



HAL
open science

**Prise en charge de l'hypotension sous anesthésie par
développement d'un moniteur de mesure non invasive de
la pression artérielle et par l'élaboration d'un modèle
PK/PD de la noradrénaline**

Jona Joachim

► **To cite this version:**

Jona Joachim. Prise en charge de l'hypotension sous anesthésie par développement d'un moniteur de mesure non invasive de la pression artérielle et par l'élaboration d'un modèle PK/PD de la noradrénaline. Cardiologie et système cardiovasculaire. Université Paris Cité, 2022. Français. NNT : 2022UNIP5098 . tel-04589657

HAL Id: tel-04589657

<https://theses.hal.science/tel-04589657>

Submitted on 27 May 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



École doctorale Hématologie, oncogénèse et biothérapies (HOB, ED 561)

Marqueurs cardiovasculaires en situation de stress (MASCOT, UMR_S 942)

Doctorat en Biothérapies et biotechnologies

Prise en charge de l'hypotension sous anesthésie par développement
d'un moniteur de mesure non invasive de la pression artérielle et par
l'élaboration d'un modèle PK/PD de la noradrénaline

Jona JOACHIM

Thèse dirigée par : Pr Étienne GAYAT

Soutenue le 10 octobre 2022

JURY

Benoit TAVERNIER	PU-PH	Université de Lille	Examineur
Romain PIRRACCHIO	Full Professor	Université de Californie à San Francisco	Rapporteur
Claire ROGER	PU-PH	Université de Montpellier	Rapporteur
Valérie BILLARD	PhD	Université Paris-Saclay	Examineur
Sandrine MILLASSEAU	PhD	Monde professionnel	Examineur
Alexandre MEBAZAA	PU-PH	Université Paris Cité	Examineur
Étienne GAYAT	PU-PH	Université Paris Cité	Directeur

REMERCIEMENTS

J'aimerais ici adresser mes sincères remerciements :

Au Docteur Fabrice Vallée qui a cru à mon projet et sans qui cela n'aurait pas été possible. Merci de mettre le côté humain au premier plan au quotidien dans ce monde où le côté technique a souvent tendance à l'emporter.

Au Professeur Gayat pour son soutien sans faille et son accompagnement quotidien.

Au Professeur Mebazaa pour sa confiance et pour son soutien tout au long de mon parcours.

A Marc Lavielle pour son aide précieuse et son expertise dans la modélisation PK/PD qui a largement contribué à ce travail.

A l'équipe MÆDISIM pour m'avoir accueilli à Saclay et m'avoir redonné goût aux mathématiques.

Au Professeur Pirracchio pour son enseignement transversal et son don de synthèse.

Au Docteur Millasseau pour ses précieux conseils et son expertise technique dans le domaine du monitoring.

Aux Professeurs Tavernier et Roger et au Docteur Billard pour avoir accepté de faire partie de mon jury et m'avoir ainsi fait bénéficier de leur enseignement et leurs expertises.

À toute l'équipe du département d'Anesthésie-Réanimation de l'hôpital Lariboisière qui m'a accompagné sur ce chemin.

Au Lariboisière Temple Orchestra pour tous les bons moments passés ensemble.

À mes deux petits garçons qui m'apportent beaucoup de joie au quotidien, qui font tout très bien et qui grandissent très vite.

À ma femme Victoire pour avoir cru en moi et pour m'avoir aidé sur le chemin malgré les épreuves pendant ces années tumultueuses. Merci de toujours être là, pour ton amour sincère et pour ta fidélité.

À ma famille et ma belle-famille

Enfin la question est là : est-ce qu'en développant de plus en plus notre appareillage nous pouvons arriver à éliminer le facteur humain, ou est-ce que nous ne faisons que le reculer ?

Ernest Kern, 1955

RESUME

Prise en charge de l'hypotension sous anesthésie par développement d'un moniteur de mesure non invasive de la pression artérielle et par l'élaboration d'un modèle PK/PD de la noradrénaline

L'hypotension artérielle sous anesthésie (en anglais, «IntraOperative Hypotension» IOH) est un phénomène fréquent. Des études récentes ont identifié l'IOH comme responsable de dommages myocardiques, d'insuffisance rénale aiguë, d'hypoperfusion cérébrale augmentant ainsi la morbi-mortalité post-opératoire. La population de patients devient de plus en plus âgée et de plus en plus fragile, or les patients les plus fragiles sont le plus exposés au risque d'IOH et sont ceux qui la tolèrent le moins bien ces épisodes. Ils sont exposés à une morbidité accrue, des défaillances d'organes et des complications post-opératoires qui peuvent avoir des séquelles à long terme dans de nombreux cas. Il a été montré dans la littérature qu'une prise en charge agressive de cette hypotension permet d'éviter un certain nombre de complications post-opératoires. En effet, la gravité des souffrances d'organes est à la fois liée à la profondeur de l'hypotension comme à la durée d'hypotension. Un traitement avec un objectif de pression artérielle permet d'en réduire l'exposition. Les moyens thérapeutiques efficaces pour traiter cette hypotension existent, notamment avec les médicaments vasopresseurs, et la mise en œuvre de cette prise en charge à large échelle se traduirait sans doute par un bénéfice de santé publique. Nous avons cependant identifié deux freins à l'application de cette prise en charge aujourd'hui, d'un côté un manque de monitoring qui soit à la fois fiable et non invasif et de l'autre côté l'absence d'outils permettant de personnaliser le traitement de l'hypotension.

La gravité de l'hypotension étant dose dépendante, le monitoring joue un rôle clé. Un brassard à tension permettant une mesure discontinue semble aujourd'hui insuffisant et un monitoring continu paraît nécessaire. Il ne paraît cependant pas raisonnable de proposer systématiquement un monitoring invasif pour des patients sans pathologie sévère sous-jacente pour des chirurgies de risque faible ou intermédiaire. Par conséquent, le monitoring doit être continu et non-invasif. Nous avons mis au point, en se basant sur des mécanismes physiologiques, une série d'algorithmes permettant l'estimation en temps réel, battement par battement, de la pression artérielle moyenne en utilisant le monitoring standard préexistant, notamment la photopléthysmographie, permettant de cette manière une utilisation systématique sans surcoût.

Le traitement de l'hypotension sous anesthésie est aujourd'hui largement basé sur des médicaments vasopresseurs. Parmi ceux-là, la noradrénaline diluée faiblement dosée s'est très rapidement établie comme un standard de facto sur les 5 dernières années. Cependant, l'utilisation de ce médicament n'est pas toujours aisée. En effet, il s'agit d'un médicament puissant avec une demie vie courte et une fenêtre thérapeutique étroite. L'absence de standardisation quant à l'utilisation peut exposer à des accidents d'utilisation et la grande variabilité interindividuelle rend difficile l'ajustement de la dose nécessaire. Nous avons développé un modèle pharmacocinétique/pharmacodynamique (PK/PD) permettant un calcul de dose individualisé par patient et pouvant servir de base pour une administration en objectif de concentration. L'administration de la noradrénaline en objectif de concentration est une méthode de choix pour uniformiser et simplifier les prises en charge tout en évitant des erreurs de dose et des fluctuations.

L'incorporation de ces deux modèles, l'un de monitoring, l'autre de traitement pharmacologique, en boucle fermée pourrait à terme automatiser la prise en charge de l'hypotension sous anesthésie.

Mots clés: Anesthésie, Hypotension, Monitoring, Intelligence artificielle, PK/PD

RESUME (anglais)

Intraoperative hypotension management using novel algorithms for noninvasive blood pressure monitoring as well as PK/PD modeling of norepinephrine

Intraoperative hypotension (IOH) is common and responsible for damage to myocardium, kidneys and brain tissue as well as increased mortality. Proactive management of IOH has been shown to prevent complications. Remaining obstacles to the effective treatment of IOH are the lack of reliable non-invasive monitoring as well as tools to personalize drug administration to treat hypotension.

In order to monitor intraoperative blood pressure, discontinuous pressure cuff measurements seem to be insufficient today. Monitoring should be both, continuous and non-invasive. We have developed algorithms based on physiology to allow the estimation of the mean arterial pressure in real time, beat to beat, using readily available standard monitoring equipment.

Treatment of IOH is nowadays largely based on vasopressors. Low-dose dilute norepinephrine has established itself as a de facto standard treatment in this domain in large parts of the world. It is a powerful drug with a short half-life and a narrow therapeutic window. No current standard for the use of low dose norepinephrine exists today and the lack of standardized drug use can lead to accidents. We developed a pharmacokinetic/pharmacodynamic (PK/PD) model that allows individualized dose calculation and can be used as a basis for a targeted controlled infusion.

The joint use of physiologic models for blood pressure monitoring and patient centered drug delivery could eventually automate the management of IOH and result in public health benefit.

Key words: Anaesthesia, Hypotension, Monitoring, Artificial Intelligence, PK/PD

PRODUCTION SCIENTIFIQUE ACQUISE DANS LE CADRE DE LA THÈSE

Articles acceptés.

- **Perfusion Index: Physical Principles, Physiological Meanings and Clinical Implications**
[1]
 - Article publié dans *Anaesthesia Critical Care & Pain Medicine* le 12 novembre 2021.
 - Auteurs: Maxime Coutrot, Emmanuel Dudoignon, Jona Joachim, Etienne Gayat, Fabrice Vallée, François Dépret

- **Noninvasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept** [2]
 - Article publié dans le *British Journal of Anaesthesia* le 11 mars 2019
 - Auteurs: Maxime Coutrot, Jona Joachim, François Dépret, Sandrine Millasseau, Helene Nougue, Joaquim Mateo, Alexandre Mebazaa, Etienne Gayat, Fabrice Vallee

- **Real-time estimation of mean arterial blood pressure based on photoplethysmography dirotic notch and perfusion index. A pilot study** [3]
 - Article publié dans *Journal of Clinical Monitoring and Computing* le 10 février 2020
 - Auteurs: Jona Joachim, Etienne Gayat, Maxime Coutrot, Sandrine Millasseau, Joaquim Matéo, Alexandre Mebazaa, Fabrice Vallée

Articles soumis

- **Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.**
 - Article soumis au *British Journal of Anaesthesia* le 26 juin 2022
 - Auteurs: Jona Joachim, Fabrice Vallée, Thomas Lefevre, Jacques Callebert, Étienne Gayat, Marc Lavielle

Articles en cours de rédaction

- **PlethoMAP: Non-invasive arterial pressure prediction for operating rooms using mechanistic and deep learning models: a comparative approach**
 - Article en cours de rédaction en vue d'une publication dans *British Journal of Anaesthesiology*
 - Auteurs: Perdereau Jade, Chamoux Thibaut, Gayat Etienne, Le Gall Arthur, Vallée Fabrice, Joachim Jona

Brevet

- Brevet FR3075590A1, US2020390347A1: Méthode de mesure de la pression artérielle moyenne [4, 5]
 - HÔPITAUX PARIS ASSIST PUBLIQUE [FR]
 - Inventeurs: VALLEE FABRICE [FR]; JOACHIM JONA [FR]; COUTROT MAXIME [FR]; MATEO JOAQUIM [FR]; GAYAT ETIENNE [FR]; MEBAZAA ALEXANDRE [FR]
 - Trophée APinnov du brevet prometteur 2021

Encadrement d'étudiants

- Master 2 de Thomas LEFEVRE
 - Master Biologie Cellulaire Physiologie et Physiopathologie, Spécialité « BiVATH »
 - Intitulé: "Dosages de Noradrénaline plasmatique pour traiter l'hypotension artérielle induite par l'anesthésie générale : Résultats préliminaires pour développer un modèle PK/PD"
 - Mémoire soutenu le 29/09/2020

- Thèse de Médecine de Thomas LEFEVRE
 - Dosages de noradrénaline plasmatique chez l'homme dans le cadre de l'hypotension artérielle induite par l'anesthésie
 - Soutenue publiquement le 11/10/2021

TABLE DES MATIERES

TABLES DES FIGURES	10
Introduction	11
CHAPITRE 1: Hypotension au bloc opératoire	12
L'hypotension sous anesthésie générale	12
Gestion de l'hypotension en pratique clinique	14
Le monitoring non invasif de la pression artérielle	15
CHAPITRE 2: Le PlethoMAP	17
Signal de Photopléthysmographie (PPG) et Indice de perfusion (PI)	17
Introduction	17
Principe de la pléthysmographie et calcul du PI	17
Déterminants de l'indice de perfusion (PI)	19
Indications cliniques	19
Du signal de photopléthysmographie à la pression artérielle moyenne: le concept du PlethoMAP	22
Introduction	22
Concept physiologique et but de l'étude	22
Méthode	23
Principaux résultats	23
Conclusion	25
Premier algorithme du PlethoMAP	25
Concept physiologique	25
Méthode	26
Principaux résultats	27
Conclusion	28
PlethoMAP : développements récents	28
Innovations	29

Méthode	30
Modèle naïf	30
Modèle mécanistique	30
Modèle de réseau neuronal	31
Principaux résultats	31
Résultats préliminaires de modélisation	32
Conclusion	32
CHAPITRE 3: Modèle PK/PD de la noradrénaline	35
Introduction	35
Rôle de la noradrénaline	35
Biosynthèse de la noradrénaline et distribution tissulaire	36
Libération de la noradrénaline	38
Concentration plasmatique	38
Propriétés physicochimiques	39
Dégradation de la noradrénaline	39
La noradrénaline exogène	40
Utilisation de la noradrénaline en pratique clinique	40
Modèle pharmacocinétique / pharmacodynamique (PKPD) de la noradrénaline en anesthésie	42
Matériel et Méthodes	42
Timing des dosages	43
Technique de dosage de la noradrénaline	44
Modèle PK	44
Modèles PKPD	46
Modèle empirique	46
Modèle basé sur les mécanismes	47
Modèle de mélange	48

Résultats principaux	48
Modèle PK	48
Modèle PK/PD : 2 types de modèles	48
Conclusion de l'article	50
CHAPITRE 4: Discussion et Perspectives	51
Perspectives PlethoMAP	51
Construction du prototype et brevet AP-HP	51
Améliorations de l'algorithme	52
Amélioration du recueil systématisé	53
Validation prospective et impact	55
Dimension entrepreneuriale	55
Perspectives Modèle PK/PD Noradrénaline	55
Perfusion à objectif de concentration	55
Entraînement temps réel	56
Asservissement aux hypnotiques	56
Boucle fermée	57
CONCLUSION	58
BIBLIOGRAPHIE	60
Annexes	65
ANNEXES 1: Articles présentés dans la thèse	65
Annexe 1.1 Article "Perfusion Index: Physical Principles, Physiological Meanings and Clinical Implications"	65
Annexe 1.2 Article "Noninvasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept"	66
Annexe 1.3 Article "Real-time estimation of mean arterial blood pressure based on photoplethysmography dicrotic notch and perfusion index. A pilot study"	67

Annexe 1.4 Article “Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.”	68
ANNEXES 2: autres documents liés au travail de thèse	69
Annexe 2.1 Étude IOCENE: Estimation de la pression artérielle moyenne	69
Annexe 2.2 Développements informatiques	70
Bibliothèque <i>dwclib</i>	70
Bibliothèque <i>InfuPy</i>	70
Bibliothèque <i>physiocurve</i>	70
Logiciel <i>GraPhysio</i>	70

TABLES DES FIGURES

	Page
Figure 1 Principe de la photopléthysmographie et du calcul de l'indice de perfusion	18
Figure 2 Déterminants de l'indice de perfusion et situations cliniques courantes	19
Figure 3 Résumé de l'utilité clinique de l'indice de perfusion	21
Figure 4 Définition de DICpleth et de PI sur la courbe de PPG	23
Figure 5 A) variation médiane de la PAM et de DICpleth et B) variation médiane de la PAM et du PI durant les 16 premières minutes de l'induction anesthésique	24
Figure 6 Illustration des trois algorithmes explorés dans l'article : en vert et en jaune les deux algorithmes basés sur DICpleth, à savoir NRA en vert et NAA en jaune ; en orange l'algorithme basé sur le PI.	27
Figure 7 Comparaison de l'estimation de la PAM par l'algorithme PlethoMAP (en bleu) au gold standard invasif par cathéter artériel (en rouge). Les ronds violets désignent les mesures par brassard. L'aire verte correspond à l'erreur d'estimation instantanée.	28
Figure 8 Structure couche par couche du réseau de neurones	33
Figure 9 « Saliency map » montrant les zones d'intérêt découvertes par le réseau de neurones sur le signal de PPG. Des couleurs plus claires signifient plus d'importance.	33
Figure 10 Comparaison des modèles sur un exemple de cas. En vert : mesure de référence obtenue par cathéter artériel invasif. En pointillée : modèle naïf. En orange : estimation par le modèle mécanistique. En bleu : estimation par le réseau de neurones profond.	34
Figure 11 Structure moléculaire de la noradrénaline	36
Figure 12 Biosynthèse de la Noradrénaline	37
Figure 13 Structure du modèle PK	46
Figure 14 Illustration graphique du modèle de circuit RLC.	47
Figure 15 Exemple de prédiction individuelle pour un patient. Points bleus : valeurs mesurées. Courbes violettes : prédiction. Panneau (a) : modèle PK. Panneau (b) : modèle Emax. Panneau (c) : modèle mécanistique.	50
Figure 16 Prototype du «PlethoMAP». Un appareil qui est connecté au moniteur patient Philips IntelliVue pour capter en temps réel les signaux de PPG, le PI et qui calcule et affiche en temps réel une estimation de la PAM par l'algorithme PlethoMAP.	51
Figure 17 Remise du prix du Brevet prometteur AP-HP 2021	52
Figure 18 Pipeline Kafka temps réel permettant la mise en place de nombreux microservices qui peuvent se nourrir et réinjecter des données en temps réel	55

Introduction

La perspective translationnelle de ce travail de thèse d'université est la mise au point d'un appareil permettant l'administration automatisée de médicaments vasoconstricteurs comme la noradrénaline au bloc opératoire afin de prévenir l'hypotension artérielle pendant la chirurgie.

Ce projet se déroule sur plusieurs étapes qui pour la plupart ont progressé de manière conjointe sur la durée de la thèse. Dans cette thèse, nous décrirons surtout les deux premières étapes du projet, à savoir 1/ la mise au point et la validation d'une méthode de monitoring non invasif et continu de la pression artérielle moyenne et puis et/ la modélisation pharmacocinétique et pharmacodynamique de la noradrénaline utilisée au bloc opératoire.

Ainsi, ce manuscrit de thèse se décompose en quatre parties:

- Une *première partie* d'introduction rappelant le contexte et la raison de lutter contre les épisodes hypotensifs au bloc opératoire.
- Nous détaillerons dans un *deuxième partie* notre solution de monitoring non-invasif de la pression artérielle moyenne (le PlethoMAP), en revenant sur l'analyse des propriétés physiologiques du signal de photopléthysmographie (PPG) et la raison pour laquelle nous avons développé cette solution et quelles sont nos avancées actuelles.
- Dans une *troisième partie*, nous détaillerons l'étude clinique (NorPharm) ayant conduit au développement du modèle PK/PD de la noradrénaline à faible concentration (parfois désignée sous le terme *babynoradrénaline*).
- Enfin, nous examinerons dans une *quatrième partie* les perspectives qui pourraient conduire à une administration automatisée de la noradrénaline au bloc opératoire pour prévenir et traiter les épisodes hypotensifs.

CHAPITRE 1: Hypotension au bloc opératoire

L'hypotension sous anesthésie générale

La problématique de l'hypotension sous anesthésie est aussi vieille que l'anesthésie elle-même et peut être retracée jusqu'à l'ère de l'anesthésie au chloroforme et à l'éther. Elle n'a pas toujours été reconnue comme néfaste. C'est ainsi que Ernest Kern écrit en 1953 dans un traité sur l'« hypotension contrôlée » [6] que “la diminution de la tension artérielle entraîne automatiquement une diminution du saignement artériel”. Il rapporte que “la plupart des auteurs considèrent qu'une tension artérielle systolique comprise entre 50 et 70 mmHg est à la fois efficace et sans danger”. Cependant, déjà à cette époque, les limites de cette pratique semblent évidentes. En effet, Kern rapporte un “pourcentage d'échecs qui oscille entre 15% et 20%”. “Le saignement veineux [...] n'est pratiquement pas affecté, il peut même [...] être augmenté”. Des effets délétères majeurs sont remarqués, en effet “la saturation du sang veineux diminue de 30% à 50% par rapport au chiffre normal”. Un auteur “rapporte deux arrêts cardiaques [...] qu'il attribue à une ischémie coronarienne” et “[...] il est possible que tous les cas malheureux n'aient pas été publiés”. Kern conclut son exposé avec beaucoup de vigilance et contre-indique notamment la pratique de l'hypotension contrôlée chez les patients coronariens, insuffisants respiratoires et rénaux, les patients souffrant de maladie d'Addison.

Si la nature des effets délétères de l'hypotension était connue dans les années 1950, nous avons aujourd'hui une meilleure notion de la gravité et de la fréquence de ces effets. En effet, l'hypotension artérielle peropératoire est une complication fréquente de l'anesthésie générale et entraîne une augmentation notable de la morbi-mortalité. Cela a été démontré plus récemment pour le risque d'insuffisance rénale aiguë, de dommage myocardique, d'accident vasculaire cérébral ischémique et de mortalité post-opératoire [7–11]. L'association entre

l'hypotension artérielle et les complications post-opératoires semble à la fois dose-dépendante et temps-dépendante [7].

Cependant, il n'existe pas à ce jour de définition précise de cette hypotension. Il semble que des valeurs de pression artérielle moyenne (PAM) inférieure à 65 millimètres de mercure (mmHg) majorent le risque de dysfonction d'organe post-opératoire [12]. Une exposition de courte durée, dès 5 minutes, à ce niveau d'hypotension entraîne un surrisque significatif de complications post-opératoires.

Le niveau de PAM à cibler pour chaque patient est difficile à évaluer. La tendance actuelle est à individualiser nos prises en charge pour chaque patient et ainsi à proposer une anesthésie « sur-mesure » [12]. C'est pour ces raisons que les recommandations actuelles sont en faveur d'une prise en charge précoce de tout épisode hypotensif durant la chirurgie. Un essai randomisé a d'ailleurs récemment montré l'efficacité d'une stratégie d'optimisation de la pression artérielle peropératoire [13]. Cette prise en charge devra bien évidemment être adaptée et ajustée à chaque patient en fonction de son risque.

Les étiologies de l'hypotension artérielle au bloc opératoire sont multiples. L'origine peut être secondaire à une baisse du tonus sympathique induite par les produits anesthésiques ou due à une hypovolémie, une hémorragie, une dysfonction myocardique voire un sepsis. L'étiologie la plus fréquemment observée au bloc opératoire est une baisse du tonus vasculaire due aux médicaments hypnotiques et morphiniques utilisés à l'induction et en entretien lors de l'anesthésie. A cette baisse du tonus artériolaire peut s'ajouter une baisse du retour veineux et ainsi une baisse du débit cardiaque. On parle ainsi d'hypotension induite par l'anesthésie ou *Intraoperative Hypotension* (IOH). Ces événements demandent une grande réactivité afin de les corriger au plus vite et imposent des contraintes de fiabilité et de réactivité au monitoring et au traitement.

Gestion de l'hypotension en pratique clinique

Comme indiqué plus haut, l'hypotension au bloc opératoire est secondaire à des mécanismes sous-jacents multiples et complexes : vasoplégie due à la sympatholyse [14] et à une diminution des catécholamines circulantes [15] induite par les agents par les agents anesthésiques, l'hypovolémie et la dysfonction myocardique.

Les stratégies actuelles de restauration de la pression de perfusion pendant l'anesthésie générale sont basées sur l'expansion volumique et/ou l'administration intravasculaire l'administration intravasculaire de vasopresseurs [16]. Ces médicaments vasopresseurs combinent souvent un effet vasoconstricteur et des effets myocardiques directs ou indirects, selon le médicament utilisé [17]. Les trois principales molécules utilisées au bloc opératoire pour corriger l'hypotension sont l'éphédrine, la phényléphrine et la noradrénaline.

L'utilisation de l'éphédrine est limitée par son effet tachycardisant et la tachyphylaxie qui limite la dose cumulée utilisable en pratique. La phényléphrine est largement utilisée pendant l'anesthésie, souvent en relais de l'éphédrine, mais cette utilisation a été récemment remise en question [18, 19]. En effet, les effets physiologiques documentés sur le débit cardiaque et la postcharge ventriculaire gauche peuvent être néfastes. De plus, la phényléphrine peut être responsable de bradycardie par l'activation du baroréflexe [20] et l'altération de la fonction de la fonction ventriculaire gauche [21, 22].

Durant ces dernières années, la noradrénaline gagne une place de choix dans le traitement de l'hypotension artérielle induite par l'anesthésie [23], avec notamment l'avènement de la noradrénaline diluée, communément appelée « babynoradrénaline », permettant une utilisation en bolus et en perfusion continue sur des voies d'abord classiques (voie veineuse périphérique). En effet, Wuethrich et al. ont montré que la perfusion continue peropératoire de noradrénaline

à faible dose chez des patients à haut risque, pouvait limiter l'expansion volumique pendant une chirurgie majeure [24, 25]. De plus, quelques d'études suggèrent un effet bénéfique de la noradrénaline à faible concentration par rapport aux autres vasopresseurs pour contrôler l'hypotension induite par la rachianesthésie chez les patientes ayant subi une césarienne [26] et chez les patients souffrant d'hypertension artérielle pulmonaire chronique [27].

Parmi les effets potentiellement délétères des vasopresseurs intraveineux, il faut noter l'augmentation de la rigidité artérielle, l'augmentation du travail du myocarde, et potentiellement la diminution du volume systolique et de la compliance artérielle. Ces altérations du couplage artériel du ventricule gauche pourraient être associées à des résultats défavorables [28–30]. Une étude récente a montré qu'un bolus de 5 µg de noradrénaline administrée dans une voie veineuse périphérique peut traiter en toute sécurité l'hypotension artérielle générale avec une moindre diminution du volume d'éjection systolique et une moindre augmentation de la rigidité artérielle, par rapport à la phényléphrine [31]. Ainsi, une faible dose de noradrénaline pourrait représenter une alternative tout à fait concevable pour traiter l'hypotension artérielle induite par l'anesthésie générale [13].

Le monitoring non invasif de la pression artérielle

Comme exposé précédemment, la durée de l'exposition à l'hypotension est directement corrélée au risque de complications post-opératoires. Ce fait plaide en faveur d'une mesure continue de la pression artérielle en per-opératoire, en particulier pour les patients à haut risque cardio-vasculaire.

Le monitoring de la pression artérielle fait évidemment partie des prérequis à la conduite d'une anesthésie. Le monitoring minimum durant l'anesthésie est réglementé en France par le code de la santé public [32] et doit comporter notamment le contrôle continu du tracé ECG, de

la saturation du sang en oxygène par photopléthysmographie et la surveillance de de la pression artérielle, “soit non invasive soit invasive, si l'état du patient l'exige”. En pratique courante, cette mesure est le plus souvent non invasive et discontinue avec une mesure toutes les 5-10 minutes. Ce délai de plusieurs minutes peut conduire à un retard diagnostic et de prise en charge des épisodes aigus d'hypotension. Même s'il existe des dispositifs non invasifs de mesure continue de la pression artérielle, les études d'interchangeabilité avec les techniques invasives ne permettent pas de conclure à l'interchangeabilité. Des études sont en cours pour mesurer l'intérêt de stratégies de correction de l'hypotension sur ces techniques non-invasives et devraient apporter des éléments nouveaux dans un avenir proche. D'ici là, un panel d'experts a récemment proposé de recommander le recours à un monitoring continu invasif de la pression artérielle chez les patients à risque modéré ou élevé [12].

CHAPITRE 2: Le PlethoMAP

PlethoMAP est le nom que nous avons donné à l'innovation maintenant breveté consistant en un algorithme d'estimation continue de la pression artérielle moyenne à partir du signal de photopléthysmographie.

Signal de Photopléthysmographie (PPG) et Indice de perfusion (PI)

Dans une revue générale publiée dans le journal *Anaesthesia Critical Care & Pain Medicine* [1], nous avons décrit les propriétés du signal de photopléthysmographie et tout particulièrement l'indice de perfusion dérivé de ce signal avec ses applications cliniques.

Introduction

Le signal de photopléthysmographie (PPG) est utilisé depuis des décennies pour surveiller la saturation en oxygène. C'est un outil non invasif, peu coûteux, simple et rapide à utiliser. Le monitoring hémodynamique à partir de ce signal est actuellement peu exploré mais a bénéficié d'un regain d'intérêt ces dernières années, notamment en anesthésie, médecine périopératoire et soins intensifs. L'indice de perfusion (PI) constitue un outil prometteur pour le clinicien.

Principe de la pléthysmographie et calcul du PI

Le principe de photopléthysmographie (PPG) est basé sur la mesure indirecte d'un volume tissulaire par les variations d'absorption de la lumière (**Figure 1**). Une source lumineuse émet un rayonnement dont l'intensité, après avoir traversé un tissu, est transformée en courant électrique par une photodiode.

Deux longueurs d'ondes sont utilisées pour la PPG: la lumière rouge, dont l'absorption est influencée par le rapport entre oxyhémoglobine et désoxyhémoglobine, et qui sert donc à calculer la SpO₂. La lumière infrarouge est peu influencée par ce rapport mais permet de détecter le caractère pulsatile du signal, correspondant au volume de sang entrant et sortant du doigt au cours du cycle cardiaque. La courbe de PPG représente cette pulsatilité obtenue par le signal lumineux infrarouge.

Après transformation de l'influx lumineux en courant électrique par la photodiode, la partie pulsatile du signal apparaît sous forme de courant alternatif (CA) et la partie non pulsatile sous forme de courant continu (CC). L'indice de perfusion (PI) du signal de PPG représente le rapport entre la composante pulsatile et la composante non pulsatile du signal infrarouge

$$PI (\%) = 100 \cdot \frac{CA}{CC}$$

Une augmentation du PI correspond donc à une augmentation relative de CA par rapport à CC. La valeur du PI est corrélée au gradient de température entre le compartiment central et le compartiment périphérique, dont le déterminant principal est la vasomotricité. Le PI est donc considéré comme un indice de vasomotricité.

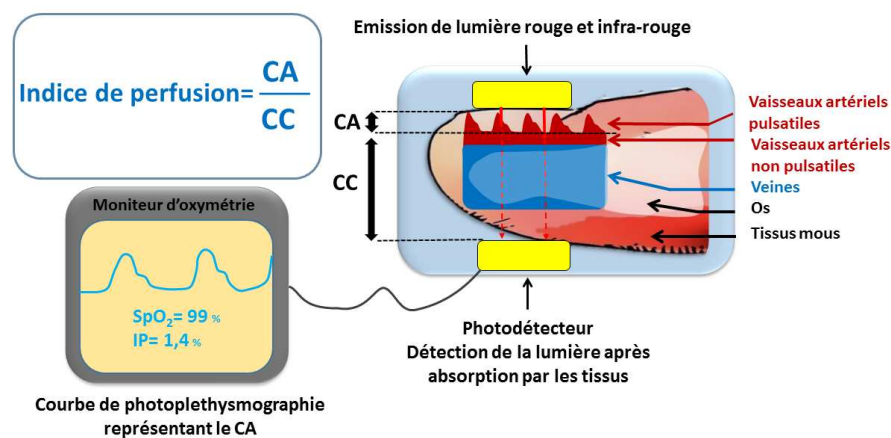


Figure 1 Principe de la photopléthysmographie et du calcul de l'indice de perfusion

Déterminants de l'indice de perfusion (PI)

Les déterminants du signal de PPG (**Figure 2**) sont complexes et font intervenir aussi bien l'hémodynamique systémique (compliance artérielle, résistances vasculaires et volume d'éjection systolique), les propriétés du tissu et du réseau vasculaire local (variables d'un patient à l'autre) ou encore le bruit environnant (lumière, mouvement). Le site de mesure influence également l'aspect de la courbe et la valeur du PI. Enfin, le traitement du signal, et donc le choix du matériel, peut également déformer de façon importante la courbe de PPG.

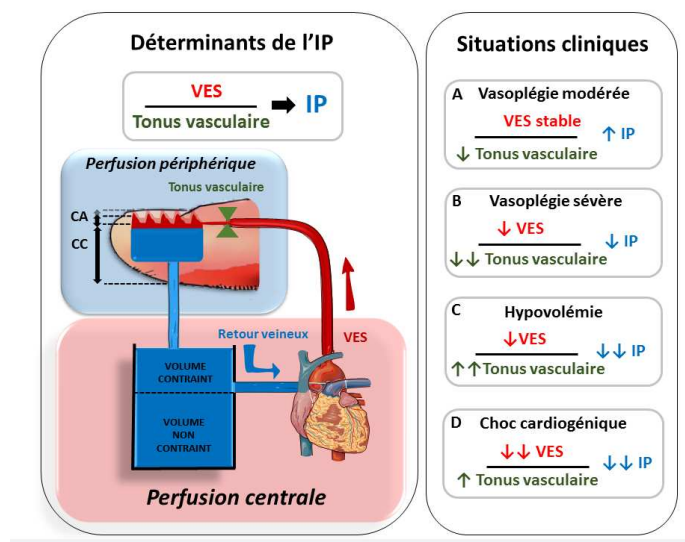


Figure 2 Déterminants de l'indice de perfusion et situations cliniques courantes

Indications cliniques

Le PI a été étudié dans différentes applications cliniques (**Figure 3**).

En anesthésie on peut citer :

- L'estimation de l'efficacité d'une anesthésie locorégionale (l'augmentation du PI permettant de détecter la vasodilatation induite par l'inhibition du tonus sympathique)
- La prédiction des variations hémodynamiques induites par une anesthésie neuro-axiale (le PI de base permettant de détecter les patients ayant un faible tonus sympathique et donc à plus haut risque d'hypotension artérielle après rachianesthésie)
- La détection d'une douleur sous anesthésie au bloc opératoire et en soins intensifs (la baisse du PI après un stimulus douloureux étant lié à l'augmentation du tonus vasculaire et de la MAP)
- La prédiction des variations de pression artérielle sous anesthésie générale
- Le pronostic anesthésique (les faibles valeurs du PI en peropératoire étant corrélées aux plus mauvais pronostics de façon indépendante)

En soins intensifs et médecine d'urgence, on retrouve :

- L'utilisation du PI comme reflet de la microcirculation locale
- L'utilisation du PI comme outil pronostic en réanimation avec plusieurs études rétrospectives montrant une corrélation entre le PI et le taux de survie
- L'étude des changements du PI en réaction à la chaleur, permettant de discriminer les altérations de microcirculation au cours du choc septique

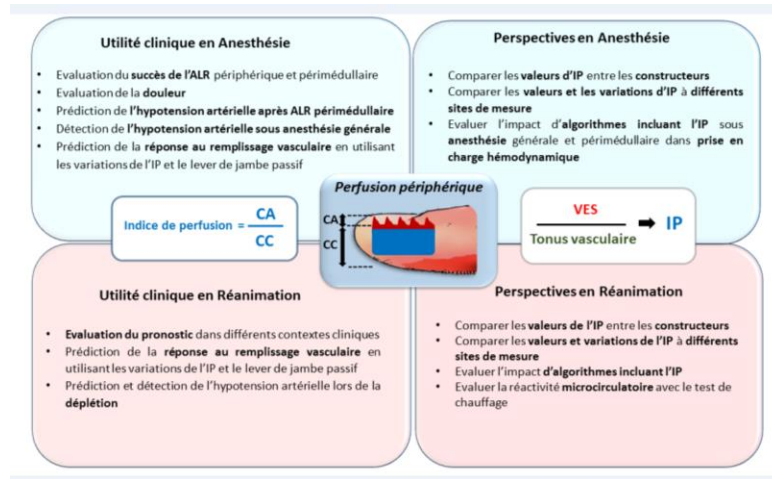


Figure 3 Résumé de l'utilité clinique de l'indice de perfusion

Du signal de photopléthysmographie à la pression artérielle moyenne: le concept du PlethoMAP

Dans un article publié dans *British Journal of Anaesthesiology* [2], nous avons rapporté le concept du PlethoMAP basé sur les variations de l'indice de perfusion et de l'onde dicrote de la PPG pour suivre les variations de la pression artérielle moyenne en continue au bloc opératoire.

Introduction

Plus de 7 millions d'anesthésies générales sont pratiquées par an en France. L'hypotension artérielle pendant l'anesthésie est un facteur de morbidité avec des conséquences à long terme potentiellement sévères. Le monitoring effectué en routine comprend une mesure de la saturation pulsée en oxygène par PPG digitale ainsi qu'une mesure discontinue, non invasive de la Pression artérielle (PA) par méthode oscillométrique. La prise discontinue de la PA, habituellement toutes les 5 minutes, entraîne un risque de méconnaissance d'épisodes d'hypotension ainsi qu'un retard à leur prise en charge. Les données de la PPG déjà en place pourraient être utilisées pour monitorer l'état hémodynamique des patients.

Concept physiologique et but de l'étude

L'oxymétrie de pouls continue au bloc opératoire permet de recueillir un signal de PPG, dont on peut facilement dériver la hauteur de l'onde dicrote (DICpleth) mais aussi l'indice de perfusion (PI) de façon non invasive et généralisable (**Figure 4**). DICpleth et PI étant corrélés au tonus vasculaire, l'objectif de l'étude était d'explorer si l'évolution de DICpleth et du PI permettait de prévoir les épisodes d'hypotension préopératoire. Il était aussi question d'analyser leur variation au cours de bolus de vasopresseurs.

Méthode

L'étude a été menée de façon observationnelle chez des patients bénéficiant d'une procédure de neurochirurgie. La PAM, DICpleth et le PI ont été recueillis à un intervalle d'une minute pendant l'induction anesthésique par AIVOC propofol et rémifentanyl. L'administration de vasopresseurs (phényléphrine ou noradrénaline) était laissée à l'appréciation du médecin pour corriger des épisodes d'hypotension.

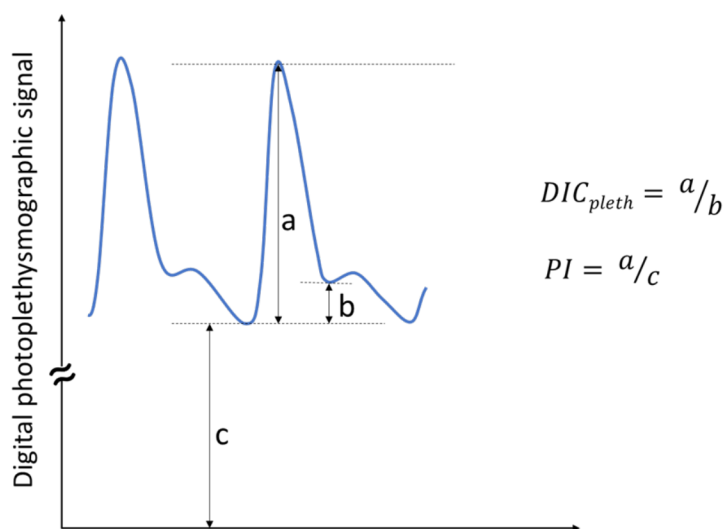


Figure 4 Définition de DICpleth et de PI sur la courbe de PPG

Principaux résultats

Il a été observé une bonne corrélation entre les variations de PAM et celles de DICpleth (**Figure 5**): $r = 0,64$ [0,59-0,69], $p < 0,0001$. Le pourcentage de concordance était de 89%. Une analyse par courbe ROC montrait qu'une baisse relative de DICpleth de plus de 22% permettait de détecter une baisse de 20% de la PAM avec une sensibilité de 77% et une spécificité de 85%.

Il a été également observé une bonne corrélation entre les variations de la PAM et le PI (Figure 5) : $r = -0,53 [-0,56 - 0,44]$, $p < 0,0001$. Le pourcentage de concordance entre les variations de la PAM et du PI était de 90%. Une analyse par courbe ROC montrait qu'une augmentation du PI de plus de 25% permettait de détecter une hypotension avec une sensibilité de 90% et une spécificité de 65%.

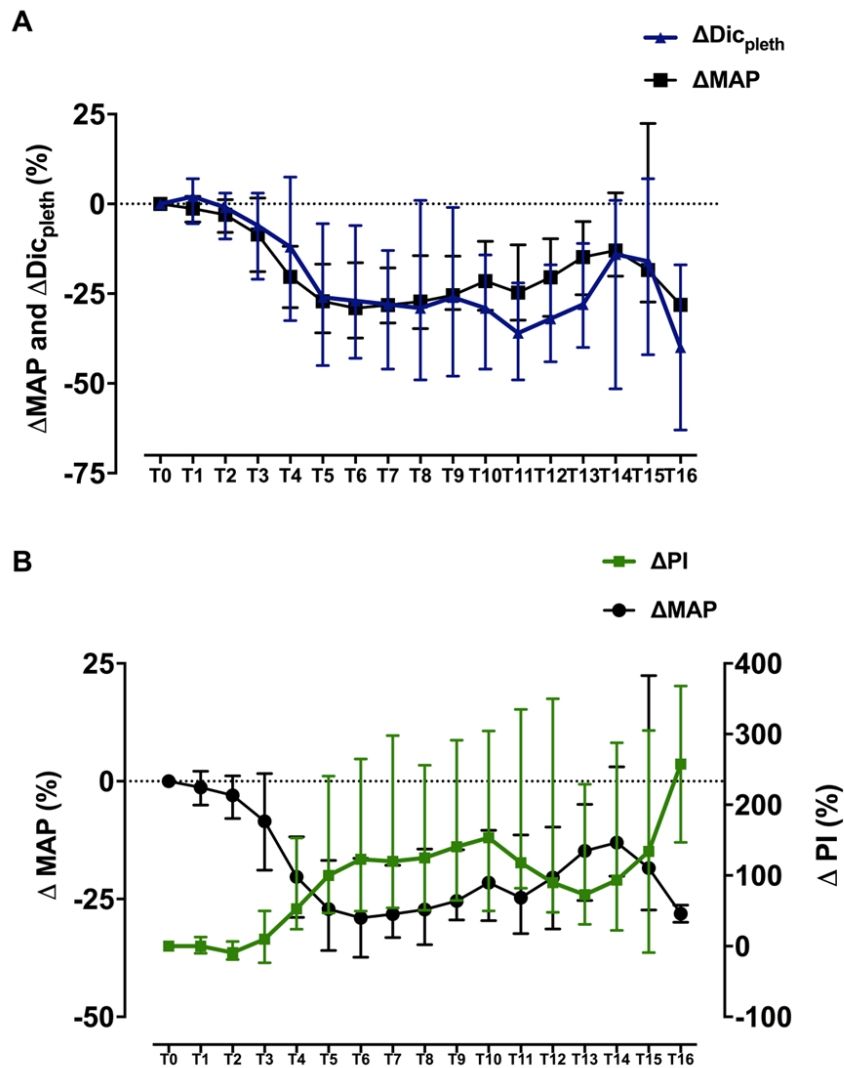


Figure 5 A) variation médiane de la PAM et de DICpleth et B) variation médiane de la PAM et du PI durant les 16 premières minutes de l'induction anesthésique

Conclusion

DICpleth et PI, mesurés à partir du signal de PPG, peuvent être utilisés pour détecter les épisodes d'hypotension au bloc opératoire. L'analyse combinée de la variation de ces deux indices peut représenter une nouvelle technique, simple et non-invasive, pour suivre les variations de pression artérielle au cours d'une anesthésie générale.

Premier algorithme du PlethoMAP

Dans un autre article original publié cette fois dans *Journal of Clinical Monitoring and Computing* [3], nous avons rapporté la mise en œuvre plusieurs algorithmes automatisés basés sur le PI et DICpleth afin de comparer leurs performances dans l'estimation en temps réel de la PAM. En effet, nous avons dans cette étude préliminaire décidé de tester trois algorithmes permettant de manière indépendante d'estimer la PAM à partir de la PPG.

Concept physiologique

Les résultats cités ci-dessus obtenus par Coutrot et al. montrent qu'il existe une relation linéaire entre la valeur de DICpleth et la PAM d'un côté et le PI et la PAM d'un autre côté.

Une relation linéaire entre deux paramètres peut être aisément décrite par la formule $y = Ax + B$, où y est la variable dépendant de x . A et B sont des paramètres. Dès lors, il est possible, en supposant $y = \text{PAM}$ et $x = \text{DICpleth}$ ou $x = \text{PI}$, d'estimer les paramètres A et B par régression linéaire. Il devient ensuite possible d'estimer la PAM en connaissant seulement DICpleth ou PI.

Nous formulons l'hypothèse qu'il serait possible d'estimer la PAM en temps réel à partir d'une mesure continue de DICpleth ou PI obtenue par analyse de la PPG. Des mesures

intermittentes de PAM par le brassard serviraient pour calibrer la relation linéaire décrite ci-dessus et calculer les paramètres A et B.

Méthode

Nous avons nommé PlethoMAP un appareil (ainsi que les algorithmes qu'il contient) permettant d'estimer la PAM en continu à partir du signal de PPG. Cette estimation est réalisée à partir d'une calibration première de la PAM par un brassard oscillométrique (PAMosc) puis d'une estimation basée sur l'analyse de l'onde de pouls de PPG.

Une analyse de l'onde de pouls basée sur la PPG a été mise en œuvre. Trois algorithmes différents ont été évalués pour estimer la PAM à partir de la PPG (**Figure 6**): deux basés sur la variation de la hauteur de l'onde dicrote et un sur le PI. Les valeurs estimées ont été comparées aux mesures ponctuelles du tensiomètre (PAMosc) et à la pression artérielle invasive (PAMinv). Il est à noter, que la hauteur relative de l'onde dicrote que nous nommons DICpleth a été nommée NRA (pour notch relative amplitude) dans ce papier, pour la différencier de NAA (notch absolute amplitude).

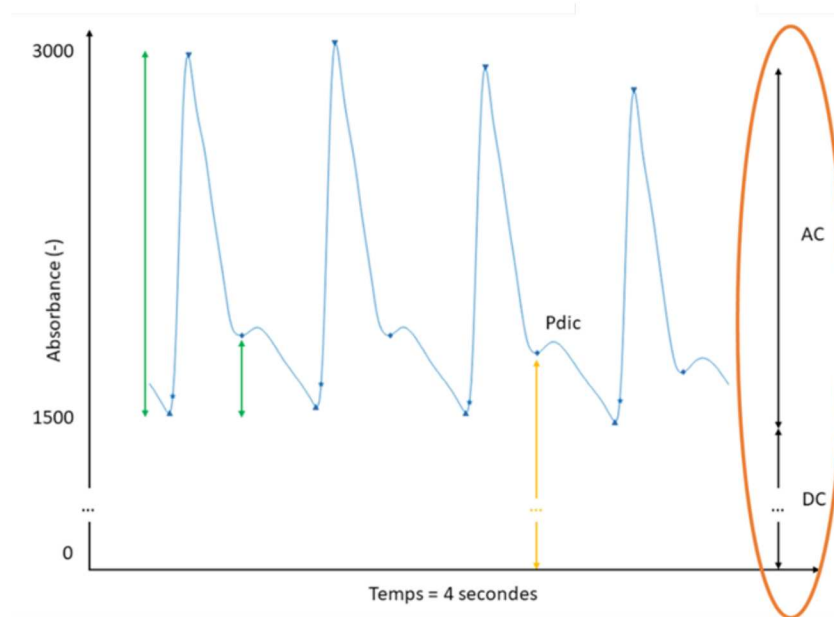


Figure 6 Illustration des trois algorithmes explorés dans l'article : en vert et en jaune les deux algorithmes basés sur DICpleth, à savoir NRA en vert et NAA en jaune ; en orange l'algorithme basé sur le PI.

Principaux résultats

46 patients ont été analysés. Par rapport à PAMosc, le biais moyen et les limites d'agrément étaient de 1 mmHg [-26 - 29], -1 mmHg [-10 - 8] et -3 mmHg [-21 - 13] pour les algorithmes 1, 2 et 3 respectivement. Par rapport à PAMinv, l'erreur absolue moyenne était de 20 mmHg [10 - 39], 11 mmHg [5-18] et 16 mmHg [9-24] respectivement.

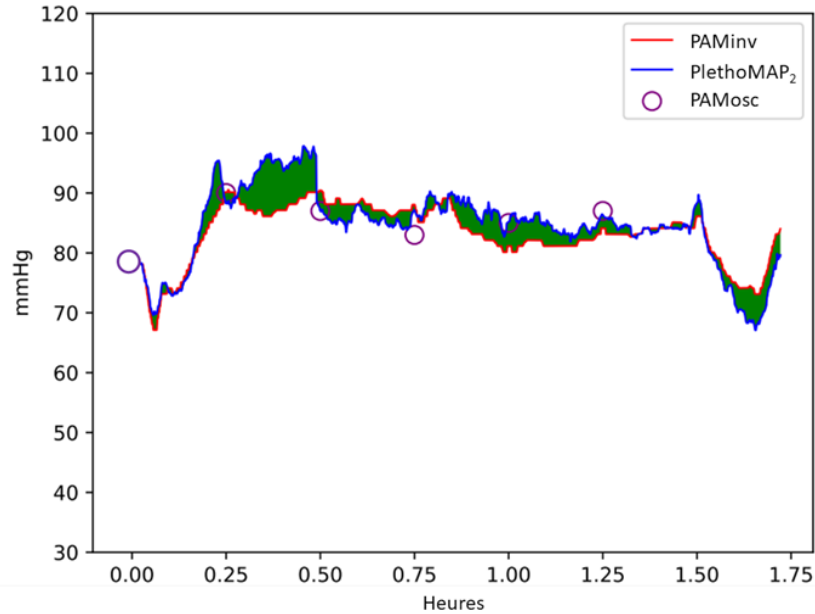


Figure 7 Comparaison de l'estimation de la PAM par l'algorithme PlethoMAP (en bleu) au gold standard invasif par cathéter artériel (en rouge). Les ronds violets désignent les mesures par brassard. L'aire verte correspond à l'erreur d'estimation instantanée.

Conclusion

L'algorithme 2, celui basé sur la hauteur absolue de l'onde dicrote ou NAA, permet l'estimation la moins biaisée par rapport au tensiomètre et à la mesure invasive. Une calibration rapprochée permet une estimation avec une faible marge d'erreur. L'estimation de la PAM battement par battement lors de l'anesthésie générale à partir de la PPG paraît possible avec une erreur moyenne acceptable de 11 mmHg.

PlethoMAP : développements récents

Ces développements font partie d'un article actuellement en cours de rédaction.

Innovations

Dans notre premier papier, nous avons pu obtenir des résultats encourageants et avons montré les relations intimes qui existent entre la pression artérielle moyenne et la PPG, notamment les paramètres DICpleth et PI obtenus à partir de celle-ci. Cependant, les algorithmes développés étaient inappropriés pour utiliser de manière conjointe l'information contenue dans DICpleth et PI. Il nous a paru nécessaire de développer un algorithme qui puisse utiliser conjointement les variables DICpleth et PI pour en déduire une meilleure estimation de la PAM. Selon les connaissances de la littérature, DICpleth est une variable qui reflète la rigidité artérielle et les résistances périphériques [33]. PI est une variable qui reflète la perfusion locale [1]. En effet, PI est une mesure directe de la partie pulsatile du signal de PPG, qui est une mesure du volume artériel au cours du temps. Par conséquent nous disposons d'une variable qui estime les résistances artérielles et une variable qui estime le débit sanguin. La modélisation la plus simple et la plus immédiate est l'utilisation de la loi d'Ohm appliqué aux écoulements fluides: $\Delta P = Q \cdot R$, avec ΔP , la pression de perfusion, Q le débit cardiaque et R , les résistances artérielles périphériques. ΔP équivaut à PAM - POD, POD étant la pression veineuse de l'oreillette droite.

Ce raisonnement mathématique a été validé par le cabinet de conseil en mathématiques *Iocène* dont le rapport figure en annexe.

De manière parallèle, en observant le signal de PPG, il nous est apparu que les modifications du signal en fonction de la pression artérielle sont complexes et qu'elles ne peuvent être résumées aux seules valeurs de DICpleth et PI. Afin d'extraire le plus d'information possible du signal de PPG, nous avons décidé d'utiliser les évolutions récentes en apprentissage par réseaux de neurones. À cette fin, nous avons construit une architecture de

réseaux de neurones convolutifs [34]. Ce type de réseau permet la reconnaissance de motifs visuels ou géométriques. Il sert de base à toutes les utilisations modernes de reconnaissances d'images mais a plus récemment été utilisé pour des applications sur séries temporelles [35].

Un des avantages supplémentaires du réseau de neurones est sa faculté d'apprendre des données de l'ensemble de la cohorte. Un réseau pré-entraîné peut par conséquent prédire la PAM sans passer par une phase de calibration par patient.

Méthode

Modèle naïf

Un modèle naïf de référence a été utilisé pour comparer les performances du réseau de neurones. Il s'agit d'un modèle qui prédit à chaque battement la valeur de PAM précédemment obtenue par brassard. Il s'agit là d'un modèle qui reflète les conditions réelles au bloc opératoire quand le brassard est la seule source de monitoring pour la PAM. Ceci constitue une référence pour tester nos modèles, en effet, un modèle doit présenter une précision strictement supérieure au modèle naïf pour être pertinent.

Modèle mécanistique

Le modèle mécanistique est basé sur la loi d'Ohm appliquée aux écoulements fluides: $\Delta P = Q \cdot R$. Le débit cardiaque Q peut être décomposé en volume d'éjection systolique du cœur gauche (SV) et fréquence cardiaque (FC). De par nos recherches en physiologie, PI était considéré comme analogue au SV et DICpleth comme analogue à R . La variable PI ne pouvait être utilisée telle quelle parce qu'elle présentait souvent des changements trop brutaux par rapport aux variations de la PAM avec un comportement exponentiel et inverse par rapport aux changements de PAM. Nous avons donc introduit la variable dérivée mPI qui est une

linéarisation du PI selon la formule $mPI = \ln\left(1 + \frac{1}{PI}\right)$. Nous avons introduit les paramètres suivants: α régit l'interaction entre SV et R, β est l'incertitude sur mPI, γ est l'incertitude sur DICpleth et δ est l'intercept qui correspond à l'incertitude sur la POD.

La formule finale obtenue est : $\widehat{PAM} = \alpha(mPI + \beta)(DICpleth + \gamma) \cdot HR + \delta$. Cette formule peut être linéarisée pour obtenir la formule linéaire:

$$\widehat{PAM} = a1 + a2 HR + a3 HR DICpleth + a4 HR mPI + a5 HR mPI DICpleth .$$

Cette forme permet l'estimation des paramètres $a1 - a5$ par des algorithmes de régression linéaire. Nous avons utilisé une régression linéaire régularisée de type LARS [36].

Modèle de réseau neuronal

Nous avons construit un réseau de neurones profond avec des entrées hétérogènes. En effet les entrées sont la courbe de PPG avec un échantillonnage relativement élevé à 125 Hz, les valeurs de HR et PI avec un échantillonnage proche de 1 Hz avec un point par battement cardiaque et les mesures intermittentes de pression non invasive par brassard. Des couches de réseaux de neurones récurrents de type Long Short Term Memory (LSTM) étaient utilisés pour capter l'information sur les tendances des valeurs de PI et HR au cours du temps. Les réseaux de neurones ont été développés et entraînés avec la plateforme PyTorch Lightning [37]. La structure du réseau de neurones est explicitée dans la **Figure 8**.

Principaux résultats

Cent dix-neuf patients ont été inclus à l'hôpital Lariboisière, dont 30 en chirurgie digestive lourde et 89 en neuroradiologie de Janvier 2015 à Septembre 2018. La durée totale d'enregistrement est de 228 heures.

Les estimations obtenues avec le modèle naïf présentaient une erreur moyenne absolue (MAE) de 8,7 [6,6 - 12,4] mmHg.

Résultats préliminaires de modélisation

Les résultats de modélisation sont préliminaires. Pour le modèle mécanistique, l'erreur moyenne absolue obtenue était de 5,2 [3,2 – 8,4] mmHg. La structure design du réseau de neurones et l'ajustement des hyperparamètres est encore en cours. Les résultats préliminaires montrent des valeurs de MAE du même ordre de grandeur que le modèle mécanistique (MAE 6,8 [4,5 - 9,6] mmHg).

Sur la courbe de PPG, le réseau de neurones accorde un poids particulièrement important à la région autour de l'onde dicrote mais également autour du pic systolique. Ceci est illustré à l'aide d'une carte de saillance (en anglais « *saliency map* ») en **Figure 9**. Ces résultats sont en accord avec notre interprétation physiologique du signal de PPG. Un exemple d'estimation de l'évolution de la PAM par le réseau de neurones est présenté sur la **Figure 10**.

Conclusion

Ces résultats montrent une amélioration nette du pouvoir prédictif à la fois du modèle mécanistique et du modèle neuronal comparé aux algorithmes simplistes de notre précédent papier. Ceci montre l'intérêt de la modélisation, aussi bien mécanistiques que statistique dans la création du PlethoMAP.

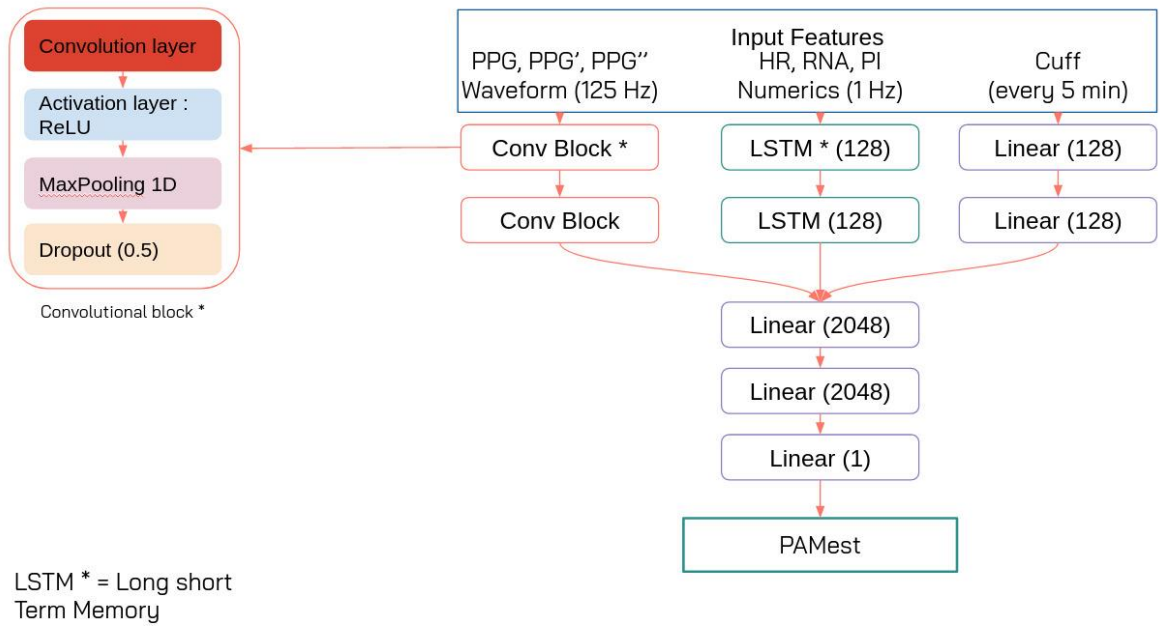


Figure 8 Structure couche par couche du réseau de neurones

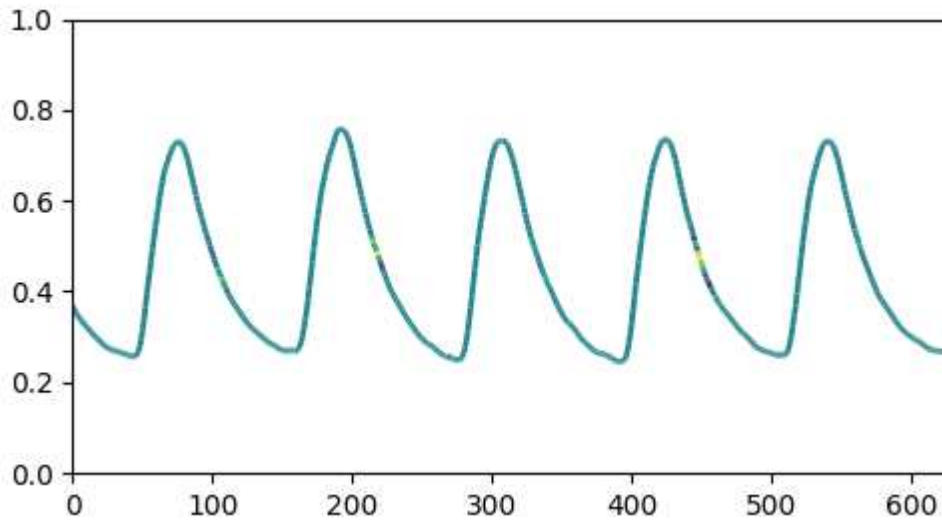


Figure 9 « Saliency map » montrant les zones d'intérêt découvertes par le réseau de neurones sur le signal de PPG. Des couleurs plus claires signifient plus d'importance.

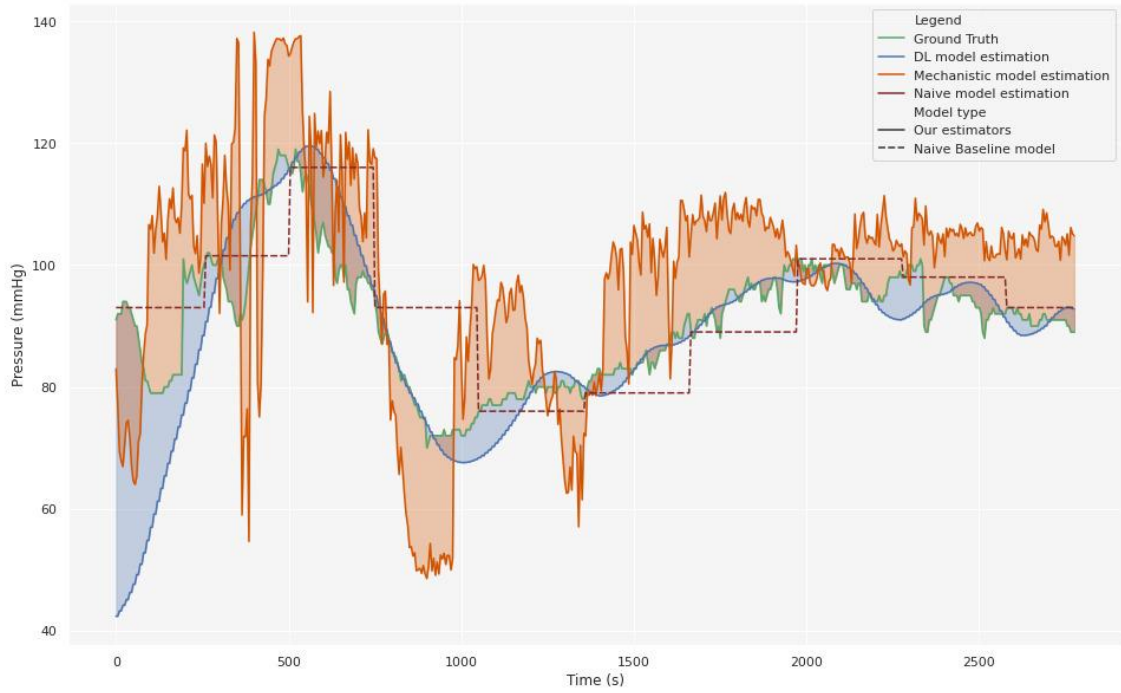


Figure 10 Comparaison des modèles sur un exemple de cas. En vert : mesure de référence obtenue par cathéter artériel invasif. En pointillée : modèle naïf. En orange : estimation par le modèle mécanistique. En bleu : estimation par le réseau de neurones profond.

CHAPITRE 3: Modèle PK/PD de la noradrénaline

Comme nous l'avons déjà dit, notre objectif est de développer des outils d'optimisation de la pression artérielle au bloc opératoire. Le développement d'un instrument comme le PlethoMAP permet d'envisager d'avoir un système de correction de l'hypotension en temps réel, potentiellement automatisé et asservi à la mesure de la PAM pour tout patient passant au bloc opératoire. Toutefois, pour ce faire, il est impératif d'avoir des informations pharmacologiques fiables du ou des médicaments couramment utilisés au bloc opératoire pour traiter l'hypotension artérielle. Nous avons fait le choix de nous intéresser à la noradrénaline à faible concentration qui semble devenir le médicament de choix pour la correction de l'hypotension artérielle au bloc opératoire.

Ainsi, Dans un article original, en cours de soumission, nous décrivons la mise au point une modélisation PK/PD de la noradrénaline faiblement dosée telle qu'elle est utilisée au bloc opératoire pour traiter l'hypotension liée à l'anesthésie.

Ce travail a également conduit à la thèse de docteur en médecine ainsi qu'au diplôme de Master 2 de Thomas Lefèvre.

Introduction

Rôle de la noradrénaline

La noradrénaline appartient au groupe des catécholamines, c'est une monoamine non substituée (**Figure 11**). Elle peut agir comme un neurotransmetteur, mais également comme une hormone, on l'appelle parfois hormone du stress". C'est cette fonction hormonale qui va nous intéresser dans ce travail.

En tant que neurotransmetteur, la noradrénaline est libérée par les neurones adrénergiques du système nerveux central, notamment le tronc cérébral. Elle est chargée de transmettre les informations sous forme d'impulsion électrique aux différentes parties du corps en relation avec l'anxiété.

En tant qu'hormone, elle est synthétisée dans les glandes surrénales à partir de l'acide aminé nommé Tyrosine puis libérée dans le sang. Parmi ses fonctions hormonales, on peut mettre en avant la stimulation de la production d'adrénaline dans le corps, provoquant une augmentation de la vigilance et de l'attention focalisée, ce qui permet une meilleure capacité de réaction comportementale face à des événements potentiellement dangereux.

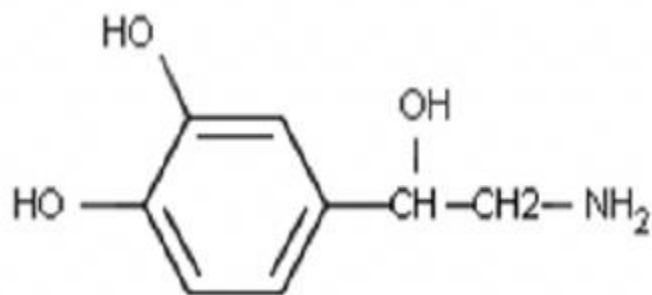


Figure 11 Structure moléculaire de la noradrénaline

Biosynthèse de la noradrénaline et distribution tissulaire

La biosynthèse de la noradrénaline se fait dans les neurones post-ganglionnaires du système nerveux sympathique et dans les cellules chromaffines de la médullosurrénale (**Figure 12**). La voie métabolique conduisant à la synthèse de la noradrénaline est identique dans les deux lieux de synthèse, partant de deux acides aminés essentiels que sont la phénylalanine et la tyrosine. L'étape limitante est celle qui transforme la tyrosine en DOPA par la L-tyrosine hydroxylase. Secondairement, la DOPA est transformée en dopamine dans le cytosol. La noradrénaline est

quant à elle produite à partir de la dopamine. Enfin l'adrénaline est produite à partir de la noradrénaline dans les cellules chromaffines de la médullo-surrénale.

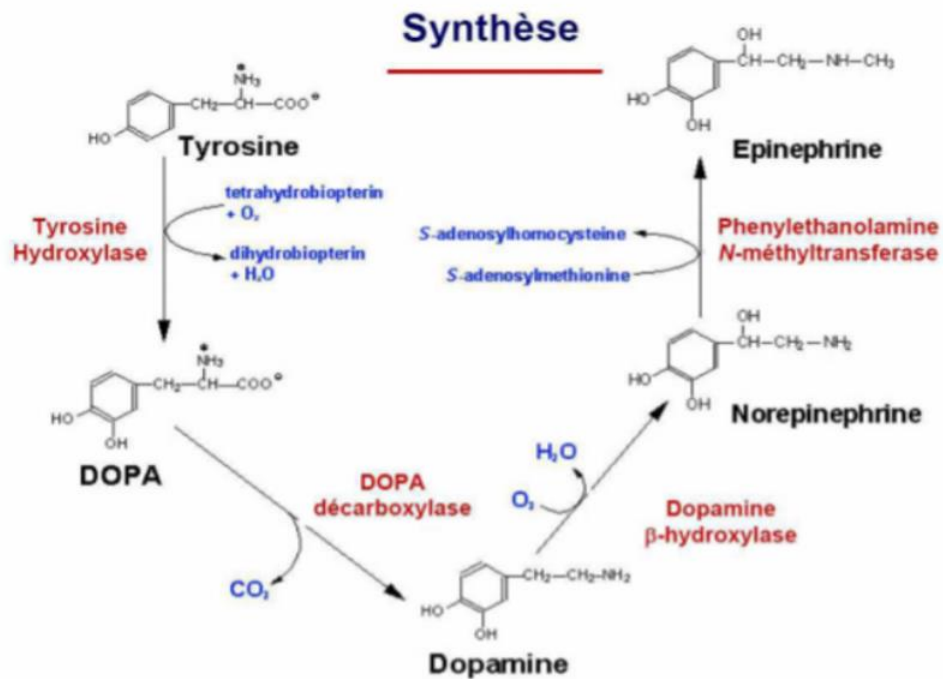


Figure 12 Biosynthèse de la Noradrénaline

La glande médullosurrénale est l'organe le plus riche en catécholamines. Elle contient beaucoup plus d'adrénaline que de noradrénaline. Les fibres post-synaptiques sympathiques synthétisent de la noradrénaline, mais pas d'adrénaline. Les tissus à forte innervation sympathique (cœur et vaisseaux) contiennent donc beaucoup de noradrénaline. Ils peuvent en outre fixer les catécholamines circulantes comme l'adrénaline. Le cerveau est, quant à lui, beaucoup plus riche en noradrénaline et dopamine et contient très peu d'adrénaline.

Libération de la noradrénaline

La libération de la noradrénaline, produite dans les neurones post-ganglionnaires, se fait par exocytose sous l'effet de l'influx nerveux du système sympathique. Cette libération est sous la dépendance de la noradrénaline elle-même ainsi que d'autres neurotransmetteurs via des récepteurs présynaptiques. Certains de ces récepteurs vont stimuler la libération (β_2 adrénergiques), pendant que d'autres vont l'inhiber (α_2 adrénergiques, muscariniques...). La noradrénaline qui n'est ni capturée ni fixée sur les récepteurs post-synaptiques rejoint la circulation systémique [38–40].

Vu que les récepteurs adrénergiques sont en contact avec des terminaisons sympathiques, il est concevable que la noradrénaline libérée agisse essentiellement sur les organes où elle est libérée et ne passe que secondairement dans la circulation générale. Cependant, la noradrénaline libérée par la glande médullosurrénale passe directement dans la circulation générale.

Concentration plasmatique

La concentration plasmatique d'une substance est la résultante d'une part de sa libération et d'autre part de sa capture par les tissus et de son catabolisme.

Dans les conditions de repos, les concentrations plasmatiques de noradrénaline sont faibles (moins de 4 nmol/L) mais elles peuvent s'élever en condition physiologique (passage en position debout, effort, stress, peur ...).

Les techniques de dosage actuelles de noradrénaline plasmatique ne peuvent différencier la noradrénaline endogène de la noradrénaline exogène.

Propriétés physicochimiques

La noradrénaline est un neurotransmetteur de petit poids moléculaire avec un caractère hydrophile. Elle ne diffuse pas à travers les membranes cellulaires mais les traversent par exocytose ou par des transporteurs transmembranaires spécifiques. Elle interagit avec des récepteurs membranaires qui activent une cascade enzymatique à l'origine d'effets cellulaires, organiques et systémiques.

Une fois libérée dans la fente synaptique sous l'effet de l'influx nerveux via le potentiel d'action et l'entrée d'ions calcium, la noradrénaline peut alors se lier aux récepteurs post-synaptiques α_1 et β et ainsi contribuer à la transduction du signal ou être recaptée en présynaptique par un transporteur membranaire sélectif NET pour être recyclée dans le neurone noradrénergique. Après passage dans la circulation systémique, la noradrénaline peut être captée par un récepteur α_2 de cellule non-neuronale, notamment les cellules musculaires lisses vasculaires, ou subir le métabolisme d'élimination enzymatique.

Dégradation de la noradrénaline

Le devenir de la noradrénaline, outre la stimulation de la cellule cible, est soit la dégradation, soit le recyclage. Les voies de dégradation de la noradrénaline sont multiples et redondantes, expliquant en partie sa très courte demi-vie. On peut décrire deux principaux compartiments différents dégradant la noradrénaline :

Le lieu de synthèse, c'est-à-dire l'espace inter-synaptique où la noradrénaline est capturée par le neurone présynaptique et, est soit dégradée par la Monoamine oxydase (MAO), soit de nouveau excrétée dans l'espace inter-synaptique [41, 42].

La dégradation extraneuronale, où la noradrénaline est capturée par des transporteurs transmembranaires des cellules post-synaptiques et est dégradée par la MAO et/ou la catéchol-O-méthyltransférase (COMT)

Les MAO et COMT sont les deux principaux enzymes de dégradation de la noradrénaline [43]. Elles sont toutes deux intracellulaires. La MAO est une désamine oxydase et se situe sur la membrane externe des mitochondries. La MAO est présente dans les terminaisons présynaptiques et astrocytaires, mais également dans le foie, le tube digestif, la paroi vasculaire et le placenta (MAO-A), ou les plaquettes et les cellules chromaffines pour la MAO-B [44]. La COMT, dont l'action est une O-méthylation, s'observe dans le cytosol. On note une grande abondance de ces 2 enzymes dans le foie et les adipocytes.

Approximativement 90% des catécholamines endogènes sont éliminées dans les urines sous forme inactive [39]. L'excrétion des métabolites inactifs se fait par les reins. Certaines observations expérimentales font état d'une élimination pulmonaire.

La noradrénaline exogène

Aussi appelée molécule sympathomimétique, car elle se lie aux récepteurs du système nerveux sympathique et a un effet agoniste, la noradrénaline exogène possède les mêmes propriétés que son équivalent endogène utilisée en tant qu'hormone. En revanche, son catabolisme est exclusivement extraneuronale, impliquant les MAO et les COMT.

Utilisation de la noradrénaline en pratique clinique

La noradrénaline exogène possède les mêmes propriétés que son équivalent endogène utilisée en tant qu'hormone. En revanche, son catabolisme est exclusivement extraneuronale, impliquant les MAO et les COMT. Les effets de la noradrénaline sont essentiellement

vasoconstricteurs veineux et artériel et, à moindre mesure inotrope positif, conduisant à une augmentation de la contractilité ventriculaire et auriculaire et de la conduction. Depuis le début des années 2000, alors que la dopamine était encore recommandée en première intention dans les états de choc, une enquête menée par la SRLF a montré une utilisation préférentielle de la noradrénaline par les praticiens. Ce changement de pratique faisait suite aux études montrant la supériorité de la noradrénaline sur la dopamine dans le rétablissement de la pression artérielle moyenne (PAM) [44, 45]. En 2010, une étude menée par l'équipe de De Baker et al comparant la noradrénaline et la dopamine chez plus de 1000 patients en état de choc a montré une tendance à la diminution de mortalité à 28 jours en faveur de la noradrénaline et un nombre significativement plus faible d'effet secondaire en faveur de la noradrénaline [46]. D'autre part, une analyse en sous-groupes incluant les chocs cardiogéniques, mettait en évidence une mortalité à 28 jours significativement inférieure dans le groupe recevant de la noradrénaline.

Ces différents résultats plaident pour une utilisation préférentielle de la noradrénaline en pratique clinique en réanimation pour prendre en charge les états de choc.

Au bloc opératoire, l'anesthésiste-réanimateur a le choix entre différents agents catécholaminergiques vasoconstricteurs afin de traiter l'hypotension artérielle induite par l'anesthésie. Parmi ces médicaments, les trois principalement utilisés sont l'éphédrine, la phényléphrine et la noradrénaline. Durant ces dernières années, la noradrénaline gagne une place de choix dans le traitement de l'hypotension artérielle induite par l'anesthésie, avec notamment l'avènement de la noradrénaline diluée ou « Babynoradrénaline » [31] permettant une utilisation en bolus et en perfusion continue sur des voies d'abord classiques (voie veineuse périphérique). De plus, la noradrénaline permet d'augmenter la pression artérielle avec un effet limité sur la baisse du débit cardiaque, en comparaison avec la phényléphrine, permettant ainsi

de préserver la perfusion d'organe [26]. L'éphédrine quant à elle n'est pas utilisée en perfusion continue en raison d'une tachyphylaxie, la rendant inefficace au-delà d'une certaine dose.

Ces résultats et l'évolution des pratiques expliquent que la noradrénaline, diluée et à faible dose, est également devenue le vasoconstricteur de choix au bloc opératoire [23].

Modèle pharmacocinétique / pharmacodynamique (PKPD) de la noradrénaline en anesthésie

La dose nécessaire de noradrénaline pour restaurer la pression artérielle ainsi que sa durée d'action est variable selon les patients. Afin de permettre une stabilité de la pression artérielle, il est nécessaire de pouvoir contrôler finement l'administration de noradrénaline et de l'adapter aux caractéristiques du patient. A l'heure actuelle, peu de travaux se sont intéressés à l'élaboration d'un modèle pharmacocinétique / pharmacodynamique (PKPD) de la noradrénaline.

Le développement d'un modèle PKPD nécessite une étude clinique incluant une administration standardisée de noradrénaline, l'analyse et la modélisation de la variabilité dans la population étudiée, l'analyse de l'effet du médicament et des dosages plasmatiques du médicament en question, ici la noradrénaline. Le but de cette étude était de développer un modèle PK/PD qui pourrait permettre la perfusion à objectif de concentration de la noradrénaline chez l'homme afin de corriger l'hypotension sous anesthésie au bloc opératoire.

Matériel et Méthodes

Cette étude a été effectuée dans le département d'anesthésie-réanimation de l'hôpital Lariboisière à Paris, entre novembre 2019 et mars 2021. Il s'agissait d'un travail prospectif

monocentrique et non randomisé. Comité d'éthique : CPP Sud-Ouest NOR-PHARM : 1-17-42 avec inscription à *ClinicalTrials*: NCT03454204. Les patients étaient informés avant l'acte chirurgical qu'ils participaient au protocole et devaient signer une feuille de consentement.

Timing des dosages

Du fait d'une connaissance limitée sur la pharmacocinétique de la noradrénaline au bloc opératoire, les timings des dosages pour l'analyse du bolus et de la perfusion continue se basent sur des données de pharmacologie générale. En ce qui concerne le bolus, la demi-vie très courte (2-3min) et les nombreuses voies de dégradation nous ont amené à décider du protocole de prélèvement exposé ci-dessous. L'analyse du bolus était obtenue à l'aide de 5 prélèvements réalisés à T0 du bolus juste avant l'administration puis T15, T30, T60 et T180 secondes.

Concernant l'administration en perfusion continue, l'état de la connaissance actuelle fait état d'une pharmacocinétique avec une élimination rapide (2-3 minutes) d'ordre 1 ou supérieur [47]. Lors d'une perfusion continue, le temps nécessaire pour atteindre 50% du plateau correspond à une demi-vie [48]. Par conséquent, à partir de 3 demi-vies nous serons à 88% du plateau.

L'administration de la noradrénaline se faisait sur une voie veineuse périphérique dédiée avec le robinet d'administration placé au plus près du cathéter et un rinçage continu par du sérum physiologique. Pour plus de précision, le bolus de 2 millilitres était réalisé par le mode bolus de la seringue électrique (Orchestra, Fresenius Kabi, Germany) et enregistré avec une précision d'un dixième de millilitre grâce au logiciel InfuPy que nous avons développé [49].

Le recueil des tubes de noradrénaline se faisait par voie artérielle avec un site de prélèvement situé au plus près du cathéter artériel.

Un échantillon de la solution noradrénaline préparée était également analysé pour obtenir la dilution et la quantité exacte de noradrénaline injectée.

Technique de dosage de la noradrénaline

Le laboratoire de biologie médicale de l'hôpital Lariboisière (Pr Callebert), possédant une expertise quant au dosage des catécholamines plasmatiques et urinaires, a été consulté en amont et son accord a été obtenu quant à sa participation au projet nous permettant ainsi d'obtenir sans difficulté un dosage plasmatique de noradrénaline lors de nos inclusions.

Les prélèvements étaient recueillis dans des tubes héparinés ou EDTA sur glace et envoyés immédiatement au laboratoire. Le refroidissement immédiat des prélèvements et la nécessité de les acheminer le plus vite possible au laboratoire se justifient du fait de la présence d'enzymes de dégradation de la noradrénaline dans le plasma (MAO et COMT). La noradrénaline plasmatique est dosée par chromatographie liquide à haute performance (HPLC) couplée à une détection électrochimique. Avant la séparation chromatographique, la noradrénaline est extraite du plasma par absorption sélective sur l'hydroxyde d'aluminium. Après élution acide, l'éluat est injecté sur un système HPLC muni d'une colonne (Chromosystems, Gräfelfing, Germany) et une phase mobile dédiée au dosage des amines biogènes. Ce système (Coularray, ESA) permet une séparation spécifique et une quantification fiable de la noradrénaline dans le plasma.

Modèle PK

La concentration plasmatique de la noradrénaline en fonction du temps était décrite en utilisant des modèles mamillaires. Des modèles de 1, 2 et 3 compartiments étaient testés. Le modèle à 3 compartiments permettait les meilleures performances. Les modèles mamillaires sont formalisés grâce à des équations différentielles qui décrivent les lois de diffusion qui

règnent entre les compartiments. La concentration du compartiment central (C_c) sert d'entrée pour le modèle PD et explique l'effet sur la pression artérielle. Le système d'équations différentielles qui définit le modèle est le suivant:

$$\begin{cases} \frac{d}{dt} A_d = -k_a A_d^\beta \\ \frac{d}{dt} A_c = k_a A_d^\beta - k_{12} A_c + k_{21} A_p - k_{10} A_c \\ \frac{d}{dt} A_p = k_{12} A_c - k_{21} A_p \end{cases}$$

La concentration plasmatique peut alors être obtenue par:

$$C_c = C_{endo} + \frac{A_c}{V_c}$$

Le modèle à 3 compartiments que nous avons analysé était composé d'un compartiment central qui correspond au plasma et d'un compartiment périphérique qui correspond à un compartiment tampon possiblement représentatif de l'endothélium.

Le compartiment dépôt servait à modéliser la convection de la noradrénaline injectée alors qu'elle s'homogénéise dans le plasma après administration intraveineuse.

A_c , A_p et A_d représentent respectivement la dose de noradrénaline dans le compartiment central, périphérique et dépôt. La constante d'absorption du compartiment A_d vers le compartiment A_c est proportionnelle à A_d^β , β étant un paramètre du modèle. k_{12} , k_{21} et k_a représentent respectivement les constantes de diffusion du compartiment central vers le compartiment périphérique et du compartiment dépôt vers le compartiment central. k_{10} est la constante d'élimination. C_{endo} est la concentration basale physiologique dans le plasma avant administration exogène. V_c est le volume du compartiment central.

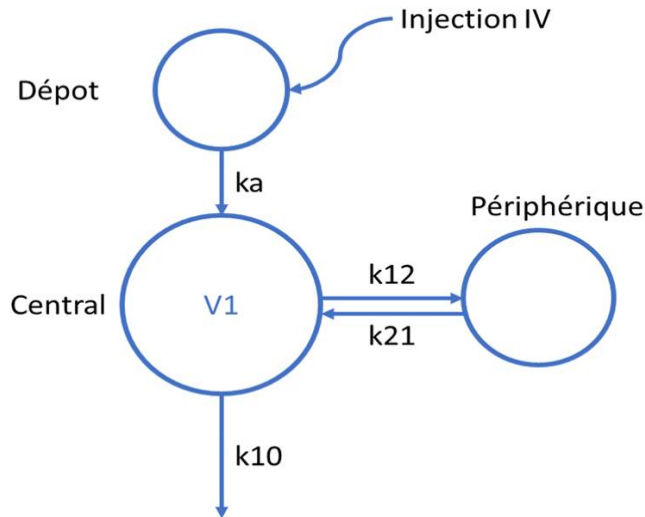


Figure 13 Structure du modèle PK

Modèles PKPD

Modèle empirique

L'une des familles de modèles de pharmacodynamie les plus courantes est celle des modèles Emax. Cette famille de modèles décrit l'effet (E - ici la pression artérielle moyenne) en termes d'effet basal lorsqu'aucun médicament n'est présent (E_0), d'effet maximal lorsque des doses croissantes de médicament ne peuvent pas entraîner une augmentation supplémentaire de l'effet (E_{max}), et de EC_{50} , la concentration de médicament qui entraîne un effet à mi-chemin entre E_0 et E_{max} . Ces paramètres du modèle sont utilisés pour paramétrer une courbe de réponse sigmoïde.

Nous avons choisi de tester une variation du modèle Emax basée sur l'équation de Hill [50].

Ce modèle peut être formulé de la façon suivante:

$$E(t) = E_0 + \frac{(E_{max} - E_0) \cdot Cc^n}{Cc^n + EC_{50}^n}$$

Le paramètre supplémentaire (n) est le coefficient de Hill. Sa valeur peut être interprétée comme les interactions entre la liaison du ligand et du récepteur en fonction des liaisons précédentes. Lorsqu'il est supérieur à 1, nous observons une liaison coopérative positive, ce qui signifie que la liaison du ligand augmente l'affinité pour une autre liaison du ligand. Lorsqu'il est inférieur à 1, on observe une liaison coopérative négative, ce qui signifie que la liaison du ligand diminue l'affinité pour une autre liaison du ligand. Lorsque la valeur est égale à 1, l'affinité du ligand ne dépend pas de la liaison du ligand préalable.

Modèle basé sur les mécanismes

La relation entre l'éjection cardiaque et la pression artérielle a été décrite à l'aide du modèle dit de Windkessel [51] depuis le début du vingtième siècle. Dans le cas le plus général, le modèle de Windkessel est équivalent à un circuit électrique RLC [52], où R représente la résistance vasculaire périphérique, C représente la compliance des grandes artères élastiques et L représente l'inertie du flux sanguin. $e(t)$ est la tension externe appliquée.

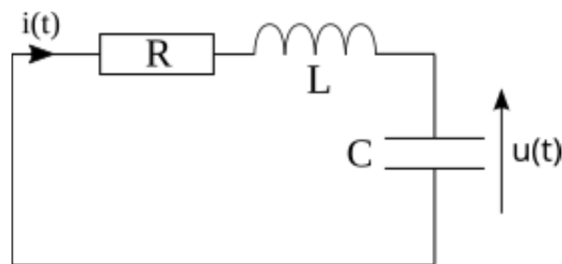


Figure 14 Illustration graphique du modèle de circuit RLC.

En appliquant la deuxième loi de Kirchhoff au circuit RLC, il est possible de dériver l'équation différentielle de la tension du système :

$$LC \frac{d^2}{dt^2} u(t) + RC \frac{d}{dt} u(t) + u(t) = e(t)$$

En utilisant l'analogie électronique-hydraulique et en prenant en compte les conditions initiales, cette équation peut être réécrite comme suit :

$$\frac{d^2}{dt^2}E + 2\zeta\omega \frac{d}{dt}E + \omega^2(E - E_0) = m \cdot (C_c - C_0)$$

E est la pression artérielle moyenne (MAP). ω est la fréquence naturelle non amortie. ζ est le rapport d'amortissement.

Modèle de mélange

Afin d'examiner s'il existe des sous-populations d'individus dont les réponses sont décrites par le modèle Emax ou le modèle Windkessel, nous avons utilisé un modèle de mélange entre sujets (BSMM). Dans ce modèle, chaque patient peut se voir attribuer un modèle structurel, Emax ou Windkessel, selon le modèle qui décrit le mieux la réponse du patient. Une probabilité p est estimée comme étant la proportion de patients décrits au mieux par le modèle Emax. Le modèle structurel choisi pour un sujet donné est Emax avec la probabilité p et Windkessel avec la probabilité 1-p. Le groupe auquel appartient un patient donné est estimé comme étant le groupe de probabilité conditionnelle la plus élevée.

Résultats principaux

Modèle PK

Les trois modèles ont été ajustés individuellement. Le modèle 3 montre un critère d'information minimal (AIC, BIC) et présente la meilleure performance pour expliquer la pharmacocinétique de la noradrénaline dans notre population.

Modèle PK/PD : 2 types de modèles

Après avoir estimé les paramètres des modèles PK et PD individuellement et après avoir sélectionné les meilleurs modèles, nous avons effectué des estimations pour les modèles PKPD conjoints en utilisant les distributions de paramètres estimées précédemment comme valeurs initiales.

Nous avons d'abord testé le modèle Emax Hill. Lors d'une inspection visuelle, nous avons noté que la qualité de l'ajustement était globalement satisfaisante, mais que plusieurs patients présentaient un "undershoot" de la pression artérielle après l'administration en bolus de noradrénaline, comme le montre l'**annexe supplémentaire 6**.

Cet effet, qui était notable chez certains patients mais pas chez tous, ne pouvait pas être modélisé à l'aide d'un modèle Emax classique, car ces modèles ne peuvent pas prédire la pression artérielle en dessous de la ligne de base (E0). Afin de modéliser le comportement observé chez certains patients, il est apparu nécessaire d'introduire un modèle de second ordre. Le modèle de Windkessel a été choisi comme modèle candidat car il a une longue histoire dans le suivi hémodynamique, est construit sur des concepts physiologiques solides et présente une dynamique de second ordre. Enfin, un modèle de mélange (BSMM) des modèles Emax et Windkessel a été testé afin d'affirmer l'existence de deux sous-populations différentes dans notre population d'étude.

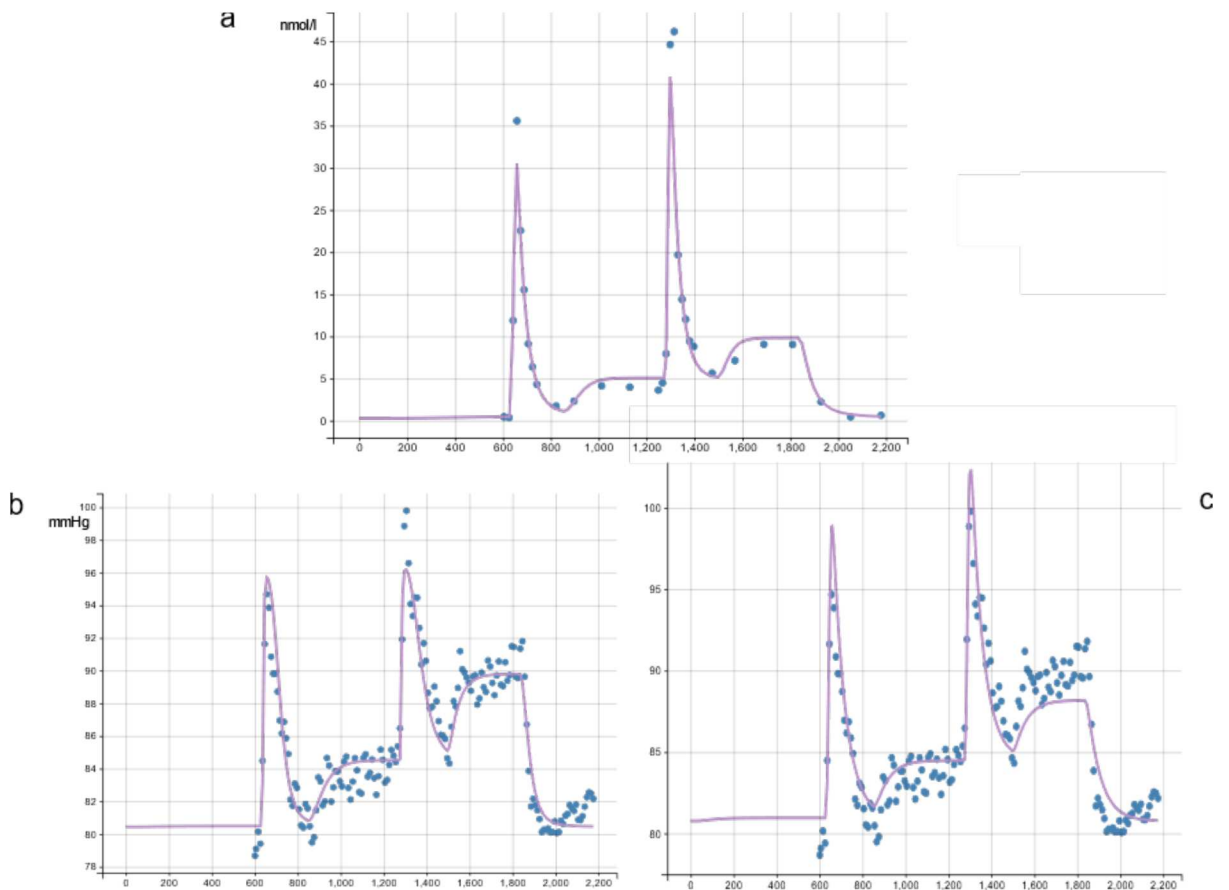


Figure 15 Exemple de prédiction individuelle pour un patient. Points bleus : valeurs mesurées. Courbes violettes : prédiction. Panneau (a) : modèle PK. Panneau (b) : modèle Emax. Panneau (c) : modèle mécanistique.

Conclusion de l'article

Les résultats de cette étude montrent qu'il est possible de développer des modèles PKPD précis pour la noradrénaline à faible dose telle qu'elle est actuellement utilisée en peropératoire. Les modèles peuvent atteindre une grande précision lorsqu'ils sont ajustés sur des patients individuels avec des erreurs moyennes aussi faibles que 1,5 mmHg. Les VPC montrent une erreur accrue dans les deux premières minutes d'enregistrement. En effet, cette période correspond à l'administration initiale du bolus. Ces données suggèrent que les modèles PKPD sont plus performants pendant la perfusion que pendant le bolus. Les tendances actuelles tendent à favoriser l'utilisation de la perfusion plutôt que du bolus car la tolérance hémodynamique semble meilleure.

CHAPITRE 4: Discussion et Perspectives

Perspectives PlethoMAP

Construction du prototype et brevet AP-HP

Afin de concrétiser les travaux réalisés autour de l'algorithme PlethoMAP, nous avons construit un appareil prototype intégrant l'algorithme PlethoMAP et pouvant estimer la PAM en temps réel en situation clinique au bloc opératoire.

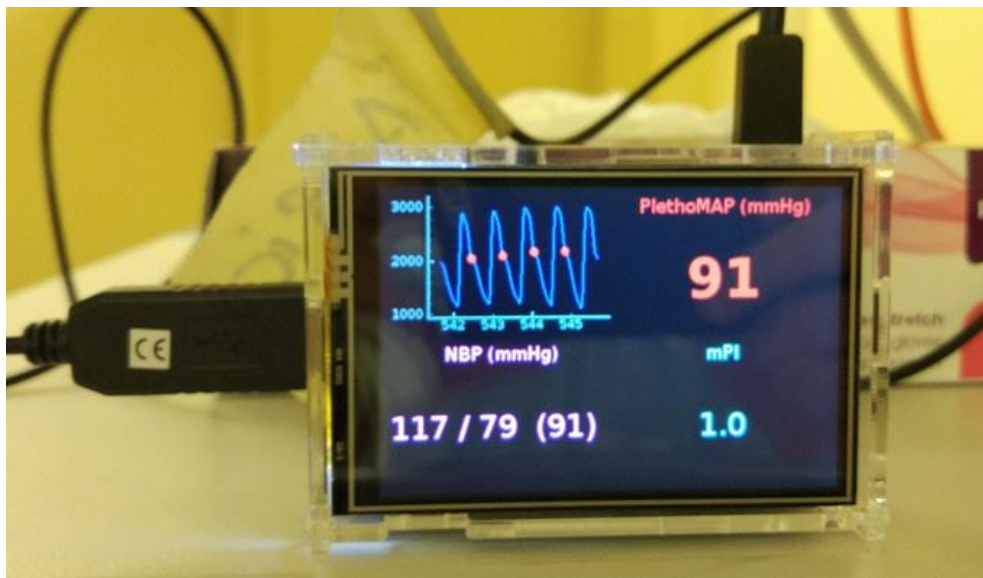


Figure 16 Prototype du «PlethoMAP». Un appareil qui est connecté au moniteur patient Philips IntelliVue pour capter en temps réel les signaux de PPG, le PI et qui calcule et affiche en temps réel une estimation de la PAM par l'algorithme PlethoMAP.

L'idée du PlethoMAP a été protégée par l'AP-HP sous le brevet portant le numéro INPI 17/62978 [4, 5]. Cette innovation a reçu le prix du Brevet Prometteur AP-HP 2021.



Figure 17 Remise du prix du Brevet prometteur AP-HP 2021

Améliorations de l'algorithme

Les techniques d'apprentissage statistique modernes permettent des innovations sensibles et des travaux sont en cours pour explorer ces pistes. Des innovations futures pourraient inclure la contextualisation pour mettre l'état physiologique actuel du patient dans un contexte qui est nourri par les données précédemment récoltées. On s'approche alors du concept de « jumeau numérique » [53].

Concernant le modèle mécanistique, une des limites les plus évidentes est la détection de l'onde dicrote qui n'est pas toujours aisée [54]. Des publications récentes semblent offrir des réponses intéressantes, permettant une détection précise de l'onde dicrote en utilisant notamment une calibration temps réel d'un modèle Windkessel [55, 56]. Il sera nécessaire de vérifier si les performances et la fiabilité de ces techniques sont suffisantes pour améliorer la détection de l'onde dicrote.

Les évolutions futures vont probablement conduire par une approche hybride, mélangeant des algorithmes mécanistiques et l'apprentissage statistique.

Amélioration du recueil systématisé

À la suite de nos premières publications, alors que nous avons des besoins croissants de recueil de données en haute-fidélité pour procéder à des vérifications physiologiques et des calibrations de modèles, nous avons entamé une collaboration avec la société Philips pour tester et aider à la mise au point d'une solution de stockage haute-fidélité et à large échelle des données des moniteurs patients (« scopes »).

Il s'agit de la solution « DataWarehouse Connect » commercialisée par Philips, qui permet l'enregistrement en temps réel de l'ensemble de données présentes sur les moniteurs patients, à savoir les chiffres mais également les courbes en haute définition et les alarmes. Cela concerne également tous les appareils tiers qui peuvent être reliés au moniteur comme des ventilateurs, des moniteurs de débit cardiaque ou d'EEG, des poussettes électriques ou encore des machines de dialyse ou d'ECMO... Toutes ces données sont enregistrées de manière synchronisée dans une base de données.

J'ai été dès le lancement en Mars 2019 le référent technique à l'hôpital Lariboisière pour la gestion de cette base de données. Nous avons progressivement augmenté l'étendue du recueil pour couvrir actuellement 20 lits de blocs opératoires et maternité et 28 lits de soins intensifs et réanimation. Le tableau ci-dessous résume l'envergure des données récoltées avec plus de 20 000 patients en chirurgie générale et plus de 3000 patients de réanimation recueillis en Mars 2022.

Clinical Unit	n Patients	Start of recording	Duration (patient days)	Average duration per patient (hours)
Central OR	11965	2019-03-15	10253	2
Orthopedics OR	707	2021-12-06	623	3
Neuroradiology	2160	2019-04-30	1835	3
PACU	9719	2020-12-15	3406	8
Maternity ward	1081	2021-12-08	1143	25
Surgical ICU	3235	2019-03-01	20945	155
CCU	329	2021-04-13	2115	154

Au moment de ces chiffres, le poids de la base de données est d'environ 20 téraoctets. Depuis octobre 2021, cette base de données est également synchronisée avec l'entrepôt de données de santé (EDS) de l'APHP grâce à l'obtention de la chaire IA AP-HP et l'engagement de deux ingénieurs données temps plein. Il est par conséquent possible aujourd'hui d'analyser ces données au sein de l'EDS, et cela de manière conjointe avec l'imagerie, la biologie, le PMSI, les comptes rendus médicaux, etc.

En parallèle, nous avons développé à Lariboisière un système permettant une analyse en flux continu (« streaming ») des données recueillies basé sur Apache Kafka [57]. Cette solution permet de traiter les données des moniteurs patients en temps réel et d'appliquer des algorithmes qui pourraient avoir un impact sur la prise en charge. Nous développons notamment un prototype pour estimer la pression artérielle moyenne en continu avec l'algorithme PlethoMAP et de retourner les estimations sur les moniteurs patients avec une latence de quelques secondes. Ainsi, ces algorithmes peuvent améliorer la prise en charge au bloc opératoire sans déploiement de matériel physique supplémentaire.

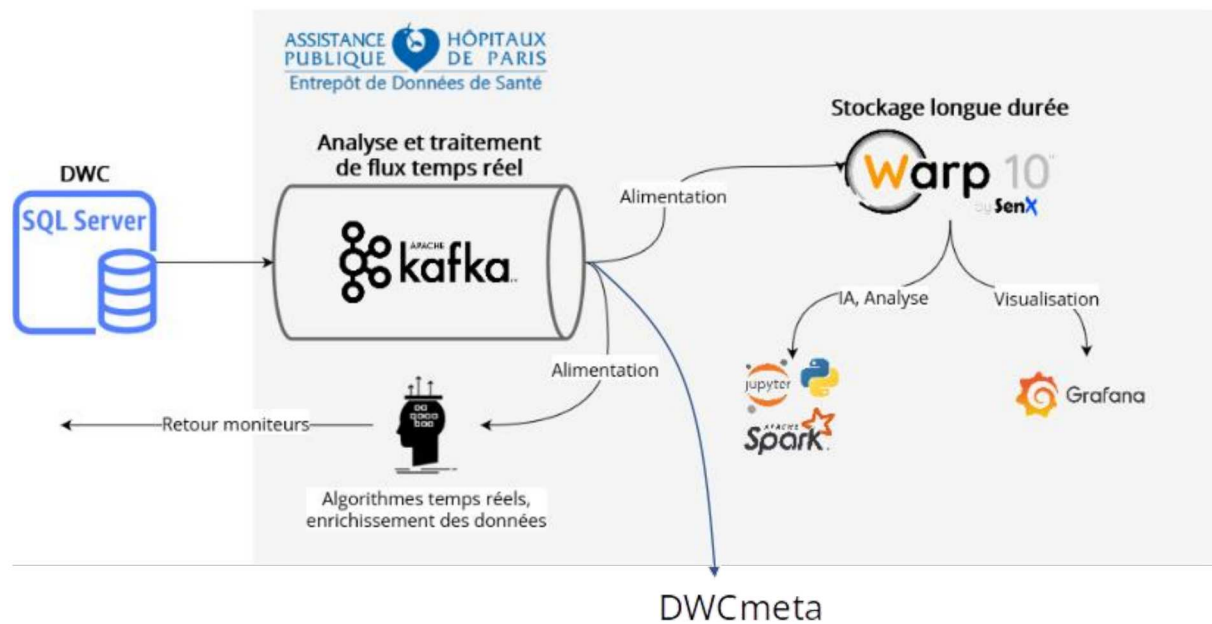


Figure 18 Pipeline Kafka temps réel permettant la mise en place de nombreux microservices qui peuvent se nourrir et réinjecter des données en temps réel

Validation prospective et impact

Nous projetons actuellement de réaliser une étude prospective d'impact qui pourrait répondre à la question si la disponibilité du PlethoMAP pourrait améliorer la prise en charge du patient par une détection et une prise en charge plus précoce de l'hypotension au bloc opératoire. Cette étude est en attente des étapes réglementaires pour l'utilisation clinique des algorithmes.

Dimension entrepreneuriale

Le projet PlethoMAP fait l'objet d'un projet de « start-up » sous le parrainage conjoint de l'AP-HP et de l'Inria.

Perspectives Modèle PK/PD Noradrénaline

Perfusion à objectif de concentration

Les perspectives pour le modèle PKPD pour la noradrénaline sont nombreuses. La plus évidente est bien entendu l'utilisation du modèle pour la perfusion de la noradrénaline à objectif de concentration, que cela soit une cible plasmatique ou une cible d'effet. Cette étape

requiert une étape mathématique parce qu'il est nécessaire d'inverser le modèle PK/PD. En effet, le modèle PK/PD permet de prédire les changements en concentration plasmatique ou de pression artérielle moyenne, sachant la dose de noradrénaline administrée. L'utilisation en objectif de concentration nécessite de résoudre le problème inverse, à savoir quelle est la dose de noradrénaline à injecter afin d'obtenir la concentration plasmatique ou l'effet désiré. Les problèmes inverses représentent une branche intéressante des mathématiques et plusieurs approches peuvent être utilisées pour répondre à cette question.

Entraînement temps réel

Le modèle PKPD présenté permet une bonne estimation de la concentration plasmatique de la noradrénaline sur la population mais les performances sont moins bonnes pour la pression artérielle moyenne. En effet, il paraît illusoire de vouloir prédire la pression artérielle uniquement sur base de la dose de noradrénaline. Une multitude d'autres facteurs sont bien entendu impliqués, notamment la dose d'hypnotiques, les comorbidités du patient, la volémie, etc. On peut améliorer la prédiction si on tente de prédire des variations de pression artérielle plutôt que la valeur absolue.

En revanche, les estimations sont excellentes lors de l'entraînement individualisé. Si on offre à l'algorithme des échantillons précédents de monitoring et notamment sa réponse à la noradrénaline, l'estimation de la pression artérielle par le modèle PKPD est exacte à l'ordre de grandeur du mmHg. Il paraît tout à fait possible de nourrir en temps réel le modèle PKPD par les données du moniteur patient. Cela peut passer par une approche bayésienne avec une erreur a priori qui est réduite au fur et à mesure que des informations supplémentaires sont disponibles. Les avancées récentes sur l'interconnexion du matériel médical rendent ce type d'application de plus en plus réaliste.

Asservissement aux hypnotiques

Ils existent aujourd'hui des modèles PKPD pour le propofol où l'effet prédit n'est non pas la sédation mais l'effet sur la pression artérielle [58, 59]. Ainsi, il devient aujourd'hui possible d'anticiper des épisodes d'hypotension après administration de propofol par la modélisation avant d'administrer le médicament au patient. D'autres études sont nécessaires à plus large échelle et notamment en étudiant l'interaction avec les opioïdes. Nous envisageons des études ultérieures dans ce sens sur notre base de données. Dès lors que l'hypotension engendrée par

l'anesthésie devient prévisible, et cela de manière individualisée pour le patient en question, et que nous disposons d'un modèle PKPD pour la noradrénaline, il devient possible d'asservir la perfusion de noradrénaline à la perfusion d'hypnotique pour prévenir en temps réel les effets d'hypotension avant qu'ils ne s'installent, prévenant ainsi l'hypoperfusion et la morbidité associée à l'hypotension.

Boucle fermée

Une application intéressante et innovante est l'administration de la noradrénaline en boucle fermée. Ce type de dispositif existe déjà dans le contexte d'études cliniques [60] et a montré son efficacité dans les études préliminaires pour traiter l'hypotension au bloc opératoire. Cependant, les dispositifs existants ne disposent pas de modélisation PK/PD et procèdent à l'élaboration de la dose de noradrénaline par des phases itératives de tentatives et d'observation. Ce type d'approche conduit à une variabilité de la pression artérielle et un retard par rapport à l'observation qui peut potentiellement être amélioré par la modélisation PKPD.

L'idée logique dans notre approche est d'utiliser le PlethoMAP comme monitoring pour la boucle fermée. Cela permettrait de réunir les travaux débutés lors de cette thèse pour aboutir à un traitement automatisé de l'hypotension sous anesthésie.

CONCLUSION

La prise en charge de l'hypotension sous anesthésie repose sur un monitoring fiable et une thérapeutique efficace par vasopresseurs. L'association de ces deux éléments paraît indispensable pour réduire la morbi-mortalité liée à l'hypotension dans la période périopératoire.

Ce travail de thèse a permis de mettre au point un système de monitoring purement non-invasif, basé sur une analyse innovante de signaux qui sont d'ores et déjà disponibles dans tous les blocs opératoires pour estimer en temps réel, battement par battement, la pression artérielle moyenne. Cette technique se base en grande partie sur l'analyse de l'onde de pouls obtenue par la photopléthysmographie. La fiabilité du monitoring a été appréhendée dans deux publications et des innovations supplémentaires sont en cours. Aucun matériel supplémentaire n'est nécessaire vu qu'il s'agit purement d'une analyse logicielle. Par rapport à d'autres solutions, cela présente un avantage en termes de coûts et de déploiement dans des zones où il est difficile de mettre en place du matériel supplémentaire pour des raisons économiques ou logistiques. De cette manière, ce monitoring répond à une problématique globale. En effet, l'hypotension sous anesthésie peut avoir des répercussions pour tout type d'anesthésie, même pour des actes mineurs dans des lieux délocalisés.

Ce travail a également permis la mise au point d'un modèle pharmacométrique de la noradrénaline faiblement dosée telle qu'elle est utilisée au bloc opératoire pour restaurer la pression artérielle. Alors que la noradrénaline est connue dans le monde médical depuis plus de 80 ans, étonnement peu de travaux se sont intéressés à sa pharmacocinétique. Dans le traitement de l'hypotension sous anesthésie, la pharmacocinétique et l'effet puissant de la noradrénaline sont particulièrement adaptés pour des corrections rapides d'hypoperfusion d'organes potentiellement délétères. Cependant, cette utilisation nécessite des précautions usage compte tenu de la fenêtre thérapeutique étroite et du risque d'accident. L'utilisation de la noradrénaline sous perfusion à objectif de concentration semble être une solution idéale pour la gestion peropératoire et la médecine personnalisée au bloc opératoire dans le contexte d'hypotension liée aux anesthésiques.

L'association de ces deux moyens devrait permettre une meilleure prise en charge des patients sous anesthésie. Des études d'impact mesurant l'effet de ces solutions innovantes de prise en charge doivent être maintenant réalisées.

BIBLIOGRAPHIE

- [1] Coutrot, M.; Dudoignon, E.; Joachim, J.; Gayat, E.; Vallée, F. and Dépret, F.: Perfusion index: Physical principles, physiological meanings and clinical implications in anaesthesia and critical care, *Anaesthesia Critical Care & Pain Medicine*, **40** (2021), no. 6, p. 100964.
- [2] Coutrot, M.; Joachim, J.; Dépret, F.; Millasseau, S.; Nougué, H.; Matéo, J.; Mebazaa, A.; Gayat, E. and Vallée, F.: Non-invasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept, *British Journal of Anaesthesia*, (2019), p. S0007091219300960.
- [3] Joachim, J.; Coutrot, M.; Millasseau, S.; Matéo, J.; Mebazaa, A.; Gayat, E. and Vallée, F.: Real-time estimation of mean arterial blood pressure based on photoplethysmography dicrotic notch and perfusion index. A pilot study, *Journal of Clinical Monitoring and Computing*, (2020).
- [4] Coutrot, M.; Gayat, E.; Joachim, J.; Mateo, J.; Mebazaa, A. and Vallée, F.: System for Measuring the Mean Arterial Pressure 2019.
- [5] Coutrot, M.; Gayat, E.; Joachim, J.; Mateo, J.; Mebazaa, A. and Vallée, F.: Méthode De Mesure De La Pression Artérielle Moyenne 2019.
- [6] Kern, E.: L'hypotension contrôlée en pratique anesthésiologique, *Acta de l'Institut d'Anesthésiologie*, **I** (1953), pp. 358–370.
- [7] Walsh, M.; Devereaux, P.J.; Garg, A.X.; Kurz, A.; Turan, A.; Rodseth, R.N.; Cywinski, J.; Thabane, L. and Sessler, D.I.: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension, *Anesthesiology*, **119** (2013), no. 3, pp. 507–515.
- [8] Bijker, J.B.; van Klei, W.A.; Kappen, T.H.; van Wolfswinkel, L.; Moons, K.G.M. and Kalkman, C.J.: Incidence of Intraoperative Hypotension as a Function of the Chosen Definition: Literature Definitions Applied to a Retrospective Cohort Using Automated Data Collection, *Anesthesiology*, **107** (2007), no. 2, pp. 213–220.
- [9] Bijker, J.B.; Persoon, S.; Peelen, L.M.; Moons, K.G.M.; Kalkman, C.J.; Kappelle, L.J. and van Klei, W.A.: Intraoperative Hypotension and Perioperative Ischemic Stroke after General Surgery, *Anesthesiology*, **116** (2012), no. 3, pp. 658–664.
- [10] Salmasi, V.; Maheshwari, K.; Yang, D.; Mascha, E.J.; Singh, A.; Sessler, D.I. and Kurz, A.: Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis, *Anesthesiology*, **126** (2017), no. 1, pp. 47–65.
- [11] Sessler, D.I.; Sigl, J.C.; Kelley, S.D.; Chamoun, N.G.; Manberg, P.J.; Saager, L.; Kurz, A. and Greenwald, S.: Hospital stay and mortality are increased in patients having a 'triple low' of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia, *Anesthesiology*, **116** (2012), no. 6, pp. 1195–1203.
- [12] Nguyen, M.; Nowobilski, N. and Guinot, P.-G.: Contrôle périopératoire de la pression artérielle, *Société Française d'Anesthésie et de Réanimation*, 2019.
- [13] Futier, E.; Lefrant, J.-Y.; Guinot, P.-G.; Godet, T.; Lorne, E.; Cuvillon, P.; Bertran, S.; Leone, M.; Pastene, B.; Piriou, V.; Mollieux, S.; Albanese, J.; Julia, J.-M.; Tavernier, B.; Imhoff, E.; Bazin, J.-E.; Constantin, J.-M.; Pereira, B.; Jaber, S. and INPRESS Study Group: Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial, *JAMA*, **318** (2017), no. 14, pp. 1346–1357.

- [14] Ebert, T.J.; Kanitz, D.D. and Kampine, J.P.: Inhibition of Sympathetic Neural Outflow During Thiopental Anesthesia in Humans:, *Anesthesia & Analgesia*, **71** (1990), no. 4, p. 319-326.
- [15] Marty, J.; Gauzit, R.; Lefevre, P.; Couderc, E.; Farinotti, R.; Henzel, C. and Desmonts, J.M.: Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans, *Anesthesia and Analgesia*, **65** (1986), no. 2, pp. 113–119.
- [16] Authors/Task Force Members:: Perk, J.; De Backer, G.; Gohlke, H.; Graham, I.; Reiner, Z.; Verschuren, M.; Albus, C.; Benlian, P.; Boysen, G.; Cifkova, R.; Deaton, C.; Ebrahim, S.; Fisher, M.; Germano, G.; Hobbs, R.; Hoes, A.; Karadeniz, S.; Mezzani, A.; Prescott, E.; Ryden, L.; Scherer, M.; Syvanne, M.; Scholte Op Reimer, W.J.M.; Vrints, C.; Wood, D.; Zamorano, J.L.; Zannad, F.; Other experts who contributed to parts of the guidelines:: Cooney, M.T.; ESC Committee for Practice Guidelines (CPG):: Bax, J.; Baumgartner, H.; Ceconi, C.; Dean, V.; Deaton, C.; Fagard, R.; Funck-Brentano, C.; Hasdai, D.; Hoes, A.; Kirchhof, P.; Knuuti, J.; Kolh, P.; McDonagh, T.; Moulin, C.; Popescu, B.A.; Reiner, Z.; Sechtem, U.; Sirnes, P.A.; Tendera, M.; Torbicki, A.; Vahanian, A.; Windecker, S.; Document Reviewers:: Funck-Brentano, C.; Sirnes, P.A.; Aboyans, V.; Ezquerra, E.A.; Baigent, C.; Brotons, C.; Burell, G.; Ceriello, A.; De Sutter, J.; Deckers, J.; Del Prato, S.; Diener, H.-C.; Fitzsimons, D.; Fras, Z.; Hambrecht, R.; Jankowski, P.; Keil, U.; Kirby, M.; Larsen, M.L.; Mancia, G.; Manolis, A.J.; McMurray, J.; Pajak, A.; Parkhomenko, A.; Rallidis, L.; Rigo, F.; Rocha, E.; Ruilope, L.M.; van der Velde, E.; Vanuzzo, D.; Viigimaa, M.; Volpe, M.; Wiklund, O. and Wolpert, C.: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), *European Heart Journal*, **33** (2012), no. 13, pp. 1635–1701.
- [17] Hollenberg, S.M.: Vasoactive drugs in circulatory shock, *American Journal of Respiratory and Critical Care Medicine*, **183** (2011), no. 7, pp. 847–855.
- [18] Thiele, R.H.; Nemergut, E.C. and Lynch, C.: The Physiologic Implications of Isolated Alpha1 Adrenergic Stimulation, *Anesthesia & Analgesia*, **113** (2011), no. 2, pp. 284–296.
- [19] Thiele, R.H.; Nemergut, E.C. and Lynch, C.: The Clinical Implications of Isolated Alpha1 Adrenergic Stimulation, *Anesthesia & Analgesia*, **113** (2011), no. 2, pp. 297–304.
- [20] Fellahi, J.-L.; Futier, E.; Vaisse, C.; Collange, O.; Huet, O.; Loriau, J.; Gayat, E.; Tavernier, B.; Biais, M.; Asehnoune, K.; Cholley, B. and Longrois, D.: Perioperative hemodynamic optimization: from guidelines to implementation—an experts’ opinion paper, *Annals of Intensive Care*, **11** (2021), no. 1, p. 58.
- [21] Goertz, W.; Lindner, K.; Seefelder, C.; Schirmer, U.; Beyer, M. and Georgieff, M.: Effect of Phenylephrine Bolus Administration on Global Left Ventricular Function in Patients with Coronary Artery Disease and Patients with Valvular Aortic Stenosis, *Anesthesiology*, **78** (1993), no. 5, pp. 834–41.
- [22] Goertz, A.W.; Schmidt, M.; Seefelder, C.; Lindner, K.H. and Georgieff, M.: The Effect of Phenylephrine Bolus Administration on Left Ventricular Function During Isoflurane-Induced Hypotension:, *Anesthesia & Analgesia*, **77** (1993), no. 2, pp. 227–231.
- [23] Mets, B.: Should Norepinephrine, Rather than Phenylephrine, Be Considered the

- Primary Vasopressor in Anesthetic Practice?, *Anesthesia & Analgesia*, **122** (2016), no. 5, p. 1707.
- [24] Wuethrich, P.Y.; Studer, U.E.; Thalmann, G.N. and Burkhard, F.C.: Intraoperative Continuous Norepinephrine Infusion Combined with Restrictive Deferred Hydration Significantly Reduces the Need for Blood Transfusion in Patients Undergoing Open Radical Cystectomy: Results of a Prospective Randomised Trial, *European Urology*, **66** (2014), no. 2, pp. 352–360.
- [25] Wuethrich, P.Y.; Burkhard, F.C.; Thalmann, G.N.; Stueber, F. and Studer, U.E.: Restrictive Deferred Hydration Combined with Preemptive Norepinephrine Infusion during Radical Cystectomy Reduces Postoperative Complications and Hospitalization Time, *Anesthesiology*, **120** (2014), no. 2, pp. 365–377.
- [26] Ngan Kee, W.D.; Lee, S.W.Y.; Ng, F.F.; Tan, P.E. and Khaw, K.S.: Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery, *Anesthesiology*, **122** (2015), no. 4, pp. 736–745.
- [27] Kwak, Y.L.; Lee, C.S.; Park, Y.H. and Hong, Y.W.: The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*: Phenylephrine and norepinephrine in pulmonary hypertension, *Anaesthesia*, **57** (2002), no. 1, pp. 9–14.
- [28] Ky, B.; French, B.; May Khan, A.; Plappert, T.; Wang, A.; Chirinos, J.A.; Fang, J.C.; Sweitzer, N.K.; Borlaug, B.A.; Kass, D.A.; St. John Sutton, M. and Cappola, T.P.: Ventricular-Arterial Coupling, Remodeling, and Prognosis in Chronic Heart Failure, *Journal of the American College of Cardiology*, **62** (2013), no. 13, pp. 1165–1172.
- [29] The Reference Values for Arterial Stiffness' Collaboration: Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values', *European Heart Journal*, **31** (2010), no. 19, pp. 2338–2350.
- [30] The CAFE Investigators; CAFE Steering Committee and Writing Committee; Williams, B.; Lacy, P.S.; Thom, S.M.; Cruickshank, K.; Stanton, A.; Collier, D.; Hughes, A.D.; Thurston, H. and O'Rourke, M.: Differential Impact of Blood Pressure-Lowering Drugs on Central Aortic Pressure and Clinical Outcomes: Principal Results of the Conduit Artery Function Evaluation (CAFE) Study, *Circulation*, **113** (2006), no. 9, pp. 1213–1225.
- [31] Vallée, F.; Passouant, O.; Le Gall, A.; Joachim, J.; Mateo, J.; Mebazaa, A. and Gayat, E.: Norepinephrine reduces arterial compliance less than phenylephrine when treating general anesthesia-induced arterial hypotension, *Acta Anaesthesiologica Scandinavica*, **61** (2017), no. 6, pp. 590–600.
- [32] Code de la santé publique - Article D712-44 Code de la santé publique no date.
- [33] Politi, M.T.; Ghigo, A.; Fernández, J.M.; Khelifa, I.; Gaudric, J.; Fullana, J.M. and Lagrée, P.-Y.: The dicrotic notch analyzed by a numerical model, *Computers in Biology and Medicine*, **72** (2016), pp. 54–64.
- [34] Lecun, Y.; Bottou, L.; Bengio, Y. and Haffner, P.: Gradient-based learning applied to document recognition, *Proceedings of the IEEE*, **86** (1998), no. 11, pp. 2278–2324.
- [35] Tsantekidis, A.; Passalis, N.; Tefas, A.; Kannianen, J.; Gabbouj, M. and Iosifidis, A.: Forecasting Stock Prices from the Limit Order Book Using Convolutional Neural Networks, 2017 IEEE 19th Conference on Business Informatics (CBI), conference '2017 IEEE 19th Conference on Business Informatics (CBI)', 2017, pp. 7–12.
- [36] Efron, B.; Hastie, T.; Johnstone, I. and Tibshirani, R.: Least angle regression, *The Annals of Statistics*, **32** (2004), no. 2, pp. 407–499.
- [37] Falcon, W.; Borovec, J.; Wälchli, A.; Eggert, N.; Schock, J.; Jordan, J.; Skafte, N.;

- Ir1dXD; Bereznyuk, V.; Harris, E.; Tullie Murrell; Yu, P.; Præsius, S.; Addair, T.; Zhong, J.; Lipin, D.; Uchida, S.; Shreyas Bapat; Schröter, H.; Dayma, B.; Karnachev, A.; Akshay Kulkarni; Shunta Komatsu; Martin.B; Jean-Baptiste SCHIRATTI; Mary, H.; Byrne, D.; Cristobal Eyzaguirre; Cinjon and Bakhtin, A.:
PyTorchLightning/pytorch-lightning: 0.7.6 release, Zenodo, 2020.
- [38] Dong, W.-X. and Ni, X.-L.: Norepinephrine metabolism in neuron: dissociation between 3,4-dihydroxyphenylglycol and 3,4-dihydroxymandelic acid pathways, *Acta Pharmacologica Sinica*, **23** (2002), no. 1, pp. 59–65.
- [39] Eisenhofer, G.; Kopin, I.J. and Goldstein, D.S.: Catecholamine metabolism: a contemporary view with implications for physiology and medicine, *Pharmacological Reviews*, **56** (2004), no. 3, pp. 331–349.
- [40] Schulz, C.; Eisenhofer, G. and Lehnert, H.: Principles of catecholamine biosynthesis, metabolism and release, *Frontiers of Hormone Research*, **31** (2004), pp. 1–25.
- [41] Danon, A. and Sapira, J.D.: Binding of catecholamines to human serum albumin, *The Journal of Pharmacology and Experimental Therapeutics*, **182** (1972), no. 2, pp. 295–302.
- [42] Gründemann, D.; Liebich, G.; Kiefer, N.; Köster, S. and Schömig, E.: Selective substrates for non-neuronal monoamine transporters, *Molecular Pharmacology*, **56** (1999), no. 1, pp. 1–10.
- [43] Axelrod, J. and Tomchick, R.: Enzymatic O-methylation of epinephrine and other catechols, *The Journal of Biological Chemistry*, **233** (1958), no. 3, pp. 702–705.
- [44] Martin, C.; Papazian, L.; Perrin, G.; Saux, P. and Gouin, F.: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock?, *Chest*, **103** (1993), no. 6, pp. 1826–1831.
- [45] Martin, C.; Viviani, X.; Leone, M. and Thirion, X.: Effect of norepinephrine on the outcome of septic shock, *Critical Care Medicine*, **28** (2000), no. 8, pp. 2758–2765.
- [46] De Backer, D.; Biston, P.; Devriendt, J.; Madl, C.; Chochrad, D.; Aldecoa, C.; Brasseur, A.; Defrance, P.; Gottignies, P. and Vincent, J.-L.: Comparison of Dopamine and Norepinephrine in the Treatment of Shock, *New England Journal of Medicine*, **362** (2010), no. 9, pp. 779–789.
- [47] Beloeil, H.; Mazoit, J.-X.; Benhamou, D. and Duranteau, J.: Norepinephrine kinetics and dynamics in septic shock and trauma patients, *British Journal of Anaesthesia*, **95** (2005), no. 6, pp. 782–788.
- [48] Absalom, A.R. and Mason, K.P. eds.: *Total Intravenous Anesthesia and Target Controlled Infusions: A Comprehensive Global Anthology*, Springer International Publishing, Cham, 2017.
- [49] Joachim, Jona: *InfuPy*, Zenodo, 2021.
- [50] Buchwald, P.: A single unified model for fitting simple to complex receptor response data, *Scientific Reports*, **10** (2020), no. 1, p. 13386.
- [51] Frank, O.: The basic shape of the arterial pulse. First treatise: mathematical analysis. 1899, *Journal of Molecular and Cellular Cardiology*, **22** (1990), no. 3, pp. 255–277.
- [52] Westerhof, N.; Stergiopoulos, N. and Noble, M.I.M.: *Snapshots of hemodynamics: an aid for clinical research and graduate education*, 2nd ed ed., Springer Verlag, New York, 2010.
- [53] Bruynseels, K.; Santoni de Sio, F. and van den Hoven, J.: Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm, *Frontiers in Genetics*, **9** (2018), p. 31.
- [54] Almeida, V.G.; Vieira, J.; Santos, P.; Pereira, T.; Pereira, H.C.; Correia, C.; Pego, M. and Cardoso, J.: *Machine Learning Techniques for Arterial Pressure Waveform*

- Analysis, *Journal of Personalized Medicine*, **3** (2013), no. 2, pp. 82–101.
- [55] Hoeksel, S.A.; Jansen, J.R.; Blom, J.A. and Schreuder, J.J.: Detection of dicrotic notch in arterial pressure signals, *Journal of Clinical Monitoring*, **13** (1997), no. 5, pp. 309–316.
- [56] Donelli, A.; Jansen, J.R.C.; Hoeksel, B.; Pedefferri, P.; Hanania, R.; Bovelander, J.; Maisano, F.; Castiglioni, A.; Ottavio, A. and Schreuder, J.J.: Performance of a real-time dicrotic notch detection and prediction algorithm in arrhythmic human aortic pressure signals, *Journal of Clinical Monitoring and Computing*, **17** (2002), nos. 3–4, pp. 181–185.
- [57] Shree, R.; Choudhury, T.; Gupta, S.C. and Kumar, P.: KAFKA: The modern platform for data management and analysis in big data domain, 2017 2nd International Conference on Telecommunication and Networks (^{TEL}-NET), conference ‘2017 2nd International Conference on Telecommunication and Networks (^{TEL}-NET)’, 2017, pp. 1–5.
- [58] Jeleazcov, C.; Lavielle, M.; Schüttler, J. and Ihmsen, H.: Pharmacodynamic response modelling of arterial blood pressure in adult volunteers during propofol anaesthesia, *British Journal of Anaesthesia*, **115** (2015), no. 2, pp. 213–226.
- [59] Su, H.; Eleveld, D.J.; Struys, M.M.R.F. and Colin, P.J.: Mechanism-based pharmacodynamic model for propofol haemodynamic effects in healthy volunteers☆, *British Journal of Anaesthesia*, **0** (2022), no. 0.
- [60] Joosten, A.; Delaporte, A.; Alexander, B.; Su, F.; Creteur, J.; Vincent, J.-L.; Cannesson, M. and Rinehart, J.: Automated Titration of Vasopressor Infusion Using a Closed-loop Controller, *Anesthesiology*, **130** (2019), no. 3, pp. 394–403.

Annexes

ANNEXES 1: Articles présentés dans la thèse

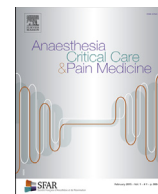
Annexe 1.1 Article “Perfusion Index: Physical Principles, Physiological Meanings and Clinical Implications”

Cet article a été publié dans *Anaesthesia Critical Care & Pain Medicine* le 12 novembre 2021 [1]. Les auteurs sont: Maxime Coutrot, Emmanuel Dudoignon, Jona Joachim, Etienne Gayat, Fabrice Vallée et François Dépret.



Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Review

Perfusion index: Physical principles, physiological meanings and clinical implications in anaesthesia and critical care



Maxime Coutrot^{a,d}, Emmanuel Dudoignon^{a,b,*}, Jona Joachim^a, Etienne Gayat^{a,b,c,d},
Fabrice Vallée^{a,b,c,d,f,g}, François Dépret^{a,b,c,d,e}

^a AP-HP, GH St-Louis-Lariboisière, Department of Anaesthesiology and Critical Care and Burn Unit, Paris, France

^b University Paris Diderot, France

^c UMR INSERM 942, Institut National de la Santé et de la Recherche Médicale (INSERM), France

^d FHU PROMICE, Paris, France

^e F-CRIN INICRCT network, Paris, France

^f Inria, France

^g LMS, Ecole Polytechnique, CNRS, Institut Polytechnique de Paris, France

ARTICLE INFO

Article history:

Available online 24 October 2021

Keywords:

Perfusion index
Haemodynamic monitoring
Non-invasive monitoring
Photoplethysmography

ABSTRACT

Photoplethysmography (PPG) has been extensively used for pulse oximetry monitoring in anaesthesia, perioperative and intensive care. However, some components of PPG signal have been employed for other purposes, such as non-invasive haemodynamic monitoring. Perfusion index (PI) is derived from PPG signal and represents the ratio of pulsatile on non-pulsatile light absorbance or reflectance of the PPG signal. PI determinants are complex and interlinked, involving and reflecting the interaction between peripheral and central haemodynamic characteristics, such as vascular tone and stroke volume. Recently, several studies have shed light on the interesting performances of this variable, especially assessing regional or neuraxial block success, and haemodynamic monitoring in anaesthesia, perioperative and intensive care. Nevertheless, no review has yet been published concerning the interest of PI in these fields.

In this narrative review will be exposed first the physiological and pathophysiological determinants of PI, and then the mean to measure this value as well as its potential limitations. In the second part, the existing data concerning usefulness of PI in different clinical settings such as operating theatres, intensive care units and emergency departments will be presented and discussed. Finally, the perspectives concerning the use of PI and mentioned aspects that should be explored regarding this tool will be underlined.

© 2021 Société française d'anesthésie et de réanimation (Sfar). Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

In the 1970s, following previous works, Takuo Aoyagi, who passed away on the 18th of April 2020, developed pulse oximetry using red and infrared lights transmission through tissues [1].

Increasing interest in non-invasive monitoring of macro-haemodynamic and microcirculation has risen in anaesthesia, perioperative and critical care. Photoplethysmography (PPG) signal, which was used during decades only to monitor oxygen

saturation, represents nowadays an interesting tool in haemodynamic monitoring.

PPG is a non-invasive tool, cheap, fast, and simple to use. However, interpretation of PPG data can be challenging: haemodynamic monitoring using PPG signal initially suffered from a large lack of knowledge and misunderstanding of its determinants, resulting in an incorrect use of this multifactorial device. However, analysis of PPG signal has benefited from regained interest in the past years and the usefulness of PPG has been highlighted by several works in anaesthesia, perioperative and critical care [2–4].

Among different components of PPG signal, perfusion index (PI), which represents the proportion of the pulsatile part of PPG, has been widely studied and stands as a promising tool for physicians. A good understanding of the principles of PPG and PI determinants as well as the knowledge of its limits is therefore

* Corresponding author at: Department of Anaesthesiology and Critical Care and Burn Unit, Saint-Louis Hospital, 1, Avenue Claude Vellefaux, Paris, France.

E-mail addresses: maxcoutrot@yahoo.fr (M. Coutrot), emmanuel.dudoignon@aphp.fr (E. Dudoignon).

Glossary of terms	
PPG	photoplethysmography
PI	perfusion index
PVI	pleth variability index
AC	alternating current
DC	direct current
SV	stroke volume
MAP	mean arterial pressure
ICU	intensive care unit
ScvO ₂	central venous oxygen saturation
P(v-a)CO ₂	arteriovenous carbon dioxide gradient
PLR	passive leg raising
CI	confidence interval

essential to optimise its correct use and performance. Physical principles and the physiological determinants of PI will be explained thereafter in this review.

Several reviews have been proposed on PPG, notably about PI respiratory variations, commonly referred to as Pleth Variability Index (PVI), and its applications [3,5-7]. However, none of the above-mentioned reviews focused on PI itself. Additionally, several new data have been published since.

This review covers the physiological and technical aspects of PPG and PI that clinicians need to understand and presents the clinical usefulness of PI in the operating theatre, perioperative and critical care.

2. How is perfusion index measured?

2.1. Principle of photoplethysmography

The principle of conventional PPG is based on indirect measurement of tissue volume variations by absorbance variations of light beams through this tissue. The oximeter probe generates incident red and ultra-red light beams, whose transmitted intensities are transformed into an electrical current by a photodetector, after penetrating a tissue (Fig. 1) [8,9].

Another PPG modality (PPG by reflection) uses reflection properties of the light in the tissue, according to the same

principle. The photodetector is then placed next to the light source to measure the reflectance of the incident beams [10].

Usually, two wavelengths are used for PPG: red light (660 nm) and infrared light (940 nm), mainly absorbed by deoxyhaemoglobin and oxyhaemoglobin, respectively. The PPG curve is obtained with infrared light absorption variations. However some PPG devices use one, or more often more than two wavelengths [11].

2.2. PI components: alternating and direct currents

Light absorption varies across the cardiac cycle. The absorption is maximal during the systole, reflecting the dilatation of vessels under the systolic pressure, i.e., the increase of arterial blood volume under the light source. The signal received by the photodetector is then decomposed into pulsatile and non-pulsatile signals. Pulsatile variations in light absorption, during systole, are commonly referred to as “alternating current” (AC). AC represents variations of absorbance or reflectance of the incident light beams due to pulsatile vessels under arterial pressure variations, i.e. the sum of the variations of the diameters of pulsatile vessels through which the light beams pass. AC then represents a volume variation measurement. It is important to underline that AC is therefore not a flow measurement in those vessels but an indirect measurement of the arterial volume variation during the cardiac cycle.

The PPG curve displayed on actual monitors represents AC, derived from the infrared light signal, after signal processing. Restitution of AC requires computer processing of the raw signal received by the photodetector by computer filters to reduce signal artifacts [8,12,13]. These manufacturer-dependent algorithms can significantly deform the PPG curve from one manufacturer to another [8,9].

On the other hand, continuous absorption is referred to as “direct current” (DC), from which AC varies. DC corresponds to light absorption from other tissues, such as non-pulsatile capillaries and venous vessels, skin, soft tissues, and bones. DC is not displayed in current practice on usual oximeter’s monitors.

2.3. PI calculation: alternating and direct currents ratio

PI represents the ratio of pulsatile light absorption on continuous light absorption, i.e., the ratio AC/DC (Fig. 1). PI, often referred to as “peripheral PI” was initially used as a quality signal

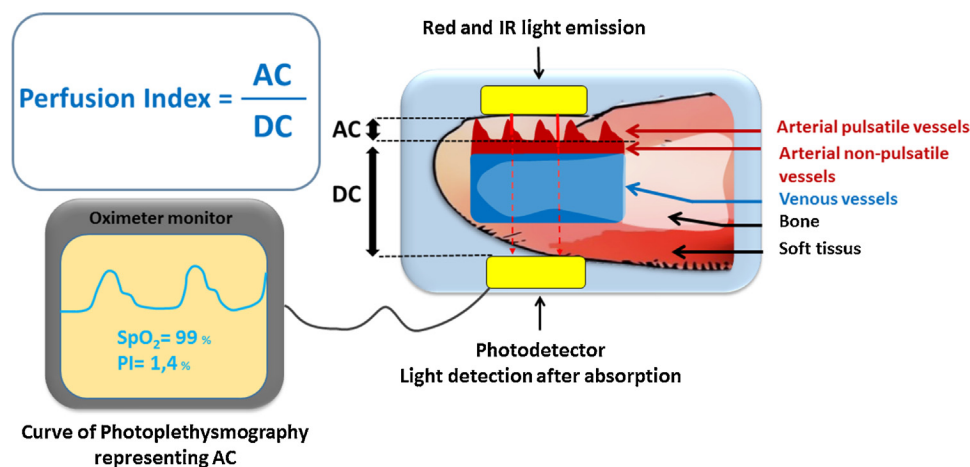


Fig. 1. Principles of photoplethysmography and PI calculation.

Fig. 1 represents the principles of PPG and PI calculation. AC corresponds to the variation of red and IR lights absorption related to the variation of diameters of pulsatile vessels (i.e. arrowed arterial pulsatile vessels on the figure). DC corresponds to the light absorption of: arterial non-pulsatile vessels, venous vessels, bone and soft tissues. PI value is calculated as the AC/DC ratio.

AC: alternating current; DC: direct current; IR: infrared light PI: perfusion index; PPG: photoplethysmography.

Table 1
Determinants of Perfusion Index and artifacts.

Physiological and pathophysiological determinants of Perfusion Index	
Systemic factors	Local factors
Factors influencing AC <ul style="list-style-type: none"> • Volaemia and venous return* • Diastolic function and inotropism* • Valvulopathy* • Vascular tone* (sympathetic, parasympathetic and non-adrenergic/non-cholinergic tones) • Arterial stiffness* • Vasoactive and cardiac medications* Factors influencing DC <ul style="list-style-type: none"> • Vascular tone* (notably venous tone) • Volaemia* 	<ul style="list-style-type: none"> • Obliterant arteriopathy • Position of the limb in relation to the heart • Vascular compression • Local temperature exposure • Local arterial compliance • Local vascular tone
Artifacts that may influence AC and DC <ul style="list-style-type: none"> • External light • Nail polish 	<ul style="list-style-type: none"> • Position of the limb • Body position • Vascular compression • Soft tissues compression • Local vascular tone
	<ul style="list-style-type: none"> • Tissues and vascular extrinsic compressions • Probe and/or patient movements

AC: alternating current; DC: direct current.

Numerous intrinsic or extrinsic factors influence AC and/or DC, and therefore their ratio, *i.e.* Perfusion Index. The main determinants are stroke volume and vascular tone, themselves influenced by many factors. Determinants of stroke volume (*) all may influence AC and PI. Volaemia, external temperature, stress, nociception, and medications (*e.g.* norepinephrine, vasodilator effect of anaesthetic drugs, etc.) are determinants of vascular tone and therefore of Perfusion Index.

* Determinants of stroke volume.

indicator for pulse oximetry [4,14]. However, PI represents the local blood volume variation during systole, and varies according to the systemic and local haemodynamic status. Hence, PI can be used for non-invasive haemodynamic monitoring.

2.4. Physiological value of PI

In healthy awake volunteers, when measured at the finger, the mean PI values (\pm standard deviation) described in two studies were $2.2\% \pm 2.0$ and $3.5\% \pm 2.4$ [15,16]. This means that AC represents only around 2%–3% of DC, and by analogy in vascular physiology, it means that the blood volume under the sensor increases by around 2% at each heartbeat. However, due to the wide variations in normal values in healthy volunteer (from $< 1\%$ to $> 10\%$), it is difficult to propose a reliable normal value of this parameter.

Determinants of PI are numerous and complex. When measured in a peripheral site, both AC and DC and their ratio, *i.e.*, PI, are the resultants of systemic and local factors, discussed below, and resumed in Table 1. The characteristics and main results of discussed studies are detailed in Supplementary Table 1.

2.5. Influence of direct current (DC) determinants

As PI represents the ratio AC/DC, any variation of DC will result in PI variation. Hence, soft tissues or venous compression (*e.g.*, by a finger clip) may decrease DC and increase PI. Likewise, congestion due to global fluid overload would have the opposite consequences. Limb position due to changes of venous filling and thus DC would also affect PI value, with an increase in DC if the limb is in a declive position (venous congestion) and the opposite in a proclive position [3]. Physiologically, DC is also not constant, and small variations are observed due to variation of venous return and sympathetic tone in patients spontaneously breathing or under mechanical ventilation [17,18]. Similarly, DC may also change in case of change in vascular tone, as under action of vasoactive drugs (*i.e.*, decrease of DC under increased vascular tone) [19].

2.6. Alternating current (AC): vascular tone versus stroke volume

Some authors have described PI as a surrogate of vascular tone only. Lima et al. showed that PI was correlated with central to toe temperature gradient – an accurate surrogate of vascular tone

[15]. Indeed, PI rapidly increased after local vasodilation induced by plexus or epidural anaesthesia, measured in the blocked area. PI was also strongly influenced by changes of vascular tone under action of vasopressors in patients under general anaesthesia (*i.e.*, decrease in PI secondary to norepinephrine infusion) [20–25].

Indeed, several recent studies suggested that stroke volume (SV) is another important determinant of PI. PI was correlated to superior vena cava flow and cardiac output in infants [26–28]. Low flow could be associated with increased vascular tone, but such data are not presented in these works. Van Genderen et al. exposed healthy volunteers to a lower body negative pressure [29]. They observed a rapid decrease of PI (from 2.2% [1.6–3.3] to 1.3% [0.9–1.7], expressed as median and interquartile), while SV decreased, and skin temperature difference between forearm and fingertip did not increase significantly. Lack of significant variation in skin temperature gradient between forearm and fingertip may be explained by the lack of power of this study (the study population comprised 25 males) or because of temperature change inertia. This suggested that PI was not only influenced by local vascular tone but also by SV itself. Another study performed in healthy volunteers showed PI variations induced by body positioning modifications (*e.g.*, Trendelenburg, 45-degree, supine, etc.) [30]. The highest values of PI were observed in Trendelenburg position ($7.8 \pm 3.8\%$). On the contrary, PI was the lowest in the sitting position ($4.5 \pm 2.5\%$), suggesting a positive relationship between PI and SV. This has been recently confirmed in a work showing that variation of PI was highly correlated to variation of SV ($r = 0.9$), and mean arterial pressure (MAP) ($r = 0.9$) during head up and down tilt test in patients under anaesthesia with low basal sympathetic tone or reactivity to position-induced hypovolaemia [31]. Additionally, other recent works further discussed, found significant correlation of cardiac index and PI variations after passive leg raising and fluid challenge [32–34]. These works confirmed the major influence of SV on PI, and the complexity of PI variations interpretation, especially in septic shock [35].

The respective influence of vascular tone and SV variations in case of vasoplegia are drawn in Fig. 2, cases A and B. Fig. 2 case A represents moderate vasoplegia (for example intraoperative hypotension secondary to anaesthetic drugs). In this case, the increase of PI (from 5 to 10%) would mainly be the consequence of a fall of arterial vascular tone (secondary to vasodilatation induced by anaesthetic drugs) without substantial SV variations

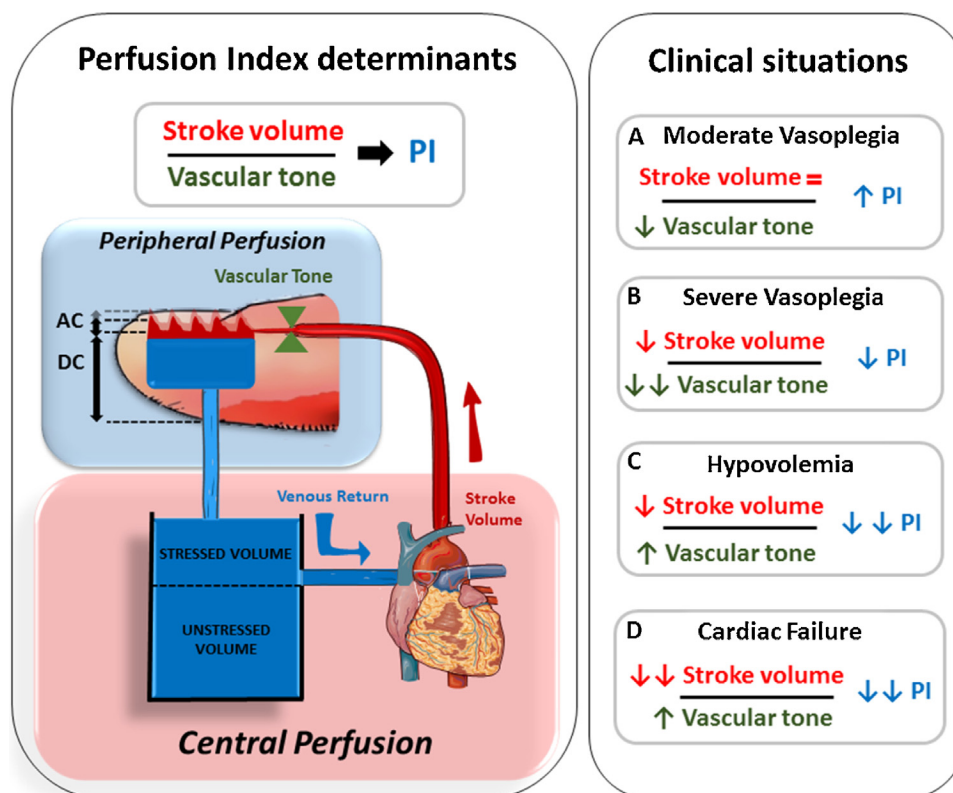


Fig. 2. Determinants of PI and typical clinical situations.

PI results from the local perfusion balance between peripheral determinants, mainly vascular tone and central determinants, *i.e.*, SV. Situation A represents the components of moderate vasoplegia: decreased vascular tone with single arterial vasodilatation, without significant variations in SV, resulting in an increase in PI. If vasoplegia becomes severe (situation B), with arterial and venous vasodilatation, the drop of stressed volume, venous return and thus SV leads to a secondary decrease in PI, despite the decrease of vascular tone.

In situation C and D, *i.e.*, hypovolaemia and cardiogenic shock, the drop of SV and the increase in vascular tone both contributes to a decrease in PI.

AC: alternating current; DC: direct current; PI: perfusion index; SV: stroke volume.

[15,19,25]. In case of severe vasoplegia (Fig. 2 case B), such as under general anaesthesia with overdose of anaesthetics leading to a significant decrease in stressed volume, venous return and thus in SV, or in case of surgical bleeding, PI decreases secondarily in comparison to Fig. 2 case A despite a low arterial vascular tone. In this case, SV would be the predominant determinant, leading to PI secondary decrease, *i.e.* “hiding” the effect of the decrease of vascular tone, on PI [29–31,33]. However, data are lacking to quantify the respective contributions of vascular tone and stroke volume in PI values and interpret its variations in such clinical situations.

On the contrary, as illustrated in the Fig. 2 case C, in case of hypovolaemia with preserved baroreceptors activation, SV will decrease and vascular tone increase. Both variations of SV and vascular tone will contribute to a decrease of AC. In such conditions, a decrease of DC secondary to the activation of the sympathetic system also participates to the drop of PI, suggesting that the decrease in AC is predominant over the decrease in DC [19,29,30]. Another comparable situation characterised by a low SV and potential increased vascular tone is cardiac failure, where both contribute also to the fall of AC, DC, and PI values (Fig. 2 case D). In this situation, PI would be typically extremely low PI (< 0.5). After inotropic drugs, an increase in SV would lead to a greater PI value [19].

2.7. Local conditions

PI measurement assesses local perfusion. The PI value varies according to the measurement site, even for clothe sites to a few

centimetres [33]. Thus, PI is highly influenced by systemic macrohaemodynamic status as well as local conditions. Since local vascular tone is mainly influenced by thermoregulation and non-thermoregulatory stimuli (*e.g.* nociception, exercise...) [36,37]. As an example, PPG waveform variation was substantially different between ear and finger after cold exposure [38]. Regional anaesthesia also illustrates the influence of local conditions: the increase in PI measured in the blocked area after regional anaesthesia is the witness of a decrease in local vascular tone, associated with an increase in local blood flow and volume at each heartbeat in the blocked region. Both the decrease in vascular tone and the increase in local blood flow and volume are contributing to the rise of AC and PI values. As for other variations of vascular tone, it is expected that DC also increase in the blocked area, although this has not been studied. In this situation, PI is a tool for local haemodynamic monitoring, but not central haemodynamic. Likewise, many local conditions must be considered to interpret PI value: local compression (soft tissues, veins and/or arteries), outside temperature variations, positions of the limbs or severe arterial abnormalities such as obliterating arteriopathy. In the conditions mentioned above, peripheral PI rather reflects local conditions than the central haemodynamic status [11,27]. However, no difference was found in basal PI in volunteers with or without vascular disease (hypertension and diabetes mellitus). On the contrary, macrohaemodynamic status (*i.e.*, cardiac index) can influence PI value depending on the measurement site. Indeed, in infants, PI tends to be higher at the right hand compared to foot for low cardiac output, and inversely for high cardiac output [26]. All these elements suggest the importance of regional perfusion

variation secondary to changes of sympathetic response and central haemodynamic status on local PI value.

2.8. Sources of errors and variations of PPG signal

One should also be aware of the classic and frequent sources of errors in the measurement of PI. Any extrinsic soft tissues and/or vascular compression could affect AC and/or DC and so the basal value of PI and/or its variations [3]. A common example is the digital compression by the clamp of PPG. The ear and finger PPG sensors are usually fitted with a clip, which prevents venous stasis and its influence on DC and thus on PI. Without a clip, forehead PPG waveform, *i.e.*, AC signal, has been described significantly affected by a strong venous signal. Therefore, venous compression by a clip may result in a more reliable arterial waveform [39]. However, the use of an external pressure on the forehead probe with a dedicated headband to suppress the impact of venous pulsation may also result in a more reliable PPG waveform. Other classical sources of errors or factors that may influence PPG waveform, such as nail polish, obesity, age, gender, ambient lights changes, course artifacts of movement of the probe, or the patient, etc., have been recently pointed out [11].

3. Clinical usefulness in anaesthesia: what are the data?

PI has been studied in the operating theatre for patients under regional or general anaesthesia in different clinical settings. The characteristics and main results of discussed studies are detailed in **Supplementary Table 1**.

3.1. PI in assessment of regional block success

At first, PI was used as an early indicator of regional anaesthesia success, using PI increase to detect vasodilation due to sympathetic tone inhibition.

PI measured at the toe was described as the earliest and 100% sensitive indicator of sympathectomy and epidural anaesthesia success compared to MAP and skin temperature [21,40]. Usefulness of PI variation after neuraxial anaesthesia in paediatric patients under general anaesthesia was also demonstrated [23,41]. PI variation was highly predictive of block success for regional plexus blocks in adults as well [20,22,42]. Variation of PI by a factor 1.55 had an area under the receiver operating characteristic curve of 0.94 for sciatic block, and area under the receiver operating characteristic curve of 1 for axillary block [20]. PI accuracy for prediction of regional block success was also higher than cold or pinprick sensations.

A recent work showed that PI performances for detection of regional block success were not different when using epinephrine as an adjuvant to local anaesthetics [43].

3.2. PI in assessment of neuraxial anaesthesia-induced haemodynamic variations

In parturients undergoing caesarean delivery after spinal-epidural anaesthesia, basal PI measured at finger location was correlated with the decline of systolic arterial pressure ($r = 0.66$) [44]. Baseline PI also showed a better correlation with systolic arterial pressure or MAP decrease than baseline heart rate, systolic arterial pressure, or MAP. The area under the receiver operating characteristics curve for baseline PI to predict arterial hypotension after spinal-epidural anaesthesia (defined as decrease in systolic arterial pressure $\geq 25\%$) was 0.87 (95% CI 0.74–0.99, $p < 0.001$), with a best threshold value of 3.5%. Similar results were found later with the same cut-off value [45]. So, a PI value greater than 3.5%

before spinal anaesthesia is a risk factor for anaesthesia-induced hypotension. One could expect that baseline PI value would also predict accurately diastolic arterial pressure decrease since vascular tone is one of the main determinants of diastolic arterial pressure. However, none of these studies evaluated the correlation between baseline PI values and diastolic arterial pressure decrease. A high PI value at baseline suggests a low basal vascular tone. Therefore, the decrease in sympathetic tone induced by spinal-epidural in patients with already low basal sympathetic tone, is more likely to induce a decrease in the stressed volume, resulting in a decrease of venous return and SV. Thus, PI is a simple tool to easily detect parturient patients with low sympathetic tone at high risk of arterial hypotension after spinal anaesthesia.

3.3. PI in assessment of nociception

As sympathetic tone is highly affected by nociceptive stimuli, PI signal has been used for nociception assessment during anaesthesia and in critical care [5]. Thus, the increase of vascular tone and MAP following nociceptive stimuli is associated with a decrease in PI [46]. Variation in PI could nevertheless be viewed only as a measurement of haemodynamic variation, *i.e.*, increase of sympathetic tone, following nociceptive stimulation. Hence, it may not be accurate in patients with external control of adrenergic receptors, such as those under high dose of vasopressors or contrarily, in case of pharmacological blockade of their sympathetic tone (*e.g.*, epidural anaesthesia or peripheral nerve blockade).

3.4. PI to detect blood pressure variation during general anaesthesia

Recent data have highlighted usefulness of PI to detect arterial hypotension during general anaesthesia. During induction of anaesthesia, PI variations were inversely correlated with MAP variations [25]. An increase of 51% or more from baseline PI detected a decrease of MAP of at least 20%. Another recent study found opposite but complementary results regarding the association between MAP and PI, in patients under general anaesthesia. Indeed, in 20 patients under general anaesthesia with head-up and head-down tilt, Højlund et al. observed that PI variations were positively correlated to MAP variations [31]. In this study, head-up tilt induced a decrease in SV correlated to MAP decrease, suggesting no significant variations in vascular tone, and resulting in a drop of PI. On the contrary, induction of anaesthesia is associated with severe drop in vascular tone. Both studies explored two major determinants of PI, reinforcing the fact that PI should be considered as the balance between SV and vascular tone, as schematically described in Fig. 2. Then, a rapid variation of PI represents an alarm signal that should warn and force the clinician to quickly check the occurrence of an arterial hypotension in patients under general anaesthesia, monitored with intermittent cuff blood pressure measurement. Kinetics of PI variation may also help clinicians to identify the mechanism of arterial hypotension and manage these situations quickly and accurately: an increase of PI suggests excessive vasodilatation (relative to excessive depth of anaesthesia for example), while a secondary decrease of PI in a patient deeply anaesthetised may reveal SV decrease (hypovolaemia and/or cardiac dysfunction).

3.5. PI and prognosis in anaesthesia

In a large recent and retrospective study, intraoperative PI was associated with severe postoperative complications or death (lower values being associated with worse outcomes) in a time-dependent manner even after adjustment for confounding variables [47]. Furthermore, they observed that the association between PI with the primary outcome was higher in patients with

MAP > 65 mmHg compared to patients with MAP ≤ 65 mmHg (OR = 1.17; 95% CI 1.09–1.27; $p < 0.001$ vs. OR = 1.07; 95% CI 1.02–1.13; $p = 0.011$; respectively), suggesting a degree of incoherence between systemic haemodynamic and microcirculation. Indeed, increasing afterload with the use of vasopressors without assessing the cause of hypotension (e.g., hypovolaemia, cardiac dysfunction. . .) could impair tissue perfusion and therefore lead to organ dysfunction. Whether targeting PI during anaesthesia could improve patient's outcome remains to be assessed in randomised controlled trials.

4. Clinical usefulness in ICU and emergency department: what are the data?

The characteristics and main results of discussed studies are detailed in **Supplementary Table 1**.

4.1. Static and dynamic values of PI in ICU patients

The first study evaluating PI in ICU was published more than 15 years ago by Lima et al. [15]. It evaluated the evolution of PI in healthy volunteers and critically ill patients with poor peripheral perfusion (i.e., capillary refill time > 2 s or central-to-toe temperature difference ≥ 7 °C). In this study, the authors observed a significant exponential relationship between PI and core-to-toe temperature difference, and significant linear correlation between changes in PI and in core-to-toe temperature difference. Then, they compared haemodynamic variables between two periods; T1 during poor peripheral perfusion and T2 during normal peripheral perfusion in the 37 critically ill patients under vasoactive medication. They observed a concordant change between T1 and T2 in PI and core-to-toe temperature difference but not with cardiac output, mean arterial pressure or dose of vasoactive agents. In this study, a PI of 1.4 best discriminated between normal and abnormal core-to-toe temperature differences in the critically ill patients (area under the receiver operating characteristics curve 0.91; 95% CI 0.84–0.98, $p < 0.001$). In this study, the authors neither looked at the relationship between PI and capillary refill time, nor between PI and prognosis (e.g., mortality). This observation suggests that PI could reflect local microcirculation status.

4.2. PI and prognosis in ICU and emergency department

Several studies have shown the negative impact of persisting macrohaemodynamic and/or microcirculatory alterations in patients with acute circulatory failure [48–50]. The hypothesis that severe and/or persistent circulatory alterations in these patients, with higher sympathetic activation, would be reflected by PI values or variations is therefore highly expected. Thus, several studies have confirmed this hypothesis and the prognostic value of PI has been evaluated in critically ill patients in different clinical settings (i.e., septic patients, after cardiac arrest, in patients with hypoperfusion, in emergency department and in neonates).

In the ICU, in different populations (e.g., septic patients, mechanically ventilated patients. . .), PI values allow a discrimination between septic patients and non-septic patients and between survivors and non-survivors [51]. Furthermore, PI was strongly associated with ICU mortality [51,52]. In patients with hypoperfusion, after 8 h of resuscitation, PI allowed a better 30-days mortality prediction than central venous oxygen saturation (ScvO₂), lactate and arteriovenous carbon dioxide gradient (P(v-a) CO₂) [53]. Subgroup analysis suggested that PI (with a 0.6% cut-off) could enable to detect patients with the worst prognosis despite ScvO₂ normalisation selecting them for adjunctive therapies, notably targeting the microcirculation. This was confirmed in

a recent study, in which PI was significantly higher in survivors compared to non-survivors after 6 h of resuscitation, suggesting that the increase of PI value in the first hours of resuscitation is associated with a better outcome [54]. However, it is impossible to assess whether the difference observed in PI between survivors and non-survivors after initial resuscitation is secondary to an improvement of macrohaemodynamic (i.e., cardiac index) or microcirculation.

The potential prognostic value of peripheral PI after cardiac arrest has been confirmed in a prospective study [55]. In this study, PI was significantly also higher in survivors than in non-survivors at day 30 in the first 30 min after return to spontaneous circulation. Similar results were again described by the same authors, including a better survival with good neurologic outcome (cerebral performance categories ≤ 2) in patients who had higher PI [56]. However, the authors did not report the cardiac index or other variable such as microcirculation variables, making difficult to interpret the PI differences between survivors and non-survivors.

In a prospective study, performances of PI were evaluated for triage of patients admitted to the emergency department for the prediction of mortality at 15 and 30 days [57]. PI was neither predictive of hospital admission, nor associated with mortality in this study. However, this may be explained by a low severity rate and lack of power of PI in this population, compared with ICU patients.

In neonates, a low PI (≤ 1.4%) was found to be accurate for detection of illness severity in the 24 h after admission [58,59]. More recently, a prospective study gave more data concerning PI values in pre-term infants [60]. Thus, PI seems promising in neonates and infants to easily detect illness severity, and has already made the object of a dedicated review [61].

Although PI appears efficient to discriminate survivors from non-survivors and septic from non-septic patients in ICU, most studies are retrospective, with PI measurement at different time points and different cut-off values, therefore the clinical use of PI as a prognostic tool remains to be explored.

4.3. Dynamic changes of PI induced by heat

More recently, PI was used with a heating challenge to monitor microvascular reactivity in patients presenting a shock [62]. PI at earlobe was significantly higher in healthy volunteers compared to shocked patients. After heating challenge, all the non-septic patients (healthy volunteers, ICU-control patients and non-septic shocked patients, i.e., cardiogenic and haemorrhagic) had similar increase in PI value. PI increase was smaller in septic shock patients after heating challenge than in non-septic patients. In a small population, there was a non-significant trend in the evolution of PI and PImax/min after heating challenge in survivors compared to non-survivors. PI variations could enable physicians to discriminate septic from non-septic patients and identify patients with a poor prognosis.

In a prospective observational study including patients under therapeutic hypothermia after cardiac arrest, Van Genderen et al. studied peripheral tissue perfusion, notably using PI before and after rewarming [63]. At admission, PI was not significantly different between survivors and non-survivors. PI became significantly different between survivors and non-survivors after rewarming similarly to other microcirculation variable (i.e., perfused capillary density and proportion-perfused vessels) assessed using a side stream dark-field imager. Interestingly, cardiac index was not different between survivors and non-survivors after rewarming, suggesting that PI differences observed between survivors and non-survivors were rather secondary to microcirculation disorders than macrohaemodynamic disorders.

5. Fluid responsiveness

The characteristics and main results of discussed studies are detailed in **Supplementary Table 1**.

5.1. PI and prediction of fluid responsiveness or fluid removal in ICU

Beurton et al. assessed whether PI variation during a passive leg-raising (PLR) test could accurately predict fluid responsiveness in ICU patients, mostly under mechanical ventilation [32]. An increase of PI > 9% induced by PLR predicted an increase of cardiac index > 10% induced by PLR with a sensitivity of 91% (95% CI 76–98%), a specificity of 79% (95% CI 63–90%) and an area under the receiver operating characteristics curve of 0.89 (95% CI 0.8–0.95). These results were confirmed in another study, which also showed that PI variations during an end-expiratory occlusion test could help to predict positive PLR [33]. However, the cut-off value of relative PI increase during end-expiratory occlusion test was very low (2.5%), compared to the PI values displayed today in most monitors with most often only one decimal place, and with respect to spontaneous variations in PI. Other authors, using the same relationship between PI and SV, studied in mechanically ventilated patients during spontaneous breathing trial (using the ratio: PI before weaning trial/PI during weaning trial), to predict weaning failure [64]. They observed that the lack of increase in PI during spontaneous breathing trial was associated with trial failure. This suggests that when PI increases during spontaneous breathing trial, patients may be on the initial vertical part of the Franck-Starling curve, *i.e.*, fluid responders, and thus at lower risk of weaning-induced pulmonary oedema. Furthermore, PI and PI variations have been used to predict hypotension during fluid removal under renal replacement therapy [65]. A PI value $\leq 0.82\%$ predicted hypotension with an area under the receiver operating characteristics curve of 0.8 ± 0.11 and PI variation (*i.e.*, decrease) during fluid removal was also predictive of hypotension. As for neuraxial anaesthesia, a low PI may be a witness of high vascular tone and/or low SV, and thus predictive of hypotension due in part to hypovolaemia induced by fluid removal. However, this study included only 23 patients and should be confirmed in a larger cohort.

5.2. PI respiratory variations and prediction of fluid responsiveness

The variability of PI is low during steady-state conditions, under deep general anaesthesia, because general anaesthesia reduces the oscillatory components of the perfusion signal related to sympathetic, myogenic activity and the component modulated by the endothelium [66]. Therefore, in this situation PI variations are mainly due to stroke volume variations. PI respiratory variations, called PVI (Pleth Variability Index), have been widely studied in mechanically ventilated patients for the prediction of fluid responsiveness, notably in the operating theatre. The physiological concept is based on tracking PI variations as a surrogate of SV variations (or pulse pressure) induced by positive pressure ventilation. Then the respiratory variations of PI could have nearly the same accuracy to predict fluid responsiveness than pulse pressure variation [67,68].

A recent meta-analysis by Liu et al. highlighted the wide range of PVI cut-off value (from 7% to 20%), depending on the studied population and ventilation settings (*e.g.*, ICU, or, tidal volume, positive end expiratory pressure. . .) to predict fluid responsiveness [69]. Furthermore, PVI is also (as it is derived from PI) largely influenced by the measurement site and seems to be more accurate to predict fluid responsiveness when measured in the forehead, less influenced by vasomotor tone than finger and earlobe [70]. Although a previous study showed reduced volume of intraoperative fluid infused and lactate levels using a PVI-guided

fluid management, a recent randomised controlled trial using a haemodynamic perioperative management based on PVI value compared to a standard management did not shorten the duration of hospitalisation [71,72]. Therefore, further studies are needed to assess whether or not PVI value is useful in haemodynamic management in the OT.

PVI could also be an accurate tool to predict fluid responsiveness in children under mechanical ventilation in the operating theatre [73]. Nevertheless, results are conflicting among the studies performed in children and further studies are required to confirm the accuracy of PVI to predict fluid responsiveness in the paediatric population [73–75].

6. Perspectives

After a wide use of PPG for decades for oximetry only, we are experiencing renewed interest and increasing use of PI in anaesthesia, perioperative and critical care. However, some important issues remain to be answered (Fig. 3). The characteristics and main results of discussed studies are detailed in **Supplementary Table 1**.

6.1. Technical aspects

Firstly, technical aspects need to be assessed, as the value of PI between manufacturers has never been evaluated and could vary significantly. Algorithms and filters used by manufacturers to process the signal could be sources of distortion of PPG signal, and influence PI performances in various clinical settings. Furthermore, these differences between monitors could also have an impact on the absolute value of PI, and could lead to misinterpretations of this value. Therefore, the adequate cut-off value could be different between manufacturers. Studies assessing PI should always indicate which PPG device has been used.

6.2. Impact of PI use in haemodynamic management during anaesthesia

If data show that PI is useful for haemodynamic monitoring, it remains to be explored whether the use of PI for haemodynamic monitoring would improve the prognosis of patients undergoing surgery. To date, no well-designed studies have been conducted. An interesting study reported the use of an algorithm integrating PI and pulse pressure variation to guide fluid administration and the use of vasopressors (*i.e.*, in the case of a hypotension event, fluids should be administered if the PI value remained steady during the 15 min before the hypotension, on the contrary the increase of the PI value should lead to the use of vasopressors). The use of this algorithm was associated with lower duration of arterial hypotension (7.7 ± 5.0 min vs. 17.1 ± 10.6 min, $p = 0.003$) and lower intraoperative fluid administration (4.3 ± 1.3 mL/kg/h vs. 7.2 ± 3.3 mL/kg/h, $p = 0.003$) [76]. However, this study suffers from several limitations. Among others, there was no algorithm in the control group and the use of an algorithm itself may have favoured an early use of vasopressors rather than fluid challenge. We could assume that another algorithm using other variables without PI may have similar effects.

PI value before neuraxial anaesthesia predicts hypotension [44,45]. Similarly, variations of PI allow real-time detection of arterial hypotension during the induction of general anaesthesia [25]. In these specific situations (*i.e.*, neuraxial anaesthesia, peripheral nerve blockade, induction of anaesthesia, etc.), modifications of PI values are due predominantly to modifications of the vascular tone. Therefore, in such cases, PI variations are a reliable reflection of sympathetic tone fluctuations. Nevertheless, the impact of PI use in these fields remains to be explored. Indeed,

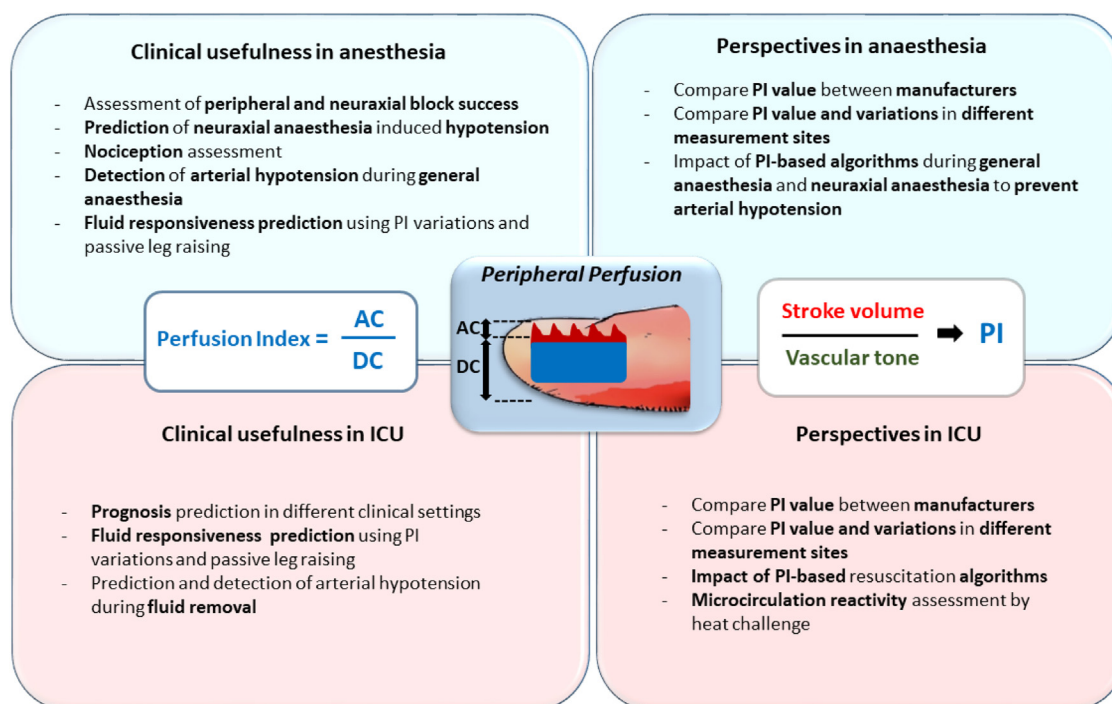


Fig. 3. Summary of clinical usefulness and perspectives of PI use in anaesthesia and critical care.

AC: alternating current; DC: direct current; IR: infrared light; PI: perfusion index; PPG: photoplethysmography; AC: alternating current; DC: direct current.

algorithms using PI for early use of vasopressor should be evaluated to prevent hypotension following neuraxial anaesthesia or induction of general anaesthesia.

6.3. Impact of PI use in haemodynamic management in ICU

In ICU, PI and its early variations are associated with prognosis. Haemodynamic situations can be complex especially in septic patients, and PI difficult to interpret [35]. In septic patients, PI can also reflect microcirculation disorders as suggested by the lower increase of PI after heating challenge [62]. However, in patients with preserved microcirculation in ICU, rapid PI variations analyses remain useful in situations in which, among PI determinants, one varies predominantly in regard to the others (e.g., PLR, fluid challenge, etc.). Comparing PI value in different measurement sites would possibly provide useful indications about local perfusion; indeed, some territories could remain poorly perfused despite normalisation of macrohaemodynamic status (i.e., MAP, cardiac index, ScvO₂). We recently described urethral PI monitoring through a modified urinary catheter [77]. Urethral PI monitoring featured a stable, reliable signal capable of measuring urethral tissue perfusion. However, in this study we neither compared urethral PI value with other measurement sites, nor specifically evaluated the effects of therapeutics (i.e., fluid challenge, vasopressors, and blood transfusion) on PI value. In a proof of concept study, comparing an early peripheral perfusion-guided fluid therapy (using capillary refill time, PI, skin temperature difference between forearm and fingertip and tissue oxygen saturation) vs. standard of care in patients with septic shock, Van Genderen et al. observed that perfusion-guided fluid therapy lead to a trend toward less fluid administration and less organ dysfunction at 72 h compared with a conventional regimen [78]. Recently, Hernandez et al., in a Bayesian reanalysis of the ANDROMEDA-SHOCK Trial, have confirmed this results, conclud-

ing that peripheral perfusion-targeted resuscitation (i.e., guided by capillary refill time) may result in lower 28-day mortality when compared with a lactate-targeted resuscitation strategy [79]. Resuscitation algorithms integrating PI for tissue perfusion assessment have also been proposed in ICU [80]. The impact on critically ill patients' outcomes of such algorithms including PI, in association with other resuscitation targets (i.e., cardiac index, mean arterial pressure, ScvO₂, capillary refill time) should be tested in large randomised controlled trials. However, in these complex situations (e.g., septic shock, haemorrhagic shock...), several determinants of PI may vary simultaneously and abruptly (i.e., increase in vascular tone due to vasopressors, increase in stroke volume due to fluid loading and/or inotropic drug introduction). This may contribute to abrupt and complex changes in PI. In these situations, PI variations are more difficult to interpret, and should probably be used as an early signal that should prompt reassessment of haemodynamic status, including stroke volume to accurately interpret PI variations.

7. Conclusion

PI is a PPG-derived variable, already given by most devices, measuring perfusion at crossroads between central and peripheral perfusion. It appears to be a useful, non-invasive additional tool for haemodynamic monitoring in anaesthesiology, perioperative and critical care for clinicians. Knowing its determinants is crucial to be able to interpret its variations. Whether the use of PI in resuscitation algorithms would improve patient outcomes remains to be explored.

Ethical statement

Reviews articles do not require ethical committee approval.

Disclosure of funding

None.

Conflicts of interest

A patent application (n° PCT IB2009/006903) is pending on variations of PcCO₂ and PI during Heating Challenge. The patent belongs to the Assistance Publique-Hôpitaux de Paris (France).

Etienne Gayat has received Consulting Fees from Magnisense, research support from Spingotex, Deltex Medical and Retia Medical.

Fabrice Vallée has received research support from Radiometer, Deltex Medical and Retia Medical.

François Dépret has received research grants from the French Ministry of Health, SFAR (Société française d'anesthésie et de réanimation), the ESICM (European Society of Intensive Care Medicine), and lecture fees Sedana medical.

Authors' contribution

Maxime Coutrot: this author drafted and approved the final version of the manuscript.

Emmanuel Dudoignon: this author drafted and approved the final version of the manuscript.

Jona Joachim: this author drafted and approved the final version of the manuscript.

Etienne Gayat: this author drafted and approved the final version of the manuscript.

Fabrice Vallée: this author drafted and approved the final version of the manuscript.

François Dépret: this author drafted and approved the final version of the manuscript.

All the authors have drafted and approved the final version of the manuscript.

Acknowledgement

The authors would sincerely thank Dr Colleen Breslin and Isabelle Taufflieb for their proofreading as well as their advice for writing this review.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.accpm.2021.100964>.

References

- [1] Aoyagi T. Pulse oximetry: its invention, theory, and future. *J Anesth* 2003;17:259–66. <http://dx.doi.org/10.1007/s00540-003-0192-6>.
- [2] Alian AA, Shelley KH. Photoplethysmography. *Best Pract Res Clin Anaesthesiol* 2014;28:395–406. <http://dx.doi.org/10.1016/j.bpa.2014.08.006>.
- [3] Reisman A, Shaltis PA, McCombie D, Asada HH. Utility of the photoplethysmogram in circulatory monitoring. *Anesthesiology* 2008;108:950–8. <http://dx.doi.org/10.1097/ALN.0b013e31816c89e1>.
- [4] Elgendi M. Optimal signal quality index for photoplethysmogram signals. *Bioengineering* 2016;3:21. <http://dx.doi.org/10.3390/bioengineering3040021>.
- [5] Korhonen I, Yli-Hankala A. Photoplethysmography and nociception. *Acta Anaesthesiol Scand* 2009;53:975–85. <http://dx.doi.org/10.1111/j.1399-6576.2009.02026.x>.
- [6] Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas* 2007;28:R1–39. <http://dx.doi.org/10.1088/0967-3334/28/3/R01>.
- [7] Murray WB, Foster PA. The peripheral pulse wave: information overlooked. *J Clin Monit* 1996;12:365–77.
- [8] Plethysmographic waveform shapes displayed by oximeters-Technical note 2008.
- [9] PHILIPS. IntelliVue Patient Monitor Philips FAST-SpO₂: Application Note n.d.
- [10] Nijboer JA, Dorlas JC, Mahieu HF. Photoelectric plethysmography—some fundamental aspects of the reflection and transmission method. *Clin Phys Physiol Meas* 1981;2:205–15.
- [11] Fine J, Branam KL, Rodriguez AJ, Boonya-ananta T, Ajmal, Ramella-Roman JC, et al. Sources of inaccuracy in photoplethysmography for continuous cardiovascular monitoring. *Biosensors* 2021;11:126. <http://dx.doi.org/10.3390/bios11040126>.
- [12] Goldman JM, Petterson MT, Kopotic RJ, Barker SJ. Masimo signal extraction pulse oximetry. *J Clin Monit Comput* 2000;16:475–83.
- [13] Oak Sang-Soo, Aroul Praveen. How to design peripheral oxygen saturation (SpO₂) and optical heart rate monitoring (OHRM) systems using the AFE4403; 2015.
- [14] Colquhoun DA, Forkin KT, Durieux ME, Thiele RH. Ability of the Masimo pulse CO-Oximeter to detect changes in hemoglobin. *J Clin Monit Comput* 2012;26:69–73. <http://dx.doi.org/10.1007/s10877-012-9335-3>.
- [15] Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med* 2002;30:1210–3.
- [16] Keller G, Cassar E, Desebbe O, Lehot J-J, Cannesson M. Ability of pleth variability index to detect hemodynamic changes induced by passive leg raising in spontaneously breathing volunteers. *Crit Care* 2008;12:R37. <http://dx.doi.org/10.1186/cc6822>.
- [17] Nitzan M, Faib I, Friedman H. Respiration-induced changes in tissue blood volume distal to occluded artery, measured by photoplethysmography. *J Biomed Opt* 2006;11040506. <http://dx.doi.org/10.1117/1.2236285>.
- [18] Shelley KH. Photoplethysmography: beyond the calculation of arterial oxygen saturation and heart rate. *Anesth Analg* 2007;105:S31–36. <http://dx.doi.org/10.1213/01.ane.0000269512.82836.c9>. tables of contents.
- [19] Jeong I, Jun S, Um D, Oh J, Yoon H. Non-invasive estimation of systolic blood pressure and diastolic blood pressure using photoplethysmograph components. *Yonsei Med J* 2010;51:345. <http://dx.doi.org/10.3349/yymj.2010.51.3.345>.
- [20] Galvin EM, Niehof S, Verbrugge SJ, Maissan I, Jahn A, Klein J, et al. Peripheral flow index is a reliable and early indicator of regional block success. *Anesth Analg* 2006;103:239–43. <http://dx.doi.org/10.1213/01.ane.0000220947.02689.9f>.
- [21] Ginosar Y, Weiniger CF, Meroz Y, Kurz V, Bdoalah-Abram T, Babchenko A, et al. Pulse oximeter perfusion index as an early indicator of sympathectomy after epidural anesthesia. *Acta Anaesthesiol Scand* 2009;53:1018–26. <http://dx.doi.org/10.1111/j.1399-6576.2009.01968.x>.
- [22] Kus A, Gurkan Y, Gormus SK, Solak M, Toker K. Usefulness of perfusion index to detect the effect of brachial plexus block. *J Clin Monit Comput* 2013;27:325–8. <http://dx.doi.org/10.1007/s10877-013-9439-4>.
- [23] Uemura A, Yagihara M, Miyabe M. Pulse oximeter perfusion index as a predictor for the effect of pediatric epidural block. *Anesthesiology* 2006;105A1354.
- [24] Sebastiani A, Philippi L, Boehme S, Closhen D, Schmidtmann I, Scherhag A, et al. Perfusion index and plethysmographic variability index in patients with interscalene nerve catheters. *Can J Anesth* 2012;59:1095–101. <http://dx.doi.org/10.1007/s12630-012-9796-3>.
- [25] Coutrot M, Joachim J, Dépret F, Millasseau S, Nougé H, Matéo J, et al. Noninvasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept. *Br J Anaesth* 2019;122:605–12. <http://dx.doi.org/10.1016/j.bja.2019.01.037>.
- [26] Corsini I, Cecchi A, Coviello C, Dani C. Perfusion index and left ventricular output correlation in healthy term infants. *Eur J Pediatr* 2017;176:1013–8. <http://dx.doi.org/10.1007/s00431-017-2920-1>.
- [27] Janaillac M, Beausoleil TP, Barrington KJ, Raboisson M-J, Karam O, Dehaes M, et al. Correlations between near-infrared spectroscopy, perfusion index, and cardiac outputs in extremely preterm infants in the first 72 h of life. *Eur J Pediatr* 2018;177:541–50. <http://dx.doi.org/10.1007/s00431-018-3096-z>.
- [28] Takahashi S, Kakiuchi S, Nanba Y, Tsukamoto K, Nakamura T, Ito Y. The perfusion index derived from a pulse oximeter for predicting low superior vena cava flow in very low birth weight infants. *J Perinatol* 2010;30:265–9.
- [29] van Genderen ME, Bartels SA, Lima A, Bezemer R, Ince C, Bakker J, et al. Peripheral perfusion index as an early predictor for central hypovolaemia in awake healthy volunteers. *Anesth Analg* 2013;116:351–6. <http://dx.doi.org/10.1213/ANE.0b013e318274e151>.
- [30] Tapar H, Karaman S, Dogru S, Karaman T, Sahin A, Tapar GG, et al. The effect of patient positions on perfusion index. *BMC Anesthesiol* 2018;18:111. <http://dx.doi.org/10.1186/s12871-018-0571-z>.
- [31] Højlund J, Agerskov M, Clemmesen CG, Hvolris LE, Foss NB. The peripheral perfusion index tracks systemic haemodynamics during general anaesthesia. *J Clin Monit Comput* 2019. <http://dx.doi.org/10.1007/s10877-019-00420-x>.
- [32] Beurton A, Teboul J-L, Gavelli F, Gonzalez FA, Giroto V, Galarza L, et al. The effects of passive leg raising may be detected by the plethysmographic oxygen saturation signal in critically ill patients. *Crit Care* 2019;23:19. <http://dx.doi.org/10.1186/s13054-019-2306-z>.
- [33] Beurton A, Gavelli F, Teboul J-L, De Vita N, Monnet X. Changes in the plethysmographic perfusion index during an end-expiratory occlusion detect a positive passive leg raising test*. *Crit Care Med* 2021;49:e151–60. <http://dx.doi.org/10.1097/CCM.0000000000004768>.
- [34] Lian H, Wang X, Zhang Q, Zhang H, Liu D. Changes in perfusion can detect changes in the cardiac index in patients with septic shock. *J Int Med Res* 2020;4803006052093167. <http://dx.doi.org/10.1177/0300060520931675>.
- [35] He H-W, Liu W-L, Zhou X, Long Y, Liu D-W. Effect of mean arterial pressure change by norepinephrine on peripheral perfusion index in septic shock patients after early resuscitation. *Chin Med J (Engl)* 2020;133:2146–52. <http://dx.doi.org/10.1097/CM9.0000000000001017>.

- [36] Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J Appl Physiol* 2010;109:1221–8. <http://dx.doi.org/10.1152/japplphysiol.00298.2010>.
- [37] Hodges GJ, Johnson JM. Adrenergic control of the human cutaneous circulation. *Appl Physiol Nutr Metab* 2009;34:829–39. <http://dx.doi.org/10.1139/H09-076>.
- [38] Awad AA, Ghobashy MA, Ouda W, Stout RG, Silverman DG, Shelley KH. Different responses of ear and finger pulse oximeter wave form to cold pressor test. *Anesth Analg* 2001;92:1483–6. <http://dx.doi.org/10.1097/0000539-200106000-00026>.
- [39] Shelley KH, Tamai D, Jablonka D, Gesquiere M, Stout RG, Silverman DG. The effect of venous pulsation on the forehead pulse oximeter wave form as a possible source of error in SpO₂ calculation. *Anesth Analg* 2005;100:743–7. <http://dx.doi.org/10.1213/01.ANE.0000145063.01043.4B>.
- [40] Kakazu CZ, Chen B-J, Kwan W-F. Masimo set technology using perfusion index is a sensitive indicator for epidural onset. *Anesthesiology* 2005;103:A576.
- [41] Xu Z, Zhang J, Xia Y, Deng X. Accuracy of pulse oximeter perfusion index in thoracic epidural anesthesia under basal general anesthesia. *Int J Clin Exp Med* 2014;7:1728.
- [42] Abdelhamid B, Emam M, Mostafa M, Hasanin A, Awada W, Rady A, et al. The ability of perfusion index to detect segmental ulnar nerve sparing after supraclavicular nerve block. *J Clin Monit Comput* 2019. <http://dx.doi.org/10.1007/s10877-019-00443-4>.
- [43] Kim D, Jeong JS, Park MJ, Ko JS. The effect of epinephrine on the perfusion index during ultrasound-guided supraclavicular brachial plexus block: a randomized controlled trial. *Sci Rep* 2020;10:11585. <http://dx.doi.org/10.1038/s41598-020-68475-4>.
- [44] Toyama S, Kakumoto M, Morioka M, Matsuoka K, Omatsu H, Tagaito Y, et al. Perfusion index derived from a pulse oximeter can predict the incidence of hypotension during spinal anaesthesia for Caesarean delivery. *Br J Anaesth* 2013;111:235–41. <http://dx.doi.org/10.1093/bja/aet058>.
- [45] Duggappa D, Lokesh M, Dixit A, Paul R, Raghavendra Rao R, et al. Perfusion index as a predictor of hypotension following spinal anaesthesia in lower segment caesarean section. *Indian J Anaesth* 2017;61:649. http://dx.doi.org/10.4103/ijaa.429_16.
- [46] Hager H, Church S, Mandadi G, Pulley D. The perfusion index as measured by a pulse oximeter indicates pain stimuli in anesthetized volunteers. *Anesthesiology* 2004;101:A514.
- [47] Agerkov M, Thusholdt ANW, Holm-Sørensen H, Wiberg S, Meyhoff CS, Højlund J, et al. Association of the intraoperative peripheral perfusion index with postoperative morbidity and mortality in acute surgical patients: a retrospective observational multicenter cohort study. *Br J Anaesth* 2021;S0007091221003561. <http://dx.doi.org/10.1016/j.bja.2021.06.004>.
- [48] Sakr Y, Dubois M-J, De Backer D, Creteur J, Vincent J-L. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004;32:1825–31.
- [49] Top APC, Ince C, de Meij N, van Dijk M, et al. Persistent low microcirculatory vessel density in nonsurvivors of sepsis in pediatric intensive care*. *Crit Care Med* 2011;39:8–13. <http://dx.doi.org/10.1097/CCM.0b013e3181fb7994>.
- [50] Ait-Oufella H, Lemoine S, Boelle PY, Galbois A, Baudel JL, Lemant J, et al. Motling score predicts survival in septic shock. *Intensive Care Med* 2011;37:801–7. <http://dx.doi.org/10.1007/s00134-011-2163-y>.
- [51] He H, Liu D, Long Y, Wang X. The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation. *Crit Care* 2013;17:R116. <http://dx.doi.org/10.1186/cc12788>.
- [52] Su L, Zhang R, Zhang Q, Xu Q, Zhou X, Cui N, et al. The effect of mechanical ventilation on peripheral perfusion index and its association with the prognosis of critically ill patients. *Crit Care Med* 2019;47:685–90. <http://dx.doi.org/10.1097/CCM.0000000000003661>.
- [53] He H, Long Y, Liu D, Wang X, Zhou X. Clinical classification of tissue perfusion based on the central venous oxygen saturation and the peripheral perfusion index. *Crit Care* 2015;19:330. <http://dx.doi.org/10.1186/s13054-015-1057-8>.
- [54] Mongkolpun W, Orbegozo D, Cordeiro CPR, Franco CJS, Vincent J-L, Creteur J. Alterations in skin blood flow at the fingertip are related to mortality in patients with circulatory shock. *Crit Care Med* 2020;48:443–50. <http://dx.doi.org/10.1097/CCM.0000000000004177>.
- [55] Savastano S, Baldi E, Molinari S, Canevari F, Corazza V, Cacciatore E, et al. Post-ROSC pulse-oximetry derived perfusion index and thirty days survival after out-of-hospital cardiac arrest. New insights from the Pavia CARE (Pavia Cardiac Arrest Registry). *Resuscitation* 2017;117:e19–20. <http://dx.doi.org/10.1016/j.resuscitation.2017.05.027>.
- [56] Savastano S, Baldi E, Contri E, De Pirro A, Sciufti F, Compagnoni S, et al. Post-ROSC peripheral perfusion index discriminates 30-day survival after out-of-hospital cardiac arrest. *Intern Emerg Med* 2020. <http://dx.doi.org/10.1007/s11739-020-02430-z>.
- [57] Oskay A, Eray O, Dinç SE, Aydın AG, Eken C. Prognosis of critically ill patients in the ED and value of perfusion index measurement: a cross-sectional study. *Am J Emerg Med* 2015;33:1042–4. <http://dx.doi.org/10.1016/j.ajem.2015.04.033>.
- [58] De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. *Eur J Pediatr* 2002;161:561–2. <http://dx.doi.org/10.1007/s00431-002-1042-5>.
- [59] Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. *Pediatrics* 1993;91:617–23.
- [60] Alderliesten T, Lemmers PMA, Baerts W, Groenendaal F, van Bel F. Perfusion index in preterm infants during the first 3 days of life: reference values and relation with clinical variables. *Neonatology* 2015;107:258–65. <http://dx.doi.org/10.1159/000370192>.
- [61] Piasek CZ, Van Bel F, Sola A. Perfusion index in newborn infants: a noninvasive tool for neonatal monitoring. *Acta Paediatr* 2014;103:468–73. <http://dx.doi.org/10.1111/apa.12574>.
- [62] Vallée F, Nougé H, Mari A, Vodovar N, Dubreuil G, Damoiseau C, et al. Variations of cutaneous capnometry and perfusion index during a heating challenge is early impaired in septic shock and related to prognostic in non-septic shock. *SHOCK* 2019;51:585–92. <http://dx.doi.org/10.1097/SHK.0000000000001216>.
- [63] van Genderen ME, Lima A, Akkerhuis M, Bakker J, et al. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival*. *Crit Care Med* 2012;40:2287–94. <http://dx.doi.org/10.1097/CCM.0b013e31825333b2>.
- [64] Lotfy A, Hasanin A, Rashad M, Mostafa M, Saad D, Mahmoud M, et al. Peripheral perfusion index as a predictor of failed weaning from mechanical ventilation. *J Clin Monit Comput* 2020. <http://dx.doi.org/10.1007/s10877-020-00483-1>.
- [65] Klijn E, Groeneveld ABJ, van Genderen ME, Betjes M, Bakker J, et al. Peripheral perfusion index predicts hypotension during fluid withdrawal by continuous veno-venous hemofiltration in critically ill patients. *Blood Purif* 2015;40:92–8. <http://dx.doi.org/10.1159/000381939>.
- [66] Landsverk SA, Kvandal P, Bernjak A, Stefanovska A, Kirkeboen KA. The effects of general anesthesia on human skin microcirculation evaluated by wavelet transform. *Anesth Analg* 2007;105:1012–9. <http://dx.doi.org/10.1213/01.ane.0000281932.09660.96>.
- [67] Chu H, Wang Y, Sun Y, Wang G. Accuracy of pleth variability index to predict fluid responsiveness in mechanically ventilated patients: a systematic review and meta-analysis. *J Clin Monit Comput* 2016;30:265–74. <http://dx.doi.org/10.1007/s10877-015-9742-3>.
- [68] Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care* 2014;18:650. <http://dx.doi.org/10.1186/s13054-014-0650-6>.
- [69] Liu T, Xu C, Wang M, Niu Z, Qi D. Reliability of pleth variability index in predicting preload responsiveness of mechanically ventilated patients under various conditions: a systematic review and meta-analysis. *BMC Anesthesiol* 2019;19:67. <http://dx.doi.org/10.1186/s12871-019-0744-4>.
- [70] Desgranges F-P, Desebbe O, Ghazouani A, Gilbert K, Keller G, Chiari P, et al. Influence of the site of measurement on the ability of plethysmographic variability index to predict fluid responsiveness. *Br J Anaesth* 2011;107:329–35. <http://dx.doi.org/10.1093/bja/aer165>.
- [71] Fischer M-O, Lemoine S, Tavernier B, Bouchakour C-E, Colas V, Houard M, et al. Individualized fluid management using the pleth variability index: a randomized clinical trial. *Anesthesiology* 2020;133:31–40. <http://dx.doi.org/10.1097/ALN.0000000000003260>.
- [72] Forget P, Lois F, de Kock M. Goal-directed fluid management based on the pulse oximeter-derived pleth variability index reduces lactate levels and improves fluid management. *Anesth Analg* 2010;1. <http://dx.doi.org/10.1213/ANE.0b013e3181eb624f>.
- [73] Desgranges F-P, Evain J-N, Pereira de Souza Neto E, Raphael D, Desebbe O, et al. Does the plethysmographic variability index predict fluid responsiveness in mechanically ventilated children? A meta-analysis. *Br J Anaesth* 2016;117:409–10. <http://dx.doi.org/10.1093/bja/aew245>.
- [74] Pereira de Souza Neto E, Grousson S, Duflo F, Ducreux C, Joly H, Convert J, et al. Predicting fluid responsiveness in mechanically ventilated children under general anaesthesia using dynamic parameters and transthoracic echocardiography. *Br J Anaesth* 2011;106:856–64. <http://dx.doi.org/10.1093/bja/aer090>.
- [75] Chen P, Chan K, Liao M, Wu C. Accuracy of dynamic preload variables for predicting fluid responsiveness in patients with pediatric liver cirrhosis: a prospective study. *Pediatr Anaesth* 2020;30:455–61. <http://dx.doi.org/10.1111/pan.13819>.
- [76] Godai K, Matsunaga A, Kanmura Y. The effects of hemodynamic management using the trend of the perfusion index and pulse pressure variation on tissue perfusion: a randomized pilot study. *JA Clin Rep* 2019;5:72. <http://dx.doi.org/10.1186/s40981-019-0291-5>.
- [77] Dépret F, Leone M, Duclos G, Futier E, Montagne M, Legrand M, et al. Monitoring tissue perfusion: a pilot clinical feasibility and safety study of a urethral photoplethysmography-derived perfusion device in high-risk patients. *J Clin Monit Comput* 2019. <http://dx.doi.org/10.1007/s10877-019-00414-9>.
- [78] van Genderen ME, Engels N, van der Valk RJP, Lima A, Klijn E, Bakker J, et al. Early peripheral perfusion-guided fluid therapy in patients with septic shock. *Am J Respir Crit Care Med* 2015;191:477–80. <http://dx.doi.org/10.1164/rccm.201408-1575LE>.
- [79] Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock: a Bayesian reanalysis of the ANDROMEDA-SHOCK trial. *Am J Respir Crit Care Med* 2020;201:423–9. <http://dx.doi.org/10.1164/rccm.201905-0968OC>.
- [80] Hariri G, Joffe J, Leblanc G, Bonsey M, Lavillegrand J-R, Urbina T, et al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. *Ann Intensive Care* 2019;9:37. <http://dx.doi.org/10.1186/s13613-019-0511-1>.

Annexe 1.2 Article “Noninvasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept”

Cet article a été publié dans le British Journal of Anaesthesia le 11 mars 2019 [2]. Les auteurs sont: Maxime Coutrot, Jona Joachim, François Depret, Sandrine Millasseau, Helene Nougue, Joaquim Mateo, Alexandre Mebazaa, Etienne Gayat et Fabrice Vallee.

Noninvasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept

Maxime Coutrot^{1,2,3,*}, Jona Joachim^{1,2}, François Dépret^{1,2,3},
Sandrine Millasseau⁴, Hélène Nougé^{1,2}, Joaquim Matéo^{1,3},
Alexandre Mebazaa^{1,2,3}, Etienne Gayat^{1,2,3} and Fabrice Vallée^{1,2,3,5}

¹Department of Anaesthesiology and Critical Care, Lariboisière Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France, ²UMR-S942, Lariboisière Hospital, Paris, France, ³University of Paris Diderot, Paris, France, ⁴Pulse Wave Consulting, Saint-Leu-la-Forêt, France and ⁵MEDISIM, Inria Paris-Saclay, Palaiseau, France

*Corresponding author. E-mail: maxime.coutrot@aphp.fr

Abstract

Background: During general anaesthesia, intraoperative hypotension (IOH), defined as a mean arterial pressure (MAP) reduction of > 20%, is frequent and may lead to complications. Pulse oximetry is mandatory in the operating room, making the photoplethysmographic signal and parameters, such as relative dicrotic notch height (Dic_{pleth}) or perfusion index (PI), readily available. The purpose of this study was to investigate whether relative variations of Dic_{pleth} and PI could detect IOH during anaesthesia induction, and to follow their variations during vasopressor boluses.

Methods: MAP, Dic_{pleth} , and PI were monitored at 1-min intervals during target control induction of anaesthesia with propofol and remifentanyl in 61 subjects. Vasopressor infusion (norepinephrine or phenylephrine) was performed when hypotension occurred according to the decision of the physician.

Results: The delta in Dic_{pleth} and PI accurately detected IOH, with areas under the receiver operating characteristic curves (AUC) of 0.86 and 0.83, respectively. The optimal thresholds were –19% (sensitivity 79%; specificity 84%) and 51% (sensitivity 82%; specificity 74%) for ΔDic_{pleth} and ΔPI , respectively. There was no difference between the ROC of ΔDic_{pleth} and ΔPI ($P=0.22$). Combining both ΔDic_{pleth} and ΔPI further improved the hypotension detection power (AUC=0.91) with a sensitivity and specificity of 84%. MAP variations were correlated with ΔDic_{pleth} and ΔPI during vasopressor infusion ($r=0.73$ and -0.62 , respectively; $P<0.001$).

Conclusions: The relative variation in Dic_{pleth} and PI derived from the photoplethysmographic signal can be used as a non invasive, continuous, and simple tool to detect intraoperative hypotension, and to track the vascular response to vasoconstrictor drugs during induction of general anaesthesia.

Clinical trial registration: NCT03756935.

Keywords: arterial hypotension; general anaesthesia; haemodynamics; intraoperative monitoring; perfusion index; photoplethysmography; pulse oximetry

Editorial decision: 19 January 2019; Accepted: 19 January 2019

© 2019 British Journal of Anaesthesia. Published by Elsevier Ltd. All rights reserved.

For Permissions, please email: permissions@elsevier.com

Editor's key points

- Photoplethysmography can be used to assess the dicrotic notch height and perfusion index during anaesthesia.
- This study sought to investigate whether relative variations in the photoplethysmographic dicrotic notch height and perfusion index are predictive for intraoperative hypotension during anaesthesia induction.
- A combination of the relative variations in dicrotic notch height and perfusion index showed a high predictive power for intraoperative hypotension.
- It is feasible to use photoplethysmography as an additional haemodynamic detection method in patients at risk of intraoperative hypotension during anaesthesia induction.

Haemodynamic stability is a major issue in the management of patients during general anaesthesia. Anaesthetic drugs may induce a rapid and deep systemic arterial blood pressure (ABP) reduction, which leads to intraoperative hypotension (IOH) episodes. IOH can contribute to complications, such as myocardial infarction, cerebral hypoperfusion, or acute kidney injury.^{1–4} These adverse events may induce higher post-surgery mortality risk, result in extended hospital stay, and are thus a source of higher hospital costs.^{5–7}

Standard haemodynamic monitoring in the operating room includes electrocardiography, assessment of the arterial oxygenation saturation by pulse oximetry, and noninvasive blood pressure measurements from an oscillometric blood pressure cuff. The major drawback of the oscillometric cuff is that it measures blood pressure at intermittent intervals only. As the blood pressure may vary quickly, especially during induction of anaesthesia, IOH should be detected in real time, as even a short hypotensive period may have deleterious consequences on vital organs.^{8,9}

Digital photoplethysmography is a noninvasive signal produced by light absorption variations caused by pulsatile blood volume variations. Similarities in the photoplethysmographic and invasive blood pressure waveforms have been described since the 1940s.^{10,11} Indices derived from photoplethysmographic signals have been used successfully to characterise the cardiovascular status in patients. Dic_{pleth} , representing the relative height of the dicrotic wave compared with the maximum peak of the waveform (Fig. 1a), has been described as the amount of reflected wave, dependent on the vascular tone. Reduction in Dic_{pleth} has been shown to be related to the reduction of vascular tone caused by vasodilator drugs, such as salbutamol or glyceryl trinitrate.¹²

Perfusion index (PI) represents the ratio of the pulsatile light absorption (i.e. the amount of blood ejected at each systole) on the continuous absorption (corresponding to the non-pulsatile vessels, bones, and soft tissues) (Fig. 1a). The PI has been described as a reliable tool for vascular tone assessment and monitoring.^{13,14} As Dic_{pleth} and PI are both related to vascular tone and are easily derived from the photoplethysmographic signal, we aimed to explore whether the combined analysis of Dic_{pleth} and PI variations would allow for an early detection of IOH during the induction of general anaesthesia.

Methods

Subjects

We conducted a single-centre, prospective, and observational study in the neuroradiology unit of the Department of Anaesthesiology and Intensive Care of Lariboisière University Hospital (Paris, France). The study has been approved by the local ethics committee (n°CE SRLF 11–356). The inclusion criteria were patients with age >18 yr old undergoing elective neuroradiological procedures. All patients were included after an oral informed consent was obtained. The exclusion criteria from the study were cardiac arrhythmia (i.e. auricular fibrillation) and pregnancy. The study was registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03756935).

Anaesthesia protocol

Before induction of anaesthesia, standard monitoring was initiated with electrocardiography, noninvasive brachial ABP measurements (Philips France, Suresnes, France) set to inflate every minute, and digital pulse oximetry (Philips France) placed on the second finger of the contralateral side to the blood pressure cuff. Bispectral index (BIS; BIS™ Quatro Sensor; Medtronic France, Boulogne-Billancourt, France) and neuromuscular block monitoring (TOF-Watch®; Alsevia Pharma, Paris, France) were also used to monitor anaesthesia. All monitoring parameters were available on a Philips IntelliVue MP60 monitor (Philips France).

Induction of anaesthesia was conducted according to our local standard of care with target-controlled anaesthesia using remifentanyl and propofol with a starting dose of 5 ng ml⁻¹ and 5 µg ml⁻¹, and adjusted to reach a BIS between 40 and 60. After the BIS decreased below 60 and loss of consciousness was observed, neuromuscular block was conducted by i.v. injection of atracurium 0.5 mg kg⁻¹. Patients were then mechanically ventilated with tracheal intubation via direct laryngoscopy (end-tidal volume=6 ml kg⁻¹ of ideal body weight, PEEP=5 cm H₂O, and ventilatory frequency and oxygen fraction to reach an end-tidal CO₂=4.7 kPa and an O₂ saturation >95%).

In agreement with our local protocol for neuroradiological patients, arterial pressure was measured every minute during induction and every 5 min after tracheal intubation and stabilisation. The anaesthetist in charge of the patient could, at any time, modify the frequency of the measurements, and treat hypotensive episodes with fluid load or vasopressor administration (phenylephrine or norepinephrine). After induction, some patients were subjected to invasive and continuous blood pressure monitoring, following our standard department management guidelines or by decision of the anaesthetist in charge of the patient.

Data collection

All monitoring parameters and curves displayed on the monitor were recorded on a computer with ixTrend® software (ixellence, Wildau, Germany). The haemodynamic parameters (heart rate, systolic arterial pressure, MAP, and diastolic arterial pressure), and photoplethysmographic parameters (Dic_{pleth} , PI, and SpO₂) were then retrospectively sampled every minute during induction. The induction period was arbitrarily defined from preoxygenation to 3 min after connection to mechanical ventilation. 'Baseline' values were obtained by averaging the two measures (1 min apart) before the anaesthetic drug injection during the preoxygenation period.

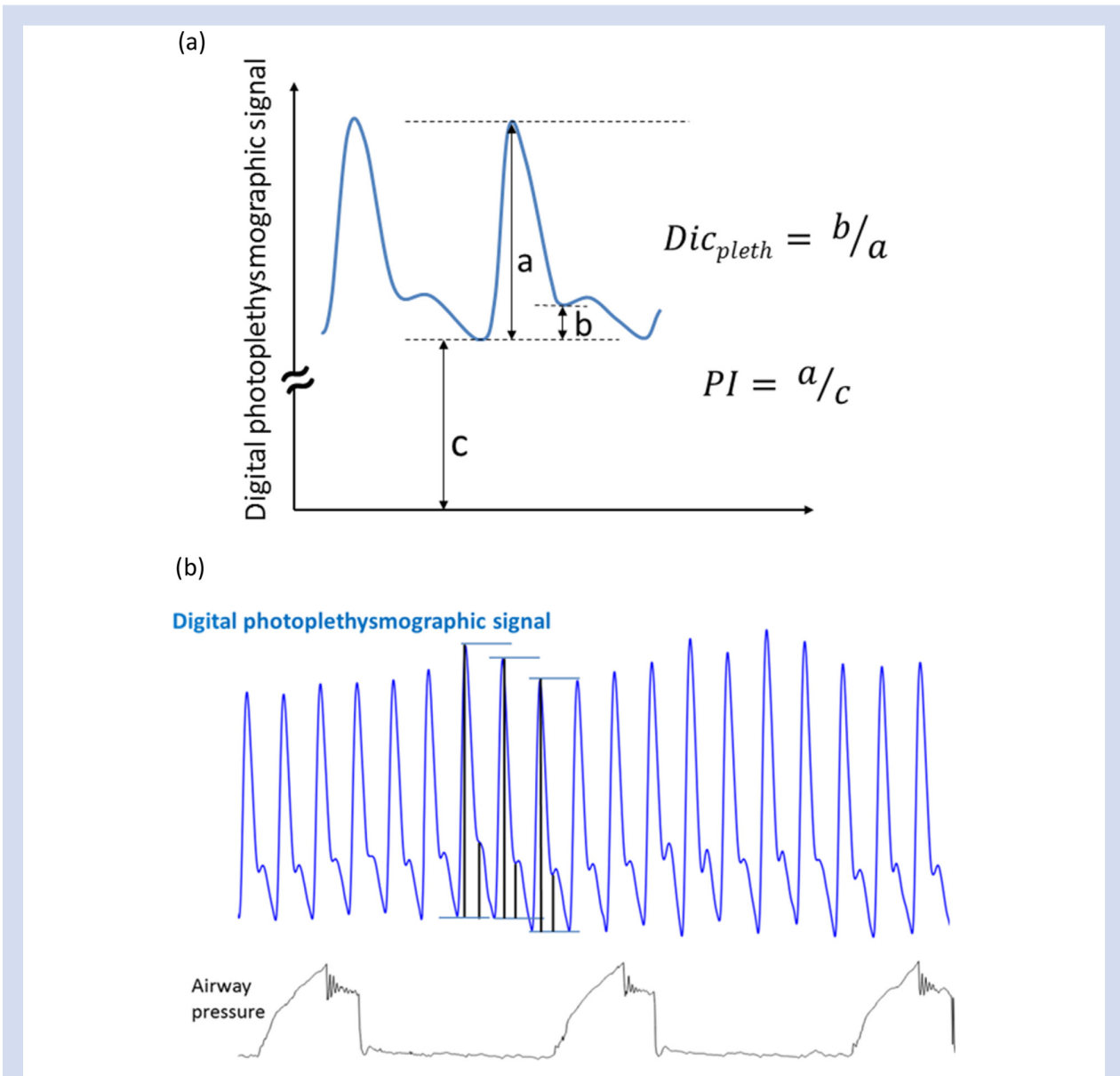


Fig 1. (a) Definition of DiC_{pleth} and PI , and (b) an example of DiC_{pleth} measurement on a real-life photoplethysmographic curve. DiC_{pleth} , relative dicrotic notch height on the digital photoplethysmographic signal (calculated as b/a ratio, by averaging the values of three consecutive complexes, at end-expiratory time); PI , perfusion index (given by the manufacturer, representing the a/c ratio). a , amplitude of the pulsatile component of the digital photoplethysmographic signal; it can also be described as the height of the systolic peak; b , height of the dicrotic notch; and c , amplitude of the steady-state component of the digital photoplethysmographic signal.

We defined 'pre-pressor' values as the measures before the vasopressor bolus during intraoperative episodes. 'Peak-pressor' values were defined as the maximum effects of vasopressor bolus, when the highest MAP was reached. In agreement with most studies, IOH was defined as a MAP reduction of more than 20% from baseline MAP.¹⁵

DiC_{pleth} and PI measurements

DiC_{pleth} was obtained from the recorded photoplethysmographic waveforms by an operator who was blinded from ABP

values. DiC_{pleth} was defined as the ratio of the height of the dicrotic notch (from nadir point of the complex to the notch) to the height of the systolic peak (from the same nadir point of the complex to the peak), measured at end-expiratory time in patients under mechanical ventilation (average of three consecutive complexes) (Fig. 1b). The PI was provided by the manufacturer and is calculated as the ratio of the pulsatile component of the photoplethysmographic signal and the continuous component.

We calculated the ΔMAP , ΔDiC_{pleth} , and ΔPI during the induction period as their relative variations (in percent) from

their baseline values. During vasopressor boluses, respective parameter variations were calculated between pre-pressor and peak-pressor measurements.

Dic_{radial} measurements

In patients with invasive monitoring during maintenance of anaesthesia, Dic_{radial} was also measured from the arterial pressure signal using the same methodology as Dic_{pleth}. The last three heartbeats of the end-expiratory period were used to calculate Dic_{radial}, from the height of the dicrotic notch to the height of the systolic peak. In those patients, Dic_{pleth}, Dic_{radial}, and their relative variations (Δ Dic_{pleth} and Δ Dic_{radial}) during vasoconstrictor administration were also analysed.

Statistical analysis

Values were expressed as median and inter-quartile range (25th; 75th percentiles). Changes of the parameters were analysed using Wilcoxon rank test. Concordance percentages between delta Δ MAP, and Δ Dic_{pleth} and Δ PI were calculated during the induction period. Areas under the curve (AUC) of the receiver operating characteristic (ROC) curve (with 95% confidence interval [CI]) of Δ Dic_{pleth} and Δ PI to detect a hypotensive episode were estimated and eventually compared using DeLong test. Youden method was used to determine the optimal Δ Dic_{pleth} and Δ PI cut-off values to detect hypotensive episodes. The ROC curve of the combination of Δ Dic_{pleth} and Δ PI was built using a logistic model. Correlation tests were performed using Spearman test. $P < 0.05$ was considered as statistically significant.

The primary aim of the study was to estimate the AUC of the ROC curve of both Δ Dic_{pleth} and Δ PI to track hypotension during induction. The sample size was determined with an expected AUC at 0.85, an expected incidence of hypotension of 80%, and the width of the CI of 1. With a power of 80%, the number of patients to include was then 62.¹⁶ The secondary objective was to evaluate the AUC of the ROC curve for the combination of Δ Dic_{pleth} and Δ PI.

A statistical analysis was performed using Prism 6.00[®] (GraphPad Software, Inc., La Jolla, CA, USA) and R 3.3.0 software (R Foundation for Statistical Computing, Vienna, Austria). Patients who had non-measurable Dic_{pleth} at baseline before induction of anaesthesia were excluded from the analysis.

Results

Subjects

From November 2014 to May 2015, 65 patients were included in the study. Before induction of anaesthesia, Dic_{pleth} was not measurable in four patients (6.2%) because of the absence of detectable dicrotic notch on the photoplethysmographic signal (Class IV waveform according to Dawber and colleagues).¹⁷

The characteristics of the 61 remaining subjects are listed in Table 1. Most subjects were ASA 2, with a mean age of 54 (39; 64) yr. Arterial hypertension, smoking, and dyslipidaemia were the most common co-morbidity encountered. The reason for neuroradiology procedures was mainly aneurysm or arteriovenous malformation scheduled embolisation.

Evolution of MAP, Dic_{pleth}, and PI during induction

The median duration of anaesthetic induction was 11 (10; 13.5) min. Overall, we recorded 720 haemodynamic data points: 61 at baseline values and 659 after anaesthetic injection, hence representing 659 variations from baseline. The MAP baseline value was 86 (79; 93) mm Hg giving an individual limit of IOH at 69 (62; 74) mm Hg. MAP decreased to 54 (48; 60) mm Hg before laryngoscopy, and rose to 72 (64; 82) mm Hg after tracheal intubation. The mean MAP on the overall induction period was 70 (64; 71) mm Hg.

Fifty-four subjects (88%) suffered from at least one hypotensive episode during anaesthesia induction, representing 323 measurements (49% of haemodynamic points). Twenty-eight subjects (46%) received one bolus of vasopressor during induction (2 phenylephrine and 26 norepinephrine). Dic_{pleth} was at 0.54 (0.45; 0.65) at baseline, decreased to 0.36 (0.19; 0.45) ($P < 0.001$), and increased to 0.46 (0.41; 0.56) after tracheal intubation. PI baseline values were 1.7 (0.9; 3) and increased to 4.4 (2.8; 6.6) ($P < 0.001$) before laryngoscopy, and then decreased to 3.6 (2.1; 5.4) after tracheal intubation. A visual representation of Δ MAP, Δ Dic_{pleth}, and Δ PI over induction time is described in Fig. 2. We found 89% concordance between

Table 1 Subjects characteristics. Data are expressed as mean (25–75) inter-quartile or number and percentage. DAP, diastolic arterial pressure; Dic_{pleth}, relative dicrotic notch height; MAP, mean arterial pressure; PI, perfusion index; SAP, systolic arterial pressure; STEMI, ST-elevation myocardial infarction

Parameter	
Subjects (n)	61
Male, n (%)	22 (36)
Age (yr)	54 (39–64)
BMI (kg m ⁻²)	25 (21–28)
ASA physical status, n (%)	
1	15 (25)
2	44 (72)
3	2 (3)
4	0 (0)
Co-morbidities, n (%)	
Arterial hypertension	20 (33)
Smoking	23 (38)
Dyslipidaemia	6 (10)
Diabetes mellitus	2 (3)
STEMI	0 (0)
Heart failure	0 (0)
Intracranial hypertension	2 (3)
Treatments, n (%)	
Beta-blockers	11 (18)
Renin blockers of renin–angiotensin system	10 (16)
Calcium blockers	5 (8)
Procedures	
Aneurism embolisation	47 (77)
Arteriovenous malformation embolisation	12 (20)
Other	2 (3)
Baseline haemodynamic parameters	
SAP (mm Hg)	127 (116–137)
DAP (mm Hg)	73 (66–80)
MAP (mm Hg)	86 (79–93)
HR (beats min ⁻¹)	67 (61–78)
Dic _{pleth}	0.54 (0.45–0.65)
PI	1.7 (0.9–3.0)

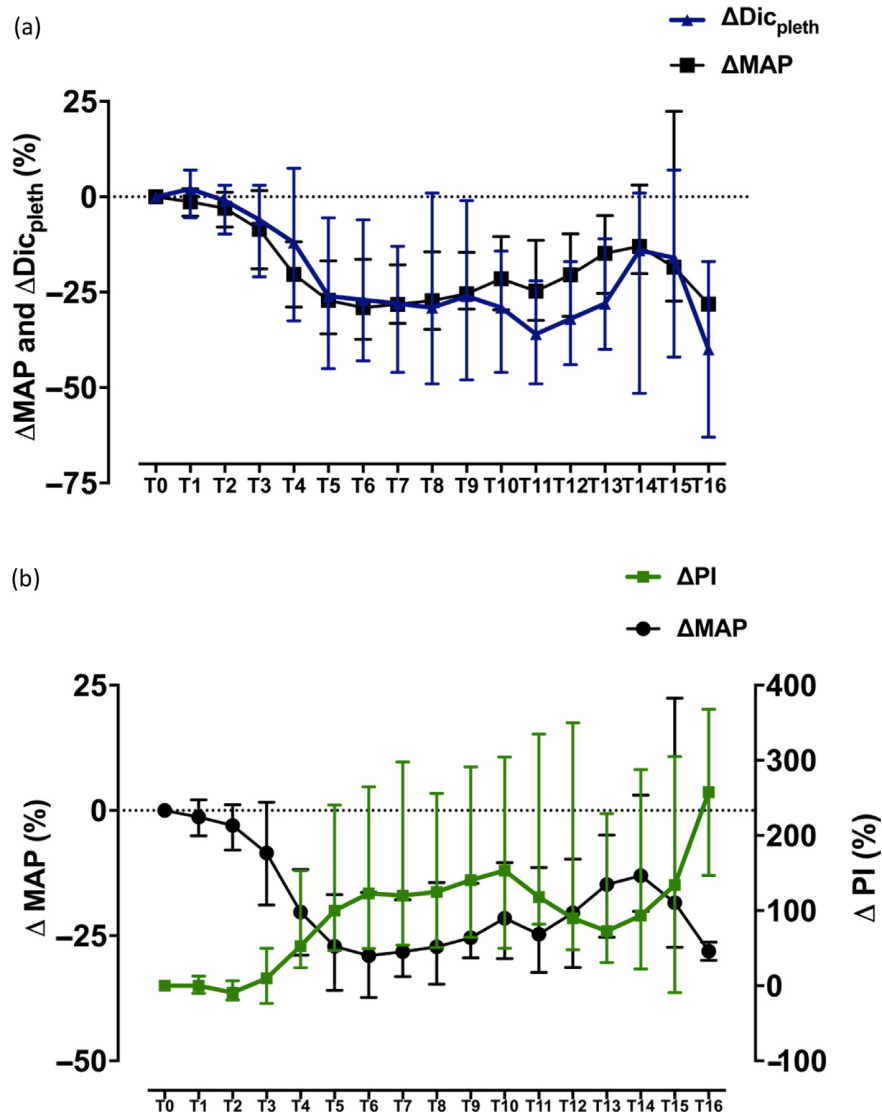


Fig 2. (a) Median Δ MAP and Δ Dic_{pleth}, and (b) median Δ MAP and Δ PI during induction of anaesthesia. Δ Dic_{pleth}, relative variation of Dic_{pleth} from baseline; Δ PI, relative variation of perfusion index from baseline; Δ MAP, relative variation of MAP from baseline. The figure represents Δ MAP and Δ Dic_{pleth} evolution during the 16 min period of induction of anaesthesia. Median MAP and Dic_{pleth} variation from baseline are represented at each minute (T'x', at 'x' min from T0) from the beginning of the induction (T0).

Δ Dic_{pleth} and Δ MAP, and 90% between Δ PI and Δ MAP (Supplementary Fig. S1).

Diagnosis performances of Δ Dic_{pleth} and Δ PI for detection of arterial hypotension

Figure 3 represents the ROC curves to assess Δ Dic_{pleth} and Δ PI performances to detect hypotensive episodes. The diagnosis performances values of Δ Dic_{pleth} and Δ PI are summarised in Table 2. The best threshold value of Δ Dic_{pleth} and Δ PI for detecting IOH were -19% and 51%, respectively. The AUC of Δ Dic_{pleth} and Δ PI were not significantly different ($P=0.22$). Combining Δ Dic_{pleth} and Δ PI to detect hypotensive episodes

improved the detection performance with an AUC of ROC curve (0.91 [95% CI: 0.88–0.95]; $P<0.001$) statistically better than Δ Dic_{pleth} and Δ PI separately ($P<0.001$ and $P=0.026$, respectively) (Table 2; Supplementary Figs S2 and S3).

Evolution of MAP, Dic_{pleth}, and PI during vasoconstrictor administration

Twenty-eight subjects (46%) received a bolus of vasopressors during induction (2 phenylephrine and 26 norepinephrine). After vasopressors, the MAP increased from 59 (50; 67) to 76 (68; 79) mm Hg (relative variation: 30% [14; 45]; $P<0.001$). Dic_{pleth} increased from 0.34 (0.25; 0.39) to 0.48 (0.35; 0.55) (relative

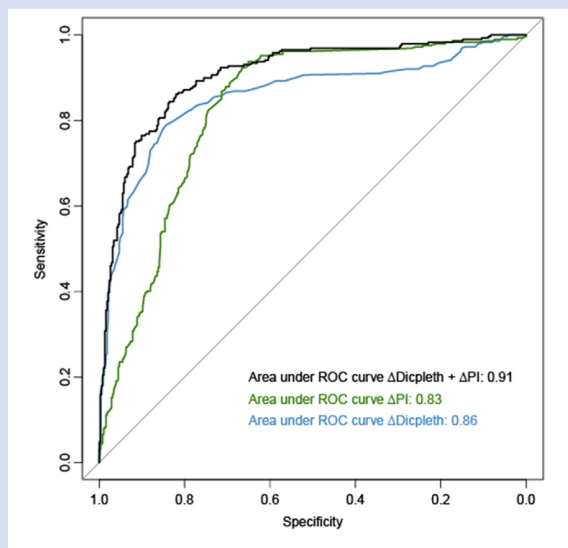


Fig 3. Receiver operator characteristic curves for Δ PI and Δ Dic_{pleth} performance to detect intraoperative hypotension. ROC, receiver operating characteristic; Δ Dic_{pleth}, relative variation of Dic_{pleth}; Δ MAP, relative variation of MAP; Δ PI, relative variation of perfusion index.

variation: 44% [17; 63]; $P < 0.001$), and PI decreased from 4.0 (3.3; 5.4) to 3.2 (1.8; 5.4) (relative variation: -28% [−44; −13]; $P < 0.001$). Δ Dic_{pleth} and Δ PI under the effect of vasopressors were strongly related to Δ MAP ($r = +0.73$; 95% CI: 0.48–0.87; $P < 0.001$ and $r = -0.62$; 95% CI: -0.81 to -0.32 ; $P < 0.001$; respectively) (Supplementary Fig. S4).

Evolution Dic_{pleth} and Dic_{radial} during vasoconstrictor administration

During maintenance of anaesthesia, 48 boluses of norepinephrine were administered to 10 patients (5 [4; 6] boluses per patient) under invasive blood pressure monitoring. Dic_{pleth} was non-measurable in two haemodynamic points, which were excluded from the analysis. The MAP increased from 70 (63; 77) to 88 (77; 98) mm Hg (relative variation: 26% [19; 34]; $P < 0.001$). Dic_{pleth} increased from 0.28 (0.17; 0.36) to 0.39 (0.25; 0.46), and Dic_{radial} from 0.32 (0.21; 0.39) to 0.40 (0.31; 0.49) (respective relative variations: 34% [20; 71]; $P < 0.001$ and 27%

[14; 46]; $P < 0.001$). Dic_{pleth} and Dic_{radial} and their relative variations were strongly correlated during vasoconstrictor administration ($r = 0.87$; 95% CI: 0.83–0.90 and $r = 0.92$; 95% CI: 0.85–0.95) (Supplementary Fig. S5).

Discussion

In our study, we describe during induction of anaesthesia the variations of two parameters issued from photoplethysmographic curves, namely, Dic_{pleth} and PI, and their performance to detect IOH under the vasoactive effects of anaesthetic drugs. Δ MAP and Δ Dic_{pleth} vary in parallel during induction of anaesthesia, whilst Δ MAP and Δ PI vary inversely, with good concordance (89% and 90%, respectively). Our study also found correlations between variations of Dic_{pleth} and MAP on one hand, and PI and MAP on the other hand, under the influence of vasoconstrictors. The main result of our study is that Δ Dic_{pleth} and Δ PI were accurate and presented similar performances to detect IOH induced by general anaesthesia. Moreover, a combined analysis of these two parameters enhanced the diagnostic performance for detecting IOH under the actions of the vasoactive effect of anaesthetics.

Dicrotic waveform variations have been described on invasive ABP and photoplethysmographic curves with changes of haemodynamic status in various clinical conditions. At the aortic level, the dicrotic notch represents the closure of the aortic valve (i.e. the end-systolic pressure), which is then followed by the dicrotic wave and the aortic elastic recoil (Windkessel effect). End-systolic pressure is dependent on afterload, which can vary quickly with changes in vascular tone, as during induction of anaesthesia caused by the vasoactive effect of anaesthetic drugs.¹⁸ A linear relationship has been described between the central dicrotic notch pressure and MAP.¹⁸ A similar relationship at the photoplethysmography level has been suggested between Dic_{pleth} and MAP.¹⁰ But, to our knowledge, no study quantified Dic_{pleth} variations to detect arterial hypotension. The photoplethysmography curve represents the pulsatile variations of light absorption measured on a tissue. It is an indirect measurement of arteriolar dilatation, and hence, of arteriolar transmural pressure variations at each cardiac cycle. It seems that ABP and photoplethysmographic waveforms have the same determinants as confirmed in a sub-analysis we performed that shows high correlation between dicrotic notch height on the photoplethysmographic signal and radial invasive ABP (ESM 5). Indeed, a transfer function has been described previously between invasive ABP and photoplethysmographic curves.¹⁹ This suggests that Dic_{pleth} could

Table 2 Diagnostic performances for Δ Dic_{pleth}, Δ PI, and Δ Dic_{pleth} and Δ PI combination to detect intraoperative hypotension episodes. AUC ROC, area under the curve of receiver operating characteristic; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; Δ Dic_{pleth}, relative variation of Dic_{pleth} from baseline; Δ PI, relative variation of perfusion index from baseline

	Δ Dic _{pleth}	Δ PI	Δ Dic _{pleth} + Δ PI
AUC ROC	0.86 (95% CI: 0.83–0.88)	0.83 (95% CI: 0.80–0.86)	0.91 (95% CI: 0.88–0.95)
P-value	<0.001	<0.001	<0.001
Threshold value (%)	−19	51	NA
Sensitivity (%)	79	82	84
Specificity (%)	84	74	84
PPV (%)	79	71	79
NPV (%)	84	85	89

be used as a surrogate parameter for the noninvasive and continuous monitoring of MAP during induction of anaesthesia. Furthermore, as the dicrotic notch pressure at the aortic level, $\text{Dic}_{\text{pleth}}$ could be used to assess vascular tone and MAP variations under vasoactive drug effect, as reported in several previous studies.^{11,12} Our results confirm this hypothesis, as we found a strong correlation between $\Delta\text{Dic}_{\text{pleth}}$ and ΔMAP under the action of vasoconstrictors. A decrease of 19% of $\text{Dic}_{\text{pleth}}$ had good performances to detect IOH with a sensitivity of 79% and a specificity of 84%.

PI represents the ratio between pulsatile and continuous components of light absorption. Lima and colleagues¹⁴ showed a strong correlation between PI and core-to-toe temperature gradient, a parameter strongly dependent on vascular tone. Some studies have described an increase of PI during reduction of vascular tone caused by sympathectomy during the onset of peripheral or epidural anaesthesia.^{20,21} PI has also been described to increase with vasoconstriction induced by central hypovolaemia during lower body negative pressure.²² The most available pulse oximeter in the operating room already displays PI. Our results showed a negative correlation between ΔPI and ΔMAP under vasopressors. ΔPI was also accurate to detect IOH, but was probably less reliable than $\Delta\text{Dic}_{\text{pleth}}$ to inform about the depth of hypotension, probably because of the complex influence of vascular tone and stroke volume on PI. Finally, our results suggest that combining both parameters could improve the detection of hypotension with a specificity and sensitivity of 84%.

Our study has some limitations. Firstly, our study included mainly ASA physical status 1 or 2 patients, for neurosurgical or neuroradiology elective procedures. None of them had cardiac failure or severe arterial diseases. However, most of the patients in our study were free of medication that may influence the arterial compliance and proprieties. Our results need to be validated in patients with higher ASA status and cardiovascular risk. However, patients with higher ASA status are more likely to require continuous invasive ABP monitoring, and hence, will not require such a simple and easy alternative to detect IOH.

Secondly, we used the standard intermittent oscillometric method for ABP measurements, which might be less reliable than invasive ABP.^{23,24} A study comparing the performance of $\Delta\text{Dic}_{\text{pleth}}$ and ΔPI to detect hypotension based on accurate continuous ABP reference would be useful. Our patients did not have cardiac output monitoring. In further studies, it would be useful to study the relationships between PI, MAP, and stroke volume to evaluate the influence of stroke volume on PI variations. These interconnected parameters are complex, and a potential reduction of stroke volume may influence variations of PI by other mechanisms than changes in vascular tone alone as during induction of anaesthesia. Finally, all the patients received total i.v. anaesthesia (propofol and remifentanyl), and the vasoconstrictor drugs used were noradrenaline and phenylephrine. Our result may not be similar with other drugs, such as ephedrine. Also, our study is based on fingertip photoplethysmographic signals. As photoplethysmographic waveform contour depends on the measurement site, our conclusion might not be applicable if photoplethysmographic signals are recorded from another site.^{25,26}

A number of factors are associated with hypotension during induction of anaesthesia and the early intraoperative period.²⁷ The relative height of the dicrotic notch and the PI, both measured from a standard pulse oximetry signal (photoplethysmography signal), could be used to detect

hypotensive episodes during induction of anaesthesia. The combined analysis of the variations of these two indices could represent a new noninvasive, simple, and easy-to-use tool to follow ABP variations during general anaesthesia.

Authors' contributions

Study design/supervision: MC, JM, FV.

Data collection: MC, JJ, FD, FV.

Data analysis/interpretation: MC, SM, HN, EG, FV.

Drafting/writing paper: MC, SM, EG, FV.

Revising/approval of final manuscript: all authors.

Acknowledgements

The authors thank all the paramedical staff of the operating room, the doctors of neuroradiology, and the whole clinical research team of the Le Temple.

Declaration of interest

AM has received speaker honoraria from Abbott, Novartis, Orion, Roche, and Servier, and fee as member of the advisory board and steering committee from Cardiorentis, Adrenomed, MyCartis, ZS Pharma, and Critical Diagnostics. EG has received consulting fees from Magnisense, and research support from Sphingotec, Deltex Medical, and Retia Medical. FV has received research support from Radiometer, Deltex Medical, and Retia Medical. SM has received consulting fees from Alam Medical, AtCor Medical, MESI Medical, and Omron.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2019.01.037>.

References

1. Lienhart A, Auroy Y, Péquignot F, et al. Survey of anesthesia-related mortality in France. *Anesthesiology* 2006; **105**: 1087–97
2. Nair BG, Horibe M, Newman S-F, Wu W-Y, Peterson GN, Schwid HA. Anesthesia information management system-based near real-time decision support to manage intraoperative hypotension and hypertension. *Anesth Analg* 2014; **118**: 206–14
3. Futier E, Lefrant J-Y, Guinot P-G, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017; **318**: 1346–57
4. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; **121**: 706–21
5. Willingham MD, Karren E, Shanks AM, et al. Concurrence of intraoperative hypotension, low minimum alveolar concentration, and low bispectral index is associated with postoperative death. *Anesthesiology* 2015; **123**: 775–85
6. Reich DL, Hossain S, Krol M, et al. Predictors of hypotension after induction of general anesthesia. *Anesth Analg* 2005; **101**: 622–8
7. Kork F, Balzer F, Krannich A, Weiss B, Wernecke K-D, Spies C. Association of comorbidities with postoperative

- in-hospital mortality: a retrospective cohort study. *Medicine (Baltimore)* 2015; **94**: e576
8. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**: 507–15
 9. Ng JLW, Chan MTV, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology* 2011; **115**: 879–90
 10. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clin Sci (Lond)* 2002; **103**: 371–7
 11. Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ. Contour analysis of the photoplethysmographic pulse measured at the finger. *J Hypertens* 2006; **24**: 1449–56
 12. Chowienczyk PJ, Kelly RP, MacCallum H, et al. Photoplethysmographic assessment of pulse wave reflection: blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus. *J Am Coll Cardiol* 1999; **34**: 2007–14
 13. van Genderen ME, Bartels SA, Lima A, et al. Peripheral perfusion index as an early predictor for central hypovolemia in awake healthy volunteers. *Anesth Analg* 2013; **116**: 351–6
 14. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med* 2002; **30**: 1210–3
 15. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KGM, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; **107**: 213–20
 16. Obuchowski NA. Sample size calculations in studies of test accuracy. *Stat Methods Med Res* 1998; **7**: 371–92
 17. Dawber T, Emerson TJ, McNamara P. Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease. *Angiology* 1973; **24**: 244–55
 18. Hébert JL, Lecarpentier Y, Zamani K, Coirault C, Daccache G, Chemla D. Relation between aortic dicrotic notch pressure and mean aortic pressure in adults. *Am J Cardiol* 1995; **76**: 301–6
 19. Millasseau SC, Guigui FG, Kelly RP, et al. Noninvasive assessment of the digital volume pulse. Comparison with the peripheral pressure pulse. *Hypertension* 2000; **36**: 952–6
 20. Ginosar Y, Weiniger CF, Meroz Y, et al. Pulse oximeter perfusion index as an early indicator of sympathectomy after epidural anesthesia. *Acta Anaesthesiol Scand* 2009; **53**: 1018–26
 21. Galvin EM, Niehof S, Verbrugge SJ, et al. Peripheral flow index is a reliable and early indicator of regional block success. *Anesth Analg* 2006; **103**: 239–43
 22. Lima A, Van Genderen M, Klijn E, Bartels S, Van Bommel J, Bakker J. Perfusion index as a predictor for central hypovolemia in humans. *Crit Care* 2011; **15**: P69
 23. Sheshadri V, Tiwari AK, Nagappa M, Venkatraghavan L. Accuracy in blood pressure monitoring: the effect of noninvasive blood pressure cuff inflation on intra-arterial blood pressure values. *Anesth Essays Res* 2017; **11**: 169–73
 24. Nakagomi A, Okada S, Shoji T, Kobayashi Y. Comparison of invasive and brachial cuff-based noninvasive measurements for the assessment of blood pressure amplification. *Hypertens Res* 2017; **40**: 237–42
 25. Allen J, Murray A. Age-related changes in the characteristics of the photoplethysmographic pulse shape at various body sites. *Physiol Meas* 2003; **24**: 297–307
 26. Cannesson M, Desebbe O, Rosamel P, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth* 2008; **101**: 200–6
 27. Südfeld S, Brechnitz S, Wagner JY, Reese PC, Pinnschmidt HO, Reuter DA, Saugel B. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth* 2017; **119**: 57–64

Handling editor: C. Boer

Annexe 1.3 Article “Real-time estimation of mean arterial blood pressure based on photoplethysmography dicrotic notch and perfusion index. A pilot study”

Cet article a été publié dans Journal of Clinical Monitoring and Computing le 10 février 2020 [3]. Les auteurs sont: Jona Joachim, Etienne Gayat, Maxime Coutrot, Sandrine Millasseau, Joaquim Matéo, Alexandre Mebazaa et Fabrice Vallée.



Real-time estimation of mean arterial blood pressure based on photoplethysmography dicrotic notch and perfusion index. A pilot study

Jona Joachim^{1,2,3} · Maxime Coutrot^{1,2,3} · Sandrine Millasseau⁴ · Joaquim Matéo^{1,3} · Alexandre Mebazaa^{1,2,3} · Etienne Gayat^{1,2,3} · Fabrice Vallée^{1,2,3}

Received: 9 August 2019 / Accepted: 10 February 2020
© Springer Nature B.V. 2020

Abstract

Hypotension during general anesthesia is associated with poor outcome. Continuous monitoring of mean blood pressure (MAP) during anesthesia is useful and needs to be reliable and minimally invasive. Conventional cuff measurements can lead to delays due to its discontinuous nature. It has been shown that there is a relationship between MAP and photoplethysmography (PPG) parameters like the dicrotic notch and perfusion index (PI). The objective of the study was to continuously estimate MAP from PPG. Pulse wave analysis based on PPG was implemented using either notch relative amplitude (MAP_{NRA}), notch absolute amplitude (MAP_{NAA}) or PI (MAP_{PI}) to estimate MAP from PPG waveform features during general anesthesia. Estimated MAP values were compared to brachial cuff MAP (MAP_{cuff}) and to radial invasive MAP (MAP_{inv}). Forty-six patients were analyzed for a total of 235 h. Compared to MAP_{cuff} , mean bias and limits of agreement were 1 mmHg (−26 to +29), −1 mmHg (−10 to +8) and −3 mmHg (−21 to +13) for MAP_{NRA} , MAP_{NAA} and MAP_{PI} respectively. Compared to MAP_{inv} , mean absolute error (MAE) was 20 mmHg [10 to 39], 11 mmHg [5 to 18] and 16 mmHg [9 to 24] for MAP derived from MAP_{NRA} , MAP_{NAA} and MAP_{PI} respectively. When calibrated every 5 min, MAP_{NAA} showed a MAE of 6 mmHg [5 to 9]. MAP_{NAA} provides the best estimates with respect to brachial cuff MAP and invasive MAP. Regular calibration allows to reduce drift over time. Beat to beat estimation of MAP during general anesthesia from the PPG appears possible with an acceptable average error.

Keywords Photoplethysmography · Noninvasive blood pressure · Mean arterial pressure · Anesthesia

1 Introduction

Intraoperative hypotension (IOH) is a major risk factor for short- and long-term perioperative morbidity and mortality. Current guidelines recommend a strategy aiming at the reduction of hypotension during anesthesia [1, 2]. Indeed, even short episodes of hypotension, lasting several minutes,

have been associated with adverse cardiovascular, neurological and renal outcomes [3–5].

Routine monitoring during anesthesia consists at least of noninvasive blood pressure and pulsated oxygen saturation (SpO_2). Blood pressure is obtained using the oscillometric method by means of a pressure cuff. This method is discontinuous by nature and can only be repeated with an interval of several minutes, leading to delayed diagnosis and treatment of IOH and eventually to prolonged exposure to the noxious event.

The oxygen saturation is routinely obtained using photoplethysmography (PPG, Fig. 1). The pulsatile part of the PPG signal directly reflects variations in the diameter of arterioles due to cyclic volume variations induced by cardiac ejection. The determinants of the overall PPG signal are complex and include systemic hemodynamics (arterial compliance, vascular resistance and systolic ejection volume), tissue and vascular properties (which vary from one patient to another)

✉ Jona Joachim
jona.joachim@aphp.fr

¹ Department of Anesthesiology, Burn and Critical Care, St-Louis-Lariboisière-Fernand Widal University Hospitals, Assistance Publique - Hôpitaux de Paris, 2 rue Ambroise Paré, 75010 Paris, France

² INSERM UMR-942, Paris, France

³ Université de Paris, Paris, France

⁴ Pulse Wave Consulting, Saint-Leu-la-Forêt, France

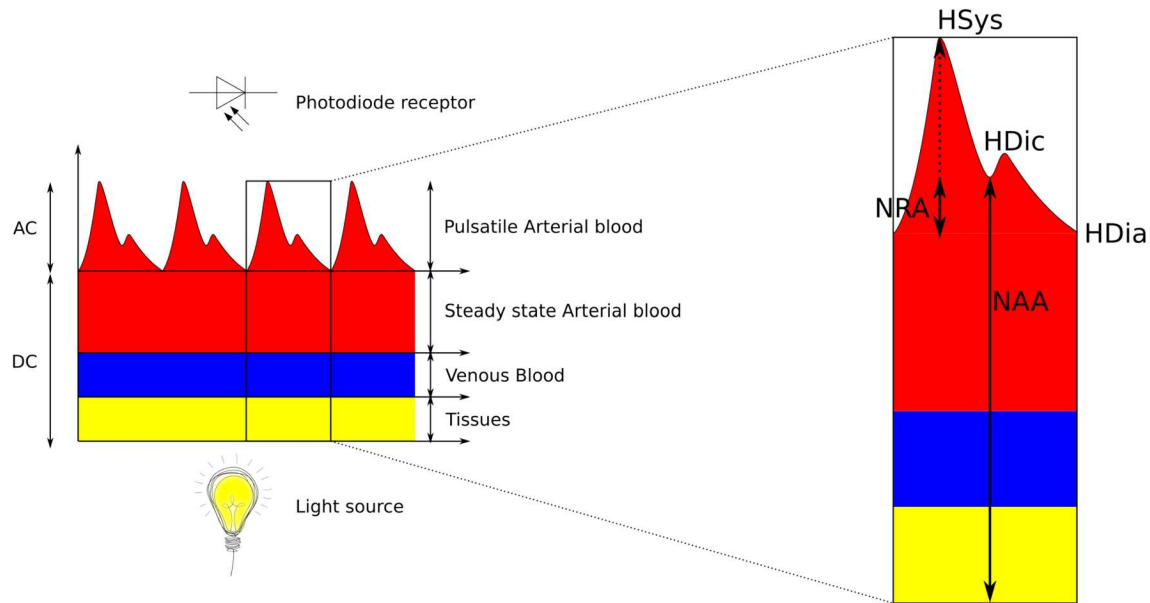


Fig. 1 Photoplethysmography signal components and definition of studied parameters in waveform analysis

as well as ambient noise (light, movement). However, for the present study, we extracted two specific parameters from PPG signal: the perfusion index (PI) and the dicrotic notch height (Hdic).

The PI is calculated by the fact that light which is received by the photodiode is transformed into electrical current. The pulsatile part of the signal appears as alternating current (AC) and the non-pulsatile part as direct current (DC). PI represents the ratio between the pulsatile (AC) component and the non-pulsatile (DC) part of the infrared signal ($PI = \frac{AC}{DC}$). An increase in PI therefore corresponds to a relative increase in the pulsatile part of the signal. PI is then correlated with vasodilation [6] and is therefore considered to be an index which reflects vasomotor tone. Local vasodilation leads to an increase in local flow, i.e. an increase in AC and therefore in PI.

The interest of the PI is twofold. First, the value of the PI is used as an indicator of signal quality. Indeed, a PI value of less than 1.4% indicates a bad PPG signal [6] and indicates to the user a poor estimation quality.

Additionally, PI provides information on the hemodynamic state and mean blood pressure (MAP) in a complementary way to the dicrotic notch values. Indeed, vascular tone directly influences PI and the value of PI is therefore correlated to vascular resistance and therefore indirectly to MAP [7].

The dicrotic notch (Hdic) is a secondary upstroke in the descending part of the pulse wave (Fig. 1). There still exists controversy regarding the physiologic origins of the dicrotic notch. It is believed that the dicrotic notch is either

secondary to the closure of the aortic valves or due the wave reflection phenomenon or a mixture of both effects [8]. Regardless, it corresponds to the end of cardiac ejection during the cardiac cycle and contains valuable information regarding the cardiovascular state. By examining the amplitude of the dicrotic notch, we can define two values: the notch relative amplitude (NRA) and the notch absolute amplitude (NAA). NRA is the relative amplitude of the dicrotic notch in the pulsatile part of the PPG signal [9]. NAA is the absolute amplitude of the dicrotic notch including the non-pulsatile part of the PPG signal and is independent of the systolic peaks and diastolic low points of the signal.

In a previous study, we investigated the correlation between MAP variations during the induction of general anesthesia in 61 patients with PI and the NRA [7]. We found a linear positive correlation between MAP and NRA variations and an inverse relationship between MAP and PI variations.

Therefore, we hypothesized that it would be possible to estimate MAP in real time from a continuous measurement of NRA, NAA and/or PI obtained by PPG analysis. Intermittent measurements of MAP by the oscillometric pressure cuff (MAPcuff) would be used to calibrate the linear relationship described above.

The aim of this “proof of concept” study was to test the feasibility of estimating MAP in real time, beat by beat, during general anesthesia only from the continuous PPG signal, with MAP_{NRA} , MAP_{NAA} or MAP_{PI} analysis, combined with intermittent pressure cuff calibration.

2 Material and methods

2.1 Definitions MAP prediction algorithms

Real time MAP estimation is based on PPG analysis combined with a linear model and periodic calibration by brachial cuff blood pressure apparatus (MAPcuff). We hypothesized that it would be possible from algorithms based on PPG curve parameters to track MAP variations in real time. In this preliminary study we decided to test three functions that could independently estimate MAP from PPG. Two were based on the dicrotic notch of the PPG signal: one based on the NRA (MAP_{NRA}) and the other based on the NAA (MAP_{NAA}). The third was based on PI (MAP_{PI}).

2.1.1 Algorithm 1: MAP_{NRA}

Algorithm 1 uses an estimation function based on the relative height of the dicrotic notch in relation to the amplitude of the pulse wave. It did not consider the non-pulsatile part (DC). The estimation was obtained by the formula $MAP_{NRA} = k1 \cdot NRA = k1 \cdot \frac{H_{dic} - H_{dia}}{H_{sys} - H_{dia}}$, where k1 was a calibration factor reevaluated after each brachial cuff measurement.

2.1.2 Algorithm 2: MAP_{NAA}

Algorithm 2 uses the absolute height of the dicrotic notch as the estimator. The H_{dic} value is a quantity without unit, the absorbance. The estimated MAP was obtained by the formula $MAP_{NAA} = k2 \cdot NAA = k2 \cdot H_{dic}$, where k2 was a calibration factor reevaluated after each brachial cuff measurement.

2.1.3 Algorithm 3: MAP_{PI}

Based on our previous study [7] where we observed that PI varies in the opposite direction as MAP, we considered the inverse of PI for MAP estimation. As the inverse of PI varies exponentially in respect to MAP, the natural logarithm (ln) allows to linearize the variations of PI. Since the ln becomes negative for values between 0 and 1, we added 1 to ensure that only positive values are obtained [10]. The value is small in magnitude. In order to present a more meaningful number to the clinician, the value is multiplied by 10.

We hence created the following empirical formula to estimate MAP from PI.

Algorithm 3 was created with the following empirical formula to estimate MAP from PI: $MAP_{PI} = 10 \cdot k3 \cdot \ln\left(\frac{1}{PI} + 1\right)$,

where k3 was a calibration factor reevaluated after each brachial cuff measurement.

2.1.4 Calibration of MAP estimates

In order to calibrate the equations to estimate MAP, beat to beat values of the variables (NRA, NAA or PI), as well as intermittent direct measures of MAP are required. We used the non-invasive pressure cuff (MAPcuff) as the reference for calibration.

2.1.5 Continuous estimation of mean arterial pressure

Once the algorithm is calibrated, MAP can be estimated beat to beat using PPG as the only signal source. The estimated MAP is then calculated by reversing the formulas explained above for each algorithm.

2.2 Patients

Data from patients included prospectively for a previous study [7] were used for the retrospective analysis of this study. This study was approved by the SRLF Ethics Committee (n°CE SRLF 11-356). This was an observational study of "routine care". Patients were included after informed consent was obtained. Patient demographics were collected through the anesthesia consultation.

2.2.1 Anesthesia protocol

General anesthesia was induced by Propofol and morphine, then maintained intravenously by Propofol (75–150 $\mu\text{g}/\text{kg}/\text{min}$) or inhaled by Sevoflurane (age-adjusted MAC) and morphine. All patients were intubated after neuromuscular blockade by Atracurium (0.5 mg/kg) and mechanically ventilated with a tidal volume of 6 to 8 ml/kg and a respiratory rate for an EtCO_2 between 35 and 38 mmHg. Patients could then be equipped with the radial arterial catheter for invasive and continuous measurement of MAP at the discretion of the clinician in charge of the patient based on patient-related and surgical risks.

2.2.2 Patient demographics

The following data were collected: age, sex, weight, height, body mass index (BMI), co-morbidities, American Society of Anesthesiology (ASA) class of anesthetic risk, usual

treatment of the patient and possible modifications for the procedure, title of the intervention procedure.

2.2.3 Hemodynamic data

All signals were recorded in real time from a standard patient monitor allowing digital export (IntelliVue MP70 Philips, Eindhoven, Netherlands). The PPG wave and invasive blood pressure curve (MAP_{inv}) recordings were obtained with a sampling frequency of 125 Hz. PI was obtained beat to beat. MAP_{cuff} recording was obtained at each measurement. This data was exported to a laptop computer connected to the patient monitor through an RS232 serial interface using the ixTrend software (ixelligence, Wildau, Germany).

2.3 Study protocol

The data was analyzed offline after the end of the procedure. Estimated figures of MAP were compared to noninvasive cuff measures and to invasive blood pressure in two different analysis steps.

2.3.1 MAP estimation drift between two pressure cuff measures

In the first part of this study, we compared the values estimated by the different algorithms to cuff pressure values (MAP_{cuff}). MAP_{cuff} was used as gold standard in this analysis. Prediction measurements were sampled for analysis right before each new pressure cuff measurement and before calibration. Thus, this analysis served to study the deviation of the estimate between two cuff measurements. The time between two brachial cuff measurements was at least 5 min. Data was sampled after anesthesia induction before surgical incision and until the end of the procedure.

2.3.2 MAP estimation comparison to invasive blood pressure

In the second part of the study, we compared continuous beat to beat MAP estimation with a continuous invasive MAP recorded at the radial artery level (MAP_{inv}) but the estimation algorithms were calibrated to brachial cuff pressure.

2.4 Statistical analysis

For MAP estimation between two pressure cuff measures, the analysis was performed using Bland–Altman diagrams. To compare continuous beat to beat MAP estimates to invasive blood pressure, several methods exist. We calculated the mean absolute error (MAE). This indicator is commonly accepted as reliable and easily interpretable [11]. It is

obtained from the formula $MAE = \frac{1}{n} \cdot \sum_{i=1}^n |MAP_{est_i} - MAP_{inv_i}|$. The MAE has the same unit as the measured values, in this case mmHg. The time interval between two oscillometric measurements (and therefore the calibration interval) was left to the clinician's discretion. A secondary analysis was performed considering only data sets with calibration interval of exactly 5 min.

Data was analyzed using software written in Python using the following libraries: numpy 1.16, pandas 0.24 and scipy 1.3.

3 Results

3.1 Patients

From November 2016 to November 2017, 58 patients were evaluated for this pilot study. The characteristics of the population are summarized in Table 1.

12 (20%) were excluded because the PPG signal was not usable due to artifacts. 11 Patients (19%) were excluded from the second analysis because no invasive blood pressure was measured. In total, the first analysis was conducted on 46 patients and the second analysis on 35 patients.

3.2 PPG MAP estimation versus cuff pressure

In the 46 patients, 613 intervals between two brachial cuff measurements were analyzed for a total of 166 h. A majority of the intervals were of 5 min ($n=357$, 58%). The longest interval was 235 min. The median value of the interval duration was therefore 5 min [5 to 15] but with an average duration of 16 ± 5 min. The results of this analysis are summarized in Table 2. Raw scatter plots showing the correlation between MAP_{cuff} and estimates are represented in Fig. 2. The coefficient of determination (R^2) was 0.34 for MAP_{NRA}, 0.84 for MAP_{NAA} and 0.47 for MAP_{PI} respectively. The algorithms were compared to MAP_{cuff} by means of the Bland–Altman method adjusted for repeated measurements [12] (Figs. 3–5). The represented circles correspond to the mean value per patient during the procedure. The size of the circles is relative to the number of measurement points per patient.

3.2.1 Algorithm 1: MAP_{NRA}

In the 46 patients over the 613 intervals, the mean bias between and MAP_{NRA} and MAP_{cuff} was 1 mmHg and the limits of agreement were -26 to $+29$ mmHg (Fig. 3).

Table 1 Characteristics of the study population

Patient demographics	Median [IQR] or n (%)
Number of patients	46
Abdominal surgery	11 (24)
Neurosurgery	5 (11)
Neuroradiology	30 (65)
Male sex	16 (35)
Weight (kg)	64 [51 to 77]
Age (years)	46 [36 to 63]
Height (cm)	162 [159 to 175]
BMI (kg/m ²)	23 [20 to 25]
HR (min ⁻¹)	68 [59 to 75]
EtCO ₂ (mmHg)	34 [33 to 35]
BIS	37 [28 to 42]
ASA score	I: 13 (28), II: 30 (65), III: 3 (7)
Cardiovascular risk factors	n (%)
Age > 55 years	30 (65)
HTA	15 (33)
Smoking	16 (35)
Diabetes	6 (13)
Dyslipidemia	5 (11)
Coronary heart disease	1 (2)

CVRF cardiovascular risk factors, *ASA* American Society of Anesthesia, *HR* heart rate, *BIS* bispectral index, *EtCO₂* end tidal CO₂

Table 2 Summary of the comparison of estimated MAP against noninvasive oscillometric MAP

	Median [IQR] or n
n	46
Total duration (h)	235
MAP _{cuff} (mmHg)	73 [69 to 78]
MAP _{NRA}	Median [IQR] or bias (LOA)
NRA (%)	28 [22 to 34]
MAP _{NRA} (mmHg)	71 [59 to 91]
Bias (mmHg)	1 (-26 to 29)
MAP _{cuff} - MAP _{NRA} (mmHg)	2.1 [-3.4 to 5.1]
MAP _{NAA}	Median [IQR] or bias (LOA)
NAA (-)	1644 [1528 to 1773]
MAP _{NAA} (mmHg)	74 [68 to 80]
Bias (mmHg)	-1 (-10 to 8)
MAP _{cuff} - MAP _{NAA} (mmHg)	0.5 [-2.1 to 2.1]
MAP _{PI}	Median [IQR] or bias (LOA)
PI (%)	4.6 [2.0 to 7.9]
MAP _{PI} (mmHg)	77 [67 to 89]
Bias (mmHg)	-3 (-21 to 13)
MAP _{cuff} - MAP _{PI} (mmHg)	-1.5 [-6 to 0.6]

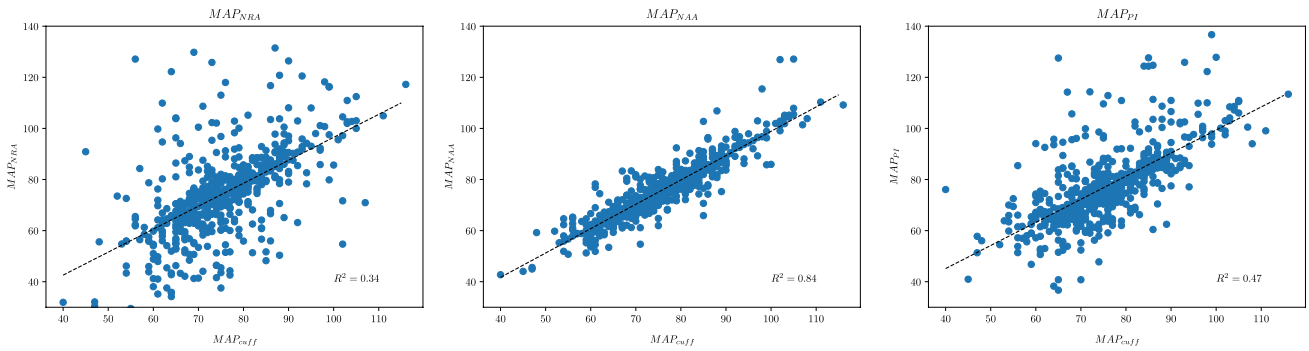


Fig. 2 Scatter plots showing the raw relation between MAPcuff and MAP_{NRA}, MAP_{NAA}, MAP_{PI} respectively. Blue points represent raw paired measurements. The black dashed line represents a linear regression best fit

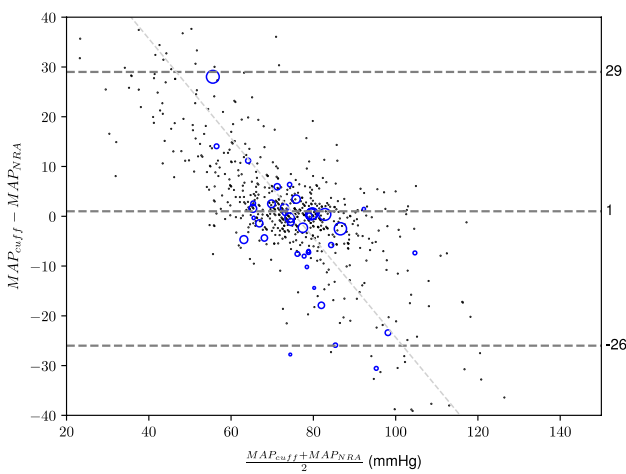


Fig. 3 Comparison of MAP_{NRA} and MAPcuff. Each blue ring represents the mean value for one patient. The ring size represents the number of individual measurements per patient. The light grey dashed line represents a linear regression best fit

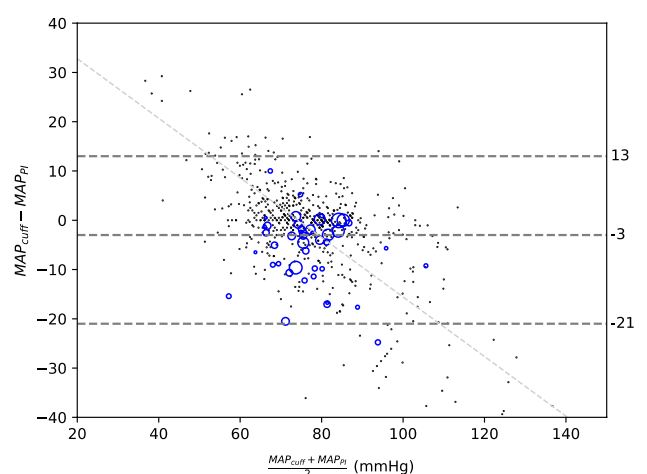


Fig. 5 Comparison of MAP_{PI} and MAPcuff. Each blue ring represents the mean value for one patient. The ring size represents the number of individual measurements per patient. The light grey dashed line represents a linear regression best fit

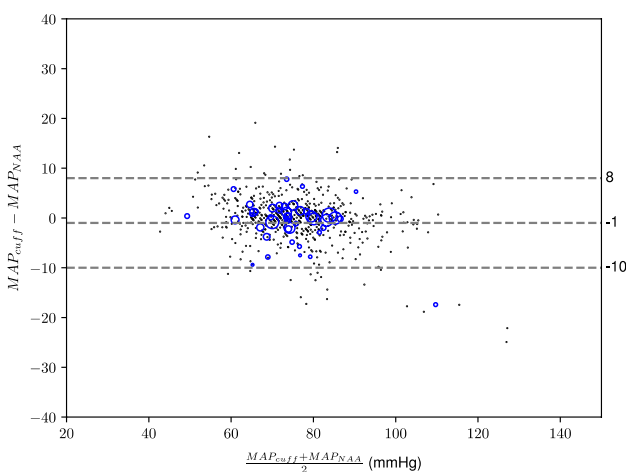


Fig. 4 Comparison of MAP_{NAA} and MAPcuff. Each blue ring represents the mean value for one patient. The ring size represents the number of individual measurements per patient

The median difference between MAPcuff and MAP_{NRA} was 2.1 mmHg [−3.4 to 5.1].

The median value of the calibration factor k1 was 438 [297 to 665].

3.2.2 Algorithm 2: MAP_{NAA}

The mean bias between MAP_{NAA} and MAPcuff was −1 mmHg and the agreement limits were −10 to +8 mmHg (Fig. 4).

The median difference between MAP_{NAA} and MAPcuff was 0.5 mmHg [−2.1 to 2.1].

The median value of the calibration factor k2 was 4.5 [4.3 to 5.0] × 10^{−2}.

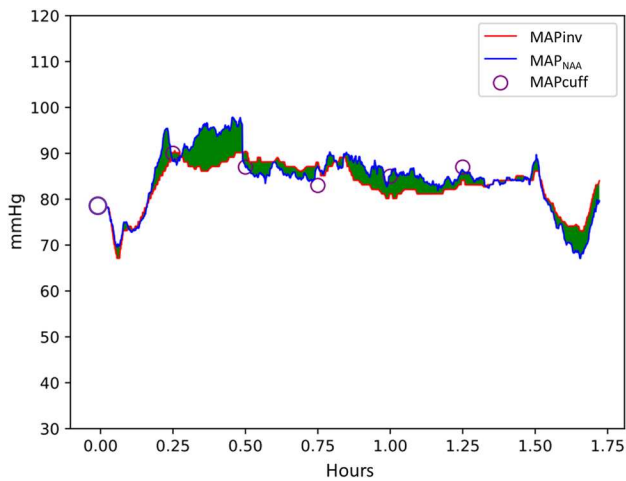


Fig. 6 Example of comparison between MAP_{Inv} and MAP_{NAA} calibrated by MAP_{cuff} . The green AUC corresponds to the MAE at each time step

Table 3 Summary of the comparison of beat-to-beat estimated MAP against invasive arterial blood pressure

	Median [IQR] or n
n	35
Total duration (h)	170
MAP_{Inv} (mmHg)	75 [67 to 82]
MAP_{cuff} (mmHg)	74 [69 to 81]
$MAP_{Inv} - MAP_{cuff}$ (mmHg)	2 [-3 to 5]
MAP_{NRA} (mmHg)	69 [49 to 86]
MAE (mmHg)	20 [10 to 39]
MAE 5 min (mmHg)	9 [7 to 18]
MAP_{NAA} (mmHg)	71 [63 to 78]
MAE (mmHg)	11 [5 to 18]
MAE 5 min (mmHg)	6 [5 to 9]
MAP_{PI} (mmHg)	74 [61 to 86]
MAE (mmHg)	16 [9 to 24]
MAE 5 min (mmHg)	10 [7 to 26]

3.2.3 Algorithm 3: MAP_{PI}

The mean bias between MAP_{PI} and MAP_{cuff} was -3 mmHg and the limits of agreement were -21 to $+13$ mmHg (Fig. 5).

The median difference between MAP_{cuff} and MAP_{PI} was -1.5 mmHg [-6.1 to $+0.6$].

The median value of the calibration factor k_3 was 32 [27 to 39].

3.3 PPG MAP estimation versus invasive pressure

In the 35 patients, beat to beat invasive MAP (MAP_{Inv}) was compared to the beat to beat PPG MAP estimation over a total recording time of 170 h which corresponded to an average of 4.8 h of recording per patient (Fig. 6).

The median value of MAP_{Inv} was 75 mmHg [67 to 82]. It ranged from a minimum of 50 mmHg to a maximum of 98 mmHg. The median value of MAP_{cuff} was 75 mmHg [69 to 81]. The difference between MAP_{Inv} and MAP_{cuff} was a median of 2 mmHg [-3 to 5]. In these 35 patients, the algorithms were calibrated 345 times.

A majority of the time intervals between two calibrations were 5 min ($n = 186$, 54%). The longest time interval was 236 min. The median value of the time between two calibrations was 5 min [5 to 45] with an average duration of 23 min.

The results of this analysis are summarized in Table 3.

3.3.1 Algorithm 1: MAP_{NRA}

Over the 170 h studied, the MAE between MAP_{Inv} and MAP_{NRA} was 20 mmHg [10 to 39].

When only analyzing dataset where recalibration was performed every 5 min, MAE is 9 mmHg [7 to 18]. This corresponds to a duration of 128 h (75% of the total time).

3.3.2 Algorithm 2: MAP_{NAA}

The MAE between MAP_{Inv} and MAP_{NAA} was 11 mmHg [5 to 18]. When only analyzing dataset where recalibration was performed every 5 min, MAE is 6 mmHg [5 to 9].

3.3.3 Algorithm 3: MAP_{PI}

The MAE between MAP_{Inv} and MAP_{PI} was 16 mmHg [9 to 24].

When only analyzing dataset where recalibration was performed every 5 min, MAE is 10 mmHg [7 to 26].

4 Discussion

4.1 Main results

The results of this pilot study suggest that MAP could be monitored beat to beat during general anesthesia using advanced analysis of signals generated by currently recommended routine equipment in the operating room, namely oscillometric pressure cuff and a PPG signal.

Our preliminary results can be summarized as follows: (I) MAP_{NAA} seems to be the most efficient; (II) MAP_{NAA} predicts the value of the cuff MAP with a deviation of 1 mmHg with recalibration every 5 min; (III) a non-invasive

calibration every 5 min allows a deviation of 6 mmHg [5 to 9] compared to invasive MAP measurement.

Further studies are needed to further develop these algorithms and to confirm these findings.

4.1.1 Comparison to cuff MAP values

The results show that MAP_{NAA} algorithm allows the smallest bias among the three algorithms evaluated. MAP_{NAA} algorithm only considers the absolute value of H_{dic} without considering H_{dia} or H_{sys} , unlike the MAP_{NRA} algorithm. As MAP_{NRA} algorithm considers the relative value of H_{dic} between diastolic and systolic values, one could intuitively think that algorithm could perform well to estimate MAP. However, we observed that the height of the systolic peak could be arbitrary and sometimes varied in the opposite direction to MAP in cases of vasoconstriction. Thus, the relative percentage of H_{dic} (NRA) is a less reliable indicator of the change in MAP than the raw value of H_{dic} (NAA).

We also noted that MAP_{NRA} as well as MAP_{PI} show proportional bias in comparison to MAP_{cuff} . Indeed, MAP_{NRA} and MAP_{PI} underestimate MAP_{cuff} for small values of MAP and overestimates MAP_{cuff} for large values of MAP. This is illustrated by the regression line on Fig. 3. Transformation of the data could be applied to compensate for under- and overestimation, however, this would limit the interpretation of the study results [13].

MAP_{PI} algorithm also provided worse MAP estimation compared to the MAP_{NAA} algorithm. We noted that despite the use of logarithm, PI variations according to MAP sometimes remained exponential. PI varies more rapidly than an exponential function in relation to MAP. Thus, the logarithm modelization may not be sufficient to linearize PI. Further studies are required to better model these interactions as a simple linear model does not explain the behavior.

4.1.2 Comparison to invasive MAP value

The error between brachial cuff MAP values and invasive radial MAP value was 2 mmHg [−3 to 5 mmHg]. The pressure amplification from the brachial to radial pressure, sometimes also called the Popeye phenomena [14] only apply to systolic pressure and hence cannot explain the difference between invasive and brachial cuff MAP. Indeed, in medium and large arteries, MAP is considered to remain constant throughout the arterial tree [15]. The difference between MAP_{cuff} and MAP_{inv} only reflects to the inherent measurement's errors of both techniques [14].

When using MAP_{inv} as the reference, MAP_{NAA} algorithm provides the smallest bias, in agreement with the comparison to MAP_{cuff} . The MAE was ± 11 mmHg [5 to 18 mmHg], which was comparable to the result obtained when comparing with MAP_{cuff} (−10 to 8 mmHg). This discrepancy with

invasive MAP could partially be due to the fact that invasive pressure signal was not filtered for noise (purging, sampling, etc.). In addition, in this invasive comparison, if we only look at the dataset for which recalibration was performed every 5 min, MAE drops to 6 mmHg [5 to 9 mmHg].

The MAE includes the error of MAP_{cuff} compared to MAP_{inv} (2 mmHg [−3 to 5 mmHg]) since the algorithms are calibrated against MAP_{cuff} .

Commercial products for continuous noninvasive digital pressure are available (Finapres, Finapres Medical Systems and ClearSight, Edwards Lifesciences). These devices are based on the Peñaz technique of vascular unloading [16], which uses PPG combined with a pressure cuff around the finger. It allows beat to beat assessment of blood pressure and MAP and also relies on regular recalibration. Previous comparison studies have reported an error of ± 13 mmHg between MAP measured invasively and with this technique [17].

This error is comparable to our MAP estimation from PPG.

While these commercial devices offer good beat to beat monitoring tool, our study shows that simple PPG analysis could lead to similar results for tracking MAP changes and for a much lower cost. However, this only holds true for MAP and such equipment are still required if systolic and diastolic blood pressure also need to be closely monitored.

4.1.3 Synthesis

MAP_{NAA} algorithm seems to be the most efficient whatever the reference comparison: cuff or invasive. Regular 5-min recalibration increases the reliability of MAP estimation from PPG.

4.1.4 Limits and perspectives

4.1.4.1 Influence of calibration reference Even when comparing to MAP_{inv} , we use brachial cuff values to calibrate our PPG estimates. Using intermittent invasive pressure might have increased accuracy of our MAP estimation for PPG. Indeed, previous studies have shown better performance of central pressure estimates when using invasive pressure [18]. Despite the fact that using brachial cuff potential adds a source of error, we however choose to use it as our aim is to describe a method to track beat to beat MAP changes in clinical routine in patient who might not have an invasive line.

4.1.4.2 Performance during hemodynamic instability Our measurements were made over fairly long periods of time, up to several hours. During these periods, we can consider that hemodynamic conditions were stable for a large part of

the time. It would be interesting to repeat the experiment during periods of hemodynamic instability with rapid variations in MAP, in order to study the reliability of algorithms under these conditions. Further studies are required to assess the trending ability of the algorithms in this setting.

4.1.4.3 Influence of the SpO₂ sensor All measurements used for this study were obtained using the Philips MP70 monitor. It is possible that the PPG signal may have different characteristics on other measurement equipment and it will be necessary to check these algorithms with equipment from other manufacturers.

4.1.4.4 Acceptable measurement error The error of MAP estimation which is acceptable was not prespecified in this study. Indeed, this preliminary study focused on feasibility of MAP estimation using only PPG waveform analysis and cuff calibration. The level of acceptable error is dependent on the use case and should ideally be fixed by the clinician according to his/her practice. The latest international recommendations by AAMI/ESH/ISO for the validation of blood pressure measuring devices specified a limit of 5 ± 8 mmHg for MAP [19]. In our study, when calibrated every 5 min, mean error (6 mmHg) is slightly above this threshold, however the confidence interval [5 to 9 mmHg] is narrower. These recommendations do not consider the case of general anesthesia and it is therefore not clear if they can be applied here.

5 Conclusion

This preliminary study shows that it is possible to estimate MAP beat to beat during general anesthesia using only standard equipment which is routinely recommended, namely oscillometric pressure cuff and PPG signal.

Among the algorithms analyzed, the most efficient one is based on the absolute value of the height of the dicrotic notch on the PPG curve. This algorithm predicts MAP value with a deviation of 1 mmHg every 5 min when compared to reference oscillometric measurement. When compared to an invasive arterial pressure, more frequent noninvasive recalibration of the PPG estimate increases the quality of estimated MAP.

Further studies are needed to confirm these results and to evaluate the relevance of these algorithms in daily clinical practice.

Acknowledgements We thank anesthetic nurses and the staff of neuro-radiology for their support in the conduct of the present study.

Authors' contribution JJ, MC, JM, AM, EG, FV conception and design of research; JJ, MC, FV, and JM performed experiments; JJ, MC, FV and EG analyzed data; JJ, MC, FV, EG and SM interpreted results; JJ, MC, FV and SM prepared figures; JJ and FV drafted manuscript; FV, EG, AM, JM and SM edited and revised the manuscript; JJ, JM, FV, EG, AM, SM and MC approved final version of manuscript.

Compliance with ethical standards

Conflict of interest Assistance Public-Hôpitaux de Paris (AP-HP) applied for a patent for the concepts exposed in this paper as well as the MAP prediction algorithms (preliminary Patent Number INPI 17/62978). Fabrice Vallée, Jona Joachim, Maxime Coutrot, Étienne Gayat and Alexandre Mebazaa are Co-inventors of said patent. Alexandre Mebazaa has received Speaker Honoraria from Abbott, Novartis, Orion, Roche and Servier and Fee as Member of Advisory Board and/or Steering Committee from Cardiorentis, Adrenomed, MyCartis, ZS Pharma and Critical Diagnostics. Etienne Gayat has received Consulting Fees from Magnisense, research support from Sphingotec, Deltex Medical and Retia Medical. Fabrice Vallée has received research support from Radiometer, Deltex Medical and Retia Medical. Sandrine Millasseau has received Consulting Fees from Alam Medical, AtCor Medical, Mesi Medical and Omron.

Ethical approval This study was approved by the SRLF Ethics Committee (n°CE SRLF 11-356). This was an observational study of "routine care".

Informed consent Patients were included after informed consent was obtained.

References

1. Société Française d'Anesthésie et de Réanimation: Stratégie du remplissage vasculaire périopératoire (2013). <https://sfar.org/strategie-du-remplissage-vasculaire-perioperatoire-2/>. Accessed 12 Dec 2019.
2. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte Op Reimer WJM, Vrints C, Wood D, Zamorano JL, Zannad F, Other experts who contributed to parts of the guidelines: Cooney MT, ESC Committee for Practice Guidelines (CPG), Bax J, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers: Funck-Brentano C, Sirnes PA, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener H-C, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancía G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European Guidelines on cardiovascular disease prevention in clinical practice (version: the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention and

- Rehabilitation (EACPR). *Eur Heart J*. 2012;2012(33):1635–701. <https://doi.org/10.1093/eurheartj/ehs092>.
3. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119:507–15. <https://doi.org/10.1097/ALN.0b013e3182a10e26>.
 4. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg*. 2005;100:4–10. <https://doi.org/10.1213/01.ANE.0000147519.82841.5E>.
 5. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S. Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology*. 2012;116:1195–203. <https://doi.org/10.1097/ALN.0b013e31825683dc>.
 6. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med*. 2002;30:1210–3.
 7. Coutrot M, Joachim J, Dépret F, Millasseau S, Nougé H, Matéo J, Mebazaa A, Gayat E, Vallée F. Non-invasive continuous detection of arterial hypotension during induction of anaesthesia using a photoplethysmographic signal: proof of concept. *Br J Anaesth*. 2019. <https://doi.org/10.1016/j.bja.2019.01.037>.
 8. Politi MT, Ghigo A, Fernández JM, Khelifa I, Gaudric J, Fullana JM, Lagrée P-Y. The dicrotic notch analyzed by a numerical model. *Comput Biol Med*. 2016;72:54–64. <https://doi.org/10.1016/j.compbiomed.2016.03.005>.
 9. Shi P, Hu S, Zhu Y, Zheng J, Qiu Y, Cheang PYS. Insight into the dicrotic notch in photoplethysmographic pulses from the finger tip of young adults. *J Med Eng Technol*. 2009;33:628–33. <https://doi.org/10.3109/03091900903150980>.
 10. Abramowitz M. Handbook of mathematical functions, with formulas, graphs, and mathematical tables. Mineola: Dover Publications, Incorporated; 1974.
 11. Willmott C, Matsuura K. Advantages of the mean absolute error (MAE) over the root mean square error (RMSE) in assessing average model performance. *Clim Res*. 2005;30:79–82. <https://doi.org/10.3354/cr030079>.
 12. Myles PS, Cui J. I. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth*. 2007;99:309–11. <https://doi.org/10.1093/bja/aem214>.
 13. Montenij LJ, Buhre WF, Jansen JR, Kruitwagen CL, de Waal EE. Methodology of method comparison studies evaluating the validity of cardiac output monitors: a stepwise approach and checklist ††This Article is accompanied by Editorial Aew110. *Br J Anaesth*. 2016;116:750–8. <https://doi.org/10.1093/bja/aew094>.
 14. Armstrong MK, Schultz MG, Picone DS, Andrew Black J, Dwyer N, Roberts-Thomson P, Sharman JE. Brachial and radial systolic blood pressure are not the same. *Hypertension*. 2019;73:1036–41. <https://doi.org/10.1161/HYPERTENSIONAHA.119.12674>.
 15. Nichols WW. McDonald’s blood flow in arteries: theoretical, experimental and clinical principles. London: Hodder Arnold; 2010.
 16. Peñáz J. Photoelectric measurement of blood pressure, volume and flow in the finger. In: Digest of the 10th international conference on medical and biological engineering, 1973, p. 104.
 17. Balzer F, Habicher M, Sander M, Sterr J, Scholz S, Feldheiser A, Müller M, Perka C, Treskatsch S. Comparison of the non-invasive Nexfin® monitor with conventional methods for the measurement of arterial blood pressure in moderate risk orthopaedic surgery patients. *J Int Med Res*. 2016;44:832–43. <https://doi.org/10.1177/0300060516635383>.
 18. Sharman JE, Marwick TH. Accuracy of blood pressure monitoring devices: a critical need for improvement that could resolve discrepancy in hypertension guidelines. *J Hum Hypertens*. 2019;33:89–93. <https://doi.org/10.1038/s41371-018-0122-6>.
 19. Stergiou GS, Palatini P, Asmar R, Ioannidis JP, Kollias A, Lacy P, McManus RJ, Myers MG, Parati G, Shennan A, Wang J, O’Brien E, European Society of Hypertension Working Group on Blood Pressure Monitoring. Recommendations and Practical Guidance for performing and reporting validation studies according to the Universal Standard for the validation of blood pressure measuring devices by the Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO). *J Hypertens*. 2019;37:459–66. <https://doi.org/10.1097/HJH.0000000000002039>.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Annexe 1.4 Article “Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.”

Cet article a été soumis au British Journal of Anaesthesia le 26 juin 2022. Les auteurs sont: Jona Joachim, Fabrice Vallée, Thomas Lefevre, Jacques Callebert, Étienne Gayat et Marc Lavielle.

British Journal of Anaesthesia

Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.

--Manuscript Draft--

Manuscript Number:	BJA-D-22-00974
Full Title:	Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.
Article Type:	Clinical Investigation
Keywords:	Hemodynamics, Hypotension, Norepinephrine, PKPD, pharmacology, TCI
Corresponding Author:	Jona Joachim AP-HP: Assistance Publique - Hopitaux de Paris PARIS, FRANCE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	AP-HP: Assistance Publique - Hopitaux de Paris
Corresponding Author's Secondary Institution:	
First Author:	Jona Joachim
First Author Secondary Information:	
Order of Authors:	Jona Joachim Fabrice Vallée Thomas Lefevre Jacques Callebert Étienne Gayat Marc Lavielle
Order of Authors Secondary Information:	
Abstract:	<p>Introduction Intraoperative hypotension is an ever-increasing burden for the fragile population under general anesthesia. Low dose peripheral norepinephrine has shown encouraging results to reduce organ dysfunction, however its current use is not standardized. Target-controlled infusion could provide a patient-centric drug therapy solution. This study aims to develop a PKPD model which would make possible target-controlled norepinephrine infusion in the perioperative context.</p> <p>Methods Patients for elective surgery needing vasopressor support to correct hypotension were included in this study from June 2018 to December 2021 in Lariboisière Hospital, AP-HP, Paris. Low dose norepinephrine was administered peripherally according to study protocol and arterial blood samples were drawn iteratively in order to measure plasma concentration over time and were synchronized with patient monitor data and arterial blood pressure. Empirical and mechanistic PKPD models were developed and tested for accuracy in the study population.</p> <p>Results Twenty-nine patients were analyzed. Time to peak effect for MAP was 74s [53 - 73]. After bolus administration, MAP increased by 24% [15 - 31], heart rate was reduced by 8% [2 - 11] and stroke volume was reduced by 8% [2 - 11]. A three compartment mamillary model showed best fit for PK data. An empirical Emax and a mechanism-based Windkessel model were tested to explain norepinephrine effect on MAP and showed similar goodness-of-fit on individual patient data.</p> <p>Conclusions A three-compartment PK model as well as empirical and mechanistic PD models can be used to accurately model norepinephrine plasma concentration and effect on MAP</p>

	over time after intravenous administration.
Suggested Reviewers:	Xavier Declèves, Professor Professor of Pharmacokinetics, Hospital Cochin xavier.decleves@aphp.fr Specialist in PKPD modeling
	Douglas Eleveld, Professor University of Groningen d.j.eleveld@umcg.nl PKPD specialist. Published on PKPD in BJA earlier this year.
	Michel Struys, Professor Chair of the Department of Anaesthesiology, Peri-operative pharmacology and medi, University of Groningen m.m.r.f.struys@umcg.nl PKPD specialist. Published on PKPD in BJA earlier this year.
Opposed Reviewers:	
Additional Information:	
Question	Response
Date of trial registration (if applicable)	03-05-2018
Date trial initiated (if applicable)	06-27-2018
Date first subject enrolled (if applicable)	06-27-2018

Dear Editors of the British Journal of Anaesthesia,

Please, find for your consideration our latest manuscript entitled « Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anesthesia. » as a clinical investigation.

Intraoperative hypotension has been identified as a major risk factor for postoperative organ dysfunction and increased mortality. Current guidelines recommend to avoid hypotension during anesthesia and low-dose dilute norepinephrine is establishing itself as a key treatment in this context. It has been shown that low-dose norepinephrine reduces the risk of postoperative organ dysfunction (Futier et al. JAMA 2017; 318: 1346–57). However, norepinephrine handling and titration can be challenging. Indeed, it is a potent drug and its routine use on peripheral venous catheters has been the source of much debate in past years. Currently, administration has not been standardized and norepinephrine is administered empirically. One way to provide standardized and patient centric norepinephrine infusion is through target controlled infusion. The basis of target controlled infusion is pharmacokinetic-pharmacodynamic (PKPD) modeling which makes it possible to calculate plasma concentration and effect on arterial blood pressure as a function of time.

In this work we develop a PKPD model for dilute norepinephrine in healthy patients. For the sake of the study, repeated plasma samples were obtained in order to measure plasma concentration and patient vitals were recorded and synchronized to norepinephrine infusion and blood samples. The data was used to fit and compare PKPD models for norepinephrine using state-of-the-art pharmacometric modeling software.

We conclude that PKPD modeling for norepinephrine is possible and provide the parameters of the identified models.

Our work is of great interest for anesthesia care providers since it can be used to estimate the required norepinephrine dose in real time, can be used in infusion pumps for target controlled infusion and has potential applications in closed loop anesthesia. As such, it could change everyday anesthesia practice.

We have never presented this work elsewhere for consideration and believe that the British Journal of Anaesthesia, with its innovation-seeking, would be our preferred outlet to share our results.

Fabrice Vallee, Thomas Lefevre, Jacques Callebert, Etienne Gayat, Marc Lavielle and Jona Joachim

CONFLICT OF INTEREST FORM

Manuscript Title: Development of a pharmacokinetic-pharmacodynamic model for low dose peripheral norepinephrine during general anaesthesia.

Author(s): Jona Joachim MD; Fabrice Vallee PhD; Thomas Lefevre MD; Jacques Callebert PhD ; Etienne Gayat PhD ; Marc Lavielle PhD

PLEASE NOTE: As an integral part of the online submission process, each manuscript must contain a declaration of interests from ALL authors. Corresponding authors are required to confirm whether they and/or their co-authors have any competing interests to declare, and to provide details of these. The corresponding author is required to complete and upload this Declaration of Competing Interests form when submitting a manuscript to BJA via our online submissions system (at <https://www.editorialmanager.com/bja/default1.aspx>). It is the corresponding author's responsibility to ensure that all authors adhere to this policy.

BJA requires disclosure by all authors of any financial interests or connections, direct or indirect, or other situations which may *raise the question of bias* in the work reported or the conclusions, implications, or opinions stated. **When considering whether you should declare a competing interest or connection please consider the competing interest test: Is there any arrangement that would embarrass you or any of your co-authors if it was to emerge after publication and you had not declared it?**

If the manuscript is published, this declaration of competing interests information may be communicated in a statement in the published paper. If an author states that there are no competing interests then a statement to this effect may be included in the published paper.

Please complete either section I or section II

I. The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated:

Printed Name (corresponding author): [Click here to enter text.](#)

Signature: _____

Date: [Click here to enter a date.](#)

OR

II. Conflict of interest statement declared by the corresponding author on behalf of all authors:

Example: *Drs A & B have received payments and travel funding from [business name] for overseas lectures. Total funding: approximately [Amount]. Dr C holds stock in [business name], the makers of [product], and is currently conducting research sponsored by this company. Dr A is also a member of the speakers' bureau for [business name].*

The authors' joint statement is as follows:

Pr Etienne Gayat has received consulting fees from Magnisense, research support from Sphingotec, Deltex Medical and Retia Medical.

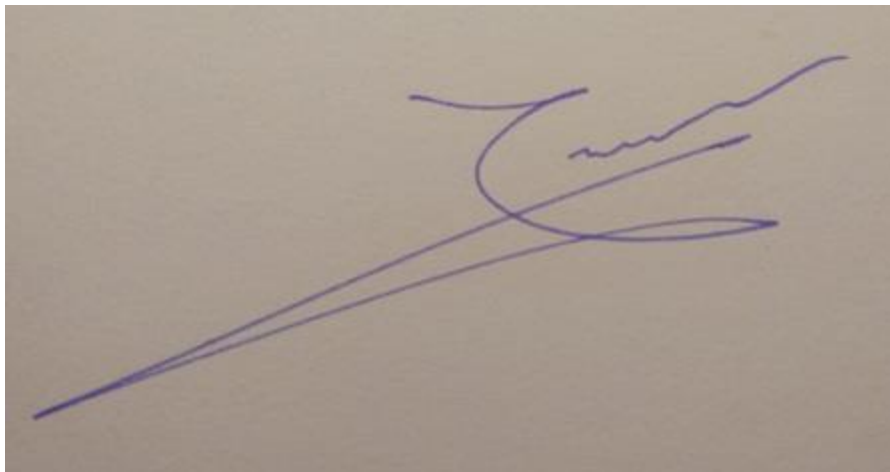
Pr Fabrice Vallée has received research support from Radiometer, Deltex Medical and Retia Medical.

Fabrice Vallée, Etienne Gayat and Jona Joachim are coinventors for patents US2020390347A1 and US10653364B2 for inventions related to blood pressure monitoring.

Drs Thomas Lefevre, Jacques Callebert and Marc Lavielle do not have any conflicts of interest to declare.

Printed Name (corresponding author): Dr Jona JOACHIM

Signature: Dr Jona JOACHIM

A photograph of a handwritten signature in blue ink on a light-colored surface. The signature is stylized and appears to be 'Jona JOACHIM'. The ink is a vibrant blue, and the background is a plain, light-colored paper or card.

Date: 06/07/2022

1
2
3
4 **Development of a pharmacokinetic-pharmacodynamic model for low**
5 **dose peripheral norepinephrine during general anaesthesia.**
6
7
8
9

10 Jona Joachim^{1,2}, MD ; Fabrice Vallee^{1,2}, PhD ; Thomas Lefevre², MD ; Jacques Callebert^{1,3},
11 PhD ; Etienne Gayat^{1,2}, PhD ; Marc Lavielle⁴, PhD
12

13 ¹ Université Paris Cité, INSERM, U942 MASCOT, F-75006, Paris, France.
14

15 ² Department of Anaesthesiology, Burn and Critical Care, St-Louis-Lariboisière-Fernand Widal University
16 Hospitals, F-75010, Paris, France.
17

18 ³ Service of Biochemistry and Molecular Biology, St-Louis-Lariboisière-Fernand Widal University Hospitals, F-
19 75010, Paris, France.
20

21 ⁴ Inria & CMAP, Ecole Polytechnique, CNRS, Institut Polytechnique de Paris, Paris, France.
22
23
24
25

26 **Running title:**

27
28 Towards target-controlled infusion for Norepinephrine.
29
30

31 **Corresponding author:**
32

33
34 Jona Joachim, jona@joachim.cc, Tel: +33 1 49 95 80 71
35

36 Department of Anesthesiology, Burn and Critical Care, St-Louis-Lariboisière-Fernand Widal
37 University Hospitals, 2 rue Ambroise Paré, 75010 Paris
38
39
40

41 If available the 16-digit ORCID of the authors

42 Jona Joachim : 0000-0002-2945-4554

43 Fabrice Vallée : 0000-0001-8204-3626

44 Etienne Gayat: 0000-0002-3334-3849
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **Authors' contribution**
5
6

7 J.J., F.V., T.L. J.C., E.G., M.L. conception and design of research; J.J., T.L., and F.V. performed
8 experiments; J.C. performed lab sample analysis, J.J., M.L and E.G. analyzed data; J.J., M.L.,
9 F.V and E.G. interpreted results; J.J., M.L. prepared figures; J.J. and M.L. drafted manuscript;
10 J.J., F.V., T.L. J.C., E.G., M.L. edited and revised the manuscript; J.J., F.V., T.L. J.C., E.G., M.L.
11 approved the final version of manuscript.
12
13
14
15

16 **Acknowledgments**
17

18 We thank anaesthetic nurses for their support in the conduct of the present study.
19
20
21
22

23 **Abbreviations**
24

25 PID controller: proportional–integral–derivative controller
26

27 MAP: mean arterial blood pressure
28

29 PK: pharmacokinetics
30

31 PD: pharmacodynamics
32

33 RLC circuit: circuit consisting of a resistor (R), an inductor (L), and a capacitor (C)
34

35 EtCO₂: end-tidal CO₂
36

37 mmHg: millimetres of mercury
38

39 LBM: lean body weight
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Abstract

Introduction

Intraoperative hypotension is an ever-increasing burden for the fragile population under general anaesthesia. Low dose peripheral norepinephrine has shown encouraging results to reduce organ dysfunction, however its current use is not standardized. Target-controlled infusion could provide a patient-centric drug therapy solution. This study aims to develop a PKPD model which would make possible target-controlled norepinephrine infusion in the perioperative context.

Methods

Patients for elective surgery needing vasopressor support to correct hypotension were included in this study from June 2018 to December 2021 in Lariboisière Hospital, AP-HP, Paris. Low dose norepinephrine was administered peripherally according to study protocol and arterial blood samples were drawn iteratively in order to measure plasma concentration over time and were synchronized with patient monitor data and arterial blood pressure. Empirical and mechanistic PKPD models were developed and tested for accuracy in the study population.

Results

Twenty-nine patients were analysed. Median time to peak effect for MAP was 74s [53 - 73]. After bolus administration, MAP increased by 24% [15 - 31], heart rate was reduced by 8% [2 - 11] and stroke volume was reduced by 8% [2 - 11]. A three compartment mamillary model showed best fit for PK data. An empirical Emax and a mechanism-based Windkessel model were tested to explain norepinephrine effect on MAP and showed similar goodness-of-fit on individual patient data.

Conclusions

A three-compartment PK model as well as simple empirical and mechanistic PD models can be used to accurately model norepinephrine plasma concentration and effect on MAP over time after exogenous administration.

Keywords:

Hemodynamics, Hypotension, Norepinephrine, PKPD, pharmacology, TCI

Introduction

With an ever-increasing number of elderly and fragile patients, intraoperative hypotension constitutes a major and increasing challenge for current anaesthesiology practice. Deleterious effects of intraoperative hypotension have been established in numerous studies for all major organs, including myocardial damage, kidney injury and adverse neurologic outcomes as well as increased post-operative mortality¹⁻⁴.

Peripherally administered low concentration norepinephrine has seen increased interest in recent years in the perioperative setting as well as in emergency departments⁵⁻⁹. Treatment of intraoperative hypotension with peripheral norepinephrine showed encouraging results in the reduction of organ damage¹⁰. As a result, peripheral Norepinephrine is rapidly becoming a standard of care around the world for treatment of hypotension in the perioperative and other settings¹¹.

Current treatment strategies are not satisfactory. Indeed, peripheral norepinephrine is currently administered manually without firmly established standards using infusion and/or boluses. These treatment strategies are not patient specific and can result in inaccurate and delayed treatment. Strategies have been developed for closed loop infusion using proportional–integral–derivative (PID) controllers^{12, 13} but only partially address this problem since the absence of pharmacometric models makes dose calculation very difficult. Indeed, Norepinephrine is a potent drug with a small therapeutic index and large interindividual response variability.

We believe that target-controlled infusion (TCI) could solve these problems by providing standardized treatment regimens based on patient specific models making it possible to correct hypotension rapidly while limiting the risk of overdose and blood pressure variability, thus improving efficacy and safety of peripheral norepinephrine treatment. However, to build such a tool, it is essential to know the pharmacological parameters of norepinephrine at low concentration.

Accordingly, this study aimed to develop a pharmacokinetic / pharmacodynamic (PKPD) model for low concentration norepinephrine suitable for target-controlled infusion during anaesthesia.

Methods

Patients

This study was approved by a research ethics committee (CPP Sud-Ouest et Outre-Mer I 1-17-42) and was registered to ClinicalTrials.gov (NCT03454204). The study was conducted from June 2018 to December 2021 in the department of anaesthesiology at Lariboisière University Hospital (Assistance publique-Hôpitaux de Paris, Paris, France). Patients were included after informed written consent was obtained. Patients were eligible when they were older than 18 years and invasive monitoring of blood pressure was indicated. Patient demographics were collected through the anaesthesia consultation. The following data

1
2
3
4 were collected and were available as covariates for the model: history of hypertension,
5 smoking, age, weight, height, body mass index (BMI), lean body mass (LBM), sex, co-
6 morbidities, American Society of Anaesthesiology (ASA) class of anaesthetic risk, usual
7 treatment of the patient and possible modifications for the procedure, title of the
8 intervention procedure.
9

11 Anaesthesia protocol

13 General anaesthesia was induced and maintained by TCI of Propofol and Remifentanil,
14 adjusted for bispectral index between 40 and 60. All patients were intubated after
15 neuromuscular blockade by Atracurium (0.5 mg/kg) and mechanically ventilated with a
16 tidal volume of 6 to 8 ml/kg and a respiratory rate adjusted to obtain $EtCO_2$ between 35
17 and 38 mmHg. Ventilation parameters were adjusted during the procedure according to
18 arterial blood gas analysis. Radial or femoral artery catheter was inserted after induction of
19 anaesthesia before skin incision. Dilute Norepinephrine tartrate at a concentration of 5
20 $\mu\text{g/ml}$ was used as a standard of care vasopressor at our institution using infusion and/or
21 bolus by syringe pump.
22
23
24

25 When patients were included in the study protocol, norepinephrine could be administered
26 according to study protocol when intraoperative hypotension occurred. An initial bolus of
27 10 μg Norepinephrine tartrate was administered, followed by further infusion or boluses at
28 the discretion of the caring physician. When continuous infusion was administered, a fixed
29 infusion rate was set and was kept constant until mean arterial pressure (MAP) stabilized
30 at a plateau, at which point a different infusion rate or bolus could be administered with
31 the same modalities. Some patients were treated with norepinephrine infusion prior to
32 data acquisition. Infusion rate needed to be constant for a least ten minutes before start of
33 acquisition in order to assure steady state conditions.
34
35
36

37 During the study protocol, care was taken that the patient was not subject to any other
38 external factors with effect on blood pressure such as other vasopressors, vasodilatory
39 drugs or excessive surgical stimulation. If any of these stimulations were present, patients
40 could be excluded because effect could not be reliably attributed to norepinephrine. In
41 particular, care was taken that patients were in steady state infusion of propofol and
42 remifentanil and the level of propofol and remifentanil was not modified during the data
43 acquisition.
44
45
46

47 Data Acquisition

48
49 Data was obtained from three different sources, connected to a single computer and
50 synchronized with the computer in order to ensure the synchronization of all signals and to
51 fit an accurate model. All systems were connected to the same network time server¹⁴ in
52 order to be in sync with universal time at a precision of 10 milliseconds.
53
54

55 Details on blood sampling procedure, technique of norepinephrine preparation and
56 infusion, and norepinephrine concentration measurements are provided in [supplementary](#)
57 [material 1, 2 and 3 respectively](#).
58
59
60
61
62
63
64
65

Patient monitor

Patient biometric data was obtained using a Philips IntelliVue MX850 bedside patient monitor (Philips, Eindhoven, The Netherlands). The device was connected to the Data Warehouse Connect storage solution (Philips, Eindhoven, The Netherlands) which enables automated database storage in real time of the data from the patient monitor for offline analysis. For the aim of this study, we used the recordings of arterial blood pressure, heart rate, cardiac output and stroke volume. Data was synchronized with universal time at a sampling rate of 1 Hz for calculated numeric values such as mean arterial blood pressure (MAP) and 125 Hz for waveform data.

Pharmacometric Modelling

Population analysis was performed with the Monolix software suite (Monolix version 2021R1. Antony, France: Lixoft SAS, 2021.) using nonlinear mixed-effect modelling. This software uses the stochastic approximation expectation maximization (SAEM) algorithm to obtain estimates of the population parameters and Bayesian inference to estimate individual parameters. Pharmacokinetic and pharmacodynamic models were expressed in the MLXTRAN language as differential equations.

Log-normal distributions were chosen for all individual parameters.

The residual error model for PK and PKPD models was chosen as a combination of a constant term and a term proportional to the prediction f : $Obs = f + (a + b \cdot f) \cdot \epsilon$.

During model building, the change in log-likelihood, information criterion and prediction error were compared between candidate models at each step.

Goodness-of-fit was evaluated using predictions vs observations plots and the individual weighted residuals (IWRES). Parameter uncertainty was estimated using importance sampling. Prediction-corrected visual predictive checks (VPC) were used to evaluate the models¹⁵.

A covariate model was considered to explain part of the parameter variability. Relevant covariates were retained on a per-parameter basis when they permitted to reduce the BIC criterion. In order to minimize BIC, the Stochastic Approximation for Model Building Algorithm (SAMBA) procedure was used¹⁶.

Pharmacokinetics (PK)

Norepinephrine plasma concentration as a function of time was described using mammillary models. Models consisting of 1, 2 and 3 compartments were fitted and compared using Monolix. Model 1 was the simplest model with only one central compartment and no peripheral compartment. Model 2 was a model with one central compartment and a depot compartment. Model 3 was a model with a central compartment, a depot compartment and a peripheral compartment.

Mammillary models are formalized by a system of differential equations which describe passive diffusion between compartment. The concentration of the central compartment

(Cc) serves as input to the PD model and explains effect on blood pressure. The system of differential equations for the model 3 was defined as follows:

$$\begin{cases} \frac{d}{dt} A_d = -k_a A_d^\beta \\ \frac{d}{dt} A_c = k_a A_d^\beta - k_{12} A_c + k_{21} A_p - k_{10} A_c \\ \frac{d}{dt} A_p = k_{12} A_c - k_{21} A_p \end{cases}$$

Plasma concentration was obtained as

$$C_c = C_{endo} + \frac{A_c}{V_c}$$

The three-compartment model which we analysed was composed of a central compartment which corresponds to the plasma volume and a peripheral compartment which corresponds to a theoretical buffer compartment possibly composed of the endothelium. The depot compartment was used to model convection of injected Norepinephrine as it homogenizes in the plasma after intravenous administration.

The absorption rate from the Ad compartment into the Ac compartment is proportional to A_d^β , β being a model parameter.

Ac, Ap and Ad stand for the amount of drug in the central, peripheral and depot compartments respectively, k_{12} , k_{21} and k_a stand for the diffusion constants between the central, peripheral and depot compartments and k_{10} is the elimination constant. C_{endo} is the baseline physiological plasma concentration before start of infusion. As such, C_{endo} is the result at equilibrium of endogenous production and elimination of Norepinephrine and can thus be considered constant. V_c is the volume of the central compartment.

A graphical illustration of the three-compartment mammillary model can be seen in supplementary appendix 4.

Pharmacodynamics (PD)

Pharmacodynamic models describe drug effect (E) in terms of drug plasma concentration (Cc). Mean arterial blood pressure (MAP) values as a function of Norepinephrine plasma concentration were considered as drug effect (E). We successively tested an empirical model, a mechanism-based model inspired by the Windkessel theory and finally a mixture model of the empirical and mechanism-based models.

PD models were tested separately by using as input the three-compartment PK model described above.

Empirical model

One of the most common family of PD models are the Emax models. This family of models describes the effect in terms of baseline effect when no drug is present (E_0), maximum effect when increasing doses of drug cannot result in further effect increase (E_{max}), and

1
2
3
4 EC_{50} , the drug concentration that results in an effect half way between E_0 and E_{max} . These
5 model parameters are used to parametrize a sigmoid response curve.
6

7 We chose to test a variation of the Emax model based on the Hill equation¹⁷. This model can
8 be formulated as follows:
9

$$10 \quad E(t) = E_0 + \frac{(E_{max} - E_0) \cdot Cc^n}{Cc^n + EC_{50}^n} \quad (1)$$

11
12
13
14 The additional parameter n is called the Hill coefficient. Its value can be interpreted as the
15 interactions between the binding of ligand and receptor based on previous bindings. When
16 n is greater than 1, we see positively cooperative binding, meaning ligand binding increases
17 affinity for further ligand binding. When n is less than 1, we see negatively cooperative
18 binding, meaning ligand binding decreases affinity for further ligand binding. When n
19 equals 1, the ligand affinity is not dependent on prior ligand binding.
20
21

22 *Mechanism-based model*

23
24 The relationship between cardiac ejection and arterial blood pressure has been described
25 using the so-called Windkessel model¹⁸ since the beginning of the twentieth century. In the
26 most general case, the Windkessel model is equivalent to an electric RLC circuit¹⁹, where R
27 represents the peripheral vascular resistance, C represents the compliance of large elastic
28 arteries and L represents inertia of blood flow. $e(t)$ is the external applied voltage.
29
30

31 A graphical illustration of the RLC circuit model can be seen in supplementary appendix 4.
32

33 By applying Kirchhoff's second law to the RLC circuit, it is possible to derive the differential
34 equation of the system voltage:
35
36

$$37 \quad LC \frac{d^2}{dt^2} u(t) + RC \frac{d}{dt} u(t) + u(t) = e(t)$$

38
39
40 Using the electronic-hydraulic analogy, this equation can be rewritten as:

$$41 \quad \frac{d^2}{dt^2} E + 2\zeta\omega \frac{d}{dt} E + \omega^2 E = m \cdot C_c \quad (2)$$

42
43 E is mean arterial blood pressure (MAP). ω is the undamped natural frequency defined as
44 $\omega = \frac{1}{\sqrt{LC}}$. ζ is the damping ratio defined as $\zeta = \frac{1}{2}R\sqrt{\frac{C}{L}}$. It is possible to calculate the half-life
45 of the effect as: $\tau = \frac{2\zeta}{\omega}$.
46
47

48 Equation 2 can be shifted in order to accommodate our initial conditions at time $t = 0$
49 when $E = E_0$ and $C_c = C_0$ resulting in equation 3 which is the final equation used for the
50 model.
51

$$52 \quad \frac{d^2}{dt^2} E + 2\zeta\omega \frac{d}{dt} E + \omega^2 (E - E_0) = m \cdot (C_c - C_0) \quad (3)$$

53
54
55
56
57
58
59
60
61
62
63
64
65

Mixture model

In order to examine whether there exist subpopulations of individuals whose responses are described by either the Emax model or the Windkessel model, we used a between-subject model mixture (BSMM) model. In this model, each patient can be attributed one structural model, Emax or Windkessel, according to which model best describes patient response. A probability p is estimated to be the proportion of patients best described by the Emax model. The structural model chosen for a given subject is Emax with probability p and Windkessel with probability $1-p$. The group to which an individual patient belongs is estimated as the group of highest conditional probability.

Results

Patients

From November 2019 to March 2021, 34 patients were included for this study. The characteristics of the population are summarized in table 1. Five patients (15%) were excluded. One patient was excluded because blood samples could not be obtained, one patient was excluded because Norepinephrine plasma samples were not interpretable, and three patients were excluded because MAP was varying due to surgical stimulation. Twenty-nine patients were analysed. Surgical indications were intracranial meningioma (32%), intracranial aneurysm (21%), other intracranial tumour (32%), spine surgery (3%), other (12%).

Descriptive hemodynamic data

For the 29 analysed patients, the total duration of data sampling was 499 minutes. During this period, 35 boluses and 82 infusions were administered.

During the entire study period, 717 plasma samples for norepinephrine were obtained and 34736 measurements of MAP were recorded.

The median concentration of dilute Norepinephrine tartrate solution prepared for IV administration (as described in supplementary appendix 1) was 5.35 $\mu\text{g/mL}$ [4.77 - 5.85].

Bolus

Baseline hemodynamic values were MAP 68 [63 - 73] mmHg, heart rate 65 [60 - 72] bpm, cardiac output 4.2 [3.3 - 5.2] L/min and stroke volume 69 [56 - 84] mL. At peak effect, after a bolus of 10 μg of norepinephrine tartrate, MAP increased by 24% [15 - 31], heart rate was reduced by 8% [2 - 11], cardiac output was reduced by 20% [15 - 28] and stroke volume was reduced by 8% [2 - 11]. Time to peak effect for MAP was 74 s [53 - 73], for heart rate 74 s [63 - 102], for cardiac output 61 s [51 - 81] and for stroke volume 61 s [51 - 72].

Infusion

During continuous infusion, effect plateau was reached after a median of 360 seconds. MAP increased 13% [9 - 20], heart rate reduced by 5% [2 - 9], cardiac output reduced by 15% [9 - 20] and stroke volume reduced by 6% [2 - 9].

PK model

The three models were fitted individually. Model 3 show minimal information criterion (AIC, BIC) and exhibits the best performance to explain Norepinephrine pharmacokinetics in our population. Values for AIC and BIC can be seen in supplementary appendix 5. Plots of prediction vs observation, IWRES and VPC are available in [supplementary appendix 8, 9 and 10](#). An example of PK model prediction is shown in [figure 1](#) panel a.

Individual PK model fits for all patients can be seen in [supplementary appendix 11](#).

PKPD Model

After estimation of parameters for PK and PD models individually and after selection of best models, we ran estimations for joint PKPD models using previously estimated parameter distributions as initial values.

We first tested the Emax Hill model. Upon visual inspection, we noted that overall goodness of fit was satisfying, however several patients presented an “undershoot” of blood pressure after bolus administration of norepinephrine as seen in supplementary appendix 6.

This effect, which was notable in some patients but not all, could not be modelled using a classic Emax model since these models cannot predict blood pressure below baseline (E0). In order to model the observed behaviour in some patients, it appeared necessary to introduce a second order model. The Windkessel model was chosen as a candidate model because it has a long history in hemodynamic monitoring, is built on solid physiologic concepts and presents second order dynamics. A comparison between Emax Hill and Windkessel fits for two patients can be seen in figure 2. Finally, a mixture model (BSMM) of both Emax and Windkessel models was tested in order to assert whether two different subpopulations existed in our study population.

Values for AIC and BIC can be seen in supplementary appendix 5. Plots of prediction vs observation, IWRES and VPC for both models are available in supplementary appendix 8-10. An example of PKPD model prediction is shown in figure 1 panels b and c.

The final values of parameters that we obtained as very as standard deviations are summarized in table 2.

Individual PKPD BSMM model fits for all patients can be seen in supplementary appendix 12.

Covariate model

A linear model between the logarithm of individual parameters and the logarithm of covariates was considered.

1
2
3
4 The general formula linking individual parameters to population parameters and
5 covariates is $\log Param = \log Param_{pop} + \beta \log Covar$.
6

7
8 Significant correlation was identified for PK model parameters between $S0$ and age, $Tlag$
9 and height, ka and height, $V1$ and lean body mass.
10

11 Significant correlation was identified for the Emax PD model parameters between $E0$ and
12 age, $Emax$ and sex and n and age.
13

14 Significant correlation was identified for the Windkessel PD model parameters between $E0$
15 and age and ω and lean body mass.
16

17 Values for β are shown in supplementary appendix 5 for the Emax Hill and Windkessel
18 PKPD models.
19
20
21

22 Discussion

23

24 The results of this study show that it is possible to develop accurate PKPD models for low
25 dose Norepinephrine as currently used intraoperatively. Models can achieve high accuracy
26 when fitted on individual patients with mean errors as low as 1.5 mmHg. VPC show
27 increased error in the first two minutes of recording. Indeed, this period corresponds to
28 initial bolus administration. The data suggests that the PKPD models perform better during
29 infusion rather than bolus. Current trends tend to favour usage of infusion rather than
30 bolus since hemodynamic tolerance appears to be better¹⁰.
31
32
33

34 Indeed, in our study we found that rebound hypotension can occur after bolus
35 administration of norepinephrine, an effect which cannot be modelled by the empirical
36 Emax model. This effect has not been previously described to our knowledge. One of the
37 potential mechanisms could be internalization of $\alpha1$ receptors due to excessive
38 stimulation²⁰ but further studies are warranted in order to explain this effect.
39
40

41 The Windkessel model is based on physiologic concepts and the model parameters may
42 have clinical interpretations. Further studies are needed to establish whether the model
43 parameters are well correlated with clinical biomarkers such as arterial stiffness.
44
45

46 Due to its nature, the Hill model cannot predict values below $E0$ and above $Emax$. It is thus
47 impossible for this model to predict values below 57.09 mmHg and above 113.52 mmHg
48 for MAP with the parameters we identified. These values are well above and below the
49 usual physiologic values but may not be adequate for extreme situations. The Windkessel
50 model does not have any hard limits on the predicted values of MAP.
51
52

53 The only known PD model for norepinephrine we found in literature was the model
54 published by Oualha et al. in a paediatric population of neonates in paediatric intensive
55 care units²¹. This model corresponds to a special case of the Emax Hill model when the Hill
56 factor n is equal to one. Forcing n to 1 resulted in worse fit (results not shown).
57

58 One of the strengths of this study was to develop and compare a mechanism-based model
59 to an empirical model. Mechanism-based PD models are seeing increased interest lately²².
60
61
62
63
64
65

1
2
3
4 Indeed, mechanism-based models provide greater insight into physiologic processes and
5 may provide means to correlate effects with physiologic and pathologic findings. Our
6 findings suggest that mechanism-based models can compete with empirical models for
7 prediction. Furthermore, we also developed a mixture model combining empirical and
8 mechanism-based models which may be used to jointly use the strength of both model
9 types.
10
11

12 **Limits and perspectives**

13
14
15 Some confusion may arise when norepinephrine concentrations are expressed in mass
16 units since it may not be clear whether norepinephrine base or norepinephrine tartrate are
17 meant. In order to avoid this kind of confusion, all concentrations have been converted to
18 amount of substance in solution in *nmol/l*. Additionally, the drug concentrations in low
19 dose norepinephrine preparations vary greatly and no standard has been agreed on. In
20 order to make interpretation of our results easier and avoid confusion, we dosed the exact
21 amount of norepinephrine which was injected in *nmol*.
22
23

24 *Study population*

25
26 It was decided to include patients in neurosurgery since these patients are routinely
27 monitored using invasive blood pressure, procedures are of long duration and peripheral
28 low dose norepinephrine is needed routinely for most patients for blood pressure
29 maintenance and cerebral perfusion pressure. These patients did not suffer severe
30 cardiovascular disease or shock. Further studies may be warranted to show if our findings
31 can be applied to a more general population.
32
33

34 *Closed loop infusion perspective*

35
36 The cardiovascular system is a complex physiological apparatus with many individual
37 processes, many of which are difficult to measure. The simple PD models we present are
38 limited in their ability to extrapolate the number of different conditions a patient may
39 present. Indeed, non-measured external factors such as level of hydration and unknown
40 cardiovascular risk factors can greatly influence the effect of Norepinephrine on blood
41 pressure. However, the models show remarkable performance for individual prediction.
42 Since arterial blood pressure is readily measured in routine, it is possible to infer patient
43 specific models in real time to estimate patient specific parameters and thus obtain a very
44 accurate model to predict future treatment. This mode of operation seems particularly
45 suited to be incorporated into closed loop infusion systems.
46
47
48
49
50

51 **Conclusion**

52
53 In this study, we successfully developed and compared pharmacokinetic /
54 pharmacodynamic (PKPD) empirical and mechanism-based models for low concentration
55 peripherally administered norepinephrine in the operating room. These results show that
56 it is possible to estimate the effects of Norepinephrine infusion on plasma concentration
57
58
59
60
61
62
63
64
65

1
2
3
4 and mean arterial blood pressure suggesting that the appropriate dose can be calculated
5 for patient specific care.
6

7 8 9 **Conflict of Interest:**

10
11 Etienne Gayat has received consulting fees from Magnisense, research support from
12 Sphingotec, Deltex Medical and Retia Medical. Fabrice Vallée has received research support
13 from Radiometer, Deltex Medical and Retia Medical.
14

15 16 17 **References**

- 18
19 1. Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in
20 patients having a "triple low" of low blood pressure, low bispectral index, and low
21 minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012; **116**: 1195–
22 203
23
- 24
25 2. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean
26 arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical
27 definition of hypotension. *Anesthesiology* 2013; **119**: 507–15
28
- 29
30 3. Bijker JB, Klei WA van, Kappen TH, Wolfswinkel L van, Moons KGM, Kalkman CJ.
31 Incidence of Intraoperative Hypotension as a Function of the Chosen Definition: Literature
32 Definitions Applied to a Retrospective Cohort Using Automated Data Collection.
33 *Anesthesiology* [Internet] 2007 [cited 2018 Mar 28]; **107**: 213–20 Available from:
34 [http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/01.anes.0000270724.408](http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/01.anes.0000270724.40897.8e)
35 [97.8e](http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/01.anes.0000270724.40897.8e)
36
- 37
38 4. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative Hypotension and Perioperative
39 Ischemic Stroke after General Surgery. *Anesthesiology* [Internet] 2012 [cited 2022 Mar 1];
40 **116**: 658–64 Available from:
41 [https://pubs.asahq.org/anesthesiology/article/116/3/658/13036/Intraoperative-](https://pubs.asahq.org/anesthesiology/article/116/3/658/13036/Intraoperative-Hypotension-and-Perioperative)
42 [Hypotension-and-Perioperative](https://pubs.asahq.org/anesthesiology/article/116/3/658/13036/Intraoperative-Hypotension-and-Perioperative)
43
- 44
45 5. Medlej K, Kazzi AA, El Hajj Chehade A, et al. Complications from Administration of
46 Vasopressors Through Peripheral Venous Catheters: An Observational Study. *The Journal of*
47 *Emergency Medicine* [Internet] 2018 [cited 2022 Jan 26]; **54**: 47–53 Available from:
48 <https://linkinghub.elsevier.com/retrieve/pii/S0736467917308636>
49
- 50
51 6. Hasanin AM, Amin SM, Agiza NA, et al. Norepinephrine Infusion for Preventing
52 Postspinal Anesthesia Hypotension during Cesarean Delivery. *Anesthesiology* [Internet]
53 2019 [cited 2022 Jan 26]; **130**: 55–62 Available from:
54 [https://pubs.asahq.org/anesthesiology/article/130/1/55/18377/Norepinephrine-](https://pubs.asahq.org/anesthesiology/article/130/1/55/18377/Norepinephrine-Infusion-for-Preventing-Postspinal)
55 [Infusion-for-Preventing-Postspinal](https://pubs.asahq.org/anesthesiology/article/130/1/55/18377/Norepinephrine-Infusion-for-Preventing-Postspinal)
56
- 57
58 7. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak
59 S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized
60
61
62
63
64
65

1
2
3
4 Trial. *American Journal of Respiratory and Critical Care Medicine* [Internet] 2019 [cited
5 2022 Jan 26]; **199**: 1097–105 Available from:
6 <https://www.atsjournals.org/doi/10.1164/rccm.201806-10340C>
7

8
9 8. Ngan Kee WD. A Random-allocation Graded Dose–Response Study of
10 Norepinephrine and Phenylephrine for Treating Hypotension during Spinal Anesthesia for
11 Cesarean Delivery. *Anesthesiology* [Internet] 2017 [cited 2022 Jan 26]; **127**: 934–41
12 Available from: [https://pubs.asahq.org/anesthesiology/article/127/6/934/19137/A-](https://pubs.asahq.org/anesthesiology/article/127/6/934/19137/A-Random-allocation-Graded-Dose-Response-Study-of)
13 [Random-allocation-Graded-Dose-Response-Study-of](https://pubs.asahq.org/anesthesiology/article/127/6/934/19137/A-Random-allocation-Graded-Dose-Response-Study-of)
14

15
16 9. Cardenas-Garcia J, Schaub KF, Belchikov YG, Narasimhan M, Koenig SJ, Mayo PH.
17 Safety of peripheral intravenous administration of vasoactive medication: Peripheral
18 Administration of VM. *Journal of Hospital Medicine* [Internet] 2015 [cited 2022 Jan 26]; **10**:
19 581–5 Available from:
20 [http://www.journalofhospitalmedicine.com/jhospmed/article/127869/peripheral-](http://www.journalofhospitalmedicine.com/jhospmed/article/127869/peripheral-administration-vm)
21 [administration-vm](http://www.journalofhospitalmedicine.com/jhospmed/article/127869/peripheral-administration-vm)
22
23

24
25 10. Futier E, Lefrant J-Y, Guinot P-G, et al. Effect of Individualized vs Standard Blood
26 Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk
27 Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA* 2017; **318**: 1346–
28 57
29

30
31 11. Mets B. Should Norepinephrine, Rather than Phenylephrine, Be Considered the
32 Primary Vasopressor in Anesthetic Practice? *Anesthesia & Analgesia* [Internet] 2016 [cited
33 2018 Mar 5]; **122**: 1707 Available from: [https://journals.lww.com/anesthesia-](https://journals.lww.com/anesthesia-analgesia/Citation/2016/05000/Should_Norepinephrine,_Rather_than_Phenylephrine,.63.aspx)
34 [analgesia/Citation/2016/05000/Should_Norepinephrine,_Rather_than_Phenylephrine,.63.](https://journals.lww.com/anesthesia-analgesia/Citation/2016/05000/Should_Norepinephrine,_Rather_than_Phenylephrine,.63.aspx)
35 [aspx](https://journals.lww.com/anesthesia-analgesia/Citation/2016/05000/Should_Norepinephrine,_Rather_than_Phenylephrine,.63.aspx)
36

37
38 12. Joosten A, Delaporte A, Alexander B, et al. Automated Titration of Vasopressor
39 Infusion Using a Closed-loop Controller. *Anesthesiology* [Internet] 2019 [cited 2021 Sep 2];
40 **130**: 394–403 Available from:
41 [https://pubs.asahq.org/anesthesiology/article/130/3/394/19189/Automated-Titration-](https://pubs.asahq.org/anesthesiology/article/130/3/394/19189/Automated-Titration-of-Vasopressor-Infusion-Using)
42 [of-Vasopressor-Infusion-Using](https://pubs.asahq.org/anesthesiology/article/130/3/394/19189/Automated-Titration-of-Vasopressor-Infusion-Using)
43

44
45 13. Desebbe O, Rinehart J, Van der Linden P, et al. Control of Postoperative Hypotension
46 Using a Closed-Loop System for Norepinephrine Infusion in Patients After Cardiac Surgery:
47 A Randomized Trial. *Anesthesia & Analgesia* [Internet] 2022 [cited 2022 Mar 1]; **Publish**
48 **Ahead of Print** Available from:
49 <https://journals.lww.com/10.1213/ANE.0000000000005888>
50

51
52 14. Martin J, Burbank J, Kasch W, Mills PDL. Network Time Protocol Version 4: Protocol
53 and Algorithms Specification [Internet]. Internet Engineering Task Force; 2010 Jun Report
54 No.: RFC 5905. Available from: <https://datatracker.ietf.org/doc/rfc5905>
55

56
57 15. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-Corrected Visual
58 Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models. *The AAPS Journal*
59 [Internet] 2011 [cited 2022 Mar 17]; **13**: 143–51 Available from:
60 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085712/>
61
62
63
64
65

- 1
2
3
4 16. Prague M, Lavielle M. SAMBA: A novel method for fast automatic model building in
5 nonlinear mixed-effects models. *CPT: Pharmacometrics & Systems Pharmacology* [Internet]
6 2022 [cited 2022 Mar 31]; **11**: 161–72 Available from:
7 <https://onlinelibrary.wiley.com/doi/abs/10.1002/psp4.12742>
8
9
10 17. Buchwald P. A single unified model for fitting simple to complex receptor response
11 data. *Scientific Reports* [Internet] 2020 [cited 2022 Jan 26]; **10**: 13386 Available from:
12 <https://www.nature.com/articles/s41598-020-70220-w>
13
14 18. Frank O. *The basic shape of the arterial pulse. First treatise: Mathematical analysis.*
15 1899. *Journal of Molecular and Cellular Cardiology* 1990; **22**: 255–77
16
17 19. Westerhof N, Stergiopoulos N, Noble MIM. Snapshots of hemodynamics: An aid for
18 clinical research and graduate education. 2nd ed. New York: Springer Verlag; 2010.
19
20 20. Cowlen MS, Toews ML. Evidence for alpha 1-adrenergic receptor internalization in
21 DDT1 MF-2 cells following exposure to agonists plus protein kinase C activators. *Molecular*
22 *Pharmacology* 1988; **34**: 340–6
23
24 21. Oualha M, Tréluyer J-M, Lesage F, et al. Population pharmacokinetics and
25 haemodynamic effects of norepinephrine in hypotensive critically ill children. *British*
26 *Journal of Clinical Pharmacology* [Internet] 2014 [cited 2016 Feb 26]; **78**: 886–97 Available
27 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239982/>
28
29 22. Su H, Eleveld DJ, Struys MMRF, Colin PJ. Mechanism-based pharmacodynamic model
30 for propofol haemodynamic effects in healthy volunteers☆. *British Journal of Anaesthesia*
31 [Internet] 2022 [cited 2022 Mar 9]; **0** Available from:
32 [https://www.bjanaesthesia.org/article/S0007-0912\(22\)00031-9/fulltext](https://www.bjanaesthesia.org/article/S0007-0912(22)00031-9/fulltext)
33
34 23. Joachim J. InfuPy [Internet]. Zenodo; 2021 [cited 2021 Aug 16]. Available from:
35 <https://zenodo.org/record/5208192>
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figures

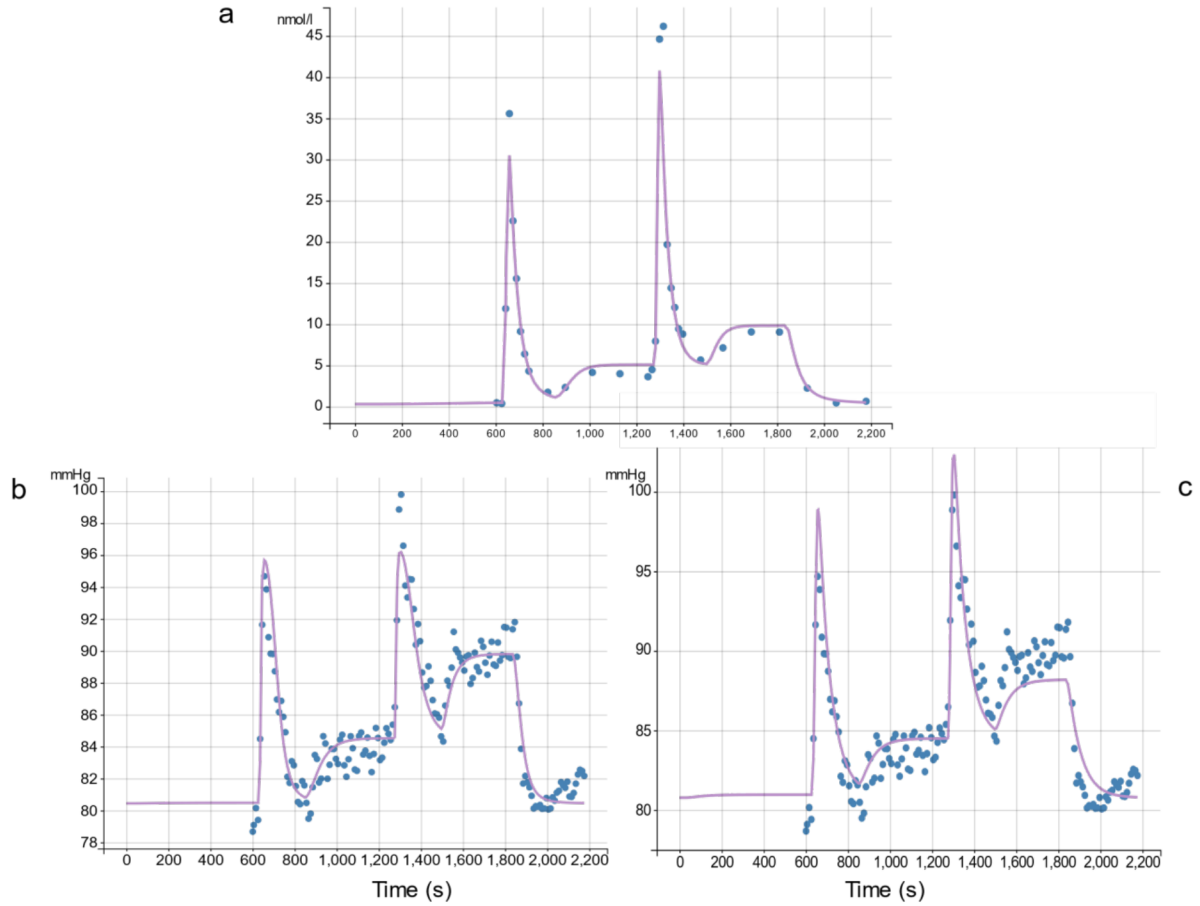


Figure 1: Example of individual prediction for one patient. Blue dots represent measurements and the purple curve represents individual prediction. Panel a. shows plasma concentrations and PK model prediction. Panels a and b show MAP over time as predicted by the Emax model (b) and the mechanistic model (c). The administration schema for this patient consisted of a pre-existing infusion at 19nmol/h followed by a bolus of 39nmol followed by an infusion of 44nmol over 427 seconds, followed by a new bolus of 39nmol, followed by an infusion of 71nmol over 340 seconds, followed by return to baseline for a procedure where temporary increase in blood pressure was required.”

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

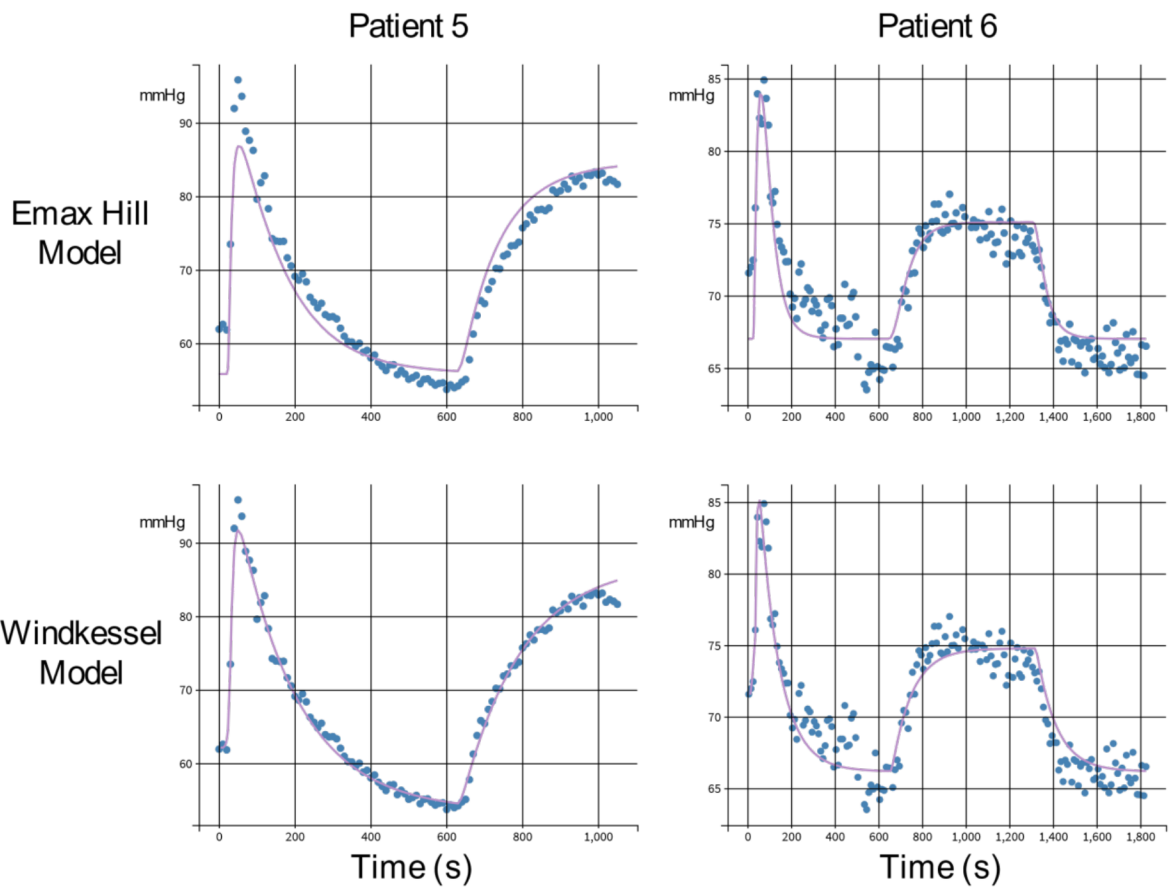


Figure 2: Example of two patients and respective predictions of Emax and Windkessel models. The undershoot in blood pressure after initial bolus is apparent in both patients and cannot be accurately modelled by the Emax model, resulting in underestimation of baseline blood pressure.”

Tables

Table 1: Patients' characteristics

	Median [IQR] or n(%)
Female	20 (69%)
Age (years)	52 [46 – 64]
Weight (kg)	71 [62 – 84]
Height (cm)	163 [158 – 173]
Body mass index (kg/m ²)	26 [22 – 29]

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

	Median [IQR] or n(%)
GFR ¹ (mL/min)	100 [88 - 128]
Hypertension	12 (41%)
Smoking	8 (28%)
Diabetes mellitus	5 (17%)
Dyslipidaemia	6 (21%)
Obesity	6 (21%)
Chronic kidney disease	2 (7%)
Prior Norepinephrine infusion	14 (48%)
Norepinephrine Plasma Baseline ² (nmol/l)	1.24 [0.59 - 1.36]

Table 2: Population parameters fitted for the PKPD mixture model

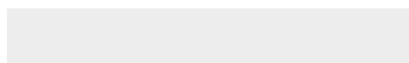
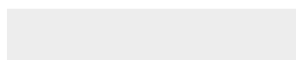
Parameter	Value	Standard deviation
C0	0.81	0.51
Tlag	25.31	0.33
ka	0.02	0.65
V1	0.49	0.36
k13	0.06	0.28
k31	0.04	0.58
k10	0.05	0.31
β	1.21	0.28
E0	57.09	0.22
E _{max}	113.52	0.51
EC50	15.7	0.59
n	1.46	0.7
ω	1.01	0.2
ζ	19.44	0.66
m	2.12	0.4

¹ Glomerular filtration rate (MDRD)

² results for patients without prior norepinephrine infusion



Click here to access/download
Supplementary Material
supplementary_appendix.docx



Supplementary material

Table of contents

Supplementary material.....	1
Supplement 1: Norepinephrine drug preparation	2
Supplement 2: Blood sampling	2
Supplement 3: Norepinephrine infusion data collection.....	2
Supplement 4: PK and PD model illustrations	3
Supplement 5: Supplementary tables	3
Supplement 6: “Undershoot” after bolus	5
Supplement 7: Raw data.....	6
Norepinephrine blood concentration for all patients	6
MAP for all patients	7
Supplement 8: Observation vs Prediction	8
Plasma concentration from PK model.....	8
Effect from PKPD models	9
Supplement 9: Residuals	10
PK model Residuals	10
PKPD model Residuals	11
Supplement 10: Visual predictive checks (VPC)	12
PK model prediction-corrected VPC	12
PKPD model prediction-corrected VPC	13
Supplement 11: Individual PK fits	14
Supplement 12: Individual BSMM PKPD fits	15

Supplement 1: Norepinephrine drug preparation

Norepinephrine dilution was done ahead of time at the bedside using an institution protocol. As per protocol, 1 ml of commercially available norepinephrine tartrate (8 mg/4 ml) was diluted in a 20 mL syringe, yielding a solution of 100 µg/ml. Of this intermediate solution, 5 ml were added to bags of 100 mL of normal saline to yield a final theoretical solution of Norepinephrine 4.76 µg/ml. Due to the manual dilution step which could potentially introduce a source of error, the final solution of dilute Norepinephrine was measured using the same technique as the patient plasma samples in order to measure the exact amount of Norepinephrine administered.

Supplement 2: Blood sampling

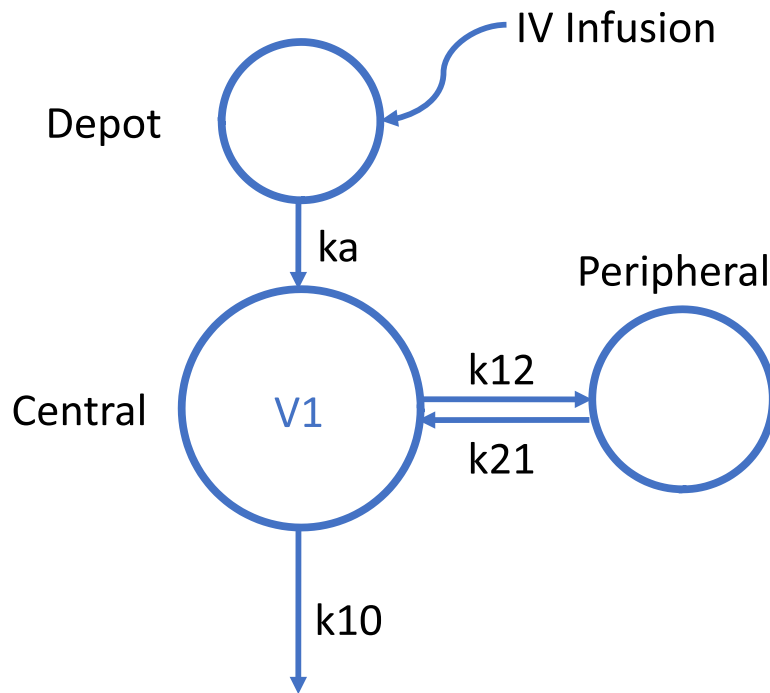
During infusion, arterial blood samples were taken regularly in order to measure plasma norepinephrine concentrations. Since we knew from experience that Norepinephrine has a very short half-life, care was taken to accurately locate the plasma samples in time. The sampling microtubes were labeled with a bar code beforehand and we designed a small software coupled to a bar code scanner which stored the sample microtube identifier together with the precise timestamp. Once the samples were drawn, the microtube was immediately scanned with the bar code scanner and then immediately put in ice in order to avoid norepinephrine degradation inside the sample tube by plasma enzymes. Microtubes of 1mL containing ethylenediaminetetraacetic acid (EDTA) were used to avoid clotting. Samples were forwarded to the biochemistry laboratory immediately after the end of the data collection.

Upon reception by the biochemistry laboratory, samples were analyzed using the standard procedure for plasma catecholamine dosage. Samples were immediately centrifuged and the obtained serum was purified. Plasma norepinephrine was extracted using selective adsorption on aluminum hydroxide. After acid elution, Norepinephrine was dosed using a specific kit (Chromsystems, Gräfelfing, Germany) by HPLC and Coulometry (CoulArray, Thermo Fisher Scientific, Waltham, MA, USA).

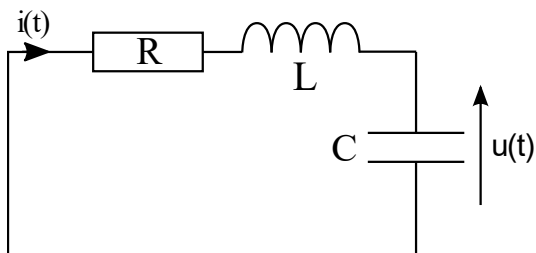
Supplement 3: Norepinephrine infusion data collection

Norepinephrine was infused using standard of care syringe pumps (Orchestra Module DPS, Fresenius Kabi, Brézins, France). The syringe pumps were interfaced using the RS232 output with an in-house developed software driver²³. Cumulative delivered volume was recorded in real time with a resolution of 0.001 ml. The measured volume data was synchronized with the computer clock. In addition to blood samples, we also took a sample of the dilute norepinephrine solution which we administered in the syringe. This was done because the norepinephrine dilution was prepared at the bedside and was potentially inaccurate. By dosing the norepinephrine solution in the drug solution, we were able to calculate precisely the amount which was administered to the patient. For each patient, the exact amount of Norepinephrine administered (converted to nmol) was considered for analysis.

Supplement 4: PK and PD model illustrations



Supplementary Figure 1: "Three compartment pharmacokinetic model"



Supplementary Figure 2: "Resistor-inductor-capacitor (RLC) electric model"

Supplement 5: Supplementary tables

PK model fit results

Compartments	AIC	BIC	BICc	-2LL
Model 1	2547	2561	2579	2527
Model 2	2450	2469	2494	2422
Model 3	2285	2313	2341	2245

Supplementary Table 1: "Information criteria for PK model fits"

PKPD model fit results

Model	AIC	BIC	BICc	-2LL
Emax Hill	18679	18716	18791	18625
Windkessel	19192	19229	19303	19138
BSMM	18666	18714	18813	18596

Supplementary Table 2: "Information criteria for PKPD model fits"

Emax Hill covariates

Parameter	Covariate	β
S0	age	1.32
Tlag	height	2.27
ka	height	1.43
V1	LBM	1.78
E0	age	-0.27
Emax	sex	-0.55
n	age	0.96

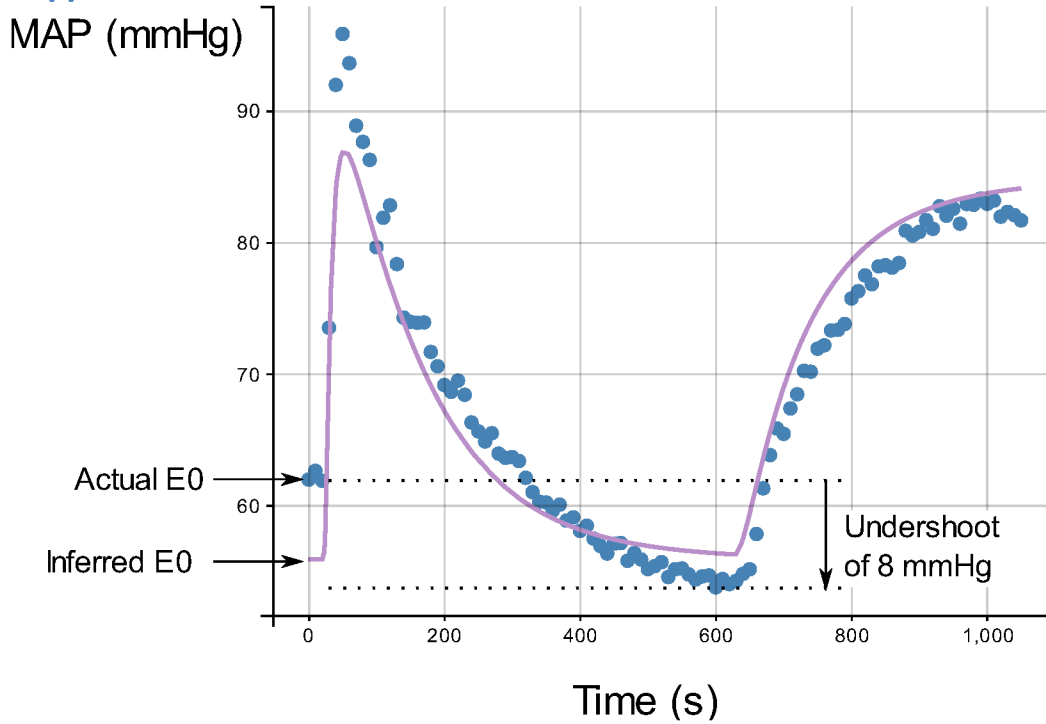
Supplementary Table 3: "Emax Hill model covariates and weights"

Windkessel covariates

Parameter	Covariate	β
S0	age	2.31
Tlag	height	2.61
ka	height	-0.39
E0	age	-0.5
ω	LBM	1.14

Supplementary Table 4: "Windkessel model covariates and weights"

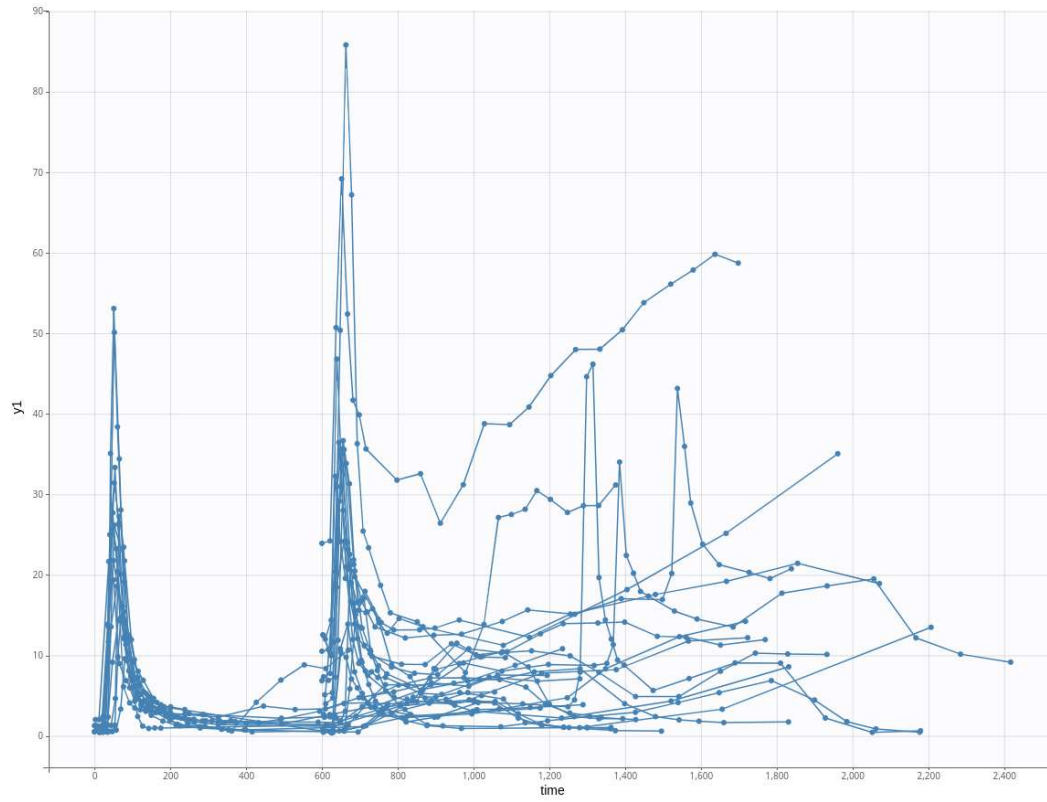
Supplement 6: "Undershoot" after bolus



Supplementary Figure 3: "Example of an individual patient who displays marked mean blood pressure undershoot of 8 mmHg after bolus administration of 10ug norepinephrine tartrate. The blue dots represent actual measured MAP values. The Emax Hill model (purple curve) is unable to account for the undershoot and infers an incorrect value for E0 in order to fit the data."

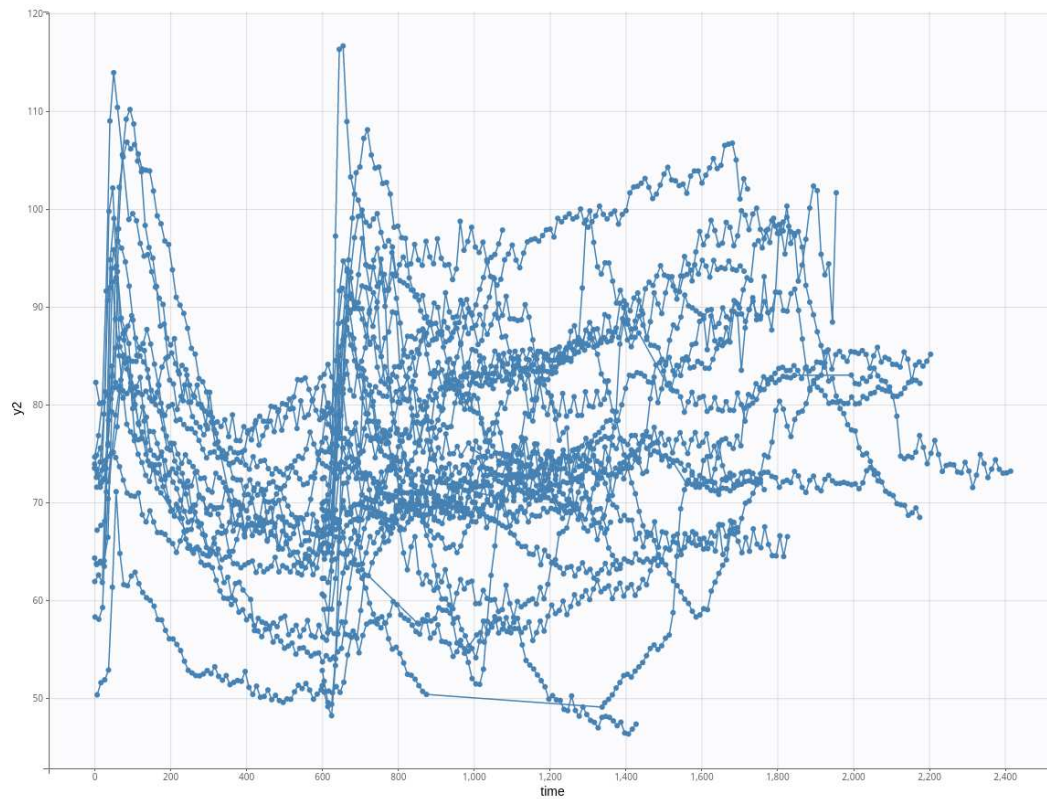
Supplement 7: Raw data

Norepinephrine blood concentration for all patients



Supplementary Figure 4: “Raw values of measured plasma concentration of norepinephrine (nmol/L) in all patients as a function of time.”

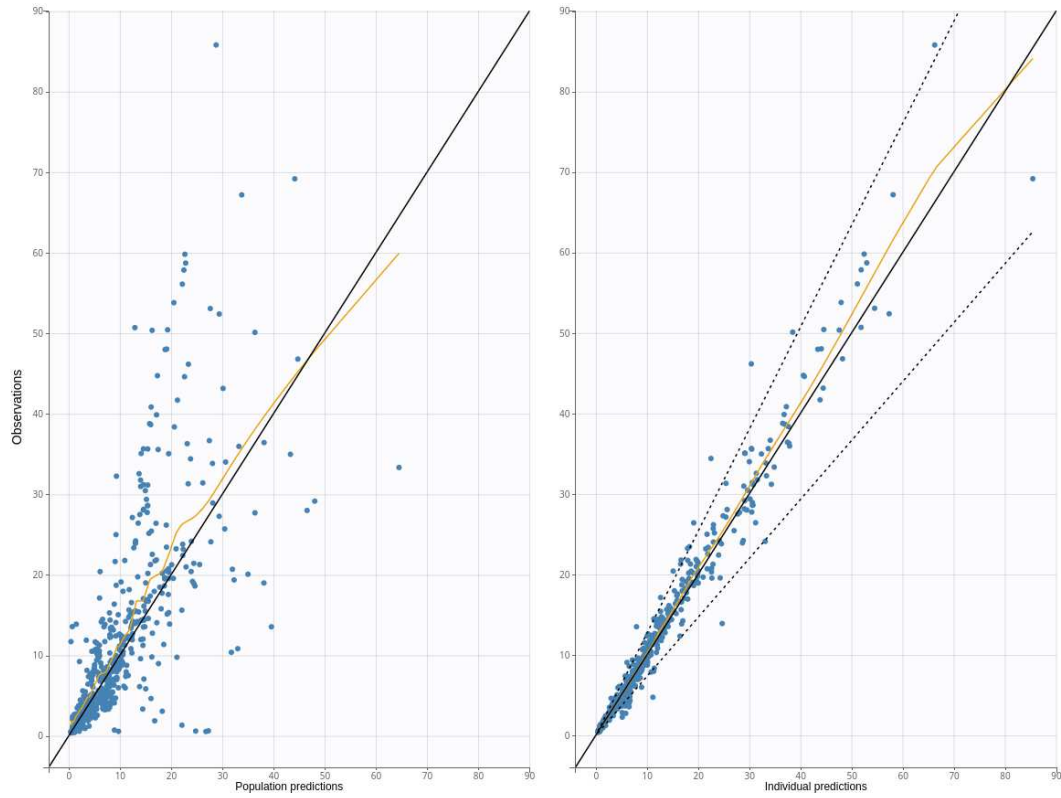
MAP for all patients



Supplementary Figure 5: “Raw values of measured mean arterial blood pressure (mmHg) in all patients as a function of time.”

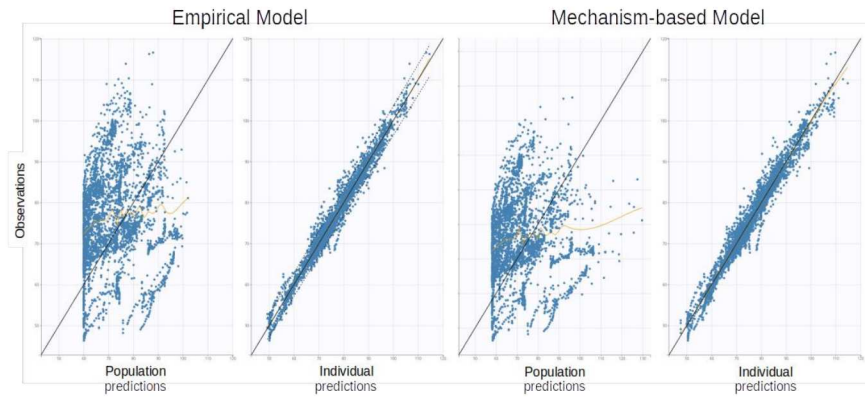
Supplement 8: Observation vs Prediction

Plasma concentration from PK model



Supplementary Figure 6: “Observation vs. Prediction plots comparing PK model predictions to actual measured plasma concentration for individual fits and population predictions.”

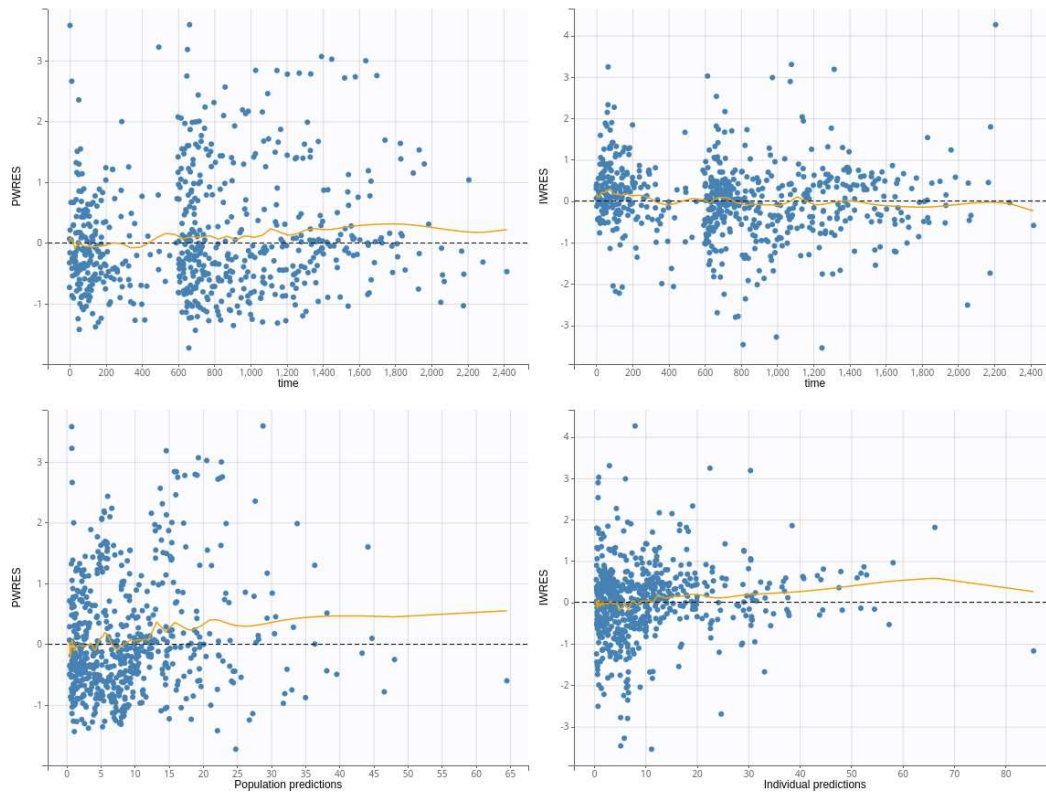
Effect from PKPD models



Supplementary Figure 7: “Observation vs. Prediction plots comparing PKPD model predictions to actual measured mean arterial blood pressure for individual fits and population predictions. Results are shown for the Empirical Emax model and the Mechanism-based Windkessel model.”

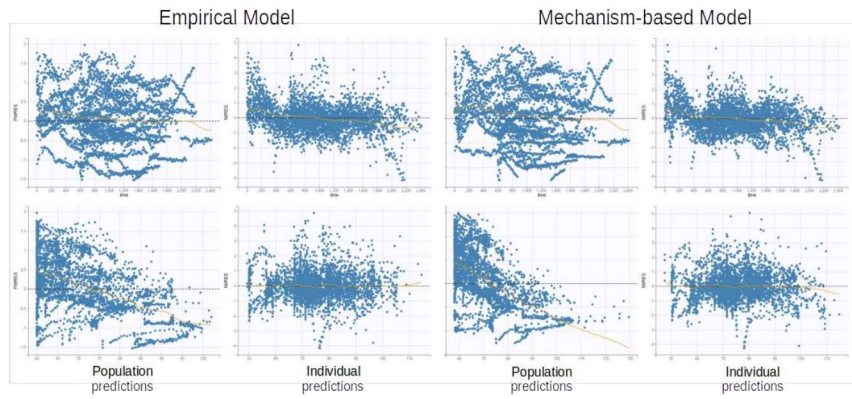
Supplement 9: Residuals

PK model Residuals



Supplementary Figure 8: “PK model population weighted (PWRES) and individual weighted (IWRES) residual plots as a function of time and predicted values.”

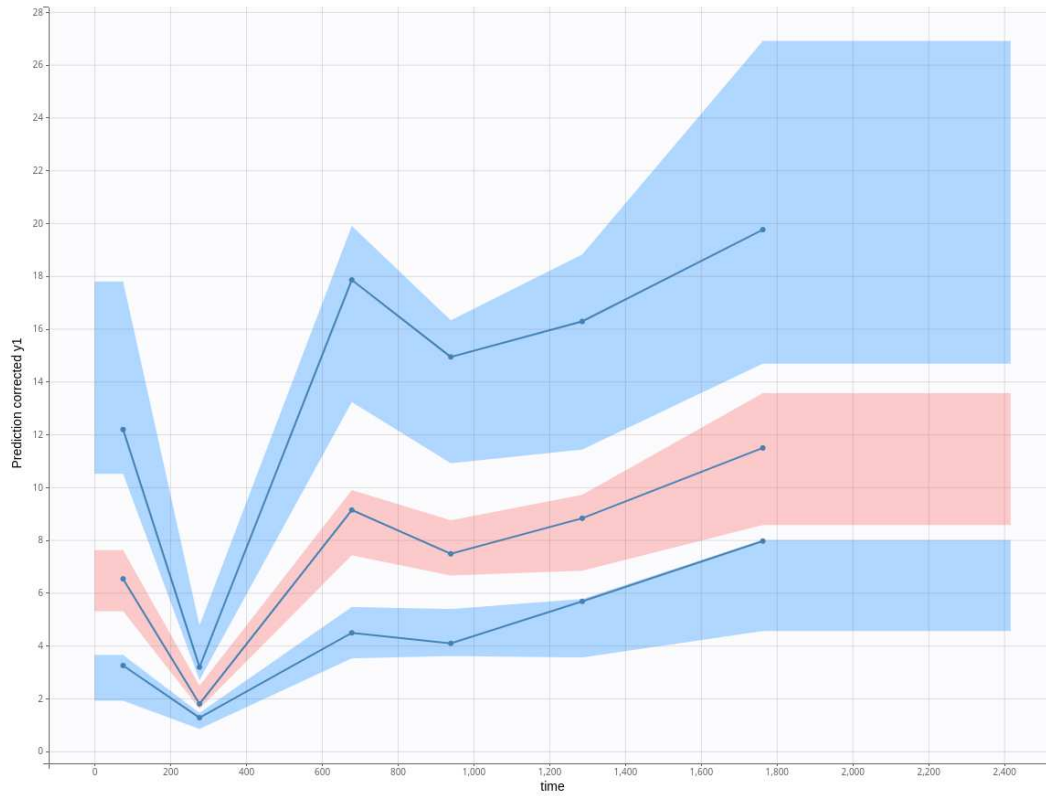
PKPD model Residuals



Supplementary Figure 9: “PKPD model population weighted (PWRES) and individual weighted (IWRES) residual plots as a function of time and predicted values.”

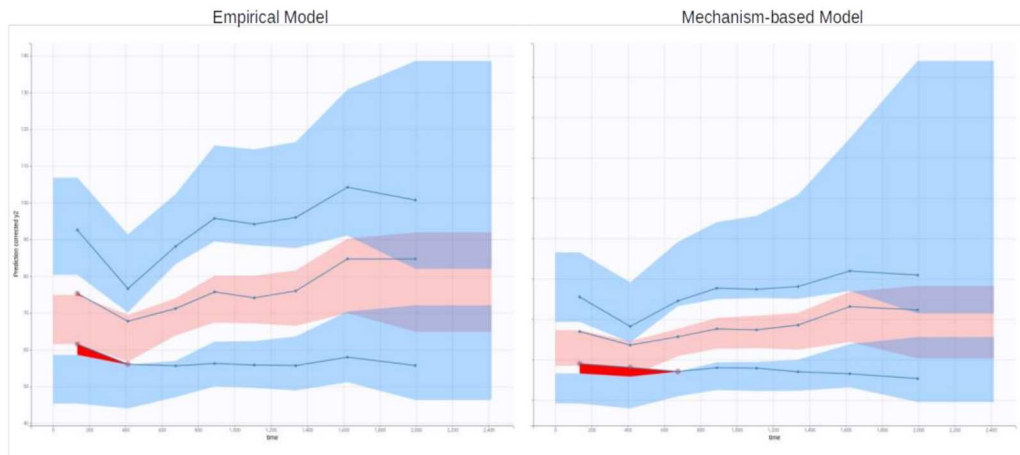
Supplement 10: Visual predictive checks (VPC)

PK model prediction-corrected VPC



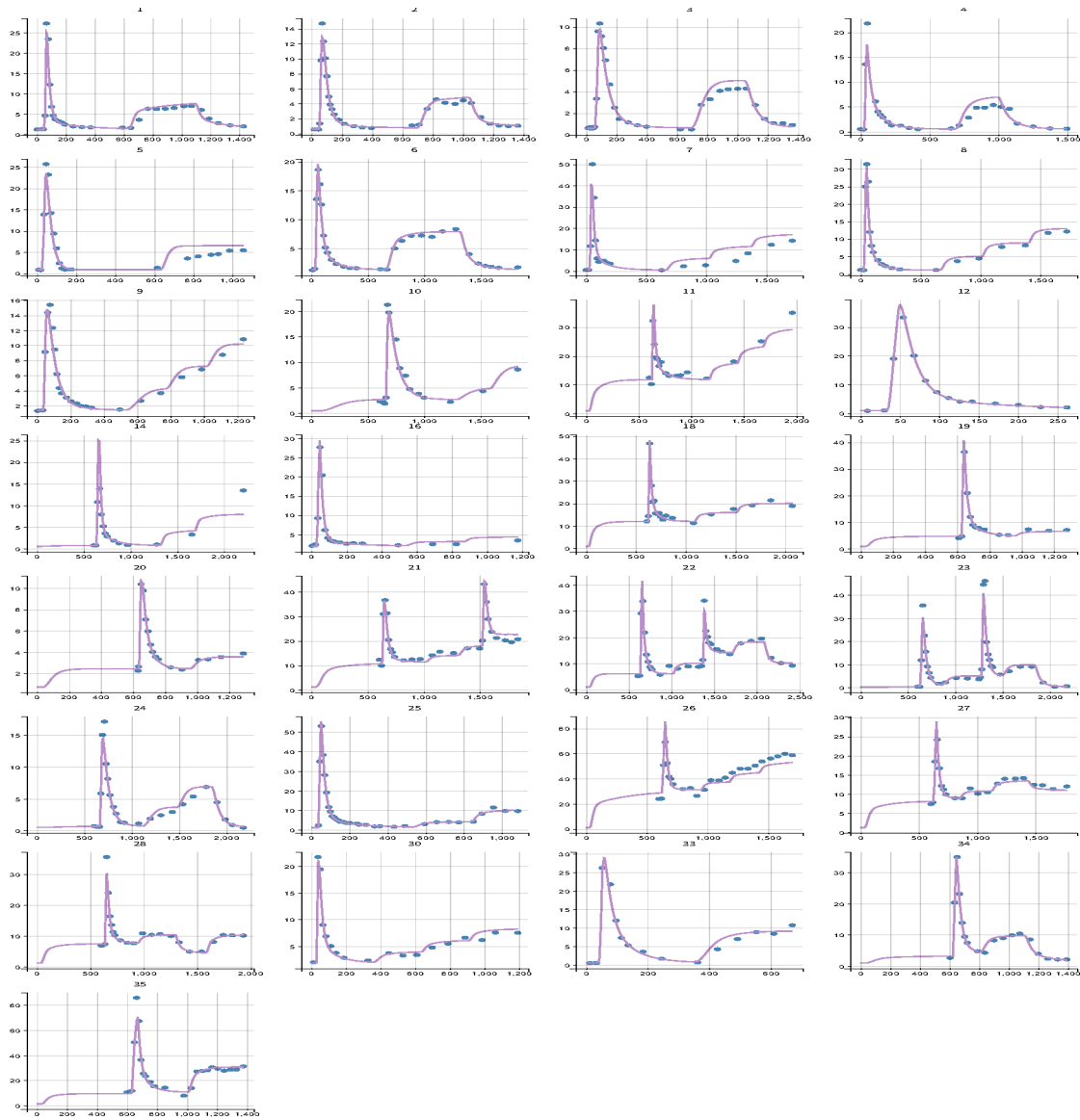
Supplementary Figure 10: “PK model Visual predictive checks (VPC). Prediction intervals for the 50th percentile are represented in pink. Prediction intervals for the 10th and 90th percentile are represented in blue.”

PKPD model prediction-corrected VPC



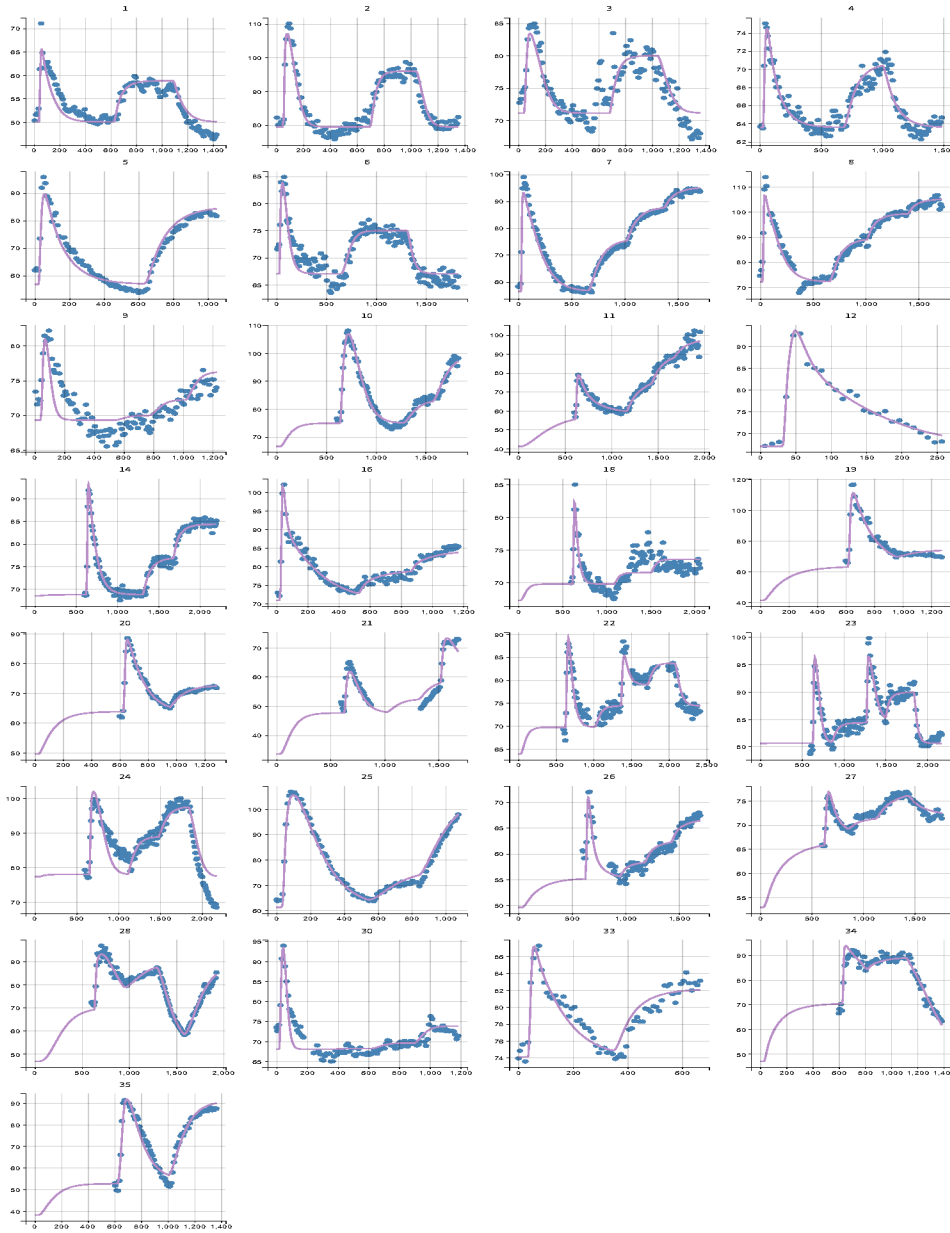
Supplementary Figure 11: “PKPD model Visual predictive checks (VPC). Prediction intervals for the 50th percentile are represented in pink. Prediction intervals for the 10th and 90th percentile are represented in blue.”

Supplement 11: Individual PK fits



Supplementary Figure 12: “Raw data for norepinephrine plasma concentrations as a function of time (blue dots) as well as individual PK model fits (purple curves) for all patients in the study cohort.”

Supplement 12: Individual BSMM PKPD fits



Supplementary Figure 13: “Raw data for mean arterial blood pressure as a function of time (blue dots) as well as individual BSMM PKPD model fits (purple curves) for all patients in the study cohort.”

ANNEXES 2: autres documents liés au travail de thèse

Annexe 2.1 Étude IOCENE: Estimation de la pression artérielle moyenne

Cette étude mathématique de l'algorithme PlethoMAP a été réalisée par le cabinet Iocène suite à notre demande pour vérifier nos modélisations mécanistiques.

Estimation de la pression artérielle moyenne

ALGORITHMME

12/02/2018

Iocène	Laure Sinègre	06 95 96 62 49
	Etienne Boilley	06 01 80 10 67
APHP	Fabrice Vallée	
	Jona Joachim	

Table des matières

1.	Contexte.....	3
1.1	Objet.....	3
1.2	Objectif.....	3
2.	Veille.....	3
3.	Calcul de la PAM.....	3
4.	Analyse des données.....	5

1. Contexte

1.1 Objet

Ce document constitue le rapport correspondant la prestation « algorithmes d'estimation de la pression artérielle moyenne ».

1.2 Objectif

Estimation de la pression artérielle moyenne à l'aide de méthode non invasive

...

Améliorer l'estimation en décomposant le signal de photopléthysmographie.

...

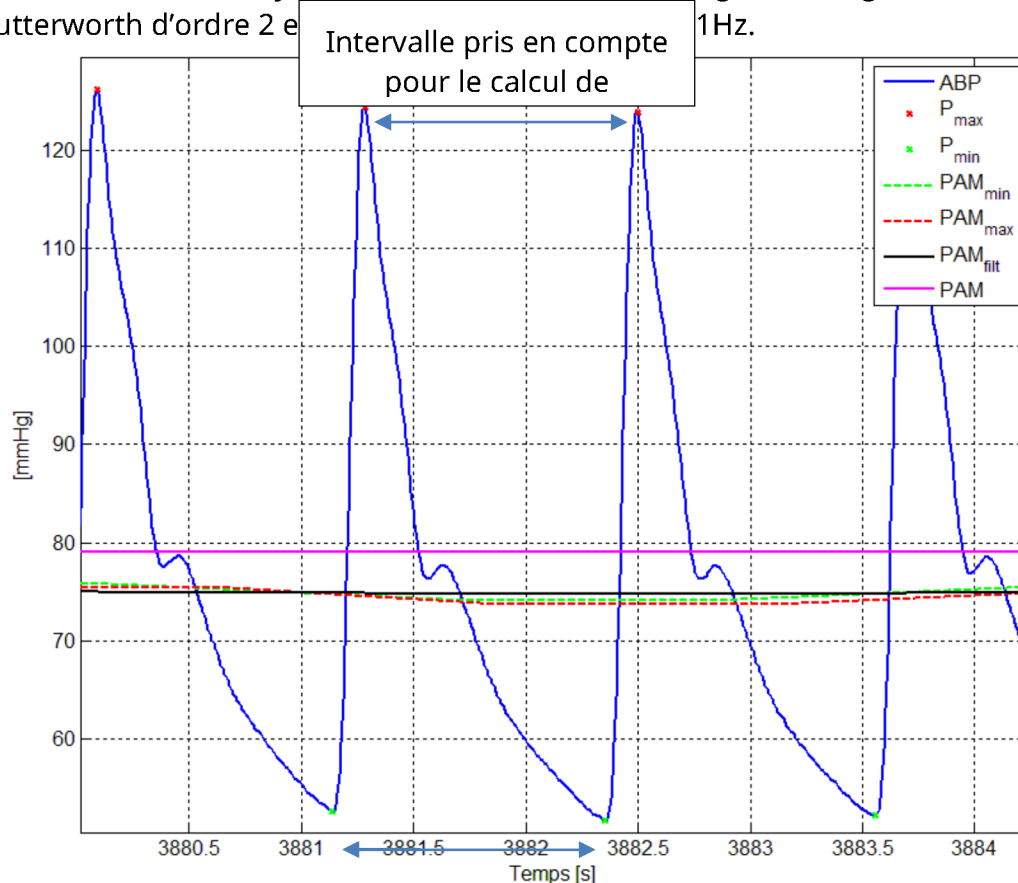
2. Veille

	Estimating blood pressure using Windkessel model on Photoplethysmogram	2014	https://www.ncbi.nlm.nih.gov/pubmed/25571008
	New photoplethysmogram indicators for improving cuffless and continuous blood pressure estimation accuracy	2018	https://www.ncbi.nlm.nih.gov/pubmed/29319536
Electronic eng. HK	Continuous and non invasive estimation of arterial blood pressure using a photoplethysmographic approach	2003	https://scinapse.io/papers/1594461330

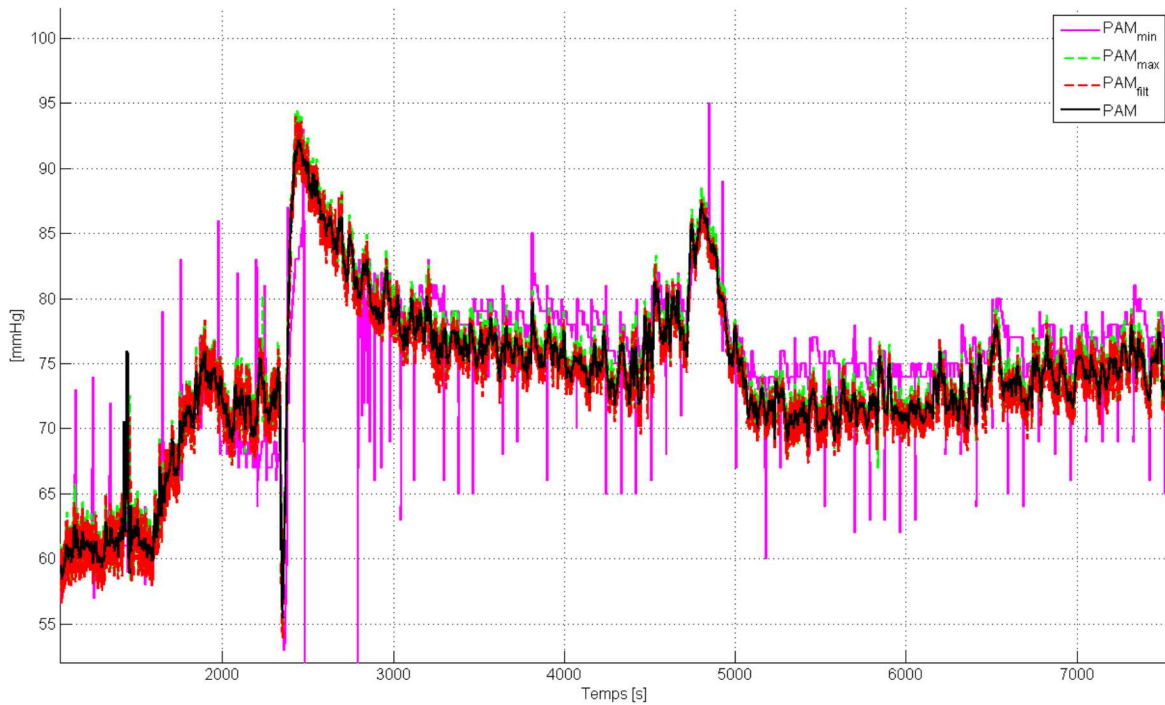
3. Calcul de la PAM

Le signal PAM présentant des pics non interprétés, nous commençons par recalculer la valeur de la pression moyenne artérielle à partir du signal ABP pris à une fréquence de 125Hz. Pour ce faire nous proposons trois calculs différents :

- PAM_max : Pression moyenne calculée à partir du signal ABP en prenant des intervalles entre deux valeurs de pression maximale
- PAM_min : idem mais en considérant les cycles entre deux valeurs de pressions minimales
- PAM_filt : Pression moyenne évaluée en filtrant le signal ABP grâce à un filtre Butterworth d'ordre 2 et à une fréquence de coupure de 1Hz.



La Figure ci-dessous présente la comparaison des 3 PAM calculés avec le signal PAM brut. On constate que les trois signaux calculés donnent des valeurs cohérentes entre elles mais distinctes de la PAM brute. Pour la suite, nous utiliserons le signal PAM_FILT qui nécessite moins de temps de calcul.



4. Analyse des données

4.1.1 Estimation de la pression moyenne en supposant une relation linéaire avec la PPG

La méthode proposée pour estimer la PAM consiste à :

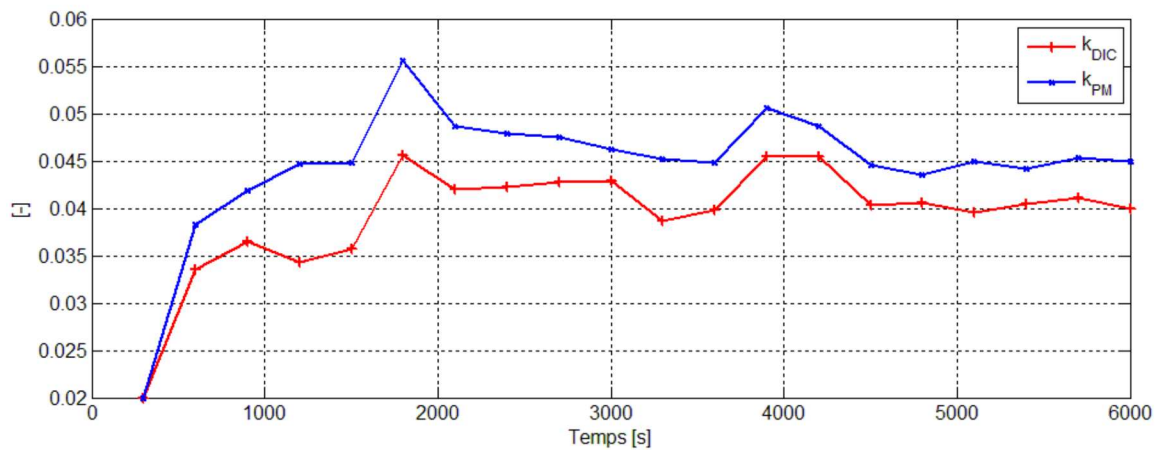
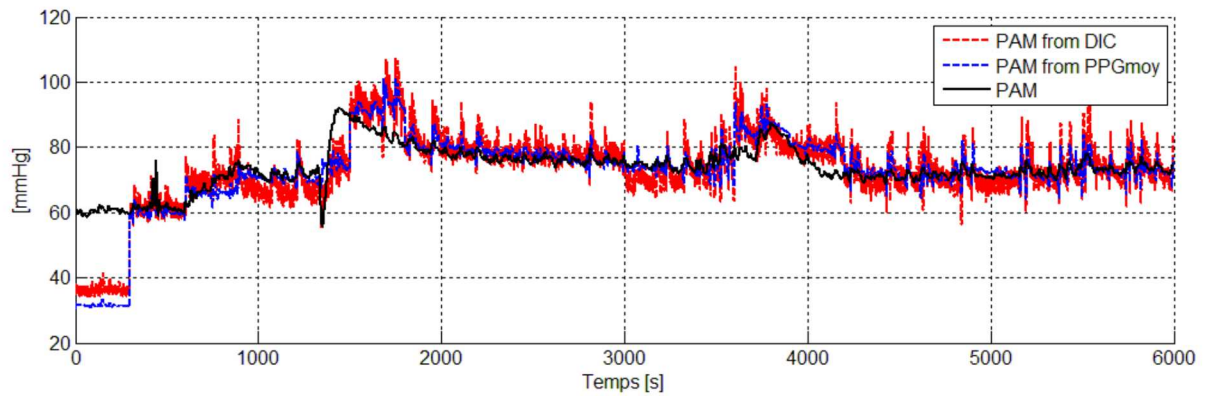
- Supposer une relation linéaire entre la PAM et la dicrote (DIC)
- Recaler ce coefficient linéaire à toutes les 5 minutes (en supposant que l'on dispose d'une mesure de la pression artérielle moyenne au brassard toutes les 5 minutes).

Afin de comprendre le rôle particulier joué par la dicrote, on propose d'utiliser cette même méthode à partir d'une autre composante du signal issu du photopléthysmographe : la moyenne du signal (calculé comme précédemment à partir d'un filtre butterworth d'ordre 2 et de fréquence de coupure 0.1Hz).

Résultats

La Figure ci-dessous présente les résultats obtenus. En bleu, l'estimation du signal à partir la PPGmoyenne et en rouge à partir de la dicrote.

Conclusion ?



4.1.2 Analyse alternative

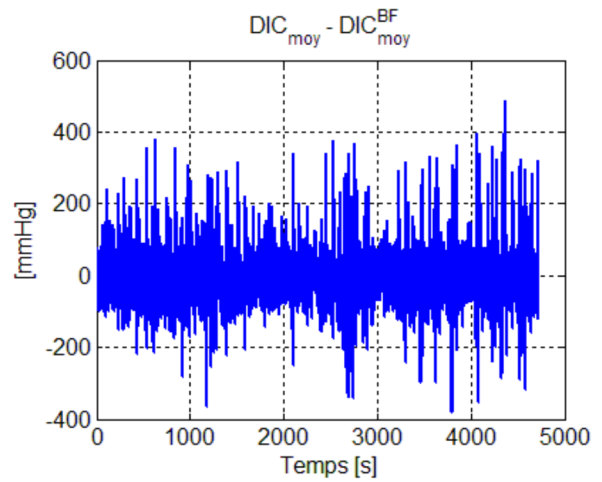
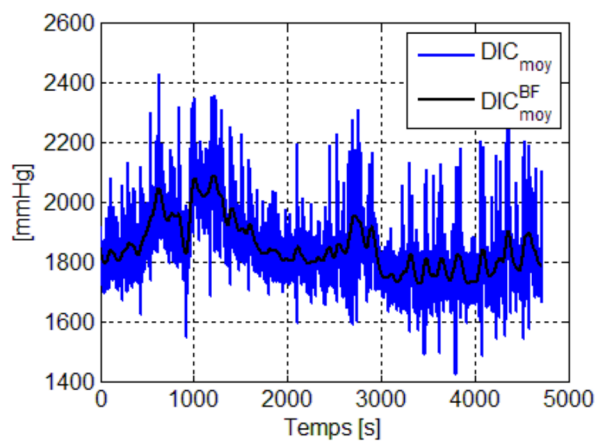
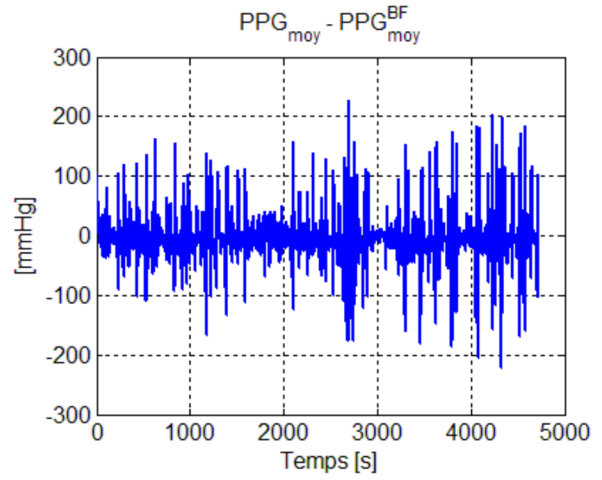
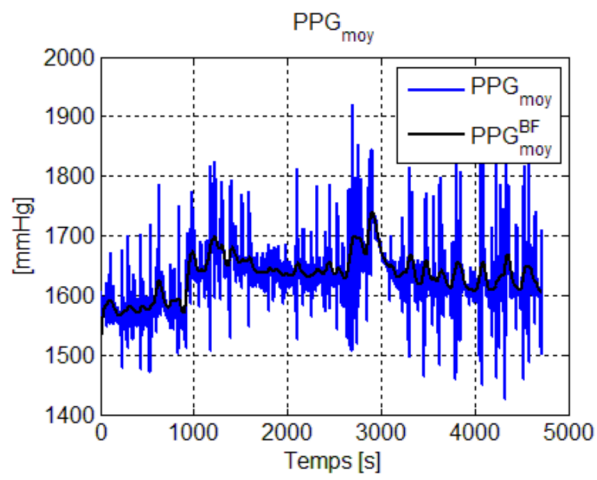
On suppose que la PAM peut être estimée sous la forme :

$$PAM_{est} = a + b PPG_{BF} + c PPG_{HF}$$

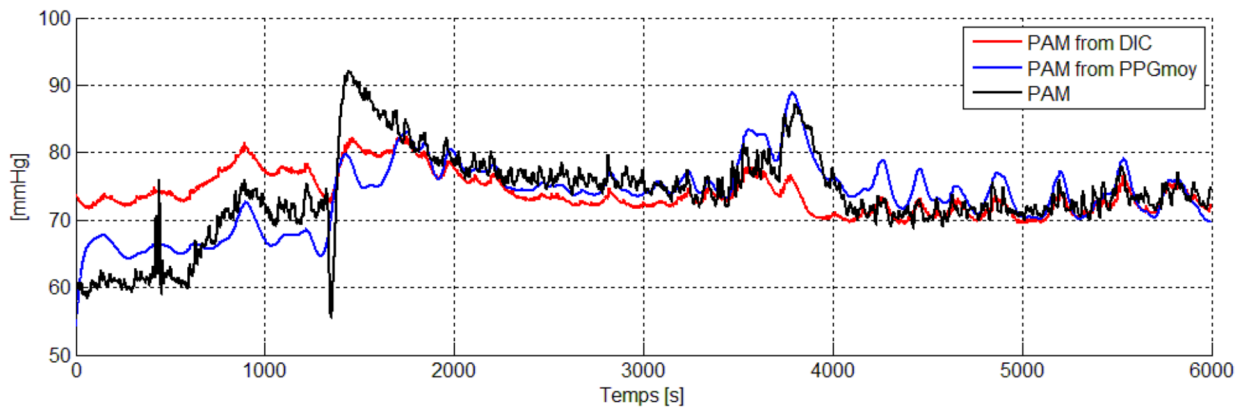
Le signal PPG pouvant correspondre soit à la dicrote soit à la moyenne de la PPG. On décompose le signal issu de la PPG en une partie basse fréquence, PPG_{BF} et une partie haute fréquence : PPG_{HF} . On considère un filtre butterworth d'ordre 2 et de fréquence de coupure 0.08Hz (voir ci-dessous la représentation des signaux filtrés).

$$PPG_{BF} = \text{Filtre}(PPG)$$

$$PPG_{HF} = PPG - \text{Filtre}(PPG)$$



Résultats



	DIC	PPMGmoy
a	10.9170	-158.0667
b	0.0025	0.0013
c	0.0340	0.1420

Conclusion ?

Estimation de la pression artérielle moyenne

ALGORITHMME

29/11/2019

Iocène	Laure Sinègre	06 95 96 62 49
	Etienne Boilley	06 01 80 10 67
APHP	Fabrice Vallée	
	Jona Joachim	

Table des matières

1.	Contexte.....	3
1.1	Objet.....	3
1.2	Objectif.....	3
2.	Traitements proposés.....	3
2.1	Analyse préliminaire.....	3
2.2	Opérations.....	4
3.	Résultats.....	7
3.1	Résultats globaux.....	7
3.2	Analyse détaillée.....	11
4.	Conclusions.....	21
4.1	Estimation de la PAM possible.....	21
4.2	Points d'amélioration.....	21
5.	Annexes.....	23
5.1	P : Suppression des points aberrants.....	23
5.2	Calcul de la fréquence à partir de <i>Pclean</i>	25
5.3	Calcul de la fréquence à partir du signal du pléthysmographe.....	26
5.4	Résultats - Figures.....	27

1. Contexte

1.1 Objet

Ce document constitue le rapport correspondant la prestation « algorithme d'estimation de la pression artérielle moyenne ».

1.2 Objectif

Estimation de la pression artérielle moyenne à l'aide de méthode non invasive

La pression artérielle moyenne doit être surveillée durant une anesthésie et maintenue entre certaines bornes. La méthode la plus simple est d'utiliser un cathéter pour avoir accès à la pression artérielle. Cette méthode étant invasive, les médecins aimeraient pouvoir parfois s'en dispenser, en particulier, lorsque le patient ne présente pas de risque particulier.

Améliorer l'estimation en décomposant le signal de photopléthysmographie.

L'idée serait de transposer l'analyse visuelle pratiquée aujourd'hui par les médecins en l'absence de mesure de pression invasive. Elle consiste à suivre l'évolution de la pression artérielle moyenne entre deux prises de pression au brassard à travers deux indicateurs :

- La forme de l'onde de pression renvoyée par photo-pléthysmographie
- L'indice de perfusion renvoyé par ce même appareil.

L'idée n'est pas de remplacer cette analyse visuelle pendant les phases critiques, en particulier, pendant l'induction. L'idée est au contraire de disposer d'un système complémentaire donnant l'estimation de la pression artérielle moyenne capable de lever des alertes pendant les phases calmes où l'anesthésie est en place.

Reconstitution de la PAM – exploitation de l'indice de perfusion

Ce travail vient en complément de celui déjà réalisé par Jona Joachim lors de sa thèse de médecine visant à reconstituer la PAM à partir de la dicrote seule. Il s'agit ici de voir s'il est possible d'améliorer cette reconstitution en exploitant également l'indice de perfusion.

Les analyses et traitements ont été réalisés à partir de 171 jeux de données acquis lors d'interventions à l'hôpital Lariboisière. Seuls 22 jeux de données sont exploités ici.

2. Traitements proposés

L'objectif est d'arriver à reconstituer la PAM à partir de :

- la pression à la dicrote
- l'indice de perfusion
- la pression au brassard (par hypothèse égale à la PAM mais prise à une fréquence basse de l'ordre d'une fois toutes les dix minutes).

2.1 Analyse préliminaire

On a :

$$PAM = SV * HR * SVR$$

Avec :

- SV : stroke volume / volume sanguin éjecté par le coeur
- HR : fréquence cardiaque
- SVR : systemic vascular resistance

Nous allons utiliser les signaux dont nous disposons pour retrouver ces grandeurs.

Fréquence cardiaque

Nous pouvons supposer que nous disposons de la fréquence cardiaque (soit qu'elle soit fournie directement par un appareil de mesure, soit retrouvée grâce à la périodicité des autres signaux).

Résistance vasculaire systémique

L'évolution de la dicrote est à l'image de la résistance du système veineux. En effet, plus le système veineux sera résistif, plus l'onde de retour sera d'amplitude importante. Comme l'idée est de travailler à partir de la mesure fournie par le pléthysmographe, c'est de là que nous tirons l'information sur la dicrote.

En effet, ce dernier nous fournit un signal O qui suit la forme de l'onde de pression.

Soit

$$dic = \frac{O_{dic} - O_{dia}}{O_{sys} - O_{dia}}$$

Nous allons exploiter dic comme étant une image de R la résistance. Par définition dic est un signal entre 0 et 1.

Remarque : les valeurs O_{dic} , O_{sys} et O_{dia} ont été identifiées a priori grâce à un algorithme ad-hoc écrit par Jona Joachim.

Volume sanguin éjecté

Nous allons utiliser l'indice de perfusion IP fournit par le pléthysmographe comme image du débit sanguin.

$$Q \ln\left(\frac{1}{IP} + 1\right) = Q_{IP}$$

Remarque : fréquence d'acquisition

Les signaux de base (pression artérielle et onde de pression fournie par le pléthysmographe) sont à 125Hz. En revanche, tous les signaux que nous allons exploiter : dic , Q et $freq$ sont des grandeurs qui ne sont définies que sur une période cardiaque, de l'ordre de 1 Hz.

2.2 Opérations

2.2.1 Principe de la reconstruction

On recherche une observation de la pression artérielle moyenne, \widehat{PAM} , sous la forme :

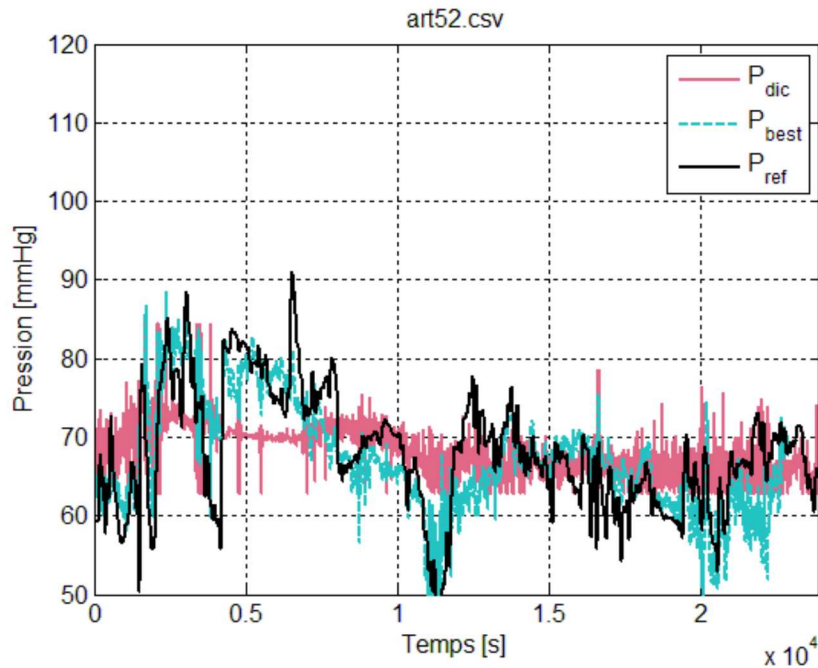


Figure 1 – Comparaison des PAM estimées à partir des fréquences/IP/dicrote (P_{best}) ou de la dicrote seule (P_{dic}).

2.2.3 Initialisation et mise à jour des paramètres à partir du brassard

Dans la pratique, l'idée est justement de s'affranchir de la mesure de pression artérielle invasive. Il n'est donc pas possible de l'exploiter. En revanche, il est possible de s'appuyer sur les mesures de pression au brassard :

- Toutes les minutes pendant quinze minutes au démarrage pour initialiser le système
- Puis toutes les dix minutes pour éviter les dérives.

Nous allons donc exploiter des informations.

Procédure :

- Nous allons donc calculer un premier jeu de paramètres à partir des informations de la première période de quinze minutes : v_a^{init} (15 points)
- Puis nous allons exploiter les informations mesurées par le brassard depuis le début de l'enregistrement pour calculer un v_a^k (15 points + k points)

Exemple de résultat

La Figure ci-dessous présente un exemple de résultats obtenus. La courbe en pointillés correspond à l'estimation de la \widehat{PAM} réalisée en supposant que l'on connaît le signal en noir (pression artérielle moyenne de référence). La courbe en continue correspond à l'estimation de la \widehat{PAM} réalisée en actualisant les paramètres v_a à chaque nouvelle mesure du brassard.

Remarque

Cette façon de fonctionner, implique que toute nouvelle donnée a de moins en moins de poids au fil du temps. C'est un inconvénient qui pourrait être contourné en fixant une

taille de fenêtre. A l'inverse, il faut que cette fenêtre soit d'une taille suffisante pour que l'on puisse identifier les 5 paramètres.

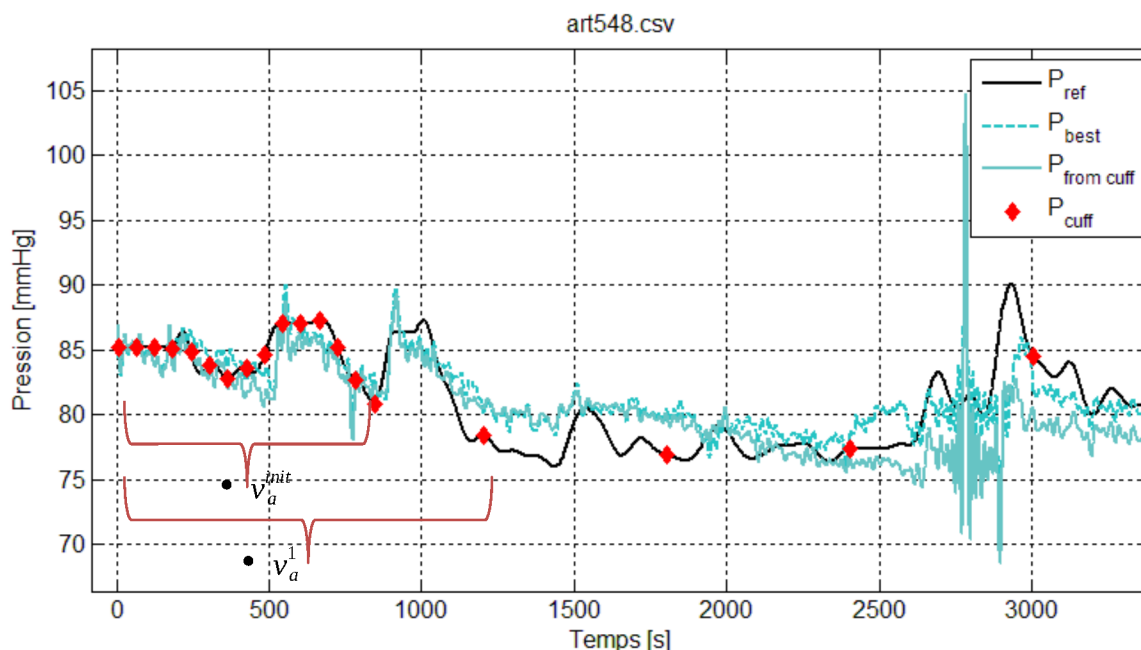


Figure 2 - Comparaison de l'estimation de pression moyenne artérielle réalisée avec les paramètres optimaux $v_a(P_{best})$ et de celle réalisée à partir de paramètres actualisés à chaque mesure de brassard (P_{cuff})

2.2.1 Estimation à partir de la dicrote seule

Dans la suite, nous allons également calculer la PAM estimée seulement à partir de la dicrote de la même manière mais en utilisant la formule suivante :

$$\widehat{PAM}_{dic} = b_1 + b_2 dic$$

3. Résultats

3.1 Résultats globaux

3.1.1 Analyse statistique

La Figure ci-après présente les résultats obtenus. Pour chaque jeu de données (désigné uniquement par son numéro) on présente la synthèse des résultats obtenus en utilisant seulement la dicrote (en rouge) ou la formule présentée précédemment (en bleu).

On constate :

- La médiane de l'erreur $|P_{est} - P_{ref}|$ est plus basse de 1 à 2 mmHg lorsque l'on utilise toute l'information (en bleu) plutôt que seulement la dicrote (en rouge)
- L'amplitude entre le 1^{er} quartile et le 3^{ème} est généralement similaire dans les deux cas.

Notons que cette représentation ne rend pas vraiment compte de la performance de l'algorithme, en effet :

- La valeur max de l'erreur paraît très importante mais ce n'est dû qu'à des problèmes d'amplification du bruit, lié, entre autre, à l'identification de la dicrote
- L'amplitude entre le 1^{er} quartile et le 3^{ème} est plus caractéristique de la forme du signal (très plat pour le jeu de données 548 par exemple) que de la performance de l'algorithme
- Cette visualisation ne permet pas de voir si les variations de la PAM estimée sont bien cohérentes avec celle de la PAM réelle.

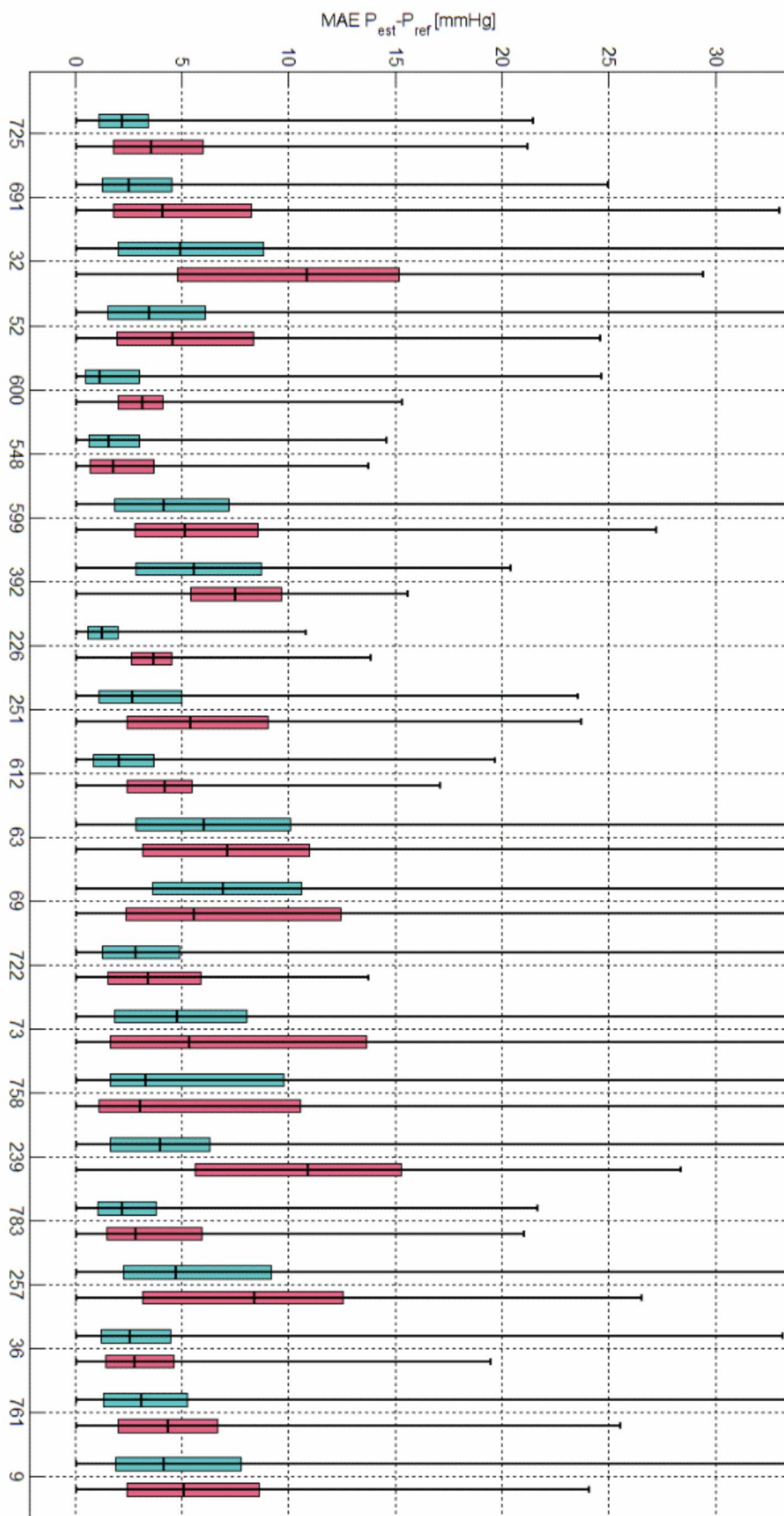


Figure 3 - Comparaison des résultats obtenus avec seulement la dicrote (en rouge) ou les 3 signaux (en bleu)

3.1.2 Analyse qualitative

Le tableau suivant présente les résultats qualitatifs. A l'œil on analyse si la qualité de la reconstruction est correcte et si la reconstruction utilisant la fréquence cardiaque et l'indice de perfusion est meilleure que celle utilisant la dicrote seule.

On constate que sur les 22 jeux analysés :

- Qualité de reconstruction
 - o 13 ont une qualité de reconstruction très satisfaisante (++)
 - o 18 ont une qualité de reconstruction assez satisfaisante (+ et ++)
- Meilleur que la dicrote seule
 - o 8 sont bien meilleurs (++)
 - o 16 sont notablement meilleurs (+ et ++)

	Qualité reconstructio n	Meilleur que dicrote seule ?	Observation	Explications
art725	++	+		
abp691	++	++		
art32	++	+	Un pic non expliqué	
art52	++	++	Un creux non expliqué	
art600	++	-		
art548	++	=		
art599	-	=	Pic et creux non expliqué	
art392	-	=	Pic et creux non expliqué	Pb identification dic.
abp226	+	+	oscillations	
abp251	-	=	non expliqué	Dicrote non interprétable
art612	-	+	non expliqué	Absence d'info IP
art63	+	+		
art69	++	+		
art722	++	++		
art73	++	++	Un creux non expliqué	
abp758	+	=		
art239	++	++		
abp783	++	++		
art257	+	+	gros creux non expliqué	Dicrote non interprétable
art36	++	++		
art761	++	+	pics non expliqués à la fin	
art9	+	++	creux non expliqué	Cause non identifiée

En bleu apparaissent les jeux de données pour lesquels la concordance est particulièrement bonne.

A l'inverse en orange apparaissent les jeux pour lesquels il y a peu de concordance et pour lesquels cela s'explique par un problème de fond : absence de données sur l'indice de perfusion ou signal de pléthysmographie inexploitable.

3.1.3 Analyse des coefficients

Reprenons la forme factorisée de la *PAM* estimée :

$$\widehat{PAM} = a_5 \left(\left(dic + \frac{a_4}{a_5} \right) \left(Q_{IP} + \frac{a_3}{a_5} \right) - \frac{a_3 a_4}{a_5^2} + \frac{a_2}{a_5} \right) freq + a_1$$

Considérons les coefficients v_a correspondant au cas optimal où l'on a utilisé la *PAM* réelle pour identifier les coefficients. La Figure ci-dessous présente l'évolution des coefficients pour les différents jeux de données.

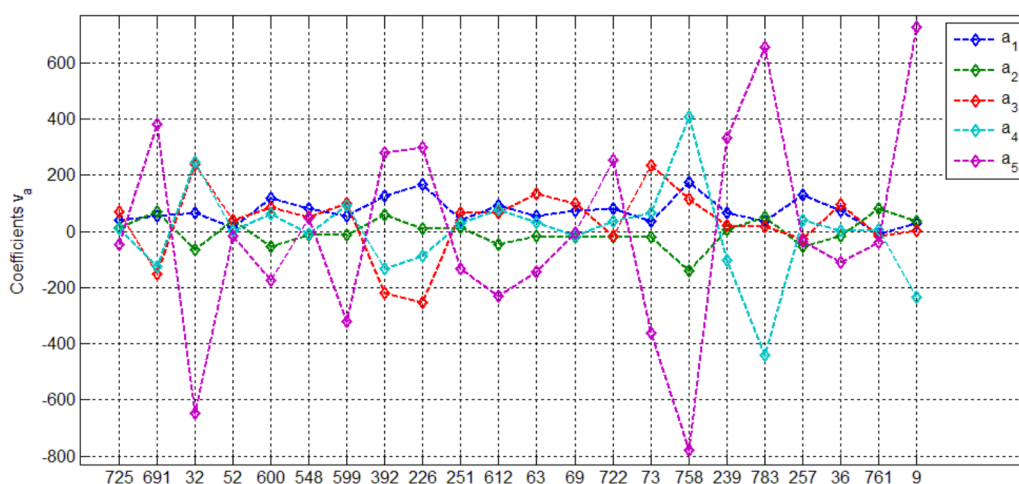


Figure 4 - Evolution des coefficients v_a pour les différents jeux de données

On constate :

- Que les coefficients sont fortement variables d'un jeu à l'autre
- Que les coefficients changent de signe
- Que généralement :
 - o $a_1 > 0$
 - o a_3 et a_4 sont de même signe
 - o a_2 et a_5 sont de même signe (opposé à celui de a_3 et a_4)

Analyse des changements de signe

Utilisant les considérations de signes, il est possible de réécrire :

$$\widehat{PAM} = +i - d \left((dic - b)(Q_{IP} - c) + \epsilon \right) freq + a$$

Avec a, b, c et d des constantes positives et $\epsilon = \frac{-a_3 a_4}{a_5^2} + \frac{a_2}{a_5}$.

Les termes peuvent s'interpréter ainsi :

- b et c correspondent à un offset

- d correspond au facteur d'échelle global
- a correspond à l'offset sur la PAM

Le changement de signe de $a_5 = +i - d$ signifie que la PAM est tantôt une fonction croissante en fonction de nos paramètres tantôt décroissante. Ce point nécessiterait d'être éclairci d'un point de vue physiologique.

Remarque

Sur la Figure ci-après présente l'évolution de ces paramètres en fonction des jeux de données. On constate que certains jeux de donnée ont des paramètres différents. Le jeu 69 en particulier pour lequel les résultats sont justement particulièrement bons.

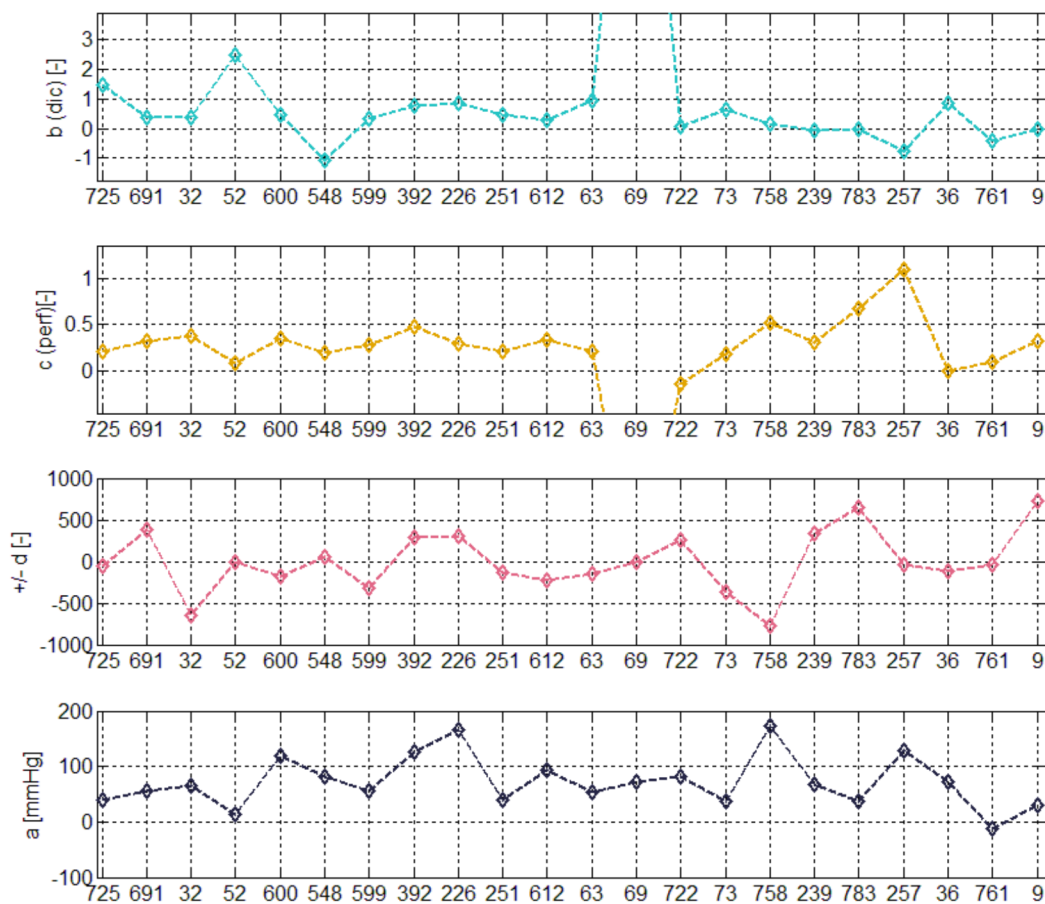


Figure 5 – Evolution des coefficients en fonction des jeux de données

3.2 Analyse détaillée

3.2.1 Fonctionnement de la reconstruction

On constate que l'exploitation de la fréquence et de l'indice de perfusion permettent d'améliorer les résultats obtenus avec la dicrote seule.

Impact de la fréquence cardiaque

art52.csv : les deux estimations de la pression moyenne artérielle sont relativement proches excepté lors de la montée très rapide en pression (voir Figure ci-dessous, le rectangle orange) qui ne s'explique qu'avec la fréquence cardiaque.

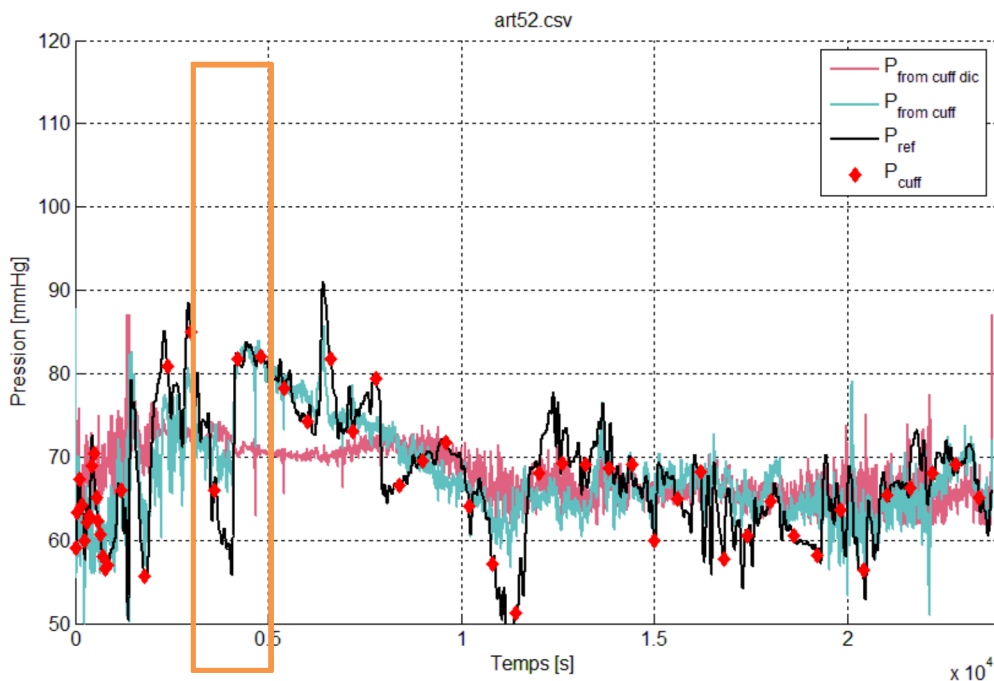


Figure 6 - Amélioration de l'estimation de la PAM grâce à la fréquence cardiaque

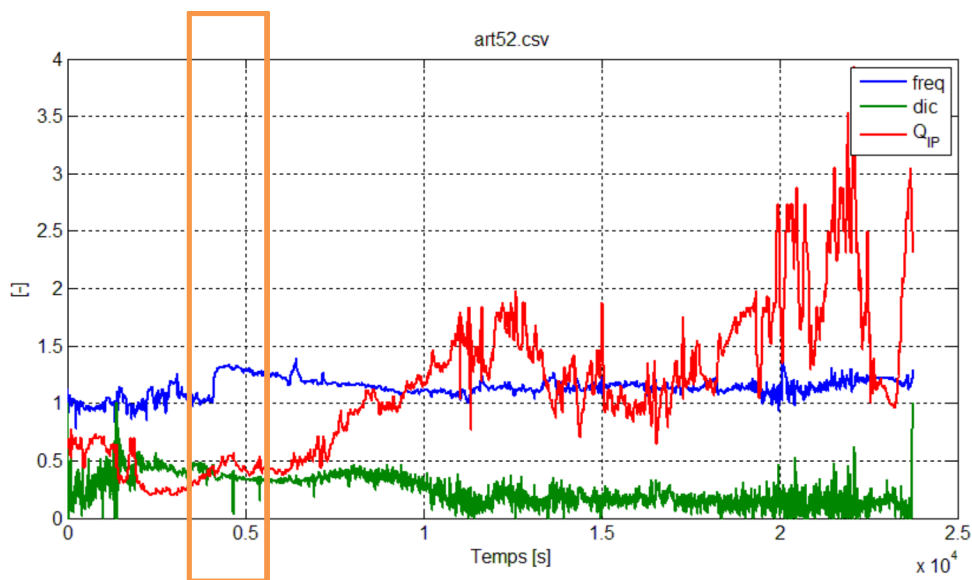


Figure 7 - Seule la fréquence cardiaque présente un à coup similaire à celui constaté sur la PAM

Impact de la perfusion

art36.csv : de la même façon le décrochement de la pression artérielle moyenne dans le rectangle orange ne s'explique qu'avec l'indice perfusion.

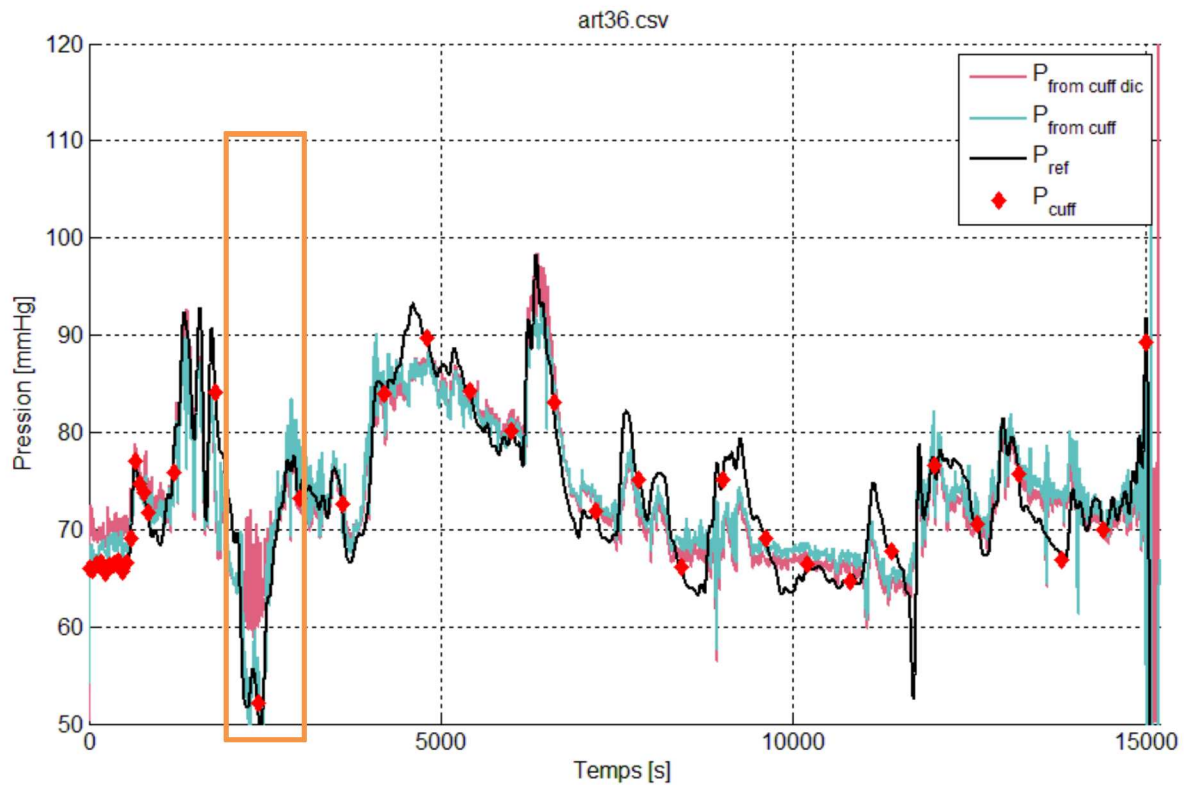


Figure 8 - Amélioration de l'estimation de la PAM grâce à l'indice de perfusion

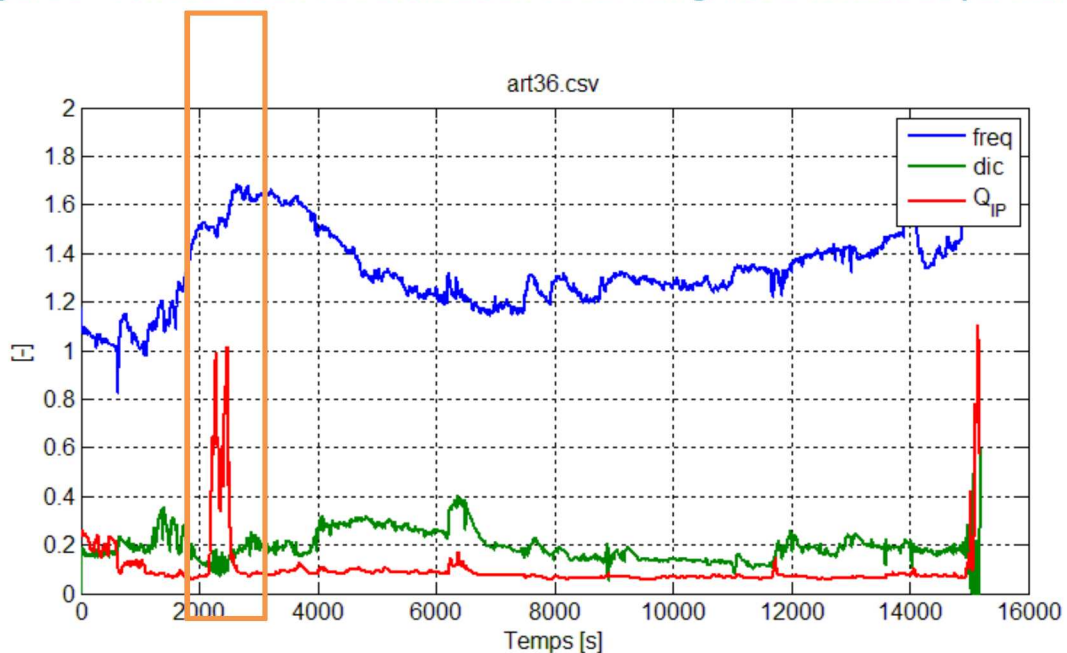
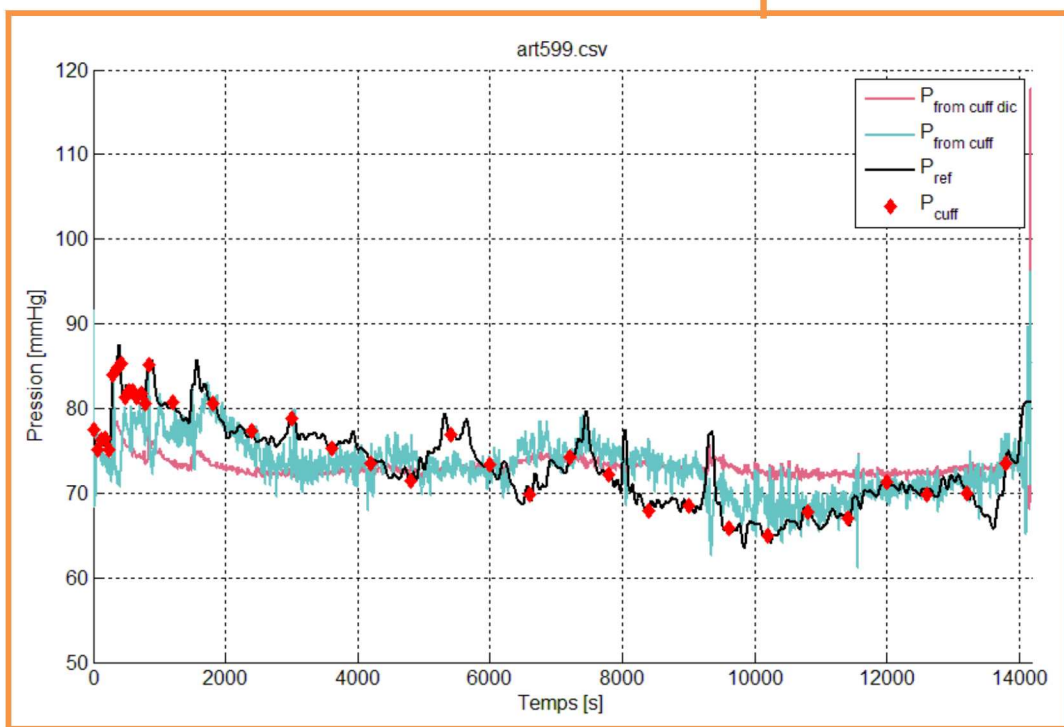
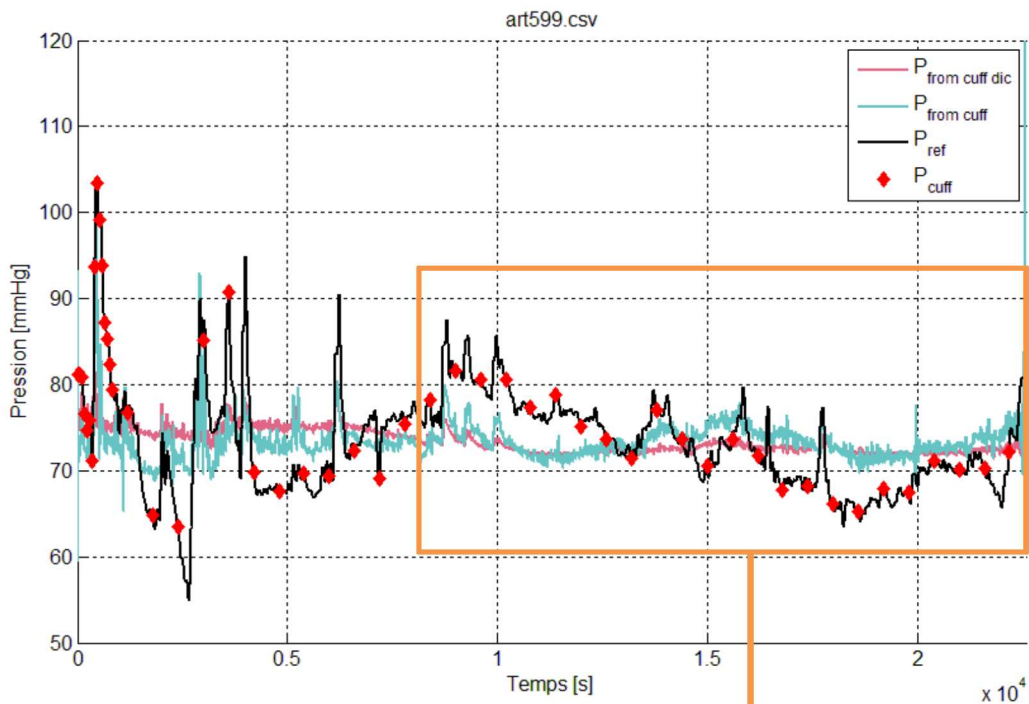


Figure 9 - Seul l'IP présente un à coup similaire à celui constaté sur la PAM

Impact de la zone d'initialisation

Sur le jeu de données art599.csv on constate que l'information est présente sur le signal reconstruit de la PAM mais avec une amplitude qui semble insuffisante.

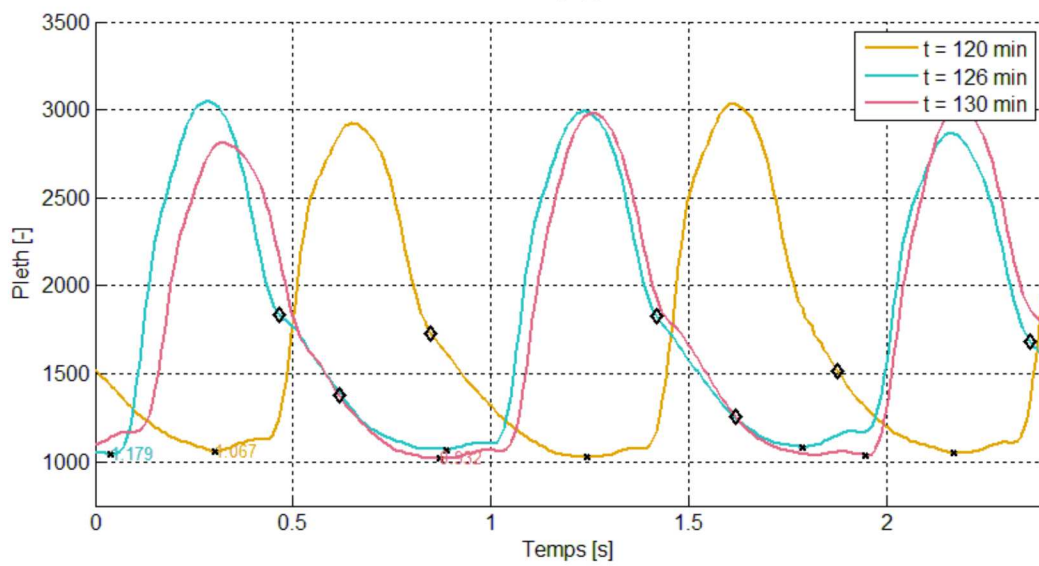
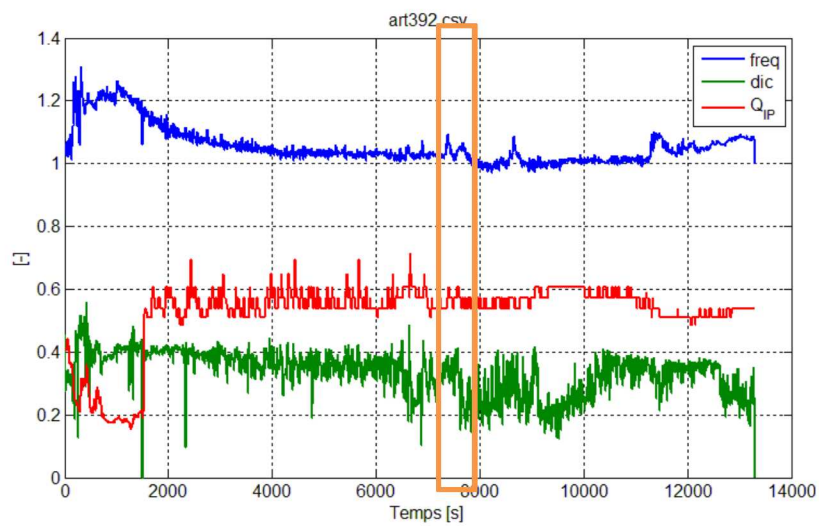
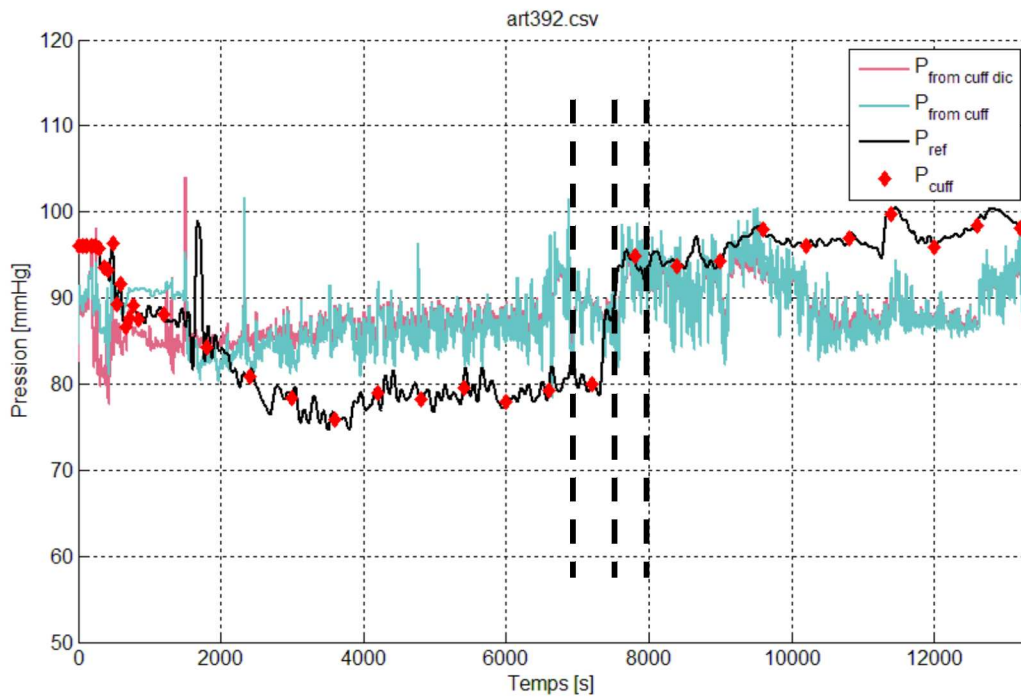
Lorsque l'on décide de changer la zone d'initialisation et de la situer autour de 8000s, on obtient de bien meilleurs résultats.



3.2.2 Problèmes identifiés

Problème d'identification de dicrote

Sur le jeu de données art392.csv on constate que l'augmentation de la pression moyenne autour de 7500s n'est pas représentée. En analysant la forme de l'onde de pression donnée par le pléthysmographe avant, pendant et après la montée de pression, on constate que la dicrote est sous évaluée après la montée de PAM (signal rouge sur le 3^{ème} graphique) ce qui correspond à la chute du signal vert sur le second graphique.



Signal d'onde de pression difficilement interprétable : trop d'oscillations

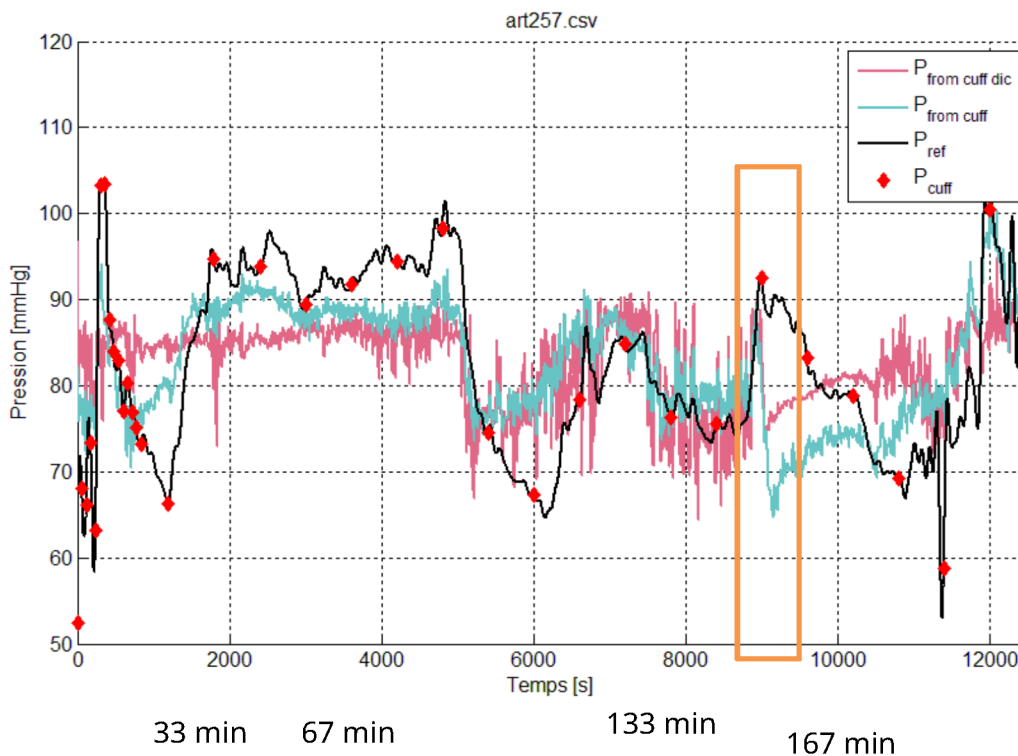
Le jeu de données art257.csv présente une relativement bonne concordance excepté autours de $t=9000s$ où l'estimation de pression chute de manière très importante à l'inverse de la PAM réelle.

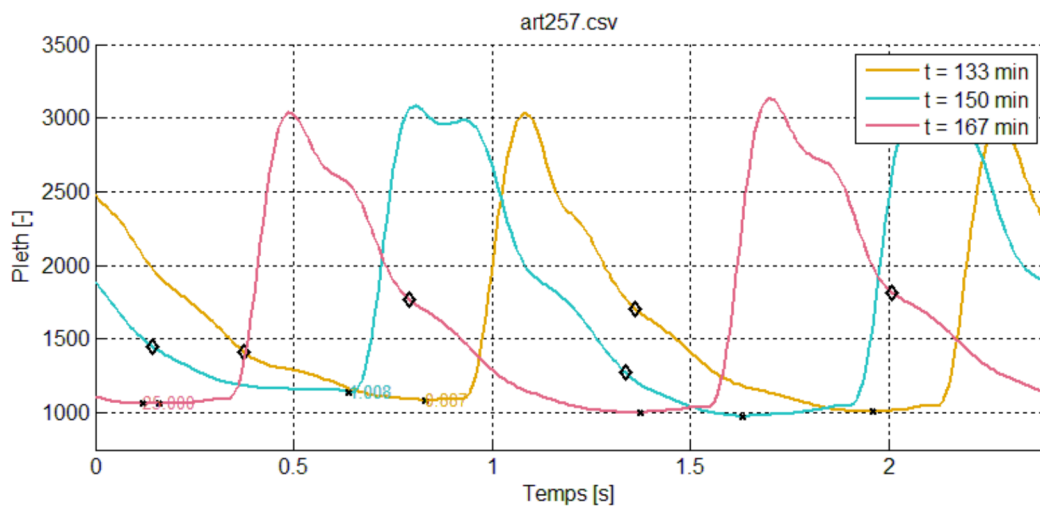
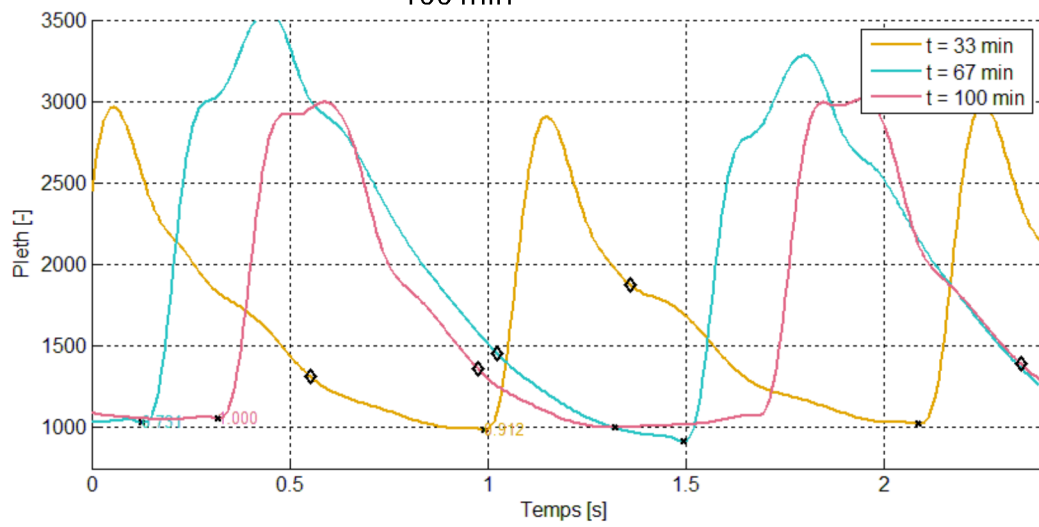
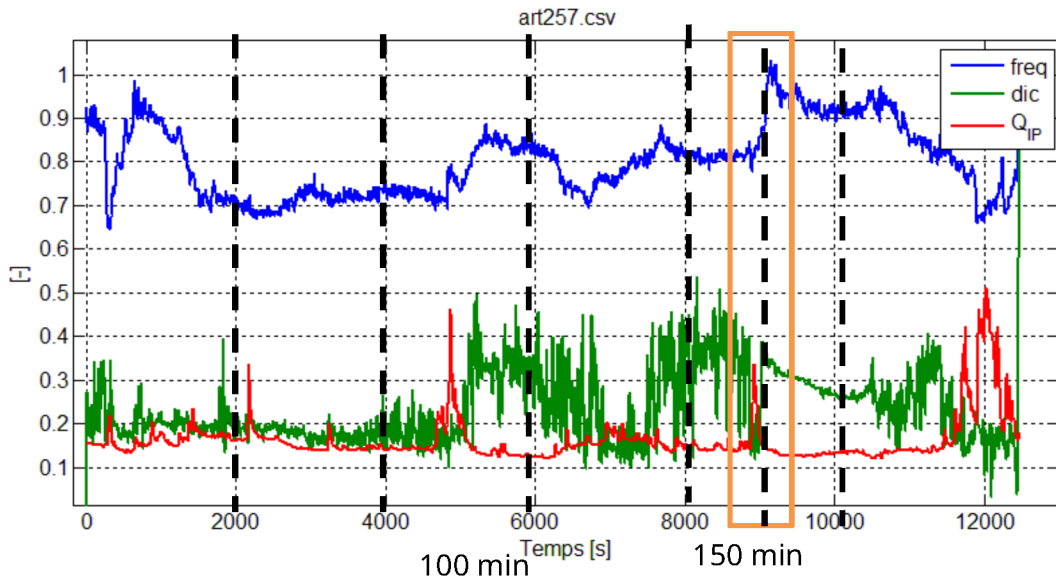
Cela peut s'expliquer par deux choses :

- La reconstruction de la PAM s'appuie essentiellement sur la fréquence, en l'utilisant en miroir, or à $t=9000s$ les deux vont dans le même sens. Cela peut être dû au fait que deux mécanismes se combattent
 - o L'augmentation du débit donc de la pression avec la fréquence cardiaque
 - o La régulation physiologique de la pression artérielle moyenne par la fréquence cardiaque

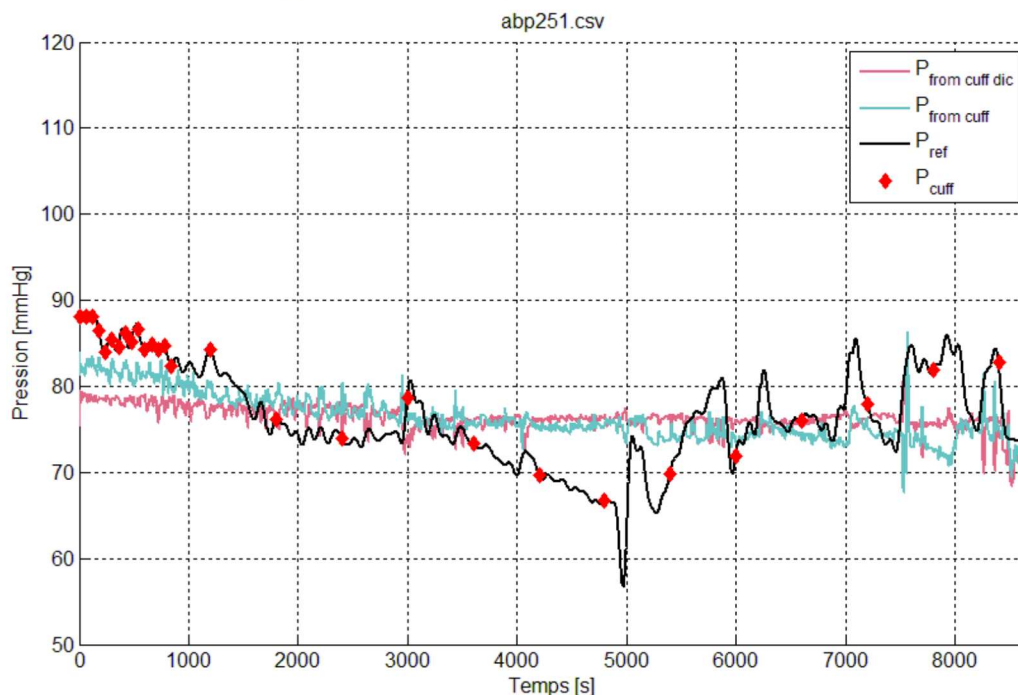
Hypothèse : Jusqu'à $t=9000s$ la fréquence est interprétée comme contrant les variations de la PAM alors que l'augmentation de la fréquence cardiaque à $9000s$ correspond à un stimulus externe

- La dicrote est difficilement interprétable car la forme de l'onde issue du pléthysmographe présente plusieurs oscillations. La détection de la dicrote n'accroche pas toujours la même.



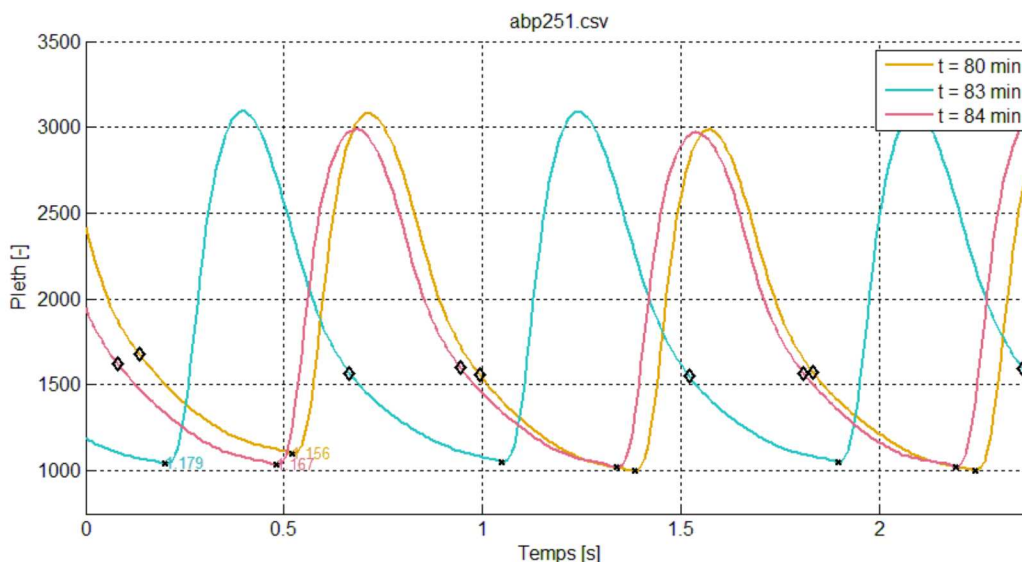


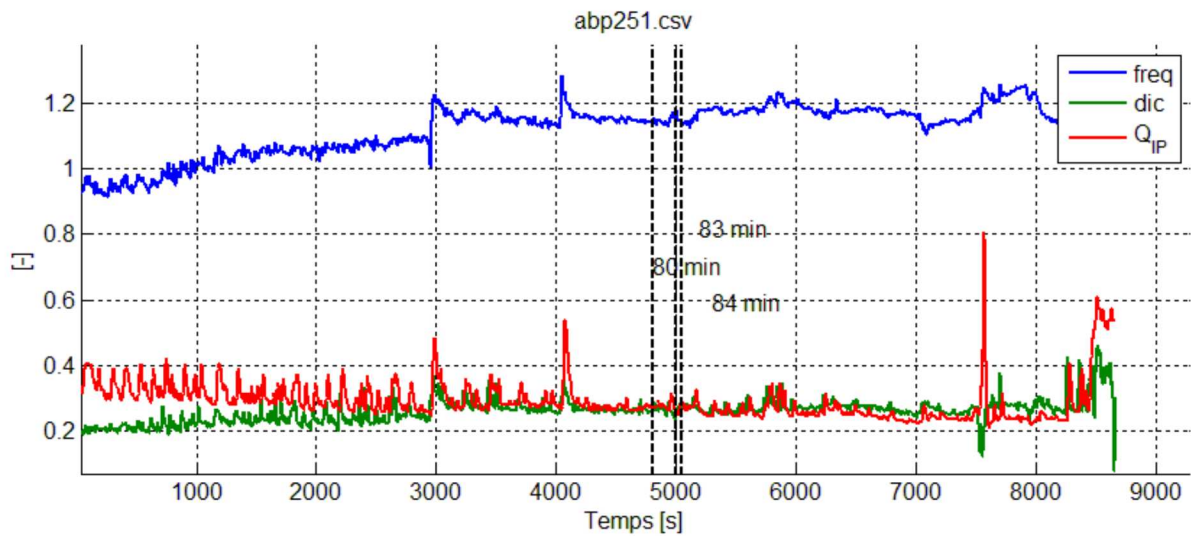
Signal d'onde de pression difficilement interprétable : trop raide



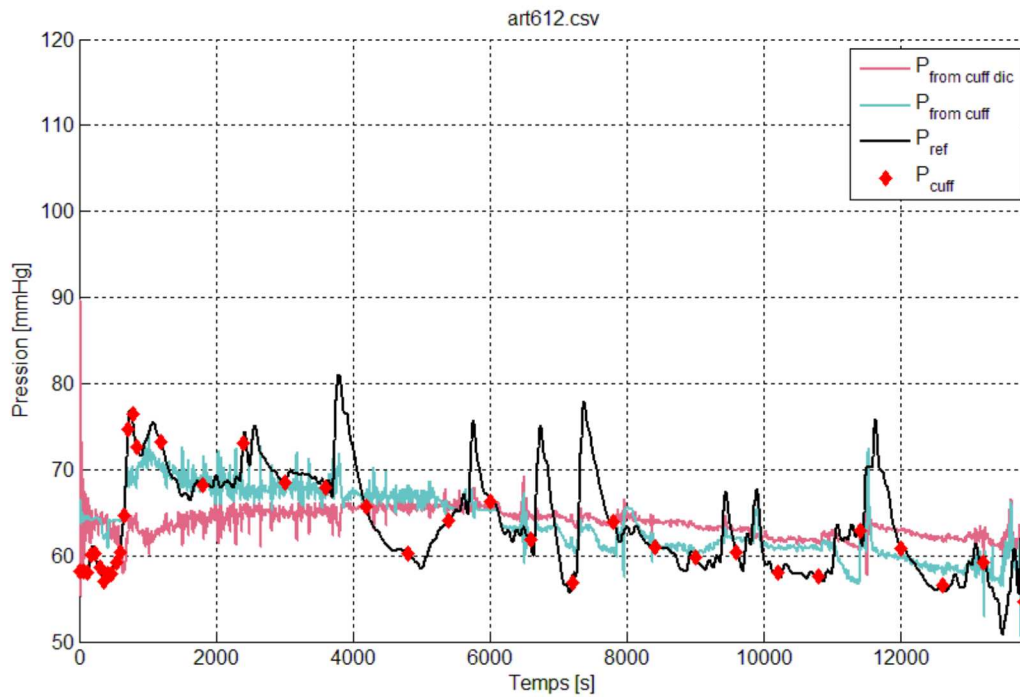
Sur le jeu de données art251.csv on constate une très mauvaise concordance, comme s'il n'y avait pas d'information à interpréter.

En s'intéressant au pic autour de $t = 5000s$ présent sur la PAM réelle mais pas sur les signaux sous-jacent, on constate que le signal issu de la pléthysmographie ne présente pas réellement de dicrote, ce qui peut expliquer le peu d'information que l'on en extrait.



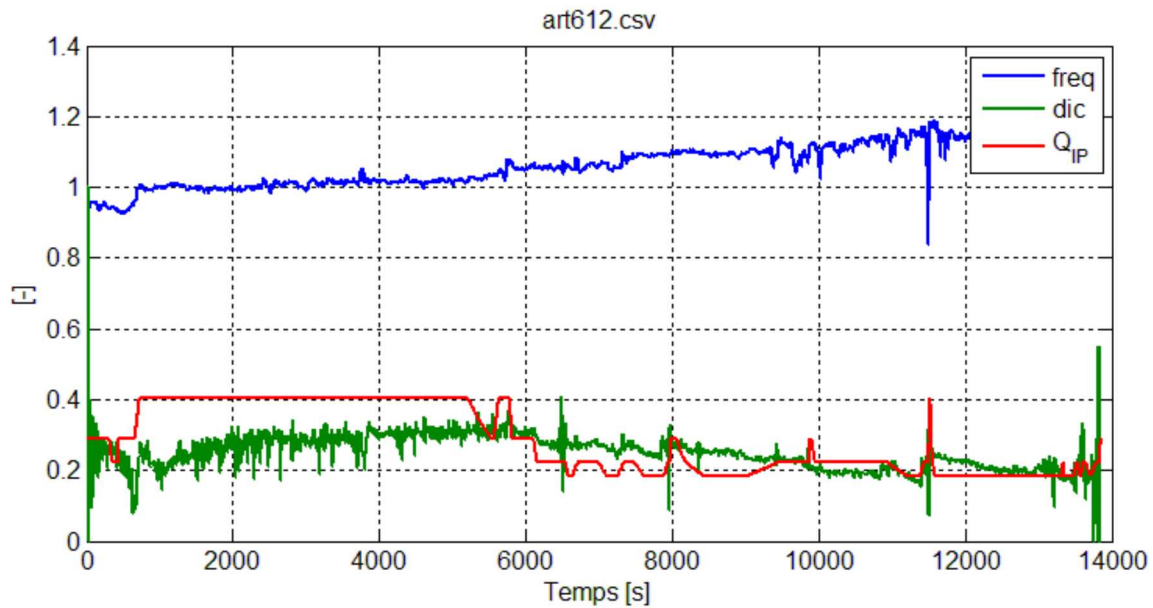


Pas de données sur l'indice de perfusion



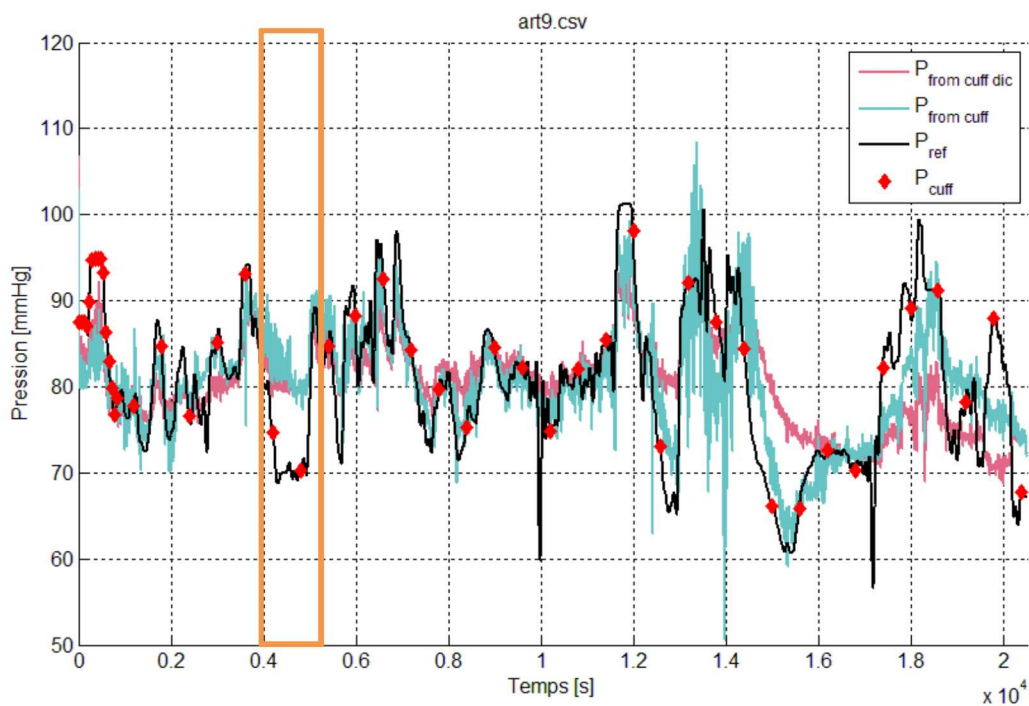
On constate sur le jeu de données art612.csv, qu'il semble y avoir peu d'information contenu dans la dicrote pour reconstruire la pression artérielle moyenne. L'ajout de la fréquence permet de retrouver l'augmentation de la PAM au début du jeu de données.

En analysant les signaux sous-jacent, on s'aperçoit qu'il n'y a quasiment pas d'information contenu dans l'indice de perfusion (problème d'acquisition ?), or il est probable que l'IP aurait contribué à expliquer les pics de la PAM.



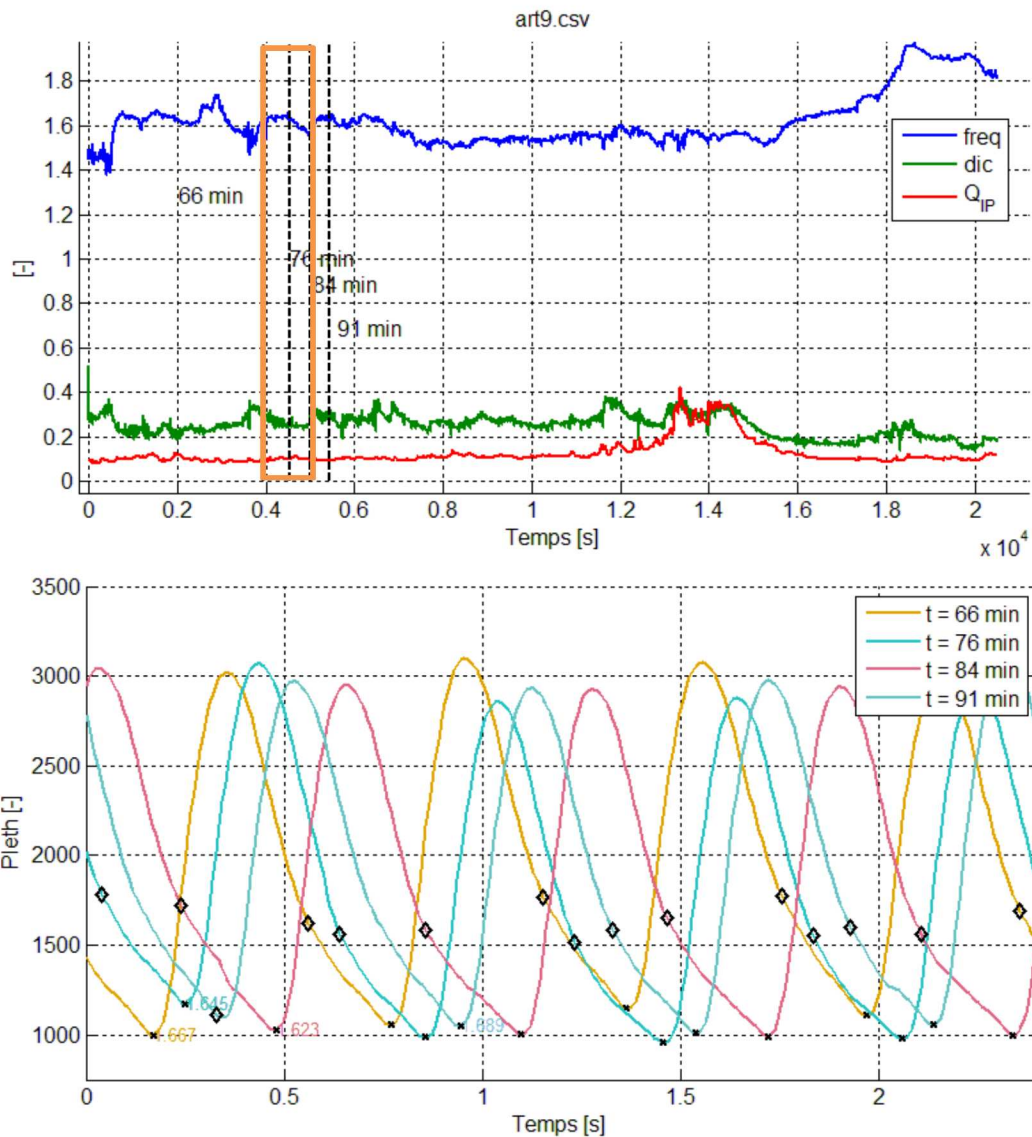
Problèmes : causes non identifiées

Le jeu de données art9.csv présente une bonne concordance excepté autours de t = 4000s.



Pour ce jeu de données nous ne disposons pas d'interprétation pour ce problème, en effet :

- Les signaux dic, freq et Q_{ip} ne semblent effectivement pas présenter de variation à t = 4000s
- La dicrote ne semble pas être significativement mal identifiée



4. Conclusions

4.1 Estimation de la PAM possible

Nous avons proposé un algorithme qui estime la pression moyenne artérielle à partir : des signaux obtenus grâce à la photopléthysmographie et à la prise de pression au brassard.

Reconstruction satisfaisante

Grâce à l'algorithme proposé, en s'appuyant sur la dicrote, l'indice de perfusion et la fréquence cardiaque, il a été possible de reconstituer la PAM de manière satisfaisante dans plus de 80% des cas.

Amélioration par rapport à l'exploitation de la dicrote seule

De plus on note une amélioration notable de la reconstitution en utilisant l'indice de perfusion et la fréquence cardiaque et non plus seulement la dicrote dans plus de 75% des cas.

Notons que l'algorithme proposé nécessite une période d'initialisation (prise ici à 15 minutes) pendant laquelle la pression est prise au brassard toutes les minutes. Notons également qu'il est important qu'il y ait des variations de la PAM durant cette période pour que l'identification des paramètres se fasse correctement.

4.2 Points d'amélioration

Besoin d'identifier les cas où la forme d'onde n'est pas standard et où l'estimation de la PAM ne peut pas fonctionner

Il existe deux cas où la dicrote risque d'être mal identifiée voire ne peut pas l'être :

- Soit la forme de l'onde de pression présente de nombreuses oscillations (cas d'une aorte très élastique) et il n'existe pas qu'un seul point d'inflexion sur la forme d'onde
- Soit, à l'inverse, la forme de l'onde de pression ne présente aucune oscillation (cas d'une aorte très rigide) et la dicrote n'existe pas à proprement parler.

Il est nécessaire de pouvoir identifier ces deux cas de figures pour pouvoir les exclure. Cela devrait pouvoir se faire grâce à l'analyse fréquentielle de la forme d'onde.

A noter qu'il pourrait être envisagé d'exploiter non plus la dicrote pas la forme de l'onde elle-même comme image de la résistance du système veineux auquel cas ces cas pourraient être réintégrer.

Besoin d'améliorer l'identification de la dicrote dans les cas où la forme d'onde est standard

Il existe des cas où malgré la forme réglementaire de l'onde de pression, l'algorithme d'identification de la dicrote ne donne pas la valeur attendue, il serait bon d'améliorer ce point ou du moins de donner un indice de qualité de l'identification pour permettre l'amélioration de l'estimation de la PAM.

Besoin de mieux comprendre certains phénomènes

Les phénomènes qui lient la PAM à la fréquence cardiaque, l'indice de perfusion et la dicrote sont loin d'être aussi simples que ceux décrits plus haut, ils peuvent faire intervenir des systèmes de régulation qui agissent à différentes échelles de temps. Les phénomènes prépondérants pouvant changer au cours de l'anesthésie, il serait bon d'analyser certains jeux de données en détail pour mieux en comprendre les ressorts et modifier l'algorithme le cas échéant.

5. Annexes

5.1 P : Suppression des points aberrants

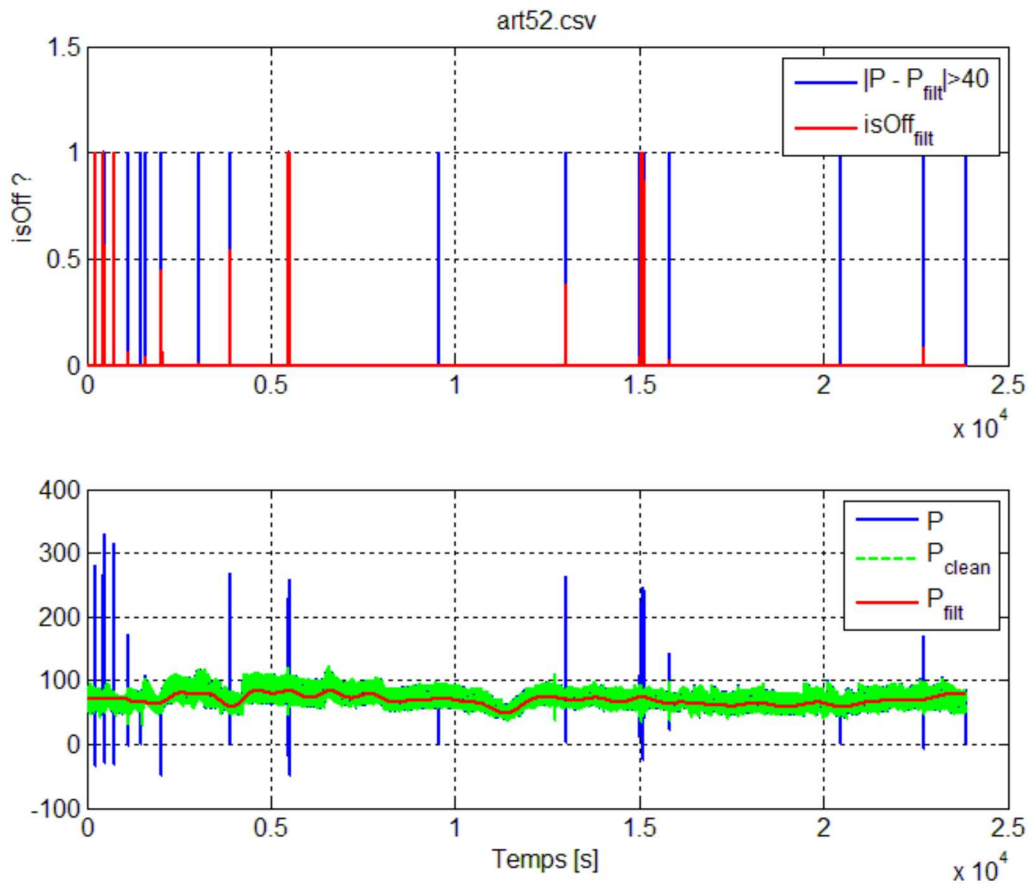
5.1.1 Prise de pression invasive sensible aux flushs

La pression est mesurée grâce à un dispositif qui doit être flushé de temps en temps. La mesure de pression n'est alors plus raccordée à la pression artérielle ce qui crée de brusque montée de pression allant jusqu'à 300mmHg.

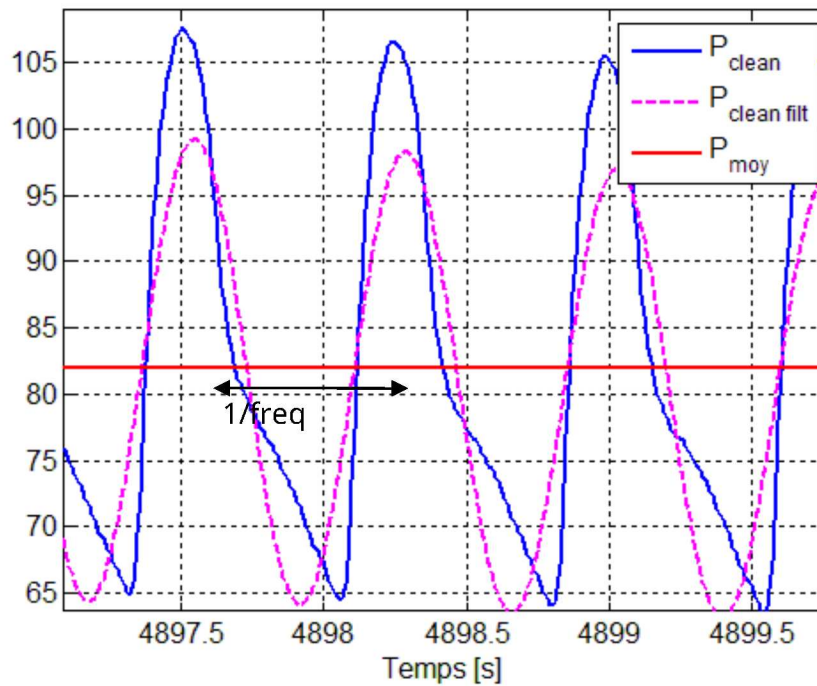
5.1.2 Traitement proposé : identification et suppression des points

Les étapes sont les suivantes :

- Filtrage passe bas de la pression P pour trouver une valeur qui servira de référence : P_{filt}
 - o passe bas de fréquence 0.005Hz (période de 3min20s)
- Identification des points de P qui sont à plus de 40 mmHg (60 ?) de la référence P_{filt} : $isOff$
- Filtrage de $isOff$ pour identifier les points situés à moins de 2 secondes d'un point aberrant
 - o Convolution avec un signal de type créneau de largeur 2 secondes
- Identification des points à garder :
 - o $P_{clean} = P(isOff_{filt} \cong 1)$



- Figure 10 - Identification des points aberrants de P grâce au signal $isOff$



- Figure 11 - Identification de la fréquence

0

5.2 Calcul de la fréquence à partir de P_{clean}

5.2.1 Calcul d'une fréquence brute

L'idée pour calculer la fréquence est d'identifier les points où la pression passe sous sa valeur moyenne. L'écart temporel entre ces points donne la période et son inverse la fréquence.

Les étapes sont donc dans un premier temps :

- Filtrage léger passe bas pour supprimer l'influence d'oscillations à des fréquences supérieures à la fréquence cardiaque : $P_{cleanfilt}$
 - o Passe bas de fréquence 1.5 Hz
- Identification de la PAM par filtrage passe base de $P_{clean} : P_{moy}$
 - o Passe bas de fréquence 0.01Hz (période : 1min40s)
- Identification des points tels que $P_{cleanfilt} < P_{moy}$
- Calcul de l'écart en temps entre ces points : $Fre q_{brut}$

5.2.2 Filtrage de la fréquence

La fréquence que l'on obtient doit encore être nettoyée. Entre autre, à cause des points que l'on a supprimés initialement de la courbe de fréquence.

Les étapes sont les suivantes :

- Suppression de tous les points de fréquence à plus de 0.1Hz de leur prédécesseur sur le signal $Fre q_{brut}$
- Sur le signal obtenu : suppression de tous les points de fréquence à plus de 0.1Hz de leur prédécesseur : $Fre q$
- Filtrage passe bas de fréquence 0.05Hz pour obtenir $Fre q_{filt}$

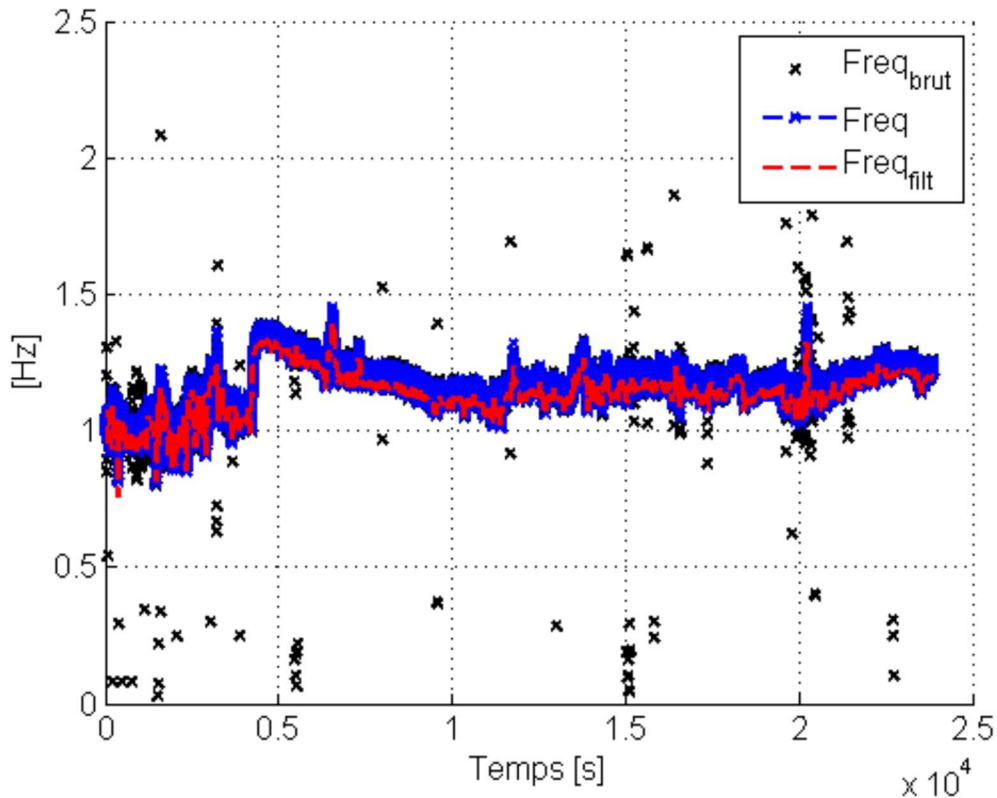


Figure 12 Suppression des points aberrants et filtrage pour obtenir la fréquence (cas art52.csv)

5.3 Calcul de la fréquence à partir du signal du pléthysmographe

5.3.1 Traitements proposés

On utilise le même principe que précédemment : on calcule la fréquence en identifiant les points où le signal sinusoïdal croise sa moyenne.

Pour cela on réalise les étapes suivantes :

- Identification de la porteuse $Plet h_{moy}$ grâce à un filtre passe bas de fréquence de coupure 0.001Hz (15 min 40s de période) appliqué au signal brut $Plet h_{brut}$
- Identification des points de croisement et calcul de la fréquence $Freq_{brut}^{Pleth}$
- Identification des points aberrants et obtention du signal $Freq_{clean}^{Pleth}$
 - o Suppression des fréquences $> 3.5\text{Hz}$
 - o Suppression des points distincts de plus de 0.1 Hz de leur prédécesseur

A noter que différentes fréquences de coupure auraient pu être utilisées.

5.3.2 Résultats

La Figure ci-après présente les résultats obtenus. On constate que sur le jeu de données art52.csv, il y a de nombreux points aberrants (croix bleues) qui sont correctement éliminés.

Une fois nettoyée, la fréquence issue du signal de pléthysmographie est très proche de celle issue du signal de pression invasive.

De même, lorsque l'on compare les deux signaux filtrés (passe-bas) on constate une très bonne correspondance. On choisit donc de garder le signal issu de la pléthysmographie (puisque c'est le seul dont on dispose à coup sûr).

5.4 Code

5.4.1 Fichiers

Les fonctions sont codées en Matlab :

scriptFreq.m	Programme principal
getFreq.m	Fonction qui permet le calcul de la fréquence cardiaque
deleteFakePoint.m	Fonction qui supprime les points aberrants

5.4.2 Structure

5.4.2.1 Du programme principal

Le programme principal est découpé en trois parties :

- *Algorithme*
 - o La première consiste à faire tourner l'algorithme sur l'ensemble des jeux de données listés dans la variable select et à stocker les résultats (erreur et paramètres calculés dans la variable cas sous la forme d'une structure).
- *Affichage des statistiques de l'ensemble des données*
 - o La seconde exploite la variable cas et affiche le graphique présentant les MAE
- *Affichage détaillé des formes d'onde*
 - o La troisième, pour un jeu de données, permet d'afficher les formes d'onde correspondant à différents indice temporel défini dans la variable vT

Lorsque le programme principal est lancé, seule la première partie est exécutée (jusqu'à return).

Les deux autres parties pourront être exécutées séparément (sélectionner le code correspondant et lancer l'exécution F5).

Mises en garde

- Il est indispensable d'avoir exécuté une fois la première partie du code sur l'ensemble des jeux de tests avant de lancer la seconde partie (graphique MAE)
- Il faut avoir chargé au moins un jeu de donnée (celui que l'on étudie) avant de lancer la troisième partie.

5.4.2.2 De l'algorithme

L'algorithme est découpé en trois parties :

- Pré-traitement : lecture et nettoyage des données
 - o Lecture du fichier excel et création de deux structures pour stocker toutes les colonnes :
 - Raw : données brutes
 - Ind : indices non nuls

- o Identification de l'intervalle temporel commun à toutes les variables, interpolation et nettoyage :
 - Time_1 : base de temps commune
 - Int : structure contenant les variables nettoyées et interpolées
- o Filtrage des variables issues de l'identification de la dicrote
 - Int_filt : structure contenant les données filtrées
 - Perf, dic et freq : correspondent à Q_{IP} , *dic* et *freq*
- Estimation de la pression moyenne
 - o Création des variables A et B
 - o Estimation des paramètres par moindres carrés :
 - Sur l'ensemble de l'acquisition : variable Z
 - Sur la période d'initialisation : Z_{init}
 - Actualisé au fur et à mesure de l'acquisition de pression par le brassard : A, B et Z_i
- Calcul des statistiques : erreur et stockage dans un tableau de la variable cas indexé par l'indice du fichier traité dans la variable select

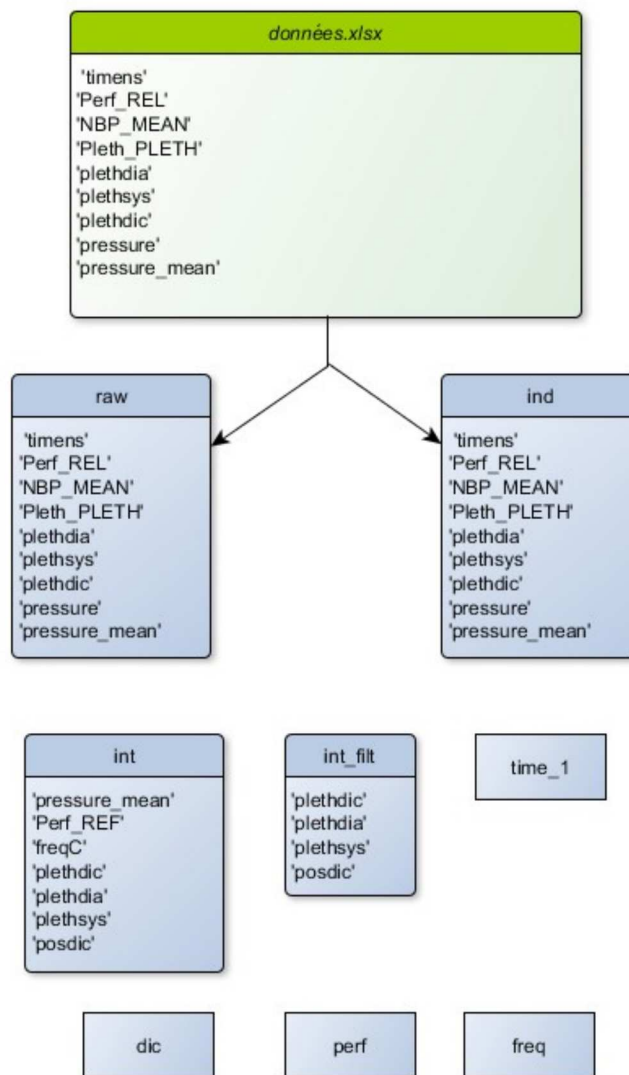
5.4.3 Variables

5.4.3.1 Paramètres

Les paramètres sont les suivants (en début de programme principal) :

Nom	Description	Valeur	Unité
cuffDelay	Délais entre 2 prises de brassard	10*60	Seconde
firstCuffDelay	Délais entre 2 prises de brassard pendant l'initialisation	1*60	Seconde
initDuration	Durée de l'initialisation	15*60	Seconde

5.4.3.2 Variables courantes



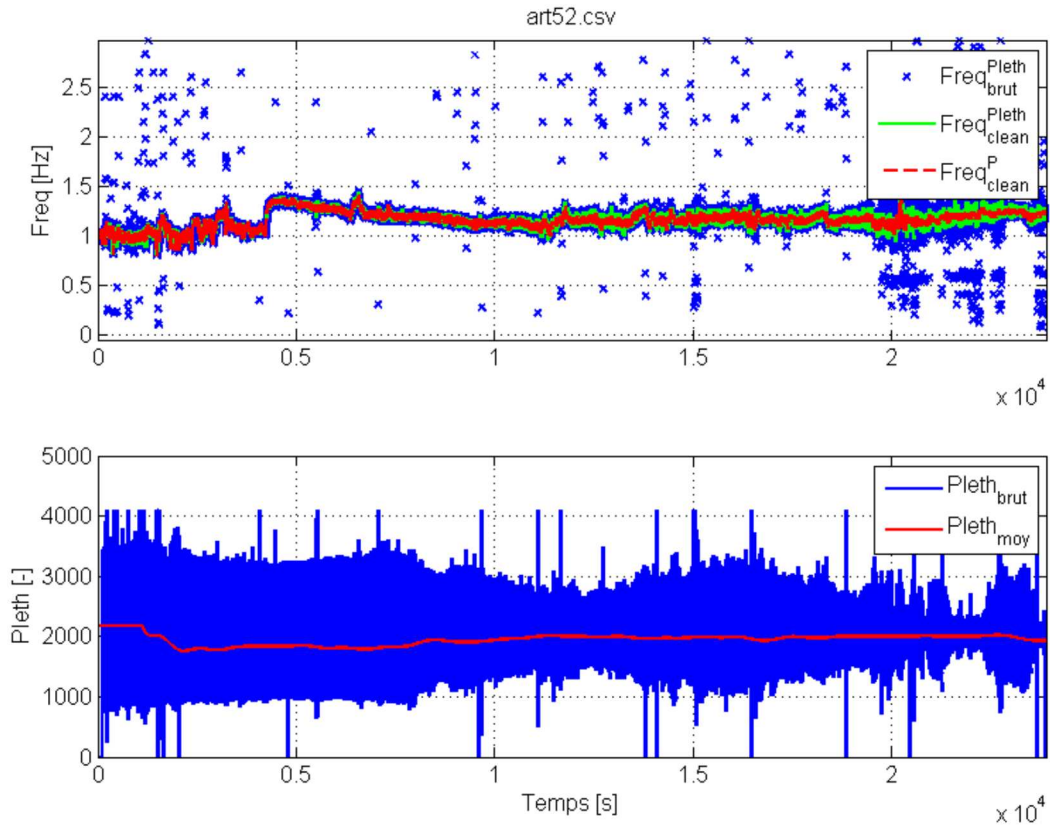


Figure 13 - Signal de pléthysmographie brut et sa porteuse (en rouge).
 Comparaison des fréquences obtenues

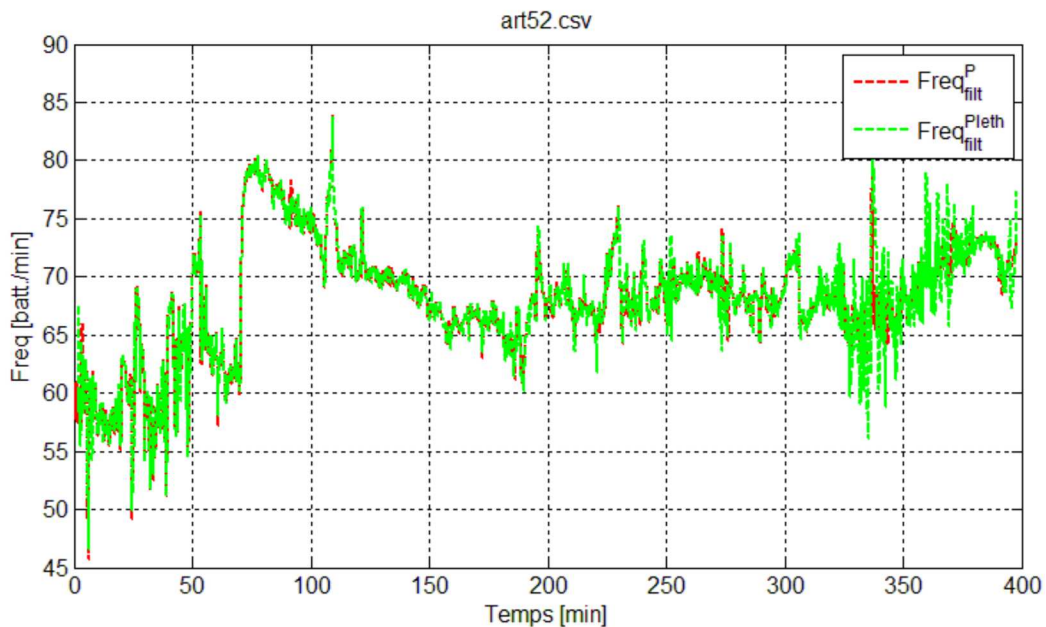
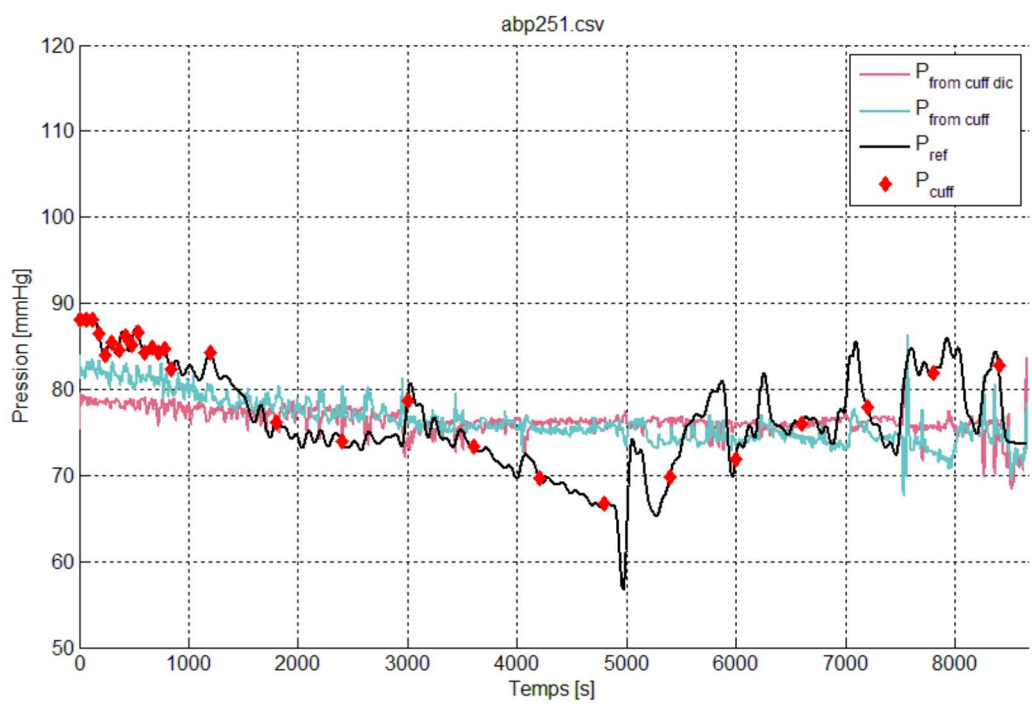
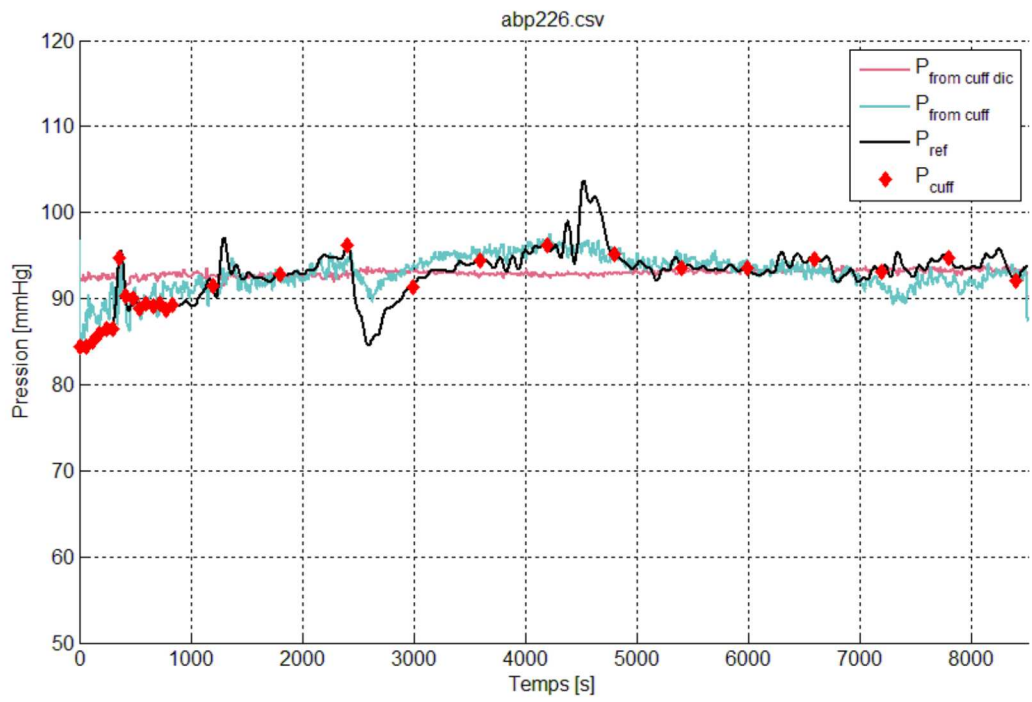
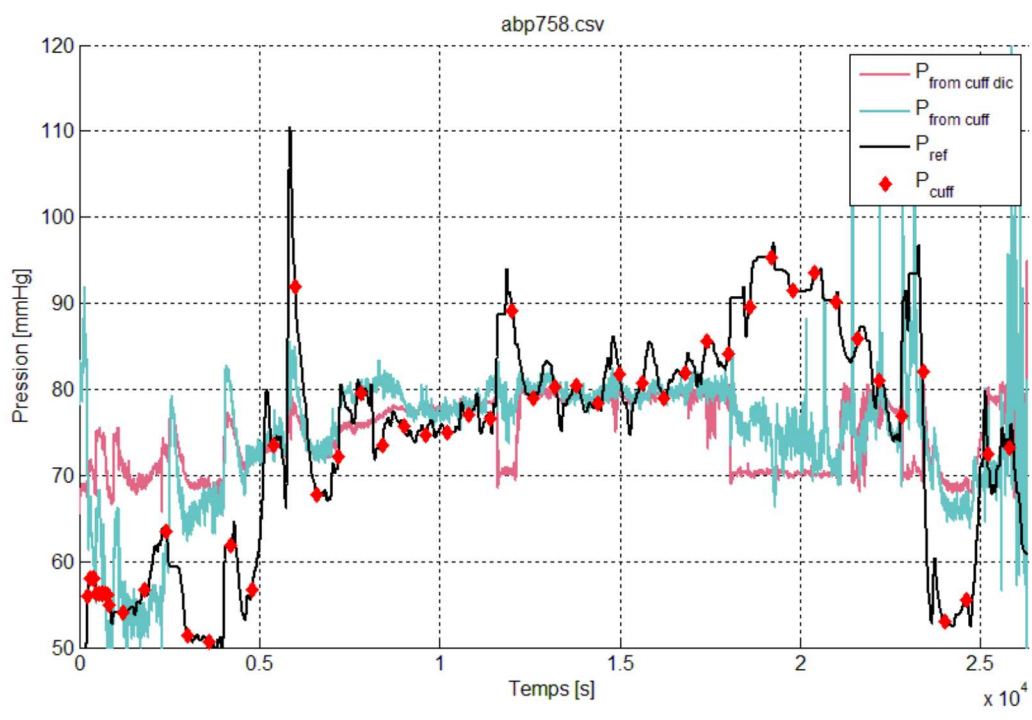
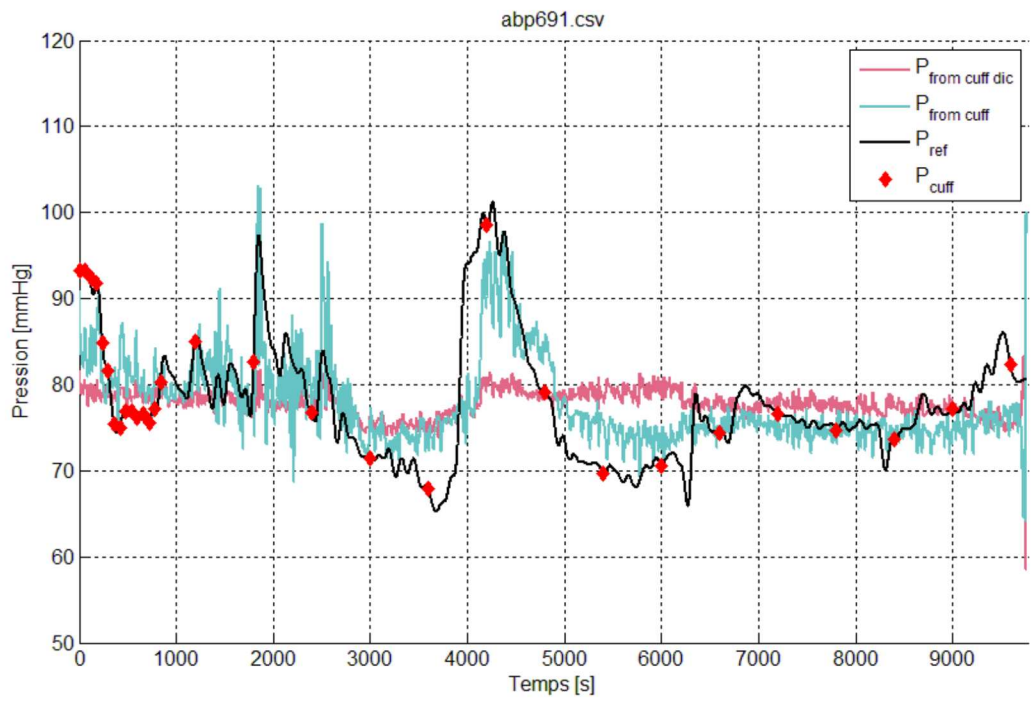
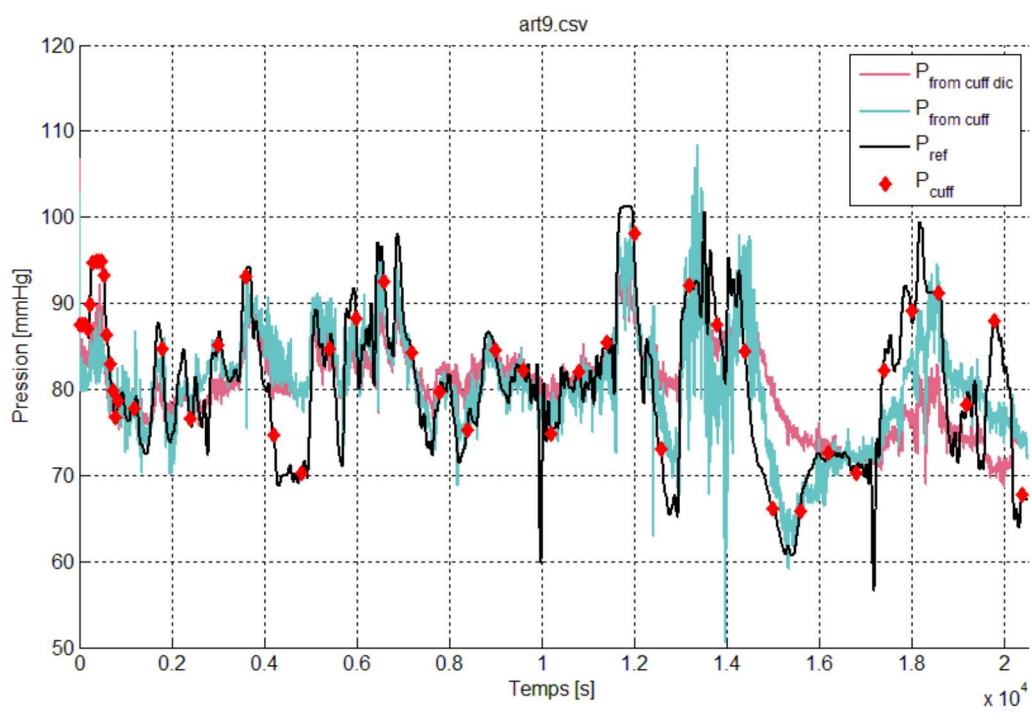
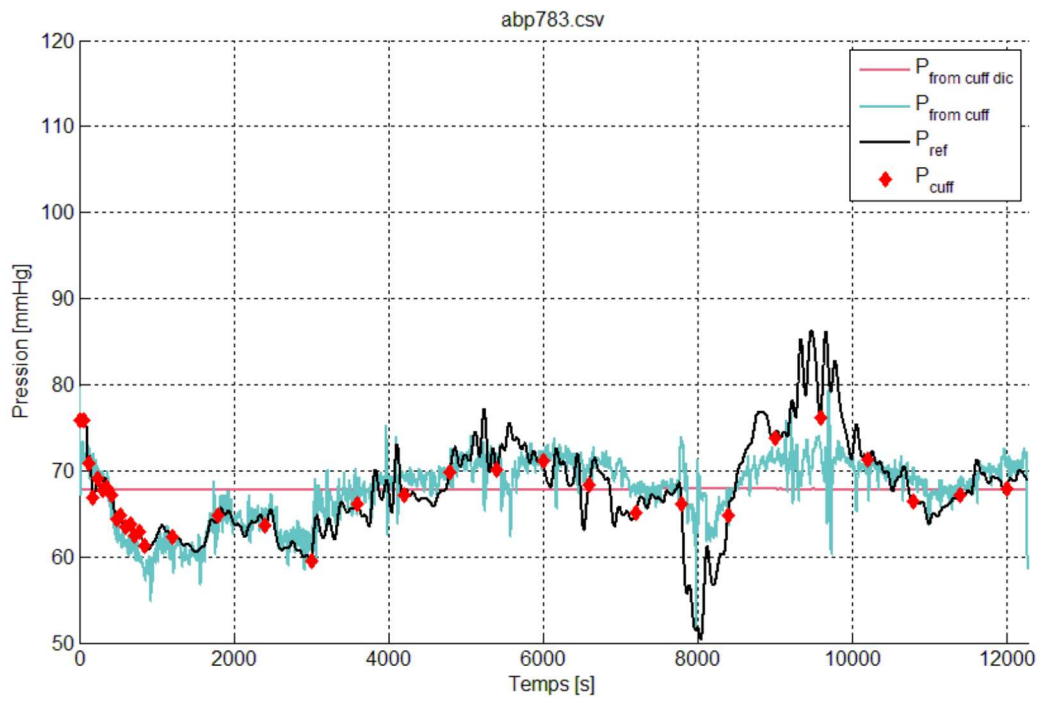


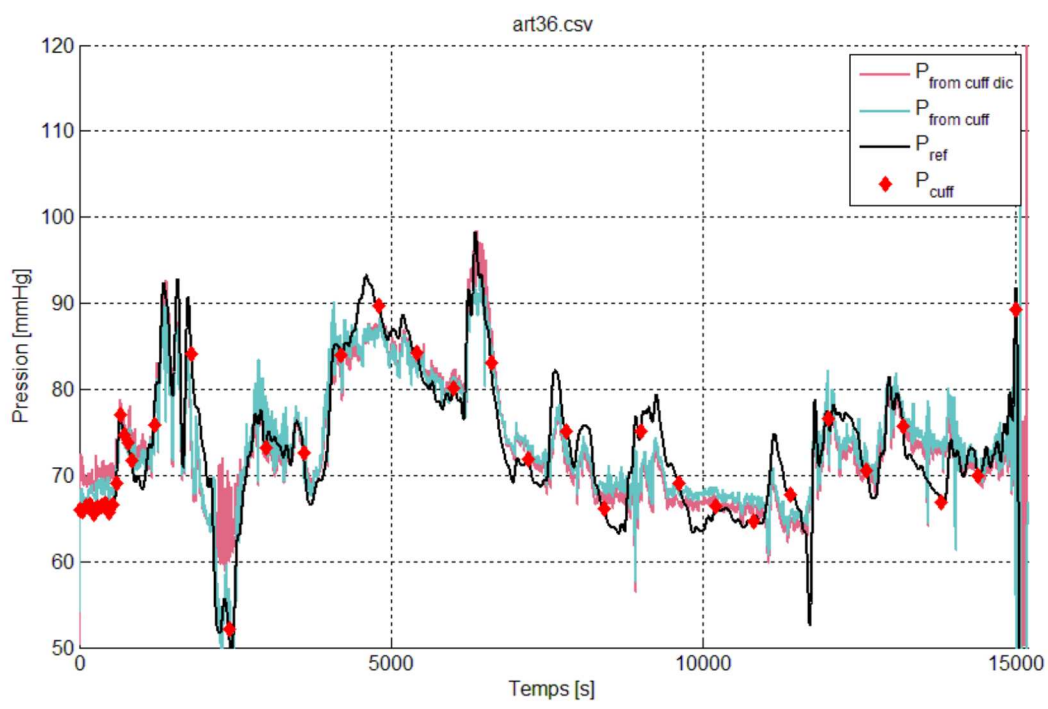
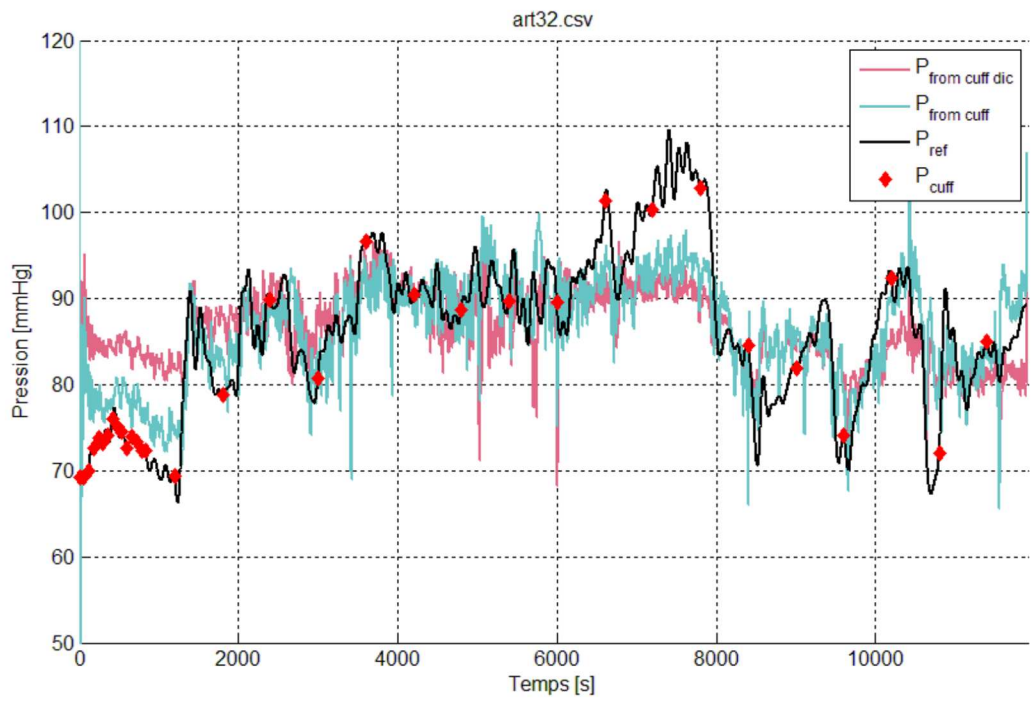
Figure 14 - Comparaison des fréquences cardiaques calculées à partir du signal de pléthysmographie et de la pression artérielle. On constate que les deux sont très proches.

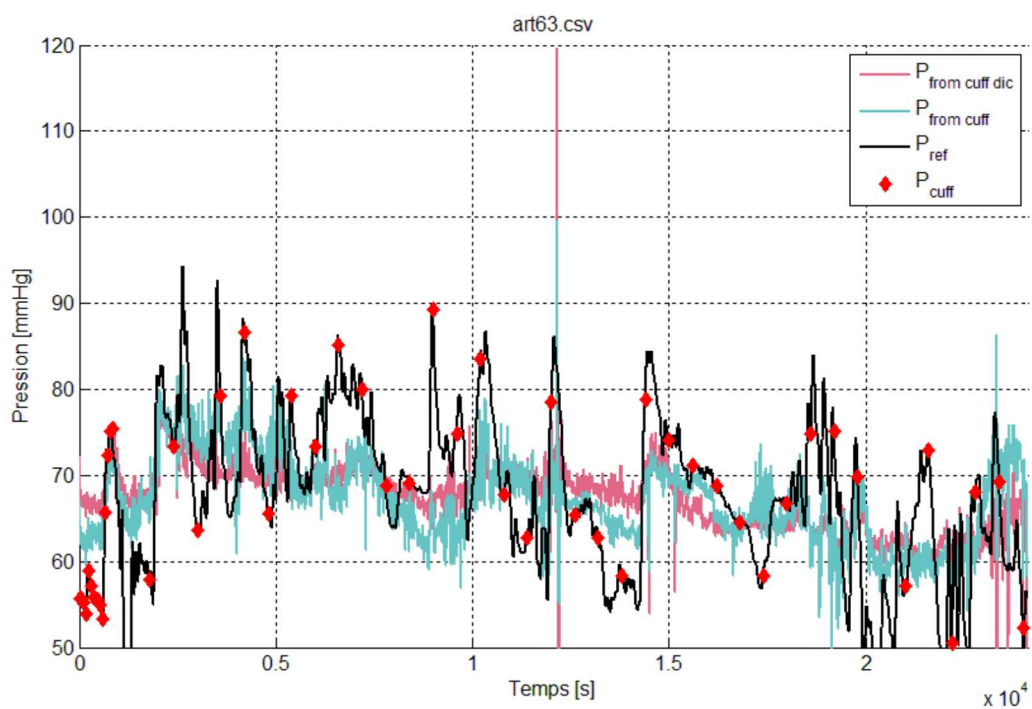
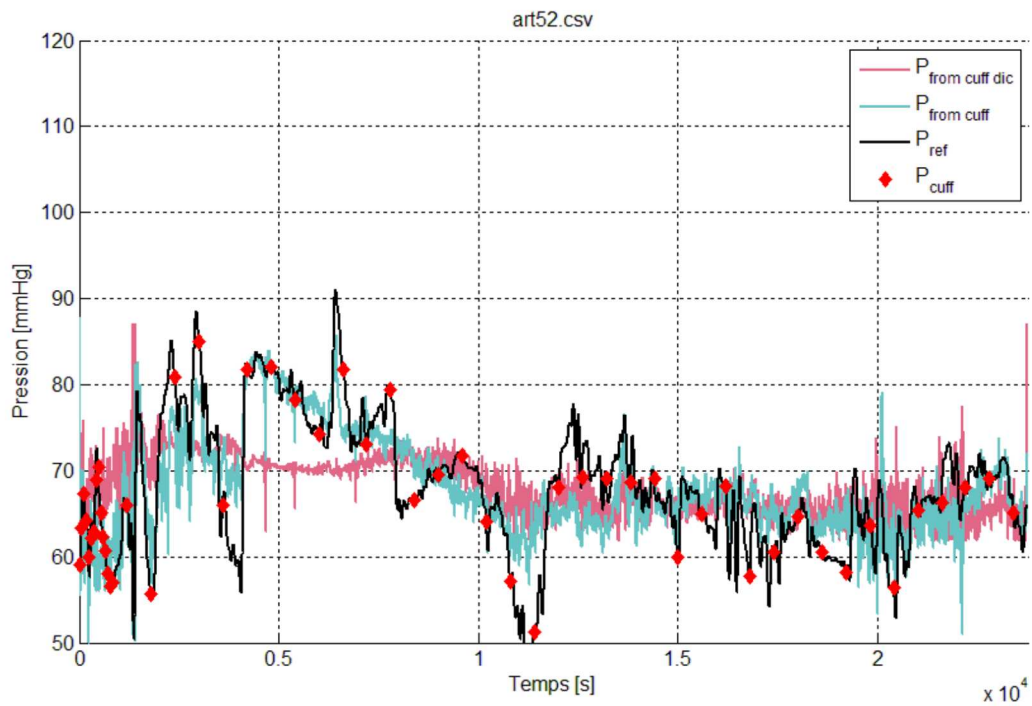
5.5 Résultats – Figures

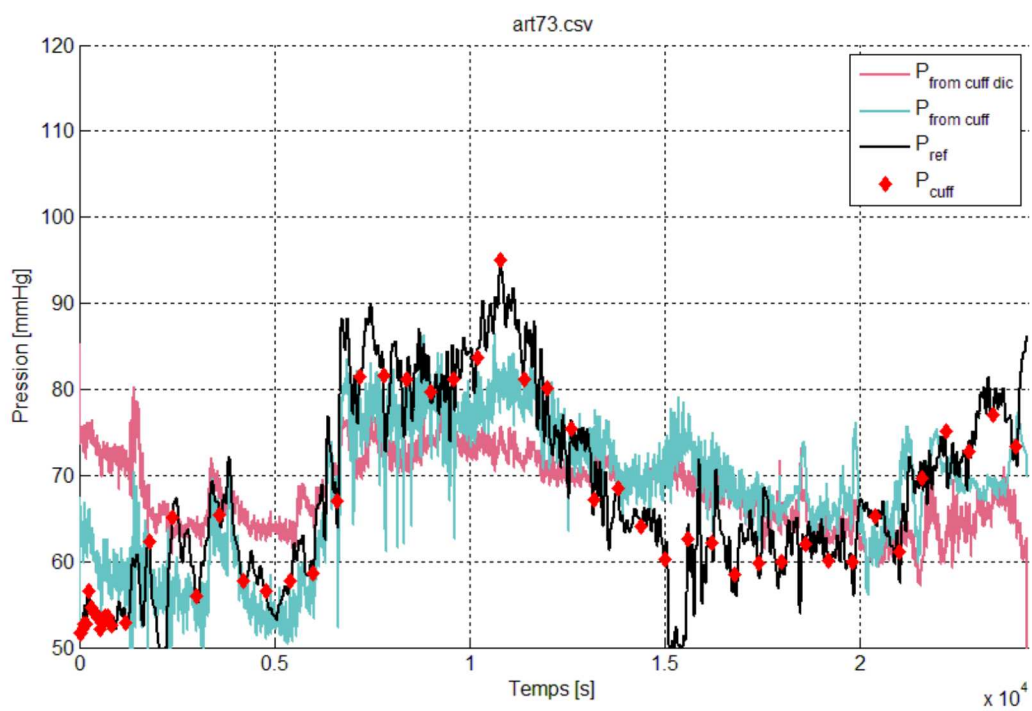
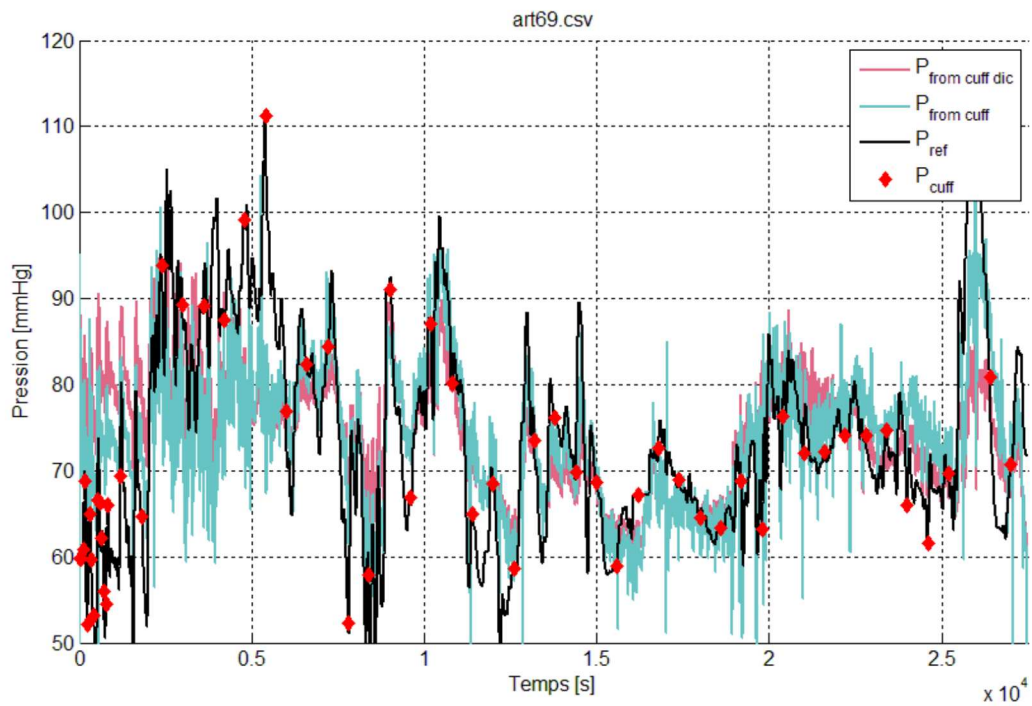


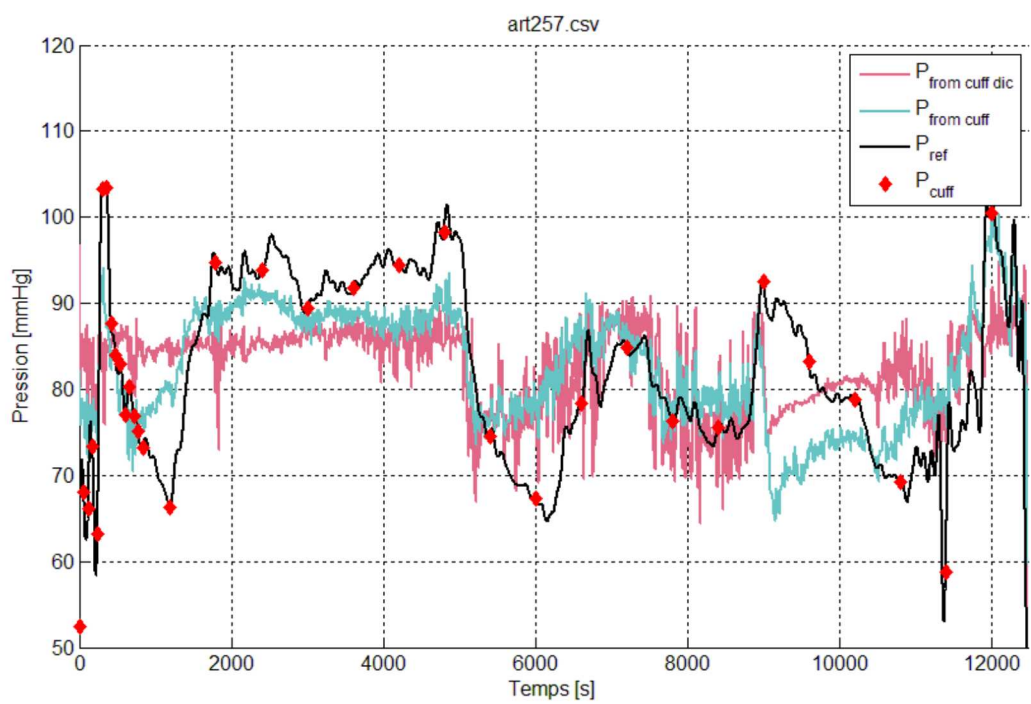
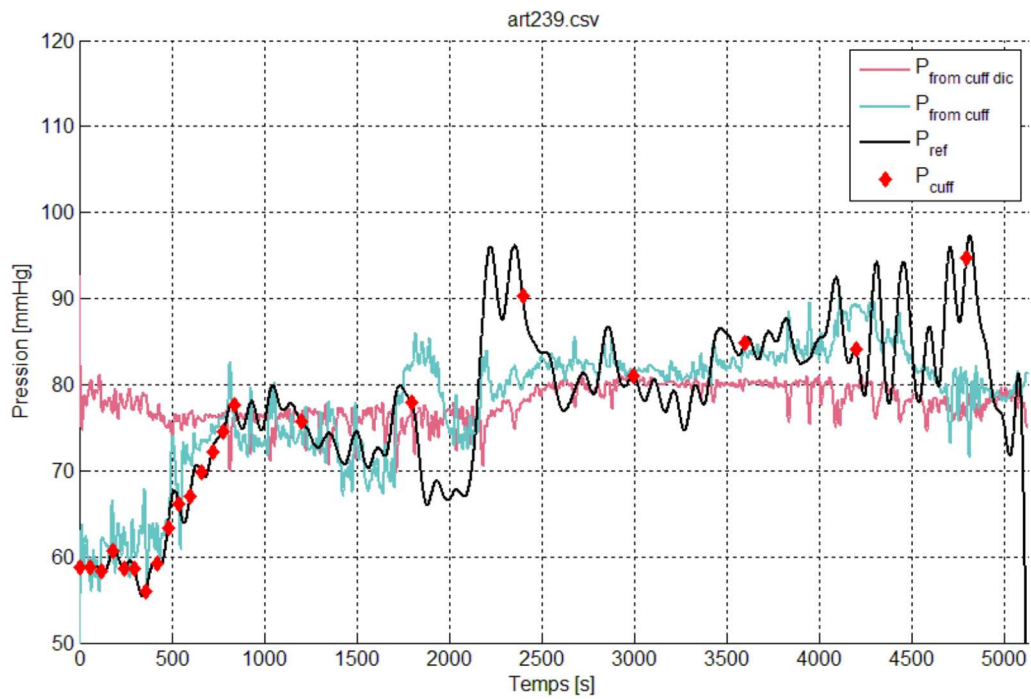


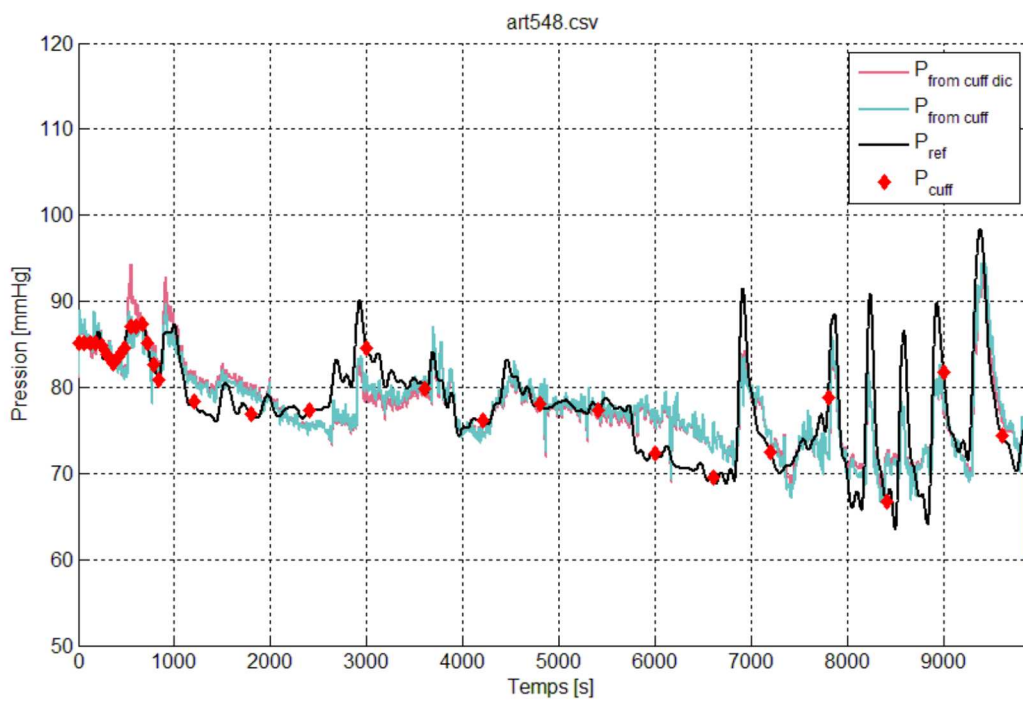
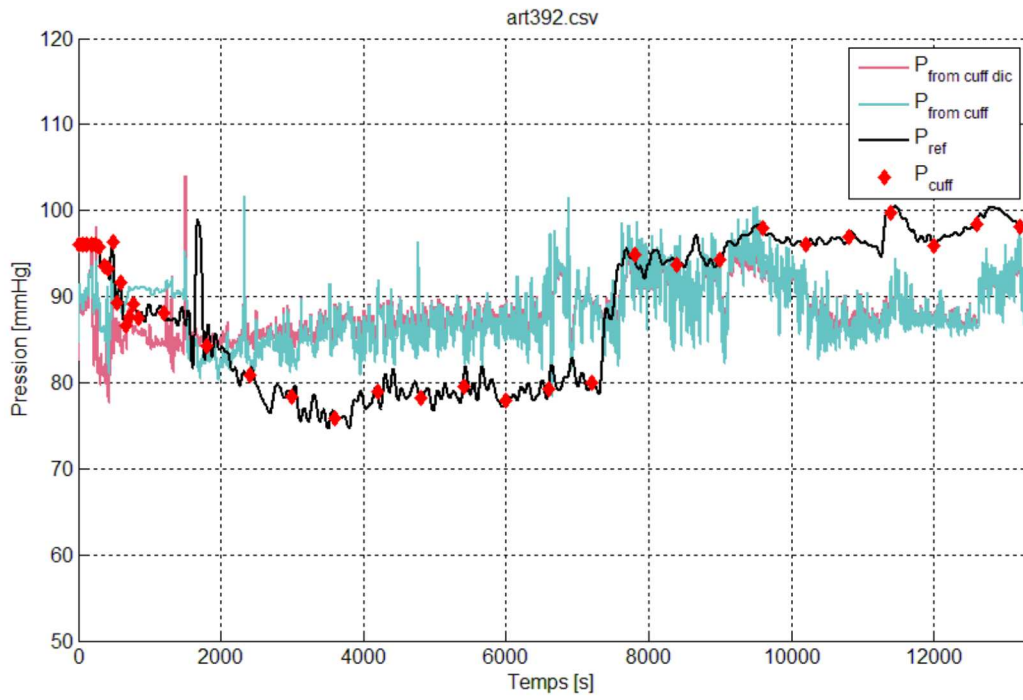


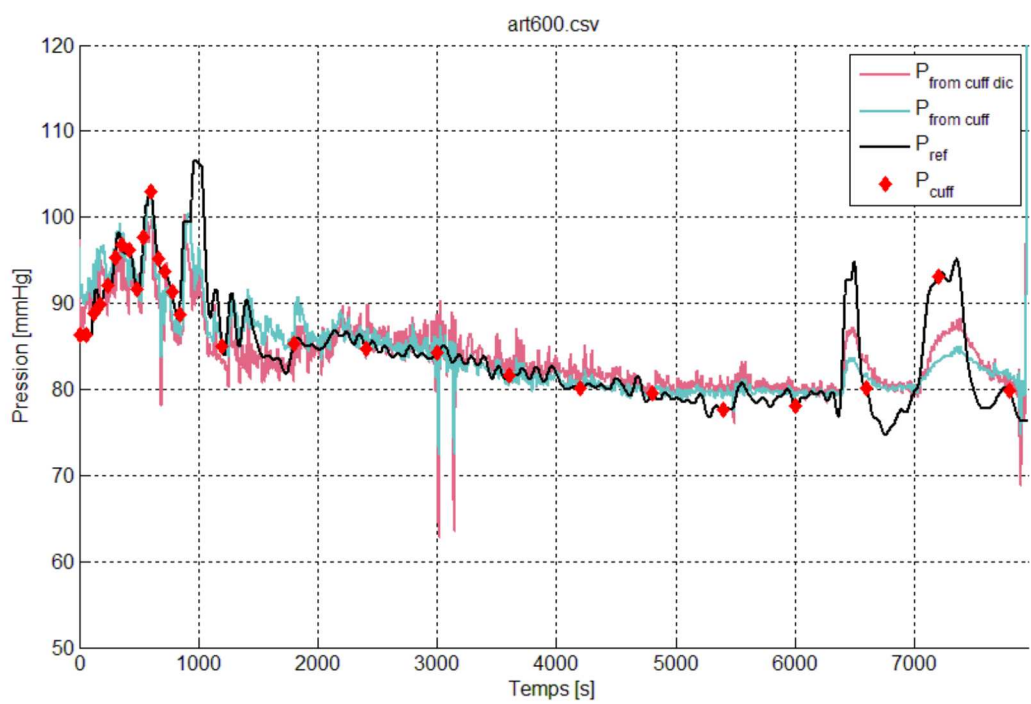
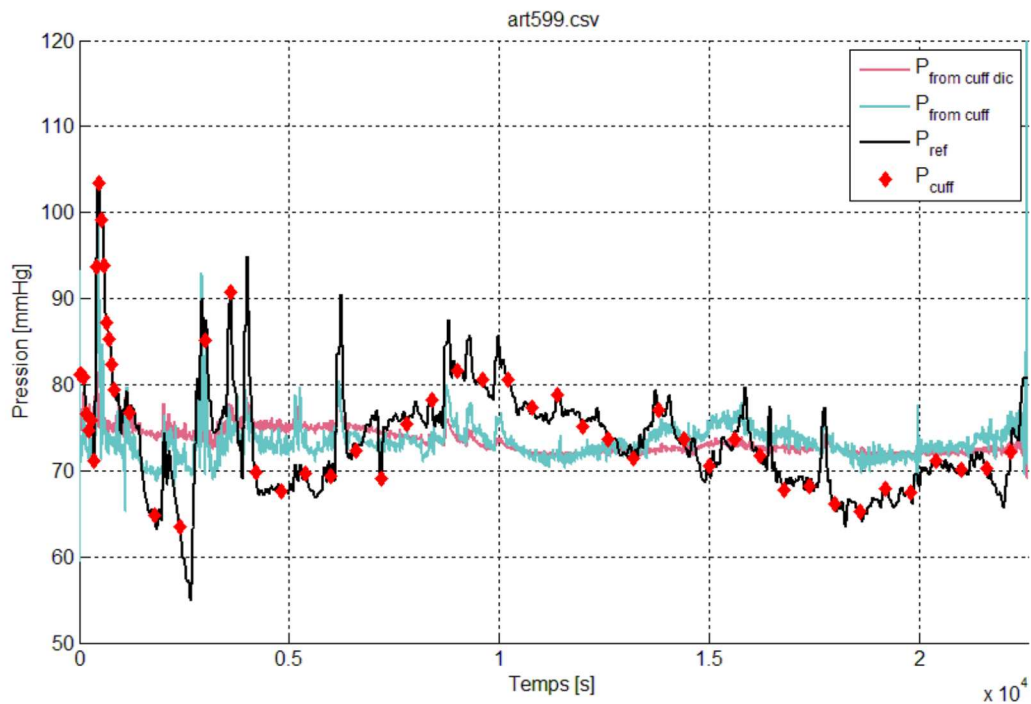


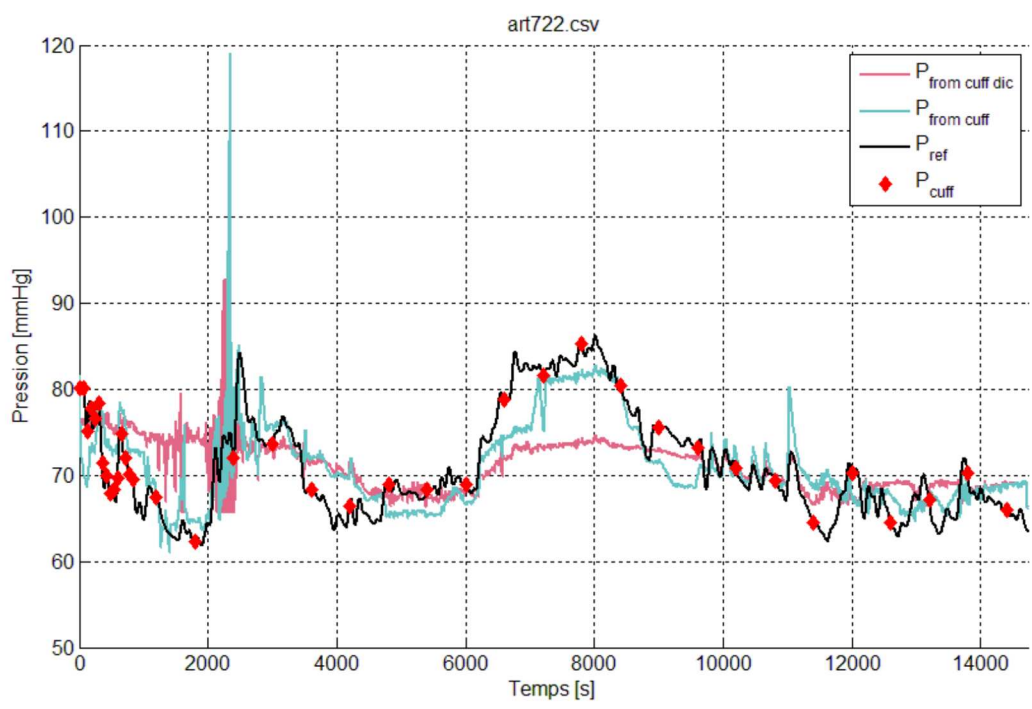
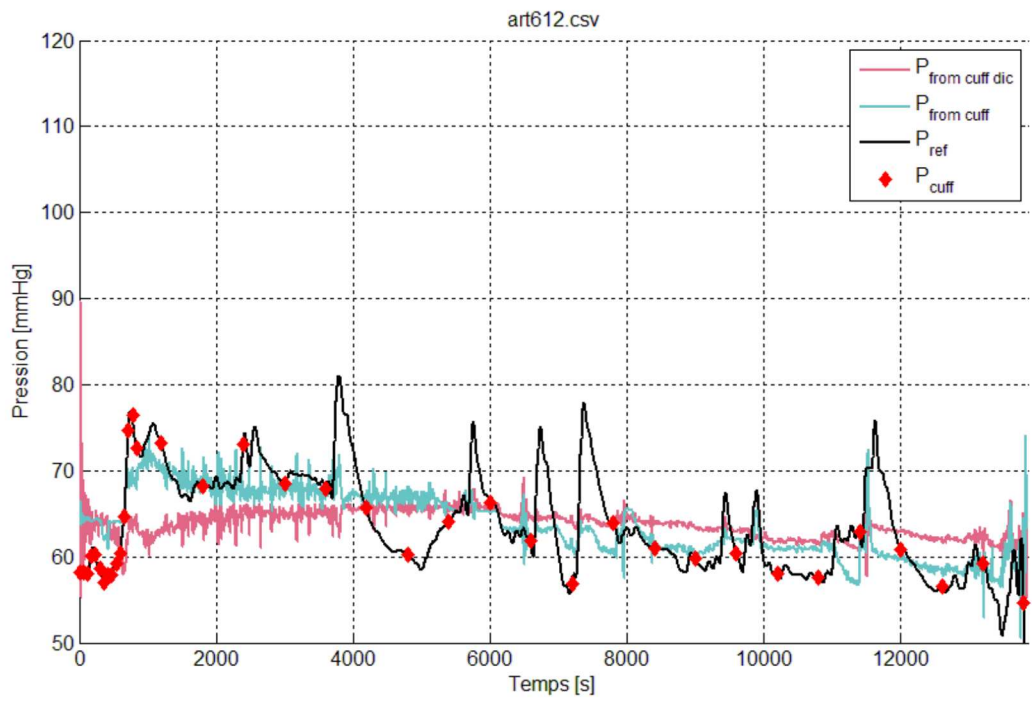


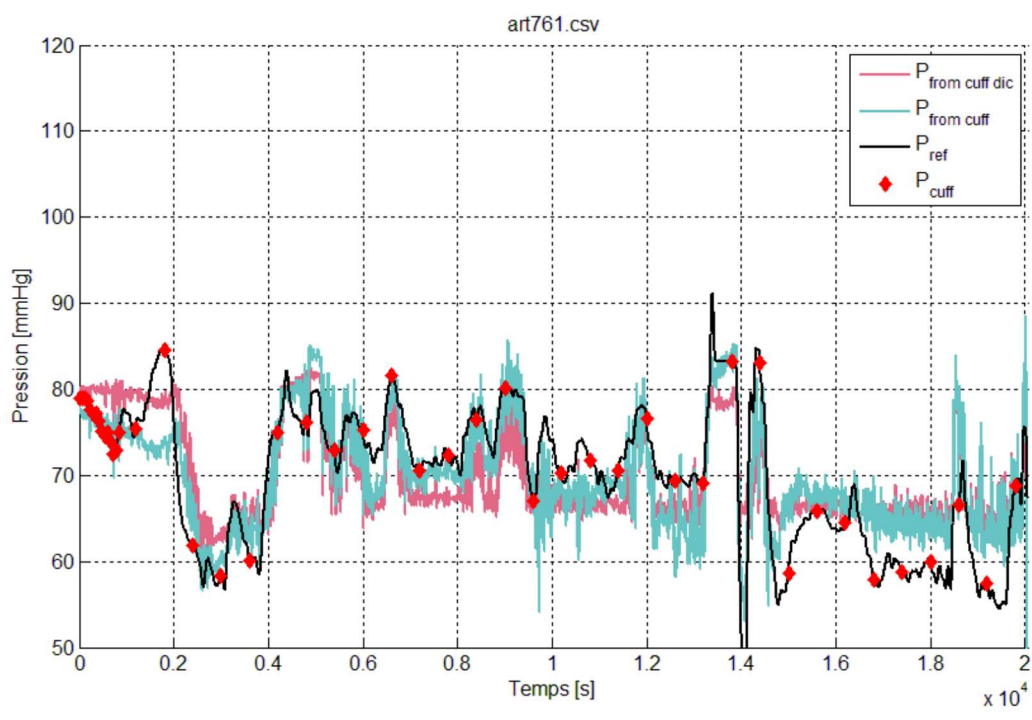
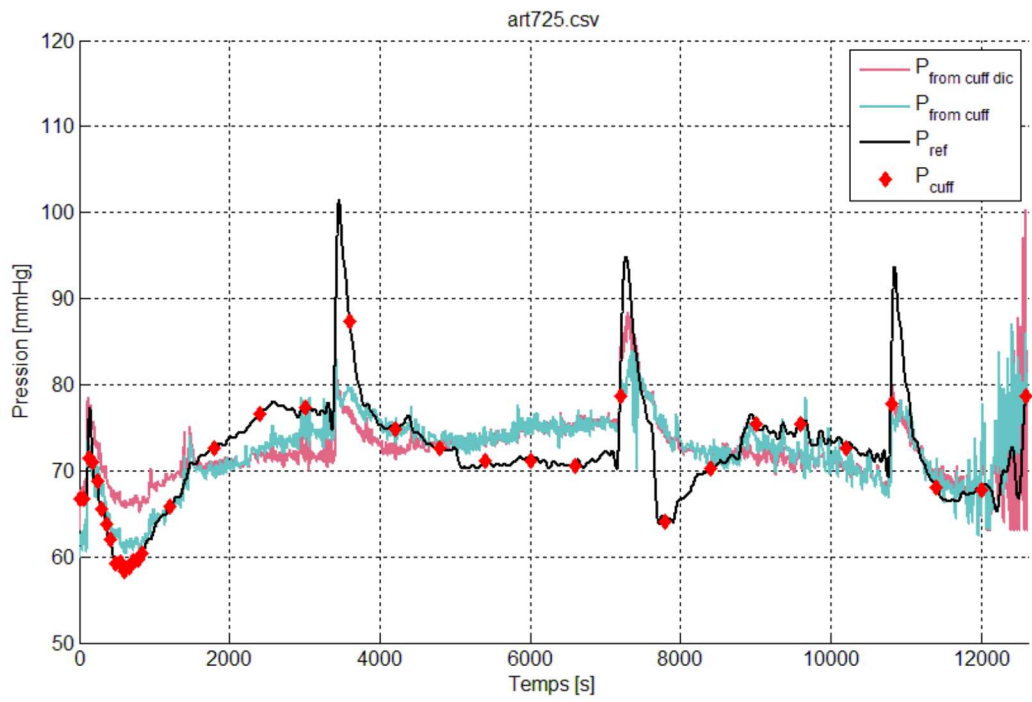












Annexe 2.2 Développements informatiques

Bibliothèque *dwclib*

dwclib est une bibliothèque de programmation pour le langage de programmation Python qui permet une requête et une analyse efficace de la base de données DataWarehouse Connect (DWC). Cette bibliothèque a été développée dans le cadre de ce travail pour permettre l'analyse des données biométriques qui permettant la calibration des algorithmes PlethoMAP et du modèle PK/PD de la noradrénaline. Le code source est disponible sous licence libre (open source) à l'adresse suivante: <https://framagit.org/jaj/dwclib>

Bibliothèque *InfuPy*

InfuPy [49] est une bibliothèque de programmation pour le langage de programmation Python qui permet d'interfacer les pompes à insuline électriques. Cette bibliothèque a été développée dans le cadre de ce travail, notamment pour interfacer les seringues électriques dans le cadre de l'étude NorPharm pour mesurer précisément la dose de noradrénaline infusée. Le code source est disponible sous licence libre (open source) à l'adresse suivante: <https://github.com/jaj42/infupy>

Bibliothèque *physiocurve*

physiocurve est une bibliothèque de programmation pour le langage de programmation Python qui intègre un certain nombre d'algorithmes que nous avons développés pour analyser des courbes de signaux biométriques. *Physiocurve* intègre notamment les algorithmes pour analyser les courbes de PPG et détecter les points d'intérêt comme le pied de l'onde et l'onde dicrote. Cette bibliothèque forme un socle commun pour les analyses des courbes, notamment pour le modèle mécanistique PlethoMAP. Le code source est disponible sous licence libre (open source) à l'adresse suivante: <https://framagit.org/jaj/physiocurve>

Logiciel *GraPhysio*

GraPhysio est un logiciel que nous avons développé pour analyser visuellement des courbes de signaux biométriques. Le logiciel permet d'afficher des signaux recueillis, notamment grâce à *dwclib*, de couper et fusionner certains signaux et de réaliser des opérations mathématiques, des interpolations ou l'application de filtres. *GraPhysio* intègre également

physiocurve pour l'analyse des ondes. Le logiciel permet d'exporter les données après traitement sous divers formats. Le code source est disponible sous licence libre (open source) à l'adresse suivante: <https://github.com/jaj42/GraPhysio>

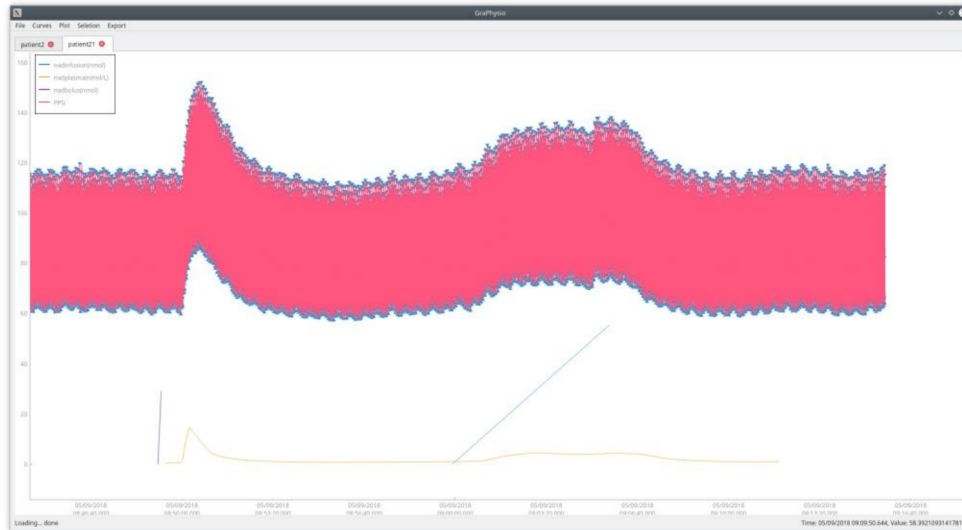
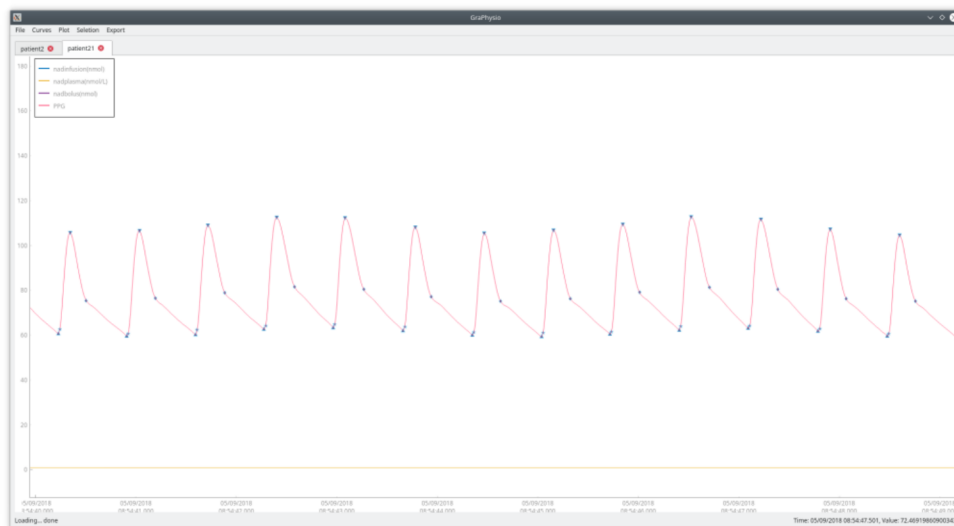


Illustration du logiciel GraPhysio montrant des données sources pour l'étude PKPD sur la noradrénaline, notamment la courbe de PPG annotée (rose), la concentration plasmatique en noradrénaline mesurée (jaune) et les perfusions de noradrénaline en volume cumulé des seringues électriques (violet et bleu)



Grossissement de la figure précédente montrant l'annotation du signal de PPG, notamment de l'onde dicrote.