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Étude de facteurs visant à favoriser l'intégration de la réanimation par circulation extracorporelle à l'arsenal de soins pour les patients souffrant d'un arrêt cardiorespiratoire extrahospitalier

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Étude de facteurs visant à favoriser l'intégration de la réanimation par circulation extracorporelle à l'arsenal de soins pour les patients souffrant d'un arrêt cardiorespiratoire extrahospitalier

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Résumé

Le taux de survie des patients souffrant d'un arrêt cardiaque extrahospitalier est inférieur à 10% même avec les meilleures pratiques en réanimation. Une nouvelle technique de réanimation, soit la réanimation par circulation extracorporelle, a été mise à l'essai et s'avère prometteuse pour améliorer le pronostic chez cette population. Par contre, des réponses à plusieurs enjeux doivent être obtenues avant de tester de façon prospective les avantages de cette technique, notamment quant aux impacts collatéraux sur les pratiques de réanimation préhospitalière qu'elle impliquerait, à la sélection des patients et aux potentielles stratégies de monitorage à utiliser chez ces patients. Cette thèse vise à répondre à ces questions avant d'éventuellement démontrer la valeur ajoutée de cette technique de réanimation et ainsi améliorer la survie pour ces patients.

Le premier volet présente les résultats de trois études de cohorte explorant les impacts qu'aurait l'incorporation de la réanimation par circulation extracorporelle sur les protocoles de soins. Les résultats d'une première étude de cohorte ont démontré que la durée des manœuvres de réanimation avancées pratiquées en préhospitalier pourrait être réduite pour permettre un départ plus rapide vers un centre hospitalier pouvant initier la réanimation par circulation extracorporelle puisqu'il n'y avait pas d'association positive entre la durée de ces manœuvres et la survie chez ces patients. Les résultats d'une deuxième étude ont démontré que de rediriger les patients en arrêt cardiaque vers les centres hospitaliers pouvant pratiquer la réanimation par circulation extracorporelle pourrait augmenter leur taux de survie. Ce bénéfice potentiel subsistait jusqu'à un ajout de 14 minutes de la durée du trajet par ambulance dû à la redirection. Troisièmement, la modification de ces deux protocoles de soins permettrait à potentiellement trois fois plus de patients de bénéficier d'une réanimation par circulation extracorporelle.

Le second volet présente les résultats de deux études visant à optimiser la sélection des patients pour une réanimation par circulation extracorporelle. Les résultats d'une première étude de cohorte descriptive ont démontré que les patients nécessitant plus de 10 défibrillations conservaient un pronostic de survie adéquat, et ainsi devraient demeurer éligible à une réanimation par circulation extracorporelle. Dans une deuxième étude de cohorte, nous avons étudié l'impact pronostique d'une conversion de rythme pendant la réanimation et avons démontré que le rythme initial était un meilleur marqueur de pronostic que la conversion du rythme. Ainsi, les patients ayant une conversion d'un rythme non-défibrillable à un rythme défibrillable ne devraient pas être retenus en première intention pour une réanimation par circulation extracorporelle, contrairement à ceux dont le rythme initial était déjà défibrillable.

Les études du troisième volet visaient à explorer l'usage d'une technologie de monitorage de l'oxymétrie tissulaire, la spectroscopie proche-infrarouge, en raison de son potentiel pour mesurer en continu le degré d'oxygénation des candidats à une réanimation par circulation extracorporelle. Une revue systématique de la littérature a démontré l'utilité pronostique de cette technologie pour les patients en arrêt cardiaque. Ensuite, nous avons décrit à l'aide d'une cohorte prospective les propriétés métrologiques de deux appareils et les facteurs associés permettant d'optimiser leur utilité dans le contexte de patients en arrêt cardiaque.

Les connaissances développées par l'entremise des études composant la présente thèse ont déjà été intégrées aux protocoles de prise en charge des patients souffrant d'un arrêt cardiaque extrahospitalier ce qui jette des bases solides pour poursuivre des recherches pour ultimement améliorer leur pronostic.

Mots-clés : arrêt cardiaque extrahospitalier, réanimation par circulation extracorporelle, organisation des soins préhospitaliers, pronostication, spectroscopie proche-infrarouge

Abstract

Despite advances in medical care, survival amongst out of hospital cardiac arrest patients remains low, with only 10% of patients surviving. The use of extracorporeal cardiopulmonary resuscitation, a novel resuscitation procedure, has recently garnered interest and showed promise to improve resuscitation outcomes. However, questions remain to be answered before this technology can be prospectively evaluated, notably regarding the collateral impacts of its implementation, appropriate patient selection and the monitoring strategies to use for these patients. The main objective of this thesis is to answer these questions to eventually improve the outcome of patients suffering from an out-of-hospital cardiac arrest.

In the first part, the results of three cohort studies exploring the potential impact of the implementation of extracorporeal resuscitation on prehospital resuscitation protocols are presented. A first cohort study showed that the duration of prehospital advanced cardiac life support could be reduced to allow for an earlier transport to an extracorporeal resuscitation centre. A second cohort study showed that patients being transported to specialized resuscitation centres might have increased survival. This increase in survival would remain despite an additional 14 minutes of prehospital transport time due to the redirection. A third study showed that prehospital redirection could triple the number of patients who could benefit from extracorporeal resuscitation.

In the second part, the results of two studies aiming to improve the selection of adequate patients for extracorporeal resuscitation are presented. A first cohort study showed that patients requiring more than 10 defibrillations still had an adequate chance at survival and should remain eligible for an extracorporeal resuscitation. A second cohort study showed that the initial rhythm was a much better prognosticating factor than subsequent rhythms. Patients with an initial non-

shockable rhythm who experience a conversion to a shockable rhythm should not be considered first-line candidates for extracorporeal resuscitation.

In the third part, three studies exploring the potential uses of near-infrared spectroscopy for the monitoring of extracorporeal resuscitation patients are presented. A systematic review was first performed and showed the prognosticating ability of this technology for patients suffering from a cardiac arrest. Then, using a prospective cohort, the metrological properties and their determinants of two frequently used near-infrared spectroscopy devices were described, in order to optimize their uses in the context of cardiac arrest.

The knowledge acquired by the studies comprised in this thesis has already been integrated in protocols guiding the care for patients suffering from an out-of-hospital cardiac arrest and has laid the foundation for the prospective evaluation of extracorporeal resuscitation for this population, which will hopefully ultimately lead to improvement in their prognosis.

Keywords : out-of-hospital cardiac arrest, extracorporeal resuscitation, emergency medical services, prognostication, near -infrared spectroscopy

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Liste des abréviations

ACEH : Arrêt cardiaque extrahospitalier

ACLS : Advanced cardiac life support

ACP : Advanced care paramedic

ACS : Acute coronary syndrome

AESP : Activité électrique sans pouls

AHA : American Heart Association

AOR : Adjusted odds ratio

AWC : Asystole with conversion to a shockable rhythm

AWoC : Asystole without conversion to a shockable rhythm

BCLS : Basic cardiac life support

BMI : Body mass index

CA : Cardiac arrest

CH : Centre hospitalier

CH R-CEC : Centre hospitalier pouvant réaliser une réanimation par circulation extracorporelle

CI : Confidence interval

CPR : Cardiopulmonary resuscitation

CPP : Coronary perfusion pressure

ELSO : Extracorporeal Life Support Organization

ECPR : Extracorporeal cardiopulmonary resuscitation

EMS : Emergency medical services

$ETCO_2$: End-tidal capnography

IAMEST : Infarctus aigu du myocarde avec élévation du segment ST

ICC : Intraclass correlation coefficient

ICP : Intervention coronaire percutanée

IHCA : In-hospital cardiac arrest

J : Joule

NIRS : Near-infrared spectroscopy

OHCA : Out-of-hospital cardiac arrest

OR : Odds ratios

PCI : Percutaneous coronary intervention

PCP : Primary care paramedic

PEA : Pulseless electrical activity

PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm

PEAwoC : Pulseless electrical activity without conversion to a shockable rhythm

pVT : Pulseless ventricular tachycardia

R-CEC : Réanimation par circulation extracorporelle

RCS : Retour de circulation spontané

ROSC : Return of spontaneous circulation

SARC : Soins avancés en réanimation cardiorespiratoire

SCA : Syndrome coronarien aigu

SD : Standard deviation

SPIR : Spectroscopie proche infrarouge

SMD : Standardized mean difference

STEMI : ST-segment elevation myocardial infarction

StO_2 : Tissue saturation in oxygen

S_w : Within-subject standard deviation

VF : Ventricular fibrillation

VT : Ventricular tachycardia

À Sylvie, ma mère, qui m'a guidé, épaulé,

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Chapitre 1. Problématique

1.1. Épidémiologie

Chaque année, plus de 50 000 Canadiens et 350 000 Nord-Américains décèdent des suites d'un arrêt cardiaque extrahospitalier (ACEH).[1-3] Malgré une amélioration des pratiques en réanimation et des soins post-réanimation, la survie suite à un ACEH demeure basse et ne s'est améliorée que de 2% (10 à 12%) depuis les 10 dernières années.[1, 3] La grande majorité de ces ACEH sont causés par un syndrome coronarien aigu (SCA); le SCA en est même la cause principale dès l'âge de 25 ans.[3, 4] Ainsi, les principaux facteurs de risque pour un ACEH sont les mêmes que ceux identifiés pour un SCA dû à de l'athérosclérose coronaire (p. ex., âge avancé, sexe masculin, tabagisme, hypertension, diabète, sédentarité).[5] Les problèmes cardiaques structuraux (p. ex., cardiomyopathie, anomalie valvulaire) sont la deuxième cause en importance d'un ACEH.[5]

1.2. Traitements initiaux

Les traitements prodigués aux patients souffrant d'un ACEH sont résumés par les différentes étapes de la 'chaîne de survie' de l'*American Heart Association* (AHA), soit la reconnaissance et l'activation des services d'urgence, l'initiation d'un massage cardiaque de qualité, l'administration rapide d'une défibrillation pour les patients dont le rythme cardiaque s'y prête, les soins préhospitaliers de base et avancés prodigués par des paramédics et, finalement, les soins avancés à l'urgence et post-réanimation.[6]

Les premiers moyens qui contribuent à améliorer la capacité des membres de la communauté à reconnaître la survenue d'un ACEH et à initier les premières étapes de la réanimation sont l'éducation et la formation de base en réanimation.[7] Les conseils prodigués par les répartiteurs

médicaux d'urgence peuvent également contribuer à la reconnaissance de l'ACEH et à ce que les témoins initient les manœuvres initiales de la réanimation.[8] À cet effet, le principal traitement que ces derniers doivent initier est un massage cardiaque de qualité.[9] Puisque le délai avant la première défibrillation est un marqueur important de survie, l'obtention d'un défibrillateur et son utilisation est la priorité suivante pour les témoins d'un ACEH.[10] L'accès aux défibrillateurs dans la communauté permet d'améliorer les probabilités que les témoins d'un ACEH puissent administrer cette première défibrillation sans avoir de formation avancée.[11, 12]

Par la suite, les paramédics prodiguent d'autres interventions. Des soins de base en réanimation sont premièrement prodigués (massage cardiaque, ventilation et défibrillation). Puis, certains paramédics ayant une formation supplémentaire traiteront le patient avec des soins avancés en réanimation cardiorespiratoire (SARC), comme la prise en charge avancée des voies aériennes et l'administration de médicaments vasopresseurs (p. ex., adrénaline) et antiarythmiques (p. ex., amiodarone).[13, 14] Par contre, l'impact sur la survie avec un bon devenir neurologique de ces interventions demeure incertain.[15-17]

Finalement, ces patients sont transportés en centre hospitalier (CH) où les manœuvres avancées en réanimation sont continuées jusqu'à l'obtention d'un retour de circulation spontanée (RCS) ou l'arrêt des manœuvres et le décès. Suite au RCS, un monitorage agressif de l'hémodynamie et une prise en charge de la température ciblée (*targeted temperature management*) seront rapidement initiés afin d'optimiser la survie neurologique.[18, 19] Étant donné la fréquence du SCA comme étiologie de l'ACEH, une angiographie coronaire sera également fréquemment réalisée, plus ou moins rapidement en fonction des résultats de l'électrocardiogramme.[18, 20]

1.3. Réanimation par circulation extracorporelle

Une nouvelle technique, la réanimation par circulation extracorporelle (R-CEC), est présentement mise en place dans certains départements d'urgence au Québec pour des populations sélectionnées de patients souffrant d'un ACEH.[3, 21-40]

La R-CEC consiste à utiliser un appareil externe pompant et oxygénant le sang afin de rétablir la circulation cardiopulmonaire. Pour ce faire, deux canules sont insérées dans une veine et une artère de gros calibre (généralement la veine et l'artère fémorale dans un contexte de R-CEC) (Figure 1). Ces canules sont reliées à un oxygénateur externe et une pompe. Ainsi, le sang désoxygéné est aspiré via la canule veineuse, réoxygéné par l'appareil et repompé par la canule artérielle. Ceci a comme avantage de perfuser le patient avec du sang parfaitement oxygéné et à un débit bien supérieur à ce qui est obtenu avec un massage cardiaque externe conventionnel.[41]

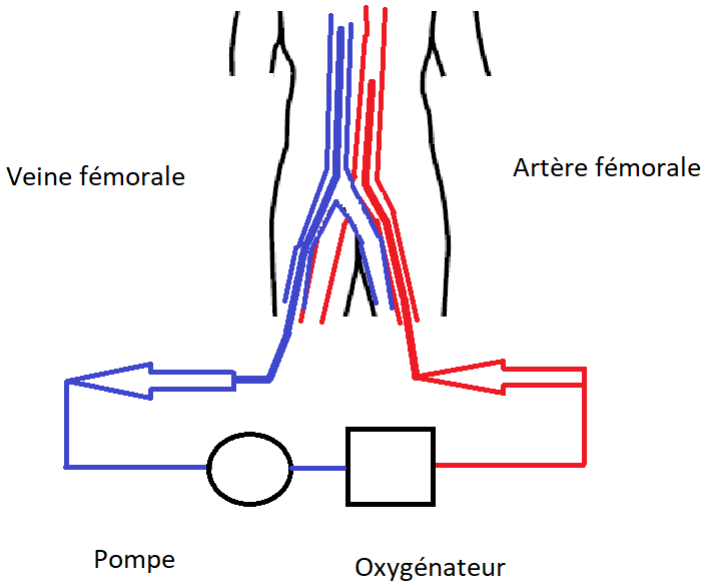

Figure 1. Schéma simplifié d'un circuit de R-CEC. Le sang est aspiré via la canule fémorale, située dans la veine fémorale, puis est oxygéné dans un circuit externe au corps, puis est repompé par la canule artérielle fémorale.

De manière générale, l'utilisation de cette technique semble associée à de meilleurs devenirs lorsque comparés à des soins standards.[42] Un taux de survie plus élevé, allant de 2 % jusqu'à plus de 50% a été rapporté avec l'utilisation de cette technique chez des patients pour qui, avant l'arrivée de la R-CEC, un arrêt de manœuvres aurait été préalablement généralement considéré.[21]

Ces évidences ont mené à une modification des recommandations de l'AHA quant à l'utilisation de la R-CEC : la R-CEC peut être considérée pour des patients sélectionnés souffrant d'un arrêt cardiorespiratoire réfractaire aux traitements conventionnels lorsqu'elle peut être mise en place de manière expéditive par des professionnels expérimentés (Classe 2b, niveau d'évidence C-LD).[3]

Cependant, suite à cette recommandation, il devient nécessaire de clarifier les modalités ou facteurs qui pourraient favoriser son implantation en pratique courante, notamment quant aux changements nécessaires à faire aux protocoles de soins afin de pouvoir mettre en place la R-CEC de manière expéditive et à la sélection de ces patients, ainsi que d'optimiser les stratégies de monitorage pouvant être utilisées pour ce faire.

1.3.1. Impacts potentiels sur les protocoles de soins de la réanimation par circulation extracorporelle

Certains protocoles de soins devront nécessairement être modifiés afin de permettre une mise en oeuvre rapide d'une R-CEC pour les patients éligibles, mais également afin d'optimiser l'accès à cette technique de réanimation.

1.3.1.1. Durée des manœuvres de réanimation

Avec l'arrivée de la R-CEC, la durée des soins de réanimation prodigués en préhospitalier devra être réduite. En effet, l'un des facteurs influençant le plus l'efficacité de la R-CEC afin d'améliorer

la survie des patients est le délai entre l'ACEH et l'initiation de la R-CEC.[4] Les meilleurs résultats sont obtenus si la R-CEC est débutée dans les 60 minutes suivant l'ACEH.[43] Puisque l'initiation de cette technique prend un minimum de 15 minutes une fois le patient arrivé à l'urgence d'un CH, il serait optimal de transporter ces patients à l'hôpital en moins de 45 minutes pour leur assurer un meilleur taux de survie.[21, 43]

À cet effet, la durée de réanimation sur la scène de l'ACEH selon les protocoles de réanimation préhospitalière actuellement utilisés au Québec varie en fonction de la formation de l'intervenant impliqué. Les paramédics de soins primaires prodiguent environ 10 minutes de réanimation sur la scène avant d'initier l'extraction vers l'ambulance et le transport vers le centre hospitalier.[44, 45] Par contre, les paramédics de soins avancés, qui peuvent administrer des médicaments par voie intraveineuse, continuent les soins pendant un minimum de 20 minutes avant l'initiation de l'extraction selon les protocoles actuels.[44, 46]

Ainsi, l'intégration de la R-CEC aurait comme effet de devoir réduire la durée des manœuvres avancées afin de permettre une arrivée en CH avant la limite des 45 minutes et ainsi maximiser son potentiel.

1.3.1.2. Destination hospitalière

Afin de maximiser le potentiel de la R-CEC, il faudrait aussi changer la destination hospitalière de certains patients souffrant d'un ACEH. En effet, les patients souffrant d'un ACEH sont généralement transportés dans l'hôpital le plus proche, étant donné leur instabilité hémodynamique extrême. Dans la région métropolitaine de Montréal, plus de 20 CH reçoivent ainsi des patients souffrant d'un ACEH et, parmi eux, seuls cinq ont les capacités de réaliser une R-CEC (CH R-CEC). En effet, puisque la technique de R-CEC s'apparente fortement à celle réalisée pendant les chirurgies cardiaques, seuls les CH ayant un département de chirurgie cardiaque et

réalisant fréquemment ces interventions disposent des professionnels expérimentés, notamment des percussionnistes, et de l'équipement nécessaire pour mettre en place un programme de R-CEC. Un défi majeur consiste à transporter de manière efficiente les patients éligibles à la R-CEC vers l'un des rares CH R-CEC, qui peuvent se trouver à une distance plus éloignée.

Ce changement de destination hospitalière pourrait avoir un impact sur les soins et le pronostic de ces patients, même en ignorant l'effet potentiel de la R-CEC. En effet, il est généralement proposé que, puisque la qualité de la réanimation peut être suboptimale durant le transport ambulancier, la durée de transport devrait également être minimale.[47] Prolonger significativement le temps de transport de ces patients pourrait ainsi leur être délétère. D'autres études ont cependant démontré que la qualité du massage cardiaque pouvait être maintenue pendant le transport des patients souffrant d'un ACEH, ce qui pourrait permettre un transport prolongé sans effet délétère important.[48] Cependant, il demeure cliniquement plausible de proposer que la durée de transport devrait être limitée puisqu'une ambulance n'est pas un endroit optimal pour prodiguer des soins de réanimation. Il reste à déterminer quelles options de transport offrent le meilleur ratio de bénéfices versus risques pour les patients souffrant d'un ACEH éligible à une R-CEC.

Le transport vers un CH R-CEC pourrait donc permettre d'avoir accès à une R-CER et pourrait aussi prodiguer d'autres avantages aux patients. En effet, tous les CH R-CEC peuvent aussi prodiguer, sur place et à toute heure du jour, tous les soins nécessaires aux patients souffrant d'un SCA, notamment une angiographie coronaire avec intervention coronaire percutanée. Puisqu'il s'agit de la cause la plus fréquence de l'ACEH, les patients transportés dans les CH R-CEC pourraient bénéficier des traitements des causes de l'ACEH. Les équipes de soins critiques (urgence, soins intensifs, anesthésie), médicales et chirurgicales traitent un plus grand nombre de patients

souffrant de pathologies critiques dans les CH R-CEC, ce qui permet aussi d'améliorer les devenirs des patients traités dans ces institutions.[49, 50]

Bref, l'intégration de la R-CEC aurait comme effet de devoir modifier la destination hospitalière pour les patients éligibles, ce qui d'un côté pourrait leur être bénéfique étant donné la possibilité d'avoir accès à une R-CEC en plus des autres capacités de traitement disponible dans les CH R-CEC, mais d'un autre coté pourrait aussi leur nuire en prolongeant leur temps de transport.

1.3.2. Sélection des patients pour une réanimation par circulation extracorporelle

Un deuxième facteur important à étudier est la sélection des patients pour une R-CEC. Ce sujet est d'une importance primordiale puisqu'il existe une très grande variabilité de survie chez les patients sélectionnés pour cette technique allant de moins de 2% à plus de 50%.[21, 29] De plus, cette technique requiert de multiples ressources humaines, administratives et économiques à son application. Afin de maximiser les bénéfices et réduire les interventions futiles, il est nécessaire de limiter ce traitement aux patients ayant un pronostic adéquat. Pour ce faire, de multiples algorithmes de sélection propres à chaque CH R-CEC sont utilisés. Ces derniers sont généralement basés sur des facteurs de pronostic des patients en ACEH.

1.3.2.1. Facteurs de pronostic chez les patients en arrêt cardiorespiratoire

Il existe de nombreux facteurs de pronostics décrits pour les patients souffrant d'un arrêt cardiorespiratoire, certaines conditions prémorbides, des facteurs péri-arrêts et d'autres post-arrêts cardiaques témoignant de l'évolution du patient et de sa réponse aux traitements. Étant donné le présent contexte (sélection des patients pour une R-CEC), les facteurs de pronostic post-arrêt cardiaque ne seront pas discutés puisqu'ils ne peuvent pas, par définition, être utilisés pour la sélection des patients pendant leur ACEH. Également, seules les caractéristiques pertinentes

aux ACEH d'origine cardiaque/médicale présumée seront présentées puisque ces arrêts cardiaques d'origine traumatique ne sont généralement pas considérés pour une R-CEC.

Les principaux facteurs de pronostics cliniques des patients en arrêt cardiorespiratoire extrahospitalier sont les facteurs d'Utstein.[51-53] Les principaux prédicteurs parmi ceux-ci sont d'avoir obtenu un RCS préhospitalier, avoir eu un rythme initial défibrillable, avoir eu un arrêt cardiaque témoigné (par un professionnel de la santé ou par une tierce personne) et avoir reçu des soins de réanimation par une tierce personne.[53] Bien qu'elles ne soient pas directement incluses dans les facteurs d'Utstein, d'autres interventions ont également été associées à une amélioration du pronostic chez les patients souffrant d'un arrêt cardiaque extrahospitalier. Notamment, avoir été défibrillé par une tierce personne par rapport à une défibrillation par le personnel préhospitalier était associé à un meilleur pronostic (délai à la première défibrillation).[54] Également, la qualité du massage cardiaque prodigué influence la survie de ces patients (profondeur et vitesse du massage cardiaque).[55]

D'autres caractéristiques prémorbides influencent le devenir de ces patients. Notamment, avoir un âge avancé est un facteur de mauvais pronostic.[56-58] Cependant, ce sont de manière plus importante l'état fonctionnel pré-arrêt cardiaque (indépendance au niveau des activités de la vie quotidienne et domestique, habiter dans une maison de retraite médicalisée), les états comorbides connus et les symptômes pré-arrêts qui semblent plus fortement associé au devenir de la réanimation que l'âge lui-même.[56-59]

Pendant l'arrêt cardiaque, certaines mesures de perfusion (capnographie expirée, oxymétrie tissulaire ou cérébrale, niveaux de lactate sanguin) ont également été associées au pronostic de la réanimation.[60-64]

1.3.2.2. Facteurs de pronostics chez les patients éligibles à une réanimation par circulation extracorporelle

Les patients ayant bénéficié d'une R-CEC ont été généralement sélectionnés selon des critères très précis ce qui empêche d'avoir un portrait précis sur l'ensemble des facteurs potentiels qui entrent en jeu. De plus, même si les facteurs de pronostic semblent très similaires à ceux chez les patients souffrant d'ACEH, il y a très peu d'écrits scientifiques ou de rapports de cas cliniques ce qui réduit la force des évidences à ce sujet.

Cependant, il existe un certain consensus à l'effet que certaines caractéristiques cliniques sont identifiées comme facteurs de bon pronostic, notamment avoir un rythme initial défibrillable, sans asystolie initiale et avoir un court délai avant l'initiation de la R-CEC ou obtenu à un moment de la réanimation un RCS.[43, 65-71] En ce qui a trait aux caractéristiques sociodémographiques, certaines études montraient une meilleure survie chez les jeunes patients et les femmes.[65-69, 72, 73] Parmi les mesures physiologiques évaluées, avoir des lactates sanguins relativement bas et un pH sanguin moins abaissé étaient également des facteurs de bon pronostic.[65, 70] Évidemment, les patients avec plus de comorbidités avaient un moins bon pronostic.[65, 74]

1.3.2.3. Algorithmes actuels de sélection des patients pour une réanimation par circulation extracorporelle

Il n'existe pas d'algorithme validé pour la sélection des candidats à une R-CEC. *L'Extracorporeal Life Support Organization* (ELSO) propose de ne pas utiliser cette technique de manière générale chez les patients souffrant d'une maladie dont le pronostic fonctionnel est d'emblée mauvais, souffrant de comorbidités significatives nuisant à la qualité de vie (trouble neurologique, néoplasie avancée, etc.), aux extrêmes de l'âge (pas de chiffre proposé) et chez les gens chez qui le pronostic, même avec l'usage d'une R-CEC est jugé très mauvais.[75, 76] L'AHA, quant à elle, recommandait de considérer (Grade 2b, niveau d'évidence C - données limitées) la R-CEC chez les

patients souffrant d'un arrêt cardiaque lorsque le délai avant le massage cardiaque est bref (pas de temps précis proposé), et si la cause de l'arrêt cardiaque est réversible, comme pour le SCA.[77, 78]

Plusieurs modèles pronostics peuvent permettre d'estimer les probabilités de survie pour les patients pour qui une R-CEC est envisagée ou a été initiée (SAVE, PREDICT VA-ECMO, ECMO-ACCEPTS).[74, 79] Cependant, les devis de ces études incluaient principalement des patients en choc cardiogénique. En effet, bien que plusieurs de ces études incluaient une proportion significative des patients ayant subi un ACEH, elles s'appliquent difficilement à ceux nécessitant un massage cardiaque continu au moment de l'initiation de la R-CEC.

En résumé, devant l'absence d'évidences fortes et étant donné l'importance des ressources requises pour offrir ce traitement, de multiples combinaisons de facteurs énoncés précédemment (âge, état comorbide, rythme initial, délai avant l'initiation du massage cardiaque, délai avant l'initiation de la R-CEC, lactatémie et niveau d'acidose, mesure de capnographie expirée, saturation tissulaire et cérébrale en oxygène) ont été utilisées afin de sélectionner les patients pour une R-CEC. Ces facteurs varient en fonction de la culture locale, des ressources disponibles et souvent des expériences antérieures avec la R-CEC. De plus, certains patients ont des caractéristiques cliniques particulières (p. ex., hypo ou hyperthermie, très grand nombre de défibrillations) qui influencent la décision des équipes traitantes à initier une R-CEC bien que ces caractéristiques n'aient pas été bien décrites dans la littérature comme facteur de pronostic chez les patients souffrant d'un ACEH.

1.3.3. Monitorage de l'oxymétrie tissulaire par spectroscopie proche infra-rouge dans le contexte d'une réanimation par circulation extracorporelle

L'oxymétrie tissulaire par spectroscopie proche infrarouge (SPIR) est une technique de monitorage non invasive mesurant la saturation des différents tissus en oxygène, notamment au niveau cérébral, mais aussi au niveau des membres (Figure 2).[80-84] Tel que mentionné précédemment, cette technique a été proposée afin de monitorer les patients souffrant d'un ACEH, notamment pour ceux-ci chez qui une R-CEC est envisagée ou initiée.[61, 81, 85, 86]

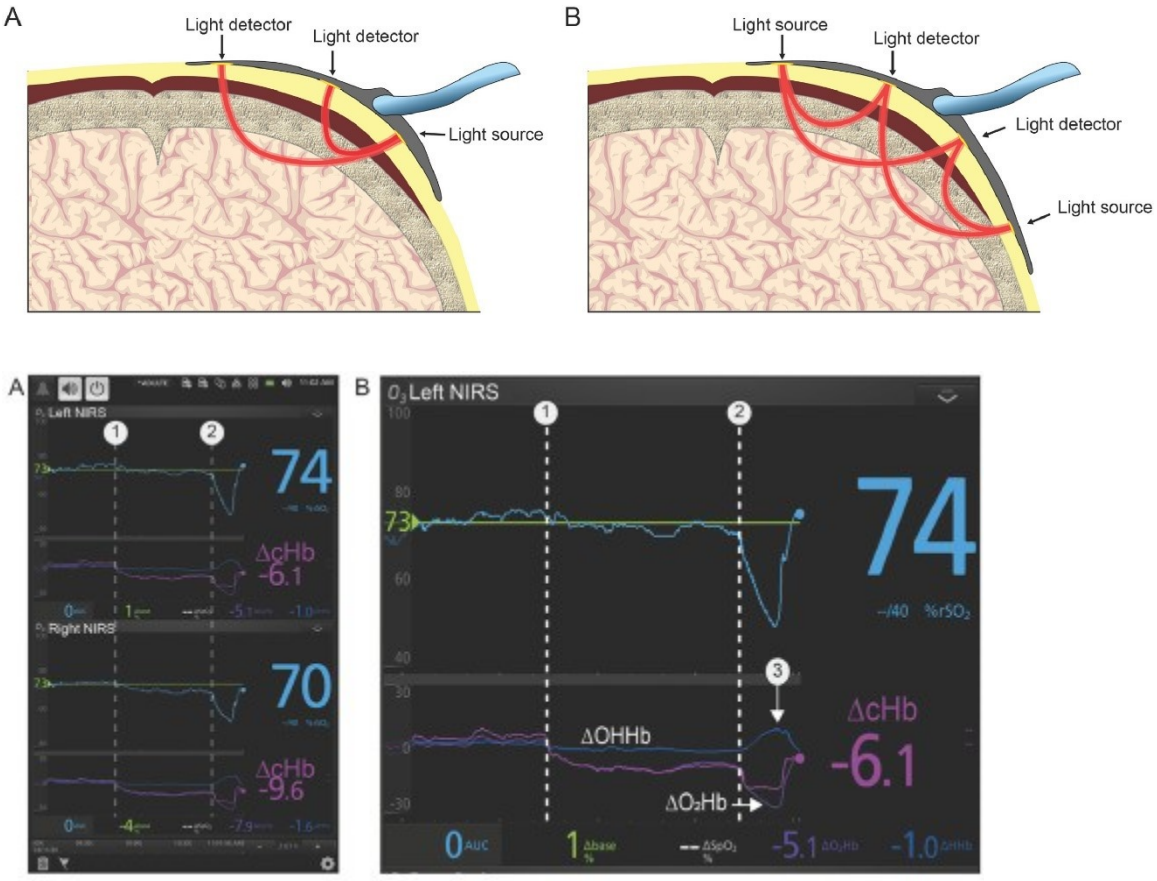

Figure 2. Appareil de monitorage par oxymétrie tissulaire via spectroscopie proche infrarouge. Les capteurs sont reliés à un moniteur qui affiche les valeurs d'oxymétrie pour chacun des sites d'intérêt. (Figures tirés avec permission de Shaaban-Ali, M., Momeni, M., & Denault, A. (2020).

Clinical and Technical Limitations of Cerebral and Somatic Near-Infrared Spectroscopy as an Oxygenation Monitor. Journal of Cardiothoracic and Vascular Anesthesia.)[87]

1.3.3.1. Principes physiques sous-jacents et mécanisme d'action

La technique de SPIR a pris son essor lorsqu'une expérience de Jöbsis en 1977 a montré deux propriétés qui rendaient ce spectre lumineux exploitable à des fins de monitorage.[88] Premièrement, les ondes du proche-infrarouge, soit entre 700 nanomètres et 1300 nanomètres, peuvent traverser les tissus corporels sans être dissipés ou absorbés de manière importante.[88] Également, certaines molécules du corps humain appelées chromophores, notamment l'oxyhémoglobine et la désoxyhémoglobine, ont différentes propriétés d'absorption dans ce registre spectral.[88] La loi de Beer-Lambert stipule que l'atténuation d'un rayon dépend de la distance parcourue par le rayon entre l'émetteur et le récepteur, la concentration des chromophores et leurs propriétés d'absorption selon la longueur d'onde. Dans les vaisseaux de plus de 1 mm (p. ex., artères, veines), la quantité d'hémoglobine est assez importante pour que tous les rayons soient absorbés. Ainsi, la variation du signal est dépendante de la quantité d'oxyhémoglobine et de désoxyhémoglobine dans les artérioles, les veinules et les capillaires.[89] Cependant, la diffusion des rayons à travers les tissus sous-cutanés contribue également à l'atténuation du signal, même dans le spectre du proche-infrarouge, et influence ainsi la mesure de saturation obtenue. Afin de contourner partiellement ce problème, la plupart des appareils de SPIR utilisés dans le contexte clinique utilisent le principe de spectroscopie multidistance (ou à résolution spatiale). En utilisant plusieurs récepteurs situés à différentes distances, différents émetteurs et plus d'une longueur d'onde, ces appareils limitent cette interférence et fournissent des valeurs de saturation plus précise du tissu d'intérêt.[90, 91] En utilisant un algorithme spécifique, les appareils de SPIR peuvent donc calculer des concentrations totales d'oxyhémoglobine, de désoxyhémoglobine et ainsi la saturation du tissu d'intérêt en oxygène

(oxymétrie tissulaire). Tout récemment, Santé-Canada a approuvé le premier appareil de SPIR avec mesures continues des changements d'oxyhémoglobine et de désoxyhémoglobine.

1.3.3.2. Utilisations possibles de l'oxymétrie dans le contexte d'un patient ayant subi un arrêt cardiaque

1.3.3.2.1. Sélection des patients

La sélection des patients pour une R-CEC est complexe et débattue.[75-77] L'oxymétrie cérébrale a été proposée comme mesure de perfusion cérébrale pouvant contribuer à la sélection des patients pour une réanimation par circulation extracorporelle.[85, 92-94] Premièrement, puisque les mesures de saturation cérébrale sont associées au pronostic des patients souffrant d'un ACEH et que les algorithmes de sélection des patients pour la R-CEC incluent ces facteurs de bon pronostic, il est plausible de proposer d'inclure ces valeurs comme une des variables entrant dans les critères de sélection de ces patients.[61, 85, 86, 92, 93] Également, la survenue d'un ACEH entraîne une ischémie cérébrale et cette ischémie cérébrale est l'une des principales causes de morbidité et de mortalité suite à l'ACEH et la R-CEC.[71] La prise de mesure de saturation cérébrale pendant la réanimation initiale pourrait potentiellement permettre de sélectionner des patients non pas uniquement à bon pronostic de survie, mais également à bon pronostic neurologique.[71, 95] Il n'existe cependant pas d'études ayant évalué formellement l'utilité de cet outil dans ce contexte particulier.

1.3.3.2.2. Évaluation de la perfusion

L'oxymétrie cérébrale et tissulaire peut être utilisée pour évaluer la perfusion locale et systémique avant et suite à l'initiation de la R-CEC tout comme elle se fait lors de l'initiation de la CEC en chirurgie cardiaque (Figure 3).[80, 82]

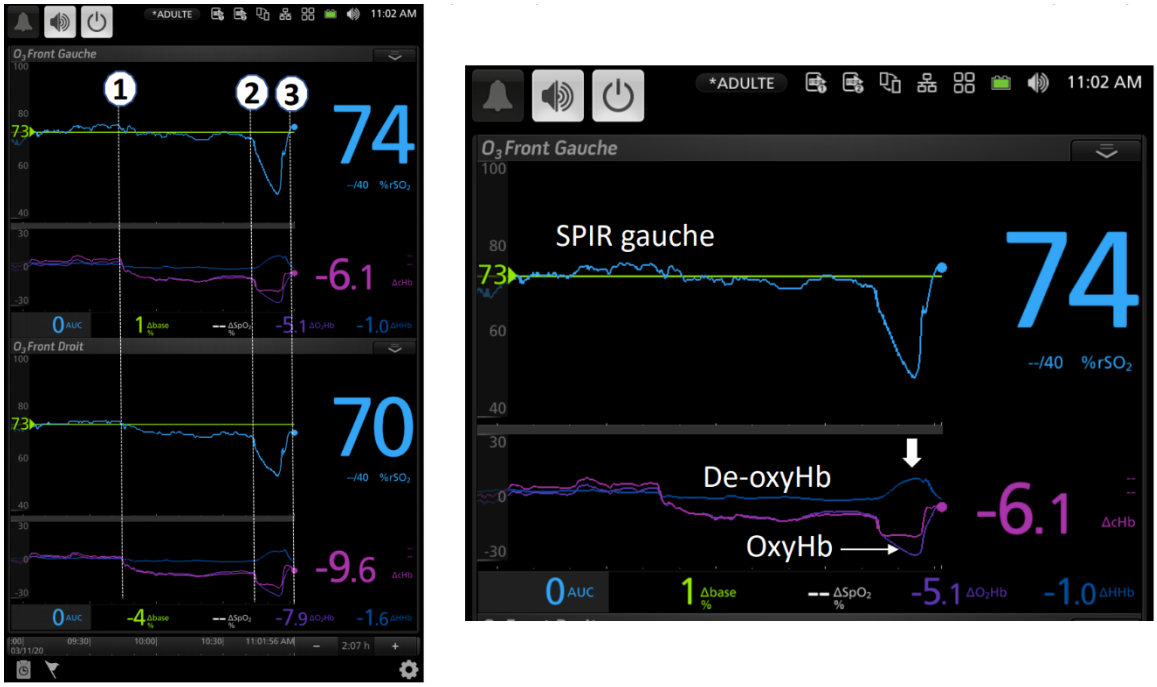

Figure 3. Exemple de monitorage par oxymétrie tissulaire pendant une chirurgie cardiaque. Au début de l'initiation de la circulation extracorporelle (1), une légère baisse de l'oxymétrie tissulaire est notée. Pendant l'arrêt circulatoire (2), une baisse importante de la saturation tissulaire est notée, et suivie rapidement d'une remontée des valeurs lors du rétablissement de la circulation (3).

À cet effet, comme pour tout outil de monitorage, son rôle est d'indiquer au clinicien qu'un processus pathologique est en cours et de l'aiguiller quant à son origine afin que la prise en charge puisse être rapide et adéquate. Ainsi, les patients ayant subi une réanimation extracorporelle peuvent être suivis par des mesures d'oxymétrie tissulaire au niveau cérébral, des membres supérieurs et des membres inférieurs. La prise en charge des patients varie en fonction de s'il s'agit d'une désaturation unilatérale, régionale ou globale (ou artéfactuelle, cf. 1.3.3.4.).[80] Quelques exemples de situations spécifiques d'anomalies notées au monitorage par SPIR sont décrites dans les paragraphes suivants. Une description plus approfondie quant à l'approche

spécifique utilisée lors de l'utilisation du monitorage SPIR dépasse le cadre de cette thèse étant donné la nature des travaux de recherche ayant été effectués.

Une désaturation unilatérale locale, qu'elle soit cérébrale ou au niveau d'un membre, est généralement causée par un processus local limitant la perfusion ou nuisant au retour veineux.[80] Dans le contexte de la R-CEC, dans le cas d'une canulation fémorale artérielle ou veineuse, on peut observer parfois une réduction de la valeur du SPIR. Cette dernière peut être secondaire à une ischémie artérielle distale à la canulation ou à une thrombose veineuse profonde (Figure 4).[82, 96] Ainsi, le monitorage par SPIR peut permettre de détecter cette ischémie et de la traiter de manière plus précoce, évitant ainsi potentiellement des complications sérieuses.

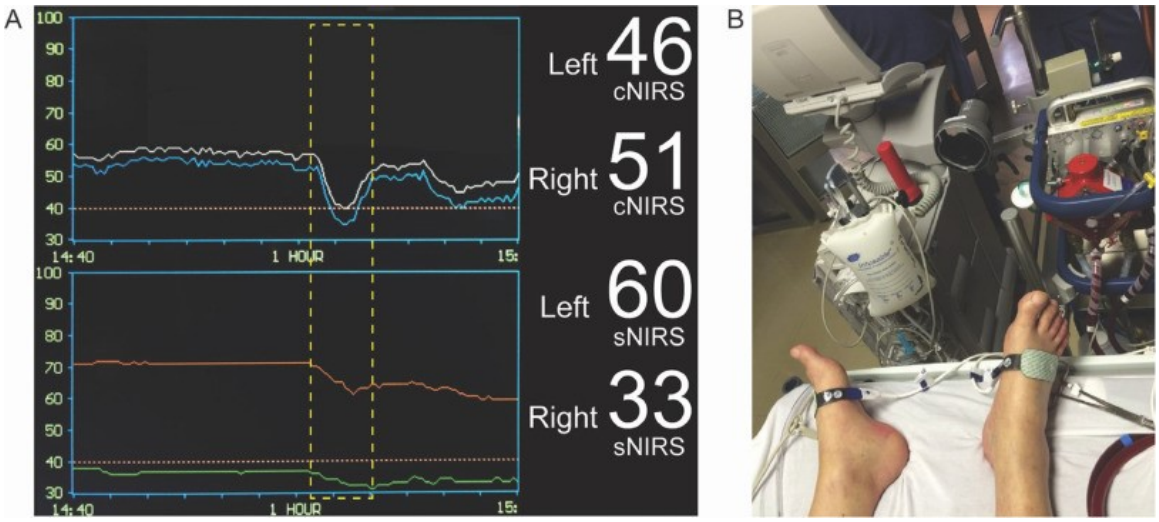

Figure 4. Asymétrie entre les valeurs d'oxymétrie somatique (60% vs 33%) chez un patient post CEC en lien avec une canulation fémorale droite. (Figure tirée avec permission de Denault, A., Ali, M. S., Couture, E. J., Beaubien-Souligny, W., Bouabdallaoui, N., Brassard, P., ... & Deschamps, A. (2019). A practical approach to cerebro-somatic near-infrared spectroscopy and whole-body ultrasound. Journal of cardiothoracic and vascular anesthesia, 33, S11-S37.)[97]

Les désaturations globales, au contraire, sont généralement causées par un processus systémique important.[80] Dans le contexte de la R-CEC, étant donné l'anticoagulation importante que ces patients reçoivent, il pourrait s'agir d'une hémorragie. Cette hémorragie limiterait par conséquent le transport d'oxygène étant donné les paramètres fixes de la pompe. Il pourrait également s'agir d'un « échec de pompe » (thrombose importante, problème mécanique) limitant significativement le débit généré. Il est intéressant de noter que, étant donné l'autorégulation cérébrale, toute insulte systémique peut se manifester initialement aux niveaux des membres.[84]

Les désaturations cérébrales peuvent être causés par de multiples facteurs affectant la livraison et la consommation d'oxygène au niveau du cerveau.[80] De manière générale, s'il s'agit uniquement d'une désaturation cérébrale, un algorithme de prise en charge détaillé a été proposé par Deschamps.[98] Une approche guidée par l'échographie a également été proposée par Denault.[97] Ainsi, différentes causes possibles d'anomalie de délivrance et de consommation d'oxygène assez fréquentes chez les patients ayant nécessité une R-CEC (hypocapnie, œdème cérébral, convulsions, hyperthermie, etc.) peuvent causer des désaturations cérébrales bilatérales et être ainsi détectées par le monitorage par oxymétrie cérébrale.[80, 98]

Une désaturation régionale notée principalement au niveau cérébral et des membres supérieurs laisse penser à un syndrome de la veine cave supérieur qui, dans le contexte d'une R-CEC, peut être d'origine mécanique si le cathéter est mal positionné et draine mal cette partie de la circulation.

1.3.3.2.3. Pronostication

Les mesures initiales d'oxymétrie tissulaire et leur évolution une fois la R-CEC enclenchée, particulièrement au niveau cérébral, pourraient potentiellement prédire le devenir neurologique

des patients.[99] En effet, les valeurs d'oxymétrie diminuent dans le cas d'une dysfonction systémique multiorganique importante, la principale cause de mortalité suite à une R-CEC.[71] À l'inverse, un cerveau ayant subi des dommages très important pourrait ne pas utiliser beaucoup d'oxygène et présenter des valeurs d'oxymétrie anormalement haute.[99] Aucune étude de grande envergure n'a cependant démontré la valeur ajoutée de cet outil comparativement aux techniques standard de pronostication suite à un ACEH.[99, 100]

1.3.3.3. Avantages

Les avantages de l'oxymétrie tissulaire par SPIR sont nombreux, particulièrement chez les patients chez qui une R-CEC est considérée ou initiée. Premièrement, il s'agit d'une mesure non invasive, pouvant être installée très rapidement, et ce même en préhospitalier.[101] Les données sont également fournies de manière continue et elles peuvent donc être immédiatement interprétées et varier en fonction de l'évolution clinique et des traitements prodigués. L'hypoperfusion est si marquée chez les patients souffrant d'un ACEH que des différences de quelques secondes avant certains traitements peuvent faire une importante différence sur leur devenir.[102] La décision d'initier la R-CEC doit également pouvoir se prendre rapidement étant donné l'impact important des délais sur leur pronostic.[71] Ainsi, un bénéfice potentiel d'obtenir une rétroaction continue et ainsi ajuster les traitements prodigués est considérable. D'autres avantages sont notables. Ainsi, les mesures fournies par les appareils ne nécessitent pas de flot artériel pulsatile. Il s'agit d'un avantage très important chez les patients souffrant d'un ACEH et suite à l'initiation de la R-CEC puisque d'autres outils de monitorage standard comme la prise de pression au brassard ou l'oxymétrie de pouls ne peuvent être utilisés chez ces patients. Également, les mesures ne sont pas affectées par le mouvement, contrairement à d'autres outils de monitorage cérébral comme l'électroencéphalographie, ce qui permet l'acquisition de mesure même lorsqu'un patient reçoit des compressions thoraciques. Finalement, cet outil peut être utilisé chez le même patient à

plusieurs sites afin de donner une évaluation globale de sa perfusion, ce qui peut permettre d'identifier plus facilement la source du problème.[80, 82, 98, 103, 104]

1.3.3.4. Limites

Il n'existe pas de mesures d'étalon-or de 'saturation tissulaire' qui permettrait de proposer des valeurs standards offrant le meilleur indicateur de saturation. Ainsi, leurs mesures sont généralement validées en utilisant un ratio de saturations jugulaire centrale et artérielle en assumant un ratio artério-veineux fixe et en ignorant le volume capillaire dans leurs calculs. Ainsi, une variation du flot sanguin et de ces volumes via vaso/venodilatation ou construction peut influencer les valeurs de saturation tissulaire sans que l'extraction ne soit significativement affectée.[80]

Quant à leur validation, les concordances observées entre les valeurs d'oxymétrie et les mesures prédites par les ratios sont adéquates, mais ne sont pas parfaites.[105] Tout comme les appareils mesurant l'oxymétrie de pouls, ces tests de validation se font chez de petites cohortes de volontaires chez qui il n'est pas cliniquement recommandé ni éthiquement acceptable de faire trop diminuer la saturation. Ainsi, leur validité est peu établie dans le spectre de valeurs observées pendant un ACEH qui sont souvent en deçà de 40%. Comme les appareils d'oxymétrie pulsée présentent une variabilité significative à ce niveau, la prudence dans l'interprétation de ces valeurs est de mise.[106] Puisque les différents appareils utilisent des algorithmes non dévoilés par les compagnies, des longueurs d'onde différentes, un nombre d'optodes différents et des distances différentes entre ces mêmes optodes, il en résulte une grande variabilité quant aux mesures 'brutes' de saturation tissulaire chez un même individu et les causes de cette variabilité n'ont jamais été explorées.[107] Également, plusieurs variables, comme la couleur de la peau du patient, son niveau d'hémoglobine ou de bilirubine, semblent pouvoir influencer les valeurs

obtenues.[105, 108-110] Ainsi, il existe une variabilité très large intra et inter individu qui rend assez difficile de déterminer un niveau critique pour une utilité clinique.[107]

De plus, la zone évaluée par les appareils d'oxymétrie tissulaire est relativement limitée (lobes frontaux antérieurs ou tissus musculaires superficiels). En effet, la pénétration maximale globale est d'environ 2 fois la distance entre les optodes émetteurs et récepteurs les plus éloignés (environ 2 cm selon les modèles).[80, 81, 111] Au niveau tissulaire, cette petite distance pourrait limiter considérablement la fidélité de la mesure si le tissu sous cutané était très épais (œdème, gras, etc.). De plus, leur position implique que seuls certains organes ou parties d'organes sont disponibles pour évaluation (p. ex., lobes frontaux du cerveau pour le monitorage cérébral). Ainsi, une ischémie critique de la fosse postérieure pourrait donc être complètement manquée par un monitorage par oxymétrie tissulaire. Dans le cas d'un arrêt cardiaque où l'ischémie est généralement globale, ceci est potentiellement moins problématique. De plus, bien que les appareils utilisant la technique de spectroscopie multidistance puissent limiter la contribution du tissu sous-cutané et interroger en grande partie les tissus d'intérêt qui sont plus profonds, la peau et les tissus superficiels semblent influencer tout de même les valeurs obtenues.[87, 112]

1.4. Résumé de la problématique

En résumé, l'ACEH est une problématique de santé importante étant donné la mortalité qui y est reliée, même avec les meilleures pratiques en réanimation. La R-CEC s'avère prometteuse pour améliorer le pronostic de ces patients, mais des incertitudes importantes demeurent quant à l'incorporation de cette technique aux soins usuels. Des réponses à plusieurs questions de recherche doivent être obtenues avant de tester de façon prospective les avantages de cette technique, notamment quant aux effets sur les pratiques de réanimation préhospitalière qu'elle

impliquerait, à la sélection des patients et aux potentielles stratégies de monitorage à utiliser chez ces patients.

Chapitre 2. Objectifs et méthodes

2.1. But des travaux présentés

Les travaux présentés dans la présente thèse visent à bâtir une base de connaissance qui permettrait l'implantation de la R-CER dans les pratiques en médecine d'urgence. Pour ce faire, trois séries d'études ont été menées. Ces dernières seront ainsi présentées sous trois volets distincts et interreliés.

Un premier volet inclut des études décrivant les impacts de l'implantation de la R-CER sur les pratiques de réanimation préhospitalière. Un deuxième volet inclut des études visant à optimiser les critères de sélection des patients qui pourraient être éligibles à une R-CEC. Un troisième volet inclut des études visant à optimiser les stratégies de monitorage à utiliser chez ces patients. Pour donner suite aux travaux réalisés dans la présente thèse, d'autres études seront nécessaires, notamment afin de démontrer de façon prospective la valeur ajoutée du R-CER sur la survie et le devenir neurologique des patients souffrant d'un ACEH.

2.2. Objectifs spécifiques et méthodes

Puisque les cinq études des deux premiers volets ont des caractéristiques communes quant à leurs méthodes, nous en décrirons d'abord les caractéristiques communes et seules les spécificités seront traitées dans les sections particulières des volets.

Les cinq études ont été approuvés par le comité d'éthique de l'Hôpital du Sacré-Cœur de Montréal (CÉR 2016-1198) et réalisés en collaboration avec Urgences-santé.

Étant donné la nature des études (rétrospective sur base de données), toute la population disponible a été incluse. Les patients adultes (18 ans et plus) traités pour un ACEH par Urgences-santé entre avril 2010 et décembre 2015 ont été inclus. Les patients dont la mort était considérée

comme évidente par les paramédics, ayant souffert d'un traumatisme ou ayant une ordonnance de non-réanimation ont été exclus.[44]

Les données ayant permis la réalisation de ces études ont été extraites à partir de trois bases de données d'Urgences-santé. Toutes les données cliniques collectées par les paramédics pour les cas d'ACEH sont déjà colligées dans une base de données utilisée à des fins d'assurance-qualité (registre d'arrêt cardiaque de style Utstein).[51] Les données quant aux dates et moments de mise en services des ambulances (heure de l'appel, heure de l'arrivée sur la scène, etc.) sont également enregistrées dans une autre base de données, tout comme les devenirs de réanimations. Les bases de données ont été combinées sur la base de plusieurs variables communes (notamment, numéro d'appel et numéro de déclaration de transport).

Parmi les variables qui peuvent avoir un impact sur la survie mentionnés dans le chapitre de la problématique, certains n'ont pu être examinés puisque non disponibles dans ces banques de données. Ces variables incluent notamment l'état fonctionnel pré-morbide des patients ainsi que leurs comorbidités, tout comme le délai avant la première défibrillation et à savoir s'ils avaient reçu un choc par un témoin à l'aide d'un défibrillateur externe automatisé.

2.2.1. Premier volet

Les études du premier volet visent à décrire trois impacts collatéraux qu'auraient l'intégration de la R-CEC sur les pratiques de soins préhospitaliers (Tableau 1). Une première étude de cohorte visait à déterminer s'il serait sécuritaire de réduire la durée des manœuvres de réanimation avancée pratiquées en préhospitalier afin de permettre un départ plus rapide vers un CH pouvant initier la R-CEC. Une deuxième étude de cohorte réalisée sur les mêmes bases de données visait à évaluer si une redirection préhospitalière, soit vers un CH R-CEC plutôt que vers l'hôpital le plus près, pourrait également influencer le devenir des patients souffrant d'un ACEH. La troisième

étude visait à simuler avec un modèle statistique l'implantation d'une redirection préhospitalière de ces patients afin d'estimer l'impact qu'aurait cette implantation sur le nombre de patients éligibles qui seraient transportés dans les CH R-CEC, afin d'optimiser ce total et de s'assurer que les CH R-CEC puissent se préparer à cette augmentation de volume.

Tableau 1 : Résumé des articles du premier volet

Volet 1	Objectif	Devis	Groupe	Exclusion	Mesure de résultats	Analyse principale
Article 1 [113]	Évaluer la sécurité de diminuer la durée des SARC	Cohorte	SARC vs Soins de base uniquement	-	Survie au congé	Régression logistique
Article 2 [114]	Évaluer le bénéfice potentiel de changer la destination hospitalière	Cohorte	CH avec ICP 24h sur 24h vs autre CH	Arrêt des manoeuvres en préhospitalier	Survie au congé	Régression logistique
Article 3 [115]	Évaluer l'augmentation du nombre de patients avec une redirection préhospitalière	Cohorte simulée	Simulation de redirection préhospitalière vs scénario actuel	RCS durant les 15 premières minutes la réanimation préhospitalière	Proportion de candidats à une R-CEC transportés à un CH R-CEC	Chi-carré de McNemar

SARC: Soins avancés en réanimation cardiorespiratoire; CH : Centre hospitalier; ICP : Intervention coronaire percutanée; RCS : Retour de circulation spontanée; R-CEC : Réanimation par circulation extracorporelle

2.2.1.1. Réduction de la durée des soins avancés en réanimation cardiovasculaire préhospitaliers

La durée entre le moment de l'ACEH et l'initiation de la R-CEC doit être réduite au maximum afin d'optimiser l'efficacité de la R-CEC.[67] Les manœuvres initiales de réanimation, comme les premières défibrillations et le massage cardiaque, doivent cependant être maintenues étant donné le bénéfice démontré de ces interventions sur le pronostic des patients souffrant d'un

ACEH.[45] Par contre, la nécessité d'un transport rapide aurait comme impact collatéral de réduire la durée des SARC prodigués durant la phase préhospitalière de réanimation.[116] Aucune évidence n'était d'ailleurs disponible au moment de débuter le présent projet doctoral quant au bénéfice potentiel de ces manœuvres chez les patients éligibles à une R-CEC. Il fallait donc initialement évaluer l'impact des SARC préhospitaliers sur le devenir des patients souffrant d'un ACEH et particulièrement des patients candidats à un R-CEC afin d'évaluer la sécurité d'une future étude prospective pour les patients qui y participeraient. Ainsi, les objectifs spécifiques de la première étude du premier volet consistaient à évaluer l'impact de prodiguer des SARC préhospitaliers à des patients souffrant d'un ACEH sur leur survie, et ce spécifiquement chez le sous-groupe de patients candidats à une R-CEC.

Ainsi, deux cohortes ont été constituées à partir des patients inclus dans la base de données principale. Les patients ayant reçus uniquement des soins de base en réanimation ont été inclus dans la première cohorte, alors que les patients ayant eu des manœuvres de réanimation par les paramédics pouvant prodiguer des SARC ont été inclus dans la deuxième cohorte.

Aux fins de cette étude, un sous-groupe de patients candidats à une R-CEC a été constitué dans chacune des deux cohortes. Pour être inclus dans ces sous-groupes, les patients devaient être âgés de 65 ans ou moins, avoir un rythme initial défibrillable, ne pas avoir obtenu de RCS après 15 minutes de réanimation initiale et avoir eu un arrêt cardiaque témoigné avec un massage cardiaque rapide.[21, 39, 40, 43, 117]

La mesure de résultat principal pour cette étude était la survie au congé hospitalier. Les mesures de résultats secondaires étaient la présence d'un RCS préhospitalier et le délai entre l'appel initial et l'arrivée à l'hôpital receveur.

Les associations entre les SARC préhospitaliers et les devenirs de réanimation ont été évaluées initialement à l'aide de chi-carré de Pearson. Des modèles de régressions logistiques multivariées ont ensuite été construits en utilisant une approche standard (méthode *enter*) afin de contrôler pour différents facteurs démographiques et cliniques pertinents, en fonction des données qui étaient disponibles.

De plus, trois analyses de sensibilité ont été réalisées afin d'évaluer la robustesse du modèle principal de régression logistique étant donné le risque inhérent de biais de sélection du devis utilisé. Premièrement, les mêmes analyses ont été réalisées en n'incluant que les patients ayant reçu des SARC moins de 11 minutes après leur ACEH afin d'éliminer les cas où des SARC aurait été prodigué à des patients déjà réfractaires aux traitements depuis une période prolongée. Dans la deuxième analyse, une variable, soit la nécessité d'une intubation préhospitalière, a été ajoutée au modèle afin d'ajuster pour la sévérité de la maladie. Finalement, une dernière variable, soit le code de priorisation préhospitalière, a été ajoutée au modèle étant donné l'auto-affectation des paramédics prodiguant des SARC en fonction de ces codes. Quant à elle, l'association entre le fait de prodiguer des SARC préhospitalier et le délai avant l'arrivée à l'hôpital receveur a été évaluée initialement à l'aide d'un test t de Student, puis par une régression linéaire multivariée, où le délai en minutes est la variable dépendante et la variable SARC est la variable indépendante d'intérêt principale), en intégrant les mêmes variables que pour les régressions logistiques précédentes.

2.2.1.2. Modification de l'hôpital de destination

Les patients souffrant d'un ACEH sont fréquemment transportés à l'hôpital le plus proche étant donné la nature critique de leur condition. Ainsi, le changement de la destination hospitalière, nonobstant l'implémentation d'une R-CEC, est un impact collatéral important d'un transport direct des patients éligibles à une R-CEC vers un CH R-CEC. Au Québec, tous les CH R-CEC peuvent

réaliser 24h sur 24 une angiographie coronaire avec intervention coronaire percutanée (ICP) et sont ainsi désignés régionalement pour recevoir des patients souffrant d'un infarctus aigu du myocarde avec élévation du segment ST (IAMEST). Puisque la cause la plus fréquente de l'ACEH est le SCA et que l'angiographie coronaire suivi d'une ICP est la manœuvre diagnostique et thérapeutique de choix pour cette maladie, il est possible que les patients transportés directement vers l'un de ces CH bénéficient des autres interventions disponibles localement, en plus de la R-CEC.[118-120] À l'opposé, une redirection vers un CH R-CEC peut impliquer également un temps de transport plus long, qui pourrait être néfaste chez un patient instable. Ainsi, les objectifs spécifiques de la deuxième étude du premier volet consistaient à évaluer l'association entre le transport des patients souffrant d'un ACEH vers un CH ayant des capacités d'angiographie et d'ICP et leurs devenirs ainsi que l'impact de deux caractéristiques cliniques (la présence d'un rythme initial défibrillable et d'un RCS préhospitalier) sur cette association. Le dernier objectif de cette étude était d'évaluer la durée acceptable de temps de redirection vers un CH ayant des capacités d'angiographie, à la place de vers le CH le plus près afin de maintenir le bénéfice de cette stratégie.

Ainsi, deux cohortes ont été constituées à partir des patients inclus dans la base de données principale en fonction de leur destination hospitalière (CH ayant les capacités de réaliser une ICP 24h sur 24h vs autre CH). Les patients n'ayant pas été transportés vers un CH ont été exclus.

La mesure de résultat principal pour cette étude était la survie au congé hospitalier. Pour le deuxième objectif spécifique de l'étude, la mesure de résultat était le délai de transport additionnel acceptable pour qu'un transport direct vers un CH ayant les capacités de réaliser une ICP demeure bénéfique.

L'association entre le type de l'hôpital de destination (CH ayant les capacités de réaliser une ICP 24h sur 24h vs autre CH) et la survie au congé a été évaluée initialement à l'aide de chi-carré de Pearson. Par la suite, un modèle de régression logistique multivariée a ensuite été construit en utilisant une approche standard (méthode *enter*) afin de contrôler pour différents facteurs démographiques et cliniques pertinents. Nous avons par la suite testé si les deux variables d'intérêt prédéfinies (présence d'un rythme initial défibrillable et présence d'un RCS préhospitalier) contribuaient significativement à cette régression. Finalement, le délai acceptable de redirection vers un CH ayant des capacités d'angiographie à la place du CH le plus près afin de maintenir le bénéfice de cette stratégie a été calculé à l'aide des rapports de côte ajustés obtenus dans le modèle principal en utilisant la formule suivante :

$$(Rapport\ de\ cotes\ ajustés[1\ minute\ de\ délai\ additionelle\ avant\ l'arrivée\ à\ l'hôpital])^{x} * (Rapport\ de\ cotes\ ajustés\ [Transport\ vers\ un\ CH\ ayant\ des\ capacités\ d'angiographie]) = 1.$$

2.2.1.3. Impact sur le nombre de patients et les durées de transport

La troisième étude du premier volet porte sur l'impact de la modification des protocoles de soins afin de favoriser le transport direct des patients éligibles à une R-CEC vers les CH R-CEC sur le nombre de patients que recevront ces CH et leur temps avant l'arrivée au CH. Il était impératif d'estimer cette augmentation de volume afin que les CH R-CEC puissent évaluer les ressources nécessaires afin de permettre une mise en œuvre optimale de la R-CEC pour cette population de patient et s'assurer de pouvoir répondre à la demande. De plus, nous devions estimer les temps de redirection d'une telle stratégie afin d'en assurer la sécurité, le tout en intégrant les résultats obtenus dans l'étude précédente. Ainsi, les objectifs spécifiques de la troisième étude du premier volet consistaient à estimer l'impact sur le volume de patients qu'aurait la mise en œuvre d'un

système de redirection préhospitalier pour les patients éligibles à une R-CEC ainsi que sur leur durée de transport avant l'arrivée au CH.

Ainsi, une étude de simulation mathématique a été conduite à partir des patients inclus dans la base de données principale. Les patients ayant obtenus un RCS durant les 15 premières minutes de leur réanimation préhospitalière ont cependant été exclus puisque ces patients ne sont généralement pas considérés pour une R-CEC.

Trois groupes de scénarios de prise en charge préhospitalière ont été simulés afin de représenter trois catégories de critères utilisés pour déterminer si un candidat est éligible ou non à la R-CEC. Des critères stricts ont été retenus dans le premier groupe (p. ex., âge de moins de 60 ans, aucun délai avant l'initiation du massage cardiaque), des critères intermédiaires dans le deuxième (p. ex., âge de moins de 65 ans, moins de cinq minutes de délai avant l'initiation du massage cardiaque) et des critères plus souples dans le troisième (p. ex., âge de moins de 70 ans, moins de 10 minutes de délai avant l'initiation du massage cardiaque). Dans chacun de ces groupes de scénarios, pour la première simulation, il était considéré que les patients éligibles à une R-CEC étaient transportés au CH le plus près (pratique usuelle sans redirection préhospitalière). Dans la deuxième simulation du même groupe, il était considéré que les patients éligibles à une R-CEC étaient transportés au CH R-CEC le plus près (pratique hypothétique avec redirection préhospitalière).

La mesure de résultat principal pour cette étude était la proportion de candidats à une R-CEC transportés à un CH R-CEC. Pour le deuxième objectif, la mesure de résultat était la durée de transport des patients.

Les données utilisées lors de cette étude ont été collectées de la même manière que pour les deux études précédentes. Plusieurs données ont cependant dû être estimées puisqu'il s'agissait de

scénarios simulés. À cet effet, pour les scénarios de redirection préhospitalière, la durée de réanimation préhospitalière était limitée à 15 minutes, le temps d'extraction (délai entre le départ de la scène et l'arrivée dans l'ambulance) était estimé à cinq minutes et le temps nécessaire à l'initiation de la R-CEC à 20 minutes. Les temps estimés de redirection ont cependant été ajustés à partir des temps de transports réels disponibles. Les méthodes d'analyses pour ce faire sont décrites en détail dans l'article de résultats.

Les proportions de candidats à une R-CEC ont été comparées à l'aide de tests de McNemar. Afin d'évaluer la robustesse des résultats, trois analyses de sensibilités ont également été réalisées; une première où les patients ayant eu un RCS préhospitalier après 15 minutes ont été exclus et deux autres où le temps nécessaire à l'initiation de la R-CEC a été augmenté à 25 et à 30 minutes. Les temps de transport ont quant à eux été comparés à l'aide de tests de t (tests de t de Student ou tests de t dépendants en fonction des comparaisons).

2.2.2. Deuxième volet

Les deux études du deuxième volet visent à raffiner les connaissances quant à la pronostication de certaines populations de patients considérés pour une R-CEC afin d'optimiser la sélection des patients pour cette technique. Une première étude de cohorte descriptive visait à préciser l'évolution pronostique des patients avec un rythme initial défibrillable nécessitant plusieurs défibrillations afin d'évaluer si un nombre maximal de défibrillations serait un facteur pronostic de survie. Dans une deuxième étude de cohorte, nous avons étudié l'impact pronostique d'une conversion d'un rythme non défibrillable à un rythme défibrillable pendant la réanimation afin d'évaluer si ces patients devraient être considérés en première intention pour une R-CEC.

Tableau 2 : Résumé des articles du deuxième volet

Volet 2	Objectif	Devis	Groupe	Exclusion	Mesure de résultats	Analyse principale
Article 1 [121]	Préciser l'évolution du pronostic en fonction du nombre de défibrillations données	Cohorte	-	Rythme initial non-défibrillable ou inconnu	Survie au congé	Courbe de probabilité dynamique
Article 2 [122]	Évaluer l'impact pronostic d'une conversion à un rythme défibrillable	Cohorte	Rythme initial défibrillable Rythme initial non-défibrillable avec ou sans conversion à un rythme défibrillable	Rythme initial inconnu	Survie au congé	Régression logistique

SARC: Soins avancés en réanimation cardiorespiratoire; CH : Centre hospitalier; ICP : Intervention coronaire percutanée; RCS : Retour de circulation spontanée; R-CEC : Réanimation par circulation extracorporelle

2.2.2.1. Évolution du pronostic avec des défibrillations répétées

Tel que discuté précédemment, les critères utilisés afin de sélectionner les patients pour une R-CEC varient énormément en fonction des milieux où cette approche est préconisée.[75, 76] À cet effet, les patients dont le rythme initial est défibrillable sont généralement considérés comme de bons candidats pour ce type de traitement.[75, 76] L'évolution pronostique de ces patients au cours de leur réanimation demeure cependant incertaine. Or, plusieurs décisions médicales importantes, notamment l'éligibilité à une R-CEC, mais aussi le moment d'initiation du transport d'un patient vers l'hôpital ou l'arrêt des manœuvres de réanimation, dépendent du pronostic estimé au moment même de la prise de décision. Bien qu'il soit probable que les patients nécessitant un nombre plus élevé de défibrillations aient un moins bon pronostic, l'évolution

précise de leur pronostic est méconnue. Une amélioration des connaissances pourrait donc bénéficier aux pratiques de réanimation, notamment quant à la sélection pour une R-CEC. Ainsi, les objectifs spécifiques de la première étude du deuxième volet étaient d'évaluer l'association entre le nombre de défibrillations préhospitalières et le devenir des patients (survie au congé hospitalier et RCS préhospitalier) souffrant d'un ACEH dont le rythme initial était défibrillable et de décrire le nombre de défibrillations requises dans le sous-groupe des patients ayant obtenu un RCS en préhospitalier.

Pour cette étude, à partir de la base de données principale, seuls les patients dont le rythme initial était défibrillable ont été inclus.

La mesure de résultat principal était la survie au congé hospitalier. La mesure de résultat secondaire était la survenue d'un RCS préhospitalier.

Pour l'objectif principal, afin que les résultats présentés puissent être utilisés par les professionnels prodiguant des soins de réanimation, la relation entre le nombre de défibrillations et le devenir des patients a été analysée d'une manière à refléter la nature dynamique de la prise de décision dans ce type de situation. Ainsi, la probabilité de survie à chaque niveau d'analyse (à chaque nouvelle défibrillation) représente les chances qu'aurait un patient de survivre à ce moment précis de la réanimation (probabilité dynamique ou Bayésienne). Par exemple, puisque tous les patients inclus ont été défibrillés au moins une fois, les résultats présentés au niveau '1 défibrillation' ont été dérivés de toute la cohorte et non pas des patients ayant reçu un total d'une seule défibrillation. De la même manière, au niveau '2 défibrillations', tous les patients ayant reçu deux défibrillations ou plus ont été inclus dans l'analyse. Cette analyse s'interprète comme le serait une courbe de Kaplan-Meier. Pour l'analyse secondaire, les patients ont été séparés en deux groupes en fonction du nombre de défibrillations qu'ils ont reçu : moins de trois ou trois et plus.

Ce seuil a été utilisé puisqu'il a déjà été proposé pour différencier les patients à bon et moins bon pronostic. [123] De plus, l'énergie des deux premières défibrillations (120 joules et 150 joules) est plus basse comparativement à celle de toutes les défibrillations subséquentes (200 joules). Les devenirs (survie au congé hospitalier et RCS préhospitalier) des patients inclus dans ces deux groupes ont été comparés à l'aide de tests de chi-carré de Pearson. Par la suite, un modèle de régression logistique multivariée a été construit de manière standard afin d'ajuster pour les covariables pertinentes disponibles et évaluer de manière indépendante l'association entre le nombre de défibrillations préhospitalières (analysée comme une variable continue) et le devenir des patients.[51] Pour l'objectif secondaire (la description du nombre de défibrillations requises pour les patients ayant eu un RCS préhospitalier), les mesures appropriées de tendances centrales et de dispersions quant au nombre de défibrillations prodiguées dans ce sous-groupe sont présentées tel que discuté précédemment.

2.2.2.2. Impact d'une conversion à un rythme défibrillable

Le rythme initial est une caractéristique clinique fréquemment utilisée pour la sélection des patients pour une R-CEC.[43, 65-71] En effet, les patients dont le rythme initial est défibrillable sont généralement considérés éligibles alors que ceux ayant une activité électrique sans pouls (AESP) initiale sont seulement parfois considérés éligibles.[43, 65-71] Peu de patients dont le rythme initial est une asystolie sont considérés éligibles pour une R-CEC. La conversion d'un rythme non défibrillable (AESP ou asystolie) à un rythme défibrillable a été décrite comme facteur de bon pronostic, mais n'est que rarement utilisée pour la sélection en vue d'une R-CEC. [124] Il n'existe, en effet, que peu d'évidences quant à l'impact des rythmes subséquents sur le pronostic des patients souffrant d'un ACEH rencontrant d'autres critères de sélection pour une R-CEC. [39, 40, 43, 125, 126] Ainsi, les objectifs spécifiques de la deuxième étude du deuxième volet consistaient à évaluer l'association entre le rythme initial, avec et sans conversion à un rythme

défibrillable, et le devenir des patients souffrant d'un ACEH, et ce spécifiquement chez le sous-groupe de patients candidats à une R-CEC.

Ainsi, cinq cohortes ont été constituées à partir des patients inclus dans la base de données principale en fonction de leur rythme initial et de l'évolution de rythme initial vers un rythme défibrillable ou non (1. rythme initial défibrillable, 2. AESP avec conversion à un rythme défibrillable, 3. AESP sans conversion à un rythme défibrillable, 4. asystolie avec conversion à un rythme défibrillable et 5. asystolie sans conversion à un rythme défibrillable). Les patients dont le rythme initial était inconnu ont été exclus de cette étude.

La mesure de résultat principal était la survie au congé hospitalier. La mesure de résultat secondaire était la survenue d'un RCS préhospitalier.

Un test de chi-carré de Pearson a initialement été utilisé pour comparer les taux de survie de chacun des cinq groupes. Par la suite, deux régressions logistiques multivariées ont ensuite été construites en utilisant une approche standard (méthode *enter*) afin de contrôler pour différents facteurs démographiques et cliniques pertinents. Le groupe auquel tous les autres étaient comparés dans cette analyse était celui comprenant les patients avec un rythme initial défibrillable puisque ces patients sont généralement considérés de manière privilégiée pour une R-CEC.[125] Deux analyses supplémentaires ont ensuite été réalisées afin d'évaluer l'impact direct d'une conversion de rythme. Pour ces deux analyses, le groupe de référence a été modifié. Il s'agissait de celui comprenant les patients avec une AESP sans conversion à un rythme défibrillable, pour la première analyse, et celui comprenant les patients avec une asystolie sans conversion à un rythme défibrillable, pour la deuxième.

2.2.3. Troisième volet

Les études du troisième volet visent à décrire et explorer les usages d'une technologie de monitorage, la SPIR, en raison de son potentiel pour monitorer les candidats à une R-CEC. La première est une revue systématique et méta-analyse sur l'utilisation de cette technologie chez les patients souffrant d'un ACEH, alors que les deux autres études sont des études de cohorte prospective menées auprès de volontaires sains visant à préciser les caractéristiques métrologiques de bases de ces appareils afin d'optimiser l'interprétation des données fournies, particulièrement chez une population pour qui les valeurs de base ne sont pas connues.

Tableau 3 : Résumé des articles du troisième volet

Volet 3	Objectif	Devis	Groupe	Inclusion	Mesure de résultats	Analyse principale
Article 1 [85]	Synthétiser les connaissances quant à l'utilisation du monitorage par SPIR en AC	Revue systématique et méta-analyse	SPIR initiale SPIR moyenne SPIR la plus haute	Monitorage de SPIR pendant AC	RCS Survie Survie avec bon devenir neurologique	Graphique en forêt
Article 2 [107]	Déterminer la fiabilité pour deux appareils de SPIR	Cohorte	INVOX Equanox	Volontaire en bonne santé	Coefficient de corrélation intra-classe	Transformation de Fisher
Article 3 [127]	Déterminer les facteurs individuels influençant la concordance entre deux	Cohorte	INVOX Equanox	Volontaire en bonne santé	Survie au congé	Modèle mixte

	appareils de SPIR

SPIR: Spectroscopie proche infra-rouge; AC : Arrêt cardiaque; RCS : Retour de circulation spontanée

2.3.3.1. Revue systématique sur la spectroscopie proche infrarouge pour les patients souffrant d'un arrêt cardiaque

Bien que la SPIR ait fait sa place dans d'autres contextes comme outil de monitorage neurologique (au bloc opératoire notamment) et qu'elle démontrait un grand potentiel pour les patients souffrant d'un ACEH et candidats à une R-CEC, il n'existait aucune recommandation ou consensus quant à son usage en réanimation cardiorespiratoire.[128-131] Les objectifs spécifiques de la première étude du troisième volet consistaient à évaluer l'efficacité de la SPIR à prédire des résultats cliniques de réanimation (RCS, survie au congé hospitalier et bon devenir neurologique) et à décrire les autres utilités étudiées de la SPIR comme outil de monitorage pendant une réanimation.

Pour ce faire, une revue systématique avec méta analyse a été réalisée. Cette revue a été enregistrée au préalable via PROSPERO (numéro CRD42015017380) et conçue afin de respecter les standards PRISMA.[132]

La stratégie de recherche a été développée avec l'aide de deux bibliothécaires médicales afin d'identifier non seulement toutes les études pertinentes ayant été publiées, mais aussi celles ne l'ayant pas encore été. Les moteurs de recherche Medline, Embase et CENTRAL ont été utilisés pour la recherche électronique, sans spécification de date ni de langue. La recherche de littérature grise a été faite à l'aide de Web of Science et Google Scholar. Les manufacturiers de SPIR et les différents auteurs des articles retenus ont également été contactés à la recherche de résultats

non publiés. Chacune des références des articles inclus a également été révisée pour assurer la plus grande couverture possible de résultats pertinents. Cette stratégie de recherche a été effectuée initialement, puis a été répétée moins d'un mois avant que les résultats obtenus ne soient soumis pour publication.

Toutes les études incluant des adultes ayant un monitoring par SPIR durant un AC non-prévu et évaluant le RCS ont été incluses, à l'exception des études de cas et des séries de cas, et ce peu importe la date ou la langue de publication. Deux réviseurs ont évalué la qualité des articles en utilisant le '*Newcastle-Ottawa scale*' et en ont extrait les données.[133] Tous les auteurs des articles retenus ont été contactés afin de valider l'interprétation qui a été faite de leurs données et pour tenter d'obtenir le maximum de données pertinentes.

Une méta-analyse a été réalisée avec Revman (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) pour chacun les résultats de réanimation, lorsqu'approprié. Lorsqu'une étude présentait plusieurs valeurs d'oxymétrie, une de ces mesures a été sélectionnée pour l'analyse principale selon l'ordre de priorisation suivant. La première valeur d'oxymétrie retenue était l'oxymétrie moyenne pendant la réanimation, si disponible, puisque cette dernière devrait théoriquement mieux refléter le niveau de perfusion atteint pendant la réanimation. Si cette mesure n'était pas disponible, la valeur initiale était retenue, puis la valeur la plus haute. Ainsi, trois sous-groupes indépendants ont été créés pour les analyses. Les résultats ont été présentés sous forme de différence moyenne normalisée afin de pouvoir comparer les sous-groupes. L'hétérogénéité a été évaluée à l'aide la statistique I^2. Étant donné les différents temps de mesure, une méta-analyse de type 'effet aléatoire' a été effectuée. Si l'hétérogénéité était supérieure à 75% s'il y avait une différence significative entre les sous-groupes, il était prévu de présenter les résultats des sous-groupes séparément (avec l'inclusion de toutes les données disponibles). Le biais de publication a été évalué avec un graphique en

entonnoir, lorsqu'approprié. Plusieurs analyses de sensibilité ont également été effectuées afin d'évaluer l'effet possible sur les résultats de la qualité des études, de la taille de l'échantillon, de la précision des appareils de SPIR et de la priorisation des temps de mesures retenus (valeur moyenne, initiale et supérieure).

2.3.3.2. Caractéristiques métrologiques de deux appareils de spectroscopie proche infrarouge chez des volontaires sains

Une autre limite importante du monitorage par SPIR consistait en, tel que décrit précédemment, l'incertitude en regard de plusieurs des caractéristiques métrologiques de base des appareils de SPIR. En effet, la fiabilité des valeurs pour un même appareil et la concordance entre les valeurs données par plusieurs appareils n'avaient été décrites que sur de petites cohortes.[105, 134-137] Bien que ces appareils soient utilisés cliniquement pour monitorer la saturation à de multiples endroits sur le corps, la majorité des études à ce sujet avait uniquement inclus des mesures prises au niveau cérébral.[105, 135] En plus de cela, les valeurs de références chez des volontaires sains n'avaient également jamais été déterminées. Finalement, aucune étude n'avait évalué le temps nécessaire pour obtenir une mesure stable, ce qui peut importer dans le contexte du monitorage d'un patient souffrant d'un ACEH. Ainsi, les objectifs spécifiques de la deuxième étude du troisième volet consistaient à déterminer la fiabilité, la concordance, les valeurs de référence et le temps nécessaire pour obtenir une mesure stable pour deux appareils de SPIR fréquemment utilisés en clinique.

Pour ce faire, une étude de cohorte prospective sur volontaires sains a été réalisée. Cette étude a été approuvée par le comité d'éthique de l'Hôpital du Sacré-Cœur de Montréal (2015-1118).

Des volontaires sains de plus de 18 ans ont été recrutés via une technique d'échantillonnage en boule de neige. La majorité d'entre eux étaient des employés de l'Hôpital du Sacré-Cœur de

Montréal. Aucun patient n'a été recruté dans le cadre de ce projet. Afin d'être éligible, les volontaires devaient ne pas être enceinte, ne prendre aucun médicament à l'exception des contraceptifs oraux, ne souffrir d'aucune maladie systémique active ou chronique, ne pas avoir de maladie de peau ou de pilosité limitant la prise des mesures, ne pas fumer, peser moins de 40 kilogrammes ou avoir un indice de masse corporelle inférieur à 18 ou supérieur à 35.

Deux appareils de SPIR ont été utilisés dans le cadre de cette étude, le INVOS 5100C avec les capteurs SomaSensor format adulte et le EQUANOX 7600 avec les capteurs Equanox Advance 8004CA.

Les données sociodémographiques de base (âge, sexe, taille, poids), les signes vitaux (pression artérielle, pouls et saturation artérielle en oxygène par oxymétrie pulsée) ainsi que la couleur de peau selon l'échelle de Fitzpatrick ont été initialement collectées.[138] Les six sites de mesures (frontal, deltoïde, avant-bras, cuisse, mollet, pied) étaient ensuite marqués à l'aide d'un crayon de chacun des côtés du corps. L'épaisseur du pli cutané était ensuite mesurée aux quatre sites auxquels cette mesure se prête (deltoïde, avant-bras, cuisse et mollet) de chacun des côtés du corps également. Aucune prise de sang n'a été effectuée chez les volontaires, ce qui signifie que leur niveau précis d'hémoglobine et de bilirubine n'était pas connu. Puisqu'uniquement des volontaires sains étaient recrutés, ces données ont été présumées comme étant dans le spectre de la normale.

Pour chacun des appareils, des mesures d'oxymétrie tissulaire ont été prises à six sites différents, des deux côtés du corps (pour un total de 12 sites par sujet). L'ordre de mesure entre chacun des deux appareils a été randomisé. À chaque site, nous avons pris une mesure de base (temps 1 (t1)) avec un premier capteur (capteur 1 (c1)) pour une mesure capteur1-temps1 (c1t1)), une deuxième mesure après une minute (temps 2 (t2)) avec le même capteur (C1) pour une mesure

capteur1-temps2 (c1t2) et une troisième mesure après une minute (temps 3 (t3)) avec un capteur différent du même modèle (capteur 2 (c2)) pour la mesure capteur2-temps3 (c2t3). Ainsi, pour chaque participant, nous avons obtenu 72 valeurs d'oxymétrie tissulaire (2 appareils * 6 sites * 3 temps * 2 côtés du corps). Le délai avant la stabilisation de chacune des mesures était noté à partir de l'apposition du capteur jusqu'à ce que l'appareil fournisse deux mesures consécutives similaires, alterne entre deux valeurs contiguës ou qu'un maximum de 20 secondes se soit écoulées depuis la première mesure.

À partir de ces mesures brutes d'oxymétrie, nous avons calculé deux indices de fiabilité, un inter-capteur (T2 vs T3) et un intra-capteur (T1 vs T2), les deux à une minute d'intervalle chacun. Ces indices ont calculés à l'aide du coefficient de corrélation intraclasse (ICC) et de l'écart-type intra-individu (S_w) à l'aide de la méthode de Blant et Altman.[139] Les comparaisons entre ICCs ont été réalisées à l'aide de la méthode de transformation de Fisher. Les comparaisons entre S_w ont été réalisées à l'aide de tests de t pour échantillon apparié. Ces mêmes tests ont été utilisés pour évaluer la comparabilité des mesures entre les deux appareils, ainsi qu'entre les différents sites et les deux côtés. Les temps nécessaires pour obtenir une mesure stable ainsi que les valeurs moyennes à chaque site ont été comparés entre les deux appareils à l'aide de test ANOVA sur mesures répétées.

Étant donné l'absence de littérature sur la puissance de tests lors de comparaisons d'ICCs dépendants et basés sur des ANOVA à deux facteurs, la taille de l'échantillon a été basée sur la précision d'un intervalle de confiance unidirectionnel pour un ICC paramétrique. Afin d'obtenir un seuil de confiance unidirectionnel de 95% et une étendue de 0,1 vers les faibles valeurs et en assumant une valeur attendue de 0,75 pour un ICC, nous avons déterminé qu'il fallait recruter 53 volontaires pour cette étude.

2.3.3.3. Influences des caractéristiques du volontaire sur la répétabilité des mesures de saturation tissulaire

Tel que discuté précédemment, la concordance entre les valeurs données par plusieurs appareils de SPIR n'avait été décrite que sur de petites cohortes.[105, 134-137] De plus, une seule étude avait exploré quels facteurs pourraient influencer cette concordance.[105] Puisqu'il avait déjà été montré que l'ischémie du tissu cutané et sous-cutané pouvait influencer la saturation cérébrale, l'hypothèse a été émise que l'épaisseur de ce tissu sous-cutané puisse expliquer une partie de cette variabilité.[112] Ainsi, l'objectif spécifique de la troisième étude du troisième volet consistait à déterminer les facteurs individuels, notamment la quantité de gras sous-cutané, influençant la concordance entre deux appareils de SPIR fréquemment utilisés.

Cette étude consiste en une analyse secondaire planifiée de la cohorte prospective décrite précédemment (cf. 2.3.3.2.). Les méthodes spécifiques relatives aux procédures y sont également décrites. La quantité de gras sous-cutané a été estimée à partir des mesures de pli cutané obtenues.

L'association entre la quantité de gras sous-cutané a été évaluée initialement à l'aide d'une corrélation de Pearson et un graphique de type 'nuage de points'. Par la suite, un modèle linéaire mixte a été construit afin d'évaluer de manière indépendante l'association entre la quantité de gras sous-cutané et des autres covariables inclues dans le modèle (âge et sexe) et la concordance entre les valeurs d'oxymétrie tissulaire. Une structure autorégressive de covariance et une correction de Bonferroni ont été utilisées pour cette analyse spécifique.

Étant donné qu'il s'agissait d'une sous-analyse de l'étude précédente, aucun calcul de taille d'échantillon n'a été calculé spécifiquement pour celle-ci.

Chapitre 3. Résultats

3.1. Premier volet

3.1.1. Volet 1 – Article 1 – Prehospital advanced cardiac life support for out-of-hospital cardiac arrest: a cohort study

3.1.1.1. Préface

Cette étude a été réalisée en collaboration avec 13 autres chercheurs. J'ai réalisé plus de 90% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Sylvie Cossette, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. La collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette et Massimiliano Iseppon. André Denault, Éric Notebaert Luc Londei-Leduc, Yoan Lamarche, Judy Morris, Éric Piette, Raoul Daoust, Jean-Marc Chauny, Catalina Sokoloff, Yiorgos Alexandros Cavayas et Jean Paquet ont également contribué à sa révision. Cette étude a été publiée dans le journal Academic Emergency Medicine en 2017 (Facteur d'impact en 2017 : 2,731).

3.1.1.2. Volet 1 – Article 1

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Prehospital advanced cardiac life support for out-of-hospital cardiac arrest: a cohort study

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Abstract

Objectives: Out-of-hospital advanced cardiac life support (ACLS) has not consistently shown a positive impact on survival. Extracorporeal cardiopulmonary resuscitation (E-CPR) could render prolonged on-site resuscitation (ACLS or basic cardiac life support [BCLS]) undesirable in selected cases. The objectives of this study were to evaluate, in patients suffering from out-of-hospital cardiac arrest (OHCA) and in a subgroup of potential E-CPR candidates, the association between the addition of prehospital ACLS to BCLS and survival to hospital discharge, prehospital return of spontaneous circulation (ROSC) and delay from call to hospital arrival.

Methods: This cohort study targets adult patients treated for OHCA between April 2010 and December 2015 in the city of Montreal, Canada. We defined potential E-CPR candidates using clinical criteria previously described in the literature (65 years of age or younger, initial shockable rhythm, absence of return of spontaneous circulation after 15 minutes of prehospital resuscitation and emergency medical services witnessed collapse or witnessed collapse with bystander cardiopulmonary resuscitation). Associations were evaluated using multivariate regression models.

Results: A total of 7134 patients with OHCA were included, 761 (10.7%) of whom survived to discharge. No independent association between survival to hospital discharge and the addition of prehospital ACLS to BCLS was found in either the entire cohort [adjusted odds ratio (AOR) 1.05 (95% confidence interval 0.84-1.32), p=0.68] or amongst the 246 potential E-CPR candidates [AOR 0.82 (95% confidence interval 0.36-1.84), p=0.63]. The addition of prehospital ACLS to BCLS was associated with a significant increase in the rate of prehospital ROSC in all patients experiencing OHCA (AOR 3.92 [95% CI 3.38-4.55], p<0.001) and in potential E-CPR candidates (AOR 3.48 [95% CI 1. 76-6.88], p<0.001) as compared to isolated prehospital BCLS. Delay from call to hospital arrival was longer in the ACLS group than in the BCLS group (difference=16 min [95% CI 15-16], p<0.001).

Conclusions: In a tiered-response urban emergency medical service setting, prehospital ACLS is not associated with an improvement in survival to hospital discharge in patients suffering from OHCA and in potential E-CPR candidates, but with an improvement in prehospital ROSC and with longer delay to hospital arrival.

Introduction

Over 300000 people suffer from out-of-hospital cardiac arrest (OHCA) each year in the United States.[1] Despite advances in medical care, survival amongst these patients remains low, with only 5-10% surviving to discharge.[1, 140] Rapid provision of Basic cardiac life support (BCLS), consisting of cardiopulmonary resuscitation and defibrillation, has been shown to increase survival.[45] Advanced cardiac life support (ACLS), which adds advanced airway management and intravenous therapy to the aforementioned, is provided on the scene whenever possible. Survival is rare in situations when there is no on-site return of spontaneous circulation (ROSC). Therefore, maximizing efforts towards achieving prehospital ROSC is generally justified, especially since the quality of the resuscitation inside of a moving emergency medical services (EMS) vehicle is often

suboptimal.[47, 141] These elements are compounded by the fact that, until recently, no additional life-saving interventions were available upon hospital arrival.

The use of extracorporeal cardiopulmonary resuscitation (E-CPR) in selected patients suffering from refractory OHCA has recently garnered interest. It incorporates an extracorporeal cardiopulmonary bypass circuit to obtain cardiopulmonary support during resuscitation.[21, 28, 33] Although physical, human and economic limitations usually restrict this novel technique's use to specialized centers, it performs favorably when compared to traditional ACLS.[35, 39, 40, 142] The time interval from arrest to E-CPR initiation is of critical importance, in accordance with most interventions performed on patients in cardiac arrest.[29, 34, 43]

Out-of-hospital ACLS has been shown to increase the rate of prehospital ROSC, but has failed to consistently show a positive impact on survival.[15, 143, 144] Recent improvements in post-cardiac arrest care with targeted temperature management and aggressive reperfusion therapy have increased the likelihood of survival amongst patients experiencing ROSC.[18] The effectiveness of prehospital ACLS at increasing survival in OHCA has never been evaluated in potential E-CPR candidates and the necessity to rapidly transport these patients to hospitals with E-CPR capability may render prolonged on-site resuscitation undesirable. In a tiered-response EMS system, the provision of prehospital ACLS in addition to BCLS may be foregone for potential E-CPR candidates, especially if associated with longer delays before hospital arrival. Contemporary data are required to determine if out-of-hospital ACLS can now improve survival among patients with OHCA prior to evaluating the possibility of implementing a change in EMS practice.

The main objectives of this study are to evaluate the impact of the addition of prehospital ACLS to BCLS when compared to isolated prehospital BCLS in all patients suffering from OHCA,

and more precisely in a targeted population: potential E-CPR candidates. We hypothesized that the addition of prehospital ACLS would be associated with higher rates of survival to hospital discharge, and this for all OHCA patients, as well as in the subgroup of potential E-CPR candidates. As a secondary outcome, we evaluated the impact of the addition of ACLS on prehospital return of spontaneous circulation (ROSC) and delay from call to hospital arrival.

Methods

Study design and setting

This cohort study was conducted using a prospectively collected registry of OHCA that was subsequently validated internally. It was carried out at the Hôpital du Sacré-Coeur de Montréal, in association with the local EMS agency (Urgences-santé) and the Université de Montréal. This study was approved by our establishment's Institutional Review Board. All data were readily anonymized.

Emergency prehospital care in the city of Montreal, Canada, is coordinated by a single public tiered-response EMS agency that employs first responders, primary care paramedics and advanced care paramedics, the latter providing ACLS on-site in situations of OHCA. Given their limited numbers, advanced care paramedics are not always available to respond to OHCA calls.

Selection of participants

The present study includes all patients aged 18 years and older treated for an OHCA (defined as prehospital absence or loss of pulse and subsequent closed chest compressions) from that database's inception in April 2010 to December 2015. Patients were excluded if their death was considered obvious according to EMS criteria (e.g. decapitation, advanced putrefaction), if the cause of the OHCA was traumatic or in cases of 'do-not-resuscitate' directives.[44]

We divided the sample of patients with OHCA according to the type of prehospital care providers that were present on-site. Patients were allocated to the ACLS or BCLS cohort depending on whether an ACLS provider was on-site during the resuscitation or not. Patients were considered potential E-CPR candidates if they met the following clinical criteria: 65 years of age or younger, initial shockable rhythm, absence of ROSC after 15 minutes of prehospital resuscitation and EMS witnessed collapse or witnessed collapse with bystander CPR.[21, 39, 40, 43, 117]

General OHCA management and EMS protocols

Whenever an OHCA is suspected during an emergency call, both first responders and primary care paramedics are dispatched to the scene in order to minimize time to defibrillation and CPR. Primary care paramedics treat patients suffering from OHCA by following a BCLS resuscitation protocol based on the American Heart Association guidelines.[44, 45] Whenever available, advanced care paramedics will self-assign to cardiac arrest cases and provide drug therapy in accordance with the current ACLS guidelines, as well as specific treatments directed at presumed etiology of the OHCA.[14, 46] In accordance with provincial law, advanced care paramedics cannot perform endotracheal intubation, but can perform other actions to secure the airway (e.g. laryngoscopic removal of foreign object, cricothyrotomy) if ventilation is ineffective. Following five analyses of the defibrillator during primary care paramedics' resuscitation or a minimum of 20 minutes of resuscitation following the initiation of drug therapy by advanced care paramedics, the patients will either be transported to the nearest hospital or the resuscitation efforts will be ceased if termination criteria are met.[44, 46]

Methods and Measurements

According to local EMS protocols, OHCA patient data are entered by the paramedic on a 'run-sheet' following every call. This information is then entered into a database which comprises

demographic (gender, age) and clinical characteristics (nature of the case, core Utstein-style data, etc.).[51] Call times are automatically saved in a separate database that we linked to the patient-care information database. Resuscitation outcome data were either transferred from discharge hospitals to the local EMS agency, or were readily available in their database. Since E-CPR resuscitation began in 2014, it is possible that some of the patients received this therapy. However, we did not have access to this information.

Outcome measures

The primary outcome measure was survival to hospital discharge. The secondary outcome measures were prehospital ROSC (minimum of 30 seconds) and delay from call to hospital arrival (minutes).

Primary Data Analysis

The entire available population was used in this study's analysis. Assuming a survival rate of 10% and 7475 victims of OHCA treated over the recruitment period, a difference of 3% in survival between both groups could be detected using a bilateral alpha of 5%, a power of 90% and 75% of the variability explained by other factors included in the model.[52]

Continuous variables are presented as means with standard deviations and categorical variables are presented as frequencies with percentages. The effect size of group differences for demographic, clinical and time variables were assessed using Cohen's d for continuous variable and Cramér's v for categorical variables.

The relationships between the addition of prehospital ACLS to BCLS compared to isolated prehospital BCLS with regards to resuscitation outcomes were first assessed using Pearson's chi-squared test. A multivariate logistic regression model was then constructed, if appropriate, using a standard approach (enter method) to control for pertinent demographic (age, gender, initial call

time moment) and clinical variables (initial rhythm, bystander CPR, witnessed arrest, presence of first responders, time from call to arrival of EMS personnel). The predictive power of the model was evaluated using a Nagelkerke R^2. Odds ratios (OR) and adjusted OR (AOR) are presented with their 95% confidence interval (CI). The same analyses were carried out for potential E-CPR candidates. Given the retrospective nature of this study, we performed three sensitivity analyses to account for possible selection bias. First, we only included patients who received prehospital care within 11 minutes of initial call time, since longer delay before the initiation of resuscitation could make ACLS interventions futile.[145] For this analysis, we defined rapid prehospital care as a delay of 11 minutes or less from call time to arrival on the scene of advanced care paramedics in the ACLS group or primary care paramedics in the BCLS group.[15] In the second analysis, we added a covariate (intubation using an esophageal tracheal airway) to the model to adjust for case severity. Intubated patients are less likely to have good outcomes, presumably because patients that experience early prehospital ROSC have a better prognosis and are thus less likely to be intubated.[141, 146] While this covariate takes place after the beginning of the resuscitation, this treatment occurs relatively early in the course of the resuscitation, and this analysis was useful to adjust for case severity. Finally, we included the medical priority dispatch system card in the model to adjust for all variables that could influence advanced care paramedics' allocation to certain call.[147] The association between prehospital ACLS and delay before hospital arrival was first assessed using a Student's t-test, which was followed with a standard (enter method) multivariate linear regression, if appropriate according to dataset property, using the covariables presented previously. Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA). Alpha levels were fixed at 0.05.

Results

During the study period (April 1st 2010 to December 31st 2015), 7134 patients met the inclusion criteria. Two thousand thirty two patients (28.5%) received on-site ACLS in addition to BCLS (ACLS group) and 5102 (71.5%) only BCLS (BCLS group). Demographic and clinical characteristics, as well as the treatments they received on-site, are presented in Table 1. In the overall sample, 1691 (23.7%) experienced on-site ROSC and 761 (10.7%) survived to discharge.

The proportions of patients surviving to discharge were similar in both groups (10.9% vs 10.6%, p=0.67). There was no significant independent association between the addition of prehospital ACLS to BCLS and survival to hospital discharge (AOR 1.05 [95% CI 0.84-1.32], p=0.68) (Nagelkerke R^2=0.36) (Table 2). Amongst the patients receiving prehospital care within 11 minutes, we found no significant independent association between the addition of prehospital ACLS to BCLS and survival to hospital discharge (AOR 1.7 [95% CI 0.92-2.04], p=0.12) (data not presented). Intubation with an esophageal tracheal airway was associated with lower survival to hospital discharge (OR 0.16 [95% CI 0.13-0.18], p<0.001). However, its addition to the multivariate logistic regression model to adjust for case severity did not significantly affect the association between patients receiving the additional ACLS therapies and survival to hospital discharge (AOR 1.10 [95% CI 0.89-1.36], p=0.39) (data not presented). Adding the initial medical priority dispatch system card to the model did not significantly affect the association between the addition of prehospital ACLS to BCLS and survival to hospital discharge (AOR 1.05 [95% CI 0.85-1.29], p=0.68) (data not presented).

Amongst the 7134 patients included in the study, 246 would have been potential E-CPR candidates (3.4%) according to the aforementioned eligibility criteria. Amongst them, 126 (51.2%) experienced on-site ROSC and 90 (36.6%) survived to discharge. We found no significant independent association between the addition of prehospital ACLS to BCLS and survival to hospital discharge (AOR 1.18 [95% CI 0.57-2.45], p=0.65) (Nagelkerke R^2=0.26) (Table 3).

The addition of prehospital ACLS to BCLS was associated with a significant increase in the rate of prehospital ROSC in all patients experiencing OHCA (AOR 3.92 [95% CI 3.38-4.55], p<0.001) (Nagelkerke R^2=0.36) and in potential E-CPR candidates (AOR 3.48 [95% CI 1.76-6.88], p<0.001) (Nagelkerke R^2=0.27) as compared to isolated prehospital BCLS (Tables 4 and 5).

The addition of prehospital ACLS to BCLS was associated with significantly longer delay from initial call to hospital arrival (difference = 14 min [95% CI 13-14], p<0.001). That association was maintained after adjusting for all confounding variables (difference = 16 min [95% CI 15-16], p<0.001) (data not presented).

Discussion

The primary objective of this study was to evaluate the association between the addition of prehospital ACLS to BCLS and survival to hospital discharge. Using an adjusted analysis, we found no significant association between the addition of ACLS therapies and the rate of survival to hospital discharge. These results were replicated when only evaluating potential E-CPR candidates, patients receiving prehospital care within 11 minutes, following adjustment for case severity and including all prehospital variables that could have introduced a selection bias between both groups. As expected, the rate of prehospital ROSC was higher in patients receiving the additional prehospital ACLS when compared to isolated prehospital BCLS. The addition of on-site ACLS was also associated with significantly longer delays to hospital arrival. The present study adds to the literature by providing an important cohort of OHCA. This large sample size granted us good power, which would have allowed us to detect a clinically significant difference in survival. More importantly, this is the first study that addresses these questions in potential E-CPR candidates. The stability of our results across all analyses adds to their value.

Prehospital ACLS was associated with an increase in prehospital ROSC, but with longer delays to hospital arrival. These observations are likely explained by two factors. First, as mentioned earlier, several ACLS interventions have been shown to increase ROSC.[148] Second, ACLS providers can perform more resuscitation acts and are allotted a longer timeframe for prehospital resuscitation before having to transport the patients than primary care paramedics are. Therefore, they have a better chance of resuscitating patients prior to their arrival to hospitals, but with much longer delays. The limited number of ACLS providers in a tiered-response EMS system can also lengthen the delay to ACLS providers' arrival on the scene, which also contributes to prolonging delays before hospital arrival.

However, we did not observe any association between prehospital ACLS and survival to hospital discharge. Our results are in agreement with many articles already published on the subject.[15, 144, 149, 150] In a retrospective cohort study published in 2015, Sanghavi et al. observed an increase in mortality with on-site ACLS.[144] However, their study did not include an adjustment for the majority of the Utstein data elements and only included patients transported to hospital.[52] On the other hand, a meta-analysis published in 2011 concluded that on-site ACLS increased survival to hospital discharge in non-traumatic OHCA.[151] The prehospital ACLS in most of the articles with positive results in this meta-analysis was provided by physician, which is not the case in our setting. In the subgroup of patients for which ACLS was provided by paramedics, the results were barely statistically significant [OR 1.23 (95%CI 1.01-1.49)]. It is possible that the addition of our results and those presented by Sanghavi et al. would change the results of that sub-group analysis.[144] Woodall et al. published the only positive trial with paramedics providing care for the patients in the meta-analysis.[143] However, their catchment area was the entirety of the state of Queensland, Australia, an area more than a thousand times less densely populated than any urban setting. It is plausible that more advanced

and prolonged prehospital resuscitation could be beneficial in rural settings where hospital transport times can be prolonged. Also, five of the six articles presenting positive results were published more than 15 years ago and BCLS resuscitation has significantly improved since then.[44, 45]

Given these conflicting results, there is no clear advantage of the addition of prehospital ACLS to BCLS as compared to prehospital BCLS alone. This is likely explained by the fact that therapies that have been proven to effectively increase survival for patients suffering from OHCA are part of the BCLS bundle (high quality CPR and early defibrillation).[152] On the other hand, most ACLS therapies (such as epinephrine and antiarrhythmic medication) have been shown to increase ROSC, but not survival to hospital discharge.[16, 148] Nevertheless, given the results presented by Bakalos et al., it is possible that, in some settings (rural areas or physician provided prehospital care), more advanced skill level may improve enough the quality of the delivered care to positively affect survival.[151, 153]

We did not identify an association between survival to hospital discharge in potential E-CPR candidates and prehospital ACLS. To our knowledge, this is the first time this has been studied in this particular population. Optimal screening, with the use of early identification parameters, and referral of potential E-CPR candidates might be one of the solutions to increase these patients' access to E-CPR. This process could be impeded by the delays before hospital transport associated with prolonged prehospital ACLS resuscitation observed in our sample. We could hypothesize that, after their identification, following a shorter period of resuscitation, whether it be ACLS or BCLS, rapidly transporting these patients to E-CPR capable centers could result in improved survival. In addition, longer prehospital resuscitation may render potential E-CPR candidates ineligible for this therapy owing to a lengthy delay to its initiation.[34, 43] This hypothesis remains unproven and can now be safely tested in future studies.

Limitations

The main limitation of this study is its observational nature. This design was the best possible design given the ethical and logistical challenges in performing a randomized controlled trial with OHCA patients. However, our results were consistent across all analyses, even following adjustment for major clinical variables and all prehospital variables that could have influenced ACLS providers's allocation to certain calls. We were limited by the information provided by the EMS run-sheets and databases, and we were unable to adjust some potentially pertinent confounders (notably etiology of the OHCA, CPR quality and hospital/post-resuscitation care). We could not effectively determine which specific ACLS or BCLS interventions were most beneficial to the patients or if a shorter delay to some interventions would have affected our results. Given how we defined our group, it is possible that some patients classified in the ACLS group received little or no ACLS specific actions during the resuscitation before sustaining ROSC. Given the direction of that potential bias (advantaging the ACLS group since these patients had a good prognosis given their early ROSC), our initial hypothesis and our results, our conclusion remains valid. This study includes one vast metropolitan region, covered by a unique EMS provider. Our results may not be generalizable to other regions, notably because of differences in geography, OHCA epidemiology or prehospital emergency care system.

Conclusion

Although associated with an increase in prehospital ROSC, the addition of prehospital ACLS to BCLS as compared to isolated prehospital BCLS in tiered-response urban EMS setting is not associated with an improvement in survival to hospital discharge in patients suffering from OHCA. It is, however, associated with an improvement in prehospital ROSC, at the price of an increase in delay to hospital arrival. These findings were reproduced in a subset of potential E-CPR candidates. A more rapid transport to hospital could potentially benefit this subgroup, especially

since high-quality CPR can be achieved during transport.[48] Future studies evaluating the benefits of rapid hospital redirection for potential E-CPR candidates are necessary and should be performed given this novel therapy's potential beneficial effect on survival.

Conflict of interest statement

Dr. André Denault is part of a speakers bureau for Masimo, Edwards and CAE Healthcare. We have no other conflicts of interest to declare.

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Tableau 4 : Table 1 Demographic and clinical characteristics of the included patients

Variables	BCLS group (n=5102)	ACLS group (n=2032)	Effect size
Age, years	69.3 (16.2)	65.8 (17.2)	-0.23
Gender, men	3179 (62.3)	1349 (66.4)	0.038
Initial call between 8 am and 4 pm Initial call between 4 pm and 12 am Initial call between 12 am and 8 am	2289 (44.9) 1542 (30.3) 1263 (24.8)	731 (36.0) 921 (45.3) 380 (18.7)	0.14
Initial prehospital triage card, cardiac arrest	2338 (47.2)	1177 (61.0)	0.124
Initial rhythm, shockable rhythm	1252 (26.3)	536 (27.8)	0.016
Unwitnessed arrest Bystander witnessed First responder or paramedic witnessed	2347 (46.0) 2076 (40.7) 679 (13.3)	975 (48.0) 948 (46.7) 109 (5.4)	0.12
No bystander CPR Bystander CPR First responder or paramedic witnessed	3144 (62.0) 1252 (24.7) 679 (13.4)	1252 (62.0) 659 (32.6) 109 (5.4)	0.13
Presence of first responders	2964 (58.1)	1264 (62.2)	0.038
Delay from call to arrival of first responders, minutes	6.4 (4.0)	6.1 (2.8)	-0.076
Delay from call to arrival of primary care paramedics, minutes	10.6 (5.3)	10.0 (4.4)	-0.11
Delay from call to arrival of advanced care paramedics, minutes	-	17.0 (7.5)	-
Delay from call to departure to hospital, minutes	32.7 (10.4)	45.7 (13.6)	1.15
Delay from call to hospital arrival, minutes	39.8 (12.2)	53.4 (15.3)	1.04
Intubation using an esophageal tracheal airway	3794 (74.4)	1596 (78.5)	0.044
Number of shocks given	0.8 (2.0)	1.4 (3.1)	0.23
Number of doses of epinephrine given	-	2.8 (2.4)	-
Number of doses of other medication given	-	0.2 (0.5)	-
Prehospital ROSC	928 (18.2)	763 (37.5)	0.21
Survival to hospital discharge	539 (10.6)	222 (10.9)	0.005

BCLS: Basic cardiac life support; ACLS: Advanced cardiac life support; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; Values are presented as mean (standard deviation) or N (%) and effect size as Cohen's d or Cramér's v, as appropriate

Tableau 5 : Table 2 Multivariate analysis for the survival to hospital discharge outcome, adjusted for prehospital ACLS, demographic and prehospital variables

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Prehospital ACLS	1.04 (0.88-1.23)	0.66	1.05 (0.84-1.32)	0.68
Age (1 year older)	0.97 (0.96-0.97)	< 0.001	0.97 (0.96-0.97)	< 0.001
Gender, male sex	1.39 (1.18-1.64)	< 0.001	0.66 (0.52-0.83)	< 0.001
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	0.94 (0.80-1.12)	0.51	0.85 (0.68-1.07)	0.16
Initial call between 12 am and 8 am	0.74 (0.60-0.91)	0.004	0.87 (0.66-1.14)	0.32
Initial rhythm, shockable rhythm	15.73 (12.98-19.06)	< 0.001	11.72 (9.24-14.86)	< 0.001
Unwitnessed arrest	*	-	*	-
Bystander witnessed	5.00 (4.06-6.16)	< 0.001	2.49 (1.90-3.27)	< 0.001
First responder or paramedic witnessed	7.64 (5.95-9.80)	< 0.001	7.10 (5.03-10.00)	< 0.001
No bystander CPR	*	-	*	-
Bystander CPR	1.92 (1.62-2.28)	< 0.001	1.21 (0.98-1.48)	0.07
First responder or paramedic witnessed	3.48 (2.84-4.26)	< 0.001	†	†
Presence of first responders	0.87 (0.75-1.01)	0.072	1.27 (1.00-1.60)	0.047
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.99 (0.98-1.01)	0.37	0.98 (0.96-1.00)	0.048

ACLS: Advanced cardiac life support; OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; CPR: Cardiopulmonary resuscitation
* Reference category † Not calculated due to collinearity

Tableau 6 : Table 3 Multivariate analysis for the survival to hospital discharge outcome, including only potential E-CPR candidates, adjusted for prehospital ACLS, demographic and prehospital variables

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Prehospital ACLS	0.55 (0.29-1.01)	0.055	0.82 (0.36-1.84)	0.63
Age (1 year older)	1.00 (0.98-1.03)	0.82	1.01 (0.98-1.04)	0.66
Gender, male sex	0.95 (0.47-1.92)	0.90	0.94 (0.40-2.25)	0.90
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	1.44 (0.79-2.60)	0.23	1.49 (0.72-3.09)	0.28
Initial call between 12 am and 8 am	1.26 (0.63-2.49)	0.51	0.85 (0.36-2.05)	0.72
Bystander witnessed + Bystander CPR	*	-	*	-
First responder or paramedic witnessed	6.97 (3.89-12.46)	< 0.001	8.15 (3.72-17.86)	< 0.001
Presence of first responders	0.59 (0.35-0.99)	0.047	1.26 (0.58-2.71)	0.56
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	1.00 (0.95-1.05)	0.96	0.98 (0.92-1.04)	0.45

E-CPR: Extracorporeal cardiopulmonary resuscitation; ACLS: Advanced cardiac life support; OR: Odds ratio; CI: Confidence interval; Adjusted Odds ratio; CPR: Cardiopulmonary resuscitation
* Reference category

Tableau 7 : Table 4 Multivariate analysis for the prehospital ROSC outcome, adjusted for prehospital ACLS, demographic and prehospital variables

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Prehospital ACLS	2.70 (2.41-3.03)	< 0.001	4.08 (3.46-4.82)	< 0.001
Age (1 year older)	0.98 (0.98-0.99)	< 0.001	0.99 (0.98-0.99)	< 0.001
Gender, male sex	1.26 (1.12-1.41)	< 0.001	0.76 (0.66-0.88)	0.001
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	0.98 (0.87-1.11)	0.75	0.75 (0.63-0.89)	0.001
Initial call between 12 am and 8 am	0.67 (0.57-0.77)	< 0.001	0.70 (0.57-0.86)	0.001
Initial rhythm, shockable rhythm	7.82 (6.90-8.86)	< 0.001	6.54 (5.54-7.71)	< 0.001
Unwitnessed arrest	*	-	*	-
Bystander witnessed	4.13 (3.62-4.71)	< 0.001	3.00 (2.51-3.59)	< 0.001
First responder or paramedic witnessed	5.02 (4.19-6.01)	< 0.001	7.28 (5.65-9.37)	< 0.001
No bystander CPR	*	-	*	-
Bystander CPR	1.71 (1.51-1.94)	< 0.001	1.07 (0.90-1.27)	0.47
First responder or paramedic witnessed	2.65 (2.26-3.12)	< 0.001	†	†
Presence of first responders	0.96 (0.86-1.07)	0.46	1.11 (0.93-1.32)	0.24
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.99 (0.98-1.00)	0.20	0.99 (0.97-1.00)	0.083

ROSC: Return of spontaneous circulation; ACLS: Advanced cardiac life support; OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; CPR: Cardiopulmonary resuscitation
* Reference category † Not calculated due to collinearity

Tableau 8 : Table 5 Multivariate analysis for the prehospital ROSC outcome, including only potential E-CPR candidates, adjusted for prehospital ACLS, demographic and prehospital variables

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Prehospital ACLS	1.47 (0.84-2.60)	0.18	2.83 (1.35-5.95)	0.006
Age (1 year older)	0.99 (0.97-1.02)	0.46	0.99 (0.96-1.02)	0.68
Gender, male sex	0.65 (0.33-1.30)	0.23	0.94 (0.40-2.25)	0.84
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	1.29 (0.73-2.28)	0.38	1.17 (0.58-2.36)	0.65
Initial call between 12 am and 8 am	1.28 (0.66-2.46)	0.47	0.95 (0.41-2.22)	0.91
Bystander witnessed + Bystander CPR	*	-	*	-
First responder or paramedic witnessed	5.86 (3.24-10.62)	< 0.001	11.40 (4.91-26.47)	< 0.001
Presence of first responders	0.72 (0.43-1.21)	0.22	1.52 (0.69-3.36)	0.30
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	1.00 (0.95-1.05)	0.97	0.99 (0.93-1.05)	0.72

ROSC: Return of spontaneous circulation; E-CPR: Extracorporeal cardiopulmonary resuscitation; ACLS: Advanced cardiac life support; OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; CPR: Cardiopulmonary resuscitation
* Reference category

3.1.2. Volet 1 – Article 2 – Impact of the direct transfer to percutaneous coronary intervention-capable hospitals on survival to hospital discharge for patients with out-of-hospital cardiac arrest

3.1.2.1. Préface

Cette étude a été réalisée en collaboration avec 21 autres chercheurs. J'ai réalisé plus de 90% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Luc de Montigny, Dave Ross, Eli Segal, Sylvie Cossette, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. La collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette et Massimiliano Iseppon. André Denault, Éric Notebaert, Luc de Montigny, Dave Ross, Luc Londei-Leduc, Yoan Lamarche, Brian Potter, Alain Vadeboncoeur, Dominic Larose, Judy Morris, Éric Piette, Raoul Daoust, Jean-Marc Chauny, François de Champlain, Eli Segal, Martin Albert, Catalina Sokoloff, Yiorgos Alexandros Cavayas et Jean Paquet ont également contribué à sa révision. Cette étude a été publiée dans le journal Resuscitation en 2018 (Facteur d'impact en 2018/2019 : 4,572).

3.1.2.2. Volet 1 – Article 2

Title: Impact of the Direct Transfer to Percutaneous Coronary Intervention-Capable Hospitals on Survival to Hospital Discharge for Patients with Out-of-Hospital Cardiac Arrest

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Conflict of interest: Dr. André Denault is part of a speakers bureau for Edwards, Masimo and CAE Healthcare.

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Aims: Patients suffering from out-of-hospital cardiac arrest (OHCA) are frequently transported to the closest hospital. Percutaneous coronary intervention (PCI) is often indicated following OHCA. This study's primary objective was to determine the association between being transported to a PCI-capable hospital and survival to discharge for patients with OHCA. The additional delay to hospital arrival which could offset a potential increase in survival associated with being transported to a PCI-capable center was also evaluated.

Methods: This study used a registry of OHCA in Montreal, Canada. Adult patients transported to a hospital following a non-traumatic OHCA were included. Hospitals were dichotomized based on whether PCI was available on-site or not. The effect of hospital type on survival to discharge was assessed using a multivariable logistic regression. The added prehospital delay which could offset the increase in survival associated with being transported to a PCI-capable center was calculated using that regression.

Results: A total of 4922 patients were included, of whom 2389 (48%) were transported to a PCI-capable hospital and 2533 (52%) to a non-PCI-capable hospital. There was an association between being transported to a PCI-capable center and survival to discharge (adjusted odds ratio=1.60 [95% confidence interval 1.25-2.05], $p<0.001$). Increasing the delay from call to hospital arrival by 14.0 minutes would offset the potential benefit of being transported to a PCI-capable center.

Conclusions: It could be advantageous to redirect patients suffering from OHCA patients to PCI-capable centers if the resulting expected delay is of less than 14 minutes.

Introduction

Approximatively 326 000 patients are afflicted annually by a non-traumatic out-of-hospital cardiac arrest (OHCA) in the United States.[1] Most of these are presumed to result from a cardiac etiology, the most frequent being an acute coronary syndrome (ACS).[118, 119] Coronary angiography with appropriate percutaneous coronary intervention (PCI) is the diagnostic and therapeutic procedure of choice in ACS and is recommended after cardiac arrest both in patients with ST-segment elevation and without ST-segment elevation on their initial 12-lead electrocardiogram (Class I, level of evidence B and Class IIa, level of evidence B, respectively).[18, 154-156] Additionally, early access to a cardiac catheterization laboratory allows for timely consideration of percutaneous hemodynamic support. However, considering the specialized resources and expertise required, such services tend to be centralized.

Given these recommendations and the fact that regionalized prehospital systems have already helped decrease morbidity and mortality in patients suffering from ST-segment elevation myocardial infarction (STEMI), it has been proposed that a similar regionalized approach for the treatment of OHCA, including direct transport to a specialized cardiac resuscitation center, might be beneficial (Class IIb, level of evidence C).[6, 157, 158] One of the main features of a cardiac resuscitation center is its ability to perform diagnostic angiography and PCI on-site at all times. Patients with an initial shockable rhythm (ventricular tachycardia or ventricular fibrillation) might benefit even more from being transported directly to a PCI-capable center owing to their higher likelihood of suffering from a significant coronary lesion amenable to PCI.[159] However, since OHCA might be a more time sensitive condition than STEMI, the increased delay before hospital arrival when bypassing primary or secondary care centers could possibly be harmful to some patients. Patients having experienced prehospital return of spontaneous circulation (ROSC) might be more stable and less affected by longer prehospital delays than those who have not. Whether

survival after OHCA can be improved by direct transfer to cardiac resuscitation centers and the transport delay that would be acceptable have yet to be determined.

The main objective of this study was to evaluate the independent impact of direct transport to a PCI-capable center on survival to discharge among patients suffering from OHCA. Secondary objectives included determining whether or not two specific prehospital characteristics (e.g. prehospital ROSC or an initial shockable rhythm) would influence this association and the acceptable incremental delay for direct transfer.

Methods

Design

This cohort study used a registry of OHCA from the region of Montreal, Canada. It was carried out in association with the Hôpital du Sacré-Coeur de Montréal, the regional emergency medical service (EMS) agency (Urgences-santé) and the Université de Montréal. It was approved by the Institutional Review Board of the Hôpital du Sacré-Coeur de Montréal and conducted in accordance with the Declaration of Helsinki. Given the nature of the study, a waiver of written informed consent from the participant was granted.

Setting

In Montreal, a single public EMS agency coordinates all prehospital care for a population of over 2 000 000 people. First responders and paramedics treat patients suffering from OHCA following resuscitation protocols based on the American Heart Association guidelines.[44-46] According to these protocols, patients suffering from OHCA are transported to the closest of the region's 20 hospitals. Seven of these centers are capable of performing PCI.

Study population

All patients aged 18 years and older treated for an OHCA from April 2010 until December 2015 were screened for inclusion. Patients with traumatic causes for arrest, 'do-not-resuscitate'

directives or with 'obviously deceased' criteria (e.g. decapitation, advanced putrefaction) were excluded from the registry described above.[44] In addition to these, patients not transported to hospital were excluded.

Study groups

The OHCA cohort was dichotomized according to the first hospital to which these patients were transported (PCI-capable vs non–PCI-capable). All PCI-capable hospitals in the region are designated STEMI centers and are therefore able to provide emergent diagnostic and interventional procedures (PCI or hemodynamic support) 24 hours a day, all year round.[160]

Study outcomes

For the primary objective and the first two secondary objectives, the outcome measure was survival to hospital discharge. For the last secondary objective, the outcome measure was the additional delay in prehospital transport time (in minutes) that would result in equipoise between the two transport strategies (nearest hospital vs PCI-capable hospital).

Data collection

According to provincial law, OHCA patient data are entered by paramedics on a 'run-sheet' following every call. This information is then entered into a database that includes demographic (gender, age) and clinical characteristics (chief complaint, core Utstein-style data, etc.).[51] Call times are automatically registered in a separate database that is linked to the patient-care information collected. Resuscitation outcome data were transferred from the discharge hospitals to the regional EMS agency.

Power and statistical analysis

With a survival rate to hospital discharge of 15%, including 4100 patients would generate more than 90% power to detect a difference of 4% in survival between groups, using a two-tailed alpha

of 5% (assuming that 75% of the variability is explained by other factors included in the model).[52]

The effect size of cohort differences for demographic, clinical and time variables were assessed using Cohen's d for continuous variable and Cramér's v for categorical variables. For Cohen's d, it was considered that an effect size of 0.2 was small, 0.5 moderate and 0.8 large.[161] For Cramér's v, it was considered that an effect size of 0.1 was small, 0.3 moderate and 0.5 large.[162] A Pearson's chi-squared test was first used to evaluate the difference in survival to discharge between both cohorts. The primary objective analysis consisted of a multivariable logistic regression model, using pertinent demographic (age, gender, initial call time moment) and clinical variables (initial rhythm, witnessed arrest, bystander cardiopulmonary resuscitation [CPR], presence of first responders, presence of advanced care paramedics, time from call to hospital arrival, prehospital intubation, presence of a prehospital ROSC). The predictive power of the model was evaluated using a Nagelkerke R^2. Interaction between the capabilities of the destination hospital (PCI-capable vs non–PCI-capable) and either of the two predefined clinical variables of interest (presence or not of a prehospital ROSC, shockable vs non-shockable initial rhythm) was tested using the same multivariable logistic regression model. If one of these interactions was significant, it was planned to perform separate multivariable logistic regression analyses for each pertinent subgroup. Finally, if a positive association was observed between survival to discharge and direct transport to a PCI-capable center, calculation of the additional acceptable prehospital delay of transport to such a center over the nearest center was to be performed using the adjusted odds ratio obtained in the main model and the following algebra formula, derived from the mathematical properties of logistic regressions $(Adjusted\ odds\ ratio\ [Delay\ of\ one\ additional\ minute\ from\ call\ to\ hospital\ arrival])^x *$

$(Adjusted\ odds\ ratio\ [Being\ transported\ to\ a\ PCI-capable\ hospital]) = 1$.[163] Given the nature of this analysis, it is not possible to provide a confidence interval for its result.

Continuous variables are presented as means with standard deviations (SD) and categorical variables are presented as frequencies with percentages. Odds ratios (OR) and adjusted OR (AOR) are presented with their 95% confidence interval (CI). Alpha levels were fixed at 0.05. Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA).

Results

Cohort description

During the study period (April 1st, 2010 to December 31st, 2015), 7134 patients met the inclusion criteria. Prehospital termination-of-resuscitation rules were applied to a total of 2212 (31%) patients who were not ultimately transported to a hospital and who were therefore excluded from the analysis. Among the remaining 4922 patients, 2389 (48%) were transported to a PCI-capable hospital and 2533 (52%) were transported to a non-PCI-capable hospital. Their demographic and clinical characteristics are presented in Table 1. Notably, there were more patients having experienced prehospital ROSC, more patients with an initial shockable rhythm, more patients treated by advanced care paramedics and less patients treated by first responders in the cohort of patients transported to PCI-capable hospitals. However, the effect sizes of these differences were only small to moderate.

Main results

Survival to hospital discharge was higher in the cohort of patients transported directly to PCI-capable hospitals (479 [20.1%] vs 282 patients [11.1%], p<0.001). This association persisted in the multivariable analysis (AOR=1.60 [95% CI 1.25-2.05], p<0.001) (Nagelkerke R^2=0.58) (Table 2). There was an interaction between the capabilities of the destination hospital (PCI-capable vs non–

PCI-capable) and prehospital ROSC (p=0.023) in terms of survival to discharge, which was not the case with the initial rhythm (shockable vs non-shockable) (p=0.095).

Therefore, separate regression models for the effect of the destination hospital on survival to hospital discharge in accordance to the presence of absence of prehospital ROSC were generated. The observed association between being transported to a PCI-capable center and survival to discharge was stronger in patients not having experienced prehospital ROSC (282 patients [2.8%] vs 19 [1.0%], p<0.001; AOR=3.24 [95% CI 1.71-6.14], p<0.001) (Nagelkerke R^2=0.13) than for those who experienced prehospital ROSC (441 patients [43.2%] vs 263 [39.5%], p=0.13; AOR=1.43 [95% CI 1.10-1.87], p=0.009) (Nagelkerke R^2=0.37) (Tables 3 and 4). There was no significant interaction between the initial rhythm and both associations (p=0.35 and p=0.14, respectively).

Using the main model, it was calculated that an increase in the delay from call to hospital arrival of 14.0 minutes was sufficient to offset the potential benefit of being transported to a PCI-capable center.

Discussion

It was demonstrated in this analysis of a large, unselected OHCA population that direct transport to a PCI-capable center was associated with a significant improvement in survival to hospital discharge. Additionally, it was observed that patients without prehospital ROSC appear to derive even greater survival benefit from direct transport to a PCI-capable hospital. The present analysis also serves as a benchmark for the acceptable time delay in prehospital transport to a PCI-capable center before transport to the nearest non–PCI-capable hospital would be preferred.

The main finding that direct transport to a PCI-capable center is associated with a survival benefit in patients suffering from OHCA is supported by prior work, and is likely at least partially explained by the fact that the most frequent cause of non-traumatic OHCA is myocardial ischemia, which

benefit from timely revascularisation.[50, 119, 160, 164-169] On the other hand, one study performed in France including only patients having experienced prehospital ROSC did not observe such an association[170]. This might be explained by the fact that medical staff provide the on-site resuscitation and might be able to diagnose and identify the adequate hospital destination for patients having experienced ROSC. Also, given the advanced prehospital care provided in France, it is possible some patients received thrombolysis on-site, which would have limited the benefit of being transported to a PCI-capable hospital. Since there was a trend toward better outcomes in bigger hospitals, it is also possible that they simply lacked the power to detect such an association. Also, these PCI-capable hospitals may benefit from acute care teams with greater experience in managing unstable patient and access to advance interventions such as hemodynamic support devices and cardiovascular surgery.[50, 125]

This study also observes that patients without prehospital ROSC benefited even more from a transport to a PCI-capable centers than those with prehospital ROSC.[164] This might be interpreted as analogous to a dose-response effect, whereby the patients with the poorest prognosis benefit most from the advanced care options available at PCI-capable centers. On the contrary, whether patients present with a shockable initial rhythm or not did not influence the association of interest. It may be hypothesized that patients with a shockable rhythm have a high likelihood of underlying significant coronary obstruction that could benefit from timely PCI. However, not presenting with such a rhythm may not adequately stratify patients, as degeneration of a shockable rhythm into a non-shockable one may occur prior to ECG recording.[159] Moreover, those without an initial shockable rhythm might have advanced underlying non-coronary disease that may also benefit from the expertise available at PCI-capable centers, such as highly experienced and higher-volume intensive care, respirology, nephrology, interventional radiology and non-cardiac surgery.

In the present study, it was observed that longer prehospital delays before hospital arrival were associated with worse outcomes following OHCA. This is contrary to the results concluded in earlier studies, where the authors concluded that the transport distance to the destination hospital was not associated with survival in patients suffering from OHCA.[171, 172] Geri et al also performed a meta-analysis which showed no association between prehospital transport time and survival.[173] Using the total time before hospital arrival may better reflect the overall complexity of the prehospital resuscitation and therefore mortality risk than transport delay alone. Indeed, it is possible that a longer total delay to hospital might be associated to worse outcome, whereas transport time or distance might not be sensitive enough to detect this association. Kragholm et al also observed no association between the bypass time to a PCI-capable centers and the outcome of patients.[169] However, they only included patients who had experienced prehospital ROSC and who are inherently more stable than patients still in cardiac arrest and who might not suffer as much from prolonged transport.

The present analysis is the first to determine the additional prehospital delay for direct transport to a PCI-capable center that would result in an equipoise between such a strategy and one of transport to the nearest hospital (14 minutes in the overall cohort). In another study, it was estimated that transporting patients with centers able to perform extracorporeal resuscitation would potentially prolong the prehospital transport time by an average of up to three minutes.[115] In Montreal's setting, five hospitals are able to perform both extracorporeal resuscitation and are also PCI-capable and two more are only PCI-capable. Therefore, the prehospital redirection delay to PCI-capable centers should be even lower. In that particular setting, direct transport to PCI-capable centers would be beneficial based on this study's findings for most if not all OHCA cases. In addition, while it was thought that the quality of the resuscitation was worse during transport than on-site, a recent study concluded that the CPR

metrics were similar in both two phases.[48] While there is a general agreement that a regionalized approach to the treatment of OHCA could be beneficial and jurisdictions that tried such an approach appear to have improved outcomes, the optimal rules and targets of such a system have yet to be determined.[6, 174, 175] The present results suggest that it may be advantageous to redirect these patients to PCI-capable centers if the expected delay is of less than 14 minutes. In an urban setting, where hospitals tend to be at a short distance from one another, redirection delays are expected to be lower than this threshold. Depending on the jurisdiction, if appropriate, patients could be redirected using the same destination protocols already in place for patients suffering from STEMI. Outside of urban settings, when redirection delays would be expected to result in an additional prehospital delay greater than 14 minutes, one would not anticipate an advantage to bypassing non–PCI-capable hospitals based on the present analysis and it might be beneficial for patients to be transported to the nearest hospital for initial resuscitation, and then rapidly transferred to a PCI-capable center for definitive management. These two strategies should be tested in prospective trials.

Limitations

The present study is observational in nature and, as such, carries a risk of bias and unaccounted-for confounding factors. For example, all patient data was derived from information available in the EMS patient record. The final medical diagnosis at hospital discharge, the status of whether patients underwent PCI or not and the neurological outcomes were not available in this analysis. In terms of the prehospital delay analysis, a few assumptions were necessary, including that the decrement relationship between mortality and prehospital delay was both linear, and similar across all prehospital phases, which may not be the case. However, linearity was adequate according to a Box-Tidwell transformation results. Also, it was not possible to calculate a confidence interval for this analysis. Since patients in this dataset were transported to the closest

hospital, it is possible that geographic difference in the *a priori* mortality risk of OHCA patients exist that could not be identified or addressed in the analysis. However, given this study's analyses were adjusted for the Utstein data elements which have been shown to predict most of the survival variability following OHCA, the relatively high number (seven and 13) of individual centers in each group, the broad geographic and demographic distribution of both PCI-capable and non–PCI-capable hospitals, the only very small to moderate effect sizes observed when comparing both cohorts, it is highly unlikely that a covariable that was not adjusted for would have significantly affected the main analysis.[52, 161, 162] Additionally, given the high degree of collinearity between PCI-capability and other characteristics, such as OHCA patient volume, university affiliation status or extracorporeal resuscitation capability, it was not possible to assess for the impact of such variables in the present study. Given the fact it was not possible to perform such an analysis, we opted to use the PCI-capable characteristic because it seemed it was the hospital characteristic with the strongest influence on outcome.[156, 167, 176] Finally, although a large and comprehensive multicenter dataset of OHCA, this study included a single metropolitan region. As such, these findings may not be generalizable to other urban regions, notably owing to the differences in geospatial organization of advanced care services, urban geography, prehospital organization and treatment standards and OHCA epidemiology. Moreover, whether patients who do not bypass the nearest hospital in non-urban settings would fare better than patients who do is not addressed by the present analysis and should be the subject of further research.

Conclusions

Direct transportation to a PCI-capable center is associated with a significant improvement in survival to discharge among patients suffering from OHCA, particularly in the absence of prehospital ROSC. If the delay is expected to be of less than 14 minutes, it could be reasonable

to redirect OHCA patients to PCI-capable hospitals. This hypothesis should be verified in a prospective trial.

Conflict of interest statement

Dr. André Denault is part of a speakers bureau for Edwards, Masimo and CAE Healthcare. All other authors have no conflict of interest to declare.

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Tables

Tableau 9 : Table 1 Demographic and clinical characteristics of the included patients

Variables	PCI-capable hospital (n=2389)	Non–PCI-capable hospital (n=2533)	Effect size
Age, years	67.1 (16.4)	67.4 (16.8)	0.014
Gender, men	1629 (68.2)	1608 (63.5)	0.050
Initial call between 8 am and 4 pm Initial call between 4 pm and 12 am Initial call between 12 am and 8 am	1021 (42.9) 846 (35.5) 515 (21.6)	1100 (43.4) 830 (32.8) 603 (23.8)	0.033
Initial rhythm, shockable rhythm	990 (45.0)	751 (32.2)	0.13
Unwitnessed arrest Bystander witnessed First responder or paramedic witnessed	658 (27.5) 1342 (56.2) 389 (16.3)	909 (35.9) 1249 (49.3) 375 (14.8)	0.090
No bystander CPR Bystander CPR First responder or paramedic witnessed	1287 (54.3) 696 (29.3) 389 (16.4)	1522 (60.3) 626 (24.8) 375 (14.9)	0.062
Presence of first responders	1147 (48.0)	1706 (67.4)	0.20
Presence of advanced care paramedics	752 (31.5)	477 (18.8)	0.15
Delay from call to hospital arrival, minutes	45.0 (14.6)	41.6 (13.8)	0.24
Intubation using an esophageal tracheal airway	1775 (74.3)	1978 (78.1)	0.045
Prehospital ROSC	1021 (42.7)	666 (26.3)	0.17

PCI : Percutaneous coronary intervention; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; Values are presented as mean (standard deviation) or N (%) and effect size as Cohen's d or Cramér's v, as appropriate

Tableau 10 : Table 2 Univariate and multivariable logistic regression model evaluating the association between the capabilities of the receiving hospital and survival to discharge (n=4922)

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Being transported to a PCI-capable hospital	2.00 (1.71-2.35)	< 0.001	1.60 (1.25-2.05)	< 0.001
Age (per additional year)	0.97 (0.97-0.98)	< 0.001	0.97 (0.97-0.98)	< 0.001
Gender, male sex	1.26 (1.07-1.49)	0.007	0.82 (0.64-1.06)	0.13
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	0.98 (0.82-1.16)	0.80	1.16 (0.90-1.51)	0.25
Initial call between 12 am and 8 am	0.76 (0.61-0.93)	0.009	1.37 (1.00-1.87)	0.051
Initial rhythm, shockable rhythm	9.13 (7.52-11.09)	< 0.001	3.72 (2.88-4.81)	< 0.001
Unwitnessed arrest	*	-	*	-
Bystander witnessed	2.72 (2.20-3.37)	< 0.001	1.37 (1.01-1.85)	0.040
First responder or paramedic witnessed	3.60 (2.79-4.63)	< 0.001	2.13 (1.42-3.20)	< 0.001
No bystander CPR	*	-	*	-
Bystander CPR	1.82 (1.52-2.17)	< 0.001	0.98 (0.76-1.27)	0.88
First responder or paramedic witnessed	2.21 (1.80-2.71)	< 0.001	†	†
Presence of first responders	0.92 (0.79-1.08)	0.30	1.38 (1.08-1.76)	0.010
Presence of advanced care paramedics	1.29 (1.09-1.53)	0.004	0.77 (0.57-1.03)	0.075
Delay from call to hospital arrival (per additional minute)	0.98 (0.97-0.98)	< 0.001	0.97 (0.96-0.98)	< 0.001
Intubation using an esophageal tracheal airway	0.13 (0.11-0.15)	< 0.001	0.37 (0.29-0.47)	< 0.001
Prehospital ROSC	39.9 (30.2-52.8)	< 0.001	26.35 (18.75-37.03)	< 0.001

OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; PCI: Percutaneous coronary intervention; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation
* Reference category † Not calculated due to collinearity

Tableau 11 : Table 3 Univariate and multivariable logistic regression model evaluating the association between the capabilities of the receiving hospital and survival to discharge including only patients not having experienced prehospital ROSC (n=3235)

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Being transported to a PCI-capable hospital	2.78 (1.60-4.84)	< 0.001	3.24 (1.71-6.14)	< 0.001
Age (1 year older)	0.97 (0.96-0.99)	< 0.001	0.97 (0.95-0.99)	< 0.001
Gender, male sex	0.86 (0.50-1.47)	0.57	0.72 (0.37-1.42)	0.34
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	0.96 (0.52-1.77)	0.88	0.89 (0.43-1.87)	0.77
Initial call between 12 am and 8 am	1.04 (0.54-1.99)	0.91	1.49 (0.71-3.11)	0.29
Initial rhythm, shockable rhythm	3.06 (1.76-5.30)	< 0.001	3.87 (2.03-7.37)	< 0.001
Unwitnessed arrest	*	-	*	-
Bystander witnessed	1.60 (0.84-3.03)	0.15	1.52 (0.72-3.21)	0.27
First responder or paramedic witnessed	2.64 (1.25-5.58)	0.011	3.58 (1.42-9.06)	0.007
No bystander CPR	*	-	*	-
Bystander CPR	0.77 (0.38-1.57)	0.47	0.57 (0.25-1.30)	0.18
First responder or paramedic witnessed	1.83 (0.97-3.45)	0.061	†	†
Presence of first responders	1.01 (0.59-1.72)	0.97	2.03 (1.06-3.91)	0.033
Presence of advanced care paramedics	1.11 (0.54-2.27)	0.79	1.15 (0.46-2.87)	0.77
Delay from call to hospital arrival (1 more minute)	0.99 (0.97-1.02)	0.54	0.97 (0.94-1.00)	0.056
Intubation using an esophageal tracheal airway	0.46 (0.25-0.84)	0.012	0.68 (0.30-1.52)	0.34

OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; PCI: Percutaneous cutaneous intervention; CPR: Cardiopulmonary resuscitation

* Reference category † Not calculated due to collinearity

Tableau 12 : Table 4 Univariate and multivariable logistic regression model evaluating the association between the capabilities of the receiving hospital and survival to discharge including only patients having experienced prehospital ROSC (n=1687)

Variables	OR (95% CI)	P value	AOR (95% CI)	P value
Being transported to a PCI-capable hospital	1.17 (0.96-1.42)	0.13	1.43 (1.10-1.87)	0.009
Age (1 year older)	0.97 (0.97-0.98)	< 0.001	0.97 (0.97-0.98)	< 0.001
Gender, male sex	1.31 (1.06-1.61)	0.012	0.86 (0.65-1.13)	0.27
Initial call between 8 am and 4 pm	*	-	*	-
Initial call between 4 pm and 12 am	0.95 (0.77-1.18)	0.66	1.21 (0.92-1.60)	0.18
Initial call between 12 am and 8 am	1.02 (0.78-1.34)	0.88	1.33 (0.94-1.88)	0.11
Initial rhythm, shockable rhythm	5.82 (4.59-7.36)	< 0.001	3.68 (2.78-4.87)	< 0.001
Unwitnessed arrest	*	-	*	-
Bystander witnessed	1.92 (1.48-2.48)	< 0.001	1.32 (0.95-1.85)	0.10
First responder or paramedic witnessed	2.84 (2.06-3.92)	< 0.001	1.90 (1.21-2.98)	0.005
No bystander CPR	*	-	*	-
Bystander CPR	1.49 (1.20-1.86)	< 0.001	1.04 (0.79-1.37)	0.80
First responder or paramedic witnessed	2.04 (1.56-2.67)	< 0.001	†	†
Presence of first responders	0.84 (0.69-1.02)	0.083	1.29 (0.99-1.68)	0.062
Presence of advanced care paramedics	0.35 (0.28-0.43)	< 0.001	0.76 (0.56-1.03)	0.076
Delay from call to hospital arrival (1 more minute)	0.96 (0.95-0.96)	< 0.001	0.97 (0.96-0.98)	< 0.001
Intubation using an esophageal tracheal airway	0.23 (0.19-0.28)	< 0.001	0.35 (0.27-0.45)	< 0.001

OR: Odds ratio; CI: Confidence interval; AOR: Adjusted odds ratio; PCI: Percutaneous cutaneous intervention; CPR: Cardiopulmonary resuscitation

* Reference category † Not calculated due to collinearity

3.1.3. Volet 1 – Article 3 – Potential impact of a prehospital redirection system for refractory cardiac arrest

3.1.3.1. Préface

Cette étude a été réalisée en collaboration avec 17 autres chercheurs. J'ai réalisé plus de 80% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Luc de Montigny, Dave Ross, Eli Segal, Sylvie Cossette, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. La collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Luc de Montigny et Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette et Massimiliano Iseppon. André Denault, Éric Notebaert, Luc de Montigny, Dave Ross, Luc Londei-Leduc, Yoan Lamarche, Judy Morris, Éric Piette, Raoul Daoust, Jean-Marc Chauny, Eli Segal, Dominic Lafrance, Catalina Sokoloff, Yiorgos Alexandros Cavayas et Jean Paquet ont également contribué à sa révision. Cette étude a été publiée dans le journal Resuscitation en 2017 (Facteur d'impact en 2017 : 5,863).

3.1.3.2. Volet 1 – Article 3

Title: Potential Impact of a Prehospital Redirection System for Refractory Cardiac Arrest

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Conflict of interest: Dr. André Denault is part of a speakers bureau for Masimo, Edwards and CAE Healthcare. We have no other conflicts of interest to declare.

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Abstract

Aim: A change in prehospital redirection practice could potentially increase the proportion of E-CPR eligible patients with out-of-hospital cardiac arrest (OHCA) transported to extracorporeal cardiopulmonary resuscitation (E-CPR) capable centers. The objective of this study was to quantify this potential increase of E-CPR candidates transported to E-CPR capable centers.

Methods: Adults with non-traumatic OHCA refractory to 15 minutes of resuscitation were selected from a registry of adult OHCA collected between 2010 and 2015 in Montreal, Canada. Using this cohort, three simulation scenarios allowing prehospital redirection to E-CPR centers were created. Stringent eligibility criteria for E-CPR and redirection for E-CPR (e.g. age < 60 years old, initial shockable rhythm) were used in the first scenario, intermediate eligibility criteria (e.g. age < 65 years old, at least one shock given) in the second scenario and inclusive eligibility criteria (e.g. age < 70 years old, initial rhythm ≠ asystole) in the third scenario. All three scenarios were contrasted with equivalent scenarios in which patients were transported to the closest hospital. Proportions were compared using McNemar's test.

Results: The proportion of E-CPR eligible patients transported to E-CPR capable centers increased in each scenario (stringent criteria: 48 [24.5%] vs 155 patients [79.1%], p<0.001; intermediate criteria: 81 [29.6%] vs 262 patients [95.6%], p<0.001; inclusive criteria: 238 [23.9%] vs 981 patients [98.5%], p<0.001).

Conclusions: A prehospital redirection system could significantly increase the number of patients with refractory OHCA transported to E-CPR capable centers, thus increasing their access to this potentially life-saving procedure, provided allocated resources are planned accordingly.

Keywords

Out of hospital cardiac arrest (OHCA)

Prehospital redirection

Cardiopulmonary resuscitation (CPR)

Extracorporeal cardiopulmonary resuscitation (E-CPR)

Emergency medical services (EMS)

Introduction

Over 300 000 people are victims of out-of-hospital cardiac arrest (OHCA) each year in the United States.[1] Despite advances in medical care, survival amongst these patients remains low, with only 5-10% surviving to discharge.[1, 140] Extracorporeal cardiopulmonary resuscitation (E-CPR), which incorporates an extracorporeal cardiopulmonary bypass circuit to obtain cardiopulmonary support during resuscitation, has recently been proposed as an effective complement to traditional resuscitation.[21, 28, 33, 35, 39, 40, 142] Because of the expertise and physical, human and economic resources required for E-CPR, its availability is often limited to dedicated, specialized centers. In addition, determining patient eligibility criteria is critical, judging by the variation observed in survival benefits (less than 2% to over 50%) seen in patient groups.[21, 29]

Changes in the organization of regional prehospital systems has successfully decreased morbidity and mortality in patients suffering from ST-segment elevation myocardial infarction and severe trauma. This is partly because of direct transport to dedicated centers, bypassing primary or secondary care centers when necessary, thereby reducing the total time to definitive care.[157, 158, 177, 178] Since refractory OHCA is also a time-sensitive condition with a low survival rate, it is plausible that, for appropriately selected patients, a similar approach could be of benefit.[29, 34, 43] Indeed, bypassing a closer hospital in favor of an advanced-care center where E-CPR is available could improve survival if the delay incurred is short, which is the case in urban settings where hospitals are clustered in the same area.

Estimating the potential effect of such a system could help allocate resources accordingly. The main objective of this study was to quantify the potential increase of the proportion of E-CPR candidates transported directly to E-CPR capable centers by simulating prehospital redirection scenarios with varying criteria. The secondary objective was to evaluate the potential effect of this redirection on the hospital transport time for E-CPR candidates.

Methods

Design and setting

This simulation study used a registry of OHCA. The data available were used to simulate scenarios in which redirection to an E-CPR capable center was guided by three different sets of inclusion criteria. These scenarios were compared to scenarios with equivalent inclusion criteria, but for which there was no prehospital redirection (i.e. transport to the closest hospital), which reflects current practice. This study was carried out in association with the Hôpital du Sacré-Coeur de Montréal, the local emergency medical services (EMS) agency (Urgences-santé) and the Université de Montréal. It was approved by the Institutional Review Board of the Hôpital du Sacré-Coeur de Montréal and conducted in accordance with the Declaration of Helsinki.

This study used data from the region of Montreal, Canada. A single public EMS agency coordinates the prehospital care for the two million citizens in the serviced area. First responders and paramedics treat patients suffering from OHCA by following resuscitation protocols based on the American Heart Association guidelines.[44-46] Patients suffering from OHCA are normally transported to the closest of the 20 local hospitals, five of which have the necessary resources and expertise to perform E-CPR.

Study population

All patients aged 18 years and older treated for an OHCA from April 2010 until December 2015 were screened for inclusion. Patients were excluded from the initial registry if their death was considered obvious according to EMS criteria (e.g. decapitation, advanced putrefaction, etc.), if the cause of the OHCA was traumatic or in cases where 'do-not-resuscitate' directives were known.[44] In addition, patients who experienced ROSC within 15 minutes of either first responders' or paramedics' arrival were excluded because these patients are generally not considered for E-CPR.

Study groups

In half of the proposed scenarios, it was considered that E-CPR candidates would be transported to the closest hospital (current practice; no prehospital redirection). In the other half, transport to the closest E-CPR capable center was simulated (hypothetical prehospital practice; with prehospital redirection) (Table 1).

Since there is no consensus on which criteria should be used to determine patient eligibility for E-CPR, clinical variables (age, initial rhythm, whether or not a shock was delivered, time to initiation of cardiac massage, total time to E-CPR initiation and hospital transport time) that have previously been used to select patients for E-CPR or that have been associated with survival following E-CPR were used.[21, 39, 40, 43, 117] In order to increase the external validity of the study, these variables were used to construct three sets of varying clinical criteria to select E-CPR candidates: one with stringent eligibility criteria, one with intermediate eligibility criteria and one with inclusive eligibility criteria (Table 1).

Outcome measurements

For the primary objective, the outcome measure was the proportion of E-CPR candidates being transported to an E-CPR capable center using the stringent eligibility criteria. For the secondary objective, the outcome measure was the hospital transport time (total transport time from scene to hospital in minutes).

Data collection and management

According to provincial law, OHCA patient data are entered by paramedics on a 'run-sheet' following every call. This information is then entered into a database that includes demographic (gender, age) and clinical characteristics (chief complaint, core Utstein-style data, etc.).[51] Call times are automatically registered in a separate database that is linked to the patient-care information database. When the data on hospital transport time was not available in the

database (e.g. on-site termination of resuscitation), it was estimated using an online geospatial service (Google Distance API, Mountain view, CA, USA).

Since the time interval from the OHCA to E-CPR initiation is of critical importance, on-site resuscitation was limited to 15 minutes.[34, 43, 68] Site extraction time was estimated at five minutes and the time to E-CPR initiation in the emergency department at 20 minutes.[21] Therefore, the time interval variable (total time before E-CPR initiation) was calculated by summing the following five procedural durations: the delay before first responders' or paramedics' arrival, the time of on-site resuscitation (15 minutes), the estimated site extraction time (5 minutes), the hospital transport time and the estimated time to E-CPR initiation in the emergency department (20 minutes).

2.6. Power and statistical analysis

The entire available population in the database was used in this study's analysis. Since discordance using McNemar's test was expected to be unidirectional, including at least 1000 patients would grant a power of 99% if using a unilateral alpha of 2.5%, to detect a relative increase of 20% in the proportion of E-CPR candidates transported to E-CPR capable centers (from 4% without prehospital redirection to 5% with prehospital redirection).[37]

Continuous variables are presented as means with standard deviations (SD) and categorical variables are presented as frequencies with percentages. To adjust the estimated hospital transport times, patients with recorded data in the database were used. An estimated transport time was calculated and compared to their actual transportation time using a dependent test and an intraclass correlation coefficient (ICC) with its 95% confidence interval (CI). A ratio of these transport times (actual and estimated) was also calculated. The estimated transport time was

subsequently adjusted using this ratio, and a dependent t-test and an ICC were then recalculated to validate this method.

For the primary objective, the proportions of E-CPR candidates transported E-CPR capable centers were compared using McNemar's test. Three sensitivity analyses were also performed: one in which patients that experienced prehospital ROSC were excluded, and two in which the estimated time to E-CPR initiation in the emergency department were increased by five and 10 minutes (estimates increased to 25 and 30 minutes respectively). For the secondary objective, hospital transport times for every E-CPR candidates in each pair of scenarios were compared using Student's t-tests. The estimated hospital transport times of patients that would have been redirected to an E-CPR capable center were then compared to their actual recorded transport time to the closest hospital using dependent t-tests.

Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA). Alpha levels were fixed at 0.025 for McNemar's tests and at 0.05 for all other analyses.

Results

Patients demographic, clinical characteristics and outcomes

During the study period (April 1st 2010 to December 31st 2015), 7134 patients met the inclusion criteria. A total of 836 (12%) patients experienced ROSC within 15 minutes of either first responders' or paramedics' arrival and were excluded from the present study. The demographic and clinical characteristics of the 6298 included patients, as well as the treatments they received on-site, are presented in Table 2. Amongst the included patients, 855 (13.6%) experienced ROSC after 15 minutes of on-site resuscitation and 297 (4.7%) survived to discharge. According to their baseline characteristics (age, initial rhythm, whether or not a shock was delivered and time to initiation of cardiac massage), 196 (3.1%) patients would have been potential E-CPR candidates

using the stringent set of clinical criteria, 274 (4.4%) using the intermediate set and 996 (15.8%) using the inclusive set (Figure 1).

Estimated transport time adjustment

A total of 1067 (16.9%) patients were actually transported to an E-CPR capable center, providing data on real time transportation. For these patients, the estimated hospital transport times were on average two minutes longer than the actual hospital transport times (10 [SD 5] vs 8 minutes [SD 6], p<0.001; ICC=0.45 [95% CI 0.39-0.49]) resulting in a ratio of real vs estimated time of 1.3 times longer. After adjustment using this ratio, there was no significant difference between the estimated hospital transport times and actual transport times (8 [SD 4] vs 8 minutes [SD 6], p=1.00; ICC (0.48 [95% CI 0.43-0.53]). For the main analysis, the actual transport time were used when available. Adjusted estimated transport times were used if actual transport times were unavailable.

Proportion of E-CPR candidates being transported to E-CPR capable centers

Prehospital redirection significantly increased the proportion of E-CPR eligible patients transported to E-CPR capable centers in each scenario, regardless of criteria stringency (stringent criteria: 48 [24.5%] vs 155 patients [79.1%], p<0.001; intermediate criteria: 81 [29.6%] vs 262 patients [95.6%], p<0.001; inclusive criteria: 238 [23.9%] vs 981 patients [98.5%], p<0.001) (Table 3). The results were not influenced by the exclusion of patients who experienced prehospital ROSC from the analyses, with an increase in the proportion of E-CPR eligible patients transported to E-CPR capable centers still observed in each scenario (stringent criteria: 19 [21.1%] % vs 70 patients [77.8%], p<0.001; intermediate criteria: 81 [29.6%] vs 262 patients [95.6%], p<0.001; inclusive criteria: 238 [23.9%] vs 981 patients [98.5%], p<0.001). Similarly, extending the time estimate for E-CPR initiation in the emergency department (from 20 to 25 and 30 minutes) also did not influence the results (estimate of 25 minutes: stringent criteria: 37 [18.9%] vs 108 patients

[55.1%], p<0.001; intermediate criteria: 75 [27.4%] vs 254 patients [92.7%], p<0.001; inclusive criteria: 228 [22.9%] vs 971 patients [97.5%], p<0.001; estimate of 30 minutes: stringent criteria: 22 [11.1%] vs 53 patients [27.0%], p<0.001, intermediate criteria: 75 [27.4%] vs 254 patients [92.7%], p<0.001; inclusive criteria: 228 [22.9%] vs 971 patients [97.5%], p<0.001).

Hospital transport time

Prehospital redirection did not significantly increase average hospital transport time of eligible candidates to E-CPR capable centers in the first two scenarios of redirection (stringent criteria: 8 [SD 5] vs 9 minutes [SD 4], p=0.21; intermediate criteria 8 [SD 6] vs 10 minutes [SD 4], p=0.073). However, hospital transport times of eligible candidates was significantly increased in the scenario with inclusive criteria (inclusive criteria: 8 [SD 6] vs 10 minutes [SD 4], p<0.001) (Table 4).

In the sample of E-CPR candidates, a total of 107 (54.6%), 181 (66.1%) and 743 (74.6%) E-CPR candidates were redirected to an E-CPR capable center in each of the stringent, intermediate and inclusive criteria scenario, respectively (patients that did not need redirection because the E-CPR capable center was the closest hospital were excluded from this analysis). In the scenario allowing redirection using stringent criteria, prehospital redirection did not significantly affect hospital transport times (8 [SD 7] vs 9 minutes [SD 3], p=0.12). However, hospital transport times of redirected patients were significantly increased in the intermediate criteria and the inclusive criteria scenarios (7 [SD 5] vs 10 minutes [SD 3], p<0.001 and 7 [SD 5] vs 10 minutes [SD 4] vs, p<0.001, respectively) (Table 5).

Discussion

The main objective of this study was to evaluate the potential impact of a prehospital redirection system for refractory OHCA on the proportion of E-CPR candidates transported to E-CPR capable centers using three sets of eligibility criteria. Prehospital redirection increased

significantly the proportions of patients in refractory OHCA transported to E-CPR capable centers, regardless of the stringency of the clinical inclusion criteria. These results were replicated with the exclusion of patients that experienced prehospital ROSC and when adjusting the estimated time to E-CPR initiation in the emergency department. Hospital transport times of E-CPR candidates redirected to E-CPR capable centers were longer when the inclusive criteria for redirection were used. The present study adds to the literature by demonstrating the potential added benefit of a prehospital redirection system towards optimizing E-CPR access and may guide the planning of resources required to compensate for additional patient flow in accordance to this potential benefit. This is also the first study to provide an estimate on the impact of such a system in terms of delay to hospital arrival for the redirected E-CPR candidates.

In each scenario of redirection, prehospital redirection allowed the majority of E-CPR candidates in accordance to their baseline characteristics (age, initial rhythm, whether or not a shock was delivered and time to initiation of cardiac massage) to be transported to E-CPR capable centers. Indeed, in an urban setting where multiple hospitals are clustered and relatively close to each other, the prolongation of the travel time associated to redirecting an eligible patient to an E-CPR capable center does not seem long enough to affect his E-CPR eligibility. Implanting such a prehospital structure would considerably increase the volume of patients who could benefit from E-CPR in designated centers. In contrast to trauma or ST-segment elevation myocardial infarction, where most patients are ultimately transferred to designated centers for treatment, most OHCA patients who are not initially transported to E-CPR capable centers will never be transferred because of the mortality associated with this condition.[1, 179, 180] In addition, the magnitude of this effect seemed to be dependent on the set of clinical criteria used to determine E-CPR eligibility, with greater increase observed with the use of more inclusive eligibility criteria.

The proportions of OHCA patients who would be eligible for E-CPR under three sets of eligibility criteria were also quantified. Using one different set of eligibility criteria each, Grunau et al. (< 60 years old, witnessed arrest, bystander CPR or time to EMS arrival < 5 min, absence of malignancy) and Poppe et al. (<75 years old, shockable rhythm, witnessed arrest with bystander CPR) had previously estimated the proportions of E-CPR candidates to be of 3% and 6%, respectively.[37, 181] All these results reflect the fact that using more or less inclusive eligibility criteria is going to affect the proportions of patients suffering from OHCA eligible for E-CPR. Given the theoretically infinite possible sets of eligibility criteria, we encourage clinicians and administrators to perform local case reviews to estimate their future caseload, weighting the odds of survival of the included patients and the available resources that could be allotted for E-CPR.[37, 181]

In our simulations, prehospital redirection did not result in a clinically significant increase in the hospital transport time of E-CPR candidates transported to E-CPR capable centers, notwithstanding a trend towards an increase or a statistically significant increase in the hospital transport time in these analyses. Long hospital transport times for patients in OHCA are considered undesirable owing to the difficulty of maintaining high quality CPR while inside a moving ambulance.[47] However, adequate CPR metrics recently have been shown to be achievable during transport using standard cardiopulmonary resuscitation.[48] Given that the prolongation in hospital transport time for redirected E-CPR candidates is rather minimal (1-3 minutes), it could be proposed that the added benefit of E-CPR in increasing survival would offset this increased delay to in-hospital care.[21, 182] As most E-CPR capable centers are academic hospitals with cardiovascular intensive care units, catheterization laboratories and cardiac surgery departments, redirected patients could also benefit from the specialized care available in these

centers.[156, 183] However, this hypothesis remains unproven and should be tested in future studies.

Limitations

The main limitation of this study is its observational and scenario-based nature. While a prospective experimental study would have been preferable, this study needed to be performed first to prepare for future ethical and logistical challenges. This study was also limited by the information provided by the EMS data. Consequently, estimates had to be used for one variable (transport time) and accounting for other significant variables, such as patients' comorbid conditions, was not possible. This study also simulates best practices time intervals for on-scene, extraction and E-CPR initiation in the emergency department, which may not be achievable for all patients in a real-world setting. Therefore, it is possible that the proportions of E-CPR candidates in each scenario was overestimated. This should not have affected the main analysis given the probable uniform distribution of this bias across all scenarios. Finally, a single large metropolitan region covered by a single EMS provider was included. Thus, the results presented may not be generalizable to other regions, notably because of differences in hospital dispersal, geography and OHCA epidemiology.

Conclusion

In an urban setting, a prehospital redirection system could potentially increase the proportion of patients with refractory OHCA who would have access to E-CPR, without significantly increasing in their hospital transport time. Future studies evaluating the benefits of rapid hospital redirection for E-CPR candidates are necessary and should be performed given this novel therapy's potential beneficial effect on survival. Resources required to carry out these studies must be planned accordingly based on the eligibility criteria selected.

Conflict of interest statement

Dr. André Denault is part of a speakers bureau for Edwards, Masimo and CAE Healthcare. We have no other conflicts of interest to declare.

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This project received funding from the 'Département de médecine familiale et de médecine d'urgence de l'Université de Montréal' and the 'Fonds des Urgentistes de l'Hôpital du Sacré-Coeur de Montréal'. Dr. André Denault is supported by the Richard I. Kaufman Endowment fund in Anesthesia and Critical Care and the Montreal Heart Foundation.

Tables

Tableau 13 : Table 1 Criteria used to select E-CPR candidates in simulation scenarios

	Stringent criteria		Intermediate criteria		Inclusive criteria	
	Without prehospital redirection	With prehospital redirection	Without prehospital redirection	With prehospital redirection	Without prehospital redirection	With prehospital redirection
Age	<60	<60	<65	<65	<70	<70
Initial rhythm	VF/VT	VF/VT	Non asystole	Non asystole	Non asystole	Non asystole
Shock given	Yes	Yes	Yes	Yes	Not necessary	Not necessary
Time before cardiac massage initiation (min)	Immediate	Immediate	<5	<5	<10	<10
Time to E-CPR initiation (min)	<60	<60	<80	<80	<100	<100
Maximum hospital transport time to an E-CPR capable center (min)	≤15	≤15	≤18	≤18	≤21	≤21
Prehospital redirection allowed	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**

E-CPR: extracorporeal cardiopulmonary resuscitation; VF: Ventricular fibrillation; VT: Ventricular tachycardia

Tableau 14 : Table 2 Demographic and clinical characteristics of the included patients

Variables	Refractory cardiac arrest cohort (n=6298)
Age, years	69.0 (16.4)
Gender, men	3965 (63.0)
Initial call between 8 am and 4 pm Initial call between 4 pm and 12 am Initial call between 12 am and 8 am	2603 (41.3) 2172 (34.5) 1515 (24.1)
Initial rhythm=VF/VT Initial rhythm=PEA Initial rhythm=Asystole	1257 (20.0) 1827 (29.0) 2824 (44.8)
Unwitnessed arrest Bystander witnessed First responder or paramedic witnessed	3162 (50.2) 1599 (25.4) 695 (11.0)
No bystander CPR Bystander CPR First responder or paramedic witnessed	1614 (51.7) 812 (25.9) 695 (22.2)
Presence of first responders	3753 (59.6)
Presence of ACP	1774 (28.2)
Time from call to arrival of first responders, minutes	6.4 (3.7)
Time from call to arrival of PCP, minutes	10.4 (5.1)
Time from call to arrival of ACP, minutes	17.2 (7.6)
Actual hospital transport time, minutes	7.3 (5.5)
Intubation using an oesophageal tracheal airway	5016 (79.6)
At least one shock given	1568 (24.9)
Number of shocks given	1.0 (2.5)
Prehospital ROSC (experienced after 15 minutes of resuscitation)	855 (13.6)
Survival to hospital discharge	297 (4.7)
Actual transport to an E-CPR capable center	1067 (16.9)

VF: Ventricular fibrillation; VT: Ventricular tachycardia; PEA: Pulseless electrical activity; CPR: Cardiopulmonary resuscitation; ACP: Advance care paramedic; PCP: Primary care paramedic; ROSC: Return of spontaneous circulation; E-CPR: extracorporeal cardiopulmonary resuscitation; Values are presented as mean (standard deviation) or N (%)

Tableau 15 : Table 3 Proportions of E-CPR candidates being transported to E-CPR capable centers in simulation scenarios

	Stringent criteria		Intermediate criteria		Inclusive criteria	
	Without prehospital redirection (n=196)	With prehospital redirection (n=196)	Without prehospital redirection (n=274)	With prehospital redirection (n=274)	Without prehospital redirection (n=996)	With prehospital redirection (n=996)
E-CPR candidates being transported to an E-CPR capable center	48 (24.5)	155 (79.1)	81 (29.6)	262 (95.6)	238 (23.9)	981 (98.5)

E-CPR: Extracorporeal cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; Values are presented as N (%)

Tableau 16 : Table 4 Hospital transport time of E-CPR candidates being transported to an E-CPR capable center in simulation scenarios

	Stringent criteria		Intermediate criteria		Inclusive criteria	
	Without prehospital redirection (n=48)	With prehospital redirection (n=155)	Without prehospital redirection (n=81)	With prehospital redirection (n=262)	Without prehospital redirection (n=238)	With prehospital redirection (n=981)
Hospital transport time, minutes	8 (5)	9 (4)	8 (6)	10 (4)	8 (6)	10 (4)

Values are presented as mean (standard deviation)

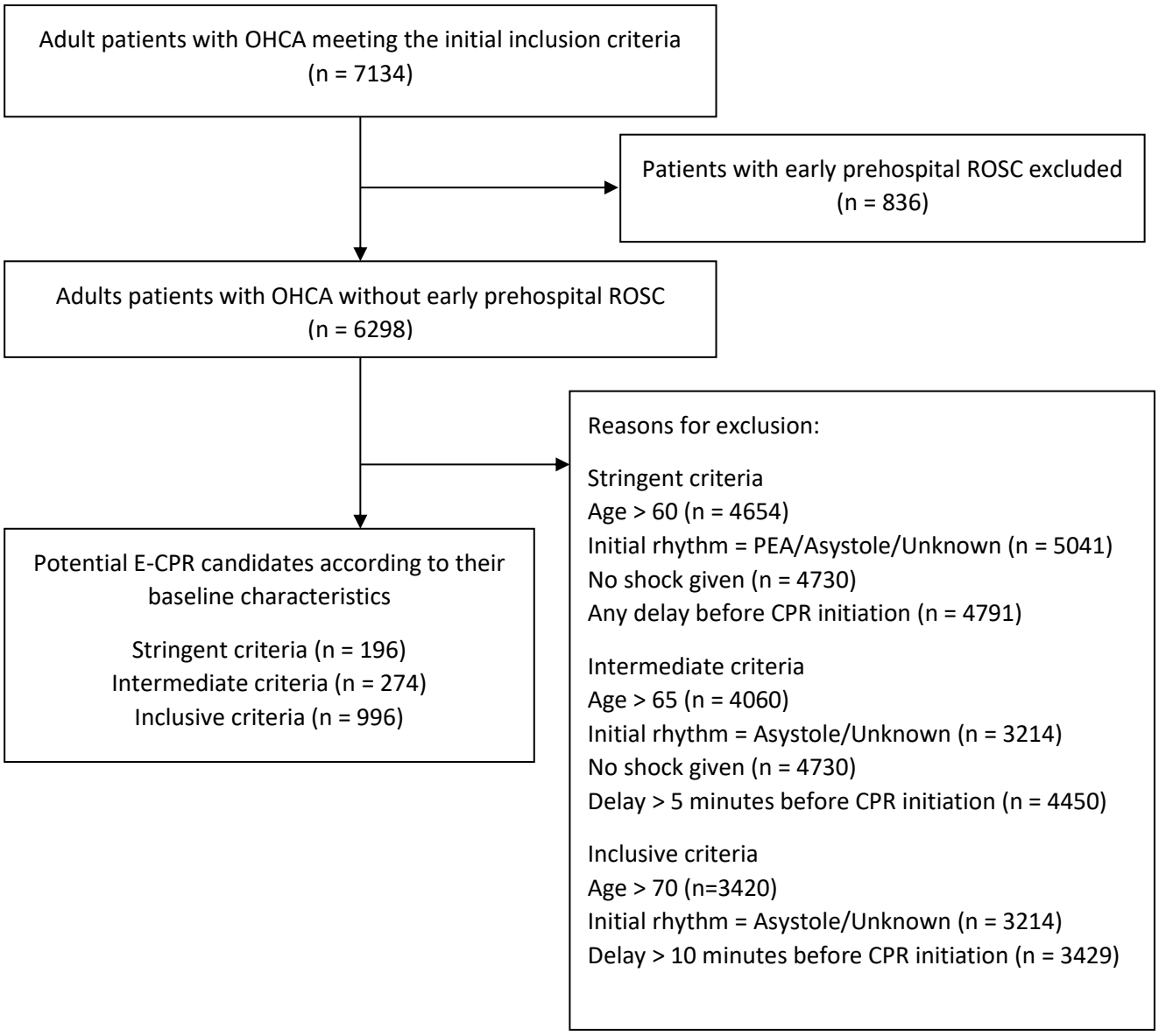
Tableau 17 : Table 5 Hospital transport times of redirected patients in simulation scenarios

	Redirected patients in the scenario using stringent criteria (n=107)		Redirected patients in the scenario using intermediate criteria (n=181)		Redirected patients in the scenario using inclusive criteria (n=743)	
	Actual transport time to the closest hospital	Estimated transport time to an E-CPR capable center	Actual transport time to the closest hospital	Estimated transport time to an E-CPR capable center	Actual transport time to the closest hospital	Estimated transport time to an E-CPR capable center
Hospital transport time, minutes	8 (7)	9 (3)	7 (5)	10 (3)	7 (5)	10 (4)

Values are presented as mean (standard deviation)

Figures

Figure 5 : Figure 1. Contribution of each baseline characteristic criterion to extracorporeal resuscitation eligibility



3.2. Deuxième volet

3.2.1. Volet 2 – Article 1 – The prognostic significance of repeated prehospital shocks for out-of-hospital cardiac arrest survival

3.2.1.1. Préface

Cette étude a été réalisée en collaboration avec 20 autres chercheurs. J'ai réalisé plus de 85% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Sylvie Cossette, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. La collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette. André Denault, Éric Notebaert, Luc Londei-Leduc, Luc de Montigny, Dave Ross, Yoan Lamarche, Brian Potter, Alain Vadeboncoeur, Raoul Daoust, Catalina Sokoloff, Martin Albert, Francis Bernard, Judy Morris, Jean Paquet, Jean-Marc Chauny, Massimiliano Iseppon, Martin Marquis, François de Champlain et Yiorgos Alexandros Cavayas ont également contribué à sa révision. Cette étude a été publiée dans le journal Canadian Journal of Emergency Medicine en 2019 (Facteur d'impact en 2018/2019 : 1,829).

3.2.1.2. Volet 2 – Article 1

The prognostic significance of repeated prehospital shocks for out-of-hospital cardiac arrest survival

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Conflict of interest: Dr. André Denault is part of a speakers bureau for Edwards, Masimo and CAE Healthcare.

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Abstract

Objectives

Patients suffering from an out-of-hospital cardiac arrest (OHCA) associated with an initial shockable rhythm have a better prognosis than their counterparts. The implications of recurrent

or refractory malignant arrhythmia in such context remain unclear. The objective of this study is to evaluate the association between the number of prehospital shocks delivered and survival to hospital discharge among patients in OHCA.

Methods

This cohort study included adult patients with an initial shockable rhythm over a 5 year period from a registry of OHCA in Montreal, Canada. The relationship between the number of prehospital shocks delivered and survival to discharge was described using dynamic probabilities. The association between the number of prehospital shocks delivered and survival to discharge was assessed using multivariable logistic regression.

Results

A total of 1,788 patients (78% male with a mean age of 64 years old) were included in this analysis, of whom 536 (30%) received treatments from an advanced care paramedic. A third of the cohort (583 patients, 33%) survived to hospital discharge. The probability of survival was highest at the first shock (33% [95% confidence interval 30%-35%]), but decreased to 8% (95% confidence interval 4%-13%) following nine shocks. A higher number of prehospital shocks was independently associated with lower odds of survival (adjusted odds ratio=0.88 [95% confidence interval 0.85-0.92], p<0.001).

Conclusions

Survival remains possible even after a high number of shocks for patients suffering from an OHCA with an initial shockable rhythm. However, requiring more shocks is independently associated with worse survival.

Introduction

Across North America, over 365,000 people suffer a non-traumatic out-of-hospital cardiac arrest (OHCA) each year.[1, 2] Rates of survival for these patients remain low, with only 5-10% of all

OHCA surviving to hospital discharge.[1, 113, 140] However, patients with an initial shockable rhythm, such as ventricular fibrillation and pulseless ventricular tachycardia, have a better prognosis than patients whose initial rhythm is non shockable (pulseless electrical activity or asystole).[52, 53, 113, 184] This may be explained by shockable rhythms being a marker of earlier intervention (i.e. prior to deterioration to asystole) or simply that the single best available therapy for patients suffering from a cardiac arrest (defibrillation), is only effective in patients with these rhythms.[14, 45, 77, 185, 186]

The efficacy of a single shock to terminate a malignant ventricular arrhythmia is reported to be over 85% when using a biphasic waveform.[185] However, because of refractory (ventricular fibrillation not responding to the initial shocks) or recurrent (returning ventricular fibrillation after a period of non-shockable rhythm) arrhythmias, more than one shock is often required.[123, 187-189] While the patients requiring more shocks may be expected to have worse outcomes, the precise prognostic implications of having a recurrent or refractory malignant arrhythmia remain uncertain and many medical decisions, such as the timing of patient transport, or the decision to cease resuscitation efforts, could be aided by more reliable early survival prognostication. This is especially true in prehospital settings with low rates of prehospital advanced cardiac life support (ACLS) for which this has not been described so far. As such, a better understanding of the implications of the number of shocks delivered could help improve prehospital resuscitation practices.[115, 190]

The main objective of this study was therefore to evaluate the association between the number of prehospital shocks delivered and the resuscitation outcomes (survival to discharge and prehospital return of spontaneous circulation [ROSC]) of patients suffering from an OHCA with an initial shockable rhythm, in a prehospital setting with low rates of prehospital ACLS. The secondary

objective was to describe the number of shocks delivered in the specific population subgroup of patients having experienced prehospital ROSC.

Methods

Study design and settings

This cohort study was derived from a registry of all OHCA occurring in the region of Montreal, Canada. It was carried out in association with the Hôpital du Sacré-Coeur de Montréal, the regional emergency medical service (EMS) agency (Urgences-santé) and the Université de Montréal and was approved by the Research Ethics Board of the Hôpital du Sacré-Coeur de Montréal with a waiver of written informed consent.

In Montreal, a single public tiered-response EMS agency coordinates all prehospital care for a population of over 2,000,000 people. First responders and paramedics treat patients suffering from OHCA using an automated external defibrillator when appropriate (ZOLL AED Pro® and ZOLL E series®, respectively, using a sequence of 120 J – 150 J – 200 J) and follow resuscitations protocols based on the American Heart Association guidelines.[44, 45] All paramedics can use an esophageal tracheal airway to assist ventilation during the resuscitation.<19, 20> In up to 25% of OHCA cases, advanced care paramedics are dispatched to provide prehospital ACLS, which includes the administration of epinephrine and amiodarone and the use of the ZOLL E series® defibrillator in manual mode.[14, 46] In accordance with provincial law, advanced care paramedics do not perform endotracheal intubation. All these defibrillators provide rectilinear biphasic waveform defibrillations.

Methods and Measurements

The methods used to collect and extract the data for the initial registry have been described previously.[113-115] Patient data are entered by the paramedic on a ‘run-sheet’ following every call. Patients suffering from an OHCA are identified using these run-sheets. The pertinent

information is then entered into a database which comprises demographic and clinical characteristics. Resuscitation outcome data were transferred from the discharge hospitals to the regional EMS agency or were readily available. The extracted data was subsequently validated.

Selection of participants

All patients aged 18 years and older treated for an OHCA between April 2010 and December 2015 with an initial shockable rhythm, either ventricular fibrillation or pulseless ventricular tachycardia, were included in the present study. Patients with traumatic causes for arrest, 'do-not-resuscitate' directives or fitting 'obviously dead' criteria (e.g. decapitation, advanced putrefaction) were excluded from both the registry and this analysis.[44]

Outcome measures

The primary outcome measure was survival to hospital discharge. The secondary outcome measure was any occurrence of prehospital ROSC of a duration of more than 30 seconds.

Statistical analyses

The entire available population with an initial shockable rhythm was used in this analysis.

Continuous variables are presented as means with standard deviations or median and Q1-Q3, as appropriate, and categorical variables are presented as frequencies with percentages.

For the main objective, in order to ensure that this analysis would be immediately applicable for physicians providing resuscitation care, the relationship between the number of prehospital shocks delivered and the probability of both resuscitation outcomes was first analyzed in a way to reflect the dynamic nature of clinical decision-making such that each level of analysis represents the likelihood of the resuscitation outcome up to that number of shocks (dynamic or Bayesian probabilities). For example, since all patients received at least one shock, the results presented at '1 shock' were derived from the entire cohort (and not from patients having received

only one shock). Likewise, at '2 shocks', all patients having received two shocks or more were kept in the analysis. This analysis can be interpreted as one would a Kaplan-Meier curve. For the alternative analysis, patients were separated in two groups according to the number of prehospital shocks they received: less than three or at least three. This cut-off has been previously proposed to differentiate patients with better and worse prognosis.[123] Moreover, the shock energy is lower with the first two shocks (120 J and 150 J) compared to all subsequent ones (200 J). Resuscitation outcomes (survival to hospital discharge and prehospital ROSC) of the patients included in these two groups were compared using Pearson's chi-squared tests. In addition, a multivariable logistic regression model was planned using a standard approach (enter method) adjusting for pertinent variables (age, sex, initial call time, bystander CPR, witnessed arrest, time from call to arrival of EMS personnel, presence of first responders, presence of advanced care paramedics, intubation using an esophageal tracheal airway) to assess the independent association between the number of prehospital shocks administered (used as a continuous variable) and the resuscitation outcomes.[51]

For the secondary objective (describing the number of shocks necessary for patients having experienced ROSC over the course of their prehospital resuscitation), the appropriate measures of central tendency and dispersion of the number of prehospital shocks administered that subgroup are presented as described above. This analysis was necessarily limited to patients having experienced ROSC in the prehospital setting. That subgroup analysis was performed because, by definition, these patients had the potential to respond to treatment they received. The association between the number of prehospital shocks administered and survival to hospital discharge was also evaluated in this same subgroup of patients using the same methods described above.

Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA). All results are presented with their 95% confidence intervals (CI).

Results

During the study period (April 1st 2010 to December 31st 2015), among 7,134 patients in the OHCA registry, 1,788 had an initial shockable rhythm and were included. Their demographic and clinical characteristics are presented in Table 1. Less than a third of the included patients (536, 30%) received treatments from an advanced care paramedic. A total of 977 patients (55%) were administered one or two prehospital shocks while 774 (45%) were administered three or more. Among all included patients, 583 (33% [95% CI 30%-35%]) survived to hospital discharge and 961 (54% [95% CI 51%-56%]) experienced prehospital ROSC (Table 2). Included patients were administered a median number of 2 shocks (Q1-Q3: 1-5) (Table 2).

The dynamic probabilities of survival and prehospital ROSC according to the number of prehospital shocks having already been delivered, irrespective of whether the previous shocks were successful, are presented in Figure 1. The probability of survival begins at 33% (95% CI 30%-35%) for patients having received at least one shock and gradually lowers to 8% (95% CI 4%-13%) following nine shocks, without a pronounced inflection point. The same is observed for the probability of prehospital ROSC, which begins at 54% (95% CI 51%-56%) and lowers to 24% (95% CI 18%-30%) following nine shocks.

Patients having received three shocks or more were less likely to survive to hospital discharge (22% vs 41%, odds ratio [OR] =0.41 [95% CI 0.33-0.50], p<0.001) than their counterparts (Table 2). They were also less likely to experience prehospital ROSC (40% vs 64%, OR=0.38 [95% CI 0.31-0.46], p<0.001) (Table 2). In multivariable logistic regression models, the number of prehospital shocks received was independently associated with lower odds of survival (adjusted OR [AOR] =

0.88 [95% CI 0.85-0.92], p<0.001; Hosmer-Lemeshow goodness of fit test: p=0.28; c-statistic=0.81) and with lower odds of prehospital ROSC (AOR=0.85 [95% CI 0.82-0.88], p<0.001; Hosmer-Lemeshow goodness of fit test: p=0.35; c-statistic=0.80) (Table 3 and Online appendix 1).

Among the 961 patients who experienced prehospital ROSC, 556 (58% [95% CI 55%-61%]) survived to hospital discharge and 320 (33%) received three prehospital shocks or more (Online appendix 2). The median number of prehospital shocks they received was 2 [Q1-Q3: 1-3] (Online Appendix 2). Among patients who experienced prehospital ROSC, patients having received three prehospital shocks or more were also less likely to survive to hospital discharge (50% vs 62%, OR=0.62 [95% CI 0.47-0.81], p<0.001) than their counterparts (Online appendix 2). In a multivariable logistic regression model, the number of prehospital shocks administered was independently associated with poorer survival to hospital discharge (AOR 0.95 [95% CI 0.89-1.00], p=0.045).

Discussion

In this large cohort of OHCA presenting with a shockable initial rhythm, the number of shocks was independently associated with lower rates of prehospital ROSC and survival to hospital discharge. Moreover, although outcomes were significantly worse with more shocks, no clear inflection point in the dynamic probabilities could be identified. These probabilities presented may well prove useful in decision modelling to guide resuscitation efforts, especially for settings with low rates of prehospital ACLS for which this had not been described so far.

In the present study, it was observed that the probability of survival to discharge in patients with an initial shockable rhythm diminishes gradually with the number of defibrillations attempts from 33% at the first to 8% at the ninth. Similarly, the probability of prehospital ROSC diminishes gradually from 54% to 26% after nine defibrillations. Interestingly, these results are similar to the

ones observed by Holmen et al. for the survival outcome (1-3 shocks=42.9% and >10 shocks=7.5%) despite differences in prehospital care between the studies.[123] Indeed, most patients received ACLS interventions in Holmen's study (73% received epinephrine) while the majority did not in the present study (17% received epinephrine). This observation would seem to corroborate the finding that prehospital ACLS does not appear to increase the medium-term outcomes of patients suffering from OHCA, even for patients with a shockable rhythm.[15, 16, 113, 123] On the other hand, Jouffroy et al. observed higher probabilities of prehospital ROSC than in the present study, perhaps explained by on-site prehospital ACLS provided by a specialized physician in that study.[187] While not clearly associated with improved survival to hospital discharge, ACLS interventions (e.g. vasopressors and antiarrhythmics) have been shown to increase the rate of ROSC.[15, 113, 148] On the other hand, Hasegawa et al. observed a slightly higher survival in their cohort compared to the present one, but only included patients with a witnessed collapse who are known to have a better prognosis.[52, 189] While these studies presented outcomes for patients having received a selected number of shocks, the present study is the only one to present probabilities that are easily usable by providers during the resuscitation.

In the current study, no clear inflection point could be observed in the dynamic probabilities of survival. On the contrary, in the studies of Hasegawa and Jouffroy, cut-offs of three and four shocks were proposed to predict survival and prehospital ROSC.[187, 189] The absence of an obvious inflection point indicates that the arbitrary use of a specific cut-off is probably not sufficiently sensitive or specific to allow them to be used independently of other factors in clinical decision-making.

The present results further our understanding of the prognostic implications of multiple shocks. One possible interpretation of this analysis is that all patients with an initial shockable rhythm, even those where a large number of shocks was administered, have chance of survival well over

the often suggested threshold of medical futility in resuscitation.[190] Indeed, survival nearing 10% is likely sufficient to conclude that such patients not be considered for prehospital termination-of-resuscitation.[123, 190, 191]

The observation that more shocks is associated with worse resuscitation outcomes is likely explained by two factors. First, requiring more shocks implies a longer period of cardiopulmonary resuscitation, which is strongly associated with the resuscitation outcomes.[192] In addition, the patients responding more rapidly to a shock might have a less severe underlying disease (e.g. infarct size, genetic predisposition) or a shorter delay before its treatment.[193-195] Nevertheless, it bears noting that a third of the patients who experienced ROSC required three shocks or more.

Another important interpretation of this analysis is that it might be critical to ensure the efficiency of first shocks. The best way to improve first-shock success is most likely to reduce the delay between circulatory collapse the initial defibrillation attempt, which likely implies both optimizing the prehospital organization of care services and increasing public access to automated external defibrillators.[11, 152, 196] Increasing the energy of initial shocks has also been proposed as a way to improve their efficiency, but evidence is lacking so far to support such a practice.[185, 197, 198] Whether adding a short acting beta-blocker to the pharmaceutical cocktail these patients receive early in resuscitation efforts or attempting a double sequential defibrillation remain a promising avenue for future research.[199-201]

Limitations

By design, all patient data was derived from information available in the EMS patient record. As such, it was not possible to know if multiple shocks were administered because of a refractory versus a recurrent arrhythmia. It is possible that patients suffering from a recurrent arrhythmia

would have a better prognosis than patients suffering from a refractory arrhythmia and, consequently, that these two populations' dynamic probability of survival differ. It was also not possible to know if some patients had received defibrillation attempts from a public-access defibrillator prior to the arrival of emergency responders. Having this data available could have flattened the dynamic probabilities curve even more and increased the difference observed between groups. Neurologic outcomes were unavailable in this study. It would have been interesting to evaluate this outcome since patients with a high number of shocks might be at a higher risk of brain ischemia and of poor neurologic outcomes than the majority of patients surviving from an OHCA. Given the nature of the prehospital system in the Montreal region, only a minority of patients received antiarrhythmic medications. While these have never been shown to increase the long-term survival of patients with OHCA, they do increase the rate of ROSC and could also influence the rate of recurring or refractory arrhythmias (and consequently shocks) which could make the present results less generalizable in settings with high rates of prehospital ACLS.[16] Additionally, although this study included a large and comprehensive multicenter dataset of OHCA, caution would be recommended in extrapolating these results to regions with differences in the geographic parameters, availability of advanced care services, treatment standards or patient demographics.

Conclusions

Survival remains possible even after a high number of shocks for patients suffering from an OHCA with an initial shockable rhythm. In a prehospital setting with low rates of prehospital ACLS, the probability of survival to hospital discharge for these patients diminishes gradually with the number of defibrillations attempts from 33% to 8% after nine shocks have been administered. There does not seem to be an evident inflection point in the probabilities of survival that would predict bad resuscitation outcomes and the number of shocks received should not influence

treatment decisions alone. Requiring more shocks is independently associated with worst outcomes in that population. Future studies should describe the dynamic probabilities of good neurologic outcomes of two specific subgroups of patients requiring multiple shocks, patients with a refractory arrhythmia and patients with a recurrent arrhythmia.

Financial support

This project received funding from the 'Fonds des Urgentistes de l'Hôpital du Sacré-Cœur de Montréal' and the 'Département de médecine familiale et de médecine d'urgence de l'Université de Montréal'.

Conflict of Interest

Dr. André Denault is part of a speakers' bureau for Edwards, Masimo and CAE Healthcare. All other authors have no conflict of interest to declare.

Tables

Tableau 18 : Table 1: Demographic and Clinical Characteristics of the Included Patients

Variables	Total cohort (n=1,788)	Two defibrillations or less (n=977)	Three shocks or more (n=774)
Age, years (mean, SD)	64 (16)	64 (16)	64 (15)
Sex, male (N, %)	1,396 (78)	734 (74)	662 (84)
Initial call between 8 am and 4 pm (N, %) Initial call between 4 pm and 12 am Initial call between 12 am and 8 am	807 (45) 631 (35) 349 (20)	448 (45) 358 (36) 190 (19)	359 (45) 273 (35) 159 (20)
Unwitnessed arrest (N, %) Bystander witnessed First responder or paramedic witnessed	375 (21) 1,170 (65) 243 (14)	213 (21) 592 (59) 191 (19)	162 (21) 578 (73) 52 (7)
No bystander CPR (N, %) Bystander CPR First responder or paramedic witnessed	908 (51) 629 (35) 243 (14)	465 (47) 336 (34) 191 (19)	443 (56) 293 (37) 52 (7)
Delay from call to arrival of EMS personnel, minutes (median, Q1-Q3)	6.1 (5.1-7.8)	5.1 (6.1-8.0)	6.1 (5.1-7.6)
Presence of first responders (N, %)	1,040 (58)	537 (54)	503 (64)
Presence of advanced care paramedics (N, %)	536 (30)	255 (26)	281 (36)
Intubation using an esophageal tracheal airway (N, %)	1,177 (66)	531 (53)	646 (82)
At least one dose of epinephrine given (N, %)	295 (17)	115 (13)	180 (23)
If given, number of epinephrine dose (median, Q1-Q3)	2 (2-5)	2 (2-5)	2 (2-5)
No dose of amiodarone given (N, %) No amiodarone given	1,688 (94)	982 (99)	706 (89)
One dose of amiodarone given (300 mg)	63 (4)	11 (1)	52 (7)
Two doses of amiodarone given (450 mg)	37 (2)	2 (0)	34 (4)

SD: Standard deviation; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical service

Tableau 19 : Table 2: Resuscitation Outcomes of Patients with an Initial Shockable Rhythm

Variables	Total cohort (n=1,788)	Two prehospital shocks or less (n=977)	Three prehospital shocks or more (n=774)	Odds ratio
Survival to hospital discharge (N, %)	583 (33)	408 (41)	175 (22)	0.41 (0.33-0.50)
Prehospital ROSC (N, %)	961 (54)	641 (64)	320 (40)	0.38 (0.31-0.46)
Number of prehospital shocks administered (median, Q1-Q3)	2 (1-5)	1 (0-2)	5 (4-8)	-

ROSC: Return of spontaneous circulation

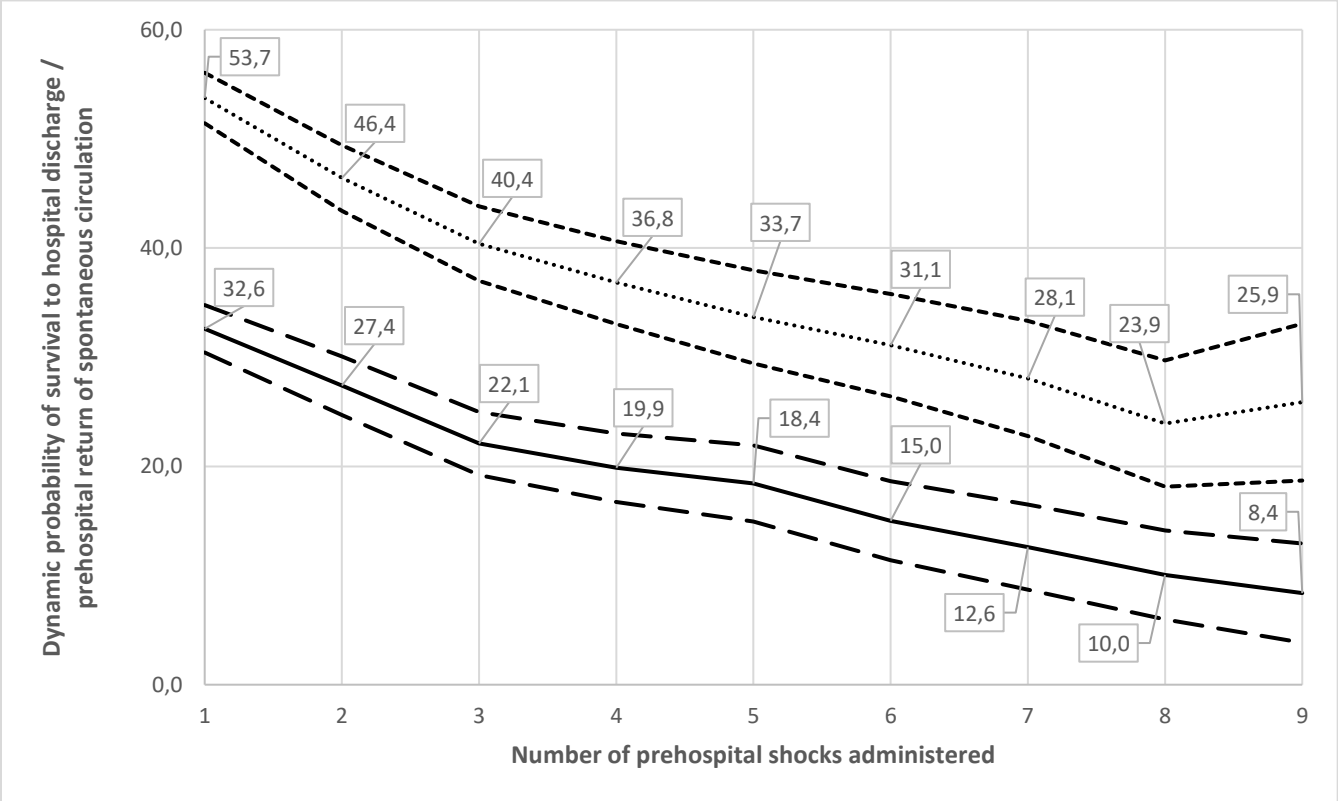
Tableau 20 : Table 3: Multivariate analysis for the survival to hospital discharge outcome, adjusted for the number of shocks, demographic and prehospital variables

Variables	AOR (95% CI)	P value
Number of shocks (1 more shock)	0.88 (0.85-0.92)	< 0.001
Age (1 year older)	0.97 (0.96-0.97)	< 0.001
Gender, male sex	0.98 (0.73-1.30)	0.87
Initial call between 8 am and 4 pm	*	-
Initial call between 4 pm and 12 am	1.01 (0.77-1.32)	0.95
Initial call between 12 am and 8 am	1.08 (0.78-1.50)	0.64
Unwitnessed arrest	*	-
Bystander witnessed	2.53 (1.80-3.57)	< 0.001
First responder or paramedic witnessed	3.73 (2.37-5.85)	< 0.001
No bystander CPR	*	-
Bystander CPR	1.26 (0.97-1.63)	0.086
First responder or paramedic witnessed	†	†
Presence of first responders	0.97 (0.75-1.25)	0.80
Presence of advanced care paramedics	1.20 (0.92-1.56)	0.19
Intubation using an esophageal tracheal airway	0.20 (0.15-0.25)	< 0.001
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.97 (0.94-1.00)	0.055

AOR: Adjusted odds ratio; CI: Confidence interval; CPR: Cardiopulmonary resuscitation
* Reference category † Not calculated due to collinearity

Figure

Figure 6 : Figure 1. Dynamic probabilities of survival to hospital discharge (full line) and prehospital return of spontaneous circulation (dotted line) with their respective confidence intervals (large dash and small dash) according to the number of prehospital shocks already administered



Online appendix

Tableau 21 : Online appendix 1: Multivariate analysis for the prehospital ROSC outcome, adjusted for the number of shocks, demographic and prehospital variables

Variables	AOR (95% CI)	P value
Number of shocks (1 more shock)	0.85 (0.82-0.88)	< 0.001
Age (1 year older)	0.98 (0.98-0.99)	< 0.001
Gender, male sex	0.78 (0.59-1.04)	0.094
Initial call between 8 am and 4 pm	*	-
Initial call between 4 pm and 12 am	0.92 (0.71-1.20)	0.54
Initial call between 12 am and 8 am	0.78 (0.57-1.08)	0.13
Unwitnessed arrest	*	-
Bystander witnessed	2.52 (1.88-3.40)	< 0.001
First responder or paramedic witnessed	4.73 (2.99-7.49)	< 0.001
No bystander CPR	*	-
Bystander CPR	1.34 (1.04-1.72)	0.022
First responder or paramedic witnessed	†	†
Presence of first responders	0.92 (0.72-1.18)	0.52
Presence of advanced care paramedics	3.88 (2.96-5.08)	< 0.001
Intubation using an esophageal tracheal airway	0.13 (0.10-0.17)	< 0.001
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.97 (0.94-0.99)	0.011

ROSC: Return of spontaneous circulation; AOR: Adjusted odds ratio; CI: Confidence interval; CPR: Cardiopulmonary resuscitation
* Reference category † Not calculated due to collinearity

Tableau 22 : Online appendix 2: Resuscitation Outcomes of Patients with an Initial Shockable Rhythm, Including Only Patients Having Experienced Prehospital Return of Spontaneous Circulation

Variables	Patients having experienced prehospital ROSC (n=961)	Two prehospital shocks or less (n=641)	Three prehospital shocks or more (n=320)	p-value
Survival to hospital discharge (N, %)	556 (58)	396 (62)	160 (50)	< 0.001
Number of prehospital shocks administered (median, Q1-Q3)	2 (1-3)	1 (0-2)	4 (3-6)	< 0.001

ROSC: Return of spontaneous circulation

3.2.2. Volet 2 – Article 2 – Prognostic impact of the conversion to a shockable rhythm from a non-shockable rhythm for patients suffering from out-of-hospital cardiac arrest

3.2.2.1. Préface

Cette étude a été réalisée en collaboration avec 18 autres chercheurs. J'ai réalisé plus de 85% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Sylvie Cossette, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. La collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette. André Denault, Éric Notebaert, Luc Londei-Leduc, Luc de Montigny, Dave Ross, Yoan Lamarche, Brian Potter, Raoul Daoust, Catalina Sokoloff, Martin Albert, Francis Bernard, Judy Morris, Jean Paquet, Jean-Marc Chauny, Massimiliano Iseppon, Martin Marquis et Yiorgos Alexandros Cavayas ont également contribué à sa révision. Cette étude a été publiée dans le journal Resuscitation en 2019 (Facteur d'impact en 2018/2019 : 4,572).

3.2.2.2. Volet 2 – Article 2

Prognostic impact of the conversion to a shockable rhythm from a non-shockable rhythm for patients suffering from out-of-hospital cardiac arrest

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Conflict of interest: Dr. André Denault is part of a speakers' bureau for Masimo and CAE Healthcare.

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Abstract

Objective

For patients suffering from an out-of-hospital cardiac arrest (OHCA), having an initial shockable rhythm is a marker of good prognosis. It has been suggested as one of the main prognosticating factors for the selection of patients for extracorporeal resuscitation (E-CPR). However, the prognostic implication of converting from a non-shockable to a shockable rhythm, as compared to having an initial shockable rhythm, remains uncertain, especially among patients that can otherwise be considered eligible for E-CPR. The objective of this study was to evaluate the association between the initial rhythm and its subsequent conversion and survival following an OHCA, for the general population and for E-CPR candidates.

Methods

This study used a registry of OHCA in Montreal, Canada. Adult patients suffering from a non-traumatic OHCA for whom the initial rhythm was known were included. The association between the initial rhythm and its subsequent conversion or not and survival to discharge was assessed using a multivariable logistic regression.

Results

Of 6681 included patients, 1788 (27%) had an initial shockable rhythm, 1749 (26%) had pulseless electrical activity (PEA) and no subsequent shockable rhythm, 295 (4%) had PEA and a subsequent shockable rhythm, 2694 (40%) had an asystole and no subsequent shockable rhythm and 155 (2%) an asystole and a subsequent shockable rhythm. As compared to patients having an initial shockable rhythm, patients in all other groups had significantly lower odds of survival to hospital discharge ($p<0.001$ for all comparisons). Univariate analyses were performed for E-CPR candidates. Among these 556 (8%) patients, more patients with an initial shockable rhythm survived than patients in all other groups ($p<0.001$ for all comparisons).

Conclusions

The initial rhythm remains a much better prognostic marker than subsequent rhythms for all patients suffering from an OHCA, including in the subset of potential E-CPR candidates.

Introduction

Over 325 000 North Americans die each year from a non-traumatic out-of-hospital cardiac arrest (OHCA).[1, 2] Among all patients who suffer from an OHCA, survival is low, with only 5-10% of all OHCA surviving to hospital discharge.[1, 113, 140] The use of extracorporeal cardiopulmonary resuscitation (E-CPR) has been proposed as a way to improve the mortality associated with OHCA since it has been shown to perform favorably when compared to traditional resuscitation.[35, 39, 40, 142] This technique incorporates an extracorporeal cardiopulmonary bypass circuit to obtain cardiopulmonary support during resuscitation.[21, 28, 33] However, given the material, human and economic resources required to provide this treatment, its use is usually limited to the patients deemed to have a good prognosis, that is without significant comorbidities and with an underlying reversible etiology for their OHCA.[76, 77]

One of the main prognostic factors used for the selection of patients for E-CPR is the initial rhythm.[29, 125, 181, 202, 203] Indeed, having an initial shockable rhythm, such as ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT), is considered a marker of good prognosis compared to having a non-shockable initial rhythm (pulseless electrical activity [PEA] or asystole).[52, 53, 113, 184] The conversion from a non-shockable rhythm to a shockable rhythm during the course of the resuscitation is also recognized as a marker of good prognosis, but it is thus far infrequently used in E-CPR selection algorithms.[124] However, the precise prognostic implications of such a conversion for both PEA and asystole, as compared to having an initial shockable rhythm, remains uncertain, especially among patients who otherwise meet E-CPR selection criteria.[39, 40, 43, 125, 126] More accurately determining the prognosis of patients

who convert to a shockable rhythm during resuscitation may help improve OHCA prognostication and patient selection for E-CPR.

The main objective of this study was therefore to evaluate the association between the initial rhythm, with or without its subsequent conversion if not initially shockable, and the resuscitation outcomes of patients suffering from an OHCA, and more precisely in a targeted population: potential E-CPR candidates.

Methods

Study design and setting

This cohort study was derived from a registry of all OHCA occurring in the region of Montreal, Canada. It was carried out in association with the Hôpital du Sacré-Coeur de Montréal, the regional emergency medical service (EMS) agency (Urgences-santé) and the Université de Montréal and was approved by the Research Ethics Board of the Hôpital du Sacré-Coeur de Montréal with a waiver of written informed consent.

In Montreal, a single public tiered-response EMS agency coordinates all prehospital care for a population of over 2,000,000 people. First responders and paramedics treat patients suffering from OHCA following resuscitations protocols based on the American Heart Association guidelines.[14, 44-46] Patients suffering from OHCA are normally transported to the closest of the 20 local hospitals, five of which have the necessary resources and expertise to perform E-CPR (cardiac surgery department and necessary equipment). During the study's period (2010-2015), E-CPR was seldom used to treat patients suffering from an OHCA in all these hospitals.

Study population

All patients aged 18 years and older treated for an OHCA between April 2010 and December 2015 were included in the present study. Patients with traumatic causes for arrest, 'do-not-resuscitate'

directives or fitting 'obviously dead' criteria (e.g. decapitation, advanced putrefaction) were excluded from both the registry and this analysis.[44] In addition, patients for whom the initial rhythm was unknown were excluded from the present study.

Methods and measurements

The methods used to collect and extract the data for the initial registry have been described previously.[113-115, 121] Patient data are entered by the paramedic on a 'run-sheet' following every call. Patients suffering from an OHCA are identified using these run-sheets. The pertinent information is then entered into a database which comprises demographic and clinical characteristics. Resuscitation outcome data were transferred from the discharge hospitals to the regional EMS agency or were readily available. The extracted data was subsequently validated.

Study groups

All included patients were divided into five groups according to the nature of their initial rhythm and its subsequent evolution for initially non-shockable rhythms: (1) initially shockable rhythm (FV or pVT), (2) PEA without conversion to a shockable rhythm (PEAwoC), (3) PEA with a conversion to a shockable rhythm (PEAwC), (4) asystole without conversion to a shockable rhythm (AwoC) and (5) asystole with conversion to a shockable rhythm conversion (AwC).

Patients were considered otherwise potential E-CPR candidates if they met the following clinical criteria: 65 years of age or younger, absence of return of spontaneous circulation (ROSC) after 15 minutes of prehospital resuscitation and EMS witnessed collapse or witnessed collapse with bystander cardiopulmonary resuscitation (CPR).[21, 39, 40, 43, 117]

Outcome measures

The primary outcome measure was survival to hospital discharge. The secondary outcome measure was occurrence of a prehospital ROSC of a duration of more than 30 seconds.

Statistical analyses

Continuous variables are presented as means with standard deviations or median and Q1-Q3, as appropriate, and categorical variables are presented as frequencies with percentages.

A Pearson's chi-squared test was first used to evaluate the difference in survival to discharge and ROSC between all five groups. The primary analysis consisted of a multivariable logistic regression model, constructed with a standard approach (enter method) using pertinent demographic (age, gender) and clinical variables (delay before EMS personnel arrival, witnessed arrest, bystander CPR, presence of first responders, presence of advanced care paramedics). The reference category used in that analysis was the group of patients with an initial shockable rhythm because these patients are generally the ones considered for E-CPR.[125] Then, two supplemental sets of analyses were performed to evaluate the influence of a subsequent rhythm conversion for patients with an initial PEA and an initial asystole. In the first one, the reference category was the group of patients with PEAwoC and, in the second one, the reference category was the group of patients with AwoC.

Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA). All results are presented with their 95% confidence intervals (CI). The alpha level was fixed at 0.05 for all comparisons.

Results

During the study period, 7134 patients suffered an OHCA, of whom 6681 (94%) had a known initial rhythm (Figure 1). Among the included patients, 1788 (27%) had an initial shockable rhythm, 2044 (31%) had PEA and 2849 (43%) had asystole. A total of 295 (14%) patients with an initial PEA and 155 (5%) patients with an initial asystole subsequently converted to a shockable rhythm during prehospital resuscitation. The demographic and clinical characteristics of all included patients are

presented in Table 1. Among the entire cohort, 1594 (24%) patients experienced prehospital ROSC and 729 (11%) survived to hospital discharge.

The probabilities of survival to hospital discharge and prehospital ROSC of all five groups are presented in Figure 1 and Table 2. Patients with an initial shockable rhythm were more likely to survive than patients in all other groups ($p<0.001$ for all comparisons). Patients with an initial PEA, regardless of subsequent shockable rhythm conversion, were more likely to survive than patients in both asystole groups (all $p=0.021$ or less). The conversion to a shockable rhythm was not associated with an improvement in survival for patients with an initial PEA (PEAwC vs PEAwoC), ($p=0.22$) or an initial asystole (AwC vs AwoC) ($p=0.89$).

Regarding the prehospital ROSC outcome, patients with an initial shockable rhythm experience prehospital ROSC more often than patients in all other groups ($p<0.001$ for all comparisons). Patients with an AwoC were less likely to experience prehospital ROSC than patients in all other groups ($p<0.001$ for all comparisons). There was no difference when comparing the three remaining groups between each other (PEAwC, PEAwoC and AwC) (all $p=0.13$ or more).

In the main multivariable logistic regression model, as compared to patients having an initial shockable rhythm, patients in all other groups had significantly lower odds of survival to hospital discharge and prehospital ROSC ($p<0.001$ for all comparisons) (Tables 3 and 4). In the first supplemental set of regression models, among patients with an initial PEA, there was no association between evolving to a shockable rhythm and survival to hospital discharge or prehospital ROSC (PEAwC vs PEAwoC) (AOR=0.74 [95% CI 0.40-1.35], $p=0.32$, and AOR=0.88 [95% CI 0.64-1.21], $p=0.44$, respectively). In the second supplemental set of regression models, among patients with an initial asystole, there was no association between evolving to a shockable rhythm and survival to hospital discharge (AwC vs AwoC) (AOR=1.37 [95% CI 0.17-10.83], $p=0.77$), but it

was however associated with higher odds of prehospital ROSC (AwC vs AwoC) (AOR=3.41 [95% CI 2.03-5.70], p<0.001).

A total of 556 (8%) patients were considered potential E-CPR candidates according to their clinical characteristics (65 years of age or younger, absence of ROSC after 15 minutes of prehospital resuscitation and EMS witnessed collapse or witnessed collapse with bystander CPR). Among these patients, 248 (45%) had an initial shockable rhythm, 201 (41%) had an initial PEA and 81 (14%) had an initial asystole. Only 26 (10%) patients with an initial PEA and five (6%) patients with an initial asystole had a subsequent shockable rhythm during their prehospital resuscitation. The probabilities of survival to hospital discharge and prehospital ROSC of all five groups are presented in Table 5. Given the small number of patients and events in some groups, only univariate analyses were performed using a Fisher's exact test. Patients with an initial shockable rhythm had better odds of survival than patients in all other groups (p<0.001 for all comparisons). No other comparisons yielded significant results (p=0.09 to p=0.80). Regarding the prehospital ROSC outcome, patients with an initial shockable rhythm were also more likely to experience prehospital ROSC than patients in all other groups (all p<0.001), with the exception of the small group comprising patients with an AwC (p=0.52). No other comparisons yielded significant results.

Discussion

In this analysis of a large, unselected OHCA population of almost all cases of a metropolitan region, it was observed that patients with an initial PEA or asystole have significantly lower odds of survival to hospital discharge or ROSC than patients with an initial shockable rhythm, regardless of subsequent conversion to a shockable rhythm. Converting to a shockable rhythm was however associated with an improvement in the odds of prehospital ROSC for patients presenting with an asystole. Rhythm conversion did not show a significant impact on survival to hospital discharge.

The present study is also the first to specifically address these questions in potential E-CPR candidates. Among potential E-CPR candidates, survival was also higher in patients with an initial shockable rhythm. No E-CPR candidate with an initial asystole survived to hospital discharge. The present study is the first one to address these questions in potential E-CPR candidates.

The initial cardiac rhythm appears to be a much better outcome predictor than subsequent rhythms in patients suffering from an OHCA. Rajan et al. also observed that the conversion to a shockable rhythm was not a strong prognostic marker as compared to the initial rhythm itself.[204] This may be explained by shockable rhythms being a marker of earlier intervention.[186] Indeed, even after a conversion to a shockable rhythm, patients having an initial non-shockable rhythm might have more severe underlying total body ischemia in relation to the duration of their arrest or the quality of their resuscitation.[186] It is also possible that their underlying illness is less easily treatable than for patients having an initial shockable rhythm, regardless of subsequent rhythm conversion.[159]

Patients who had an initial asystole experienced prehospital ROSC more often after conversion to a shockable rhythm, which was not the case for patients with an initial PEA. This is in keeping with the findings of Luo et al's in their recent literature review.[124] Luo et al also observed that the conversion from an initial asystole to a shockable rhythm was associated with an increase in survival, which we did not observe in our cohort.[124] Asystole consists of a lack of both perceivable electrical and mechanical activity in the heart, patients with PEA may have persistent organized mechanical activity despite ongoing circulatory collapse. As such, conversion from a lack of activity to any electrical activity (i.e. a shockable rhythm) may be a good prognostic marker, conversion of an organized PEA to a disorganized rhythm such as VF may not have the same positive prognostic significance.

To the best of our knowledge, this is the first study to show that the initial rhythm is a better marker of prognosis than subsequent rhythms among patients in refractory cardiac arrest who would otherwise be potential candidates for E-CPR. This finding adds to the current evidence that the initial rhythm is a marker of good prognosis among patients undergoing E-CPR and supports using the initial rhythm in the selection of patients for E-CPR.[70] In addition to this, we believe that E-CPR selection criteria should be adapted to the local environment. Where resources are more limited, offering E-CPR only to those with an initial shockable rhythm would be reasonable. In settings with more resources available, extending indications to those with initial PEA may be appropriate. Our findings do not support extending E-CPR to those presenting with asystole given the low likelihood of a favorable outcome.[203] The results of our analysis do not support altering the decision to provide E-CPR based on subsequent rhythm conversion for initial non-shockable rhythms and this is in keeping with the current literature.[70] Whether such a dynamic strategy could be beneficial will require appropriately powered prospective studies.

Limitations

The present study is observational in nature and, as such, is subject to ascertainment bias and unmeasured confounding. As all data were derived from prehospital record, the timing of conversion, the final diagnosis and the neurologic outcomes were not available for analysis. While there was a large number of patients in the overall study, the number of E-CPR candidates was relatively small and there were comparatively few events in this group, particularly in certain rhythm categories. As such, the results in this sub-cohort must be interpreted with caution. It was not possible to know exactly how many patients received E-CPR, although it is probable given the period studied that no patient underwent that therapy. Consequently, the impact of that treatment for these patients remains uncertain. It is also possible that the patients who had an asystole as an initial rhythm had less aggressive treatment and that a part of the observed results

are due to a self-fulfilling prophecy bias. However, the prehospital treatment patients received were protocol based and a prolonged period of resuscitative efforts must be completed before termination of resuscitation can be considered, which minimizes that potential bias. Finally, although this study included a large and comprehensive multicenter dataset of OHCA, caution should be recommended in extrapolating these results to patients suffering from an in-hospital cardiac arrest, or to regions with differences in the availability of prehospital advanced care services, treatment standards or patient demographics.

Conclusions

The initial rhythm is a much better prognostic marker than subsequent rhythms for patients suffering from an OHCA. This finding also held for the subset of patients considered potential E-CPR candidates. For patients with an initial asystole, the conversion to a shockable rhythm is associated with an improvement in survival, but the overall prognosis for patients with initial asystole remained poor. Future studies are necessary to determine whether or not E-CPR might be appropriate for patients presenting with initial PEA.

Financial support

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Conflict of Interest

Dr André Denault is part of a speakers' bureau for Masimo and CAE Healthcare. He is supported by the Montreal Institute Foundation and the Richard I. Kaufman Endowment Fund in Anesthesia and Critical Care. All other authors have no conflict of interest to declare.

Tables

Tableau 23 : Table 1: Demographic and clinical characteristics of the included patients

Variables	Initial shockable rhythm (n=1788)	PEAwoC (n=1749)	PEAwC (n=295)	AwoC (n=2694)	AwC (n=155)
Age, years (mean, SD)	64 (16)	70 (16)	71 (16)	69 (17)	70 (16)
Sex, male (N, %)	1396 (78)	1011 (57)	204 (69)	1554 (58)	100 (65)
Unwitnessed arrest (N, %)	375 (21)	593 (34)	102 (35)	1997 (74)	98 (63)
Bystander witnessed	1170 (65)	792 (45)	167 (57)	652 (24)	56 (36)
First responder or paramedic witnessed	243 (14)	364 (21)	26 (9)	45 (2)	1 (1)
No bystander CPR (N, %)	908 (51)	972 (56)	179 (61)	1966 (73)	119 (77)
Bystander CPR	629 (35)	405 (23)	88 (30)	667 (25)	35 (23)
First responder or paramedic witnessed	243 (14)	364 (21)	26 (9)	45 (2)	1 (1)
Delay from call to arrival of EMS personnel, minutes (mean, SD)	7 (4)	7 (5)	7 (5)	7 (5)	7 (4)
Presence of first responders (N, %)	1040 (58)	1086 (62)	210 (71)	1601 (59)	99 (64)
Presence of advanced care paramedics (N, %)	536 (30)	449 (26)	106 (36)	765 (28)	69 (45)
Intubation using an esophageal tracheal airway (N, %)	1177 (66)	1423 (81)	262 (89)	2078 (77)	138 (89)
At least one dose of epinephrine given (N, %)	295 (17)	317 (18)	84 (29)	441 (16)	60 (39)

PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm; SD: Standard deviation; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical service

Tableau 24 : Table 2: Probabilities of survival to hospital discharge and prehospital ROSC among patients with an OHCA according to the initial rhythm and its subsequent evolution

Variables	Initial shockable rhythm (n=1788)	PEAwoC (n=1749)	PEAwC (n=295)	AwoC (n=2694)	AwC (n=155)
Survival to hospital discharge (N, %)	583 (33)	116 (7)	14 (5)	15 (1)	1 (1)
Prehospital ROSC (N, %)	961 (54)	409 (23)	69 (23)	127 (5)	28 (18)

ROSC: Return of spontaneous circulation; OHCA: Out-of-hospital cardiac arrest; PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm

Tableau 25 : Table 3: Multivariate analysis for the survival to hospital discharge outcome, adjusted for the groups according to the nature of their initial rhythm and its subsequent evolution, demographic and prehospital variables

Variables	AOR (95% CI)	P value
Initial shockable rhythm	*	
PEAwoC	0.15 (0.12-0.18)	< 0.001
PEAwC	0.12 (0.067-0.21)	< 0.001
AwoC	0.017 (0.010-0.030)	< 0.001
AwC	0.020 (0.003-0.15)	< 0.001
Age (1 year older)	0.97 (0.96-0.97)	< 0.001
Gender, male sex	0.68 (0.56-0.84)	< 0.001
Unwitnessed arrest	*	-
Bystander witnessed	1.96 (1.53-2.51)	< 0.001
First responder or paramedic witnessed	4.52 (3.31-6.19)	< 0.001
No bystander CPR	*	-
Bystander CPR	1.22 (1.00-1.50)	0.056
First responder or paramedic witnessed	†	†
Presence of first responders	0.93 (0.82-1.20)	0.93
Presence of advanced care paramedics	1.00 (0.82-1.23)	1.00
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.97 (0.94-0.99)	0.011

AOR: Adjusted odds ratio; CI: Confidence interval; PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical services
* Reference category † Not calculated due to collinearity

Tableau 26 : Table 4: Multivariate analysis for the prehospital ROSC outcome, adjusted for the groups according to the nature of their initial rhythm and its subsequent evolution, demographic and prehospital variables

Variables	AOR (95% CI)	P value
Initial shockable rhythm	*	
PEAwoC	0.25 (0.21-0.29)	< 0.001
PEAwC	0.24 (0.18-0.33)	< 0.001
AwoC	0.051 (0.041-0.064)	< 0.001
AwC	0.18 (0.12-0.29)	< 0.001
Age (1 year older)	0.99 (0.98-0.99)	< 0.001
Gender, male sex	0.73 (0.63-0.84)	< 0.001
Unwitnessed arrest	*	-
Bystander witnessed	2.12 (1.79-2.50)	< 0.001
First responder or paramedic witnessed	4.04 (3.20-5.11)	< 0.001
No bystander CPR	*	-
Bystander CPR	1.14 (0.97-1.33)	0.11
First responder or paramedic witnessed	†	†
Presence of first responders	0.97 (0.83-1.12)	0.97
Presence of advanced care paramedics	3.97 (3.42-4.62)	<0.001
Delay from call to arrival of EMS personnel (1 more minute before their arrival)	0.97 (0.96-0.99)	0.004

ROSC: Return of spontaneous circulation; AOR: Adjusted odds ratio; CI: Confidence interval; PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical services

* Reference category † Not calculated due to collinearity

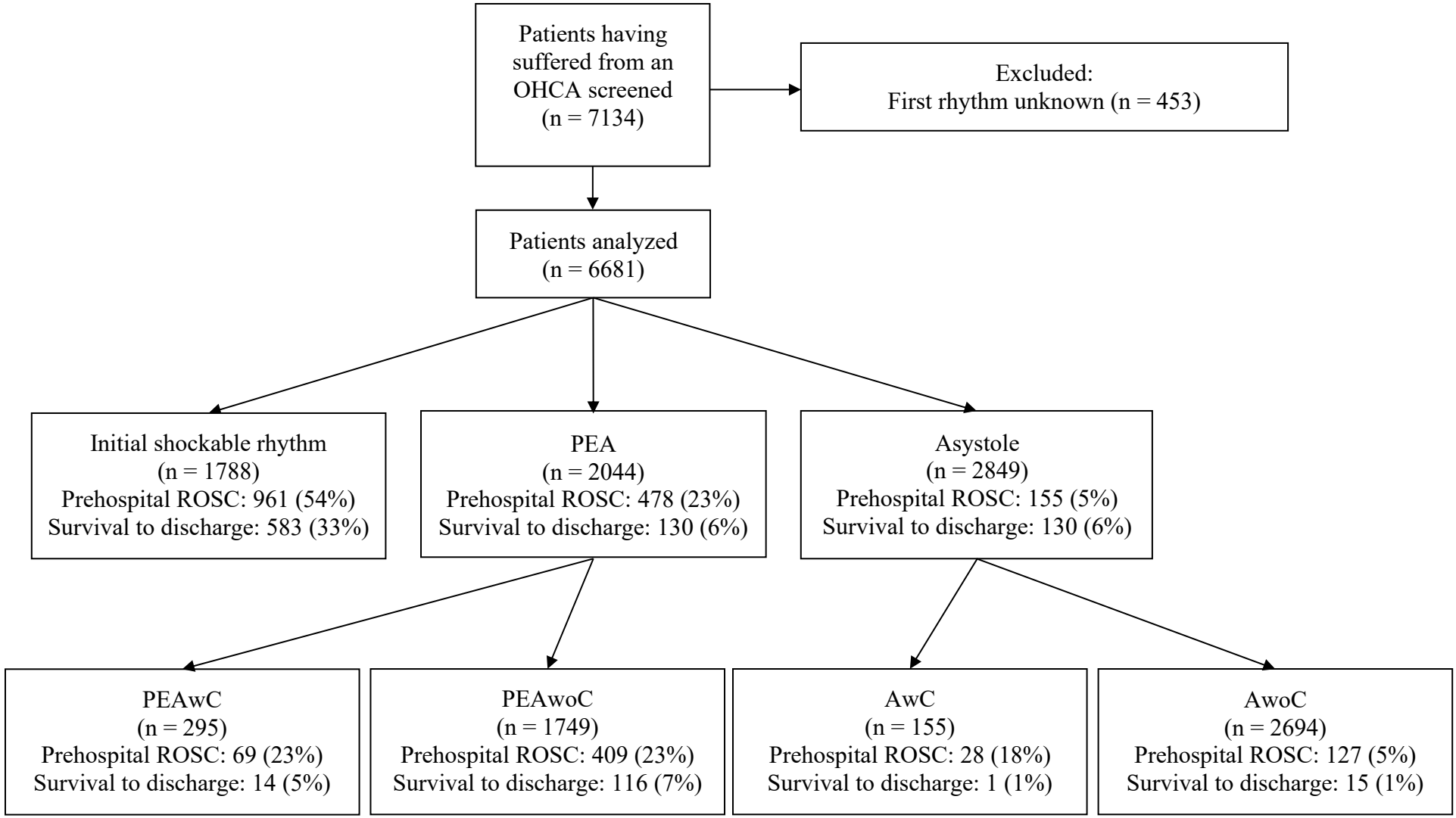
Tableau 27 : Table 5: Probabilities of survival to hospital discharge and prehospital ROSC among patients with an OHCA according to the initial rhythm and its subsequent evolution, including only potential E-CPR candidates

Variables	Initial shockable rhythm (n=248)	PEAwoC (n=201)	PEAwC (n=26)	AwoC (n=76)	AwC (n=5)	P value
Survival to hospital discharge (N, %)	91 (37)	9 (5)	1 (4)	0 (0)	0 (0)	<0.001
Prehospital ROSC (N, %)	128 (52)	33 (16)	4 (15)	11 (15)	2 (40)	< 0.001

ROSC: Return of spontaneous circulation; OHCA: Out-of-hospital cardiac arrest; E-CPR: Extracorporeal resuscitation; PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm

Figure

Figure 7 : Figure 1. Utstein diagram. OHCA: Out-of-hospital cardiac arrest; ROSC: Return of spontaneous circulation; PEA: Pulseless electrical activity; PEAwC : Pulseless electrical activity with a conversion to a shockable rhythm; PEAwoC : Pulseless electrical activity without a conversion to a shockable rhythm; AwC : Asystole with a conversion to a shockable rhythm; AwoC : Asystole without a conversion to a shockable rhythm


Patients having suffered from an OHCA screened (n = 7134)
Excluded: First rhythm unknown (n = 453)
Patients analyzed (n = 6681)
Initial shockable rhythm (n = 1788) Prehospital ROSC: 961 (54%) Survival to discharge: 583 (33%)
PEA (n = 2044) Prehospital ROSC: 478 (23%) Survival to discharge: 130 (6%)
Asystole (n = 2849) Prehospital ROSC: 155 (5%) Survival to discharge: 130 (6%)
PEAwC (n = 295) Prehospital ROSC: 69 (23%) Survival to discharge: 14 (5%)
PEAwoC (n = 1749) Prehospital ROSC: 409 (23%) Survival to discharge: 116 (7%)
AwC (n = 155) Prehospital ROSC: 28 (18%) Survival to discharge: 1 (1%)
AwoC (n = 2694) Prehospital ROSC: 127 (5%) Survival to discharge: 15 (1%)

3.3. Troisième volet

3.3.1. Volet 3 – Article 1 – Near-infrared spectroscopy monitoring during cardiac arrest: a systematic review and meta-analysis

3.3.1.1. Préface

Cette étude a été réalisée en collaboration avec cinq autres chercheurs. J'ai réalisé plus de 80% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec Éric Notebaert et Jean-Marc Chauny. La stratégie de recherche a été développée en collaboration avec Éric Notebaert, Monique Clar et Danielle Rose. La sélection des articles a été réalisée en collaboration avec Massimiliano Iseppon et Éric Notebaert. L'extraction des données a été réalisée en collaboration avec Massimiliano Iseppon et Éric Notebaert. Les analyses et leurs interprétations ont été effectuées en collaboration avec Sylvie Cossette et Jean-Marc Chauny. L'article a été écrit en collaboration avec Sylvie Cossette et Massimiliano Iseppon. André Denault, Éric Notebaert et Jean-Marc Chauny ont également contribué à sa révision. Cette étude a été publiée dans le journal Academic Emergency Medicine en 2016 (Facteur d'impact en 2017 : 2,731).

3.3.1.2. Volet 3 – Article 1

This is the peer reviewed version of the following article: Cournoyer, A., Iseppon, M., Chauny, J. M., Denault, A., Cossette, S., & Notebaert, É. (2016). Near-infrared Spectroscopy Monitoring During Cardiac Arrest: A Systematic Review and Meta-analysis. Academic Emergency Medicine, 23(8), 851-862., which has been published in final form at https://doi.org/10.1111/acem.12980. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving

Title: Near-infrared spectroscopy monitoring during cardiac arrest: a systematic review and meta-analysis

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Meeting: Preliminary results were presented as a poster at the 32nd Congress of the Association des Médecins d'Urgence du Québec in La Malbaie, Québec, Canada, November 12-13th 2015.

Preliminary results have also been accepted as a 'lightening oral' presentation at the Society for Academic Emergency Medicine Annual Meeting in New-Orleans, USA, May 10-13th 2016.

Preliminary results have also been accepted as an oral presentation at the Canadian Association of Emergency Physicians Annual Conference in Quebec, Canada, June 4-8th 2016.

Financial support: This project received internal funding from the Fond des Urgentistes de l'Hôpital du Sacré-Coeur de Montréal. This project won the first prize at the 32nd Congress of the Association des Médecins d'Urgence du Québec and is also promised a resident research award from the Canadian Association of Emergency Physicians Annual Conference. The main author also received a travel grant for its presentation at the 32nd Congress of the Association des Médecins d'Urgence du Québec.

Conflict of interest: Dr Denault is part of a speakers bureau for Masimo, Edwardds and CAE Healthcare.

Abstract word count: 337

Word count (excluding abstract, tables and figures): 5189

Abstract

Background

Tissue oximetry using near-infrared spectroscopy (NIRS) is a non-invasive monitor of cerebral oxygenation. This new technology has been used during cardiac arrest (CA) because of its ability to give measures in low blood flow situations. The aim of this study was to assess the evidence regarding the association between the types of NIRS measurements (mean, initial and highest

values) and resuscitation outcomes (return of spontaneous circulation (ROSC), survival to discharge and good neurologic outcome) in patients undergoing cardiopulmonary resuscitation.

Methods and results

This review was registered (Prospero CRD42015017380) and is reported as per the PRISMA guidelines.

Medline, Embase and CENTRAL were searched. All studies, except case reports and case series of fewer than five patients, reporting on adults that had NIRS monitoring during CA were eligible for inclusion. Two reviewers assessed the quality of the included articles and extracted the data. The outcome effect was standardized using standardized mean difference (SMD).

Twenty non-randomized observational studies (15 articles and five conference abstracts) were included in this review, for a total of 2436 patients. We found a stronger association between ROSC and mean NIRS values (SMD 1.33 [95% confidence interval (CI) 0.92-1.74]) than between ROSC and initial NIRS measurements (SMD 0.51 [95% CI 0.23-0.78]). There was too much heterogeneity amongst the highest NIRS measurements group to perform meta-analysis. Only two of the 75 patients who experienced ROSC had a mean NIRS saturation under 30%. Patients who survived to discharge and who had good neurologic outcome displayed superior combined initial and mean NIRS values than their counterparts (SMD 1.63 [95% CI 1.34-1.92]; SMD 2.12 [95% CI 1.14-3.10]).

Conclusions

Patients with good resuscitation outcomes have significantly higher NIRS saturations during resuscitation than their counterparts. The types of NIRS measurements during resuscitation influenced the association between ROSC and NIRS saturation. Prolonged failure to obtain a NIRS saturation higher than 30% may be included in a multi-modal approach to the decision of terminating resuscitation efforts (Class IIb, Level of Evidence B-Non randomized).

Keywords

Near-infrared spectroscopy, cardiopulmonary resuscitation, heart arrest, meta-analysis, prognosis

Background

Near-infrared spectroscopy (or tissue oximetry) (NIRS) is a non-invasive optical technique that uses near-infrared spectrum photons (700 to 1300 nanometers) to calculate hemoglobin saturation. It operates on the Beer-Lambert principle, which stipulates that the concentration of a substance can be measured based on the degree of light absorption in a tissue. NIRS uses an infrared-emitting diode with multiple-wavelength photons absorbed by chromophores (components of hemoglobin). Oxyhemoglobin and deoxyhemoglobin have different absorption properties in this spectrum.[88] Unlike pulse oximetry - which only measures the arterial saturation of hemoglobin - NIRS measures the oxygen saturation in all vessels smaller than 1 mm (including arterioles, capillaries and venules).[89] Tissue oximeters use an algorithm to calculate the total concentration of oxyhemoglobin and deoxyhemoglobin, thus providing a value for mixed oxygen saturation in tissues. Other major differences with pulse oximetry are that NIRS monitoring is not dependent on pulsatile flow and can provide readings in instances of low blood flood, such as cardiac arrest.

During cardiac arrest (CA) and resuscitation, low cerebral perfusion leads to hypoxic-ischemic brain injury.[205] This is one of the major reasons for disability after successful cardiac resuscitation.[95] Given that cerebral NIRS devices can measure the mixed oxygen saturation in the superficial part of the frontal lobes when placed on the cranium, interest in their use during CA monitoring has recently increased, both to guide the quality of cardiopulmonary resuscitation (CPR) and as a tool for individual prognostication (return of spontaneous circulation (ROSC), survival to discharge, neurologic outcome). This increase in interest was observed despite the

costs associated to its use, which can be estimated as being around 20 000$ per oximeter and 80$ per disposable sensor. However, there is disagreement amongst users as to which values are most useful amongst the three most often reported types of NIRS measurements (mean, initial and highest values). Some researchers and clinicians prefer to use the resuscitation's mean NIRS saturation as a guide, while others consider only the initial or highest measurements obtained as useful. In clinical practice, the mean value can be estimated by taking the initial saturation measured and incorporating the trend of ensuing values obtained during the resuscitative efforts. In other words, a patient with an initially measured NIRS saturation of 25% will have a higher mean NIRS value if it trends up to 40% than if it goes down to 20% throughout the resuscitation. Which of these types of measurements – mean, initial or highest – provides the best information during CA, however, is unclear. To better evaluate the evidence available on the subject, we performed a systematic review and meta-analysis of the currently available literature on NIRS monitoring in cardiac arrest. We hypothesized that higher NIRS values would be associated with better clinical outcomes, and that the strength of this association would differ depending on the types of NIRS oxygen saturation values used.

Methods

This review was registered (Prospero CRD42015017380) and is reported as per the PRISMA guidelines.[206]

Objectives

The main research objective was to identify the association between tissue oximetry and multiple outcomes (ROSC, survival, good neurologic outcome) in CA. We also examined the impact of the type of the NIRS oximetry measurements on that association.

The secondary research objective was to describe other potential uses of cerebral and somatic oximetry monitoring during CA.

Search methods

The search strategy was developed by two investigators (AC, EN), with the help of healthcare librarians. It aimed to find both published and unpublished studies. There were no language or time restrictions. MedLine, Embase and CENTRAL databases were searched from their inception using a specifically designed search strategy (online only supplemental method). Grey literature was searched using Web of Science and Google Scholar (online only supplemental method). NIRS manufacturers and authors of included citations were contacted about unpublished results. Finally, the reference list of all identified articles and main review articles were reviewed in search of additional studies. The search was initially performed on June 3rd 2015 and was repeated on September 18th 2015 to ascertain that no new literature was published in the interim.

Selection criteria

Following the automatic removal of duplicates, remaining citations were screened by two independent reviewers for potentially pertinent publications (AC, MI). Discrepancies regarding the selection of articles retained for full-text review were resolved by discussion with a third reviewer (EN). We included both in-hospital and out-of-hospital CA, as long as resuscitative efforts were undertaken and the arrest was not planned (e.g. part of a cardiac or vascular surgery protocol, testing of a defibrillator threshold, etc.). We excluded cases for which extracorporeal CPR was utilized for all analyses pertaining to the ROSC outcome because ROSC is not clearly defined in the setting of extracorporeal CPR. These cases, however, were included in the analyses regarding survival and neurologic outcome.

For the main research question, we considered studies that included the following outcome measures: ROSC, survival to discharge and neurological outcome. For the secondary research question, we considered all studies addressing the quality of CPR or other potential uses of NIRS during CA.

We considered all types of experimental and epidemiological studies. Given the observational nature of the research question, we included cohort and case-control studies. However, case series and case reports with fewer than five patients were not retained because we believe their inclusion would introduce too much bias, rendering the results difficult to interpret.

Methodological quality

All selected papers were assessed by two independent reviewers (AC, MI) for methodological validity prior to inclusion in the review. The risk of bias was evaluated using an adapted version of the Newcastle-Ottawa scale (online only Figure 1).[133] Discrepancies were resolved by discussion with a third reviewer (EN). Abstracts were automatically considered to be at high risk of bias because of the risk of abstract-to-publication discrepancies.

Data collection and analyses

Data for all reported outcomes was extracted from every paper included in the review. We attempted to contact every author to verify its accuracy.

For outcomes reported in multiples studies, results were pooled in a meta-analysis using Revman (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All oximetry measures were collected and subject to double data entry. When more than one site for oximetry measurement was reported in a study, only cerebral values were retained given they should theoretically better reflect the extent of the neurologic insult. For the purpose of this study, NIRS saturation at patient's arrival in the emergency department, at rescuers arrival on the scene or taken as soon as possible after the beginning of the resuscitation were considered as the initial NIRS measurement. The highest NIRS saturation obtained during the resuscitative efforts, but prior to ROSC, were considered the highest NIRS measurement. The average of all NIRS saturation values obtained during the entirety of the CA, excluding values taken after ROSC, was considered the mean NIRS value. For the main analysis, we opted to use the mean NIRS value

whenever possible because we believe it better estimates the level of tissue perfusion achieved by resuscitative efforts. When this information was not available, the initial NIRS measurement was used. If both mean and initial NIRS measurements were unavailable, the highest NIRS value assessed during CA was used for inclusion in data analysis. While the highest tissue oxygenation values reached had the greatest potential for predicting ROSC, we assumed that some of the values would inevitably represent post-ROSC situations, since ROSC is sometimes initially unrecognized.[207] Also, initial NIRS measurements might be less reliable, as it is subject to suboptimal sensor apposition and initial oximeter calibration limitations. This resulted in three independent subgroups that followed a clearly predetermined priority sequence (e.g. 1. Mean, 2. Initial 3. Highest). Effect sizes, expressed as standardized mean differences (SMD) with their 95% confidence intervals, were calculated for analysis. Because three different types of measurements were included, SMD were used because they allowed for the standardization of the results from different studies to a uniform scale. In three articles, only the median for each group was available.[93, 208, 209] Therefore, the mean needed to be estimated from the median values using Wan's technique for its integration in the meta-analysis.[210] When necessary, subgroups of the original studies were combined using the formulae provided by the Cochrane Handbook.[211] Heterogeneity was assessed statistically using I^2. A random effect model was retained to better account for the differences in design amongst the included studies. Heterogeneity was also explored, notably using subgroup differences (different NIRS measurements). If the I^2 was over 75%, there would be no meta-analysis done and the results would be described qualitatively, unless that heterogeneity was readily explained by subgroup differences. In such a situation, subgroups were also presented separately with all available data resulting in three non-independent meta-analyses.

Assessment of publication bias and sensitivity analyses

As per recommended by the Cochrane Handbook, for each meta-analysis of more than 10 articles, a funnel plot was done to assess publication bias.[211] For analyses performed on fewer than 10 articles, we assessed the reporting bias qualitatively.

We performed multiple sensitivity analyses excluding studies published more than three years ago, studies with a moderate/high risk of bias and those at a high risk of bias, smaller studies (n < 25), studies not using relative NIRS oximeters (all but FORE-SIGHT and Equanox) and studies including in-hospital CA. Other sensitivity analyses conducted were for patients who experienced extracorporeal CPR and for whose initial rhythm was a shockable one, when such information was available. Finally, in order to ascertain that our decision to prioritize mean NIRS values (over first and highest measurements) wouldn't influence our results, we included sensitivity analyses that accounted for every other possible priority sequence for available NIRS measurements.

Results

Result of the research

The electronic search strategy yielded 3275 unique citations (Figure 1). A title and abstract screening left 100 potentially eligible citations. The search of grey literature, as well as the second search done one month prior to submission, yielded an additional eight citations for a total of 108 included for the full-text review. After inspection of the full texts and communication with the authors (12 authors responsible for 54 of the 108 citations under evaluation provided a reply), 88 citations were excluded for the following reasons: availability of more recently published data from the same cohort (51), absence of NIRS values or outcome evaluated (23) and NIRS measurements taken after ROSC (14) (online only Table 1). Twenty studies (19 concerning to the main objective) were included in the final analysis.

Included studies

All included texts were non-randomized observational studies written in English. There were 15 full-text articles and five conference abstracts (Table 1). Most included studies measured oximetry levels on the forehead, with only one measuring it on the abdomen.[212] Multiple types of somatic oximeters were used. The absolute oximeters Equanox (Nonin Medical, Plymouth, MN, USA) and Fore-sight (Casmed, Branford, CT, USA) were used in five and one study respectively, while the relative oximeters INVOS (Covidien, Mansfield, MA, USA), NIRO (Hamamatsu Photonics, Hamamatsu City, Japan) and TOS (Tostec, Tokyo, Japan) were used in ten, three and two studies respectively. Two studies used two different types of oximeters. All 19 studies included in the quantitative review evaluated the ROSC outcome, while only seven evaluated the survival and four the neurologic outcome. Eight studies presented the resuscitation's mean NIRS values, 11 presented the initial NIRS measurements obtained and eight the highest NIRS measurements. Four studies presented two of these NIRS measurements and two others provided data for each of the three measurements used in this meta-analysis. Finally, 14 studies included patients suffering only from out-of-hospital CA, four studies reported only on in-hospital CA and two studies included both. No studies presented sex-specific or racial-specific data. The aforementioned characteristics are presented in table 1.

No study presented data that was adjusted for potential covariates. The authors of three studies provided access to unpublished data, allowing us to include them in additional analyses for which their published data would not have permitted.[92, 213, 214]

Risk of bias of included studies

Amongst the included studies, only the five abstracts were evaluated as being at high risk of bias.[60, 93, 215-217] Nine of the remaining studies were at intermediate risk of bias[208, 212,

218-224] and six were at low risk of bias[92, 209, 213, 214, 225, 226]. The description of the risk of bias for each included study is presented in Table 1 and specified in the online data supplements.

Main results

ROSC

A total of 2436 patients, 640 (28.1 %) of whom achieved ROSC, were included in the 19 studies we considered for the meta-analysis. As mentioned earlier, whenever a study presented data for multiple measurements, we retained the mean value (n=8) when available, followed by the initial measurement (n=7) when available, and ultimately the highest measurement (n=4) when neither mean nor initial NIRS saturation were available. This resulted in three independent types of measurement subgroups in a same analysis.

For the main analysis, using the method described above, the I^2 for overall heterogeneity was 87% which was explained by a statistically significant difference between timing subgroups (Chi^2=26.14, p<0.00001) (Figure 2). The highest NIRS measurements were a better predictor of ROSC (SMD 3.46 [95% confidence interval (CI) 2.31-4.62], p<0.00001) than the mean values (SMD 1.33 [95% CI 0.92-1.74], p<0.00001), which proved superior to initial measurements (SMD 0.45 [95% CI 0.02-0.88], p=0.04). As planned, because of the high heterogeneity, we pursued the analyses by evaluating each subgroup separately. In those analyses, no prioritization sequence was necessary because subgroups were evaluated separately. This increased the number of studies in each subgroup because all studies that reported more than one type of NIRS measurements could be included in more than one analysis.

Highest measurements

Out of 271 patients who were included in the eight studies that presented the highest NIRS saturation measurements and addressed the ROSC outcome, 91 (33.6 %) achieved ROSC. In that subgroup, heterogeneity was too high for meta-analysis (I^2=89%). This can be explained by the fact that four studies showed a large difference in highest oximetry measurements between patients who experienced ROSC and those who did not[93, 212, 216, 218], while three studies showed a much smaller difference[214, 219, 221] (Table 2).

Mean values

A total of 336 patients, 137 (40.8 %) of which achieved ROSC, were included in the eight studies that presented values for mean NIRS saturation and addressed the ROSC outcome. Patients who achieved ROSC had higher mean NIRS values than patients who did not (SMD 1.33 [95% CI 0.92-1.74], p<0.00001), with moderate heterogeneity remaining in this subgroup (I^2=49%) (Figure 3). Also, amongst the six studies that allowed for such a calculation to be done, only two patients out of 75 (2.7%) that achieved ROSC had mean NIRS saturation under 30%. Those two patients did not survive to discharge.[208, 209, 219, 224-226] In another study, patients that achieved ROSC spent a median of 2% (range 0 to 36%) of their CA time with under 30% of NIRS saturation.[214]

Initial measurements

Out of 2067 patients included in the 11 studies that presented values for initial NIRS saturation and addressed the ROSC outcome, 529 (25.6 %) achieved ROSC. However, in two studies, the standardized mean difference could not be estimated due to the fact that there was no variance in one of the groups compared. In one of those two studies, all non-ROSC patients had the minimal value on the oximeter (i.e. 15), representing an absence of perceivable cerebral oxygenation. In the other one, only one patient experienced ROSC. In the remaining nine studies, patients who achieved ROSC had significantly superior initial NIRS saturation values than patients

who did not (SMD 0.51 [95% CI 0.23-0.78], p=0.0003), with moderate heterogeneity in this subgroup (I^2=44%) (Figure 4).

Survival to discharge

Out of the 1919 patients who were included in the seven studies that addressed the survival to discharge outcome, a total of 54 (2.8 %) survived to discharge (Figure 5). Amongst the three studies presented the resuscitation's mean NIRS saturation values, only one reported parameter that could be estimated (the standard deviation (SD) must be different from zero in compared groups for a SMD to be calculated). Similarly, amongst the four studies presented initial NIRS saturation values, only two had parameters that could be estimated. Patients who survived to discharge had superior combined mean or initial NIRS values than patients who did not (SMD 1.63 [95% CI 1.34-1.92], p<0.00001) (Figure 5). When evaluated separately, differences in mean NIRS saturation values were not significant between survival groups (SMD 1.14 [95% CI -0.05 to 2.33], p=0.06), while differences in initial NIRS saturation measurements were significant (SMD 1.66 [95% CI 1.36-1.96), p<0.00001]. Unlike the ROSC outcome, there was no heterogeneity in the initial subgroup or between both subgroups (I^2=0%).

Good neurologic outcome

Only 27 (1.5 %) patients had a good neurologic outcome out of 1838 in the four studies that addressed the neurologic outcome. Two studies presented mean oximetry values during resuscitation and two others presented initial values. However, only two studies provided meta-analyzable data. Genbrugge *et al.* reported mean NIRS values and the effect observed was not significant in that study.[226] However, Nishiyama *et al.* reported initial NIRS measurements and the overall effect was significantly positive.[92] Patients with good neurologic outcome had superior combined mean or initial NIRS values than patients who did not (SMD 2.12 [95% CI 1.14-

3.10], p<0.00001) (Figure 6). When evaluated separately, differences in mean NIRS saturation values were not significantly different between neurologic outcomes groups (SMD 1.34 [95% CI -0.10 to 2.79], p=0.07), while initial values were (SMD 2.44 [95% CI 2.02-2.86], p<0.00001). Heterogeneity was moderate between subgroups (I^2=51%).

Other uses of NIRS during CPR

Three studies can be used to assess the usefulness of NIRS at guiding resuscitative efforts during CPR.[215, 219, 227] Kano *et al.* observed that NIRS values during defibrillation followed by ROSC were higher than those observed during defibrillation not followed by ROSC (51.6 [SD 4.2] vs 36.6 [SD 7.7]). They foresaw the potential use of NIRS monitoring, as opposed to an algorithm based on time, to determine when and who to defibrillate during resuscitation.[215]

Koyama *et al.* presented a NIRS-derived waveform variable that could follow the status and depth of ongoing cardiac massage. They postulated that the quality of the cardiac compressions could potentially be quantified using NIRS.[227] However, this was not confirmed by Kämäräinen *et al.*[219]

Sensitivity analyses and publication bias

We found no clear asymmetry in the funnel plot used to evaluate publication bias in the 19 studies addressing the ROSC outcome (Figure 7). For the other two outcomes, after inspection of the results and nature of the studies, we found no evidence of a publication bias. Only 115 patients experienced extracorporeal CPR amongst all identified studies. For this group of patients, there was no difference in NIRS values between patients who survived to discharge or who had a good neurologic outcome and their counterparts. All other sensitivity analyses, notably those excluding studies published more than three years ago, studies with a moderate/high risk of bias and those at a high risk of bias, smaller studies (n < 25), studies not using relative NIRS oximeters (all but FORE-SIGHT and Equanox), studies including in-hospital CA and studies including patients whose

initial rhythm was shockable, yielded no additional information. Sensitivity analyses done to evaluate the impact of the priority sequence for the type of NIRS measurements retained for analyses showed results consistent with the ones already presented, regardless of which order was used (online only Figures 2-19).

Discussion

The present meta-analysis sought to evaluate the association between different types of tissue oximetry monitoring measurements (mean, initial and highest values) and resuscitation outcomes (ROSC, survival to discharge and good neurologic outcome) during CA. As hypothesized, higher cerebral oximetry saturations during resuscitation were associated with better outcomes. The association of NIRS saturation with ROSC varied depending on the type of measurement used; mean values being a better predictor of ROSC than initial measurements. There was too much heterogeneity within the highest measurement group to perform meta-analysis. This could be explained by possible contamination produced by post-ROSC measures in some of the studies and the lower quality of the articles in that subgroup, as shown in the sensitivity analyses. Also, a cut-off mean NIRS saturation value of 30% during resuscitation has been identified as a marker of futility. There was no difference between the type of measurement used when examining the survival to discharge or the neurologic outcome. This is likely explained by the fact that a suboptimal resuscitation resulting in a neurologic insult, regardless of the moment, will affect the long-term prognosis. However, the lack of studies addressing this particular outcome may have prevented the present analysis from identifying a possible underlying difference. Also, the sensitivity analyses showed that results did not differ when smaller or older studies were excluded. Therefore, despite advances in care and technology, the results presented can be applied to the current population of cardiac arrest.

The results of the present study showed some similarities and some differences with those

recently published by Sanfilippo *et al*.[61] Similar in both meta-analyses are the observed associations between ROSC and higher, mean and initial oximetry values. The strength of those associations was slightly different in the two studies. The present study adds to the literature by demonstrating a significant association between the type of NIRS measurement during CA and the magnitude of the differences between the ROSC and non-ROSC patients. These new findings may be explained by four methodological differences. Firstly, the present study examined 12 additional studies that were not part of Sanfilippo's review, which accounted for only seven studies. This resulted in a greater variety and representability of patients and contexts, making our results more applicable to the different uses of NIRS technology in CA. Also, Sanfilippo chose to include only studies that presented mean and initial oximetry measures, while studies presenting the highest oximetry measures were excluded. Despite the high heterogeneity between these studies, the result presented is the only one available so far and is therefore useful for a large number of clinician using NIRS to such avail.[212, 216, 218, 223] Thirdly, instead of using the median, we used Wan's technique, a more precise statistical method, to estimate the mean and SD.[209, 210, 226] Lastly, one study was included in both of Sanfilippo's subgroups, which might have prevented them from finding a significant difference between the subgroups.[225]

The new findings described in the present study make a difference in the way this technology can be used during CA. Notably, it suggests clinicians should favor mean values over initial measurements for the evaluation of ROSC prognosis during resuscitation. While the mean values might not be as easily accessible during the resuscitative efforts, the results of the present study emphasize the importance of considering the trend of NIRS saturation during CPR. Indeed, a patient with a low initial NIRS saturation that rapidly trends upward may have a better prognosis than one who starts with a higher measurement and trends rapidly downward, similarly to what

has been described with capnography.[63] Also, a patient who, despite optimal resuscitation efforts, fails to achieve a NIRS saturation value of 30% has an extremely poor chance of ROSC. This information should be included in a multi-modal approach to the decision of terminating resuscitation (Class IIb, Level of Evidence C-Limited Data).[228] This study also adds to the literature by demonstrating that higher NIRS saturations during CA are strongly associated with survival and good neurologic outcomes.

The ability of NIRS to predict ROSC is likely explained by it being a surrogate measure of coronary perfusion pressure (CPP), since a higher CPP during CA has been shown to increase the oxygen tension in the brain.[229] To achieve ROSC, CPP must be maintained over 15 mmHg and ideally over 20.[230, 231] However, this vital information requires invasive monitoring that is rarely available during CA, especially in the out-of-hospital and emergency department setting. The diastolic pressure could help us estimate CPP, but it also requires invasive monitoring. End-tidal capnography ($ETCO_2$) is a well-accepted surrogate marker for cardiac output, coronary perfusion pressure and as an immediate prognostic tool during CA.[63, 64, 231, 232] However, many confounding factors can alter $ETCO_2$ and its prognosticating ability.[232, 233] Furthermore, $ETCO_2$ cannot be used as a surrogate for brain insult. In one study, the maximum NIRS value was superior to $ETCO_2$ in predicting the futility of the resuscitation.[234] In another study, NIRS was more specific, but less sensitive than $ETCO_2$ at predicting ROSC.[60] However, there was no clear NIRS cut-off value that would provide adequate sensitivity or specificity for this outcome due to the significant variability of the values for each brand of NIRS monitors.[135]

The results regarding the ability of NIRS to identify patients who will survive and those who will have good neurologic outcomes is probably better explained by its ability to assess neurologic injury and cerebral blood flow, seeing as how neurologic injury is one of the major contributors to disability after successful cardiac resuscitation.[95, 235] While NIRS can only measure the

oxygen content of the most superficial parts of the frontal lobes, it is probable that, given the global injury caused by cardiac arrest, saturation values measured in these regions of the brain are representative of the oxygenation of the remainder of the brain tissue. The low rates of survival to discharge (2.8 %) and of good neurologic outcomes (1.5%) in the study population, compared to the rates observed in the literature (e.g. 7.6%), can be explained by the fact that most of the patients included suffered from out-of-hospital CA and did not experience ROSC in the field, a population known to have a poor prognosis.[53, 141]

We also described the usefulness of NIRS monitoring at guiding resuscitative efforts during unplanned CA. Three very small studies addressed this issue, with conflicting results.[215, 219, 220] Indeed, despite all the differences we demonstrated regarding NIRS values in patients with good and bad outcomes, whether or not acting on these values can improve the patients' prognosis remains uncertain. However, the same can be said of the three other generally accepted measures of CPR prognostication (CPP, diastolic blood pressure and $ETCO_2$), no studies having ever shown that acting on their measures (e.g. by giving medication or improving cardiac massage quality) would lead to better patients' outcome.[14, 231] Nevertheless, the use of one of these techniques to monitor physiologic responses during CA is recommended by the American Heart Association.[14, 231] The clear differences in NIRS values between patients with good and bad outcomes presented in this study – coupled with its dynamic reactivity to resuscitative efforts and its ability to predict futility – are reasons why NIRS could be used as another non-invasive physiological metric to follow during CPR. Furthermore, the results of the present study showed that NIRS values were also associated with survival and neurologic outcomes, which is an improvement over the evidence available for the other monitoring techniques mentioned above.[14] This allows for the hypothesis that actions improving NIRS values could also contribute to improving patient-centered outcomes.[14, 231] That being said, future studies are needed to

evaluate which actions improve NIRS values during resuscitation and how NIRS based resuscitation could benefit both survival and neurologic outcomes.

Limits

Firstly, only two of the studies included more than 100 participants, only one of which was multi-center. On the other hand, nine of the studies retained for analysis included fewer than 25 participants. Also, the overall number of survivors and patients with good neurologic outcomes was low, limiting the strength of the conclusions drawn for the more patient-centered outcomes (survival and neurologic outcomes). This is also the case for patients suffering from in-hospital CA or for that underwent extracorporeal CPR, which represented only a minority of the patients analyzed and likely differ from the standard out-of-hospital CA population. Despite these limits, the results were still statistically significant in the in-hospital CA populations and clinically meaningful. This was not the case, however, for the patients treated with extracorporeal CPR and clinicians should use NIRS with caution when treating that population. Additionally, values from the post-ROSC period could have contaminated some of the results of studies presenting highest NIRS saturation values during resuscitation, biasing the results towards a greater difference between ROSC and non-ROSC groups. Albeit to a lesser extent, this is also true for studies presenting mean NIRS values. Also, no study presented adjusted results to other predictors of CA such as the Utstein data elements.[52] Finally, no study evaluated other types of measurement which could have proven useful to clinicians regarding the best measurement of cerebral oximetry to use to predict resuscitation outcomes (such as, for example after 20 minutes of effective resuscitation).[63]

Conclusion

Patients experiencing ROSC, surviving to discharge and surviving with good neurological outcome after CA have higher NIRS value than their counterparts. The mean values during resuscitation

are more strongly associated with ROSC than the initial values, and clinician should therefore seriously take into account the NIRS saturation trends measured during resuscitative efforts when using this technology. Prolonged failure to obtain a NIRS saturation greater than 30% may be included in a multi-modal approach to the decision of terminating resuscitation (Class IIb, Level of Evidence C-Limited Data). There was too much heterogeneity within the highest measurement group to perform meta-analysis. NIRS monitoring is a promising tool that could serve as an easy-to-install and non-invasive surrogate marker of perfusion for hemodynamic-directed resuscitation. However, future studies evaluating which resuscitative actions (e.g. medications, CPR or an improvement in its quality) best improve NIRS saturation values and could contribute to improving patient outcomes. Randomized-controlled trials should follow in order to evaluate how NIRS guided-resuscitation will result in observable benefits both on survival and neurologic outcomes.[224]

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Disclosures

Dr. André Denault is part of a speakers bureau for Masimo, Edwards and CAE Healthcare.

Tables

Tableau 28 : Table 1. Characteristics of Included Studies

Study	Type of article	Level of risk of bias	Number of patients	Types of measurement	Type of oximeter	Location of CA	Outcome
Ahn 2013[225]	Full text article	Low	50	Mean and initial	Equanox 7600	IHCA and OOHCA	ROSC
Asim 2014[218]	Full text article	Intermediate	23	Highest	INVOS 5100c	OOHCA	ROSC
Ehara 2013[93]	Abstract	High	34	Initial and highest	TOS-OR	OOHCA	ROSC and survival
Fukuda 2014[213]	Full text article	Low	69	Initial	INVOS 5100c	OOHCA	ROSC and survival
Genbrugge 2015[214]	Full text article	Low	49	Mean, initial and highest	Equanox 7600	OOHCA	ROSC, survival and neurologic outcome
Ibrahim 2015[208]	Full text article	Intermediate	27	Mean and initial	INVOS 5100c	IHCA	ROSC
Kalkan 2015[212]	Full text article	Intermediate	34	Highest	INVOS 5100c	OOHCA	ROSC
Kämäräinen 2012[219]	Full text article	Intermediate	9	Mean, initial and highest	INVOS 5100c	IHCA	ROSC and survival
Kano 2014 * [215]	Abstract	High	19	-	NIRO-200NX	OOHCA	-
Kano 2014[216]	Abstract	High	95	Highest	NIRO-200NX	OOHCA	ROSC
Koyama 2013[227]	Full text article	Intermediate	15	Initial	NIRO	OOHCA	ROSC
Meex 2013[221]	Full text article	Intermediate	14	Initial and highest	Equanox 7600 and Fore-Sight	IHCA and OOHCA	ROSC
Mullner 1995[222]	Full text article	Intermediate	6	Initial	INVOS 3100	OOHCA	ROSC, survival and neurologic outcome
Nakahori 2008[217]	Abstract	High	24	Initial	TOS96	OOHCA	ROSC
Newman 2004[223]	Full text article	Intermediate	16	Highest	INVOS 3000	OOHCA	ROSC
Nishiyama 2015[92]	Full text article	Low	1773	Initial	INVOS 5100c	OOHCA	ROSC, survival and neurologic outcome
Parnia 2014[209]	Full text article	Low	34	Mean	Equanox 7600 and INVOS	IHCA	ROSC
Parnia 2012[224]	Full text article	Intermediate	15	Mean	INVOS	IHCA	ROSC
Schewe 2014[226]	Full text article	Low	10	Mean	Equanox 7600	OOHCA	ROSC
Singer 2015[60]	Abstract	High	142	Mean	NA	OOHCA	ROSC

* : Only included in the qualitative synthesis; IHCA: In-hospital cardiac arrest, OOHCA: Out-of-hospital cardiac arrest, ROSC: Return of spontaneous circulation

Tableau 29 : Table 2. Differences in highest NIRS measures during resuscitation between patients achieving ROSC and those who do not (Non-ROSC)

Study	ROSC Highest NIRS			Non-ROSC Highest NIRS			SMD (95% CI)
	Mean	SD	n	Mean	SD	n	
Asim 2014[218]	69.3	15.81	7	28.1	10.20	16	3.29 (1.92-4.66)
Ehara 2013[93]	67.6	6.26	14	49.6	9.62	17	2.11 (1.21-3.01)
Genbrugge 2015[214]	52	14	19	40	16	30	0.77 (0.18-1.37)
Kalkan 2015[212]	70.7	10.74	13	24.2	8.93	21	4.70 (3.33-6.08)
Kämäräinen 2012[219]	56.4	17.76	7	41	36.73	2	2.74 (2.12-3.37)
Kano 2014[216]	64.3	11.4	21	41	7.4	74	0.64 (-0.98-2.26)
Meex 2013[221]	43	18	6	45	13	8	-0.12 (-1.18-0.94)
Newman 2004[223]	16	2	4	15	0	12	Not estimable

NIRS: Near-infrared spectroscopy; ROSC: Return of spontaneous circulation; SD: Standard deviation; SMD: Standardized mean deviation; 95% CI: 95% confidence interval

Figures

Figure 8 : Figure 1. Flow diagram of the systematic search

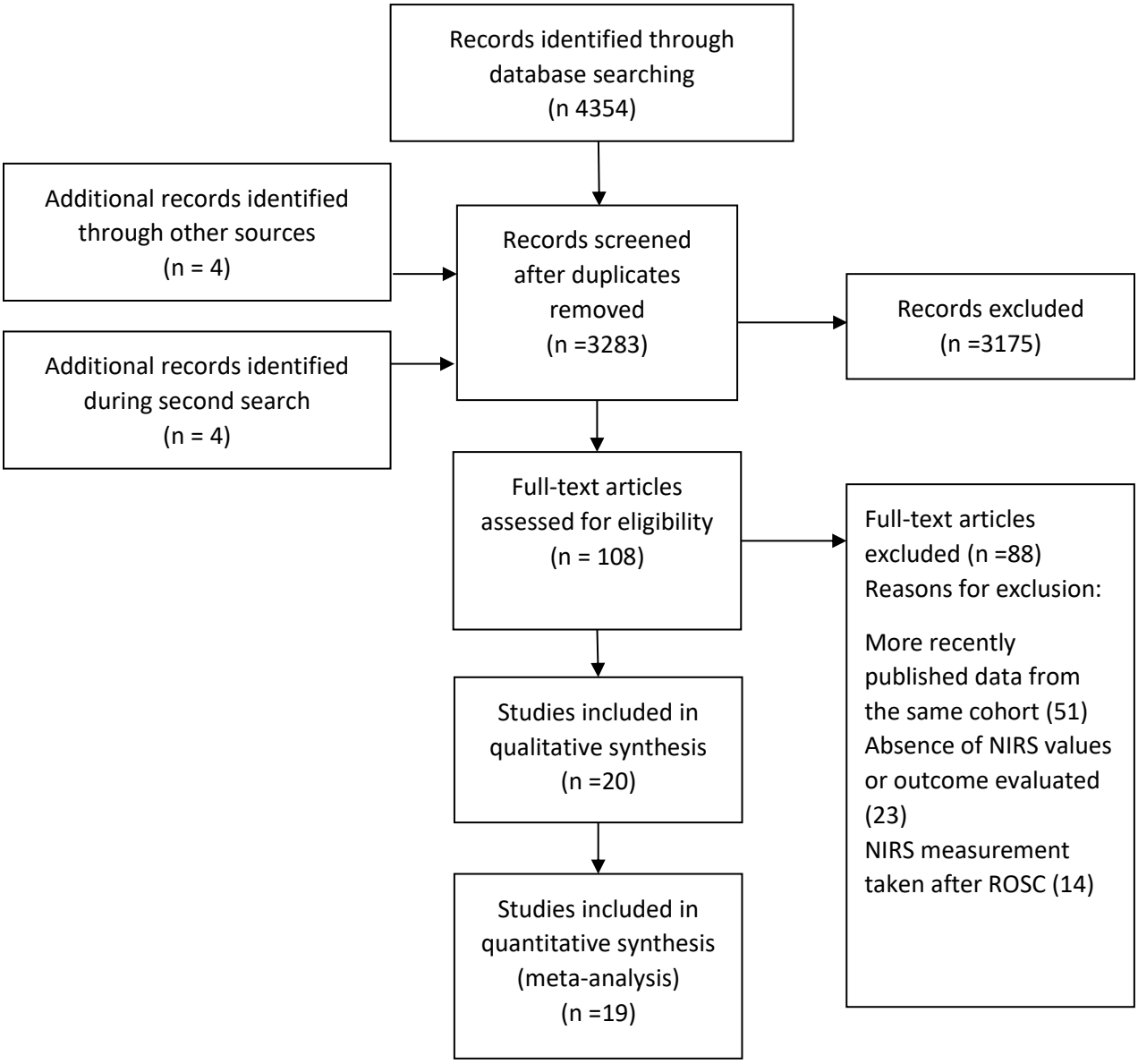


Figure 9 : Figure 2. Meta-analysis evaluating the association between the transport to a cardiac resuscitation center and survival

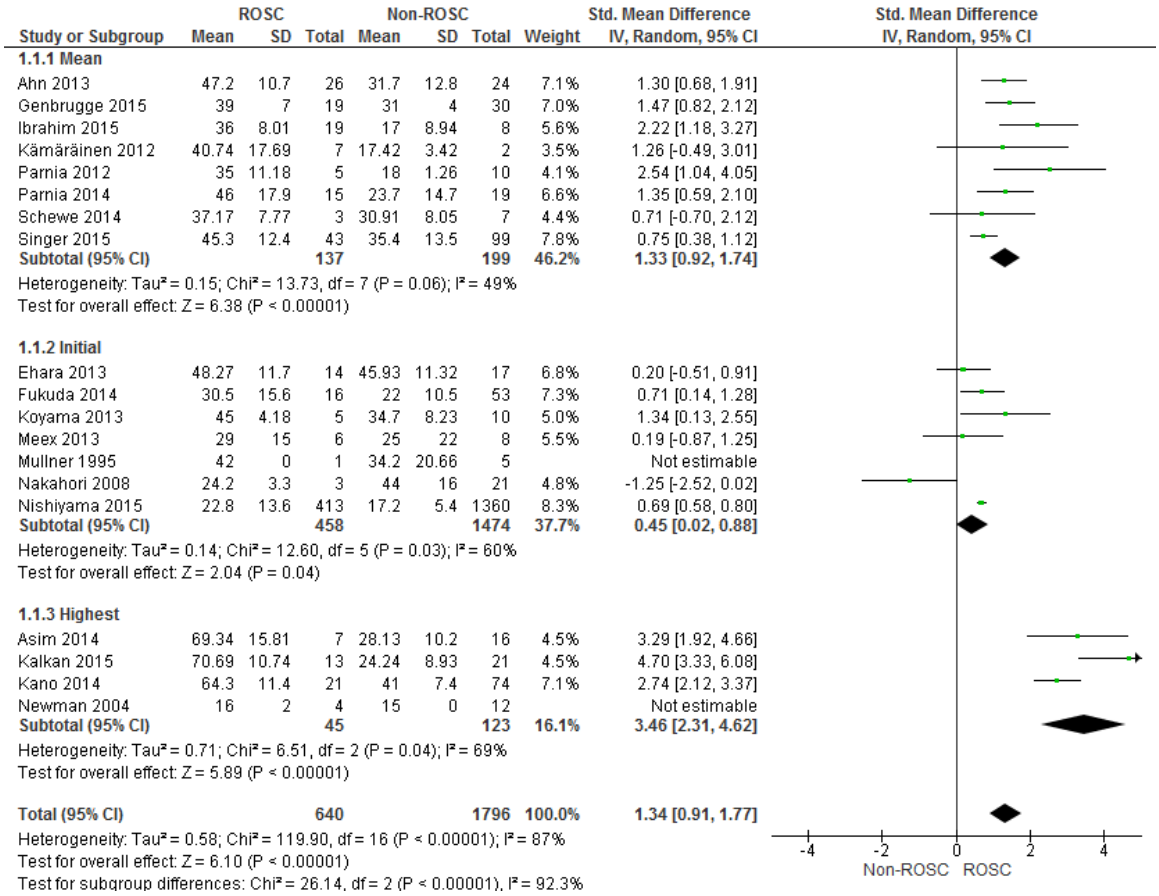


Figure 10 : Figure 3. Meta-analysis evaluating the association between the transport to a cardiac resuscitation center and survival with a good neurologic outcome

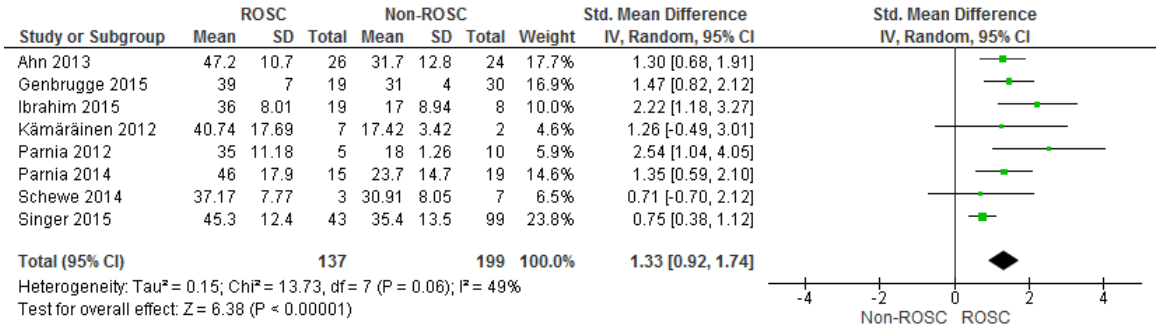


Figure 11 : Figure 4. Differences in initial NIRS measures between patients achieving ROSC and those who do not (Non-ROSC)

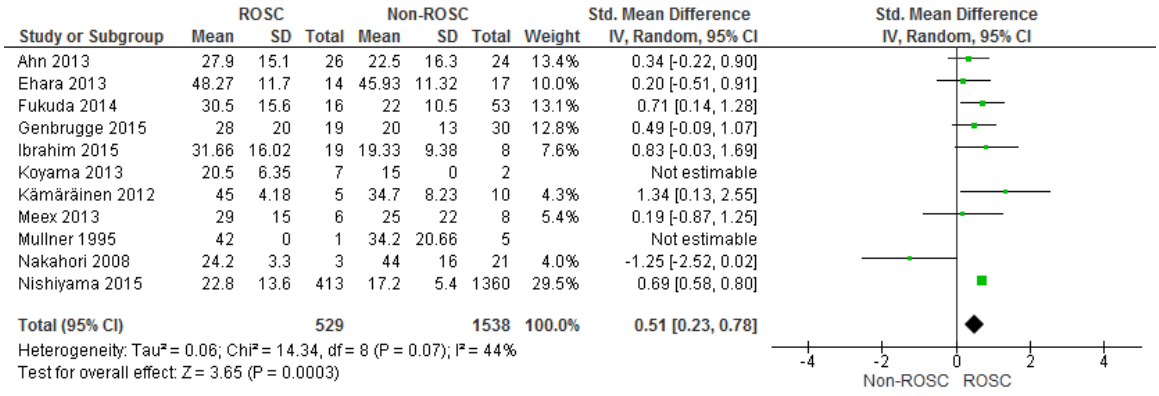


Figure 12 : Figure 5. Differences in NIRS measures between patients surviving to discharge and those who do not

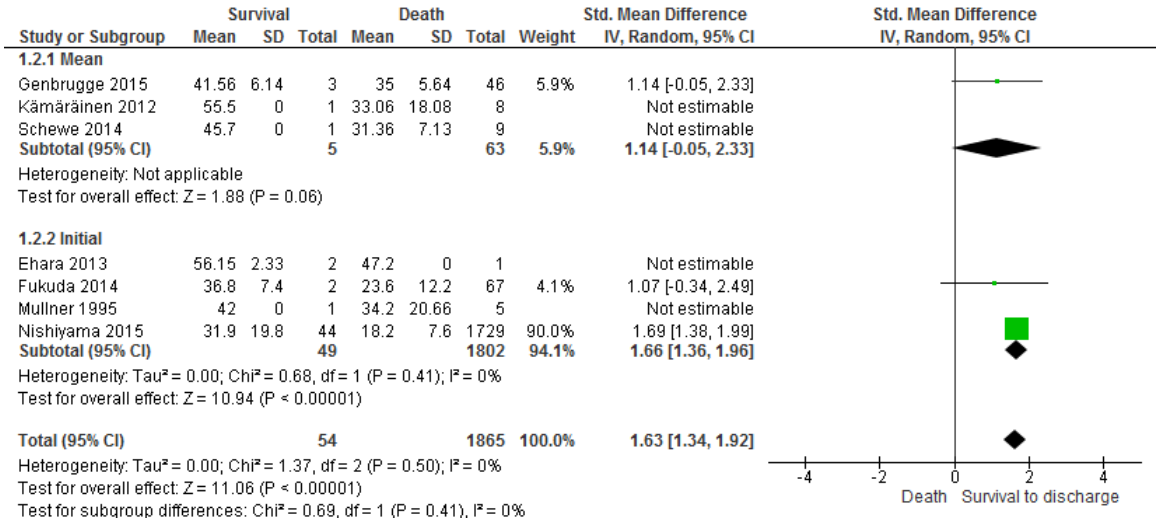


Figure 13 : Figure 6. Differences in NIRS measures between patients with a good neurologic outcome and those with a bad outcome

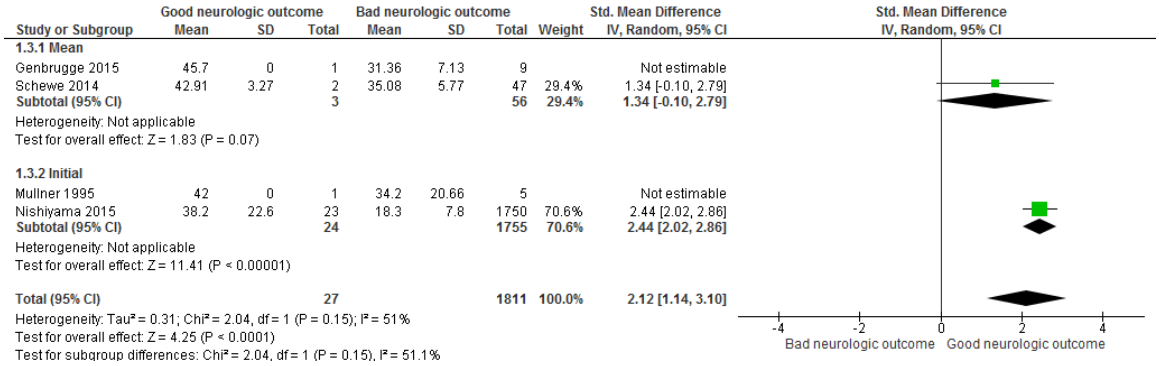
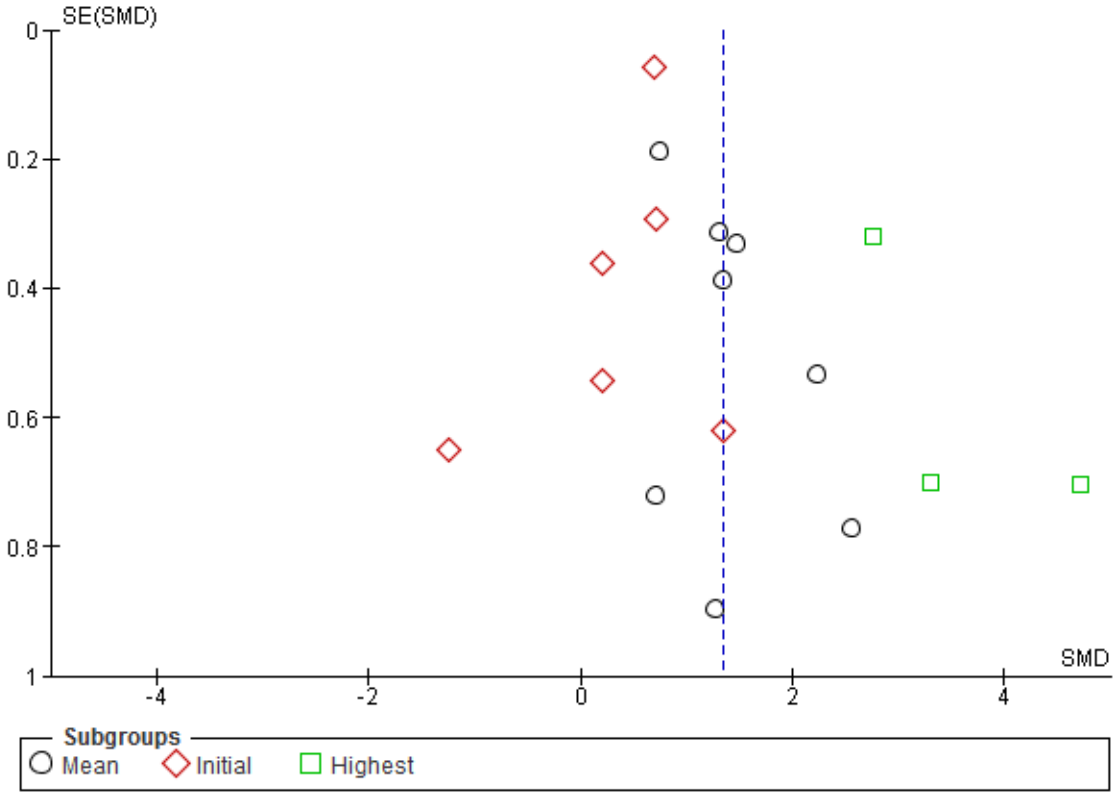


Figure 14 : Figure 7. Funnel plot for the evaluation of publication bias



3.3.2. Volet 3 – Article 2 – Reproducibility, interchangeability of measures, time to measure stabilization, and reference values of two tissue oximeters in healthy volunteers

3.3.2.1. Préface

Cette étude a été réalisée en collaboration avec sept autres chercheurs. J'ai réalisé plus de 90% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Éric Notebaert, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. Le recrutement, ainsi que l'expérience et la collecte des données a été réalisée de manière indépendante. La taille d'échantillon a été déterminée par Annick Fortier et les analyses ont été réalisées en collaboration avec elle. Leurs interprétations ont été effectuées en collaboration avec Annick Fortier et Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette et Massimiliano Iseppon. André Denault, Éric Notebaert, Raoul Daoust et Jean-Marc Chauny ont également contribué à sa révision. Cette étude a été publiée dans le journal Journal of Biomedical Optics en 2016 (Facteur d'impact en 2016 : 2,849).

3.3.2.2. Volet 3 – Article 2

Reproducibility, interchangeability of measures, time to measure stabilization and reference values of two tissue oximeters in healthy volunteers

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Abstract. This study aimed to compare two tissue oximeters, the INVOS 5100c and the Equanox 7600, in terms of their reproducibility and the interchangeability of their measures. In a randomized order, three measurements were taken at six different sites on both sides of the body in 53 healthy volunteers. Intra-class correlations (ICC) and within-subject standard deviation (S_w) were calculated for each device. The ICCs were compared using Fisher r-to-z transformation and the S_w were compared using paired-sample t-tests. We found no difference between the reproducibility of the INVOS (ICC=0.92 [95% confidence interval (CI) 0.90-0.93] and Equanox (ICC=0.90 [95% CI 0.88-0.93]) in terms of ICCs (p=0.06). However, the Equanox (Sw=1.96 [95% CI 1.91-2.02]) showed a better S_w than the INVOS (S_w=2.11 [95% CI 2.05-2.17]) (p=0.019). Also, when compared directly in stable condition, the readings produced by the two oximeters varied considerably (ICC 0.43 [95% CI 0.36-0.49]). When taken individually, both tissue oximeters displayed good reproducibility, the Equanox being slightly better than the INVOS in terms of

absolute reproducibility. However, when compared, the oximeters showed poor inter-devices agreement. Reference values were also described.

Keywords: near-infrared spectroscopy, tissue oximetry, reproducibility, inter-device agreement, reference values.

*First author

1 Introduction

Patients presenting hemodynamic instability should be aggressively managed without delay.[236, 237] This often involves the use of invasive monitoring tools, such as arterial lines or central venous catheters, in order to monitor tissue perfusion. Although they provide useful information, these tools are often unavailable and require time to install. During resuscitation, the utility of laboratory values is blunted by the fact that they provide static information on a continuously evolving clinical process. The time required to access these values can result in outdated information that provides little real-time feedback on the efficacy of the resuscitation. Near–infrared spectroscopy (NIRS) is a non-invasive, continuous and painless method of monitoring the oxygen saturation of hemoglobin in any given superficial tissue (tissue saturation) and, as such, can be used as a way of detecting tissue hypoperfusion. Unlike pulse oximetry, which only measures the arterial saturation of hemoglobin, NIRS measures the saturation in all vessels smaller than 1 mm (arterioles, capillaries, and venules).[89] NIRS devices can also provide saturation measures in situations of circulatory arrest, as they do not depend on pulsation to provide its readings. Tissue perfusion (and saturation) is affected in situations of hemodynamic instability.[85, 238, 239] Thus, the quantification of tissue saturation by NIRS oximetry could prove to be an interesting surrogate measure for tissue perfusion and a useful tool in guiding resuscitation in settings where more invasive tools are unavailable, such as when out of the

hospital or in the emergency room. They can also prove to be an interesting addition to other specialities of critical care, such as anaesthesiology and the intensive care.

NIRS technology was developed after an experiment by Jöbsis, which showed that light spectrum could be used as away to monitor patients. This is based on two unique properties. The first is that near–infrared photons (i.e., photons with a 700 to 1300 nm wavelength) have the capacity to go through organic tissues without being significantly absorbed. The second is that oxyhemoglobin and deoxyhemoglobin have different absorptions properties along this wavelength spectrum, allowing them to be differentiated.[88] Using the Beer-Lambert law and an algorithm, NIRS devices calculate the total concentration of both these molecules, thus providing a value representing tissue saturation in oxygen (StO2).

While this technology is promising, it has been proposed that an eventual standardization of NIRS oximeters would be useful to future development of this technology and the expansion of its use in critical care. One of these areas is the reproducibility of tissue oximeters, which has not been thoroughly studied. Current data has shown that the difference between two successive measurements can be quite large, although some oximeters have shown better reproducibility than others.[134, 136, 137, 240, 241] Also, newer tissue oximeters have only been studied with forehead and forearm readings in adults, other sites have been included in past clinical research.[134, 136]

The main objective of this study was to compare the reproducibility of two commonly used tissue oximeters, the INVOS 5100c (Covidien, Mansfield, MA, USA) and the Equanox 7600 (Nonin Medical, Plymouth, MN, USA). For the primary outcome, we hypothesized that the Equanox would display a better reproducibility than the INVOS owing to its more recent development. The effects of sensor switching, measurement site and side of body (left vs. right) on reproducibility

were evaluated as secondary outcomes. The second objective was to describe the interchangeability of the oximeters and sides of the body to provide similar raw tissue saturation measurements. The third objective was to assess the time necessary for each of the oximeters to provide a stable value for tissue oximetry. Finally, the last objective was to describe and compare reference values for NIRS saturation for all sites evaluated.

2 Methods

2.1 Design and setting

This prospective cohort study was conducted at the Hôpital du Sacré-Coeur de Montréal, in association with the Université de Montréal, Canada. It was submitted and approved by its Ethics Committee prior to enrolment.

2.2 Population and sample

A convenience sample was comprised of healthy adult volunteers. Recruitment was conducted via snowball sampling, mainly amongst hospital employees between March and April 2015. Exclusion criteria included pregnancy, active or chronic systemic illness, the use of medication other than oral contraceptives, skin disease, very coarse hair overlying measurement sites, active smoking, substance use, weight less than 40 kg or a body mass index lower than 18 or higher than 35. All recruited volunteers signed informed consent waivers prior to their inclusion in the study.

2.3 Material

The two tissue oximeters we used in this study both use the multidistance spectroscopy technology. By using multiple light-emitting diodes, sensors at varying distances and multiple wavelengths, they are able to measure variations in the absorption of the near-infrared

photons.*[90, 91]* This allows them to blunt superficial tissue's contribution to their readings, better representing the target tissue (brain, muscle, etc.) saturation.

The INVOS 5100C with adult SomaSensor has two light-emitting diodes (730 and 810 nm) at one position and two receptors at distances of 30 and 40 mm. The EQUANOX 7600 with Equanox Advance 8004CA sensors uses eight light-emitting diodes split in groups of four (730, 760, 810 and 880 nm) at two positions separated by 60 mm. It uses two receptors placed between the emitting groups. Each receptor is 20 mm proximal to an emitting group and 40 mm distal to the other. The INVOS estimates that the mixed arterio-venous oxygen saturation it measures is fixed at 25:75, while the Equanox estimates it is 30:70.

2.4 Measures of cerebral and somatic oximetry

Prior to measures being taken, participants were asked to provide their basic sociodemographic characteristics and their phototype, using the Fitzpatrick phototyping scale.[138] At the beginning of the experiment, participants were asked to lie on their backs while their vital signs and skinfold thickness (using a Harpenden Skinfold Caliper) were measured. Six sites (forehead, deltoid, forearm, knee, calf and foot) on both sides of the body were then marked with either a pen or tape to ensure that the same exact location was used for each sensor throughout the measure collection (cf Fig. 1).

The order in which each tissue oximeters was used was randomized. The sensors were placed on each of the measurement sites until the reading was stable. A stable reading was defined as an identical value in two consecutive measurements, measures alternating between two contiguous values, or a maximum delay of 20 seconds from the first reading. In the latter case, the last recorded value was retained. The time delay to stabilisation was noted. If a measure was not provided within 30 seconds of sensor apposition, the sensor, cables and connections were

verified. Should the oximeter persist in its failure to provide a measure, its functionality was tested on the experimenter. In instances where the oximeter provided a measure on the experimenter but not on the subject, the data was considered as missing, and the experimenter proceeded to the next site with the same sensor. Values from various measurement sites were taken in a predetermined order (forehead, deltoid, forearm, knee, calf then foot) with a first sensor (s1). Once all sites had been evaluated on both sides of the body (t1), the process was repeated at 5 minutes (t2) a second time with the same sensor (s1) to evaluate the intra-sensor reproducibility. After the second run, the procedure was repeated a third time at 10 minutes (t3) with a different sensor of the same oximeter model (s2) to assess the inter-sensor reproducibility. The same procedure was then used for the second oximeter. Because up to 24 measures would ultimately need to be taken with the same sensor, it was decided that the sensors would be held in place manually by the experimenter instead of using the adhesive, in order to avoid skin irritation. That being said, great care was taken neither to compress the sensors nor to expose them to ambient light during measurements, so as to avoid impacting the values measured. Every measure was either collected or supervised by the primary author (AC). This process was repeated for each of the two oximeters. A total of 72 measures were recorded for each subject in the study (six sites per side of the body, three values per site for each of the two oximeters).

2.5 Sample size determination

The measurement reproducibility for each oximeter was assessed using the intraclass correlation coefficient (ICC). Given the absence of literature on the power required for a test for the comparison of dependant ICCs based on two-way ANOVAs, we based our sample size calculation on the precision of a unidirectional confidence interval (CI) for a parametric ICC. An ICC is a correlation coefficient whose value varies between 0 and 1. It is used to assess reproducibility

and depends not only on the differences observed between the repeated measurements, but also on the variation between pairs of the sample. An ICC over 0.75 is considered an indicator of good reproducibility, while an ICC under 0.40 represents poor reproducibility. For an expected ICC value of 0.75, we concluded that 53 participants needed to be recruited in order to obtain a one-sided 95% CI (computed using the large sample normal approximation) for an ICC based on two measurements, given that the CI will extend about 0.1 towards the low values from the observed ICC. A good precision for the CI of the ICCs was assumed to be associated with good statistical power for the comparisons of ICCs.

2.6 Statistical analysis

Collected data was held and managed at Hôpital du Sacré-Coeur de Montréal. Statistical analyses were done both at the aforementioned hospital and the Montreal Health Innovations Coordinating Center, using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

2.6.1 Main objective

Both intra-sensor and inter-sensor ICCs and their respective 95% CI were calculated for each individual measurement site and for each side of the body, thus providing 24 ICC values (95% CI) for each oximeter. Overall intra-sensor and inter-sensor ICCs (95% CI) were also calculated for each oximeter. To complement the analysis of reproducibility we calculated global intra-sensor and inter-sensor within-subject standard deviation (S_w) (% and 95% CI), mean bias (%) and limits of agreement (%) for each oximeter using the Bland-Altman method.[139] To compare our results with the currently available literature on the forearm site, we also calculated both oximeters forearm intra-sensor S_w. Plots of Identity and Bland-Altman plots were used to illustrate the data. S_w are also a measure a reproducibility and represent the standard deviation of repeated measurements in an individual. Whereas variations within the sample influence the ICC (making

it a marker of relative reproducibility), they do not influence the S_w, making it a marker of absolute reproducibility. A lower S_w represents a better reproducibility than a higher S_w. Mean bias represent the average difference between two repeated measurements. A mean bias close to zero is a sign of good concordance. Limits of agreement represent the range of values in which the difference between repeated measurements will be comprised 95% of the time. A smaller range of limits of agreement represent better reproducibility than a wider range of limits of agreement.

The primary outcome of the main objective was the comparison of the global inter-sensor ICCs between the INVOS and Equanox. We retained the inter-sensor ICC instead of the intra-sensor ICC because it represents the reproducibility of the oximeter and its sensor combined. Comparisons of ICCs were done using the Fisher's r-to-z transformation method. All other ICC comparisons (INVOS vs Equanox intra-sensor and intra-sensor vs inter-sensor for both oximeters) were secondary outcomes. Also as secondary outcomes, S_w comparisons (INVOS vs Equanox inter-sensors, INVOS vs Equanox intra-sensor and intra-sensor vs inter-sensor for both oximeters) were done using paired sample t-tests.

Lastly, for the main objective, global ICCs, S_w, mean bias and limits of agreement were also calculated for each site of sensor application and side of the body. Comparisons of ICCs between sites of sensor application and between sides of the body were done using the Fisher's r-to-z transformation method while comparisons of S_w between sites of sensor application and between sides of the body were done using paired sample t-tests.

2.6.2 Second to fourth objectives

For these objectives, the average of the three values for both tissue saturation and time to measure stabilization obtained (c1t1, c1t2 and c2t3) on each of the 12 sites were used. For our

second objective, we describe the interchangeability of the devices and sides of the body by comparing individual raw tissue saturation measurements. This comparison was done by calculating ICCs, S_w, mean bias and limits of agreement presented as descriptive statistics.

For our third objective, we collected data on the time necessary for both oximeters to give a stable value and, for our fourth objective, we described the reference values for each site and side of the body for each oximeter. For comparisons of time to measure stabilization and reference values between the two oximeters, three-way repeated measure ANOVA were used.

3 Results

3.1 Baseline characteristics

Fifty-three healthy volunteers were included in this study, with ages ranging between 20 and 81 years old. With the exception of oral contraceptives (n=14), none took any medication on a regular basis. No patients enrolled had a chronic or active illness. Participant characteristics are presented in Table 1.

On 23 occasions (21 [1.1%] with the INVOS and two [0.1%] with the Equanox), despite otherwise functioning normally, the oximeters failed to provide a saturation value. No adverse reactions were observed during the course of the trial.

3.2 Measures of reproducibility

3.2.1 INVOS

Inter-sensor ICCs for the INVOS oximeter ranged from 0.78 to 0.91, while the intra-sensor ICCs ranged from 0.76 to 0.96 (cf Table 2). Global ICCs for the INVOS oximeter, as well as

S_w, mean bias and limits of agreement are presented in Table 3, Fig. 2 and Fig. 3. The INVOS forearm intra-sensor S_w was 2.97% (95% CI 2.77-3.18) (data not shown).

3.2.2 Equanox

Inter-sensor ICCs for the Equanox oximeter ranged from 0.73 to 0.94, while intra-sensor ICCs ranged from 0.77 to 0.96 (cf Table 4). Global ICCs for the Equanox oximeter, as well as S_w, mean bias and limits of agreement are presented in Table 5, Fig. 4 and Fig. 5. The Equanox forearm intra-sensor S_w was 2.68% (95% CI 2.50-2.87) (data not shown).

3.2.3 Comparisons of reproducibility between the two oximeters

For the primary outcome of our main objective, we found no significant difference when comparing both oximeters in terms of global inter-sensor ICC using the fisher r-to-z transformation (p=0.06) (cf Tables 3 and 5). For the secondary outcomes, using the same method, we also found no significant difference between the two oximeters in terms of global intra-sensor ICCs (p=0.78). However, the intra-sensor ICC of the Equanox was better than its inter-sensor ICC (p=0.003), which was not the case for the INVOS (p=0.42) (cf Tables 3 and 5). Using the Bland-Altman method, the Equanox displayed a significantly better inter and intra-sensor S_w than did the INVOS (p=0.019 and p<0.001, respectively). Again, the intra-sensor S_w of the Equanox was better than its inter-sensor S_w (p<0.001), while no such difference was found for the INVOS (p=0.28) (cf Tables 3 and 5 and Fig. 2-5). Both oximeters displayed adequate consistency across the range of observed results, as shown by the similarities displayed in dot dispersion around the reference line of the Bland-Altman plots (Fig. 3 and 5).

3.2.4 Comparisons of reproducibility between sides of the body and sites of measurement

Lastly, for the main objective, ICCs and S_w were similar when comparing both sides of the body (p=0.58 and p= 0.74, respectively). When comparing ICCs, amongst all possible comparisons between sites, the knee site displayed better ICCs than all the other sites (p ranging from 0.005 to <0.001). Also, the deltoid and calf sites were superior to the forearm site (p=0.009 and p<0.001, respectively). Using the Bland-Altman method, measures from the knee and calf sites had better S_w than did all other sites (p-values ranging from 0.005 to <0.001). Furthermore, the forehead, deltoid and foot had better S_w than the forearm site (p-values ranging from 0.002 to <0.001) (cf Table 7).

3.3 Interchangeability of the oximeters and sides of the body to provide similar raw tissue saturation measurements

For the second objective, tissue saturation measures provided by the two oximeters varied considerably (ICC 0.43 [95% CI 0.36-0.49], Bias -0.77 [Limits of agreement -19.88 to 18.34]). When evaluated together, all tissue saturation measurements from the Equanox showed less variation (SD 8.0) than the ones from the INVOS (SD 10.2). Thus, in comparison to the INVOS' tissue saturation measurements, the Equanox generally displayed higher tissue saturations when in the lower saturations range (e.g. around 40 to 60%) and lower tissue saturations in the higher saturation range (e.g. around 75 to 90%). This can be appreciated in Fig. 6 in the Bland-Altman plot by noticing that the dot cloud seems to follow a negative linear regression. On the other hand, the tissue saturations varied much less when we compared the readings from the left and right sides of the body (ICC 0.91 [95% CI 0.89-0.92], Bias -0.34 [Limits of agreement -7.94 to 7.25]) (cf Fig. 7). Those results are similar to the ones previously described for inter and intra-sensor reproducibility (cf Tables 3 and 5 and Fig. 2-5).

3.4 Time necessary for measure stabilization

For the third objective, the time necessary for stabilization of the oximetry measures were calculated using mean values for each site in each of the study participants. The Equanox displayed a quicker time to stabilization than the INVOS (4.7 seconds [SD 1.4] vs 9.5 seconds [SD 3.3], $p<0.0001$). All other comparisons done (between measurement site and side) were not considered clinically significant (data not shown).

3.5 Reference values

Four the last objective, reference values for each tissue oximeters calculated using the mean values of each site for each volunteer are presented in Table 7. They ranged from 58.6 (SD 8.8) to 77.0 (SD 7.4). Using a 3-way repeated measures ANOVA (oximeter * side * site), small to no differences were observed between sides of the body. However, the differences were substantial when comparing sites and oximeters (e.g. INVOS left deltoid [77.0%] vs INVOS left foot [58.6%], $p < 0.0001$).

4 Discussion

The present study sought to compare the reproducibility of two commonly used tissue oximeters. Both oximeters exhibited good reproducibility. Interestingly, no differences were observed when ICCs were used to assess this metrological characteristic, but the Equanox displayed better reproducibility when the Bland-Altman method was used, displaying smaller S_w and limits of agreement. The reproducibility also varied amongst measurement sites, but not between each side of the body. Despite the good intra-oximeter reproducibility, the interchangeability of raw saturation value between both oximeter was deficient, reflecting poor inter-oximeter agreement. To our knowledge, this is the first time that that both of these characteristics (reproducibility and interchangeability) were evaluated for tissue saturation at sites other than the forehead and the forearm, or for multiple sites of the body. The wide range of observed values in our experiment

allowed a good appraisal of these characteristics. In addition, we showed the Equanox was faster at providing a stable saturation measurement than the INVOS was, a characteristic that had never been evaluated in these two devices. Finally, reference values for the two oximeters used were also described for the first time at sites most often currently used in clinical practice.

The Equanox showed better absolute reproducibility, as reflected by better S_w values than the INVOS, but similar relative reproducibility, as reflected by the similar ICC values. This is likely explained by the fact that, as explained earlier, the ICC is a correlation coefficient and therefore takes into account the variability and range of the observed measures, thus providing a relative measure, while the S_w and limits of agreement are absolute measures of reproducibility. The Equanox also provided a smaller range of observed values across the measurement sites and sides of the body than did the INVOS. Based on these results, the Equanox could be favoured over the INVOS, especially when NIRS monitoring is used intermittently or in unstable conditions, since good reproducibility of a device is more important in these conditions than in continuous or stable monitoring. That being said, the magnitude of the differences observed in terms of reproducibility between the two oximeters is quite small and should not be the sole determinant of the type of oximeter used. Other issues that should be considered include price, versatility, convenience or institutional preferences. The Equanox's intra-sensor reproducibility was better than its inter-sensor reproducibility. This should encourage clinicians using this device to use a single sensor per patient whenever possible.

These results contrast in some aspects with prior published studies. Firstly, studies evaluating NIRS reproducibility only presented S_w values, and not ICCs, making ICC comparisons impossible. These studies reported S_w ranging from 3 to 7%.[134, 136, 137, 240, 242-245] Notably, in three different studies, Hyttel-Sorensen observed S_w of 5.4% [136], 2.9% [134] and 4.0% [244] using value measured on the forearms of healthy adults using the INVOS. We, on the other hand,

observed slightly lower S_w of 3.0% for the same measurement site. As for the Equanox, an S_w of 4.6% was observed in the sole study it was used in, as compared to the 2.7% S_w we observed.[134] Therefore, the reproducibility observed in our study is amongst the better values previously mentioned in the available published data. This is possibly because we standardized the data collection procedures and technique. In our experiment, all measurement sites were marked, participant body position was stable and all measurements were taken or directly supervised by the same investigator (AC). This may have contributed to our better measures of reproducibility, which are similar to the best values observed by Hyttel-Sorensen.[134] This emphasizes the necessity to be both familiar and rigorous with the procedure used when NIRS monitoring is utilized, especially in case where intermittent measures are taken. The Fore-Sight (Casmed, Branford, CT, USA), another oximeter less commonly used that we did not evaluate, compared favourably to both the INVOS and Equanox in terms of reproducibility in other experiments. In light of our results, this oximeter likely merits more rigorous evaluation in further studies of reproducibility.[105, 134, 243]

We identified variations in the reproducibility between measurement sites, but not between sides of the body. Variations in the reproducibility between measurement sites had already been observed in a paediatric study, which only included measures from the forehead and arm.[244] This should influence the way intermittent monitoring with this technology is done. Indeed, when intermittent peripheral NIRS monitoring is used to assess body perfusion, such as in the intensive care unit, the knee and calf sites should be favoured over other sites because of their better reproducibility. Of course, this does not apply when upper extremity specific saturations are warranted, such as in situations where upper extremity ischemia is suspected.

Despite similar mean values in both samples, inter-oximeter agreement was poor on an individual basis, with limits of agreement of ± 19%. This is even larger than what had already been observed

in multiple settings and between other brands of oximeters.[135, 246-249] This is likely explained by the measurements over sites - such as the deltoid, knee or foot - for which this had never been evaluated. Moreover, it is probable that ischemia worsen disagreements between oximeters' readings.[247] Thus, our results seem to reinforce the fact that readings from different brands of oximeters are not interchangeable, and that absolute thresholds of clinically significant ischemia are oximeter-specific, and need to be studied individually. This high variability is likely caused by the fact that each type of NIRS oximeter has unique characteristics (number of light-emitting diodes and receptors, distances between diodes, wavelengths used). This will influence the size and depth at which the underlying tissue is evaluated (wide distances between emitters and receptors increase the volume of tissue evaluated).[250, 251] Moreover, tissue oximeters use a specific algorithm to calculate the overall concentration of oxyhemoglobin and deoxyhemoglobin.[252] This is explained by the absence of a recognized gold-standard for tissue oxygenation which led to lack of standardization for the NIRS technology.

On the other hand, inter-side agreement was much better with limits of agreement of ± 8%, a value that is somewhat smaller than what has been previously observed in the cardiac and vascular surgery population.[253] This difference is probably explained by the assumed absence of significant vascular disease in our sample of healthy volunteers, a characteristic that could potentially create asymmetry limbs perfusion. This description could help guide clinicians when caring for a healthier population when searching for perfusion asymmetry between limbs.

The Equanox was quicker to give a stable reading than the INVOS. While the difference observed (~ 5 seconds) might not be clinically relevant in a hospital setting, the Equanox could be favored if this technology is used as a triage assessment tool in mass casualty events, helping to identify patients who require emergent, life-saving interventions.[239, 254]

Finally, we described the reference values for the INVOS and Equanox at most sites used in clinical practice. The variations observed between sites can be explained by the perfusion status of these sites, but also of the nature of the tissue evaluated (brain, muscle, connective tissue, fat, etc.). These results will likely help clinicians when using this technology at less conventional sites. The results observed in the present study were similar to most results described previously in healthy volunteers.[134-136] Davie and Fellahi observed higher tissue saturations in their experiment on the forehead and calf, respectively.[112, 248] This could be explained by different sensor positioning and smaller sample size (n=12 and 20). Interestingly, patients with stable severe systemic disease about to undergo cardiac surgery seem to have similar cerebral saturation as healthy volunteers.[253, 255] This suggests that only critical systemic insults will affect baseline cerebral saturations.[255] The possible determinants of raw tissue saturations across all measurements sites (for example age, comorbidity, skin color, body mass index or skinfold thickness) will need to be better studied and defined in future studies.[105]

4.1 Limitations

The majority of the patients recruited were Caucasian and, since melanin concentration has been shown to affect NIRS values, our results might not be applicable to patients with darker skin pigmentation, especially in situations of low tissue saturations (< 40%).[105] Also, despite a wide range of tissue saturation being observed amongst the different sites in our study, the results may not be generalizable in cases where extremely low levels of tissue saturation are measured (< 40%), such as during cardiac arrest, especially since the variation of the reproducibility of other oximetry devices, such as pulse oximetry, is uncertain in these situations.[85, 106] Furthermore, since the readings of the oximeters we used have been shown to be influenced by ambient light, sensor apposition was verified with great care, but it is always possible this could have affected

some of the measures we took.[256] This, however, is a limitation that will also be present in real-life NIRS use. Even though we took great care in ensuring that the volunteers were comfortable during data collection, it is possible that some may have experienced changes in body temperature. Given the influence of superficial tissue on the readings of some oximeters, some of the measures could have been affected by this, especially with measures from the lower extremity.[112] Since this study did not evaluate dynamic reproducibility, our results should not be used by clinicians using NIRS in such a way. Also, while many are currently available on the market, only two tissue oximeters were evaluated in the course of this study. Finally, since it is still unsure how tissue saturation of each peripheral site will vary in situations of in vivo low perfusion, peripheral monitoring of tissue saturation using NIRS should be incorporated in a multi-modal approach to the evaluation of perfusion.

5 Conclusion

In summary, the Equanox could be favoured over the INVOS, especially when NIRS monitoring is used intermittently or in unstable conditions, mainly because of its slightly better absolute reproducibility. The knee and calf sites displayed better reproducibility and could potentially be favoured in situations where NIRS monitoring at these sites is clinically indicated. The description of reference values and normal range of asymmetry for each measurement site will help clinicians identify situations of abnormal perfusions. The differences in observed tissue saturation between devices suggests that clinicians should use the same device for each patient when possible. Also, tissue saturation thresholds are not interchangeable from one NIRS oximeter to another, given their poor inter-oximeter agreement. NIRS offer new avenues for assessing perfusion in an array of clinical situations in which non-invasive monitoring is required. However, an eventual

standardization of NIRS oximeters will be essential to future development of this technology and the expansion of its use in critical care.

Acknowledgments

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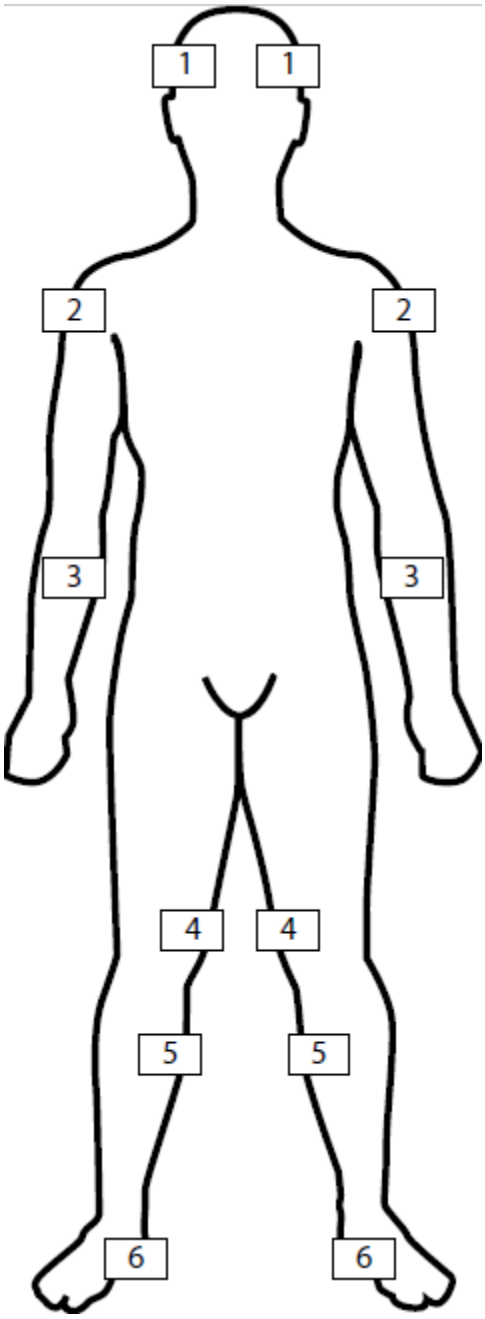
Caption List

Figure 15 : Fig. 1 Sites of tissue saturation measurements. 1. Forehead: above the eyebrow, long side perpendicular to the body axis and following the median line of the face. 2. Deltoid: at the height of the head of the humerus, long side perpendicular to the body axis and centered on the coronal plane of the body. 3. Forearm: distally to the elbow crease, centered on the palmar face of the forearm and long side perpendicular to the body axis. 4. Knee: on the medial side of the thigh at the base of the junction between the patella and the vastus medialis of the quadriceps, long side parallel to the leg axis and just medial to the patella. 5. Calf: on the medial line of the calf, 3 cm below the articular line of the knee and long side parallel to the leg axis. 6. Foot: on the medial line of the plantar face, long side parallel to the leg axis and proximal side just distally to the heel.


1
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6

Figure 16 : Fig. 2 Plot of identity describing the inter-sensor (a) and intra-sensor (b) reproducibility of the INVOS oximeter.

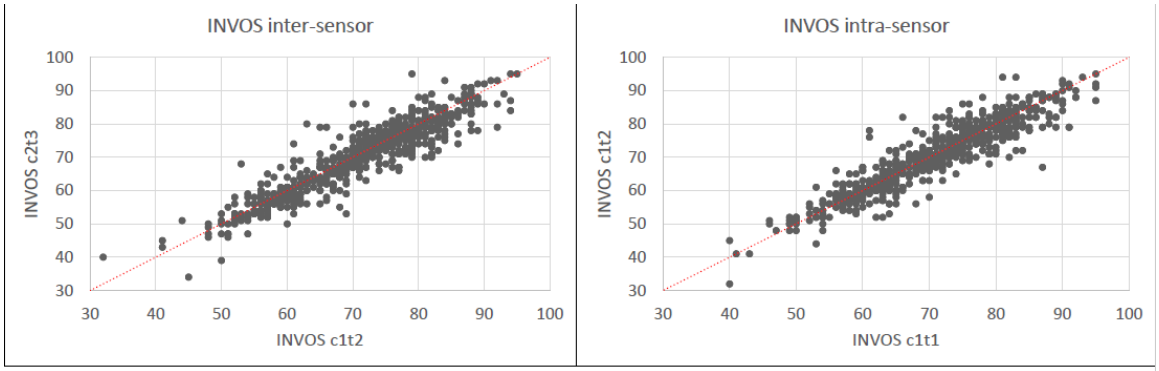
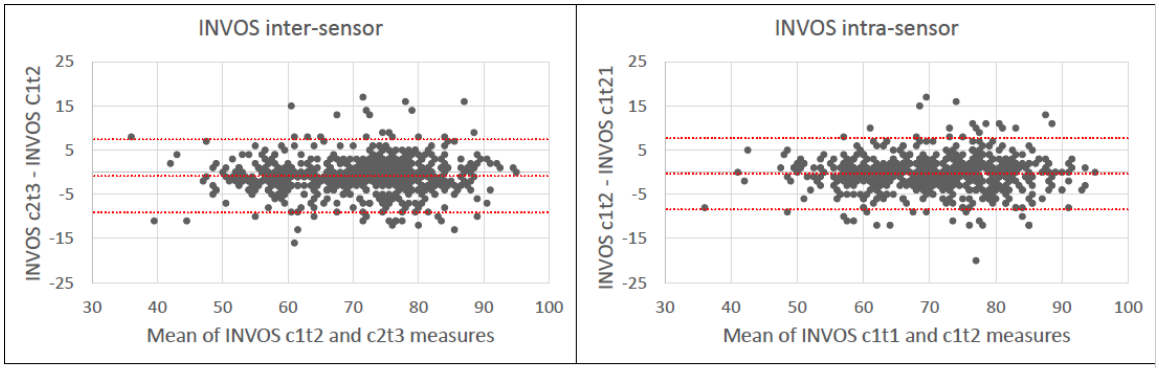
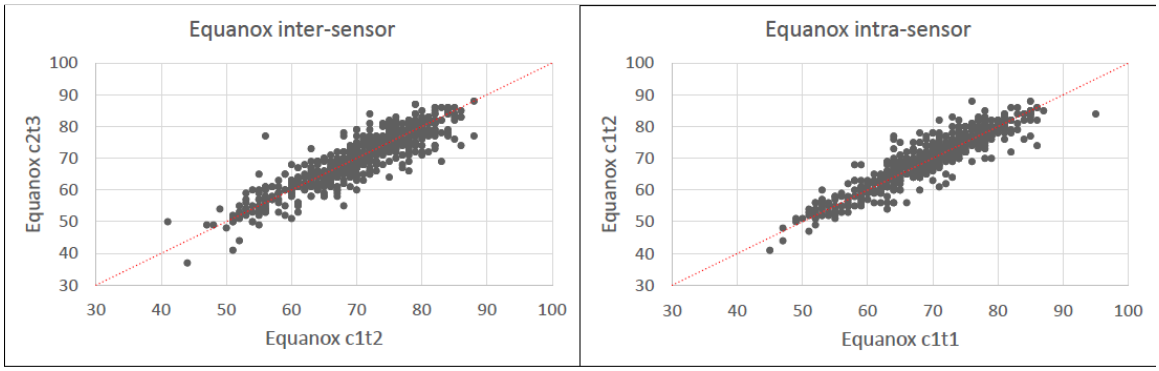


Figure 17 : Fig. 3 Bland-Altman plot describing the inter-sensor (a) and intra-sensor (b) reproducibility of the INVOS oximeter.



(a) (b)

Figure 18 : Fig. 4 Plot of identity describing the inter-sensor (a) and intra-sensor (b) reproducibility of the Equanox oximeter.



(a) (b)

Figure 19 : Fig. 5 Bland-Altman plot describing the inter-sensor (a) and intra-sensor (b) reproducibility of the Equanox oximeter.

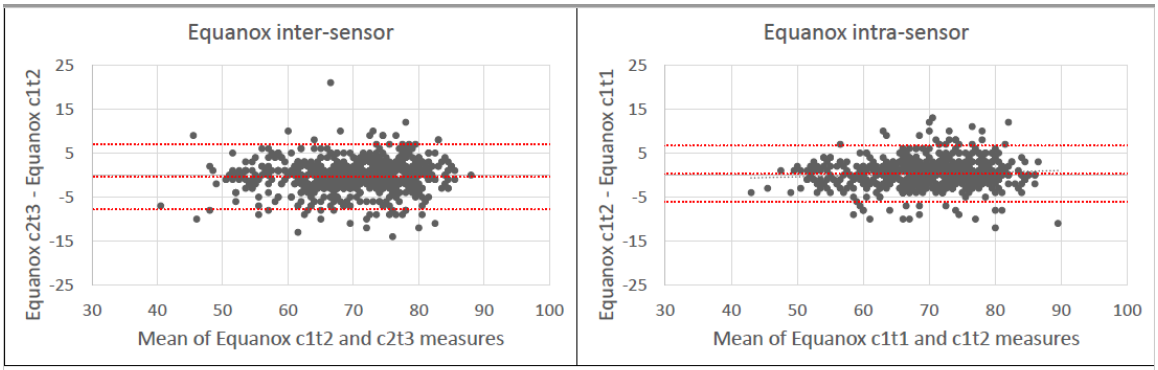
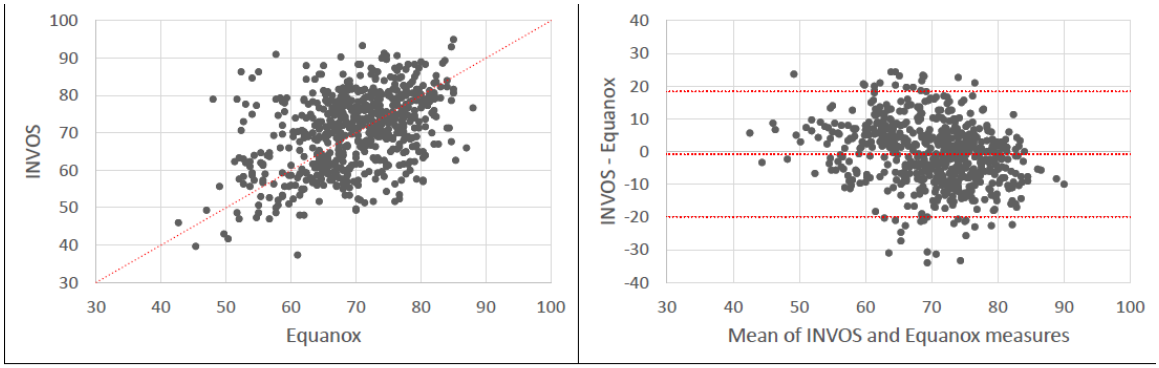
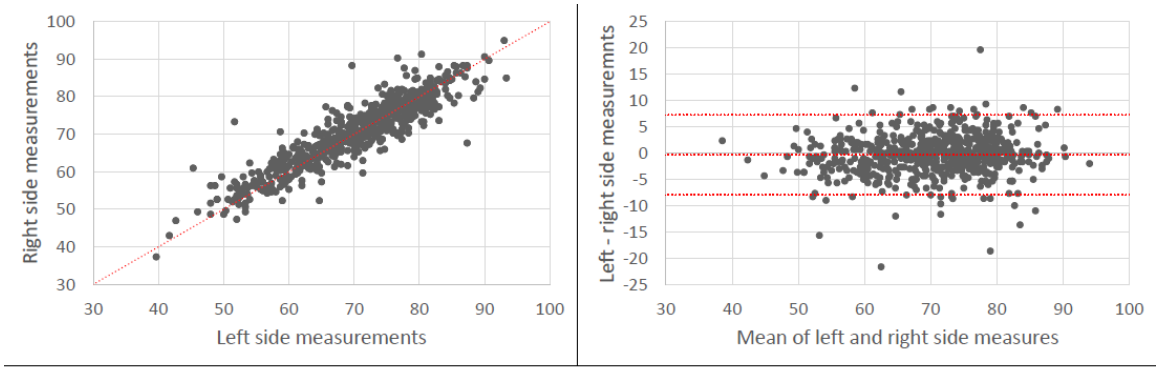


Figure 20 : Fig. 6 Plot of identity (a) and Bland-Altman plot (b) describing the interchangeability amongst two tissue oximeters.



(a) (b)

Figure 21 : Fig. 7 Plot of identity (a) and Bland-Altman plot (b) describing the interchangeability between the oximetry readings of the left and right side.



(a) (b)

Tableau 30 : Table 1 Characteristics of the 53 healthy volunteers.

Variables	Mean (SD) or N (%)
Age, years	31.5 (9.6)
Gender, men	27 (51.9)
Height, m	1.69 (0.10)
Weight, kg	69.4 (12.4)
BMI, kg/m^2	24.2 (3.1)
Blood pressure	120/75 (11/9)
Pulse	72 (13)
Pulse oximetry	98 (1)
Fitzpatrick phototyping scale [138]	
I	4 (7.6)
II	24 (45.3)
III	20 (37.7)
IV	1 (1.9)
V	0 (0)
VI	4 (7.6)
Skinfold measurement location, mm	
Left deltoid	17.9 (7.6)
Right deltoid	17.9 (8.0)
Left forearm	6.8 (3.8)
Right forearm	6.9 (3.0)
Left thigh	16.4 (9.0)
Right thigh	16.8 (10.3)
Left calf	12.8 (6.9)
Right calf	12.1 (6.9)

SD :Standard deviation; BMI : Body mass index

Tableau 31 : Table 2 Calculated measures of reproducibility of the INVOS oximeter (ICC and 95% CI).

	Inter-sensor		Intra-sensor	
	Left	Right	Left	Right
Forehead	0.91 (0.84-0.95)	0.83 (0.72-0.90)	0.91 (0.86-0.95)	0.88 (0.79-0.93)
Deltoid	0.84 (0.73-0.90)	0.84 (0.69-0.91)	0.86 (0.76-0.92)	0.90 (0.83-0.94)
Forearm	0.78 (0.65-0.87)	0.86 (0.76-0.92)	0.81 (0.68-0.88)	0.78 (0.65-0.87)
Knee	0.92 (0.87-0.96)	0.94 (0.91-0.97)	0.92 (0.87-0.95)	0.92 (0.86-0.95)
Calf	0.89 (0.82-0.93)	0.91 (0.86-0.95)	0.93 (0.88-0.96)	0.82 (0.71-0.89)
Foot	0.88 (0.78-0.94)	0.88 (0.80-0.93)	0.96 (0.93-0.98)	0.92 (0.86-0.95)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval

Tableau 32 : Table 3 Global measures of reproducibility of the INVOS oximeter.

		ICC and 95% CI	S_w and 95% CI (%)	Mean bias and limits of agreement (%)
INVOS	Inter-sensor	0.92 (0.90-0.93)	2.11 (2.05-2.17)	-0.85 (-9.11 to 7.41)
	Intra-sensor	0.92 (0.91-0.93)	2.22 (2.16-2.29)	-0.35 (-8.42 to 7.72)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval; S_w: Within-subject standard deviation

Tableau 33 : Table 4 Calculated measures of reproducibility of the Equanox oximeter (ICC and 95% CI).

	Inter-sensor		Intra-sensor	
	Left	Right	Left	Right
Forehead	0.76 (0.62-0.85)	0.73 (0.57-0.84)	0.82 (0.71-0.89)	0.77 (0.63-0.86)
Deltoid	0.89 (0.91-0.93)	0.92 (0.86-0.95)	0.95 (0.92-0.97)	0.87 (0.78-0.92)
Forearm	0.78 (0.65-0.87)	0.77 (0.63-0.86)	0.82 (0.72-0.89)	0.79 (0.66-0.97)
Knee	0.94 (0.90-0.97)	0.93 (0.89-0.96)	0.96 (0.93-0.97)	0.95 (0.92-0.97)
Calf	0.92 (0.87-0.95)	0.90 (0.83-0.94)	0.95 (0.92-0.97)	0.93 (0.88-0.96)
Foot	0.86 (0.76-0.91)	0.82 (0.71-0.89)	0.91 (0.86-0.95)	0.88 (0.81-0.93)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval

Tableau 34 : Table 5 Global measures of reproducibility of the Equanox oximeter.

		ICC and 95% CI	S_w and 95% CI (%)	Mean bias and limits of agreement (%)
EQUANOX	Inter-sensor	0.90 (0.88-0.91)	1.96 (1.91-2.02)	-0.39 (-7.78 to 7.00)
	Intra-sensor	0.92 (0.91-0.93)	1.67 (1.63-1.72)	0.32 (-6.07 to 6.72)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval; S_w: Within-subject standard deviation

Tableau 35 : Table 6 Comparison of measures of reproducibility of two tissue oximeters between sides and sites.

		ICC and 95% CI	S_w and 95% CI (%)	Mean bias and limits of agreement (%)
Left	Inter-sensor	0.91 (0.90-0.92)	2.10 (2.05-2.16)	-0.49 (-8.43 to 7.45)
Right	Inter-sensor	0.91 (0.89-0.92)	2.08 (2.02-2.13)	-0.75 (-8.49 to 6.99)
Forehead	Inter-sensor	0.86 (0.83-0.89)	2.16 (2.05-2.26)	-0.81 (-9.06 to 7.43)
Deltoid	Inter-sensor	0.88 (0.84-0.91)	2.07 (1.97-2.17)	-0.84 (-8.41 to 6.73)
Forearm	Inter-sensor	0.81 (0.76-0.86)	2.86 (2.72-3.00)	-1.23 (-11.35 to 8.89)
Knee	Inter-sensor	0.94 (0.92-0.95)	1.54 (1.47-1.62)	-0.17 (-5.86 to 5.52)
Calf	Inter-sensor	0.91 (0.88-0.93)	1.72 (1.63-1.80)	0.27 (-6.36 to 6.89)
Foot	Inter-sensor	0.87 (0.83-0.90)	2.20 (2.09-2.30)	-0.94 (-8.72 to 6.83)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval; S_w: Within-subject standard deviation

Tableau 36 : Table 7 Absolute values of two tissue oximeters by site and side of the body (mean (SD)).

		INVOS	EQUANOX
Forehead	Left	66.1 (9.4)	72.8 (4.38)
	Right	66.6 (9.1)	71.4 (4.63)
Deltoid	Left	77.0 (7.4)	71.5 (7.96)
	Right	76.3 (7.4)	71.9 (6.75)
Forearm	Left	74.1 (7.7)	69.3 (7.17)
	Right	74.8 (8.5)	69.8 (7.19)
Knee	Left	74.2 (8.0)	71.0 (8.46)
	Right	74.2 (8.1)	72.0 (7.69)
Calf	Left	73.2 (8.3)	72.50 (7.25)
	Right	73.4 (7.4)	73.52 (7.24)
Foot	Left	58.6 (8.8)	60.84 (6.99)
	Right	59.6 (8.3)	61.69 (6.35)

3.3.3. Volet 3 – Article 3 – Association between the quantity of subcutaneous fat and the inter-device agreement of 2 tissue oximeters

3.3.3.1. Préface

Cette étude a été réalisée en collaboration avec huit autres chercheurs. J'ai réalisé plus de 90% du travail ayant mené à cette publication. L'étude a été conçue en collaboration avec André Denault, Jean Paquet, Éric Notebaert, Raoul Daoust et Jean-Marc Chauny. Le financement a été obtenu en collaboration avec André Denault, Éric Notebaert et Sylvie Cossette. Comme pour l'article précédent, le recrutement, ainsi que l'expérience et la collecte des données a été réalisée de manière indépendante. Les analyses ont été réalisées en collaboration avec Jean Paquet. Leurs interprétations ont été effectuées en collaboration avec Jean Paquet et Sylvie Cossette. L'article a été écrit en collaboration avec Sylvie Cossette Jean Paquet et Massimiliano Iseppon. André Denault, Éric Notebaert Raoul Daoust, Martin Marquis et Jean-Marc Chauny ont également contribué à sa révision. Cette étude a été publiée dans le journal Journal of Cardiothoracic and Vascular Anesthesia en 2019 (Facteur d'impact en 2018 : 1,882).

3.3.3.2. Volet 3 – Article 3

Title: Association between the quantity of subcutaneous fat and the inter-device agreement of two tissue oximeters

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Structured abstract

Objective

This study aimed to evaluate the association between the quantity of subcutaneous fat (assessed by skinfold thickness) and the inter-device agreement of two tissue oximeters.

Design

This is a prospective cohort study.

Setting

This study was conducted in a tertiary care academic urban hospital.

Participants

Healthy volunteers were recruited.

Interventions

All patients recruited had their tissue saturations and skinfold thickness measured at four different sites (shoulder, forearm, knee and calf) on both sides of the body using two tissue oximeters, the INVOS 5100c and the Equanox 7600.

Measurements and Main Results

Higher skinfold measures were associated with an increase in the difference between measures provided by both oximeters (Slope=-0.59, Pearson correlation coefficient=-0.51, p<0.001). This observed association persisted in a linear mixed model (-0.48 [95% confidence interval (CI)-0.61 to -0.36], p<0.001). The sex of the volunteers also influenced the inter-oximeter agreement (Women:-5.77 [95%CI -8.43 to -3.11], p<0.001), as well as the forearm sites (Left forearm:-7.16 [95%CI -9.85 to –4.47], p<0.001; right forearm:-7.01 [95%CI -9.61 to -4.40], p<0.001).

Conclusion

The inter-device agreement of the two studied oximeters is correlated to the quantity of subcutaneous fat. Monitoring using tissue oximetry should be interpreted with great care when sensors are placed on sites with a significant quantity of subcutaneous fat. In addition to the monitoring of cerebral oximetry, following the variations of saturations at the same peripheral site seems to remain the most secure way to use that technology for the monitoring of critically ill patients.

Keywords

Near-infrared spectroscopy, tissue oximetry, inter-device agreement, subcutaneous fat

1 Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive and continuous method of monitoring the oxygen saturation of hemoglobin in any given superficial tissue (tissue saturation). This technique

was developed after an experiment by Jöbsis, which showed that light spectrum could be used as a way to monitor tissue oxygenation.[88] The quantification of tissue saturation by NIRS oximetry has been proposed as a tool measure for tissue perfusion, and a guide during resuscitation. It has been particularly used in settings where more invasive tools are either unavailable, not sensitive or specific enough, cannot be installed quickly, or when real-time feedback is required for the adequate resuscitation of the patients. As such, it has become a common monitoring modality during cardiac and non-cardiac surgery, as well as in the intensive care unit or during cardiopulmonary resuscitation.[80, 85, 239, 257-260]

While this technology is promising, it has been proposed that an eventual standardization of NIRS oximeters would be useful to the future development of this technology and expanding its use in critical care.[81, 105, 107] Indeed, it has been shown that the difference between the measurements provided by different oximeters for the same individual can be quite large.[107, 134-136, 247] The possible explanations for these large inter-device agreements are numerous. First, there is no accepted gold standard for tissue oximetry. Also, the wavelengths, number of and distance between optodes, and mathematical algorithm for each oximeter vary. In addition, little is known about the specific patient characteristics that could affect the inter-device agreement, especially at measurement sites other than the forehead, which is the one most frequently used clinically.[80, 105] Since ischemia of the subcutaneous tissues has been shown to significantly impact the measurements of tissue oximetry, the quantity of subcutaneous fat could influence the inter-device agreement at sites where fat accumulation is more likely than on the forehead.[112, 261]

The main objective of this study was to evaluate the association between the quantity of subcutaneous fat (assessed by skinfold thickness) and the inter-device agreement of two

commonly used tissue oximeters, the INVOS 5100c (Covidien, Mansfield, MA, USA) and the Equanox 7600 (Nonin Medical, Plymouth, MN, USA), in healthy volunteers.

2 Methods

2.1 Design and setting

The present study is a planned secondary analysis of a prospective cohort study which was conducted at the Hôpital du Sacré-Coeur de Montréal, Canada, in association with the Université de Montréal, Canada.[107] It was submitted and approved by its Ethics Committee prior to enrollment.

2.2 Population and sample

Healthy adult (≥ 18 years old) volunteers were recruited for this study. Exclusion criteria included pregnancy, active or chronic systemic illness, the use of medication other than oral contraceptives, skin disease, very coarse hair overlying measurement sites, active smoking, substance use, weight less than 40 kg or a body mass index lower than 18 or higher than 35. Written informed consent was obtained prior to their inclusion in the study.

2.3 Material

Two tissue oximeters both using the multidistance spectroscopy technology were used in the present study. This should allow them to relatively blunt the contribution of superficial tissue to their readings, better representing the target tissue saturation.[81, 112]

The INVOS 5100C with adult SomaSensor has two light-emitting diodes (730 and 810 nm) at one position and two receptors at distances of 30 and 40 mm. The EQUANOX 7600 with Equanox Advance 8004CA sensors uses eight light-emitting diodes split in groups of four (730, 760, 810 and 880 nm) at two positions separated by 60 mm. It uses two receptors placed between the emitting groups. Each receptor is 20 mm proximal to an emitting group and 40 mm distal to the other. The

INVOS assumes that the mixed arterial to venous oxygen saturation ratio is fixed at 25:75, while the Equanox assumes it is 30:70.

2.4 Procedures

The specific procedures used to acquire the sociodemographic characteristics, skinfold thickness and tissue oximetry measures have been described previously.[107] Following their recruitment, the volunteers answered a simple questionnaire and their skinfold thickness was measured using a Harpenden skinfold caliper by the same skilled experimenter. Then, the same experimenter took sequential oximetry measurements across the body using the two oximeters (INVOS 5100c and Equanox 7600 in a randomized order) while the volunteers were in a supine position. For the present study, the tissue oximetry and skinfold thickness measurements of four sites (deltoid, forearm, knee and calf) on both sides of the body were used (Figure 1). The sensors were placed on each of the measurement sites, which were marked to ensure that the sensor placement were spatially coincident, until the reading was stable (defined as an identical value in two consecutive measurements, measures alternating between two contiguous values) or after a maximum delay of 20 seconds from the first reading. To improve the intra-oximeter reliability of the measurements, a total of three measures were performed at each specific site with both oximeters. The average of these measurements was used throughout this study. All measures were performed under the direct supervision of the primary author (AC). No ischemia was created during all the experiment.

2.5 Statistical analyses

The entire available population was used in the present study.

Continuous variables are presented as means with standard deviations and categorical variables as frequencies with percentages. The inter-device agreement between the two oximeters is described using an intraclass correlation coefficient.

For the main objective, the association between the quantity of subcutaneous fat (assessed by skinfold thickness) and the inter-device agreement (absolute difference between the oximetry values provided by the two oximeters) was first assessed with a Pearson's correlation and a scatter plot. Subsequently, a linear mixed model was used to evaluate the impact of the subcutaneous fat and other covariables (age, sex) on the inter-device agreement while adjusting for the repeated measurements across different sites for the same volunteers. An autoregressive covariance structure was used to model variance and correlations between site measurements since association lessens as sites get further apart. A Bonferroni correction was used to control for the multiple comparisons performed across the measurement sites. The association between the quantity of subcutaneous fat and the oximetry measurements of both oximeters were also described.

Statistical analyses were performed using SPSS Statistics 23 (IBM, Chicago, USA). All results are presented with their 95% confidence intervals (CI).

3 Results

3.1 Baseline characteristics

From January to March 2015, 53 healthy volunteers were included in this study with ages ranging between 20 and 81 years old, on which a total of 848 measures were taken. With the exception of oral contraceptives (n=14), none took any medication on a regular basis. Participant characteristics, as well as their skinfold and oximetry measurements are presented in Table 1. Most volunteers (48, 91%) had relatively light skin tone (Fitzpatrick phototyping scale I-III).[138]

Despite the average oximetry measurements being similar across the entire cohort, the tissue saturation measures provided by the two oximeters varied considerably when considering each individual (Intraclass correlation coefficient: 0.16 [95%CI 0.07-0.27]).

3.2 Main results

Both oximeters were affected differently by skinfold thickness (Equanox: Slope=-0.034, p<0.001; INVOS: Slope=0.046, p<0.001). The Equanox generally provided lower values than the INVOS when the skinfold thickness was high. In the unadjusted analysis for repeated measurements, a correlation was observed between the skinfold thickness and the inter-device agreement (Pearson correlation coefficient = -0.51, p<0.001; Slope=-0.59 [95%CI -0.69 to -0.50]) (Figure 2). Higher skinfold measures were associated with an increase in the difference between measures provided by both oximeters.

This observed association persisted in a linear mixed model (-0.48 [95% CI -0.61 to -0.36], p<0.001). The sex of the volunteers also influenced the inter-oximeter agreement (Women:-5.77 [95% CI -8.43 to -3.11], p<0.001). On the contrary, the age of the volunteer did not influence the inter-device agreement (-0.02 [95% CI -0.16-0.11], p=0.72). The inter-device agreement was also affected by the measurement sites (p<0.001). Measurements taken on the forearm had a worse inter-device agreement than those taken at other sites (Left forearm:-7.16 [95% CI -9.85 to –4.47], p<0.001; right forearm: -7.01 [95% CI -9.61 to -4.40], p<0.001). Measurements taken at other sites did not affect the inter-device agreement (p=0.11 to p=71). Also, the side of measurement did not influence this association (p=1.00 for all four comparisons).

For the Equanox, there was a negative independent association between increasing skinfold thickness and (-0.40 [95% CI -0.50 to -0.31], p<0.001) and tissue saturation, which was not the case for the INVOS (0.07 [95% CI -0.03 to 0.19], p=0.19).

4 Discussion

This study demonstrated that the quantity of subcutaneous fat impacted the inter-device agreement of two commonly used tissue oximeters, the INVOS 5100c and the Equanox 7600. The measurement sites and the sex of the volunteers also influenced that measure. These findings may well prove useful in the selection of patients for whom tissue monitoring using NIRS may be useful.

The quantity of subcutaneous fat can negatively affect the inter-device agreement of tissue oximeter. This is likely explained by the fact that there is significant superficial tissue contamination for NIRS measurements.[112, 262-264] In these studies, the INVOS seemed to be more affected by extracranial ischemia than the other devices. However, in the present study, we did not observe an association between the quantity of subcutaneous fat and the baseline saturation measurements for the INVOS. The varying distances between the closest optodes on the sensors might contribute to the oxymeters' ability to differentiate layers, with closer optodes improving this ability. However, using liquid optical phantoms, another research group observed that the quantity of lipid in the liquid phantom only slightly affected the readings of tissue oximeter.[265] While it seems clear that the quantity of subcutaneous fat differently affects the readings of tissue oximeters, it remains unsure if it is the interference of subcutaneous fat itself or simply the increasing distance between the optodes and the tissue of interest that influences NIRS measurements. Also, although NIRS oximeters are frequently used as tissue oximeters, they were originally developed as brain monitors. The algorithms they use are therefore based on the assumption that the light is going through the skull and some variations in other situations can be expected. This could also explain some of the difference observed in the current study.

The sex of the volunteers also affected the inter-device agreement. Bickler et al. also made the observation that the volunteers' sex affected the bias of multiple NIRS devices to different

degrees.[105] This is mostly likely explained by difference in soft tissue composition and thickness between men and women, which could affect independently of the skinfold measurement the distance between the sensors and the tissue of interests and also possibly alter the scattering and absorption of light along the way.[266, 267] In addition, given that both of these experiences were performed in healthy volunteers, this could be explained by the differences of normal hemoglobin concentration between men and women, a factor that has been associated with lower NIRS value.[110, 268] Indeed, in the same phantom experiment by Kleiser et al., the hemoglobin concentration of the liquid affected differently the tested oximeters.[265] This could be particularly relevant when monitoring patients actively bleeding or with hemodilution when going on cardiopulmonary bypass.[269]

There was a worse inter-device agreement on the forearms than at any other measurements site. Given the generally lower skinfold thickness measured on forearms, this could be explained by the differences in interpretation of the signals coming from the muscle itself, due to the different mathematical algorithms used by each oximeter to compute the saturation measurements.

The present study confirms that NIRS monitors do not provide an unbiased estimate of tissue saturation and that they are affected differently by specific patients' characteristics. In order for this technology to be used efficiently in critical care, standardization of NIRS oximeters is essential to this technology's future development. Also, given the impact of the subcutaneous fat on these measurements, spatial resolution of the devices should be improved to measure the tissue of interest as much as possible. Specific 'tissue' algorithms could also be developed to improve the validity of the NIRS somatic measurements. In the meantime, following the saturation's variation at the same site seems to remain the most secure way to use this technology to monitor critically ill patients, ideally at the available site with the best agreement. Frequency domain and time domain NIRS might eventually limit these problems given their theoretically superior accuracy and

spatial resolution.[270] Indeed, an improvement in spatial resolution would limit the contribution of more superficial tissue to the oximetry measurements, such it has been described in the present study, but this remains to be proven.

4.1 Limitations

Despite a wide range of skinfold thickness and tissue saturation being observed in the present study, the results may not be generalizable in cases where very high skinfold thickness or extremely low levels of tissue saturation are measured, such as in morbidly obese patients or during cardiac arrest.[85, 271] A better quantification of the subcutaneous tissue depth might have been obtained if an ultrasound machine had been used instead of skinfold caliper. Also, since the majority of the recruited patients were Caucasian, it was therefore not possible to evaluate if the skin concentration of melanin affected the inter-oximeter agreement.[105] Given only healthy volunteers were recruited, it was also not possible to assess for other specific factors which could affect the inter-device agreement of tissue oximeter, such as the hemoglobin, bilirubin, and carbon dioxide levels.[108, 110, 272]

5 Conclusion

The quantity of subcutaneous fat, as well as the sex of the volunteers and the measurement sites, impacted the inter-device agreement of two commonly used oximeters. Given these findings, monitoring using tissue oximetry should be interpreted with great care when there is a significant quantity of subcutaneous fat. In addition to the monitoring of cerebral oximetry, following the variations of saturations at the same peripheral site seems to remain the most secure way to use that technology for the monitoring of critically ill patients.

Acknowledgments

Conflict of interest: Dr. André Denault is part of a speakers' bureau for Edwards, Masimo and CAE Healthcare. All other authors have no conflict of interest to declare. Funding: This project received full funding from the "Fonds des Urgentistes de l'Hôpital du Sacré-Coeur de Montréal" and the "Département de Médecine Familiale et de Médecine d'Urgence de l'Université de Montréal". No support of any kind was received from the industry for this particular study.

Tableau 37 : Table 1 Baseline characteristics, skinfold and oximetry measurements of the 53 healthy volunteers.

Variables	Mean (SD) or N (%)
Age, years	31.5 (9.6)
Gender, men	27 (51.9)
BMI, kg/m^2	24.2 (3.1)
Fitzpatrick phototyping scale [138]	
I	4 (7.6)
II	24 (45.3)
III	20 (37.7)
IV	1 (1.9)
V	0 (0)
VI	4 (7.6)
Skinfold measurements, mm	
Left deltoid	17.9 (7.6)
Right deltoid	17.9 (8.0)
Left forearm	6.8 (3.8)
Right forearm	6.9 (3.0)
Left thigh	16.4 (9.0)
Right thigh	16.8 (10.3)
Left calf	12.8 (6.9)
Right calf	12.1 (6.9)
Tissue oximetry measurements, INVOS/Equanox, %	
Left deltoid	77.0 (7.3) / 71.5 (8.0)
Right deltoid	76.3 (7.4) / 71.9 (6.8)
Left forearm	74.1 (7.6) / 69.3 (7.2)
Right forearm	74.8 (8.5) / 69.8 (7.2)
Left thigh	74.2 (8.0) / 71.0 (8.5)
Right thigh	74.2 (8.1) / 72.0 (7.7)
Left calf	73.2 (8.3) / 72.5 (7.2)
Right calf	73.4 (7.4) / 73.5 (7.2)

SD :Standard deviation; BMI : Body mass index

Figures

Figure 22 : Fig. 1. Sites of tissue saturation measurements.

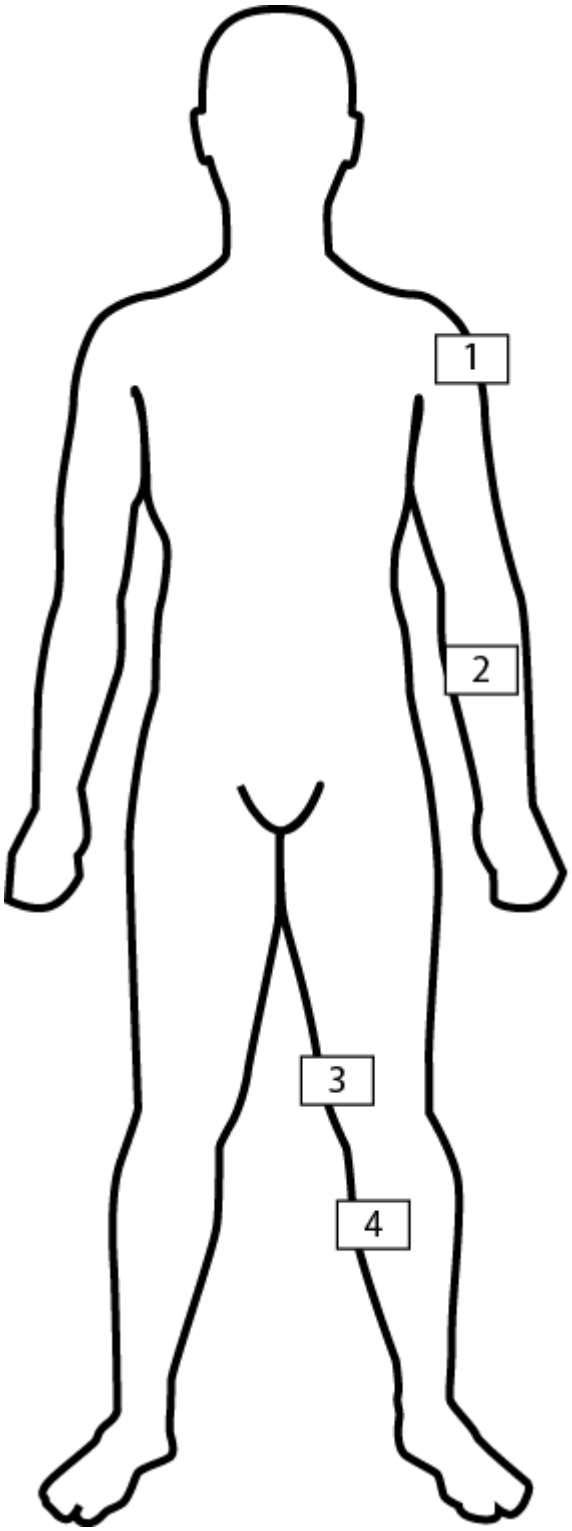


Figure 23 : Fig. 2. Plot of identity illustrating the inter-device agreement of two tissue oximeters.

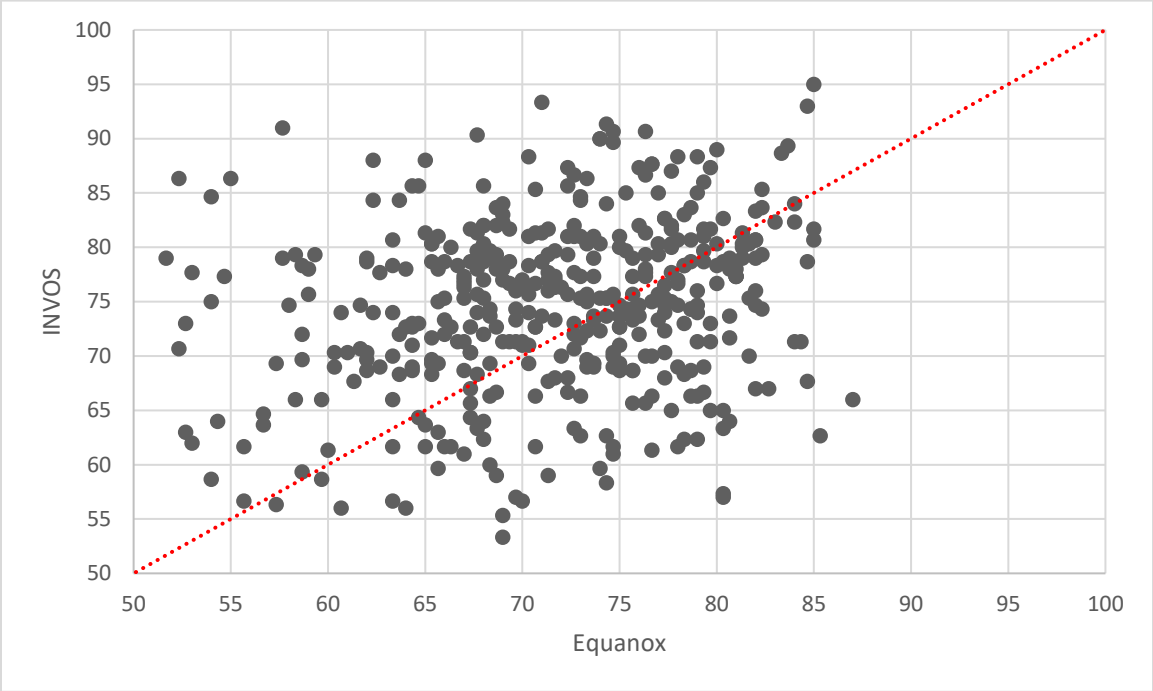
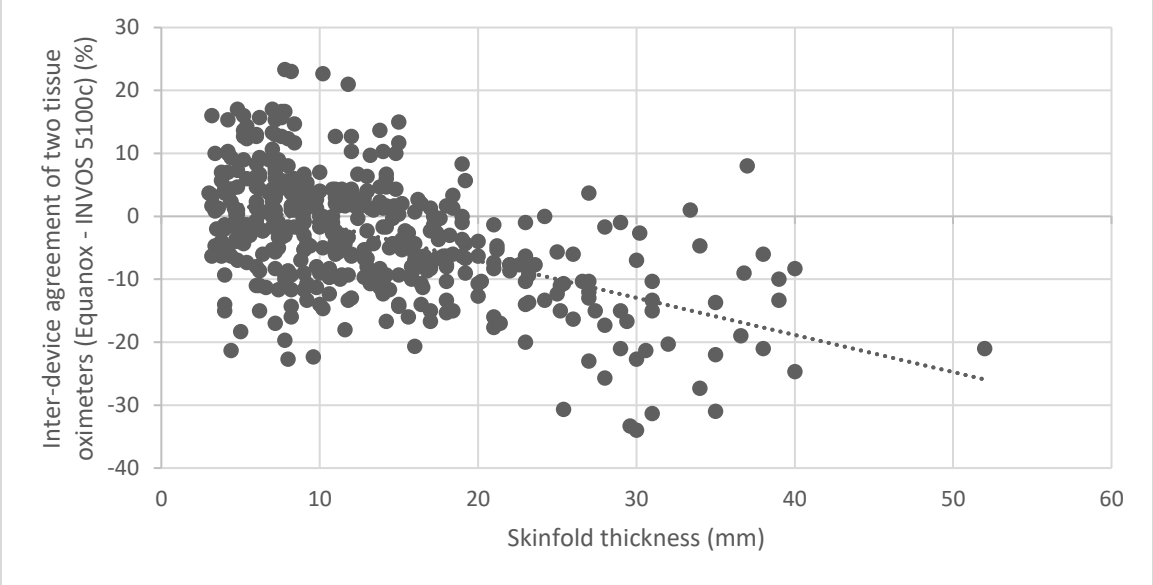


Figure 24 : Fig. 3. Scatterplot illustrating the association between skinfold thickness and the inter-device agreement of two tissue oximeters.



Chapitre 4. Discussion

Les travaux présentés dans la présente thèse visaient à bâtir une base de connaissance qui permettrait l'implantation de la R-CER dans les pratiques en médecine d'urgence.

4.1. Premier volet

Dans le premier volet, nous avons décrit trois impacts collatéraux qu'auraient l'intégration de la R-CEC sur les pratiques de soins préhospitaliers. À cet effet, nous avons observé que l'ajout de SARC aux soins de base en réanimation n'était pas associé à la survie au congé des patients éligibles à une R-CEC.[113] Les SARC préhospitaliers étaient cependant associés à une augmentation du taux de RCS préhospitalier, mais au prix d'une augmentation de la durée de transport avant l'arrivée à l'hôpital.[113] Par ailleurs, nous avons montré qu'il y avait une association favorable entre le transport direct vers un CH désigné pour des soins cardiovasculaires et la survie des patients souffrant d'un ACEH.[114] Nous avons également montré que ce bénéfice persistait jusqu'à une augmentation de la durée de transport de 14 minutes avant l'arrivée au CH.[114] Nous avons ensuite montré que la quantité de patients éligibles à une R-CEC augmenterait significativement en intégrant un système de redirection préhospitalière pour ces patients, sans que leur durée de transport n'augmente de manière significative.[115] Nous avons également observé que la quantité de patients éligibles à une R-CEC pourrait varier beaucoup en fonction des critères de sélection utilisés.[115] Considérées ensemble, ces nouvelles connaissances nous ont amenés à conclure qu'il serait sécuritaire et potentiellement bénéfique de réduire la durée de réanimation préhospitalière pour des patients sélectionnés et de les rediriger rapidement vers un CH R-CEC.

Tel que discuté précédemment, le risque principal en lien avec l'établissement d'un tel système découle de la proposition de réduire la durée des SARC préhospitaliers dans le but de réduire le

délai avant l'accès au R-CEC dans un CH-C-REC. En effet, de nombreuses études, tout comme la nôtre, ont observé une augmentation du taux de RCS avec l'ajout de SARC ou d'un traitement à l'aide d'adrénaline pour les patients souffrant d'un ACEH, ce qui est généralement considéré comme positif bien que le RCS ne soit pas une bonne mesure de résultat centrée sur le patient.[15, 273-276] D'autres chercheurs ont aussi observé une augmentation de la survie au congé avec l'ajout de SARC ou d'adrénaline en préhospitalier.[143, 273-276] Par contre, l'impact des SARC sur la survie au congé hospitalier est débattu dans la littérature.[15, 144, 273-276] Plusieurs différences organisationnelles ou méthodologiques expliquent que des études antérieures aient observé un plus grand bénéfice aux SARC par rapport aux soins de réanimation base alors que dans notre étude, ces différences n'ont pas été observées. Premièrement, la majorité des études incluent dans les méta-analyses dataient de plus de 15 ans.[273, 274] Puisque la qualité des soins de base fournis aux patients et des soins post-réanimation s'est nettement améliorée depuis ce temps, il est possible, qu'actuellement, les différences entre les SARC et les soins de base soient minimes alors que ces différences étaient plus importantes il y a 15 ans. De plus, dans certaines études, des médecins prodiguaient les SARC en préhospitalier alors que, dans notre étude, les SARC étaient prodigués par des paramédics. il est possible que l'efficacité accrue de la SARC dans les études antérieures aient été dues, du moins en partie, à la formation plus avancée des intervenants et non pas seulement au fait de prodiguer des SARC.[151] Un autre facteur pouvant influencer l'efficacité des SARC est un délai plus long entre l'ACEH et leur initiation.[275, 277] Dans notre étude, nous avons observé que le délai était relativement long avant l'initiation des SARC et ceci a pu aussi contribuer à réduire la différence d'effet entre la SARC et les soins de base. Finalement, certaines études antérieures incluaient des zones rurales, où le délai avant l'arrivée à l'hôpital est généralement plus élevé, et le bénéfice potentiel d'une initiation rapide de SARC est plus élevé.[143] Par ailleurs, il n'existe à ce jour pas d'évidence quant au bénéfice des SARC

préhospitaliers pour augmenter le taux de survie avec un bon devenir neurologique, la seule vraie mesure de résultat centrée sur le patient pour l'ACEH.[273, 274] Quant aux patients éligibles à une R-CEC, à notre connaissance, aucune autre étude n'a été recensée concernant spécifiquement l'efficacité des SARC chez cette population. Nos résultats concordent cependant avec d'autres observés dans la littérature. En effet, les chercheurs ayant réalisé des analyses spécifiques chez les patients avec un rythme initial défibrillable, qui sont habituellement ceux considérés pour une R-CEC, n'ont généralement pas observé de bénéfice des SARC et de l'adrénaline.[276, 278]

Ainsi, il nous apparaît sécuritaire de proposer réduire la durée des SARC pour les patients éligibles à une R-CEC. En effet, les évidences disponibles suggèrent qu'il n'y a pas de bénéfice significatif au niveau de la survie avec un bon devenir neurologique pour ces patients des SARC préhospitalier.

Le deuxième risque potentiel pour les patients qui seraient redirigés vers un CH R-CEC consiste en l'augmentation de leur temps de transport ambulancier. En effet, puisque la qualité de la réanimation était possiblement moins bonne dans une ambulance, la durée des temps de transport était limitée au maximum pour ces patients.[47] Nous avons calculé que le bénéfice de la redirection vers un CH R-CEC serait maintenu jusqu'à un augmentation de 14 minutes comparativement au transport vers l'hôpital le plus proche.[114] Nous avons également réalisé une simulation statistique pour évaluer l'effet d'une redirection vers un CH R-CEC pour des patients éligibles et avons observé que cette redirection n'augmenterait que très peu leur temps de transport.[115] Ainsi, cette augmentation marginale des durées de transport (1-3 minutes) n'est pas cliniquement significative étant donné les bénéfices potentiels d'une telle redirection. Plusieurs autres études ont également montré qu'il n'y avait pas d'effet délétère important à prolonger le temps de transport des patients souffrant d'un ACEH.[169, 171-173] De plus, il a été

récemment démontré qu'il est possible de maintenir une réanimation de qualité pendant un transport ambulancier.[48] Nous avons aussi réalisé une sous-analyse montrant que la survie diminue plutôt lorsque la durée de réanimation sur place est allongée et non pas si la durée du transport ambulancier est allongée.[279] Ainsi, il apparaît raisonnable de suggérer prolonger au maximum de 14 minutes le temps de transport des patients éligibles à une R-CEC afin de permettre une redirection en CH R-CEC, ce qui est facilement réalisable en milieu urbain, et particulièrement à Montréal où la grande majorité des temps de transport sont de 14 minutes ou moins.

La redirection vers un CH R-CEC pourrait avoir d'autres bénéfices en plus de la R-CEC elle-même. En effet, nous avons observé un bénéfice entre un transport direct vers un centre offrant des soins spécialisés en médecine cardiovasculaire, que sont tous les CH R-CEC, pour les patients ayant subi un ACEH.[114] Trois revues de littérature, dont une à laquelle nous avons contribué, ont également corroboré cette observation.[280-282] Ces résultats s'expliquent, entre autres, par les capacités de traitements supplémentaires et de l'expérience dont disposent les CH R-CEC. En effet, la cause la plus fréquente d'un ACEH est le SCA, dont la modalité diagnostique et thérapeutique privilégiée est l'angiographie coronaire avec intervention coronaire percutanée.[1, 119, 160] Puisque le délai entre l'événement et l'initiation du traitement peut avoir une importance pour les patients ayant subi un ACEH, la possibilité de réaliser cette intervention sur place pourrait améliorer les chances de survie de ces patients.[283-286] De plus, les CH R-CEC sont tous des centres universitaires tertiaires traitant un nombre élevé de patients souffrant de pathologie sévère, incluant l'ACEH, et disposant de capacités chirurgicales étendues. Bien que l'évidence demeure faible quant à l'association entre ces spécificités hospitalières et le pronostic des patients souffrant d'un ACEH, il demeure plausible que la présence de professionnels plus expérimentés en raison d'un volume de traitement plus élevé leur soit bénéfique.[176, 286, 287]

Ainsi, il pourrait y avoir un bénéfice surajouté à la redirection des patients souffrant d'un ACEH, incluant ceux éligible à une R-CEC, vers un CH R-CEC étant donné les autres capacités de traitement disponibles dans ces centres et de l'expérience de leur personnel à condition que ce délai de redirection soit inférieur à 14 minutes tel que discuté précédemment.

La réorganisation du système de transport préhospitalier pour permettre une telle redirection augmenterait l'accès à la R-CEC pour les patients éligibles. En effet, nous avons observé que l'établissement d'un système de redirection pourrait augmenter significativement le nombre de patients éligibles à une R-CEC transporté rapidement dans un CH R-CEC.[115] En milieu urbain, la distance est courte entre les hôpitaux ce qui fait que le délai de redirection vers un CH R-CEC l'est également et ne nuit pas à l'éligibilité d'un patient à la R-CEC.[115] L'ampleur de l'augmentation du nombre de patients pourrait varier en fonction de la nature des critères d'inclusion (entre 322% et 412% d'augmentation dans notre étude).[115] D'autres études ont déjà évalué la proportion des ACEH qui seraient candidats à une R-CEC et leurs résultats varient en fonction des critères utilisés (entre 6 et 31%).[37, 181, 288, 289] Dans tous les cas, la proportion de patients éligibles à une R-CEC transportés au bon hôpital pourrait augmenter avec une réorganisation des soins préhospitaliers ayant cet objectif en vue.

En résumé, les connaissances issues du premier volet nous permettent de proposer qu'il serait sécuritaire et même potentiellement bénéfique de limiter la durée de réanimation préhospitalière sur la scène avant l'initiation de l'extraction pour des patients sélectionnés et de les rediriger vers un CH R-CEC, soit la première étape en vue d'évaluer prospectivement quels seraient les impacts de l'implantation de la R-CER dans les pratiques en médecine d'urgence pour les ACEH. De plus, nos résultats concordent avec les évidences disponibles dans la littérature ce qui ajoute à la solidité de nos recommandations. Ces trouvailles permettront l'évaluation

prospective d'une telle stratégie pour les patients éligibles à une R-CEC afin d'évaluer le bénéfice pour ces patients.

4.2. Deuxième volet

Dans le deuxième volet, nous avons raffiné les connaissances quant à la pronostication de certaines populations de patients considérés pour une R-CEC afin d'optimiser la sélection des patients pour cette technique. Plus spécifiquement, nous avons montré que les patients ayant reçu un grand nombre de défibrillations gardaient un potentiel de survie supérieur à 5% et pourraient donc demeurer candidats à une R-CEC.[121] Nous avons ensuite montré que les patients en ACEH dont le rythme se convertissait à un rythme défibrillable n'avaient pas une aussi bonne survie que si leur rythme initial lui-même était défibrillable. Ceci nous a amené à suggérer que les patients avec un rythme initial défibrillable devraient continuer d'être considéré en première intention pour la R-CEC.[122] Les nouvelles connaissances acquises lors du deuxième volet nous ont permis de préciser le pronostic de deux populations particulières de patients afin d'optimiser la sélection des patients pour une R-CEC afin d'optimiser les résultats de l'implantation de cette technique de réanimation en médecine d'urgence.

La sélection en vue d'une R-CEC est un processus complexe et d'une importance primordiale considérant la variabilité de survie chez les patients sélectionnés pour cette technique.[21, 29] Nous avons observé que les patients souffrant d'un ACEH avec une arythmie ventriculaire persistante gardaient un pronostic de survie de plus de 5% même après une dizaine de tentatives de défibrillations.[121] D'autres études ont également observé des taux de survie de plus de 5% chez des populations similaires de patients.[123, 187, 189] Ceci s'explique, du moins en partie, par le fait qu'une réanimation de qualité est nécessaire afin de maintenir une arythmie (versus tomber en asystolie). Bien que le taux de survie diminue après chaque tentative de défibrillations,

nous n'avons pu mettre en évidence de point de césure qui nous permettrait d'énoncer avec une sensibilité et spécificité optimales que de continuer la réanimation de ces patients est futile.[121] Dans le même ordre d'idée, il est difficile de déterminer avec certitude le moment auquel le transport vers un CH R-CEC et l'initiation de la R-CEC devrait se faire pour ces patients. En effet, il n'est pas justifié d'initier un transport vers un CH R-CEC et une R-CEC si les taux de RCS et de survie en continuant la réanimation sur place sont meilleurs que ceux théoriquement obtenus à l'aide d'une R-CEC. Malgré la variabilité des résultats obtenus par les différents programmes de R-CEC, il est cependant possible d'affirmer que la R-CEC pourrait être considérée après un minimum de trois à cinq tentatives de défibrillations pour la majorité des cohortes s'étant intéressée à ceci.[202, 290] Ainsi, bien que la survie diminue après chaque tentative de défibrillations chez les patients souffrant d'un ACEH, leur pronostic de survie demeure de plus de 5% et ils devraient être considérés pour une R-CEC après un nombre de défibrillations dépendant des résultats observés par le programme de R-CEC local.

Nous avons ensuite montré que les patients en ACEH dont le rythme se convertissait à un rythme défibrillable n'avaient pas une aussi bonne survie que si leur rythme initial lui-même était défibrillable.[122] Nous en concluons que les patients avec un rythme initial défibrillable devraient être considérés en première intention pour la R-CEC.[122] Ceci se justifie par le fait que bien que la conversion d'une asystolie à un rythme défibrillable soit à meilleur pronostic que de demeurer en asystolie, ces patients ont un pronostic bien inférieur à celui des patients ayant un rythme initial défibrillable.[124, 204, 291] En effet, un rythme initial défibrillable représente probablement une réanimation précoce et, par le fait même, un moins grand fardeau ischémique.[186] Nous avons également montré que, chez les patients souffrant d'un ACEH avec d'autres bons facteurs de pronostics, le rythme initial demeurait un marqueur de pronostic extrêmement fort et que la survie était pratiquement nulle pour ces patients s'ils étaient

retrouvés en asystolie.[122] Ainsi, les patients avec un rythme initial défibrillable devrait être privilégiés pour une R-CEC, alors que les patients avec une asystolie devrait être exclus.

En résumé, les connaissances issues du deuxième volet nous ont permis de préciser le pronostic de deux populations de patients potentiellement candidats à la R-CEC. Étant donné l'importance de la sélection des patients pour cette nouvelle option thérapeutique, ces nouvelles connaissances pourront favoriser l'évaluation prospective d'une stratégie d'implantation de la R-CER dans les pratiques en médecine d'urgence pour les ACEH.

4.3. Troisième volet

Dans le troisième volet, nous avons décrit et exploré les usages d'une technologie de monitorage, la SPIR, en raison de son potentiel pour évaluer en temps réel les candidats à une R-CEC. Nous avons montré que les patients avec de meilleure valeur de SPIR avaient un meilleur devenir suite à un ACEH.[85] Nous avons ensuite observé que les appareils de SPIR avaient une bonne fiabilité en plus de décrire les valeurs normales pour plusieurs sites de mesure utilisés en clinique.[107] Nous avons également montré que les deux appareils de SPIR utilisés présentaient cependant un mauvais accord entre eux.[107] Finalement, nous avons montré que la quantité de gras sous-cutané était l'un des facteurs principaux influençant l'accord des mesures entre les deux appareils étudiés de SPIR.[127] Les connaissances issues lors du troisième volet nous ont permis de conclure que le monitorage par SPIR pourrait être utile afin d'optimiser la prise en charge des patients bénéficiant d'une R-CEC. Par contre, les appareils de SPIR devront être standardisés avant que les valeurs 'absolues' ne puissent guider avec précision la prise en charge de ces patients.

Nous avons montré que les valeurs de SPIR cérébrales étaient associées au pronostic des patients souffrant d'un ACEH.[85] Deux autres récentes revues systématiques ont également confirmé cette association.[61, 86] Il a également été proposé que le monitorage par SPIR pourrait être

utile pour la sélection et le suivi des patients nécessitant une R-CEC.[103, 292] Par contre, il semble plus facile de déterminer une catégorie de patients à très mauvais pronostic en utilisant ces appareils qu'à prédire quels seront les patients à bon pronostic.[86] La tendance que prennent les valeurs cérébrales de SPIR pendant la réanimation (et ainsi leur valeur moyenne) semblent également mieux prédire le RCS que la valeur absolue prise à un moment ou un autre de la réanimation.[85, 86, 293] Les raisons sous-tendant cette association demeurent incertaines. En effet, puisque l'impact de la qualité de la réanimation sur les valeurs cérébrales de SPIR n'est pas évident, il a été proposé que cette amélioration des valeurs pourrait aussi refléter un RCS subclinique ou une meilleure tolérance à l'ischémie cérébrale dans les circonstances.[86, 219, 221, 224, 294-297] Pendant la réanimation, l'utilisation de la SPIR, pour l'évaluation pendant la réanimation ou à la suite d'une réanimation, en comparaison à d'autres outils de monitorage, comme la capnographie expirée ou l'électroencéphalogramme en continu demeure incertain.[60, 298, 299]

Dans le même ordre d'idée, nous avons décrit la répétabilité et l'interchangeabilité des mesures de deux appareils de SPIR chez des volontaires sains, ainsi que les valeurs normales à tous les sites utilisés en pratique.[107] À cet effet, il est surprenant que ces appareils soient couramment étudiés et utilisés comme outil de monitorage, mais que leurs qualités métrologiques soient si peu étudiées.[97, 300] Nos observations quant à la relativement bonne répétabilité des mesures de SPIR sont concordantes avec la littérature publiée à ce sujet.[134, 136, 244] Également, plusieurs autres auteurs ont également décrit une mauvaise interchangeabilité des valeurs données par différents appareils de SPIR. [135, 246-249, 301] Ceci s'explique principalement par le fait qu'il n'existe pas de mesure 'étalon-or' à laquelle les appareils de SPIR pourraient être standardisés. De plus, chaque appareil de SPIR est de conception unique de par son nombre d'émetteurs et de récepteurs, distances entre ces émetteurs et récepteurs, longueurs d'onde

utilisées et même quant aux algorithmes utilisées pour calculer les valeurs d'oxymétrie elles-mêmes.[81] Ainsi, ces observations nous ont permis de conclure qu'il est plus sécuritaire d'utiliser toujours la même marque d'appareil pour un patient donné. La tendance que prennent les valeurs est probablement un marqueur plus fiable que tout seuil absolu de désaturation, surtout si ce seuil a été établi avec un autre appareil de SPIR.

Dans le même ordre d'idée, nous avons observé que la quantité de gras sous-cutané, le sexe et le site de mesure étaient les principaux facteurs influençant l'accord entre deux appareils de SPIR fréquemment utilisés. Il avait déjà été observé dans une autre étude que le sexe des participants influençait l'accord entre appareil de SPIR.[105] Tel que mentionné précédemment, il est impossible de déterminer laquelle des caractéristiques conceptuelles génère principalement ces trouvailles et module l'influence des tissus superficiels sur les mesures d'oxymétrie.[81, 112, 262-264] Également, puisque les appareils de SPIR utilisent un algorithme ayant été initialement conçu pour calculer une mesure d'oxymétrie cérébrale, il est probable que ces algorithmes performent moins bien lors qu'ils calculent des mesures d'oxymétrie somatique. Ces trouvailles renforcent nos conclusions précédentes, à savoir que le suivi de la tendance des mesures à un même site, avec un même appareil de SPIR, est probablement plus fiable qu'une mesure absolue prise isolément.

En résumé, les connaissances issues du troisième volet nous ont permis de synthétiser la littérature quant à l'utilisation de la SPIR chez les patients souffrant d'un ACEH et d'améliorer les connaissances quant aux qualités métrologiques de ces appareils. Ces trouvailles favoriseront l'étude future de la SPIR chez les patients bénéficiant d'une R-CEC en médecine d'urgence afin d'optimiser les résultats obtenus. Ainsi, bien que cette technologie soit prometteuse, de meilleures études prospectives seront cependant nécessaires avant que des valeurs seuils

spécifiques puissent être utilisées afin de sélection des patients pour une R-CEC ou de les pronostiquer avec certitude.

4.4. Résumé et perspectives futures

L'ensemble des travaux réalisés dans la présente thèse a permis de jeter une base solide de connaissances permettant une évaluation prospective d'une implantation de la R-CEC dans les pratiques en médecine d'urgence. En effet, les travaux réalisés dans le cadre de la présente thèse ont ajouté aux connaissances les éléments suivants, rendant cette évaluation possible. Nous avons pu conclure du premier volet qu'il serait sécuritaire et potentiellement bénéfique de réduire la durée de réanimation préhospitalière pour des patients sélectionnés et de les rediriger rapidement vers un CH R-CEC. Nous avons pu améliorer, lors du deuxième volet, la pronostication de certaines populations de patients considérés pour une R-CEC afin d'optimiser la sélection des patients pour cette technique. Ainsi, nous avons observé que les personnes souffrant d'un ACEH nécessitant plus de 10 défibrillations devraient demeurer candidats à une R-CER, mais que ceux dont le rythme non défibrillable s'est converti à un rythme défibrillable ne devraient pas être des candidats de première intention. Dans le troisième volet, nous avons pu démontrer la capacité pronostique d'une technologie de monitorage, la SPIR, pour les patients souffrant d'un AC. Nous avons ensuite décrit les caractéristiques métrologiques de deux de ces appareils de SPIR afin de permettre une meilleure interprétation des valeurs par les cliniciens utilisant ces appareils comme outil de monitorage.

À la suite de ce que nous avons étudié dans le premier volet, une évaluation prospective à grand échelle d'une stratégie de redirection rapide vers un CH R-CEC pour les patients éligibles à une R-CEC nous apparaît nécessaire. Il serait également intéressant d'évaluer, dans les villes où le contexte géographique le permet, quelles autres caractéristiques hospitalières influencent la

survie, et chez quelles populations de patients. Cette évaluation prospective nous permettra également de monitorer l'équilibre entre le nombre de patients et la capacité à répondre à la demande des milieux hospitaliers pouvant réaliser les R-CER. Suite aux travaux réalisés dans le deuxième volet, d'autres études seront nécessaires pour identifier chez différentes populations en ACEH quels devraient être les critères de sélection à privilégier afin de maximiser les bénéfices d'une telle intervention tout en maintenant cette pratique de soins réaliste dans un contexte de ressources limitées. En effet, il est probable que certains patients avec une AESP pourraient bénéficier d'une R-CEC. L'utilisation de bases de données plus importantes, comme celle du *Canadian Resuscitation Outcomes Consortium* ou du *Resuscitation Outcomes Consortium* pourrait potentiellement permettre de déterminer une sous-population d'ACEH avec AESP pour qui il serait utile d'évaluer prospectivement une stratégie de transport rapide en vue d'une R-CEC. Aussi, d'autres études devront également être réalisés afin d'évaluer l'impact coût-bénéfice de la R-CEC, autant en termes de ressources humaines que financières, en fonction des critères de sélection utilisés, le tout sur les patients subissant un ACEH, mais aussi pour l'ensemble du CH, notamment quant à la disponibilité des pompes pour la chirurgie cardiaque et des lits de soins intensifs. Ceci permettra d'optimiser la pertinence de ces nouvelles procédures complexes de réanimation et d'améliorer globalement les soins de santé prodigués. Suite aux travaux du troisième volet, nous concluons que l'utilisation de la SPIR pourrait également contribuer à l'évaluation et au monitorage des patients éligibles ou bénéficiant d'une R-CEC. Cependant, des progrès devront être réalisés afin que les appareils deviennent plus performants, entre autres pour améliorer la fiabilité des données collectées. Cependant, ces travaux d'ingénierie devront probablement être réalisés par les compagnies elles-mêmes vendant ces appareils. À la suite d'une amélioration technologique, une démonstration de la fiabilité de ces appareils, chez des volontaires sains, mais aussi chez des patients en ACEH permettra finalement l'intégration de la

SPIR à l'intérieur d'une approche multimodale de monitorage pour les patients éligibles ou bénéficiant d'une R-CEC. Évidemment, d'autres modalités de monitorage émergentes, comme l'électroencéphalographie en continu, pourront également être étudiées afin d'améliorer nos capacités à sélectionner et monitorer ces patients.[302]

L'opérationnalisation de l'intégration d'une nouvelle pratique médicale comme la R-CEC doit être soigneusement préparée. L'évolution des pratiques en réanimation cardiorespiratoire est généralement assez lente et l'intégration de la R-CEC représente un virage que l'on observe rarement et pour lequel nous devons nous préparer minutieusement. En effet, Bougouin et al. ont tout récemment publié leur expérience de 525 cas de R-CEC, dont 136 ont même été initiées en préhospitalier.[303] Leurs résultats suggèrent qu'il n'y a aucun bénéfice à la R-CEC par rapport à la réanimation standard. Cependant, dans leur étude, les patients n'étaient pas randomisés et les critères de sélection pour une R-CEC laissés à la discrétion du médecin traitant, ceci entraînant un très important biais de sélection dont il est impossible de se défaire lors de l'analyse des résultats.[303] De la même manière, tous les résultats présentés par les différents programmes de R-CEC sont influencés par ces biais et leurs résultats varient beaucoup.[21, 29, 303, 304]

Ainsi, l'ensemble de ces résultats convergent vers la proposition que l'évaluation prospective randomisée de cette technique de réanimation devra être réalisée, afin d'obtenir des résultats convaincants qui permettraient d'influencer la pratique en médecine d'urgence. En avril 2020, déjà, sept essais randomisés sont enregistrés sur le site *Clinicaltrials.gov* afin d'évaluer les impacts de la R-CEC chez les patients souffrant d'un ACEH. Les résultats de ces études ne sont malheureusement pas encore disponibles, mais contribueront éventuellement à optimiser l'opérationnalisation du système de soins préhospitaliers pour maximiser la survie avec un bon devenir neurologique pour les patients souffrant d'un ACEH. Des données locales permettront

également de comparer les résultats québécois à ceux de ces études, afin d'en apprécier la validité.

Les travaux présentés dans la présente thèse ont permis de bâtir une base solide de connaissance ayant rendu possible l'étude locale de l'implantation de la R-CEC en médecine d'urgence. En effet, nous avons initié une étude actuellement en cours au Québec (Approbation éthique à l'Hôpital du Sacré-Cœur de Montréal : MP-32-2017-1448) visant à évaluer prospectivement la faisabilité et l'efficacité d'une modification de la prise en charge préhospitalière des patients avec ACEH et candidats à une R-CEC. À l'aide d'un devis avant-après, nous évaluons actuellement si ces patients peuvent être transportés vers les CH R-CEC en moins de 45 minutes et quel en sera l'impact sur leur survie avec un bon devenir neurologique. Les modifications proposées de la prise en charge préhospitalière des ACEH pourront permettre à plus de patients de bénéficier localement d'une R-CEC. Une deuxième étude (Approbation éthique à l'Hôpital du Sacré-Cœur de Montréal : MP-32-2019-1606) également en cours vise à déterminer les capacités de l'oxymétrie cérébrale à prédire le pronostic de patient recevant une R-CEC à deux moments, soit pendant l'ACEH avant l'initiation de la R-CEC afin d'évaluer la sélection des patients et durant les 72 heures suivant l'initiation de la R-CEC afin d'évaluer la pronostication des patients. Les résultats de cette étude visent à identifier rapidement les patients avec les meilleurs pronostics et ainsi améliorer le délai entre l'ACEH et la R-CEC. Également, une pronostication rapide de ces patients permettrait de diminuer les coûts en lien avec cette technique tout en offrant les meilleurs soins et ressources pour les patients non sélectionnés. Les résultats de ces deux études locales et ceux qui seront publiés par les groupes de recherche ayant déjà des essais randomisés en cours sur la R-CEC nous aiguilleront certainement vers un essai clinique randomisé prospectif qui répondra à une des lacunes dans la littérature.

Les résultats présentés ici ont déjà permis des applications pratiques des connaissances générées. Notamment, les patients souffrant d'un ACEH dans la région de Montréal et Laval sont transportés directement vers un CH offrant des soins spécialisés en médecine cardiovasculaire s'ils avaient un rythme initial défibrillable et ont obtenu un RCS préhospitalier. Ce protocole est en voie d'être révisé afin que tous les patients ayant subi un ACEH soient dirigés vers ces CH.

Il est également important de mentionner que la R-CEC a le potentiel d'améliorer le devenir que pour une faible proportion de tous les patients souffrant d'un ACEH. Déjà en milieu urbain où les ressources sont potentiellement disponibles, seule une minorité des patients est éligible à ce traitement. Nous savons qu'en milieu rural, étant donné l'absence de soins spécialisés cardiovasculaire et des longs temps de transports ambulanciers, aucun patient ne pourra bénéficier d'une R-CEC.[37, 181, 288, 289] Il est possible que les techniques soient éventuellement simplifiées grâce à l'amélioration de la technologie et ainsi disponibles à plus large échelle. Étant donné les coûts associés à cette intervention, il faudra aussi s'assurer de maintenir également du financement pour d'autres interventions plus simples, mais potentiellement plus efficace au point de vue populationnel, comme l'enseignement de la réanimation de base au membre du public et un meilleur accès à une défibrillation rapide.

Chapitre 5. Conclusion

Le taux de survie des patients souffrant d'un ACEH demeure bas et ne s'améliore que très peu. Les travaux présentés dans la présente thèse visaient à bâtir une base de connaissances qui permettrait l'implantation de la R-CER dans les pratiques en médecine d'urgence.

Les connaissances issues du premier volet nous ont permis de conclure qu'il serait sécuritaire et même potentiellement bénéfique de limiter la durée de réanimation préhospitalière sur la scène avant l'initiation de l'extraction pour des patients sélectionnés et de les rediriger de manière efficiente vers un CH R-CEC. Dans le deuxième volet, nous avons précisé le pronostic de deux populations de patients candidats à la R-CEC afin d'optimiser la sélection des patients pour cette thérapie. L'ensemble des connaissances issues du troisième volet nous ont permis de synthétiser la littérature quant à l'utilisation de la SPIR chez les patients souffrant d'un ACEH et d'améliorer les connaissances quant aux qualités métrologiques de ces appareils.

Ces résultats présentés ont déjà influencé les pratiques en réanimation préhospitalière et certaines catégories de patients souffrant d'un ACEH sont désormais transportées directement vers un centre spécialisé en médecine cardiovasculaire au Québec

Les résultats des études de la présente thèse et celles des deux études en cours, couplées au reste de littérature qui sera publiée, contribueront certainement à façonner l'utilisation de la R-CEC en réanimation au Québec pour les prochaines années.[305]

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