, p value less than 0.001. After correction, 95% ($n = 62$) of children had an estimated $Paco_2$ at ± 5 mm Hg.
Conclusion: Our model developed provides an accurate estimation of the $Paco_2$ using end-tidal Co_2 and noninvasive variables. Studies are needed to validate the equation in PICUs. (*Pediatr Crit Care Med* 2016; 17:1117–1123)
Key Words: carbon dioxide; mechanical ventilation; pediatrics; respiratory monitoring; volumetric capnography

*See also p. 1180.

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In spontaneous ventilation, central respiratory command adjusts the ventilation to maintain arterial pH and $Paco_2$ constant (1). In the case of severe respiratory distress, patients are mechanically ventilated and ventilation is no longer controlled solely by the central respiratory command, and caregivers adjust ventilation through changes in ventilator settings using arterial blood gas analysis at regular intervals. Arterial blood gases (ABG) are invasive, painful (in the absence of arterial line), and offer only a snapshot of the respiratory status.

Recent studies have demonstrated that oxygen saturation (Spo_2) can be used to estimate Pao_2 in mechanically ventilated children when Spo_2 is of 97% or below (2–4). $Paco_2$ may also be estimated noninvasively from the end-tidal partial pressure of Co_2 ($Petco_2$). In healthy subjects, $Petco_2$ is close to the $Paco_2$ values (5–7). In patients with hemodynamic instability or pulmonary injury, $Petco_2$ value may significantly diverge from $Paco_2$ (5, 8, 9). In such conditions, $Petco_2$ is not used routinely in the PICU as a noninvasive predictor of the $Paco_2$ for ventilator setting modifications (10).

Many conditions may affect the correlation between $Paco_2$ and $Petco_2$ in critically ill patients. In patients with

cyanotic heart diseases, Fletcher (11) demonstrated that the gradient between $Paco_2$ and $Petco_2$ mainly depends on the extent of right to left shunt and increases by 2–3 mm Hg for every 10% drop in Spo_2. De Vries et al (12) validated a corrective equation of the $Petco_2$ based on Spo_2 values in these patients. In patients mechanically ventilated without intracardiac right to left shunt, the gradient between $Paco_2$ and $Petco_2$ depends on heterogeneity of ventilation-to-perfusion (V/Q) ratio in the lung (13–15), on physiologic dead space—which includes intrapulmonary shunt and alveolar dead-space (14, 16, 17)—and on pulmonary blood flow (14, 18). Under certain conditions, the difference between $Paco_2$ and $Petco_2$ may exceed 15 mm Hg (16). To better assess noninvasively the gradient between $Paco_2$ and $Petco_2$, volumetric capnography (VCap) can be used. VCap is the representation of expired Co_2 over the volume of one tidal breath (**Fig. 1**) (19, 20). VCap may provide qualitative information on pulmonary blood flow (14, 15), dead space (17, 21), and V/Q mismatch (22–24).

The aim of this study was to determine independent noninvasive variables commonly available at the bedside, including VCap, that would allow accurate prediction of $Paco_2$ in mechanically ventilated children.

MATERIAL AND METHODS

This prospective observational study was performed in a 24-bed university-affiliated hospital PICU between May 2013 and September 2014. The study was approved by Sainte-Justine Hospital Institutional Review Board number 3622.

Population

Children under 18 years hospitalized in the Sainte-Justine PICU (Montreal, QC, Canada) undergoing invasive mechanical ventilation were eligible to participate. The inclusion criteria were as follows: body weight greater than 3 kg, invasive mechanical ventilation (i.e., with endotracheal tube) more than 6 hours, arterial cannula previously inserted for invasive arterial blood pressure monitoring, arterial blood gas prescribed by the attending physician. Exclusion criteria were as follows: gestational age less than 36 weeks, hemodynamic instability (fluid administration or increasing use of catecholamine in the last hour or serum lactates > 2.2 mmol/L), high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, air leak around the endotracheal tube more than 20%, cyanotic heart disease, primary pulmonary hypertension, palliative care, pregnancy, research assistant unavailable for the study, and VCap monitor unavailable.

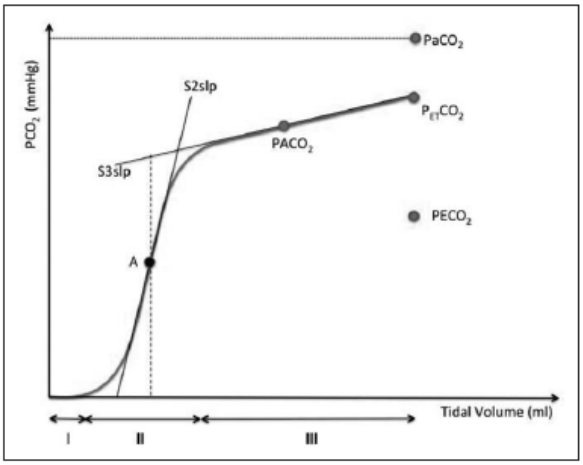

Figure 1. Volumetric capnography curve and main parameters. $PACo_2$ = alveolar partial pressure of Co_2, $Petco_2$ = end-tidal partial pressure of Co_2, $PECo_2$ = mixed expired partial pressures of Co_2, S2slp = slope S2 phase, S3slp = slope S3 phase.

Monitoring

We carried out continuous cardiorespiratory monitoring (heart rate, Spo_2, and invasive arterial blood pressure) with an Intellivue MP70 monitor (Philips Healthcare, Markham, ON, Canada). VCap and $Petco_2$ values were obtained via a dedicated Flow/Co_2 sensor (Capnostat 5 mainstream pediatric; Philips Healthcare, Markham, ON, Canada) routinely placed at the *Y* piece of the respirator and connected to a Respironics NM3 monitor (Philips Healthcare, Markham, ON, Canada).

Study Protocol and Recordings

All patients in the PICU were screened daily for eligibility and eligible patients were reviewed by the research assistant with the attending medical team. Capnostat Flow/Co_2 sensor (Capnostat 5; Philips Healthcare, Markham, ON, Canada) was connected at least 60 minutes prior to the ABG prescribed by the attending physician and data were recorded over 10 minutes before ABG analysis. The Co_2 sensor was calibrated before each use as recommended by the manufacturer's instructions. The capnograms were recorded and stored on a computer. Data from the ventilator, demographic, clinical, and biologic data were stored continuously in the electronic medical records (ICCA; Philips Healthcare, Markham, ON, Canada). Pressure measurements were expressed at body temperature and pressure saturated.

Variables Studied, Statistical Analysis, and Sample Size Calculation

The $Paco_2$ was considered as the dependent variable and we elaborated an equation using a linear model to predict $Paco_2$ from noninvasive data available at the point of care with clinically acceptable precision. This clinically acceptable precision was ± 5 mm Hg of the measured $Paco_2$ and was defined according to the Clinical Laboratory Improvement Amendments recommendations (25). Candidate predictors of $Paco_2$ (independent variables) included $Petco_2$ and patient demographic and clinical characteristics, data from the ventilator, and data from VCap that were defined prior to the study by a panel of six intensivists (26). The variables selected included $Petco_2$, FIo_2, Spo_2/FIo_2, α angle between slope S2 (S2slp) and slope S3 (S3slp) (Fig. 1) (27), capnographic index (KPIv), that is, the ratio of S3slp on S2slp (KPIv = S3slp/S2slp × 100) (24, 28), and mean

airway pressure (MAP). Prediction equations were constructed via multiple linear regression analyses to identify predictor variables of $Paco_2$. Residual analysis was conducted to confirm normality, linearity, and equal variance of the regression model. Data from the VCap were analyzed breath-by-breath using specific software (FlowTool 3.0.3; Philips Healthcare, Markham, ON, Canada). Aberrant data (negative slope, double analysis) and breath with tidal volume (V_t) outside of the flow sensor calibration range (< 30 mL) or less than 80% from median V_t (28) were excluded manually. Children with more than 60% aberrant breaths were excluded. As $Paco_2$ and capnographic data are not on the same time domain, the mean values of 5 minutes of VCap data before the arterial sampling were used. From the data provided automatically by the VCap, several independent variables were calculated using equations previously reported in the literature: α angle between S2slp and S3slp, KPIv, alveolar partial pressure of Co_2 ($PACo_2$), that is, the midpoint of S3slp (17) and Bohr's deadspace volume (V_d) on V_t ratio ($V_d/V_t = [PACo_2 - PECo_2]/PACo_2$), where $PECo_2$ is mixed expired partial pressures of Co_2 (Fig. 1) (17).

A sample size of 65 patients was estimated to provide 80% power with a two-sided α level of 5% to detect a medium effect size R^2 of at least 0.20 with a linear regression model containing up to seven predictors. A two-tailed p value of less than 0.05 was considered to be significant. Bland and Altman analysis was not used because $Paco_2$ was the reference and because we used the same sample for the predictive equation and the presentation. Categoric data were expressed as number (%) and continuous data as the median with the interquartile range. Statistical analyses were performed using SPSS v22 software (IBM, New York, NY).

RESULTS

A total of 75 patients were included and 10 patients were excluded at the time of the analysis because of V_t less than 30 mL (n = 6) or more than 60% aberrant curves or change in the ventilator settings during the recording (n = 4). The final study population included 65 patients. The median age was 65 months (21–150 mo) with a median weight of 19 kg (11–33 kg). The demographic data at inclusion are presented in **Table 1**. We analyzed 7,563 breaths and retained 6,713, which represent 88.7% ± 13.3% of the total registered breaths. The main clinical data, biologic data, and ventilator settings

TABLE 1. Patient Characteristics at Study Inclusion

Clinical Characteristics	Patients (n = 65)
Demographic characteristics	
Male, n (%)	41 (63)
Age (mo)	65 (21–150)
Weight (kg)	19 (11–33)
Reasons for PICU admission, n (%)	
Postoperative care	26 (40)
Acute medical cause	31 (48)
Acute surgical cause including trauma	8 (12)
Chronic condition, n (%)	
Acyanotic heart disease	15 (23)
Respiratory disease	11 (17)
Respiratory indices	
Pao_2/Fio_2	277 (222–391)
Oxygenation index	3 (2–5)
$Pao_2/Fio_2 < 300$, n (%)	38 (58)
Score	
Pediatric Risk of Mortality	9 (5–14)
Pediatric Logistic Organ Dysfunction	11 (1–12)

Data are presented as the median with the interquartile range, unless otherwise specified. Oxygenation index = (Fio_2 [%] × mean airway pressure [cm H_2O])/Pao_2 (mm Hg).

TABLE 2. Ventilatory Settings, Clinical and Biologic Data During Recordings

Clinical and Biological Data	Patients n = 65
Ventilatory modes, n (%)	
Volume assist control ventilation	31 (48)
Pressure assist control ventilation	10 (15)
Pressure support ventilation	13 (20)
Synchronized intermittent volume control ventilation	9 (14)
Neurally adjusted ventilatory assist	2 (3)
Ventilator's parameters	
Fio_2 (%)	40 (30–51)
TV (mL/kg)	6.8 (5.8–8.2)
Positive end-expiratory pressure (cm H_2O)	5 (5–7)
Peak inspiratory pressure (cm H_2O)	18.6 (15.4–24.3)
Mean airway pressure (cm H_2O)	8.7 (7.5–12.8)
Clinical parameters	
Heart rate (beats/min)	112 (90–135)
Respiratory rate (breaths/min)	24 (16–30)
Oxygen saturation (%)	99 (97–100)
Biologic parameters	
$Paco_2$ (mm Hg)	44.8 (38.8–49)
Pao_2 (mm Hg)	112 (90–140)
Hemoglobin (g/L)	95.5 (85–109)

Data are presented as the median with the interquartile range, unless otherwise specified.

are summarized in **Table 2**. A total of 25 children (38.5%) had acute respiratory distress syndrome (ARDS) according to the definition of the Pediatric Acute Lung Injury Consensus Conference (29) and five of them had severe ARDS (oxygenation index, ≥ 16). In total, 38 children had a Pao_2-to-FIO_2 ratio less than 300 mm Hg. Three children were intubated for severe asthma. The mean gradient between $PaCO_2$ and $PetCO_2$ ($PaCO_2$ – $PetCO_2$) was 3.35 mm Hg and the range was −5.2 mm Hg to 23.5 mm Hg (**Figs. 2*A*** and **3*A***).

Among the 24 candidate predictors, the best model included four independent variables (**Supplemental Digital Content 1, Table**, http://links.lww.com/PCC/A299): the $PetCO_2$, the MAP, the FIO_2, and the KPIv ($p < 0.001$). The resulting equation (also called "best model") was as follows: noninvasive estimated $PaCO_2$ ($P_{ni}CO_2$) = 0.859 + 0.827 × $PetCO_2$ (mm Hg) + 0.310 × MAP (cm H_2O) + 0.081 × FIO_2 (%) + 0.529 × KPIv (**Figs. 2*B*** and **3*B***). The coefficient of determination (R^2) was 0.90 (**Table 3**). The equation was built after exclusion of one outlier with low MAP due to high inspiratory effort. The mean gradient between $PaCO_2$ and $P_{ni}CO_2$ ($PaCO_2$ – $P_{ni}CO_2$) was 0.13 ± 2.56 mm Hg. The model was independent of the V_d/V_t ratio (R^2 = 0.034; p = 0.0142) (**Supplemental Digital Content 2, Fig**, http://links.lww.com/PCC/A300). The predictive equation without including variables from the VCap was $P_{ni}CO_2$_b = −1.525 + 0.876 × $PetCO_2$ (mm Hg) + 0.442 × MAP (cm H_2O) + 0.117 × FIO_2 (%). The coefficient of determination of this model was R^2 equal to 0.84 (**Figs. 2*C*** and **3*C***). The mean gradient between $PaCO_2$ and $P_{ni}CO_2$_b was 0.13 mm Hg ± 3.1 mm Hg.

With the best model, 95% (n = 62) of children had an estimated $PaCO_2$ at ± 5 mm Hg of the measured $PaCO_2$ versus 75% (n = 49) using $PetCO_2$ only.

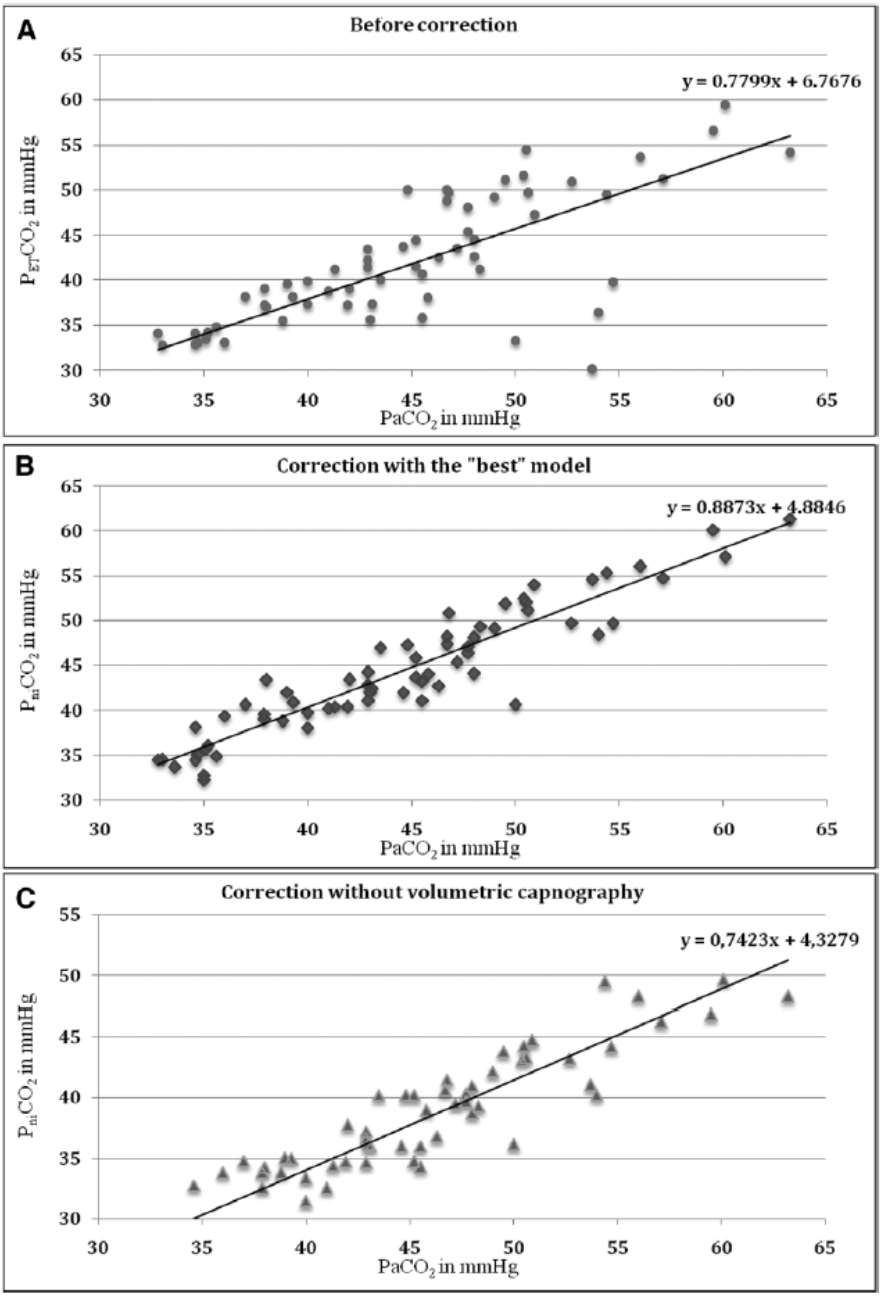

Figure 2. End-tidal partial pressure of Co_2 ($Petco_2$) versus measured value of $Paco_2$ and correlation line before correction (**A**), after correction with the "best" model (**B**) and after correction with the model without variable from the volumetric capnography (**C**) in 65 children.

DISCUSSION

Our study reports the accurate and noninvasive estimation of $PaCO_2$ using $PetCO_2$, ventilation parameters, and one parameter from VCap, in mechanically ventilated children. Our model provides an estimation of $PaCO_2$ with an accuracy of ± 5 mm Hg in 95% of the children. The three variables (MAP, KPIv, and FIO_2) combined with $PetCO_2$ led to a 0.28 increase in the coefficient of determination in comparison with the $PetCO_2$ alone.

TABLE 3. Prediction of $Paco_2$ From Stepwise Linear Regression

Model	R^2	SE of the Estimate	p
$Petco_2$	0.627	4.51	< 0.001
$Petco_2$ + KPIv	0.815	3.20	< 0.001
$Petco_2$ + KPIv + Fio_2	0.883	2.57	< 0.001
$Petco_2$ + KPIv + Fio_2 + mean airway pressure	0.901	2.38	< 0.001

KPIv = capnographic index, that is, the ratio of slope S3 phase on slope S2 phase (Fig. 1), $Petco_2$ = end-tidal partial pressure of Co_2.

Noninvasive estimation of $Paco_2$ is a real challenge to limit blood sampling especially in pediatric population (30). De Vries et al (12) validated a corrective equation with an R^2 of 0.94. These results were obtained in an homogeneous population of patients with cyanotic heart disease, in whom right to left shunt was the major determinant of the gradient between $Paco_2$ and $Petco_2$ (alveolar ventilation was considered to be normal). In a recent study, Khemani et al (9) described a model to derive and estimate $Paco_2$ and pH in children with ARDS. Their algorithm was built on retrospective data without the use of VCap and only 67.5% had a predictive value at ± 5 mm Hg of $Paco_2$. Alternatively, transcutaneous Co_2 monitoring ($TcPco_2$) can estimate $Paco_2$ but is not frequently used in pediatric intensive care (31) and has several limitations. Sites of measure of $TcPco_2$ require regular changes to avoid burns (32) and also have a prolonged calibration and stabilization time that varies with devices (32, 33).

VCap provides extensive information to improve the ventilator management of patient with ARDS (i.e., dead space, alveolar volume). Therefore, an accurate estimation of the $Paco_2$ may be useful and relevant in this context. The expired Co_2 changes almost instantaneously and is sensitive to alteration in blood Co_2 tension. Differences between $Paco_2$ and $Petco_2$ are known to be associated with severity of pulmonary disease (22). Besides the increase in alveolar dead space (also called "true deadspace"), intrapulmonary shunt (34, 35) and the wide heterogeneity of V/Q ratio may explain the increase in the gradient between $Paco_2$ and $Petco_2$. This mechanism may be more important in children with lung disease especially during ARDS.

Our model included additional parameters correlated with the pulmonary status. Fio_2 and MAP are included in the oxygenation index and in the oxygenation saturation index, previously described as markers of severity in children with ARDS (2–4). Our model also included the KPIv, defined as the ratio of the slope of S3 to the slope of S2. The shape of VCap curve (slope, α angle, and KPIv) has been described in several studies as markers of ventilation distribution, airway resistance, and ventilation perfusion (18, 20, 22, 23). The KPIv provides an overview of the ventilation perfusion heterogeneity (24, 28). Ventilation perfusion mismatch is probably one of the main determinants of the gradient between arterial and end-tidal Co_2 during ARDS that explains the pertinence of integrating the KPIv in the model (22). However, with our model the impact of V_d-to-V_t ratio increase was controlled (**Supplemental Digital Content 2, Fig,** http://links.lww.com/PCC/A300). Yamauchi et al (36) demonstrated that the gradient between arterial and end-tidal Pco_2 was also dependent on the Fio_2 in healthy adults, essentially because the alveolar dead space increases with higher Fio_2. The presumed mechanism is that high Fio_2 results in the redistribution of blood flow preferentially away from less perfused alveoli to already well-perfused alveoli. In our study, such a gradient was observed exclusively in patients with lung disease, consequently the effect of increased Fio_2 in well-aerated alveoli is uncertain (**Supplemental Digital Content 3, Fig.**, http://links.lww.com/PCC/A301).

Unlike most studies that derived clinical prediction models (9, 12), our study was a prospective study. Additionally, our model was built with a population representative of the children admitted to a PICU (postoperative, asthma, ARDS, and restrictive lung disease). Our model takes into account the clinical condition of the patient and may be used in all children, independently of their lung condition. As a result, the overall population has a relatively mild lung disease and only few children have a $Paco_2$ with extreme values. This strategy was used to ensure that our model does not over-correct "healthy" children but may be also a limitation. The model should be tested in patients with various conditions as provided in the multicenter validation study.

Our study has several limitations. First, it was a single center study and therefore there is a need to validate the model in other centers. Second, our model could be less accurate in patients with major inspiratory effort. During mechanical ventilation, the pressure applied to the respiratory system (transpulmonary pressure) is the pressure provided by the ventilator and the pressure generated by the patient. This implies that MAP only reflects the characteristic of the respiratory system if the patient does not generate a high pressure. Third, children with low V_t (< 30 mL) were excluded. Thus, children with a weight less than 4 kg (or V_t < 30 mL) cannot benefit from the use of this model. We expect that we will be able to build another model for these infants, using neonatal sensors and slope calculation based on mathematical function (37) or linear regression (18, 33). VCap monitor provides in real time all the data and the curve. For the study, we used a dedicated software to extract the data (FlowTool 3.0.3; Philips Healthcare, Markham, ON, Canada) with automatic calculation of the slope. To be clinically useful, the equation should be implemented in a monitor or ventilator to display the value in real time (based on the mean values of 5 min of VCap data). This will be discussed with manufacturers after a multicentric validation study. Finally, situations that preclude expired Co_2 monitoring (high-frequency oscillatory ventilation, significant air leaks, and extracorporeal live support) are also limitations, and measurement of $TcPco_2$ seems particularly suited to these cases.

In conclusion, our corrective equation developed in this pilot study provides an accurate estimation of the $Paco_2$ using

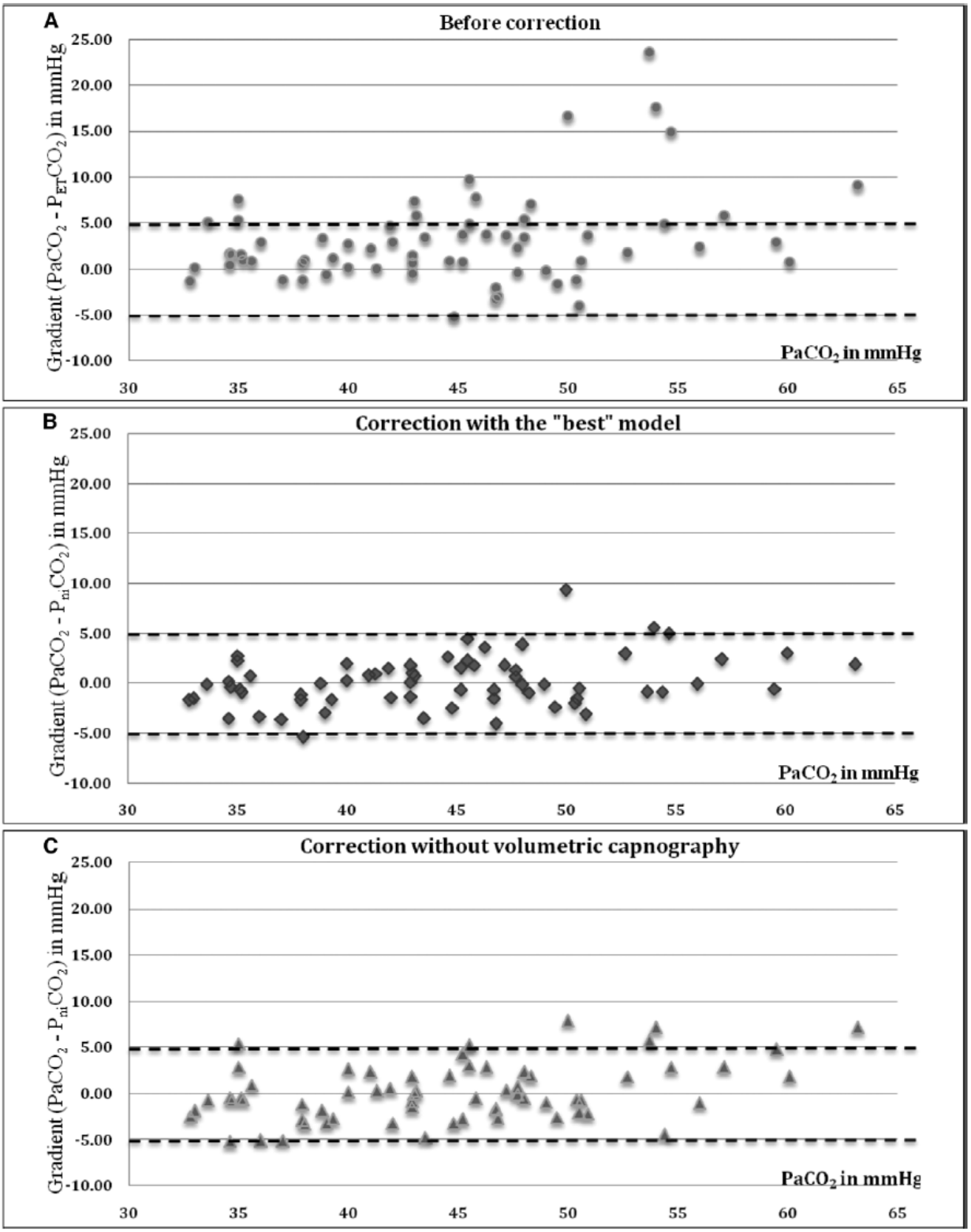

Figure 3. Gradient versus measured value of $Paco_2$ before correction (**A**), after correction with the "best" model (**B**) and after correction with the model without variable from the volumetric capnography (**C**) in 65 children. $Petco_2$ = end-tidal partial pressure of Co_2.

noninvasive variables including VCap. We plan to validate it in our PICU but also further studies are needed to validate its use in other PICUs (external validation). Our study is one of the steps of a program that aims to develop explicit computerized protocols and a closed loop system that adapts mechanical ventilation settings according to noninvasive parameters (38). As pH and $Paco_2$ are key invasively measured parameters used to adjust ventilation, the validation of our equation that noninvasively estimates $Paco_2$ is our crucial next step.

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D. Clinical decision support system for traumatic brain injury management.

Computerized Decision Support System for Traumatic Brain Injury Management

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Abstract

Mortality and morbidity related to traumatic brain injury (TBI) present a major health care burden. Patients with severe TBI must be managed rapidly and efficiently to minimize secondary brain injury potentially leading to permanent sequelae. This is especially important in young patients, whose brain is still in development, making them particularly susceptible to secondary insults. The complexity of both brain injury pathophysiology and the intensive care unit environment makes the management of these patients challenging, with a risk of delayed response and/or patient instability contributing to worsened outcome. Computerized assistance in TBI appears likely to improve patient management, by helping clinicians quickly analyze and respond to ongoing clinical changes and optimizing patient status by guiding management. Currently, computerized decision support systems (CDSSs) do not feature continuous medical assistance with individualized treatment plans. This review presents new developments in CDSSs specialized in TBI. We also present the framework for future CDSSs needed to improve TBI management in real time, taking into account individual patient characteristics.

Keywords
- brain injury
- head trauma
- intensive care unit
- pediatric intensive care unit
- computerized decision support system
- neurocritical care

Introduction

Traumatic brain injury (TBI) is a major health problem.[1] These injuries can be sustained during motor vehicle accidents, falls, high-intensity sports, or projectile blasts to the head. TBI leads to 108 to 332 new intensive care admissions per 100,000 population every year.[2] Roughly 40% of those with severe TBI will succumb to their injuries, making it the first cause of mortality in adolescents and young adults.[2] Furthermore, children with severe TBI are at high risk of developing long-term sequelae, such as partial or complete palsy, coordination impairment, learning difficulties, social behavior disorder, and memory or language impairment. The impact of these comorbidities is heightened in children, limiting their social and academic development, and leading to decreased long-term economic contribution. In 2007, the lifetime cost per case of severe TBI was estimated at up to U.S. $400,000.[2]

Important progress has been made in the understanding of brain injury, but the pathophysiology of TBI remains extremely complex and difficult to operationalize at the bedside.[1] After the initial trauma, irreversible brain lesions occur immediately, known as primary lesions. In the following hours and days, the combination of patient instability with the acutely injured brain tends to generate additional lesions known as secondary lesions. To minimize the morbidity associated with TBI, the primary goal of critical care management in the first hours is to prevent the extension of these secondary injuries.[3] To achieve this, the patient's homeostasis is maintained with close monitoring of hemodynamic and respiratory functions, as well as hematologic and electrolyte balance.[4] In addition, multimodal cerebral monitoring is used

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to detect early warning signs including intracranial hypertension, brain ischemia, cerebral metabolic crisis, and loss of vascular autoregulation, which are associated with unfavorable outcome.[5,6] A precise analysis of brain status is fundamental to appropriately guide the treatment of these patients. Each treatment for intracranial hypertension has specific effects on brain equilibrium and can be harmful when used in inappropriate situations (e.g., hyperventilation lowers intracranial pressure (ICP) by decreasing cerebral blood flow, which can be harmful if cerebral perfusion is decreased or acceptable if hyperemia prevails).

The specific analysis of brain status is complex and requires a high level of expertise. Moreover, intensive care units (ICUs) are busy work environments, where an overwhelming amount of patient information needs to be processed quickly by the health care specialists to provide accurate clinical decisions.[7] This becomes critical in severe TBI cases, given the rapid and optimal management needed to minimize secondary brain injury and sequelae.

The Miller principle states that humans can only take into consideration two variables efficiently in their decision-making process, and that this capacity is fully lost when dealing with more than seven variables.[8] Considering this, and the abundant amount of data generated in the ICU, it is appropriate to consider that the use of computerized decision support systems (CDSSs) could be beneficial in assisting ICU physicians in the decision-making process. CDSSs have been shown to be helpful in the ICU, for instance in the context of mechanical ventilation weaning.[9] When applied to the management of TBI, the potential benefits of CDSSs may include (1) standardization and optimization of the management of TBI patients even when the expertise of the medical team varies (e.g., decisions are frequently taken by residents, especially during the nights), (2) decreasing the reaction time to a change in patient condition, (3) improving understanding of individual patient patterns in pathophysiology, and (4) reducing the workload of the medical team. A CDSS would be especially useful in hospitals lacking specialized neurological ICUs, as is the case for most pediatric ICUs.

In this article, we review the evidence regarding available CDSSs designed for improving the TBI management. We also propose some features that appear critical for future CDSS development, and finally discuss the perspectives that could be achieved using machine-learning techniques.

Data Acquisition System in ICU

To fully appreciate both the potential contribution and the complexity of CDSSs in the management of children with severe TBI, it is necessary to understand some aspects of the care of these patients. Unlike adults, the brain of young children is still undergoing development, which makes it particularly vulnerable to secondary insults following severe TBI.[4] Rapid and efficient management of the injury becomes essential to favor positive outcome and reduce sequelae. To do so, the medical team has to closely monitor the patient's condition and cerebral status. This task involves the monitoring of multiple physiological signals. Some of these are continuously acquired by different sensors and their values presented on physiological monitors—for example, mean arterial pressure, temperature, pulse oxymetry (SpO_2), end-tidal CO_2, ICP, brain tissue oxygenation ($PbtO_2$), continuous electroencephalography, while other variables are measured only intermittently (e.g., transcranial Doppler, cardiac echography). The temporal evolution of these data and correlation between them provide additional important information, such as the status of cerebral vascular autoregulation. In addition, laboratory test results and ongoing pharmacotherapy must also be considered in the evaluation. Overall, there is a tremendous amount of data, sometimes conflicting, that clinicians must prioritize, analyze, and manage in their clinical decision making. The physician's personal experience plays a large role in the filtering of information and their decision making.[10] Less experienced clinicians may be less comfortable dealing with an overload of data, potentially increasing the chances of error. In addition, unplanned rapid clinical deterioration requires prompt decision making around the clock, which can be problematic in a busy ICU. Other than the quantity of data in ICUs, its presentation to clinicians can also be a factor promoting errors. Text display in medical records can increase the probability of error in ICUs,[11] while properly designed graphical display methods have been shown to help the medical staff make faster and more accurate decisions,[12–14] and facilitate finding links between associated medical events.[15]

One of the main advantages of using a CDSS in a critical care environment is its ability to regroup different datasets under one interface, and to display them in an easily interpretable manner, avoiding additional information overload. The overall goal is to help clinicians rapidly draw a general portrait of the patient's clinical status. The quality and pertinence of information presentation plays a major role in problem solving,[16–21] and taking the physician's cognitive process[18,20] into account is therefore essential in the development of a CDSS. A clinician-centered designed CDSS would be easier to implement in an ICU, a key parameter for reducing human factor errors.[22,23]

To efficiently assist the clinician, a CDSS should be fed with all available data entering in the decision process. In the case of CDSS in critical care environment, where the assessment of the patient's state has to be made in real time, the system needs to continuously gather the most recent available data. The development of a database is an important step toward the implementation of CDSS, in particular during the design, calibration, validation, and auto-learning process. The creation of the database itself can represent a major challenge in the ICU due to the multiple possible types of entries (various monitors, ventilator, electronic pumps, laboratories, medical notes, pharmacy data, imaging, etc.). The data should be entered in the database at the highest sampling frequency supported by the equipment, to avoid losing valuable information.[24] This demands high storage and computational capacity, which can require high budget allocations.[25] Assuring the data security and validity, managing possible communication problems between medical devices from different manufacturers, and the choice of the data structure

are all important considerations when developing a large-scale ICU database. The properly validated and annotated database becomes an important source of knowledge for the CDSS improvement. The database analysis by signal-processing techniques could lead to a better understanding of the TBI pathophysiology, and help develop and validate more robust mathematical models for the patient status analysis and the decision-making process.

The importance of physiological signal database for future research on complex pathophysiological pathways has led to several initiatives to make TBI-related data more accessible. The Brain Monitoring with Information Technology (BrainIT) project[26] is a European endeavor that aims to centralize TBI clinical data from different institutions, and make it research accessible to its members. The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) project[27] is a similar international collaborative group that promotes data sharing in the aim of developing TBI outcome predictors.

Computerized Clinical Support System in TBI

CDSSs have been used in the medical field for a long time. One of the first CDSSs implemented in the 1970s, the MYCIN system,[28] was used to identify the type of bacteria causing specific infections, and recommend the proper antimicrobial therapy. While this system used multiple pre-programmed medical rules to take the best decision possible, more recent CDSSs are now based on more intelligent and complex algorithms. Although not specifically designed for TBI, several systems have been developed for use in ICUs. Kamaleswaran et al[29] proposed a web-based platform that centralizes and analyzes physiological data, as well as electronic medical records in neonatal ICUs. Stylianides et al[30] developed a software that collects a database of vital signs in real time, by extracting from different medical devices. A customizable display of physiological signals facilitates interpretation and permits real-time annotations. The software also records the alarms produced by the medical devices and summarizes them on its own interface.

Of note, monitor-generated alarms are not always useful. They are mostly triggered by simple rules, usually when one physiologic signal exceeds a threshold. As a result, despite being frequently activated, they do not always reflect a medically relevant problem. They therefore tend to be ignored and can become an unnecessary source of stress for the medical team.[31] For this particular reason, one goal of CDSSs should be to avoid excessively frequent and irrelevant alerts. The integration of more sophisticated decision-making tools should result in more intelligent and clinically relevant alerts.[32]

In the specific context of TBI, a CDSS could facilitate the interpretation and diagnosis of very complex conditions, provide recommendations to improve the adherence to guidelines, and individualize patient management. A CDSS could also substantially reduce the intensivists' workload and increase their efficiency. For instance, determining optimal cerebral perfusion pressure (CPP) when managing a patient with severe TBI should take the patient's autoregulation status in account, which can be complex and time consuming. A CDSS can easily compute the brain's autoregulation coefficient (PRx), a validated indicator of autoregulation,[33,34] and rapidly provide clinically important recommendations regarding the adjustment of optimal CPP. Similarly, the automatic analysis of physiological signal time series can help identify specific patterns or predictors associated with outcome. For example, the variability of ICP is associated with long-term outcome in brain injury,[35] and a decrease in ICP approximate entropy is associated with a risk of intracranial hypertension.[36]

As listed in ►**Table 1**, a few CDSSs aiming to improve TBI management have been previously described. Wilson et al[37] have developed a CDSS specialized for neurological ICUs. Data from different sensors are gathered and processed, and alerts can be triggered based on pre-programmed medical rules. For example, an alert of high ICP in TBI would be activated when ICP exceeds 20 mm Hg, and CPP is below 60 mm Hg for more than 360 seconds. While this method produces more meaningful alerts compared with simple threshold triggering, it is limited to a specific problem (intracranial hypertension) and does not take into account other variables of the patient condition, which could influence the choice of the predetermined ICP and CPP targets (e.g., brain oxygenation or perfusion, autoregulation status).

iSyNCC is another CDSS developed for neuro-ICUs.[38] Its originality stems from its ability to predict the evolution of a physiological signal. This represents a step toward personalized treatment plans such as predicting the upcoming values of ICP over a short period of time to facilitate the anticipation of the problem (in time and in magnitude). It can also be used to compare the patient's response (after a treatment) to the predicted response, reflecting the patient's sensitivity to a treatment.

The ICM+ software developed by Smielewski et al[39] at the Cambridge University is widely used in the TBI field. Similarly to aforementioned systems, it collects physiological data in real time, displays them on a user-friendly interface, facilitating their analysis. Gomez et al[40] have also developed a toolbox for the analysis of TBI-related signals. This toolbox continuously calculates the PRx, mean velocity index (Mx), CPP, and the critical closing pressure. This software enables the calculation of monitoring indexes believed to individualize treatment; however, they do not provide any diagnostic evaluation or management recommendations.

Dora et al[41] developed a system that recommends medical treatment based on inputs. By considering the initial ICP, CPP, pupillary reaction, and the Glasgow score, the algorithm computes a list of 10 different treatments with associated certainty score. The algorithm is based on expert opinion and a probabilistic approach. Only 35% of recommendations were considered appropriate, likely because they were derived from limited baseline variables.

Wu et al[42] designed a modular CDSS that includes a TBI module. Based on real-time data processing, this system detects deviations from accepted guidelines for TBI management, and suggests treatment adaptation. The algorithm,

Table 1 Existing CDSSs developed for improving the management of patients with TBI in intensive care unit

Author	Year	Characteristics	Main strengths and limitations
Wilson et al[37]	2013	- Data gathered from different neurocritical care sensors in real time - Alarm activated by preprogrammed medical rules	Strength: improve the detection of intracranial hypertension with more meaningful alerts Limitations: limited to intracranial hypertension
Feng et al,[38] iSyNCC	2011	- Continuous data acquisition from neurocritical care medical devices - Prediction of physiological signal evolution	Strength: short-term prediction of signal evolution can facilitate anticipation Limitations: limited physiologic variables, no recommendation tool
Smielewski et al,[39] ICM+	2008	- Collects data in real time - Friendly interface facilitating signal analysis - Calculation of autoregulation parameters	Strength: facilitate the assessment of the precise brain status, including data from multimodal monitoring, favoring an individualized management Limitations: no comprehensive diagnostic classification, no recommendation for management
Gomez et al[40]	2010	- Real-time data collection and processing - Calculation of multiple indices regarding ICP, autoregulation status, perfusion status, CPP, and critical closing pressure	Strength: facilitate the assessment of the precise brain status, including data from multimodal monitoring, favoring an individualized management Limitations: no comprehensive diagnostic classification, no recommendation for management
Dora et al[41]	2001	-Recommends medical treatment based on initial ICP, CPP, pupils, and Glasgow coma score	Strength: management recommendations are available Limitations: limited quantity of variables entered in the system; the level of appropriateness of the recommendations is limited
Wu et al[42]	2009	- Real-time data acquisition and processing - Detects care deviation from medical guidelines - Suggests treatment adaptation based on ICP, CPP, and arterial blood pressure	Strength: management recommendations are available Limitations: limited quantity of variables entered in the system, recommendations not personalized based on a complete evaluation of the brain status

Abbreviations: CDSSs, computerized decision support systems; CPP, cerebral perfusion pressure; ICP, intracranial pressure; TBI, traumatic brain injury.

however, takes into account a limited quantity of variables (ICP, CPP, and arterial blood pressure), and does not adapt the recommendations to more complex pathophysiological patterns (in particular the status of brain perfusion and autoregulation), which are critical to individualize the management.

Other TBI-specific computerized algorithms have been designed to detect the severity of brain injury[43,44] or estimate patient prognosis.[45,46] Although they do not aim to optimize patient care, these tools could be useful as outcome prediction is difficult in the acute phase in ICU.

The development of more ambitious and integrative CDSSs in TBI is ongoing.[47] One project, coordinated by Moberg ICU solutions,[47] aims to facilitate the management of a patient with TBI from the time of injury, through transportation to the hospital and during its ICU stay. Similarly, the TBIcare project initiated in Europe several years ago is developing a CDSS that could provide personalized care to TBI, taking into account complex patient pathophysiological features.[48] Currently, no details or results have been published for either project.

Proposal of a CDSS in Severe TBI

Some important limitations of the systems presented earlier are the lack of specific diagnosis and recommendation capabilities; implementation of simple models using too few variables to achieve accurate results; and management recommendations that are absent, or limited to a few rules derived from guidelines for TBI care, without adaptation to the patient's specific condition. In accordance with recent international recommendations concerning the use of computer-aided monitoring systems in the neurocritical monitoring field,[32] we propose several characteristics that should be considered in the development of future CDSSs for the management of patients with TBI.

The medical management of patients with TBI has to be made on continuous basis. A real-time system connected to a dynamic database would be of great value, allowing the continuous evaluation of the patient-specific conditions, and the ability to compare one situation to a large database of previous similar conditions.

The primary role of a CDSS is to assist clinicians in their decision process, facilitating the identification and detection of specific conditions and providing them with appropriate clinical recommendations. To achieve a good acceptability, it is crucial that the CDSS algorithms take into account the clinician's cognitive clinical decision process. A rule-based system, with rules developed and widely accepted by medical specialists, should therefore be at the heart of the design. It will improve the understanding and trust in the CDSS, and facilitate its implementation in the ICU. The terminal user should also be able to adapt the algorithm rules or thresholds. It is also important that the system provides explanations and justifications regarding the diagnosis established and the suggested treatment, which would improve the acceptability of these outputs and favor the clinician training.

One major challenge in designing the rules is the understanding and replication of the decision-making process of clinicians. Clinical decisions are made based on scientific knowledge, experience, and intuition suggesting that the rules are not always strict and thresholds are not always fixed values. As such, fuzzy logic has proved to be a great tool in the design of expert systems,[49] and is well adapted for medical decisions.[50–52] The adaptability of implemented rules is also crucial to allow for inter-physician variability. One must also track the reasons why some decisions by the CDSS are denied by the clinician, to improve the CDSS recommendation process. Moreover, once a proper amount of validated data is recorded into the database, machine-learning tools will permit to reassess or recalibrate the rule basis. The CDSS should therefore be able to learn long term, based on patient behavior and clinician response to each of its decisions, to adjust the decision-making process accordingly.

To aid the medical staff in identifying the diagnostic step and consecutively adhere to the management recommendations, the CDSS should classify the state of the patient into a clearly designated category. For instance, the clinician should understand immediately if the TBI patient is in a controlled situation, or if the patient's brain seems at risk of ischemia, hyperhemia, and/or if a moderate or severe intracranial hypertension is present. By clearly assigning the brain pathophysiological condition, with the proper justification for this classification, the CDSS should more rapidly facilitate the recognition of complex condition, even by less trained physicians. This should also lead to a better acceptance of the recommendations, and reduce clinician stress, allowing them to focus on subtle details in critical situations. The prediction of the patient's ongoing clinical state will favor anticipatory rather than a posteriori reactions.

To facilitate the rapid interpretation by the medical team, the patient's status should be illustrated using specific and clear graphical display, exhibiting various pathophysiological conditions and the ongoing clinical state. This provides a visual indication of the dynamic evolution of the patient's state.

The validation of CDSS accuracy is a challenge. Retrospective patient data could be used to design and test the system. The data utilized to train the system algorithms should represent a wide range of conditions. Once the CDSS performances are validated on retrospective data against medical experts' decisions, prospective studies should evaluate the CDSS behavior in a real clinical environment. Finally, clinical trials should explore the impact of CDSS use on patient management, initially with simple objectives (e.g., percentage of adherence to guidelines) and subsequently with assessment of patient outcome.

Future Perspectives

As discussed in previous sections, the amount of data generated in ICUs is enormous. An initial challenge is centralizing and storing this information to provide an infrastructure for research. Big data mining is a very active field,[53] particularly pertinent for medical data in the ICU.[54–56] Data mining can help uncover links between variables, to help in the development of optimal strategies. Applying data mining techniques to well-structured TBI databases could generate a better understanding of complex brain conditions and aid in selecting the most significant variables to consider in TBI management. Furthermore, feature selection techniques such as genetic algorithms, frequently used in optimization problems, can be used to select, among several rules, the set of rules that provide the best accuracy. Forecasting of time series in physiological signals could also have major implication in the development of CDSS in TBI.[57–59] As previously stated, effective forecasted data would anticipate and accelerate the clinician's response, optimizing patient status for longer periods than conventional management.

In conclusion, CDSSs are crucial to improve the management of patients with TBI. CDSSs are still at an early stage in the field of TBI, but recent technologies should overcome the barriers and challenges of ICU environment, leading to the development of efficient systems. Collaboration between neurocritical care medical specialists, Information Technologies (IT) specialists, biomedical engineers, and companies is of outmost importance to prepare and validate optimal CDSS that will be reliable, efficient, and easy to implement. These future systems should have the power to decrease the impact of this major health problem on the patient, their family, and society.

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E. Editorial R. Wetzel : First get the data, then do the science!

First Get the Data, Then Do the Science!*

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This editorial's title belies our training and experience requiring careful definition of what data to collect for prospective studies and the dangers of secondary retrospective analysis of data collected for other purposes. But we live in a new era. The advent of modern computer central processing units, vast, inexpensive data storage, and new machine learning techniques for analyzing big data present an unprecedented opportunity to learn from the critical care processes and the documentation of how critical illness happens to children. The promise of big data, artificial intelligence, and a revolution in healthcare is all around us (1, 2). The reality is somewhat less conclusive (3). The really hard work of aggregating, analyzing, and learning from clinical data in a disciplined fashion and then understanding how to apply such knowledge still requires a great deal of doing. As clinical data systems become increasingly digital, there exists the opportunity to computationally analyze these data (4). Unfortunately, the lack of suitable, accessible clinical PICU data for analysis delays development in this area.

In this issue of *Pediatric Critical Care Medicine*, Brossier et al (5) are to be commended for the hard work required to organize a system to capture PICU data collected as part of clinical care. Such databases will be useful for future clinical and data science research, simulation and eventually for clinical decision support. This article is not research in the classical sense that it presents new information that will directly guide care. One then may ask: "what use is it?" This article's purpose was to describe a data acquisition process from the bedside to an electronic database to serve multiple purposes. Some may see this article as merely reporting the obvious or think that their electronic health record (EHR) is already capturing these data in a useful, accessible format. Nevertheless, many who think so will be disillusioned when they seek data, attempt to access it, and use it to the many ends necessary to move healthcare into the data science era of big data analytics, machine learning, and artificial intelligence. Although useful for clinical care, what is found in EHRs frequently is insufficient to meet our future data needs. Further, access to the data is not made simple by the industry players who too often treat the data as proprietary information. Clinicians and scientists must be at liberty to use these data for clinical, administrative, and research purposes without undue restraint (1, 6). The meticulous description of a prospective, premeditated, nontrivial system to capture data for multiple purposes from the care process, without impeding care, is the value of this article. This was not simply caching

*See also p. e189.

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EHR data. Rather, the investigators painstakingly and prospectively determined capture techniques to assure data fidelity and quality for future work. We all should emulate them!

Why? In healthcare, we have a plethora of "natural" experiments captured in our EHRs but frequently throw away the data. Hippocrates admonished us to learn from the patients, and today patients generate large amounts of data about their condition, responses, and outcomes (7). There is an ethical imperative to capture "all of the data"—every heartbeat, every breath, to analyze for the benefit of our future patients. If we do not, we will fail to learn from the evidence before our eyes and fail our future patients. The terms "reusable patients," "perpetual patients," or "virtual patients" (5, 8), perhaps somewhat inelegantly, mean that clinical data remain available for all time to guide further research, improve treatment, and provide training. This neo-empiricist approach will not supplant classical medical trials but provides an alternative by learning from the vast amount of clinical data we now have.

Prospectively collected pediatric critical care data have been useful for hypothesis testing, quality improvement, and better understanding our care process (9, 10). The Virtual Pediatric System, LLC project which prospectively collects data from all admissions to member ICUs contains over 1.3 million episodes and has been used in hundreds of papers and presentations, some applying advanced machine learning techniques (11–13). These demonstrate the potential of premeditated, prospectively gathered and retrospectively analyzed data. Brossier et al (5) report automated, granular data collection already used for multiple publications. The automated collection of these clinical data, melded with further clinical data, will have an even greater impact on our understanding of critical illness in children.

How reliable are data captured this way? Although secondary use of clinical data and big data analytics applied to EMR data is promising, the quality of the data must be considered (6, 14). Are the data valid, precise, and accurate? Do they accurately reflect the patient's condition? Often, clinical data have erroneous values beyond physiologic possibility, or often disconnected, artifact prone monitor data. There is ample evidence that what is recorded is not what the monitors displayed (6, 14). Are these clinician data smoothing, do the nurses validate representative samples, how are ridiculous and erroneous values eliminated? How do we analyze such obviously messy data? These are all serious matters requiring attention before using the data for analysis, learning, and decision support. Nevertheless, these are the data that intensivists base care on—albeit filtered through experience and reason. Understanding the importance of accurate data collection will hopefully provide the impetus to assure future data accuracy. Although not adequately addressed in this article, the authors assure us that a validation article is on the way.

The Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) database has met this need in adult critical care; it does not contain sufficient PICU data (15). Acquiring these data from the primary sources in a useful format is the start. Organizing these data in a defined open structure with defined semantic architecture, a common ontology and ready interpretability is also necessary (16). Making these data accessible to adequately trained clinician investigators and collaboratively sharing the data with others interested in data science research, building models to develop simulation and decision support systems useful back at the bedside closes the loop (17). The Virtual Pediatric Intensive Care Unit is organizing a data collaborative among national PICUs to provide a data resource of EHR data to combine and make accessible data similar to that reported here (http://collaborative.vpicu.net). Prospectively initiating large multisite data collaborations will, in addition to being a force multiplier, allow removal of inherent center and/or regional biases and enable a more representative data source to meet the big data promise in pediatric critical care.

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