



Arrêt cardiaque réfractaire aux traitements pharmacologiques : quelle solution proposer pour améliorer la circulation systémique et cérébrale.

Sebastian Voicu

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Arrêt cardiaque réfractaire aux traitements pharmacologiques: quelle solution proposer pour améliorer la circulation systémique et cérébrale?

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Dirigée par Professeur **Jacques Callebert**
Co-dirigée par Professeur **Patrick Henry**
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Résumé et mots-clés / Abstract and keywords

La thèse « Arrêt cardiaque réfractaire aux traitements pharmacologiques: quelle solution proposer pour améliorer la circulation systémique et cérébrale? » a montré que l'amélioration de la fonction circulatoire peut être obtenue à plusieurs étapes de la prise en charge de l'arrêt cardiaque.

La première étude du travail, sous la forme d'une étude expérimentale à double randomisation, a montré que l'assistance circulatoire type extracorporel life support ECLS apporte un bénéfice sur la mortalité dans la prise en charge de l'arrêt cardiaque réfractaire chez le cochon, et que l'adrénaline administrée en intraveineux lors de la réuscitation prolongée n'améliore pas la survie des animaux.

La deuxième étude a montré que la canulation pour l'ECLS peut être réalisée rapidement par voie percutanée à l'aide d'un repérage échographique et en utilisant des guides rigides en salle de cathétérisme cardiaque chez les patients en arrêt cardiaque réfractaire, permettant l'initiation de l'ECLS dans des centres dotés de salle de cathétérisme sans chirurgie cardiovasculaire.

La troisième étude a retrouvé que l'état de choc et le pH artériel $< 7,11$ sont des critères pronostiques identifiant les patients qui, après un arrêt cardiaque, présentent une reprise d'une circulation spontanée mais sont à risque de décéder d'insuffisance circulatoire réfractaire au traitement par catécholamines.

La quatrième étude a montré que la stabilisation de la fonction circulatoire par l'ECLS peut être suivie par une meilleure récupération de la fonction ventriculaire gauche en modulant la postcharge, par un dispositif pulsatile diminuant le débit de l'ECLS lors de la systole cardiaque.

Enfin, l'optimisation de la circulation cérébrale nécessite en plus de l'optimisation de la circulation systémique, le contrôle de l'interaction entre la pression en gaz carbonique et le débit sanguin cérébral qui est amélioré par une normalisation de la pression en gaz carbonique en stratégie pH-stat. Cette stratégie mesure la pression en gaz carbonique à la température réelle du patient au lieu de la température de référence 37° comme dans la stratégie alpha-stat.

L'ensemble de ces résultats, pouvant être appliqués à différentes étapes de la prise en charge d'un patient présentant un arrêt cardiaque, pourraient permettre l'amélioration du pronostic des patients.

Mots-clé : arrêt cardiaque, arrêt cardiaque réfractaire, état de choc, catécholamines, assistance circulatoire, extracorporel life support, canulation percutanée, assistance circulatoire pulsatile synchrone, circulation

cérébrale, pression partielle en bioxyde de carbone.

The doctoral dissertation « Cardiac arrest refractory to pharmacological treatments : what solution to improve systemic and cerebral circulation ? » showed that circulatory function improvement can be achieved at several stages of the management of cardiac arrest patients.

The first study of the dissertation, a double randomization experimental study, showed that extracorporeal life support - ECLS type circulatory assistance improves mortality in refractory cardiac arrest in pigs, and intravenous administration of epinephrine during prolonged resuscitation does not improve survival.

The second study showed that cannulation for ECLS can be performed rapidly by the percutaneous technique using echography guidance and stiff wires in the catheterization laboratory in refractory cardiac arrest patients allowing for ECLS initiation in centres with catheterization laboratories but without cardiovascular surgery.

The third study found that circulatory shock and arterial $\text{pH} < 7.11$ are prognostic criteria identifying patients who, after a cardiac arrest, have return of spontaneous circulation but are at risk of death from circulatory failure refractory to catecholamine treatment.

The fourth study showed that hemodynamic stabilization by ECLS can be followed by a better recovery of the left ventricular function by modulating afterload using a pulsatile device lowering ECLS output during systole.

Finally, optimization of the cerebral circulation requires besides optimization of the systemic circulation, the control of the interaction between carbon dioxide partial pressure and cerebral circulatory output, which is improved by normalizing carbon dioxide partial pressure in pH-stat strategy. This strategy measures partial pressure of carbon dioxide at the real temperature of the patients instead of the theoretical 37° reference temperature as in alpha-stat strategy.

All these results can be applied at different stages of the management of cardiac arrest patients and may improve their prognosis.

Keywords : cardiac arrest, refractory cardiac arrest, circulatory shock, catecholamines, circulatory assistance, extracorporeal life support, percutaneous cannulation, synchronized pulsatile circulatory assistance, cerebral circulation, carbon dioxide partial pressure.

1 Introduction

1.1 Arrêt cardiaque – un problème majeur de santé et un défi physiologique

L'arrêt cardiaque (AC) abordé dans ce travail est défini selon les recommandations des sociétés savantes comme un événement létal non traumatique, inattendu, survenant dans l'heure suivant l'apparition de symptômes de maladie chez un individu en état de santé apparente, désigné également dans la littérature par le terme « sudden death »(1). De point de vue clinique il s'agit d'un état de « mort apparente » qui s'installe rapidement après l'arrêt de la fonction mécanique cardiaque, de la circulation sanguine et lors duquel le pouls, la conscience, et la fonction respiratoire sont absents(2). En absence de mesures rapides de réanimation cardiopulmonaire permettant de maintenir un débit circulatoire minimal, des lésions cérébrales irréversibles suivies de lésions de l'ensemble de l'organisme s'installent. Lorsque l'AC a bénéficié de manœuvres de réanimation cardiopulmonaire permettant une reprise de l'activité circulatoire, le terme « AC récupéré » ou « mort subite avortée », « aborted sudden death » est utilisé(1), ayant pour implication clinique le succès des thérapeutiques mises en route lors de la réanimation cardiopulmonaire.

L'AC est un problème majeur de santé publique car il est responsable de 25% des 17 millions de décès de causes cardiovasculaires dans le monde entier(3). Aux États-Unis, une étude épidémiologique a enregistré 420 000 cas d'AC par an(4), alors qu'en Europe des données de 2005(5) indiquent 275 000 cas d'AC par an. Plus récemment, l'incidence de l'AC extrahospitalier a été estimée entre 24 et 104 cas par 100 000 habitants et par an en Europe, et environ 60 cas par 100 000 habitants par an en France(6). Parmi les patients ayant présenté un AC, des données récentes montrent une survie très faible, de seulement 10,3% en moyenne(6).

Cette faible survie est le résultat d'une part, de la destruction cérébrale rapide lors de l'hypoxie cellulaire liée à l'AC(7) et d'autre part de la difficulté de maintenir une fonction circulatoire

satisfaisante par le massage cardiaque externe, technique connue et utilisée depuis plus d'un demi-siècle, décrite initialement par Kouwenhoven et al., Figure 1(8).

Figure 1 Technique du massage cardiaque décrite en 1960 par Kouwenhoven et al(8).

Après l'arrêt de la circulation sanguine, les réserves énergétiques des cellules myocardiques diminuent progressivement avec le temps. Si, dans les premières minutes un geste unique comme la défibrillation peut réverser l'AC et permettre la reprise d'une circulation sanguine efficace, passé un seuil critique, cette reprise de la fonction cardiaque et de la circulation sanguine nécessitera des interventions supplémentaires comme le massage cardiaque externe, l'administration de médicaments inotropes et vasopresseurs et d'autres traitements dont la complexité augmente avec le temps passé en AC.

La survie très réduite après un AC est également liée aux difficultés de maintenir une fonction circulatoire adaptée aux besoins après la reprise d'une circulation spontanée chez ces patients qui présentent très souvent une défaillance circulatoire et cardiaque associées(7,9,10). Pour éviter l'apparition de lésions cérébrales graves et irréversibles, incompatibles avec la survie, et pour permettre la meilleure récupération neurologique possible, il est essentiel d'assurer le retour d'une circulation systémique et cérébrale efficace dans les plus brefs délais et ensuite une fonction circulatoire adaptée aux besoins.

Le retour d'une circulation efficace dépend de multiples facteurs, comme l'état physiologique du patient et la cardiopathie sous-jacente, la réversibilité de la cause de l'AC, la présence d'un témoin de l'événement, et la réalisation des gestes de base comme le massage cardiaque et les chocs électriques externes, faisant partie de la « chaîne de la survie » et permettant la reprise de la fonction cardiaque et la perfusion d'organes(11,12).

Après la reprise d'une circulation spontanée dans les suites d'un AC, l'homéostasie et l'équilibre hémodynamique sont menacés par des dysfonctionnements majeurs d'organes vitaux, dont la

réversibilité, le traitement et le pronostic sont très variables.

La rapidité d'installation de lésions de l'ensemble des organes dont le plus sensible est le cerveau, la difficulté de restaurer une contractilité cardiaque et une circulation efficace après les premières minutes post AC, et le traitement des défaillances d'organes suivant la reprise d'une circulation spontanée, sont des éléments majeurs du grand défi physiopathologique et thérapeutique représenté par l'AC.

1.2 Physiopathologie de l'arrêt cardiaque

1.2.1 Consommation des réserves énergétiques cellulaires et réversibilité de l'arrêt cardiaque

Lors de l'apparition d'un AC, les réserves énergétiques cellulaires dont la principale forme est l'adénosine triphosphate (ATP), continuent à diminuer car la consommation énergétique des cellules persiste, malgré l'arrêt total de la circulation sanguine. Cette phase a été désignée comme la phase « électrique » de l'AC, qui dure quelques minutes(13). Lors de cette phase, dans le cas de la fibrillation ventriculaire, un choc électrique externe est la seule intervention nécessaire pour la reprise d'une activité cardiaque, puisque les ressources myocytaires d'énergie ne sont pas épuisées. Lorsque les ressources cellulaires d'énergie diminuent en dessous d'un seuil critique, un simple choc électrique ne suffira pas pour reprendre une activité cardiaque, car son résultat sera soit une asystolie soit une dissociation électromécanique. Cette phase est la phase dite « circulatoire », lors de laquelle il est nécessaire de réaliser 1,5 à 3 minutes de massage cardiaque selon la technique dont les bases ont été décrites par Kouwenhoven(8), pour améliorer les réserves énergétiques cellulaires permettant ensuite au choc électrique d'être suivi d'une activité contractile efficace(13). Finalement, si le patient reste en AC pendant 8 à 10 minutes, les cellules entreront dans la phase dite « métabolique » caractérisée par l'apparition des lésions ischémiques cellulaires qui nécessiteront un

support d'organes plus complexe pour réverser les lésions(13).

Lors de l'absence de circulation sanguine, les organes et tissus sont soumis à un effondrement rapide de l'apport en oxygène et présentent lorsque cet état se prolonge au-delà de quelques minutes, des lésions liées à l'anoxie – lésions d'ischémie. Lors de la reprise d'une circulation efficace, la restitution de l'apport en oxygène nécessaire à la reprise de la production d'énergie et à la survie cellulaire, crée par elle-même des lésions cellulaires de reperfusion. Ces lésions d'ischémie et reperfusion représentent une caractéristique commune des AC de différentes causes.

1.2.2 La lésion d'ischémie-reperfusion

L'ischémie-reperfusion cellulaire a été étudiée de façon détaillée dans plusieurs organes dont principalement le cœur en raison du problème majeur de santé représenté par l'infarctus aigu du myocarde(14), mais les principes d'installation de cette lésion restent valables pour l'ensemble de l'organisme.

1.2.2.1 Effets de l'ischémie

L'arrêt de la circulation sanguine engendre une diminution brutale de la disponibilité de l'oxygène au niveau cellulaire et mitochondrial, suivie d'un arrêt rapide de la production d'ATP par les mitochondries et l'activation du métabolisme anaérobie. Le métabolisme anaérobie permet par la glycolyse, de produire une faible quantité d'ATP, deux molécules par molécule de glucose, et deux molécules d'acide lactique, qui sera responsable de l'apparition d'une acidose intracellulaire et systémique. Le milieu intracellulaire devient plus riche en protons, phosphates et potassium et le gaz carbonique intracellulaire s'accumule en absence de circulation sanguine(15–17).

La diminution rapide de la concentration d'ATP et l'apparition d'une acidose intracellulaire sont accompagnées d'anomalies du fonctionnement de l'ensemble des cellules de l'organisme à des moments variables, les plus rapidement atteintes étant les neurones, à l'origine de la perte de

connaissance survenant quelques secondes après l'AC. Dans le myocarde, les réserves de glycogène sont épuisées et les granules de glycogène disparaissent après environ 2,5 heures(18).

En absence de traitement, l'ischémie persistante a pour effet l'apparition de la nécrose cellulaire, un premier mécanisme de mort cellulaire. La nécrose est caractérisée par un œdème cellulaire accompagné par la rupture de la membrane et la libération du contenu cellulaire dans le milieu extérieur. La rupture membranaire est favorisée par la déplétion en ATP, l'inactivité des ATP-ases membranaires, l'activation de diverses protéases intracellulaires comme la calpaïne activée par le calcium. La nécrose est également favorisée par les lésions mitochondriales qui permettent l'ouverture d'un canal de haute conductance « mitochondrial permeability transition pore » (MPT) par le calcium et radicaux libres, ce qui inactive les mitochondries et fait perdre à la cellule la capacité de synthétiser de l'ATP, Figure 2.

Figure 2 Interactions entre l'augmentation du calcium intracellulaire et l'ouverture du pore mitochondrial.

A L'apparition d'une acidité intracellulaire due au métabolisme anaérobie augmente l'activité du cotransporteur $\text{Na}^+\text{-H}^+$, et augmente la concentration de Na^+ intracellulaire activant le cotransporteur $\text{Na}^+\text{-Ca}^{2+}$ qui sortira le Na^+ et transportera le calcium dans la cellule. L'accumulation de Ca^{2+} cytoplasmique favorise l'accumulation de Ca^{2+} mitochondrial ce qui stimule l'ouverture du pore MPT - mitochondrial permeability transition pore. Lorsque la reperfusion normalise le pH intracellulaire, le MPT s'ouvre et déclenche des lésions mitochondriales aboutissant à la mort cellulaire. NHE – échangeur $\text{Na}^+ - \text{H}^+$; ATP – adénosine triphosphate. Selon Murphy, Steenberg 2008(14). B, C Schéma du pore mitochondrial de transition de perméabilité (MTP) fermé (B) et ouvert (C). Selon Bernardi et al, 2015(19).

L'ouverture du MTP, canal non-sélectif, dissipe le gradient de protons à travers la membrane mitochondriale empêchant ainsi la synthèse d'ATP et déclenchant également l'apoptose, le deuxième mécanisme de mort cellulaire(20).

En absence de traitement, l'ischémie a pour effet l'activation des voies de l'apoptose (mort cellulaire programmée) par l'activation des protéines de la famille Bax, Fas, etc., qui aboutissent à une activation des protéines de la famille des caspases et à des lésions programmées de l'ADN et de divers composants cytoplasmiques(21). Cette mort programmée fragmente la cellule en corps apoptotiques qui sont par la suite phagocytés, processus associé à une faible réaction inflammatoire. Néanmoins, lorsqu'un cœur sain est exposé à une ischémie totale pendant 20 minutes et 2 heures de reperfusion, 38% des cellules cardiaques sont mortes, mais seulement 4% par le mécanisme de l'apoptose, le reste par le mécanisme de la nécrose(14). La surexpression de certaines protéines telle que Bcl₂ est capable de réduire le pourcentage de nécrose de plus de moitié et le pourcentage d'apoptose de plus de deux tiers(22). Ces données suggèrent qu'une modulation de certaines voies intracellulaires pourrait améliorer les lésions ischémiques, mais actuellement aucune de ces voies n'est utilisée en thérapeutique de l'AC chez l'homme.

Un troisième mécanisme semble être impliqué dans la lésion ischémique : l'autophagie, processus de phagocytose du contenu cytoplasmique dont il n'est pas clairement établi s'il joue un rôle favorisant ou s'opposant à la mort cellulaire(23,24).

1.2.2.2 Effets de la reperfusion

La reperfusion est caractérisée par la reprise d'une circulation sanguine avec rétablissement d'un apport d'oxygène et nutriments au niveau cellulaire qui se produit après les modifications cellulaires apparues pendant la période d'ischémie. La reperfusion génère des lésions cellulaires diffuses et surtout une lésion mitochondriale consistant essentiellement en l'ouverture du pore mitochondrial de transition de perméabilité (Figure 2). Ces lésions sont générées par deux mécanismes principaux – l'accumulation de calcium intracellulaire, et la genèse de radicaux libres.

Pendant l'ischémie, les ions de sodium entrent dans la cellule par le cotransporteur Na⁺-H⁺ activé par la production de protons due au métabolisme anaérobie. L'accumulation de Na⁺ et la

dépolarisation cellulaire activent le cotransporteur $\text{Na}^+\text{-Ca}^+$ qui commence à fonctionner dans sens inverse du sens physiologique, faisant alors entrer le Ca^{2+} dans la cellule et sortir les ions de Na^+ (Figure 2), augmentant ainsi la concentration de calcium cytoplasmique. Lors de l'ischémie et reperfusion, il existe également une dysfonction de la pompe de calcium située dans la membrane du réticulum sarcoplasmique SERCA (sarco/endoplasmic reticulum ATP-ase). Le fonctionnement de SERCA dans des conditions physiologiques permet de capter le calcium cytoplasmique et le stocker dans le réticulum sarcoplasmique. Lors de l'ischémie-reperfusion, son dysfonctionnement rend le transport du calcium plus difficile et favorise davantage l'accumulation de calcium dans le cytoplasme(20). Cette accumulation massive de calcium cytoplasmique favorise l'entrée de calcium dans la mitochondrie à travers un canal (système uniport) pour le calcium qui peut être inhibé par le ruthénium. Cette accumulation de calcium constitue le signal d'ouverture du pore mitochondrial MTP (Figure 2). Néanmoins, le MTP reste fermé si le milieu intracellulaire est acide. Lorsque la reperfusion a lieu, le pH intracellulaire redevient rapidement normal et le MTP s'ouvre, entraînant la lésion mitochondriale et finalement la mort cellulaire(14). L'ouverture du MTP annule le gradient électrique et le gradient en protons à travers la membrane mitochondriale et libère dans le cytoplasme le cytochrome c. Ce processus initiant l'apoptose, induit un œdème mitochondrial et la rupture de la membrane mitochondriale, aboutissant à la mort cellulaire par l'absence de production d'ATP(14). L'ouverture du pore MTP peut être inhibée par diverses molécules comme la cyclosporine, mais une étude récente utilisant la cyclosporine rapidement après un AC avec rythme non choquable n'a pas montré de bénéfice(25).

Lors de la reperfusion, une augmentation de la pression partielle en oxygène dans les tissus, augmente la production de radicaux libres, essentiellement par une anomalie dans la chaîne de transport des électrons mitochondriale, et par la xanthine oxydase. L'anion superoxyde O_2^- est le principal radical libre produit(14), les radicaux hydroxyle et peroxyde d'hydrogène étant dérivés ensuite du superoxyde.

Un des mécanismes de production de radicaux libres lors de la reperfusion est le dysfonctionnement

mitochondrial. Lors de la période d'ischémie, un excès de succinate apparaît par perturbation du cycle de Krebs et par le métabolisme des purines. Lors de la reperfusion, le succinate va rapidement être métabolisé en fumarate par le complexe 2 mitochondrial ce qui va générer de l'ubiquinol en excès dans la membrane mitochondriale (Figure 3). Rapidement, l'ubiquinol en excès et les protons en excès inversent le fonctionnement du complexe 1 de la chaîne mitochondriale par rapport au fonctionnement physiologique (Figure 3)(26). Les électrons seront alors cédés aux molécules d'oxygène générant ainsi l'anion superoxyde. Néanmoins, lorsque l'ensemble du succinate a été métabolisé, les mitochondries reprennent leur fonctionnement physiologique. Les radicaux libres générés sont responsables de lésions membranaires, de la destruction du monoxyde d'azote, vasodilatateur majeur nécessaire à la bonne reperfusion(27) et jouent un rôle important dans la peroxydation des lipides membranaires, la dénaturation des protéines et enzymes cellulaires(28,29) et dans l'activation du pore mitochondrial MPT(30).

Figure 3 Mécanisme proposé pour la production de radicaux libres par les mitochondries lors de la reperfusion

En haut de la figure - fonctionnement normal de la chaîne mitochondriale. Lors de l'ischémie (panneau du milieu) une quantité importante de succinate est générée. Lors de la reperfusion (schéma en bas de la figure), le succinate est transformé en fumarate et l'ubiquinol (Q) en excès s'accumule entraînant avec l'excès de protons, le fonctionnement inverse du complexe I qui génère alors des anions superoxyde et d'autres radicaux libres (ROS). PNC – cycle du métabolisme des purines; CAC – cycle de Krebs Δp – gradient transmembranaire en protons. Selon Chouchani et al(26).

Une autre source de radicaux libres est la xanthine oxydase. Celle-ci métabolise des dérivés des purines, la xanthine et l'hypoxanthine en produisant également l'anion superoxyde et du peroxyde d'hydrogène. Pendant la période d'ischémie, les substrats de la xanthine oxydase s'accumulent dans le cytoplasme par la transformation de l'ATP en ADP, AMP, adénosine, inosine et finalement en hypoxanthine. En présence de ces substrats, la xanthine oxydase devient très active et génère lors de la reperfusion des radicaux libres participant à la lésion d'ischémie-reperfusion(31). Les voies activées lors de l'ischémie et reperfusion sont représentées dans la Figure 4.

Figure 4 Voies activées par l'ischémie-reperfusion impliquées dans la mort cellulaire

ATP – adénosine triphosphate, Ca-calcium, $\Delta\Psi$ -gradient électrique transmembranaire mitochondrial, ROS - radicaux libres d'oxygène, Mito Ca - calcium intramitochondrial, MPT - mitochondrial permeability transition pore, Cyto c – cytochrome c. Selon Murphy et al.(14)

Dans le domaine de l'AC, lors de la reperfusion systémique, les lésions d'ischémie-reperfusion pourraient être favorisées par une pression partielle en oxygène trop élevée. En effet, dans une étude expérimentale chez le rat, la ventilation mécanique avec une fraction inspirée en oxygène de 50%

après réanimation cardiopulmonaire a montré une meilleure durée de survie, une meilleure fonction cardiaque et une plus faible peroxydation lipidique par rapport à l'administration d'oxygène pur(32). Des résultats en faveur de la toxicité de l'oxygène sur les neurones ont également été observés dans des études expérimentales chez le chien(33,34). Des études observationnelles chez l'homme concernant l'hyperoxémie définie comme $\text{PaO}_2 > 300 \text{ mmHg}$ ont fourni des résultats contradictoires en ce qui concerne l'effet délétère, en revanche aucun bénéfice clinique de l'hyperoxémie n'a été observé(35,36).

Si les lésions d'ischémie-reperfusion sont une caractéristique commune aux AC en général, certaines particularités importantes comme la rapidité d'une reprise de la circulation spontanée et les moyens nécessaires pour réussir à réverser l'AC, dépendent des causes ayant conduit à l'AC. En effet, un AC peut survenir après une pathologie cardiaque comme l'infarctus aigu de myocarde qui est la cause la plus fréquente(9,37,38), ou après des causes respiratoires, neurologiques, infectieuses, hémorragiques, toxiques, hypothermie, noyade, ce qui rend les conséquences de l'AC sur différents organes et systèmes très diverses en termes de physiopathologie, aspects cliniques et mesures thérapeutiques.

1.2.3 Principales causes d'arrêt cardiaque

Les causes de l'AC ont été classifiées en causes médicales ou « internes » (incluant les causes cardiaques, anaphylactiques, la crise d'asthme, l'hémorragie gastro-intestinale), et les causes externes comme les causes traumatiques, intoxications (médicamenteuses ou autres substances), noyade, électrocution, et causes asphyxiques externes (corps étranger, pendaison, strangulation) (39).

Cet travail se concentre sur l'AC de causes internes et notamment présumées cardiaques, ou « sans cause extracardiaque évidente »(38).

La cause la plus fréquente de survenue d'un AC est l'apparition d'un infarctus aigu du myocarde ou

syndrome coronaire aigu, qui se produit par l'occlusion d'une artère coronaire entraînant une ischémie myocardique aiguë(40). Cette occlusion artérielle est en général due à l'apparition d'une thrombose coronaire, généralement au niveau d'une plaque d'athérome compliquée. L'occlusion coronaire entraîne l'arrêt du flux sanguin et engendre une ischémie aiguë dans le territoire correspondant, avec une déplétion rapide de l'ATP et des réserves énergétiques intracellulaires entraînant rapidement l'apparition d'un dysfonctionnement des pompes transmembranaires notamment de la $\text{Na}^+\text{-K}^+$ ATPase. Ce dysfonctionnement entraîne la diminution de la concentration de potassium et une accumulation de sodium dans les cellules. Ainsi, les canaux de sodium responsables de la dépolarisation myocardique restent partiellement inactifs, le potentiel d'action devient plus faible, et une inhomogénéité de la dépolarisation et du potentiel transmembranaire de repos apparaissent(41). Cette inhomogénéité associée à l'accumulation de calcium intracellulaire entraîne des troubles du rythme cardiaque dont l'apparition d'une fibrillation ventriculaire représente la forme la plus menaçante(11,40), car elle s'accompagne d'un arrêt brutal de la fonction cardiaque. Les arythmies ventriculaires générées par de séquelles d'infarctus du myocarde sont également une des causes fréquentes d'AC dans le cadre d'une cardiopathie ischémique, et dans une étude française, 18% des patients ont eu comme cause d'AC une séquelle d'infarctus(9). Le myocarde situé entre la séquelle fibreuse et le myocarde sain contient des cellules instables sur le plan électrique qui peuvent générer des extrasystoles ventriculaires, des tachycardies ventriculaires, et même une fibrillation ventriculaire(1).

Une autre cause importante d'AC est l'hypoxémie due à des maladies respiratoires ou à l'œdème aigu pulmonaire, compliqués d'une diminution de la pression partielle artérielle en oxygène suffisamment importante pour engendrer une diminution de la production d'ATP myocardique et l'apparition d'abord d'une bradycardie extrême et par la suite d'une disparition complète des dépolarisations et contractions cardiaques, l'asystolie. Cette cause d'AC a été observée dans une étude française réalisée dans notre centre chez 13% des patients(9).

De façon plus rare, des maladies rythmologiques type syndrome de Brugada, syndrome du QT long,

dysplasie arythmogène du ventricule droit ou fibrillation ventriculaire idiopathique peuvent déclencher un AC par tachyarythmie chez 4% des patients dans une autre étude réalisée dans notre centre(37). L'AC peut survenir par une tachyarythmie due à une cardiopathie dilatée chez 4% des patients(9). D'autres causes plus rares d'AC sont l'embolie pulmonaire grave documentée chez 2% des patients(9), et des causes diverses comme l'hémorragie intracrânienne, les troubles hydroélectrolytiques comme l'hypokaliémie, la bradycardie extrême due à un bloc atrioventriculaire complet, la tamponnade péricardique, la dissection aortique etc. Ces causes rares ont été identifiées chez environ 15% des patients dans notre centre(9).

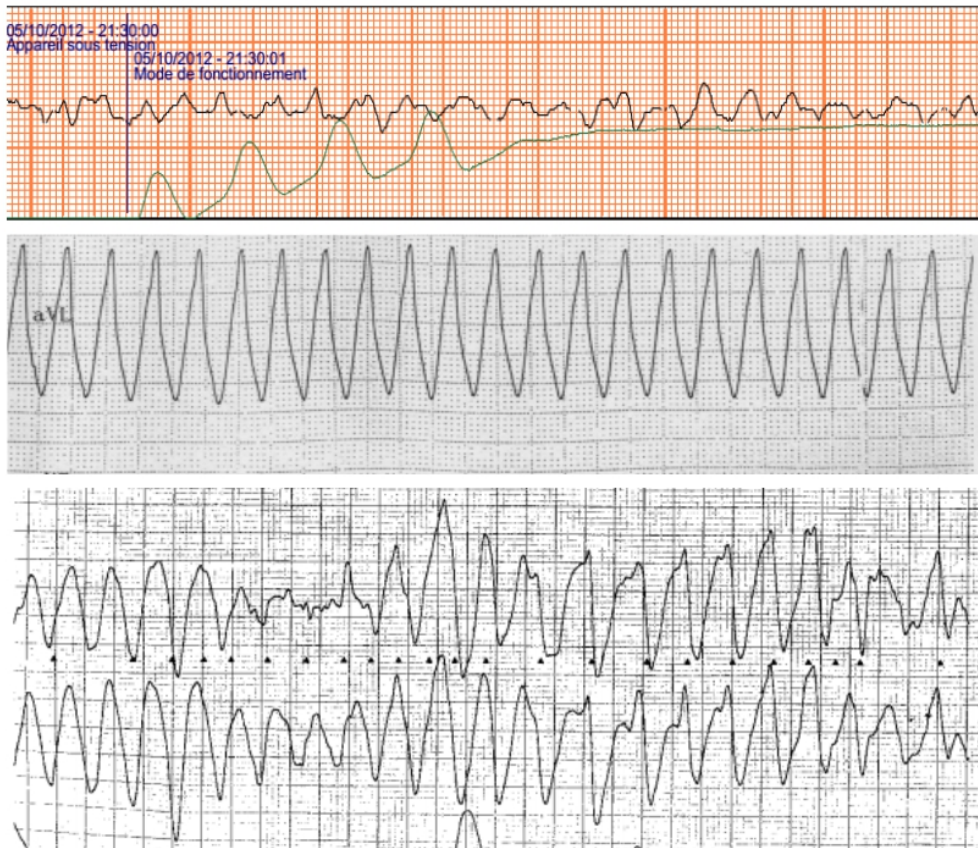
1.2.4 Le rythme initial de l'arrêt cardiaque

Un arrêt de la fonction de pompe cardiaque peut se produire par différentes anomalies du rythme cardiaque qui peuvent être des tachyarythmies - rythmes choquables comme la fibrillation ventriculaire et la tachycardie ventriculaire sans pouls, ou rythmes non-choquables comme l'asystolie, la bradycardie extrême et la dissociation électromécanique. Ces types de rythme cardiaque ont été définis comme étant les rythmes responsables de l'AC par consensus international des sociétés savantes sur la façon de rapporter les données relatives à l'AC, initialement lors de la conférence d'Utstein en Norvège, 1991(2). Ces recommandations sont réactualisées périodiquement, la dernière actualisation datant de 2015(39).

La fibrillation ventriculaire représente une dépolarisation incoordonnée des ventricules sans contraction ventriculaire et sans débit cardiaque. Lorsqu'un AC apparaît pendant un infarctus aigu du myocarde, le plus fréquemment le rythme responsable est la fibrillation ventriculaire(42), Figure 5. Le risque de fibrillation ventriculaire après une occlusion artérielle est très important entre la 2^e et 10^e minute après occlusion et entre la 15^e et 20^e minute, et son apparition peut être précédée par une tachycardie ventriculaire polymorphe(43). Un autre moment très vulnérable sur le plan rythmique est le moment de la reperfusion spontanée ou thérapeutique. Récemment, l'incidence de la fibrillation ventriculaire comme rythme initial de l'AC diminue et est estimée à 20%(44) des

rythmes cardiaques enregistrés initialement à la prise en charge de l'AC. Ce pourcentage est probablement plus important, jusqu'à 76%(45) lorsque le rythme est enregistré rapidement après l'apparition de l'AC correspondant à l'effondrement du patient. En raison de la consommation des réserves énergétiques cellulaires, ce rythme se transforme en asystolie en quelques minutes expliquant la présence d'asystolie lorsque le premier enregistrement du rythme est fait tardivement après l'effondrement du patient. La différence entre ces deux rythmes est significative de point de vue clinique car la présence de fibrillation ventriculaire est associée à un taux de réussite de la réanimation cardiopulmonaire supérieur à celui de l'asystolie(12).

Figure 5 Exemple de fibrillation ventriculaire, tachycardie ventriculaire monomorphe et tachycardie ventriculaire polymorphe



De haut en bas: fibrillation ventriculaire enregistrée par un défibrillateur semi-automatique lors d'un arrêt cardiaque; tachycardie ventriculaire monomorphe rapide sur cicatrice d'infarctus; tachycardie ventriculaire polymorphe lors d'un infarctus aigu du myocarde.

La tachycardie ventriculaire(42) peut générer un AC lorsque la fréquence de la tachycardie est élevée (Figure 5) car le délai de remplissage du ventricule est très court, le volume télédiastolique est diminué, par conséquent le volume d'éjection systolique devient insuffisant pour maintenir une perfusion systémique et cérébrale suffisante. Un autre facteur déterminant la diminution du débit cardiaque est la contractilité cardiaque, qui dans la plupart des situations de tachycardie ventriculaire est diminuée en raison d'une pathologie cardiaque sous-jacente. La situation la plus fréquemment responsable de la tachycardie ventriculaire est la cardiopathie ischémique. La plupart du temps il s'agit d'une cardiopathie ischémique chronique avec cicatrice fibreuse d'infarctus

donnant naissance à un circuit de ré-entrée. Le circuit de ré-entrée est en général situé à la zone de transition entre la cicatrice et le myocarde sain(46). Ce type de tachycardie ventriculaire est en général monomorphe, l'ensemble des QRS ayant le même aspect(40), Figure 5. Une tachycardie ventriculaire à QRS variable « polymorphe » avec des QRS variables d'un battement à l'autre est rencontrée lors de l'ischémie myocardique aiguë et peut être également à l'origine de l'AC (Figure 5).

En dehors de la cardiopathie ischémique, la fibrillation et tachycardie ventriculaires peuvent apparaître lors de maladies cardiaques plus rares comme la cardiomyopathie hypertrophique, la myocardite aiguë, la cardiopathie dilatée, le syndrome de Brugada, le syndrome de QT long, la dysplasie arythmogène du ventricule droit. La fibrillation ventriculaire et la tachycardie ventriculaire peuvent être également idiopathiques ou être générées par des causes extracardiaques comme les troubles électrolytiques sévères notamment l'hypokaliémie, des toxiques, l'hypothermie sévère ou l'électrocution.

Alors que la fibrillation ventriculaire et la tachycardie ventriculaire sont caractérisées par leurs aspects électrocardiographiques typiques, les rythmes non-choquables ont reçu des définitions spécifiques.

L'asystolie a été définie comme une période d'au moins 6 secondes sans activité électrique d'amplitude supérieure à 0,2 mV qui est l'amplitude habituelle de la dépolarisation atriale(39).

La dissociation électromécanique a été définie comme l'absence totale de pouls avec un rythme électrocardiographique ventriculaire à fréquence normale ou diminuée, et la bradycardie extrême a été définie comme la présence de pouls avec une bradycardie sévère, sans seuil défini, et perfusion systémique très diminuée(39).

La dissociation électromécanique, l'asystolie et la bradycardie extrême sont rencontrées dans des maladies cardiaques comme le bloc atrioventriculaire, bloc sinoatrial, tamponnade cardiaque, ou dans des maladies extracardiaques comme les maladies responsables d'hypoxémie profonde, l'embolie pulmonaire, l'hyperkaliémie, l'hypertension intracrânienne sévère.

Les travaux expérimentaux présentés ici se concentrent sur l'AC de cause cardiaque ayant comme rythme initial une fibrillation ventriculaire avec et sans infarctus aigu du myocarde, et les études ayant inclus des patients, sur l'AC sans cause extracardiaque évidente(9,37,38,47).

1.3 Prise en charge initiale de la victime de l'arrêt cardiaque

La réversibilité de l'AC avec récupération d'une bonne fonction cérébrale est possible uniquement si le patient reste en état d'arrêt circulatoire complet seulement quelques minutes après le début de l'AC(12). Pour cette raison, les manœuvres effectuées pour assurer la reprise d'une circulation systémique doivent être rapides et efficaces pour offrir un maximum de chances de survie. Pour permettre un maximum d'efficacité des mesures de traitement de l'AC, des sociétés savantes réunies sous le nom de International Liaison Committee on Resuscitation – ILCOR, publient régulièrement des recommandations actualisées pour la prise en charge de l'AC, basées sur les connaissances accumulées dans le domaine de la réanimation cardiopulmonaire. Ces recommandations permettent une homogénéisation des pratiques et permettent de réaliser les soins les plus appropriés et en accord avec les connaissances acquises dans le domaine de la réanimation cardiopulmonaire.

Ces recommandations réunissent plusieurs mesures fondamentales de prise en charge sous le nom de « chaîne de la survie » qui sont applicables aux patients présentant un AC d'origine cardiaque ou « hypoxique/asphyxique »(11).

1.3.1 La chaîne de la survie et la réanimation cardiopulmonaire "de base", basic life support

Le premier maillon de la chaîne de la survie est représenté par la reconnaissance rapide l'AC et l'appel des secours. Pour les personnes qui ne sont pas des professionnels de santé, un sujet qui ne répond pas aux stimulations et ne respire pas normalement(11) doit être considéré en AC. Dans ce cas, les témoins doivent appeler le service d'urgences pour demander de l'aide(12) et ensuite débiter le massage cardiaque qui est alors la priorité absolue.

Le deuxième maillon de la chaîne de la survie est la réalisation rapide de la réanimation cardiopulmonaire par massage cardiaque, sans respiration artificielle si la personne qui réanime est non entraînée à la réanimation cardiopulmonaire, et accompagné par des respirations si la personne qui réanime est entraînée dans la réanimation cardiopulmonaire. Le massage cardiaque doit être réalisé avec une amplitude de compression de la cage thoracique de 5-6 cm et une fréquence de 100-120/min(12). Entre les compressions thoraciques, le thorax doit être parfaitement décomprimé. Les personnes entraînées à la réanimation cardiopulmonaire doivent également réaliser des insufflations pulmonaires d'environ 1 seconde, avec un rapport compressions thoraciques : respirations de 30:2, sans interrompre le massage cardiaque pendant plus de 10 secondes(12). Ces manœuvres assurent une circulation sanguine malgré l'absence de contractions cardiaques, en attendant la reprise d'une circulation sanguine spontanée. Le massage cardiaque pourrait assurer au début de la réanimation cardiopulmonaire un débit circulatoire similaire au débit normal s'il est réalisé par des professionnels entraînés, et environ un tiers du débit normal s'il est réalisé par des personnes non entraînées(47), d'autres études ayant estimé son efficacité à environ 40% du débit cardiaque de repos(49). Néanmoins, l'efficacité du massage cardiaque diminue avec le temps de réanimation cardiopulmonaire(50), raison pour laquelle le retour d'une circulation efficace doit être assuré le plus rapidement possible. Un massage cardiaque immédiat par les témoins peut doubler ou tripler la survie des patients(51,52).

Le troisième maillon de la chaîne de la survie est représenté par la défibrillation. Comme un nombre important de patients en AC présentent un rythme choquable comme la fibrillation ventriculaire et plus rarement, environ 1%(44) une tachycardie ventriculaire, la défibrillation est un geste qui permet de retrouver un rythme cardiaque spontané et ainsi d'améliorer la survie avec un bon état neurologique(45). Les chocs électriques externes doivent être réalisés par les personnes non entraînées à la réanimation cardiopulmonaire, à l'aide d'un défibrillateur externe automatique s'il est disponible, celui-ci délivrant le choc sans autre intervention de la part de la personne qui réanime. La défibrillation par les professionnels de santé est en général réalisée à l'aide d'un défibrillateur

non automatique, par un choc électrique externe biphasique de 150-200 Joules après évaluation du rythme cardiaque.

La réanimation cardiopulmonaire et la défibrillation sont organisées dans des cycles de 2 minutes de réanimation cardiopulmonaire suivis par une période de quelques secondes pour l'évaluation du rythme cardiaque et la réalisation d'un choc électrique si indiqué, à l'aide du défibrillateur automatique ou manuel(12). Les interruptions du massage cardiaque doivent être réduites au minimum.

Ces séquences de réanimation cardiopulmonaire sont utilisées par les témoins des AC mais aussi par des professionnels de santé à la phase initiale de la réanimation cardiopulmonaire et sont réunies sous le terme de « basic life support ».

Ces recommandations ont été respectées dans les études expérimentales et cliniques présentées dans cette thèse.

1.3.2 Réanimation cardiopulmonaire "avancée", advanced life support

A l'arrivée des secours médicalisés, les manœuvres de réanimation cardiopulmonaire recommandées sont réunies sous le terme de « advanced life support ». Ces manœuvres peuvent être réalisées uniquement par des professionnels de santé. Les professionnels de santé intervenant en France sont des médecins et infirmiers mais dans d'autres pays d'Europe et du monde y compris aux États-Unis, ce sont des paramédicaux ayant reçu une formation spécifique qui interviennent sur le terrain pour la prise en charge de l'AC. Certaines études ont montré une supériorité de la survie lorsque l'intervention est réalisée par des médecins(53,54), alors que d'autres ont montré une équivalence entre la prise en charge par des médecins versus des paramédicaux(55).

La prise en charge est synthétisée dans l'algorithme de la Figure 6, élaboré par les sociétés savantes qui s'applique à l'ensemble des situations d'AC mais cet algorithme peut présenter des modifications et particularités en fonction des circonstances spéciales rencontrées, comme la noyade et l'hypothermie.

L'algorithme distingue les rythmes choquables – fibrillation ventriculaire et tachycardie ventriculaire, des rythmes non choquables – asystolie, bradycardie extrême et dissociation électromécanique(44), pour des raisons pratiques liées à la réalisation des chocs électriques externes.

1.3.2.1 La prise en charge des rythmes choquables

Les rythmes choquables, fibrillation ventriculaire et tachycardie ventriculaire sont présents chez environ 20% des patients en AC et peuvent également apparaître lors de la réanimation cardiopulmonaire des patients avec des rythmes initialement non choquables dans environ 25% des cas(44). Les recommandations prévoient la réalisation de la réanimation cardiopulmonaire avec un ratio compressions – ventilation de 30:2 pendant des cycles de 2 minutes et un choc électrique externe après chaque cycle de 2 minutes si le rythme choquable est encore présent (Figure 6)(44).

Figure 6 Algorithme de prise en charge d'un AC avec rythme choquable et non choquable selon Soar et al.(44)

Les rythmes choquables (partie gauche de la figure) bénéficient d'une réanimation cardiopulmonaire et d'un choc électrique externe toutes les 2 minutes si le trouble du rythme persiste. Les rythmes non choquables (partie droite de la figure) bénéficient de réanimation cardiopulmonaire seule sans choc électrique. Les deux types de rythme bénéficient d'administration d'adrénaline 1 mg en bolus toutes les 3 à 5 minutes. CPR - réanimation cardiopulmonaire, VF – fibrillation ventriculaire, VT - tachycardie ventriculaire, PEA - dissociation électromécanique.

Après un choc électrique, la réanimation cardio-pulmonaire doit être continuée sans vérifier le pouls car très peu de patients présentent un pouls immédiatement après le retour en rythme sinusal, la plupart nécessitant environ 2 minutes de massage cardiaque avant d'avoir un pouls palpable(44).

Un des aspects importants à souligner est la nécessité d'interrompre le moins longtemps possible la réanimation cardiopulmonaire car même des pauses de 5 à 10 secondes avant les CEE peuvent

diminuer les chances de retour en rythme sinusal(56).

L'énergie des chocs électriques externes doit être supérieure ou égale à 150 joules pour le premier et entre 150 et 360 joules pour les suivants, pour les défibrillateurs biphasiques(44). Lors des manœuvres décrites, un accès vasculaire pour l'administration de médicaments par voie intraveineuse doit être réalisé. Si l'accès veineux n'est pas disponible, une voie intraosseuse doit être mise en place.

Après le troisième choc électrique externe une première injection intraveineuse de 1 mg d'adrénaline doit être réalisée et cette injection doit être répétée toutes les 3 à 5 minutes en cas d'absence de reprise d'une circulation spontanée(44). L'amélioration de la pression de perfusion coronaire apparaît environ 70 à 90 secondes après l'injection d'adrénaline si le massage cardiaque est correctement effectué(57). L'adrénaline a un rôle vasoconstricteur artériel et veineux, permettant une augmentation de la pression de perfusion par augmentation des résistances vasculaires et a un rôle inotrope positif qui augmente la contractilité cardiaque en cas de reprise d'une circulation spontanée.

L'administration d'adrénaline lors de la prise en charge des AC a montré une amélioration de la reprise d'une circulation spontanée sans augmenter le taux de survie à la sortie de l'hôpital(58). L'analyse de sous-groupes dans cette étude par Olasveengen et al.(58) a montré que l'efficacité de l'adrénaline était observée essentiellement chez les patients avec des rythmes non choquables. D'autres études rétrospectives concernant l'adrénaline lors de la réanimation cardiopulmonaire ont montré une aggravation du pronostic(59,60) mais la littérature est discordante sur cet aspect car une autre étude rétrospective réalisée sur un grand effectif de patients a montré une légère amélioration du pronostic neurologique(61). Une étude française récente(62) a montré également une aggravation du pronostic neurologique, mais dans l'attente de nouvelles données randomisées, l'adrénaline continue de faire partie de l'algorithme proposé par les sociétés savantes pour la prise en charges des AC avec rythme choquable.

Un des travaux expérimentaux présentés ici s'intéresse à l'effet de l'adrénaline à des doses répétées

selon les recommandations, dans la réanimation cardiopulmonaire des AC réfractaires et son rôle dans la survie des animaux d'expérience, et dans la reprise d'une circulation spontanée.

Après le troisième choc électrique, l'administration d'amiodarone 300 mg doit être également réalisée pour augmenter les chances de défibrillation ultérieure grâce à son effet antiarythmique. Une autre dose de 150 mg doit être administrée après le cinquième choc électrique. L'amiodarone a été considérée comme l'antiarythmique de choix car elle semblait augmenter les chances de défibrillation par rapport au placebo(63) et par rapport à la lidocaïne(64). Néanmoins, une étude randomisée récente(65) dans l'AC extrahospitalier avec un rythme initial choquable, n'a pas mis en évidence de différence de survie entre l'amiodarone, la lidocaïne et le placebo dans la prise en charge de la fibrillation ventriculaire ou tachycardie ventriculaire résistantes à au moins un choc électrique externe. De plus, cette étude n'a pas montré de différence significative entre le pourcentage de reprise de circulation spontanée à l'arrivée à l'hôpital, entre le groupe amiodarone et le groupe lidocaïne.

L'algorithme de prise en charge des rythmes choquables a été respecté dans les travaux expérimentaux présentés ici, et par les équipes médicales d'urgence intervenant sur le terrain dans la prise en charge des patients inclus dans les études cliniques présentées dans cette thèse.

1.3.2.2 La prise en charge des rythmes non choquables

La présence d'un rythme électrique non choquable nécessite une prise en charge similaire aux rythmes choquables (Figure 6), mais sans réaliser de choc électrique externe ni d'injection d'amiodarone. La réanimation cardiopulmonaire est réalisée avec le même rapport compression : ventilation de 30 : 2 et le pouls est vérifié toutes les 2 minutes. Contrairement à la prise en charge des rythmes choquables, l'adrénaline doit être administrée dès qu'un accès veineux ou intraosseux est disponible, à répéter toutes les 3 à 5 minutes(44). Si l'analyse du tracé ECG entre les cycles de réanimation cardiopulmonaire montre l'apparition d'un rythme choquable, la réanimation sera

continué selon l'algorithme pour les rythmes choquables. L'algorithme de prise en charge des rythmes non choquables a été respecté par les équipes médicales d'urgence intervenant sur le terrain dans la prise en charge des patients inclus dans les études cliniques présentées dans cette thèse.

1.3.2.3 Une solution dans les réanimations cardiopulmonaires prolongées - les dispositifs automatisés de massage cardiaque

Le massage cardiaque est une manœuvre thérapeutique dont l'efficacité diminue avec le temps, une des causes étant la fatigue des personnes réalisant la réanimation cardiopulmonaire. La fatigue diminue la qualité du massage cardiaque ce qui diminue les chances de reprise d'une circulation spontanée par diminution de la perfusion d'organes y compris coronaire. Pour éviter cette situation, des dispositifs mécaniques de massage cardiaque ont été conçus, ainsi 45% des systèmes médicaux d'urgence aux États-Unis utilisaient ce type de dispositifs en 2008(66). Plusieurs études randomisées ont évalué l'efficacité de ces dispositifs. Une étude randomisée évaluant le dispositif LUCAS (Lundt University Cardiac Arrest Solutions) n'a pas montré d'amélioration de la survie à 30 jours(66), une autre étude a même montré une diminution de la survie avec un bon état neurologique(68). Plusieurs méta-analyses et registres comparant le massage cardiaque manuel avec le massage cardiaque utilisant des dispositifs mécaniques ont mis en évidence des résultats discordants et potentiellement des effets délétères(69–71). Récemment, une étude multicentrique réalisée sur des mannequins incluant dans le protocole de l'étude le transport similaire à la « vraie vie », a démontré une meilleure fréquence et profondeur des compressions thoraciques lors du massage cardiaque par LUCAS par rapport au massage cardiaque manuel et a conclu à une possible supériorité du massage cardiaque automatique lors de la réanimation cardiopulmonaire nécessitant le transport des patients(72).

Au vu de ces données, l'utilisation de ces dispositifs est recommandée surtout dans des conditions de réanimation cardiopulmonaire difficiles et prolongées(44), le massage cardiaque manuel étant

préférée en général au massage cardiaque automatique lors des réanimations cardiopulmonaires de brève durée.

Les dispositifs automatisés de massage cardiaque externe ont permis de transporter plus facilement à l'hôpital les patients en AC réfractaire aux manœuvres de réanimation cardiopulmonaire. Dans une des études présentées ici, le transport vers l'hôpital des patients en AC réfractaire, pour la mise en place d'assistance circulatoire, a été fait sous massage cardiaque automatique.

Des dispositifs automatisés de massage cardiaque externe ont été utilisés dans les deux travaux expérimentaux présentés dans cette thèse lors de la réanimation cardiopulmonaire des animaux d'expérience, pour d'une part réaliser un massage cardiaque d'efficacité comparable entre les groupes « contrôle » et les groupes « intervention », et pour reproduire d'autre part les conditions d'un massage cardiaque lors d'un AC prolongé.

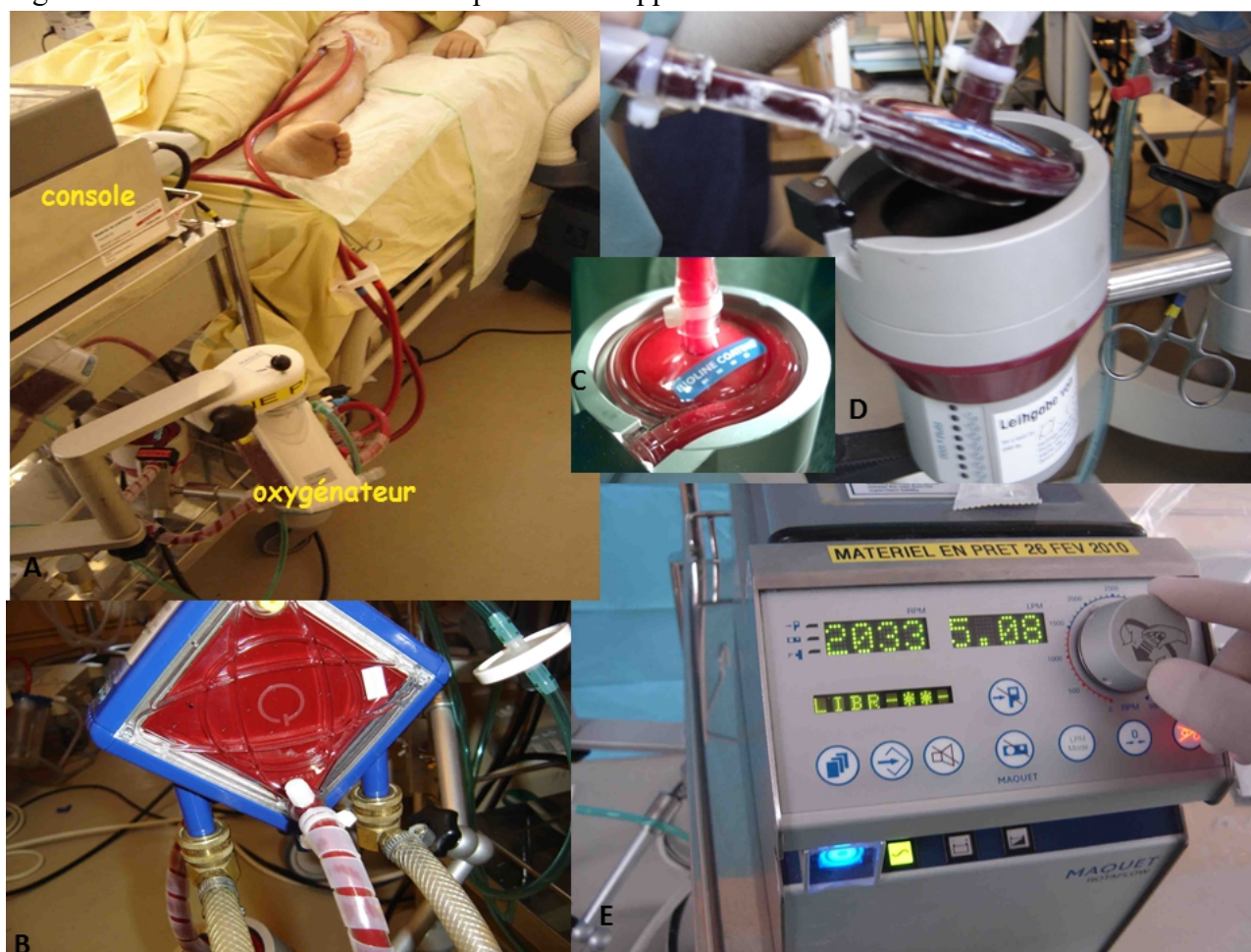
1.3.2.4 Utilité de l'assistance circulatoire type Extracorporeal Life Support lors de la réanimation cardiopulmonaire avancée

L'assistance circulatoire – extracorporeal life support (ECLS) est un support cardiaque et pulmonaire artificiel (Figure 7). Elle est constituée d'une pompe à turbine et d'un oxygénateur de sang intégrés à un circuit qui se connecte au patient grâce aux canules veineuse et artérielle. La canule veineuse est habituellement insérée au niveau de la veine fémorale commune jusqu'au niveau de l'oreillette droite et la canule artérielle est insérée habituellement au niveau de l'artère fémorale commune jusqu'au niveau de l'artère iliaque commune ou aorte descendante distale. Le rôle de la canule veineuse est d'aspirer le sang veineux de l'oreillette droite. Le sang entraîné par la pompe traverse l'oxygénateur, se charge en oxygène, est épuré du gaz carbonique, et est réinjecté par la canule artérielle au niveau de l'artère iliaque générant un flux sanguin rétrograde, orienté vers le cœur (Figure 7). Cette technique est recommandée par les sociétés savantes chez les patients qui n'ont pas de reprise d'une circulation spontanée après les manœuvres d'advanced life support, et qui

ont présenté un AC devant un témoin, chez qui l'ECLS peut être implémentée dans les 60 minutes après l'effondrement, lorsqu'il existe peu de comorbidités et lorsqu'il existe une cause réversible, comme l'infarctus du myocarde, l'embolie pulmonaire ou l'hypothermie(44).

L'ECLS a été utilisée dans les deux études expérimentales et une des études cliniques présentées dans ce travail.

Figure 7 Circuit et console d'extracorporel life support – ECLS



A- circuit d'ECLS connecté au patient par des canules artérielle et veineuse fémorales gauches. B – oxygénateur artificiel intégré au circuit. C, D – pompe intégrée au circuit assurant la circulation sanguine. E – console permettant de contrôler le débit sanguin.

1.4 Prise en charge des patients après la réanimation cardiopulmonaire

Après la réanimation cardiopulmonaire initiale et le retour d'une circulation spontanée, les patients sont transportés à l'hôpital pour la poursuite des soins qui auront pour but la stabilisation des

fonctions vitales, l'identification et le traitement de la cause initiale de l'AC, le traitement des complications, et la prévention de l'aggravation des lésions d'ischémie-reperfusion. Les patients sont transférés en général vers la structure la plus proche capable de réaliser les démarches diagnostiques et les thérapies indiquées. Environ 40-50% des patients qui présentent un retour de circulation spontanée et sont transportés à l'hôpital survivent et quittent l'hôpital(73).

1.4.1 Le syndrome "post arrêt cardiaque" ou "post-réanimation cardiopulmonaire"

Après le retour d'une circulation spontanée, les patients présentent un « syndrome post-arrêt cardiaque » qui regroupe les lésions cérébrales, la dysfonction myocardique post AC, la réponse systémique à l'ischémie-reperfusion généralisée et la pathologie ayant déclenché l'AC(73). Une grande importance est attribuée aux lésions neurologiques qui sont responsables d'environ deux tiers des décès après le retour d'une circulation spontanée(7,74) et se manifestent par l'apparition de convulsions, myoclonies, encéphalopathie postanoxique(73). Les lésions cérébrales peuvent être aggravées par l'hypotension, l'hypercapnie ou l'hypocapnie, par l'hypoxémie ou l'hyperoxémie, par l'hyper ou l'hypoglycémie, l'hyperthermie, l'hyponatrémie, ou par les convulsions(73). Les efforts de la prise en charge hospitalière sont dirigés vers la prévention de l'aggravation des lésions cérébrales et vers le contrôle le plus précis possible de ces facteurs endogènes d'agression cérébrale. Un des travaux exposés dans la présente thèse explore l'influence de la pression partielle en bioxyde de carbone (CO_2) sur la circulation cérébrale lors de la prise en charge hospitalière.

1.4.2 Gestion de l'oxygénation, de l'épuration du gaz carbonique et de la ventilation mécanique

En raison du risque de lésions induites par l'hyperoxémie comme suggéré par des études

observationnelles(75) et expérimentales(76), la gestion de la ventilation mécanique et de l'administration d'oxygène est faite pour obtenir une saturation de l'hémoglobine entre 94 et 98%. Des méta-analyses portant sur l'influence de l'hyperoxémie sur la fonction cérébrale ont trouvé des résultats discordants(36) mais une étude dans l'infarctus du myocarde a montré une aggravation des lésions myocardiques par l'hyperoxémie(77) suggérant une saturation cible en oxygène de 94-98% lors de la prise en charge(73).

L'oxygénation n'est pas le seul paramètre lié à la fonction respiratoire qui influence les lésions cérébrales, car le gaz carbonique influence directement la circulation cérébrale. En effet, l'hypocapnie induit une vasoconstriction cérébrale et peut aggraver les lésions ischémiques(78,79) en raison de la diminution du débit sanguin cérébral, ce qui peut aggraver le pronostic neurologique des patients selon des études observationnelles(80,81). En revanche, l'hypercapnie modérée pourrait être associée avec une amélioration du pronostic selon des données également observationnelles(81,82). En raison de l'influence majeure du gaz carbonique sur la circulation cérébrale, il est recommandé de maintenir une pression partielle en CO₂ normale(73).

Une des études présentée ici se concentre sur l'influence de la ventilation mécanique sur la pression partielle en CO₂ et son influence sur la circulation cérébrale chez les patients en hypothermie thérapeutique après un AC.

1.4.3 Prise en charge en salle de cathétérisme pour reperfusion coronaire après un arrêt cardiaque

Devant un AC sans cause extracardiaque évidente, la présence d'un syndrome coronaire aigu est très probable, une étude récente ayant retrouvé une incidence de 49%(83). Dans des études publiées par notre équipe, la prévalence des syndromes coronaires aigus a été de 31 à 37%(9,37,47).

Devant la présence d'un sus-décalage du segment ST à l'électrocardiogramme, les recommandations sont en faveur de la reperfusion coronaire en urgence. Cette attitude se justifie par la prévalence

élevée des syndromes coronaires aigus dans cette population, plus de 50% mais pouvant aller jusqu'à plus de 80% dans certaines études(38,47,84), et par la survie avec de bons résultats neurologiques des patients qui ont bénéficié d'une coronarographie en urgence(9,85).

Chez les patients qui ne présentent pas de sus-décalage du segment ST à l'électrocardiogramme, l'utilité de l'angiographie coronaire en urgence est plus discutée, la prévalence des syndromes coronaires aigus ayant été estimée à 37% dans une étude récente(87). Certains auteurs sont en faveur de la réalisation d'une coronarographie systématique après un AC(83,88), d'autres ne retrouvent pas de bénéfice de la coronarographie systématique après un AC sans sus-décalage du segment ST à l'électrocardiogramme(89). Des études randomisées en cours, évaluent le bénéfice de la coronarographie dans cette situation clinique.

Dans les études présentées dans cette thèse, la coronarographie a été réalisée pour l'ensemble des patients présentant un AC sans cause extracardiaque évidente, qui ont été accueillis à l'arrivée à l'hôpital en salle de cathétérisme cardiaque.

1.4.4 Contrôle thermique après un arrêt cardiaque

La présence de fièvre après un AC est associée à un pronostic neurologique défavorable(90–92), car l'hyperthermie augmente le métabolisme cérébral, la vitesse de production de radicaux libres, favorise les lésions dues à l'excitotoxicité dans les premières heures après un AC, et même après cette période par neuroinflammation, diminution du seuil épileptogène et augmentation de la perméabilité de la barrière hémato-encéphalique(93). Plusieurs études expérimentales ont suggéré que l'hypothermie thérapeutique modérée entre 32°C et 34°C après un événement ischémique pourrait limiter les dégâts neuronaux(94), et plusieurs études randomisées chez l'homme ont exploré l'effet de l'hypothermie thérapeutique après un AC(95–98).

L'hypothermie thérapeutique avec une température cible entre 32 et 34° a été comparée à une stratégie de contrôle thermique conventionnel assurant une température cible normale de 37°C dans

deux études randomisées(95,96). La stratégie hypothermie a été supérieure par rapport à la stratégie conventionnelle en améliorant la survie avec un bon état neurologique, ainsi l'hypothermie thérapeutique est recommandée comme moyen thérapeutique majeur après un AC. Le concept d'hypothermie thérapeutique a été remplacé récemment par le concept de « targeted temperature management » (contrôle thermique) après l'étude de 2013 montrant l'absence de différence de survie avec bon état neurologique entre le groupe avec hypothermie thérapeutique à 33°C et le groupe avec un contrôle thermique strict à la température cible de 36°(98). Dans cette étude les deux groupes ont bénéficié d'un contrôle thermique très strict et très proche de la cible pendant 24 heures et la fièvre a été prévenue jusqu'à la 72^e heure après l'AC.

Au vu de ces données, il est recommandé de maintenir la température des patients constante entre 32 et 36°C, pendant au moins 24 heures, ceci étant recommandé chez les patients ayant présenté un rythme initial choquable, et conseillé chez les patients ayant présenté un rythme initial non choquable, car cette population a été peu représentée dans les études randomisées(73).

La grande majorité des patients inclus dans les travaux observationnels présentés ici ont bénéficié d'un contrôle thermique selon les recommandations des sociétés savantes.

La gestion de la température a également des implications profondes sur la gestion de la pression partielle en gaz carbonique qui influence de façon très étroite la circulation cérébrale. Cette interaction a été étudiée dans un des travaux exposés ici, qui permet d'évaluer la gestion optimale de la pression en gaz carbonique pour optimiser la circulation cérébrale lors de l'hypothermie.

1.4.5 Prise en charge de la circulation systémique après un arrêt cardiaque

L'état circulatoire post réanimation cardiopulmonaire peut s'accompagner d'une hypotension artérielle multifactorielle post AC, qui nécessite souvent un traitement par remplissage vasculaire, administration intraveineuse de catécholamines, notamment noradrénaline en raison d'une

vasoplégie et/ou dobutamine en raison d'une dysfonction myocardique dans le contexte d'une réaction systémique inflammatoire apparentée au sepsis(73,99).

Si le traitement par noradrénaline, dobutamine et le remplissage vasculaire ne permettent pas d'assurer une bonne fonction circulatoire, une option thérapeutique est l'utilisation d'assistances circulatoires mécaniques comme l'Impella® (Abiomed, USA)(100,101) ou l'ECLS(102). Néanmoins, les critères précis d'utilisation de ces moyens d'assistance lors de l'insuffisance circulatoire post AC ne sont pas bien définis par les sociétés savantes(44,73).

Une des études exposée dans cette thèse se concentre sur des facteurs pronostiques de défaillance circulatoire sévère pour tenter de trouver des critères permettant d'améliorer les indications d'utilisation des moyens d'assistance circulatoire mécanique après un AC.

1.4.6 Prise en charge de la circulation cérébrale après un arrêt cardiaque

Après le retour d'une circulation spontanée, chez une partie des patients (environ 35%) le débit sanguin cérébral n'est pas régulé de façon physiologique, et varie avec la pression artérielle, exposant le cerveau à des périodes d'hyper débit ou diminution du débit sanguin(103). Cette régulation anormale est retrouvée surtout chez les patients qui présentent une hypertension artérielle chronique(104), et il est recommandé de maintenir la pression artérielle des patients au niveau de leur pression artérielle habituelle sans pouvoir recommander l'utilisation de moyens de monitoring spécifiques de la circulation cérébrale comme le doppler transcrânien ou la saturation veineuse du bulbe jugulaire(73,105–107). Plusieurs facteurs influencent la circulation cérébrale, comme la pression systémique, le débit cardiaque, la pression partielle en gaz carbonique, la pression intracrânienne. Une des études présentées dans ce document se concentre sur la relation entre la perfusion cérébrale et la pression partielle en gaz carbonique chez les patients hospitalisés en réanimation post AC, après la reprise d'une circulation spontanée et traités par hypothermie

thérapeutique (contrôle thermique à environ 33°C).

1.4.7 Scores permettant d'évaluer l'état neurologique après un arrêt cardiaque

Les patients réanimés après un AC, ne présentant pas un réveil adapté rapide, sont traités selon les recommandations de l'ILCOR avec intubation, ventilation mécanique et sédation, permettant la réalisation du contrôle thermique. Ultérieurement, une partie des patients présentent un réveil adapté et reprennent une vie relationnelle avec l'environnement. L'état neurologique des patients est évalué dans la littérature par des scores de performance cérébrale. Jennet et Bond(108) ont établi un score d'évaluation de la performance cérébrale de 1 à 5, « Cerebral Performance Category ». Le meilleur résultat neurologique est le CPC1, le patient étant conscient et capable de poursuivre son travail antérieur, même si certains déficits neurologiques ou psychologiques peuvent être mis en évidence par des tests très fins. Le score CPC2 est considéré ensemble avec le CPC1 comme étant un bon résultat neurologique et correspond à un patient conscient, autonome et indépendant pour les activités de la vie courante, et capable de travailler dans un milieu protégé. Le score CPC3 correspond à un patient conscient et dépendant de l'entourage pour les actes de la vie courante en raison des séquelles cérébrales post AC. Le score CPC4 correspond à un patient comateux (patient inconscient) ou à un état végétatif, un patient réveillé mais n'interagissant pas avec l'environnement. Le score CPC5 correspond à un patient en état de mort encéphalique ou décédé.

Une autre échelle permet d'apprécier le degré de séquelles après un AC, l'Overall Performance Category - OPC(109), les deux scores, CPC et OPC sont utilisés en pratique clinique(110).

Les données cliniques présentées dans ce travail de thèse ont évalué la performance neurologique des patients selon le score CPC.

2 Problématique de l'insuffisance circulatoire après un arrêt cardiaque et justification du travail

2.1 Les défaillances d'organes responsables de décès après un arrêt cardiaque

La prise en charge des patients après un AC a pour but de permettre non seulement la survie, mais aussi la récupération neurologique avec un score CPC 1 ou 2, ce qui représente un « bon résultat neurologique ». Néanmoins, certains patients décèdent et d'autres présentent des lésions cérébrales anoxiques sévères, les rendant dépendants de l'entourage pour les actes de la vie courante (score CPC3 à la sortie de l'hôpital). Ces patients peuvent ultérieurement, grâce à la rééducation fonctionnelle, s'améliorer et évoluer vers un score CPC2 et vivre de façon autonome(9,110). Si pour les patients CPC3 ou CPC2 la rééducation fonctionnelle peut améliorer la performance neurologique, pour les patients CPC4 (en état végétatif ou comateux) cette amélioration n'est en général pas possible. Ces patients évoluent en général vers le décès, la défaillance neurologique étant responsable d'environ 68% des décès après hospitalisation(7), et de façon similaire, de 65% des décès selon une étude française(74).

Après le retour d'une circulation spontanée, l'hypotension artérielle doit être évitée en raison du risque d'aggravation des lésions neurologiques et systémiques(73). Cet aspect est important, car la défaillance circulatoire est fréquente lors de l'AC(74,111,112), et représente le mode de décès chez 23%-35% des patients décédés. Le décès de cause circulatoire survient en général rapidement lors de la prise en charge, avant toute possibilité d'évaluation neurologique des patients, alors qu'une partie d'entre eux pourraient avoir des lésions compatibles avec un bon état neurologique. La fonction circulatoire représente donc une cible thérapeutique importante, avec un double effet potentiel, d'une part l'amélioration de la perfusion systémique et cérébrale, et d'autre part la diminution des décès de cause circulatoire.

2.2 Physiopathologie de l'insuffisance circulatoire après un arrêt cardiaque

Après un AC, une instabilité hémodynamique nécessitant l'administration de catécholamines apparaît chez plus de 50% des patients(47,113) dans les premières 72 heures suivant l'AC. Les patients à risque d'insuffisance circulatoire sont ceux qui ont présenté un délai long jusqu'à la reprise d'une circulation spontanée et ceux qui ont reçu des doses élevées d'adrénaline lors de la réanimation cardiopulmonaire(99,113). Dans une étude française ayant inclus 165 patients, le seul facteur associé en analyse multivariée à l'apparition d'une instabilité hémodynamique, a été la dose d'adrénaline administrée lors de la réanimation cardiopulmonaire(113). Cette insuffisance circulatoire, pouvant associer une défaillance cardiogénique à une vasodilatation, apparaît en général 4 à 7 heures après l'AC, et se manifeste par hypotension, diminution de l'index cardiaque et diminution de la pression veineuse centrale nécessitant un remplissage vasculaire important(113). L'insuffisance circulatoire est présente pendant environ 72 heures, au delà desquelles les catécholamines peuvent être progressivement sevrées. La dysfonction myocardique accompagnant cette insuffisance circulatoire est réversible(113).

Cette dysfonction myocardique est potentiellement liée à la peroxydation lipidique et aux lésions oxydatives de l'ADN lors de l'AC(114), à une diminution de la sensibilité des myofibrilles au calcium, et à une diminution de la fonction myofibrillaire, non compensée par la libération importante de calcium sarcoplasmique après l'AC, comme suggéré par une étude expérimentale(115).

2.3 Les options thérapeutiques pharmacologiques pour l'amélioration de la fonction circulatoire après un arrêt cardiaque

L'insuffisance circulatoire après un AC a des caractéristiques communes avec le sepsis(111), pouvant associer une vasodilatation et une dysfonction cardiaque. Ces deux processus engendrent

une diminution de la pression artérielle et de la perfusion systémique pouvant aller jusqu'à l'insuffisance multiple d'organes(10). Le traitement de l'insuffisance circulatoire comprend l'amélioration de la précharge par remplissage vasculaire, l'administration de vasoconstricteurs en cas de vasodilatation systémique, l'amélioration de la contractilité cardiaque par des médicaments inotropes positifs, l'angioplastie coronaire en cas de syndrome coronaire aigu, et l'assistance circulatoire mécanique si les mesures précédentes n'ont pas été suffisantes(73,116).

Le traitement par remplissage est guidé de façon clinique, échographique et selon des signes de précharge dépendance comme la variation respiratoire de la pression pulsée chez les patients intubés(117), ou l'épreuve d'élévation des jambes(118). Si le patient est déjà en surcharge hydrosodée ou si le remplissage vasculaire n'a pas permis la restauration d'une pression et débit satisfaisants, un traitement par inotropes et/ou vasopresseurs est alors indiqué(116,119).

Les outils de monitoring hémodynamique, PiCCO[®], Vigileo-FloTrac[®] et l'échographie cardiaque permettent de diagnostiquer une diminution de la contractilité cardiaque et/ou du débit cardiaque et guident la thérapie pour le traitement par dobutamine en cas de dysfonction cardiaque systolique, permettant d'améliorer la contractilité. Si l'insuffisance circulatoire est de cause mixte, vasoplégique et cardiogénique, le traitement par noradrénaline est également indiqué, permettant de rajouter son effet vasoconstricteur(73,116,120) et d'améliorer la pression artérielle.

Lorsque le monitoring hémodynamique montre une diminution des résistances vasculaires périphériques sans dysfonction cardiaque, la catécholamine de choix est la noradrénaline pour son effet prépondérant vasoconstricteur(73). L'utilisation d'adrénaline est indiquée selon l'avis des experts pour les chocs réfractaires à l'association dobutamine et noradrénaline(116). D'autres molécules peuvent être utilisées dans le traitement de l'insuffisance circulatoire, comme la dopamine, la milrinone, l'enoximone, mais leur rôle dans le traitement de l'insuffisance circulatoire post AC n'est pas bien défini par les sociétés savantes(73).

2.4 Les options d'assistance mécanique lors d'une insuffisance circulatoire réfractaire aux moyens pharmacologiques

Malgré leur effet puissant inotrope positif, le traitement par dobutamine et adrénaline est parfois insuffisant pour améliorer l'index cardiaque et la pression artérielle malgré des doses élevées, et dans ce cas l'option thérapeutique permettant d'améliorer l'état hémodynamique est l'assistance circulatoire mécanique. Plusieurs moyens d'assistance circulatoire mécanique sont disponibles en cas de défaillance circulatoire malgré un traitement bien conduit par catécholamines.

2.4.1 Le ballon de contrepulsion aortique

Le ballon de contrepulsion aortique est un dispositif développé dans les années 1960 pour améliorer la fonction circulatoire et la pression de perfusion coronaire des patients en état de choc cardiogénique(121,122). Le ballon de contrepulsion est inséré par voie percutanée au niveau de l'aorte thoracique et consiste en un ballon qui se gonfle lors de la diastole et se dégonfle lors de la systole cardiaque. Malgré une utilisation fréquente du ballon de contrepulsion, une étude récente à large échelle, IABP SHOCK(121,122), qui a inclus des patients en état de choc cardiogénique y compris post AC, n'a pas montré d'amélioration du pronostic par l'utilisation de ce dispositif. Ainsi, les recommandations de la Société Européenne de Cardiologie sur la prise en charge de l'état de choc cardiogénique ne considèrent plus le ballon de contrepulsion aortique comme une indication de routine(114). Les recommandations de l'ILCOR sur la prise en charge post réanimation cardiopulmonaire ne mentionnent pas ce dispositif comme étant une option thérapeutique dans la prise en charge de l'insuffisance circulatoire post AC(73).

2.4.2 L'utilisation de l'Impella®

Impella® est un dispositif d'assistance circulatoire percutanée monoventriculaire gauche qui peut être inséré au niveau fémoral. Il consiste en une turbine qui permet d'aspirer le sang à partir du ventricule gauche et l'éjecter au niveau de l'aorte ascendante. Plusieurs modèles d'Impella® sont

disponibles, pouvant assurer un débit maximal de 2,5 L/min pour Impella 2.5™ (Figure 8), 3,5 L/min environ pour l'Impella CP® et environ 5 L/min pour Impella 5.0™, cette dernière version nécessitant une insertion fémorale chirurgicale.

Figure 8 Le dispositif d'assistance circulatoire ventriculaire gauche Impella 2.5™

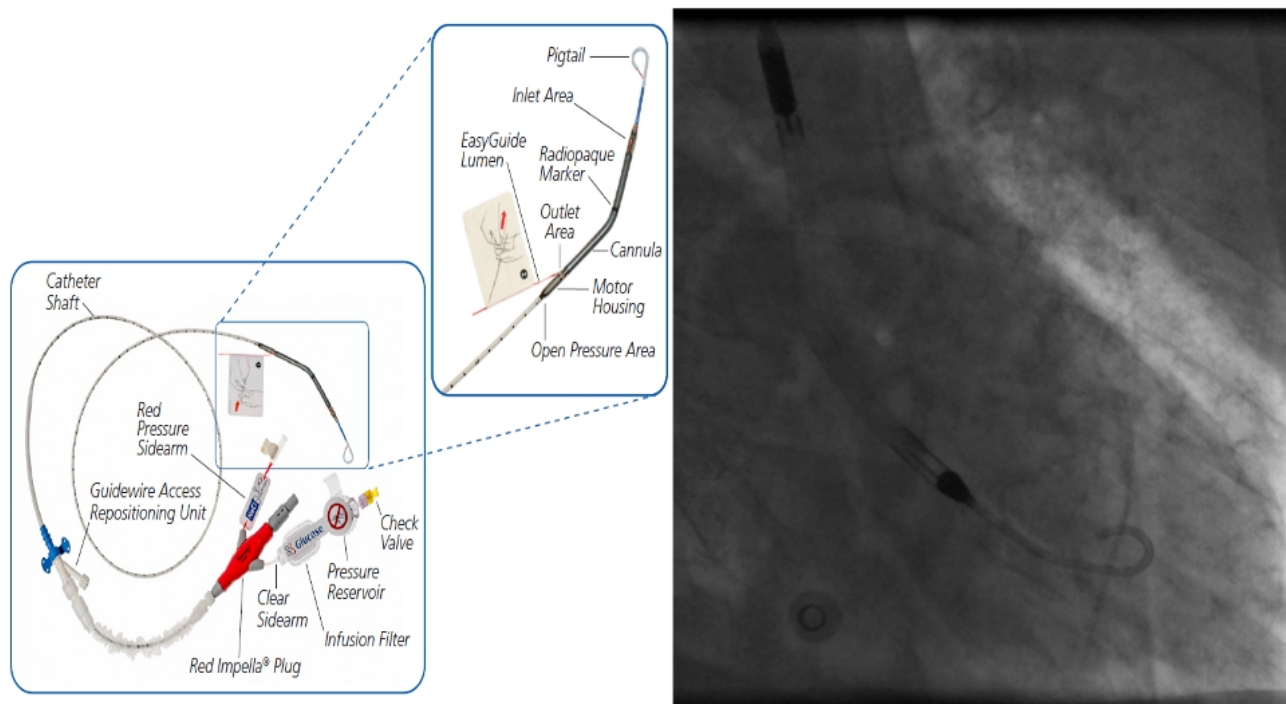


Image de gauche: le dispositif dans son ensemble, image présentée par le fabricant. Le sang est aspiré par la partie d'admission - « inlet area » et éjecté par la partie « outlet area » au niveau de l'aorte ascendante. Motor housing – localisation du moteur. A droite, image de la partie du dispositif placée au niveau du ventricule gauche et de l'aorte ascendante.

Le dispositif Impella 2,5™ est utilisé pour l'angioplastie coronaire complexe en dehors du choc cardiogénique et de l'AC, avec une amélioration de la mortalité selon certaines études(125), mais l'expérience dans le domaine de l'AC est relativement limitée. Plusieurs cas cliniques d'utilisation de l'Impella®(126,127) ont été rapportés, et une étude rétrospective a montré une bonne faisabilité, de 97%, de la mise en place de l'Impella 2,5™ post AC, sans différence de survie en comparaison avec le ballon de contrepulsion aortique(101). Dans une étude française non randomisée, ayant

inclus 22 patients en état de choc cardiogénique après un infarctus aigu du myocarde, compliqués dans 41% des cas d'un AC, le dispositif Impella 2,5TM a été associé à une survie d'environ 59% à 6 mois et 55% à 12 mois(100). Cette survie est comparable ou légèrement supérieure à la survie de 49% à 12 mois dans le groupe traitement médical, et 48% à 12 mois dans le groupe ballon de contrepulsion, de l'étude IABP SHOCK(124).

L'utilisation de l'Impella 2,5TM dans l'AC associé à un état de choc reste relativement restreinte, et les indications de ce dispositif ne sont pas bien définies dans le contexte de l'AC(73). Étant donné le risque d'effets adverses du dispositif, comme les complications vasculaires au point d'insertion ou l'hémolyse intravasculaire, son utilisation doit toujours faire l'objet d'une évaluation détaillée du rapport bénéfice-risque.

2.4.3 Utilisation de l'assistance circulatoire type Extracorporeal Life Support

L'ECLS est une assistance circulatoire biventriculaire et pulmonaire, ou cœur poumon, qui prélève le sang par une canule veineuse insérée en général par la veine fémorale commune, et dont l'extrémité est située au niveau de l'oreillette droite. Le sang traverse un oxygénateur et après oxygénation est réinjecté par une canule artérielle au niveau de l'artère iliaque, la direction du flux sanguin étant rétrograde, vers le cœur (Figure 7). En supplant la fonction cardiaque et pulmonaire et en assurant un débit sanguin jusqu'à environ 5L/min, ce dispositif permet une perfusion systémique en attendant la récupération myocardique, l'amélioration de la fonction des organes vitaux et l'évaluation de l'état neurologique après un AC.

Dans le cas de l'AC ne répondant pas aux manœuvres de réanimation cardiopulmonaire, sans reprise d'une circulation spontanée - l'AC réfractaire, l'ECLS est recommandée comme thérapie de sauvetage(44,73). La littérature est riche en études observationnelles rétrospectives et prospectives concernant l'utilisation de l'ECLS dans l'AC réfractaire, mais des études randomisées sur le sujet

manquent(128–138). Étant donné les complications liées à ce dispositif comme le saignement et le risque d'infection au site d'insertion, le risque de thromboembolie systémique, l'hémolyse intravasculaire, son utilisation doit également faire l'objet d'une évaluation minutieuse de la balance bénéfice-risque.

Une des études expérimentales réalisées dans le cadre de cette thèse se concentre sur le rôle de l'ECLS dans la prise en charge de l'AC réfractaire dans un modèle porcin, et tente de donner une réponse expérimentale à la question de l'utilité de l'ECLS dans l'AC réfractaire. Cette étude aborde également par une double randomisation le sujet de l'intérêt de l'adrénaline dans la réanimation des AC réfractaires.

Si l'ECLS est utilisée dans la situation de l'AC réfractaire selon les recommandations récentes, cette technique n'est pas discutée par les recommandations(44,73) dans la situation de l'AC ayant répondu aux manœuvres de réanimation cardiopulmonaire initiales et compliqué ultérieurement d'une instabilité circulatoire sévère potentiellement menaçant la vie du patient. L'ECLS est néanmoins indiquée lors de l'insuffisance cardiaque aiguë réfractaire au traitement médical en dehors du contexte d'AC(116,139,140).

Récemment, une étude française a montré une survie de 28% avec un bon état neurologique, CPC1, après traitement par ECLS, des patients en état de choc cardiogénique survenant après un AC(104).

Dans cette étude, l'ECLS a été mise en route 7,4 heures après l'AC, mais les critères de sélection des patients n'ont pas été définis préalablement, l'indication d'assistance circulatoire étant posée par les médecins en charge du patient en fonction de leur expérience et de l'évaluation clinique des patients.

Un des travaux présentés se concentre sur l'identification de facteurs pronostiques à l'arrivée à l'hôpital, permettant d'identifier les patients qui présenteront une insuffisance circulatoire réfractaire au traitement par catécholamines. Dans cette population, certains patients pourraient bénéficier de façon précoce d'un traitement par assistance circulatoire et ainsi éviter la dégradation hémodynamique et ses conséquences.

2.4.3.1 Effets de l'assistance circulatoire type Extracorporeal Life Support sur la fonction cardiaque et la postcharge

L'utilisation de l'assistance circulatoire dans le contexte de l'AC est un concept relativement ancien. Une première série de 6 cas d'AC réfractaires survenus pendant des procédures chirurgicales, et traités par assistance circulatoire au bloc opératoire a été publiée en 1966(141). Un patient de cette série a survécu sans séquelles neurologiques, les autres étant décédés.

L'ECLS représente une assistance circulatoire miniaturisée et un outil efficace pour améliorer la circulation systémique même dans des cas extrêmes comme l'AC réfractaire(128,129,132,138,142–144). Néanmoins, par sa position dans le système circulatoire humain, l'ECLS a plusieurs effets non-physiologiques. Un premier effet est l'augmentation importante de la postcharge du ventricule gauche(145,146). Lorsque le sang est réinjecté dans le système artériel, cette réinjection se fait par la canule artérielle insérée dans l'artère fémorale commune et dont l'extrémité se trouve en général au niveau de l'artère iliaque commune. Ce débit sanguin, en général entre 3 et 5 L/min, est dirigé de façon non-physiologique, rétrograde, vers l'aorte ascendante et le cœur. Ce débit sanguin orienté dans le sens inverse par rapport au débit physiologique, augmente la postcharge cardiaque, et induit un deuxième effet non-physiologique, l'augmentation de la pression télédiastolique du ventricule gauche. Ces effets ont été étudiés et documentés dans la littérature(145,146) et favorisent l'apparition d'un œdème pulmonaire parfois majeur, pouvant nécessiter des techniques de sauvetage pour son traitement, comme la septostomie atriale ou la mise en place d'un dispositif supplémentaire comme le ballon de contrepulsion intraaortique ou l'Impella®(147–149). Cette augmentation de la postcharge augmente également la consommation d'oxygène myocardique et pourrait dans le contexte de l'AC retarder la récupération de la fonction myocardique. Or, il a été montré que la diminution de la postcharge est un des facteurs thérapeutiques les plus importants permettant l'amélioration de la contractilité cardiaque, et même la survie des patients avec insuffisance cardiaque chronique(150). Un des travaux présentés ici, se concentre sur l'effet de la diminution expérimentale du débit de l'ECLS lors de la systole cardiaque, sur la fraction d'éjection du

ventricule gauche et sur la pression capillaire pulmonaire. Cette diminution du débit systolique de l'ECLS a été obtenue lors de la systole cardiaque par un dispositif transformant le flux continu de l'ECLS en flux pulsatile.

2.5 Optimisation de la circulation cérébrale après un arrêt cardiaque

La circulation cérébrale est influencée par de multiples facteurs dont la pression artérielle systémique, le débit sanguin systémique, la pression intracrânienne et les résistances vasculaires des vaisseaux cérébraux(103). La circulation cérébrale a des mécanismes d'autorégulation par vasoconstriction et vasodilatation permettant de maintenir constant le débit sanguin cérébral, mais dans des situations extrêmes, l'autorégulation peut être dépassée(79,151). Assurer alors un débit sanguin et une pression systémique satisfaisants est une étape majeure dans l'optimisation de la circulation cérébrale, mais les résistances vasculaires cérébrales sont très fortement influencées par la pression partielle en gaz carbonique(80,152,153). L'interaction entre la pression en gaz carbonique et la circulation cérébrale est compliquée par l'utilisation de l'hypothermie thérapeutique, qui modifie la solubilité du gaz carbonique par rapport à la température standard de 37°C(93). La cible selon les recommandations actuelles, est d'assurer une pression artérielle en gaz carbonique normale(73). Néanmoins, lorsque la température corporelle des patients est très différente de 37°C, (par exemple 33°C comme dans le cas de l'hypothermie thérapeutique), la pression partielle artérielle en gaz carbonique diffère significativement entre la mesure faite à 37°C et la mesure faite à la température réelle de 33°C. Il n'existe pas actuellement de recommandation sur la façon optimale de normaliser la pression en gaz carbonique, à la température standard de 37°C (stratégie alpha-stat) ou à la température réelle du patient (stratégie pH-stat).

Le dernier travail de cette thèse explore l'interaction entre la pression en gaz carbonique et la circulation sanguine cérébrale en prenant en compte l'effet de l'hypothermie modérée thérapeutique.

2.6 Justification et aspects abordés par la recherche dans le présent travail

Le présent travail se focalise sur l'amélioration de la fonction circulatoire, car jusqu'à 35% des patients décèdent précocement à cause de l'insuffisance circulatoire(7,73), celle-ci constituant une cible thérapeutique importante. L'insuffisance circulatoire peut être identifiée à toutes les étapes de la prise en charge des patients, la forme la plus extrême étant représentée par l'AC résistant aux manœuvres de réanimation cardiopulmonaire, identifié comme AC réfractaire.

La première étude présentée dans ce travail se concentre sur l'intérêt de l'assistance circulatoire dans l'AC réfractaire et l'intérêt de l'utilisation prolongée de l'adrénaline en bolus intraveineux lors de la réanimation cardiopulmonaire des AC réfractaires. Cette étude a été réalisée sur un modèle animal d'AC réfractaire chez le cochon.

Un deuxième aspect du traitement de l'insuffisance circulatoire abordé ici est la possibilité de mettre en route dans des délais courts, l'assistance circulatoire type ECLS, chez des patients en situation d'AC réfractaire, par canulation percutanée en salle de coronarographie, sans recours à la technique chirurgicale. Des résultats encourageants de la méthode percutanée de canulation permettraient une diffusion plus large de l'assistance circulatoire par ECLS dans l'avenir, dans les centres dotés de cardiologie interventionnelle.

Si suite aux manœuvres de réanimation, les patients ont repris une circulation spontanée, leur fonction circulatoire peut se dégrader ultérieurement malgré un traitement par catécholamines bien conduit, et cette dégradation circulatoire est responsable d'environ un tiers des décès intrahospitaliers. La troisième étude présentée se charge de retrouver, dès l'arrivée des patients à l'hôpital, les facteurs pronostiques permettant d'identifier les patients à haut risque de décès par insuffisance circulatoire, et qui pourraient bénéficier précocement des moyens d'assistance circulatoire mécanique.

Lors de la phase hospitalière, après la mise en place d'une assistance circulatoire artérioveineuse de type ECLS, celle-ci peut ralentir la récupération de la contractilité cardiaque car le flux sanguin de l'ECLS diminue la fraction d'éjection du ventricule gauche, selon une étude récente(145). La

postcharge augmentée par l'ECLS peut également augmenter la pression capillaire pulmonaire et prédisposer à un œdème pulmonaire(145,146). La quatrième étude présentée dans ce travail évalue l'effet de la diminution de la postcharge liée à l'ECLS, sur la récupération de la fonction ventriculaire gauche et la pression capillaire pulmonaire. Cette étude expérimentale est réalisée sur un modèle d'AC chez le cochon.

Finalement, après l'obtention d'une fonction circulatoire systémique satisfaisante pour la perfusion d'organes, l'optimisation de la circulation cérébrale nécessite également la prise en compte de l'interaction entre la circulation cérébrale, la pression en gaz carbonique et la température corporelle des patients, cette relation étant plus complexe en cas de traitement par hypothermie thérapeutique. La cinquième étude présentée évalue l'interaction entre la circulation cérébrale et la pression artérielle en gaz carbonique lors d'une hypothermie thérapeutique en vue de l'optimisation de la circulation cérébrale des patients après un AC.

3 Matériel et méthodes

Dans cette thèse, plusieurs options d'amélioration de la fonction circulatoire ont été évaluées par deux études expérimentales chez le cochon et trois études observationnelles chez des patients ayant présenté un AC. Les matériels et méthodes généraux sont présentés ici, les matériels et méthodes spécifiques sont détaillés dans les chapitres correspondant à chaque étude.

3.1 Matériel et méthodes - travaux expérimentaux

Les deux études expérimentales présentées ici ont été réalisées chez le cochon de taille réduite en raison de la physiologie proche la physiologie humaine et en raison de l'anatomie du système cardiovasculaire proche de l'anatomie cardiovasculaire humaine. Cette ressemblance y compris de la taille cardiaque et longueur de l'aorte a permis d'utiliser des dispositifs médicaux employés dans la prise en charge des patients, comme les canules artérielles et veineuses et les circuits de l'ECLS, les cathéters veineux et artériels et le matériel de cardiologie interventionnelle. Pour éviter la variabilité induite par le genre, uniquement des femelles ont été incluses dans les études rapportées dans cette thèse. Les protocoles expérimentaux ont reçu l'accord des comités d'éthique des institutions correspondant aux laboratoires, Université de Minnesota, Minneapolis, États-Unis, et Institut National de Recherche Agronomique, INRA, Jouy-en-Josas, Île-de-France, France.

L'ensemble des procédures a été réalisé par du personnel qualifié dans l'expérimentation animale dans le respect des recommandations sur l'expérimentation animale, détaillées dans chaque travail.

Les animaux ont été initialement anesthésiés par une injection intramusculaire de kétamine ou kétamine-xylazine suivie, après intubation, d'une anesthésie par isoflurane environ 1% permettant de réduire au minimum l'inconfort des animaux.

Les procédures expérimentales ont été réalisées sous anesthésie efficace continue, permettant la mise en place des cathéters, des canules d'ECLS et des cathéters de procédures interventionnelles coronaires. L'ensemble des procédures interventionnelles coronaires ont été réalisées sous contrôle fluoroscopique par des cardiologues expérimentés.

L'AC expérimental a été déclenché par la stimulation du ventricule droit à l'aide d'une sonde

d'électroentraînement positionnée sous contrôle fluoroscopique. Le massage cardiaque mécanique nécessaire dans les deux études expérimentales a été réalisé en utilisant des moyens mécaniques pour diminuer la variabilité de l'efficacité du massage cardiaque entre les groupes contrôle et les groupes « intervention » et pour reproduire le massage cardiaque mécanique utilisé dans la réanimation cardiopulmonaire humaine. A la fin des procédures expérimentales, les animaux ont été mis à mort sans interrompre l'anesthésie générale.

3.2 Matériel et méthodes - travaux cliniques

Les trois études réalisées en clinique humaine présentées ici sont des études observationnelles qui ont inclus des patients ayant présenté un AC, âgés de plus de 18 ans dans notre centre, l'Hôpital Lariboisière, Paris, France. Les études ont été réalisées en respectant les principes de la Déclaration de Helsinki 2008 de l'organisation Mondiale de la Santé, et ont reçu l'accord du Comité d'éthique de notre institution. Les patients et les familles des patients admis dans notre institution ont donné l'accord pour l'utilisation des données médicales de façon anonyme à but scientifique. Les patients inclus de façon prospective et/ou leurs familles ont été informés du recueil de données et de l'inclusion, et ont donné leur accord pour l'inclusion.

Les données recueillies ont été obtenues par la consultation des bases de données cliniques, biologiques et d'imagerie de l'hôpital Lariboisière, et des dossiers médicaux des patients.

Les patients inclus dans les études présentées dans cette thèse ont été victimes d'un AC et ont bénéficié d'une prise en charge selon les recommandations contemporaines des sociétés savantes sur la prise en charge de l'AC. Les patients ayant présenté un AC ont été en général pris en charge initialement soit par le service d'aide médicale urgente – SAMU, soit par les pompiers qui ont appliqué les mesures de réanimation cardiopulmonaire de base. Dès son arrivée, le personnel médical et infirmier a réalisé la réanimation cardiopulmonaire avancée avec accès veineux, administration de médicaments y compris l'adrénaline, intubation et ventilation mécanique. Nos patients présentant un AC extrahospitalier sans cause extracardiaque évidente, ont été accueillis à l'arrivée à l'hôpital, directement en salle de cathétérisme cardiaque et ont bénéficié d'une

coronarographie avec angioplastie si indiquée.

En réanimation, un contrôle thermique avec une cible de température en général à 33° a été réalisé, de même qu'une optimisation de la fonction circulatoire avec remplissage vasculaire et administration de catécholamines en cas d'insuffisance circulatoire, selon les recommandations des sociétés savantes. L'état neurologique des patients à la sortie de l'hôpital a été évalué dans les études présentées ici par le score Cerebral Performance Category - CPC(108).

4 Rôle de l'assistance circulatoire et de l'adrénaline dans la réanimation cardiopulmonaire de l'arrêt cardiaque réfractaire – travail expérimental

4.1 Introduction

La prise en charge de l'AC réfractaire ne répondant pas aux manœuvres de réanimation cardiopulmonaire pourrait bénéficier d'un traitement par ECLS comme mesure de sauvetage, mais des données expérimentales ou cliniques randomisées en faveur de l'efficacité de l'assistance circulatoire ne sont pas disponibles. Plusieurs études rétrospectives cliniques ont comparé la prise en charge des AC réfractaires avec, et sans utilisation de l'ECLS(127–129), avec des résultats contradictoires. Le traitement par adrénaline lors de la réanimation cardiopulmonaire des AC réfractaires, n'a pas été évalué dans des modèles expérimentaux, et en pratique, l'adrénaline est en général administrée selon les recommandations valables pour le traitement de l'AC non réfractaire(44). L'utilité de l'ECLS et de l'adrénaline en bolus répétés dans la prise en charge de l'AC réfractaire doit être évaluée pour adapter au mieux le traitement dans ce contexte. L'évaluation de ces deux thérapies est difficile en clinique humaine, en raison de la difficulté de réaliser des randomisations en contexte d'urgence, et en raison des difficultés logistiques imposées par l'utilisation de l'ECLS dans le contexte de l'AC réfractaire. Néanmoins, des études randomisées sont actuellement en cours à ce sujet en République Tchèque et en Autriche.

Nous avons réalisé une étude expérimentale avec une double randomisation, adrénaline versus placebo, et utilisation de l'ECLS versus réanimation cardiopulmonaire conventionnelle chez des cochons ayant subi un AC réfractaire, dans un modèle expérimental très proche de l'AC réfractaire humain. Ce modèle a compris d'abord le déclenchement d'un infarctus myocardique expérimental compliqué d'une fibrillation ventriculaire, suivi d'une période de « no flow », période d'AC sans massage cardiaque ni ventilation artificielle, similaire à l'AC humain. Une période de réanimation cardiopulmonaire prolongée a suivi, « low flow », correspondant à la période de réanimation

cardiopulmonaire initiale et au transport des patients à l'hôpital sous massage cardiaque, et finalement, une période de traitement par ECLS ou poursuite de la réanimation conventionnelle, correspondant à la prise en charge intrahospitalière des patients.

Le critère principal de jugement a été la mortalité dans le groupe adrénaline versus placebo et la mortalité dans le groupe ECLS versus le groupe réanimation cardiopulmonaire conventionnelle. Cette étude à double randomisation a été réalisée en collaboration avec l'équipe du Professeur Demetris Yannopoulos à l'Université de Minnesota, Minneapolis, Etats-Unis.

4.2 Role of epinephrine and extracorporeal membrane oxygenation in the management of ischemic refractory ventricular fibrillation - a randomized trial in pigs

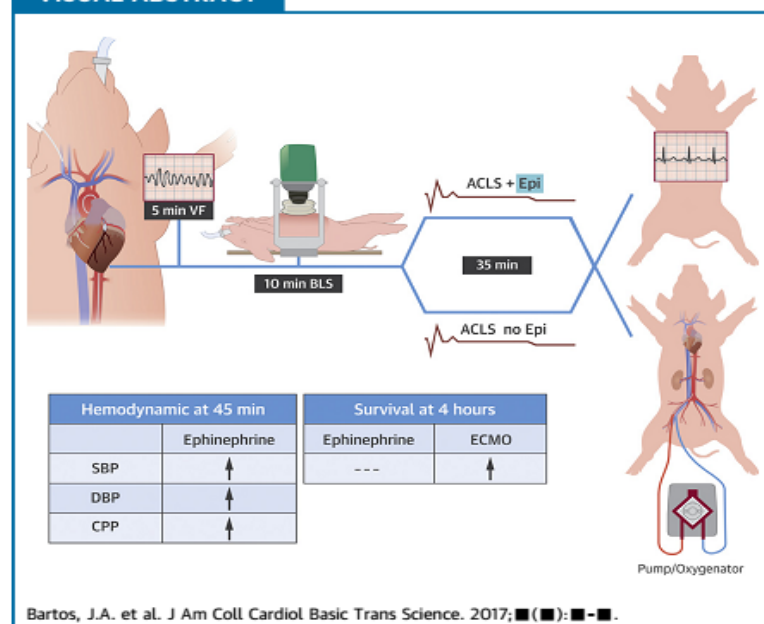
PRECLINICAL RESEARCH

Role of Epinephrine and Extracorporeal Membrane Oxygenation in the Management of Ischemic Refractory Ventricular Fibrillation

A Randomized Trial in Pigs

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VISUAL ABSTRACT



HIGHLIGHTS

- The Minnesota Resuscitation Consortium has established a protocol for rapid transport of patients with refractory out-of-hospital VF cardiac arrest to the cardiac catheterization laboratory for rapid evaluation and stabilization often requiring ECMO. This protocol provides new challenges to treatment paradigms that were created to rapidly achieve return of spontaneous circulation in the field.

- A porcine model of refractory VF cardiac arrest was developed, including initiation of VF using endovascular occlusion of the proximal LAD followed by 5 min of untreated VF. Resuscitation begins with 10 min of high-quality CPR followed by 35 min of ACLS and reconstitution of coronary flow.
- A 2 × 2 study design was used with animals randomized to use of epinephrine or placebo during ACLS and then again randomized to ECMO or no ECMO at the time of reinitiation of coronary flow.
- ECMO-facilitated coronary reperfusion and hemodynamic stabilization improved 4-h survival compared with CPR-facilitated reperfusion and standard ACLS in a porcine model of refractory VF cardiac arrest.
- Repeated epinephrine boluses provided in accordance with standard ACLS protocols increased systemic blood pressure and coronary perfusion pressure but provided no benefit in survival compared with placebo.
- Over 50% of the animals receiving ECMO met criteria for decannulation at 4 h, suggesting that rapid cardiac and hemodynamic recovery is possible in severely injured animals treated with ECMO.

ABBREVIATIONS
AND ACRONYMS**ACLS** = advanced cardiac life support**BLS** = basic life support**CA** = cardiac arrest**CCL** = cardiac catheterization laboratory**CPP** = coronary perfusion pressure**CPR** = cardiopulmonary resuscitation**ECMO** = extracorporeal membrane oxygenation**EPI** = epinephrine**LAD** = left anterior descending artery**PCI** = percutaneous coronary intervention**ROSC** = return of spontaneous circulation**VF** = ventricular fibrillation

SUMMARY

Extracorporeal membrane oxygenation (ECMO) is used in cardiopulmonary resuscitation (CPR) of refractory cardiac arrest. The authors used a 2 × 2 study design to compare ECMO versus CPR and epinephrine versus placebo in a porcine model of ischemic refractory ventricular fibrillation (VF). Pigs underwent 5 min of untreated VF and 10 min of CPR, and were randomized to receive epinephrine versus placebo for another 35 min. Animals were further randomized to left anterior descending artery (LAD) reperfusion at minute 45 with ongoing CPR versus venoarterial ECMO cannulation at minute 45 of CPR and subsequent LAD reperfusion. Four-hour survival was improved with ECMO whereas epinephrine showed no effect. (J Am Coll Cardiol Basic Trans Science 2017;■:■-■) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The Minnesota Resuscitation Consortium (MRC) has modified the advanced cardiac life support (ACLS) treatment algorithm (1) by establishing the first reported protocol in the United States to treat patients with out-of-hospital refractory ventricular fibrillation (VF) (2). The protocol includes early transport

by emergency medical services to a cardiac catheterization laboratory (CCL) with intent to receive extracorporeal membrane oxygenation (ECMO)-facilitated coronary revascularization (angioplasty) (2). Initial treatment and transport of out-of-hospital VF arrest patients to the CCL often requires 45 to 60 min.

There are currently no controlled clinical trials or published animal models of ischemic VF demonstrating improved survival when ECMO is utilized to facilitate percutaneous coronary intervention (PCI) instead of cardiopulmonary resuscitation (CPR). The effect of epinephrine (EPI) use in this setting is also unknown.

Therefore, we developed a porcine model of prolonged CPR with refractory ischemic VF that simulated our MRC clinical protocol (3) and implemented a randomized 2 × 2 factorial design to test 2 hypotheses: 1) use of EPI in prolonged resuscitation improves short-term 4-h survival; and 2) ECMO-facilitated reperfusion improves short-term 4-h survival and cardiac function compared with CPR-facilitated reperfusion with no ECMO support.

METHODS

This 2 × 2 randomized experimental study in pigs was performed at the University of Minnesota and approved by the Institutional Animal Care and Use Committee. All studies and animal care complied with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals (protocol number: 12-11). All studies and procedures were performed by a qualified, experienced research team in farm-bred female Yorkshire pigs. A certified and licensed veterinarian assured the studies were performed in accordance with the National Research Council's Guidelines.

PREPARATORY PHASE. We used 33 pigs with an average weight of 44 ± 3 kg. The surgical preparation under aseptic conditions, anesthesia, data monitoring, and recording procedures used in the present study have been described elsewhere (3-5). Briefly, pigs were anesthetized with intramuscular ketamine (1,000 mg) followed by inhaled isoflurane at a dose of 0.8% to 1.2%. Endotracheal intubation was secured with a 7.0-mm endotracheal tube. Animals were ventilated with room air using volume-controlled ventilation with a tidal volume of 10 ml/kg (Narkomed, Telford, Pennsylvania). The respiratory rate was adjusted to maintain a partial pressure of carbon dioxide in arterial blood (PaCO₂) of 36 to 42 mm Hg. A partial pressure of oxygen in arterial blood (PaO₂) of at least 80 mm Hg (blood oxygen saturation >95%) was maintained prior

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to VF initiation. Core temperature was measured with an esophageal temperature probe with normothermia ($37^{\circ} \pm 0.5^{\circ}\text{C}$) maintained prior to VF initiation using a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota). Therapeutic hypothermia was initiated after the resuscitation with a target temperature of 34°C using a Blanketrol cooling blanket (Cincinnati Sub Zero, Cincinnati, Ohio).

The aortic blood pressure was recorded continuously with a Millar catheter (Mikro-Tip Transducer, Millar Instruments, Houston, Texas) placed through an 8-F left femoral arterial sheath into the descending thoracic aorta. A second Millar catheter was inserted into the right atrium through an 8-F sheath placed into the right external jugular vein to record central venous pressure. All sheaths were placed percutaneously using ultrasound guidance.

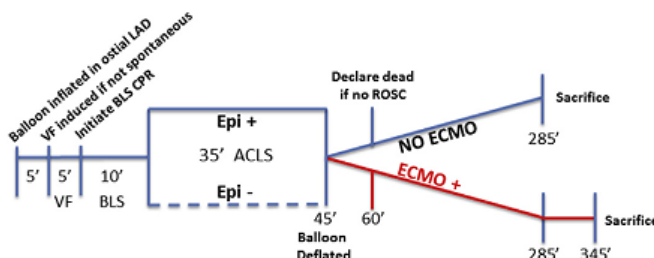
To prevent thrombosis due to endovascular instrumentation, an intravenous heparin bolus of 100 U/kg was administered every 60 min. Hemodynamic data were continuously monitored and recorded (LabVIEW 2015, National Instruments, Austin, Texas). Coronary perfusion pressure (CPP) was calculated as the difference between diastolic blood pressure and right atrial pressure. During CPR, CPP was calculated during the decompression phase. End-tidal carbon dioxide, tidal volume, minute ventilation, and blood oxygen saturation were continuously measured (COSMO Plus, Novamatrix Medical Systems, Wallingford, Connecticut). Electrocardiograms (ECGs) were continuously recorded.

EXPERIMENTAL PROTOCOL. After anesthesia and instrumentation, 6-F arterial and venous sheaths were placed in the right femoral artery and vein. A second 8-F left femoral arterial sheath was placed for coronary procedures. The timeline of the experimental protocol is shown in [Figure 1](#).

CORONARY OCCLUSION PROTOCOL. The coronary occlusion protocol has been described previously (3,6,7). A 6-F Amplatz Left 0.75 short-tipped guide catheter was engaged into the left main coronary artery under fluoroscopic guidance. A Balance Middle-weight coronary guidewire (Abbott Vascular, Santa Clara, California) was advanced into the distal part of the left anterior descending artery (LAD). Acute coronary occlusion was induced using a 4.0 mm $\times$ 16 mm balloon inflated at 6 to 8 atm in the ostial LAD proximal to the first diagonal with angiographic evidence of complete coronary flow obstruction.

INDUCTION OF VF AND INITIATION OF CPR. If spontaneous VF did not occur within 5 min of balloon occlusion, VF was electrically induced at 5 min using a pacing wire inserted through the right jugular vein

FIGURE 1 Schematic Representation of the Randomized 2 $\times$ 2 Protocol Including Epi and ECMO Randomization



Each experiment began with endovascular balloon occlusion of the ostial left anterior descending artery (LAD). If ventricular fibrillation (VF) did not occur spontaneously, it was induced electrically after 5 min. Ventilations were then halted and no treatment was provided for 5 min. High-quality cardiopulmonary resuscitation (CPR) was then initiated for 10 min of basic life support (BLS), representing first-responder CPR. Animals were then randomized to receive epinephrine (Epi) 0.5 mg intravenous or saline placebo every 5 min for the 35 min of advanced life support (ACLS). At minute 45 of CPR, the animals were again randomized into the CPR-facilitated group (no extracorporeal membrane oxygenation [NO ECMO]) or the ECMO+ group. In the NO ECMO group, the LAD balloon was deflated and resuscitation continued for up to 15 more min. If no return of spontaneous circulation (ROSC) was achieved, the animal was declared dead. If ROSC was achieved, the animal was maintained for 4 h. ECMO+ animals were cannulated for venoarterial ECMO followed by LAD balloon deflation and resuscitation continued. If ROSC was not achieved within 15 min, the animal was declared dead. If ROSC was achieved, the animal was maintained for 4 h, at which time it was assessed for suitability for decannulation. ECMO+ pigs meeting criteria for decannulation were maintained for 1 more hour, assessed again for decannulation criteria, and then sacrificed at hour 5.

sheath into the right ventricle with stimulation of the myocardium at 300 cycles/min. Once VF was initiated, ventilation ceased and no treatment was provided for 5 min. This period represents the average time from an emergency call to first-aid arrival in the state of Minnesota for patients suffering cardiac arrest (CA). After 5 min of untreated VF, all animals received high-quality CPR with active chest decompression and an impedance threshold device (8). Chest compressions were performed using a specially designed automated device enabling control of compression and decompression amplitude. Compressions were supplied at a rate of 100 compressions/min with a 50% compression-decompression duty cycle using a servomotor-driven piston with a neoprene suction cup that provides adequate area for compressions. Compression depth was set to 20% of the anteroposterior diameter or 2 inches, whichever was greater. The animals were treated with active compression-decompression and impedance threshold device to optimize perfusion for prolonged CA (8). Chest compressions were paused only for defibrillation in the CPR-facilitated group until return of spontaneous circulation (ROSC) was achieved. In the ECMO-facilitated group, chest compressions

were continuous until ECMO was placed. Ventilation during CPR was performed using zero positive end-expiratory pressure and a tidal volume of 6 ml/kg at a rate of 10 breaths/min.

RANDOMIZATION. At the start of ACLS CPR, animals were randomized to receive either EPI or no EPI. At the end of ACLS CPR, they were further randomized to receive either ECMO-facilitated reperfusion or CPR-facilitated reperfusion (no ECMO). These randomizations resulted in 4 groups: EPI-, ECMO- (n = 8); EPI+, ECMO- (n = 8); EPI-, ECMO+ (n = 8); and EPI+, ECMO+ (n = 9).

DURATION OF CPR AND RESUSCITATION EFFORTS. Resuscitation efforts were performed to closely simulate the out-of-hospital and in-hospital phases of the MRC clinical protocol. We describe each phase in detail subsequently.

Out-of-hospital CPR. The initial phase of CPR was termed basic life support (BLS), incorporating high-quality CPR alone. After 10 min of BLS, ACLS was initiated, which included continued high-quality CPR in addition to EPI, as determined by the experimental group. All animals randomized to EPI+ received 0.5 mg of intravenous EPI diluted in 5 ml of normal saline flushed in with an additional 5 ml of normal saline. EPI was given at the initiation of the ACLS phase and every 5 min thereafter. Animals randomized to EPI- received 10 ml of normal saline at the same time intervals. Investigators were blinded to drug therapy allocation. ACLS was continued for 35 min (45 min of total CPR). The duration of BLS and ACLS CPR corresponded to the care received by refractory VF CA patients from initial treatment by BLS providers, subsequent ACLS treatment, first EPI dose, emergency medical services transport, and admission to the CCL (2).

Cardiac catheterization-based resuscitation. After 45 min of CPR, pigs randomized to ECMO-facilitated reperfusion had ECMO cannulas inserted with ongoing CPR similar to the MRC clinical protocol. A 15-F arterial cannula was inserted in the right common femoral artery and a 21-F venous cannula was inserted in the right femoral vein and advanced as close to the right atrium as the length of the torso of the pigs allowed under direct fluoroscopy. Once on ECMO support, the LAD balloon was deflated and vessel patency was verified by angiography. Animals with CPR-facilitated reperfusion had their LAD balloon deflated at minute 45. On average, that occurred 5 min earlier than in the ECMO+ group.

Post-coronary reperfusion management. Animals without ECMO support. After LAD reperfusion (balloon deflation) in the ECMO- group, intravenous amiodarone 40 mg was given and CPR was continued

up to 15 min with defibrillations every 3 min until ROSC. Animals in the EPI+ group continued to receive intravenous EPI 0.5 mg every 5 min during this phase. EPI- animals continued to receive saline as a control instead of EPI. ROSC was defined as an organized ECG rhythm with mean arterial pressure >60 mm Hg (9). If ROSC could not be achieved after 15 min, CPR was terminated and the pig was declared dead (total resuscitation duration of 60 min). Animals who had ROSC were maintained using fluid resuscitation and intravenous EPI to maintain mean arterial pressure >60 mm Hg. EPI- animals received intravenous EPI as needed after ROSC. Sodium bicarbonate infusion was used for metabolic acidosis as needed.

Animals with ECMO support. For ECMO+ animals the same strategy was used. ROSC was defined as an organized ECG rhythm with mean arterial pressure >60 mm Hg. EPI+ animals continued to receive intravenous EPI 0.5 mg every 5 min during this phase whereas EPI- animals continued to receive saline as a control. If defibrillation attempts were unsuccessful after 15 min while on full ECMO support following LAD reperfusion, the animals were declared dead. If defibrillation was successful, animals were maintained using fluid resuscitation and intravenous EPI to maintain mean arterial pressure >60 mm Hg. Sodium bicarbonate infusion was used for metabolic acidosis as needed.

MANAGEMENT OF ECMO. The ECMO+ animals received ECMO support similar to MRC patients (2) using the CARDIOHELP System (Maquet Cardiovascular, Wayne, New Jersey) combining an oxygenator and an integrated centrifugal pump. The number of pump rotations per minute was adjusted to obtain maximum stable ECMO flow without venous collapse. Target flow was 2.8 to 3.5 l/min with venous pressure not exceeding -100 mm Hg. Fluid resuscitation and continuous intravenous EPI were administered to maintain mean arterial pressure >60 mm Hg as necessary. Gas exchange and blood gases were managed via the ECMO circuit.

ECHOCARDIOGRAPHIC EVALUATION. Transthoracic echocardiograms were acquired at baseline, 1 h, and 4 h in surviving animals. Parasternal long- and short-axis views were obtained and analyzed by clinical cardiologists blinded to the intervention (4).

ARTERIAL BLOOD GASES AND LACTIC ACID ASSESSMENT. Arterial blood gas measurements (Gem 3000, Instrumentation Laboratory, Bedford, Massachusetts) were obtained at baseline, and every 5 min after initiation of CPR until 45 min of CPR were complete. Arterial blood gases were then collected every hour starting at 1-h post-LAD revascularization

until death or sacrifice at 4 h. Lactic acid was quantified using the same samples at the same intervals.

STUDY ENDPOINTS. The primary study endpoint was survival at 4 h after completion of the ACLS phase of CPR (Figure 1). This time began with LAD reperfusion in the ECMO- animals and ECMO cannulation in the ECMO+ animals. ECMO- animals were considered survivors if they maintained a mean arterial pressure >60 mm Hg with an organized ECG at the end of the 4 h. In ECMO+ groups, survival was defined as an organized ECG rhythm, a mean arterial pressure >60 mm Hg, ECMO flow at least 60 ml/kg, and improving lactic acid blood levels with or without evidence of pulsatility (9).

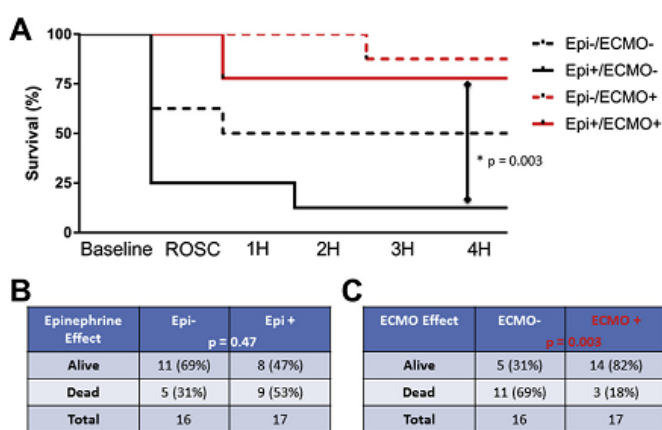
The secondary endpoints included ROSC (as discussed previously), suitability for ECMO decannulation, hemodynamics, left ventricular ejection fraction (LVEF), and arterial blood lactic acid levels. ECMO+ animals that survived were further evaluated for ECMO decannulation with an ECMO turn down. Animals were deemed suitable for decannulation if they met 2 criteria: 1) sustained mean pulsatile aortic pressure of more than 60 mm Hg with a pulse pressure of >20 mm Hg on <1.5 l/min of ECMO support; and 2) LVEF >30% by echocardiographic evaluation. Animals meeting these criteria were left at the lowest flow rate for another hour with continuous observation. The decannulation criteria were again assessed at hour 5 to ensure stable hemodynamics. At the end of 5 h, the ECMO was turned off and surviving animals were euthanized. Animals surviving to 4 h but failing to meet decannulation criteria were considered meeting the primary endpoint of 4-h survival.

STATISTICAL ANALYSIS. Values were expressed as mean $\pm$ SEM and percentages. The statistical analysis was performed with GraphPad Prism 7 (GraphPad Software, La Jolla, California). A 2-way analysis of variance was used to evaluate lactic acid curves. Unpaired *t* test was used to compare numerical values and chi-square test was used to compare categorical values from the 2 different groups of animals. The effect of EPI (EPI+) and ECMO (ECMO+) on 4-h survival was assessed with Fisher's exact test. The interaction of EPI and ECMO was tested with a logistic model including an interaction term. The survival of each group over time was assessed using Kaplan-Meier survival curves analyzed with a Mantel-Cox test. A *p* value of <0.05 was considered significant.

RESULTS

SURVIVAL TO 4 H. Survival curves for all groups are shown in Figure 2A, with group analysis in Figures 2B and 2C.

FIGURE 2 Clinical Outcomes by Group

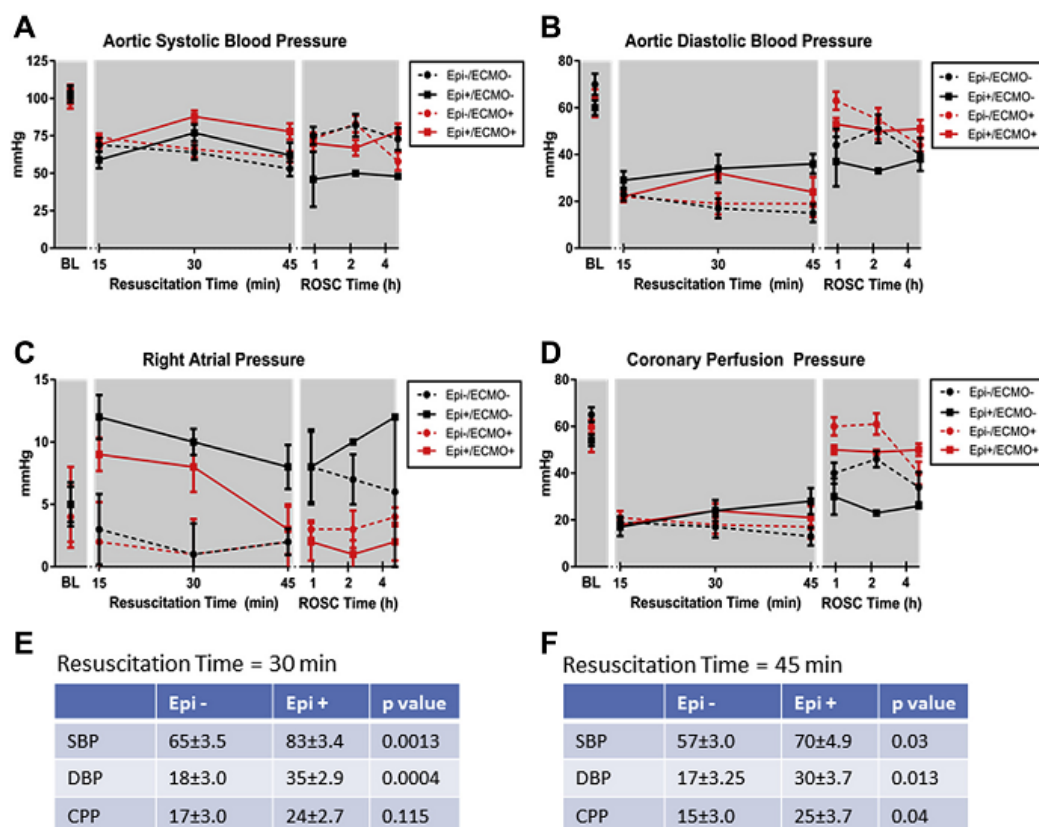


(A) Kaplan-Meier survival curves demonstrating survival at each time point noted. Survival tables showing alive and dead animals at 4 h based on the presence or absence of (B) Epi or (C) ECMO. The *p* values are noted. There was no interaction between Epi and ECMO treatments (*p* = 0.77). Abbreviations as in Figure 1.

EPI effect. There was no significant difference in 4-h survival between animals receiving EPI versus placebo (EPI+ 47% vs. EPI- 69%; *p* = 0.47) (Figure 2B).

ECMO effect. Animals randomized to ECMO support with ECMO-facilitated reperfusion had significantly improved 4-h survival (ECMO+ 82% vs. ECMO- 31%; *p* = 0.003) (Figure 2C). The primary ECMO effect appeared to be achievement and maintenance of ROSC, accomplished in 100% of ECMO+ animals versus 44% of ECMO- animals (*p* = 0.001). There was no interaction between EPI and ECMO (*p* = 0.77 for interaction). However, a significant difference was observed between the survival curves of the EPI+, ECMO- and EPI+, ECMO+ groups, suggesting that ECMO may be particularly beneficial when EPI is given during resuscitation (*p* = 0.003).

HEMODYNAMICS. There were no significant differences in hemodynamics between any of the groups during the initial 10 min of CPR (BLS phase) (Figures 3A to 3D). However, after 30 min of CPR, EPI+ animals had significantly higher aortic pressures (systolic blood pressure 83 mm Hg vs. 65 mm Hg, *p* = 0.0013; diastolic blood pressure 35 mm Hg vs. 18 mm Hg, *p* = 0.0004) compared with EPI- animals (Figures 3E and 3F). These differences continued through completion of the ACLS phase at 45 min of CPR. At 45 min of CPR, the CPP had also become significantly higher in EPI+ compared with EPI- animals (25 mm Hg vs. 15 mm Hg; *p* = 0.04). Initiating ECMO led to physiologic CPP and circulating blood flow. The effect was sustained from LAD balloon deflation to 4 h.

FIGURE 3 Hemodynamic Monitoring at Baseline, During Prolonged CPR, and After ROSC for Each Study Group

The (A) aortic systolic blood pressure, (B) aortic diastolic blood pressure, (C) right atrial pressure, and (D) coronary perfusion pressure (CPP) were measured throughout prolonged CPR and after ROSC was achieved. All pressures were measured in mm Hg. The mean pressures for no Epi (Epi-) and Epi (Epi+) animals at (E) 30 min and (F) 45 min are shown in table form with p values as shown. There was no significant difference between the ECMO- and ECMO+ groups. Error bars and error values in the tables represent SEM. BL = baseline; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Figure 1.

ARTERIAL BLOOD GASSES AND LACTIC ACID LEVELS.

There were no significant differences between groups in any arterial blood gas component (Table 1). EPI led to significantly higher lactic acid levels at the end of the out-of-hospital ACLS phase of CPR and around 45 min of resuscitation (Figure 4). Lactic acid levels recovered in all groups during the 4-h ROSC phase. Although this decrease was similar between groups, the CPR-only (ECMO-) groups had substantial attrition of the sickest animals at the ROSC and 1 h time points, which may reduce the observed lactic acid levels. The low numbers of surviving ECMO- animals did not allow for statistical comparisons.

ROSC. All animals that achieved ROSC were successfully defibrillated after LAD reperfusion, well after 45 min of CPR. Animals receiving ECMO+ had

higher rates of ROSC versus ECMO- pigs (100% vs. 44%; $p = 0.0003$). There were no significant ROSC differences in EPI+ versus EPI- animals (65% vs. 81%, respectively; $p = 0.438$).

LEFT VENTRICULAR FUNCTION. In all surviving animals, LVEF decreased from $62 \pm 7\%$ at baseline to $25 \pm 12\%$ at 1 h after LAD reperfusion. The LVEF recovered to $37 \pm 8\%$ at hour 4. LVEF was independent of treatment groups. No differences were detected between treatment groups due to the limited number of survivors in the ECMO- groups.

DECANNULATION. Of the 7 animals that survived to 4 h in the EPI+, ECMO+ group, 4 met criteria for decannulation (44% of the overall group), whereas 5 of 7 animals in the EPI-, ECMO+ group (63% of

TABLE 1 Arterial Blood Gas Results at Baseline, During Prolonged CPR, and After ROSC

	Baseline	15 min	30 min	45 min	60 min	2 h	4 h
EPI-, ECMO-		CPR	CPR	CPR	ROSC	ROSC	ROSC
pH	7.47 ± 0.07	7.33 ± 0.18	7.25 ± 0.21	7.17 ± 0.29	7.34 ± 0.05	7.39 ± 0.10	7.40 ± 0.15
PaCO ₂	44 ± 2.5	33 ± 3.9	36 ± 5.7	38 ± 4.3	42 ± 7.5	39 ± 4	43 ± 4.5
PaO ₂	97 ± 6.1	99 ± 4.6	127 ± 14.3	72 ± 23.2	107 ± 36	99 ± 29	95 ± 46
HCO ₂	31 ± 2.1	18 ± 2.9	15 ± 1.4	12 ± 1.79	23 ± 3.5	23 ± 2.5	27 ± 3
%SaO ₂	98 ± 6.1	94 ± 6.1	95 ± 2.5	90 ± 2.9	97 ± 2.5	98 ± 9	96 ± 5.5
EPI+, ECMO-		CPR	CPR	CPR	ROSC	ROSC	ROSC
pH	7.48 ± 0.04	7.36 ± 0.04	7.31 ± 0.04	7.25 ± 0.04	7.28 ± 0.07	7.24	7.21
PaCO ₂	41 ± 3.2	31 ± 2.5	27 ± 3.2	36 ± 2.5	30 ± 8.6	29	32
PaO ₂	105 ± 9.6	241 ± 30.7	189 ± 22.5	151 ± 29	189 ± 64	135	152
HCO ₂	30 ± 1.8	18 ± 2.1	13 ± 1.4	14 ± 1.4	13 ± 2.1	11	10
%SaO ₂	98 ± 2.5	99 ± 2.5	99 ± 1.8	94 ± 3.2	97 ± 5	96	99
EPI-, ECMO+		CPR	CPR	CPR	ECMO	ECMO	ECMO
pH	7.48 ± 0.04	7.36 ± 0.004	7.32 ± 0.07	7.28 ± 0.01	7.28 ± 0.07	7.29 ± 0.04	7.27 ± 0.12
PaCO ₂	39 ± 1.4	30 ± 3.2	30 ± 5.4	34 ± 3.2	32 ± 1.4	30 ± 1.8	30 ± 2.7
PaO ₂	107 ± 8.9	103 ± 4.3	135 ± 12.5	138 ± 17	290 ± 35	291 ± 29	292 ± 42
HCO ₂	29 ± 0.71	16 ± 2.5	14 ± 1.1	14 ± 2.5	15 ± 1.4	15 ± 2.5	14 ± 2.3
%SaO ₂	98 ± 2.1	96 ± 2.9	95 ± 3.2	88 ± 5	100 ± 0	100 ± 0	100 ± 0
EPI+, ECMO+		CPR	CPR	CPR	ECMO	ECMO	ECMO
pH	7.47 ± 0.03	7.32 ± 0.07	7.27 ± 0.03	7.26 ± 0.07	7.29 ± 0.04	7.32 ± 0.04	7.36 ± 0.08
PaCO ₂	38 ± 1.3	38 ± 2.3	44 ± 4.3	43 ± 2.7	42 ± 1.2	46 ± 1.9	44 ± 1.2
PaO ₂	103 ± 7.7	206 ± 25	163 ± 13.3	176 ± 37.7	227 ± 31	322 ± 36	272 ± 36
HCO ₂	31 ± 0.67	23 ± 1.67	20 ± 0.67	19 ± 1	22 ± 1.9	22 ± 1.9	22 ± 1.9
%SaO ₂	98 ± 0.33	99 ± 1	91 ± 3.3	99 ± 3.3	100 ± 0	100 ± 0	100 ± 0

Values are mean ± SEM. Data are shown per group assigned by the 2 × 2 study design. All partial pressures are shown in mm Hg. There are no error values noted for the EPI+, ECMO- group at 2 h and 4 h because only 1 animal survived to those time points in that group.

%SaO₂ = oxygen saturation in arterial blood; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; EPI = epinephrine; PaCO₂ = partial pressure of carbon dioxide in arterial blood; PaO₂ = partial pressure of oxygen in arterial blood; ROSC = return of spontaneous circulation.

the overall group) were suitable for decannulation ($p = \text{NS}$). All animals meeting criteria for decannulation at hour 4 also met criteria at hour 5.

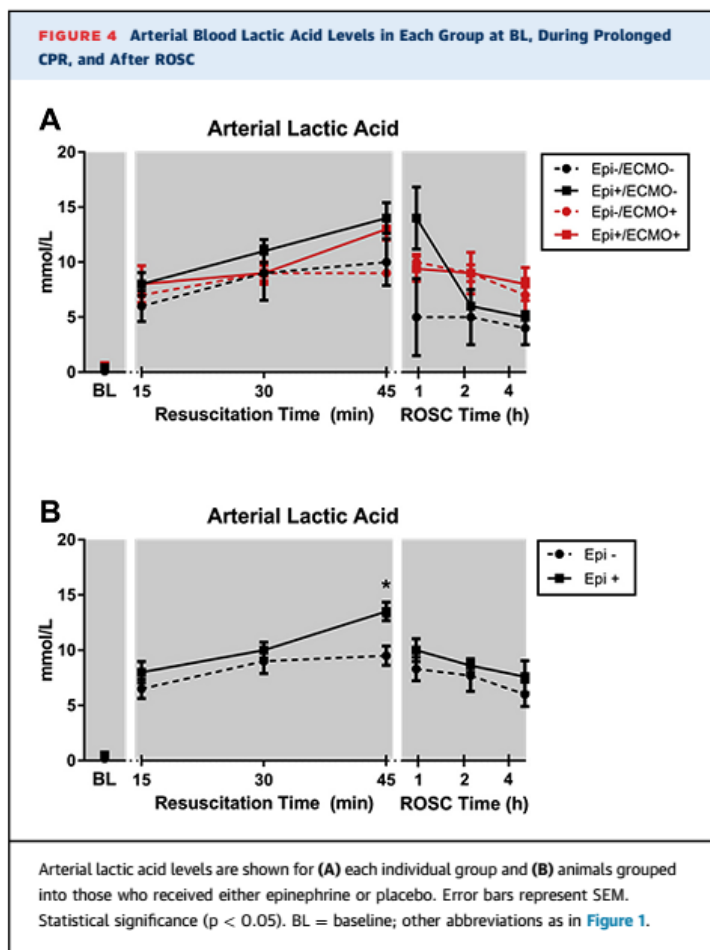
DISCUSSION

This study demonstrates that ECMO-facilitated reperfusion significantly improves short-term survival compared with CPR-facilitated reperfusion without ECMO support in the setting of refractory VF caused by coronary ischemia. Our study helps substantiate the scientific hypothesis providing the foundation for the MRC protocol (2).

In addition, this study shows that the use of EPI in the setting of ischemic refractory VF offered no advantage, as it failed to improve survival or ROSC rates compared with placebo. Further, EPI-treated animals had higher arterial blood lactic acid levels at the completion of the ACLS period before ECMO initiation or LAD reperfusion. Higher arterial lactic acid level was associated with worse prognosis in our clinical MRC protocol (2) and could be considered a marker for poor outcomes.

Cardiac function was similar in surviving animals of all groups. Even animals that did not have ECMO support had some degree of acute left ventricular function recovery within 4 h. The number of surviving ECMO- animals was small (1 for EPI+ and 4 for EPI- treated animals), preventing statistical comparisons. Cardiac functional recovery as assessed by LVEF was significantly faster (4 h) than that observed for humans encountering a similar injury in our MRC protocol (≥ 72 h) (2). This significant difference in our porcine model may limit the translation of cardiac function recovery results to humans.

Several previously published studies have evaluated ECMO as a resuscitation tool in different animal models of CA (10-16). They found improved clinical outcomes using ECMO, but the experimental models did not attempt to reproduce refractory CA triggered by acute myocardial infarction. Coronary ischemia is an important aspect of our model because it is the main cause of VF CA (17,18). Further, presence of arterial occlusion influences ROSC rate (19). Timing of coronary reperfusion and resulting degree of



myocardial damage also potentially influence subsequent left ventricular functional recovery (19,20).

Prolonged CPR (45 min) was associated with a very low ROSC rate in the ECMO- group. Prolonged CPR combined with coronary ischemia decreases the probability of ROSC in humans (20,21). The significant ROSC rate and subsequent survival advantage in the ECMO+ group seen in our study supports the use of ECMO-facilitated PCI compared with CPR-facilitated PCI. This is an important finding because the role of ECMO in human CA is debated, with no randomized studies, and retrospective studies yielding conflicting results (22). Further, this experimental model provides an avenue for additional refinement and experimentation with regard to the therapies provided.

Lactic acid level on arrival to the CCL has been associated with poor outcomes in our MRC protocol experience (2). In this animal study, all surviving animals demonstrated improving lactic acid levels. However, the significant attrition of animals in the

ECMO- groups over time likely selects for lower lactic acid levels, thus producing falsely normalizing values. Despite having higher CPP and aortic pressures, animals that received intravenous EPI during the ACLS phase had higher lactic acid levels at 45 min of CPR. This may represent reduced overall perfusion during CPR, reduced local perfusion due to vasoconstriction, increased transport of lactic acid out of tissues (23), or enhanced glycolysis induced by EPI (24). ECMO+ animals exhibited improving lactic acid levels during the 4 h post-ECMO. However, the rate of decline in arterial lactic acid levels was reduced compared to the surviving animals without ECMO. This may be due to the ability of ECMO to salvage animals that have sustained a more severe injury, whereas those animals do not survive in the ECMO- group. Alternatively, the arterial ECMO cannula may be partially or totally occluding the common femoral artery in ECMO+ animals, leading to leg ischemia and lactic acid production. Whereas in humans a distal perfusion cannula would be placed in the superficial femoral artery distal to the access for the large arterial cannula, the distal vasculature is too small to accommodate this in pigs, leaving their limb potentially ischemic.

STUDY LIMITATIONS. This study has several limitations. First, our animal model may have limited translatability to humans, despite remarkable similarities to our MRC clinical population.

The model of coronary ischemia imperfectly represents real-life conditions, with simulated revascularization consisting only of balloon deflation. To our knowledge, no model incorporating atherosclerosis, calcification, or thrombus associated with coronary occlusion is currently available in pigs (25,26). In addition, no defibrillations were provided during the ACLS phase, resulting in prolonged resuscitation for all animals. This may cause inclusion of animals that would otherwise have achieved ROSC, which may reduce the observed injury and minimize the differences between groups. This would likely limit the observed effectiveness of ECMO. Prior studies performing standard ACLS in this same model of ischemic VF have demonstrated a low ROSC rate, suggesting a minimal impact in this study (3). This may also eliminate the injury typically caused by repeated defibrillation in clinical situations. Although this injury is not thought to be the predominant factor in cardiac dysfunction after prolonged CA, its contribution cannot be assessed in this study. All animals were treated the same with regard to defibrillation, independent of their treatment group, such that comparisons represent the effects of the experimental treatments. The use of anesthesia, required

for animal studies, may also limit the differences observed in the study. Inhaled anesthetic agents, including isoflurane, which was used in this study, can provide cardioprotective effects (27). As this was used consistently in all animals, it may negate differences in cardiac outcomes observed between the 2 groups. In addition, this study did not include neurologic assessment. Potential leg ischemia caused by ECMO cannula femoral artery occlusion complicates assessment of long-term survival. However, the size of the pigs used for the study was limited, as larger pigs have very long torsos, such that the venous ECMO cannula cannot drain the right atrium reliably, and smaller animals have prohibitive femoral artery sizes for cannulation. Finally, this study might have been underpowered for an interaction between EPI and ECMO in survival given the minimal effect and trend toward worse outcomes observed with EPI.

CONCLUSIONS

ECMO-facilitated coronary reperfusion significantly improved 4-h survival compared with CPR-facilitated reperfusion in a pig model of ischemia-induced refractory VF CA and prolonged CPR. ECMO support enabled cardiac recovery and hemodynamic stability within 4 h. EPI use during prolonged CPR did not affect survival.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CA causes severe systemic injury, which worsens as the duration of resuscitation efforts increases. ECMO has been used to provide hemodynamic support to halt progressive injury and bridge the patient to recovery after prolonged refractory CA. Stabilization with ECMO also allows further diagnostic and therapeutic interventions including coronary angiography to proceed to address the underlying etiology of the CA. EPI, commonly used during resuscitation efforts, may not provide benefit during prolonged arrest when the effects of repeated EPI doses may cause additional injury.

TRANSLATIONAL OUTLOOK: ECMO significantly improves short-term survival with hemodynamic stabilization after refractory VF CA and prolonged CPR. Although further studies are necessary to assess the potential long-term benefits, 53% of animals treated with ECMO were stable for decannulation at 4 h supporting the use of ECMO as a temporary bridge to recovery. EPI use did not provide any benefit to survival in this model of prolonged CA. As ECMO is more widely incorporated into clinical care and treatment of prolonged CA becomes feasible, reassessment of commonly used therapies will be necessary to evaluate their effects in prolonged arrest.

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4.3 Discussion

Cette étude a montré pour la première fois dans un modèle d'AC réfractaire chez le cochon que l'utilisation de l'ECLS améliore la survie, et que l'adrénaline en bolus répétés n'est pas associée à une amélioration du pronostic.

Le modèle d'AC réfractaire chez le cochon utilisé dans cette étude est très proche de la pathologie humaine. Nous avons d'abord réalisé un infarctus du myocarde expérimental par inflation d'un ballon au niveau de l'artère interventriculaire antérieure suivi d'une période de fibrillation ventriculaire sans massage cardiaque pendant 5 minutes correspondant à la période de no-flow. Cette période a été suivie d'une réanimation cardiopulmonaire de 10 minutes correspondant aux premiers secours accordés par les témoins et ensuite d'une période de 35 minutes de « advanced life support » correspondant à la réanimation cardiopulmonaire réalisée par les professionnels de santé(138). Cette période de 35 minutes a fait l'objet d'une première randomisation avec un groupe traité avec des bolus d'adrénaline et un groupe traité sans adrénaline. A la fin de cette période la revascularisation de l'infarctus du myocarde a été réalisée par déflation du ballon au niveau de l'artère interventriculaire antérieure(154). A la suite de cette période une deuxième randomisation a été réalisée pour le traitement par ECLS. Dans le groupe réanimation cardiopulmonaire conventionnelle, celle-ci a été continuée par des chocs électriques externes et bolus d'adrénaline pendant encore 15 minutes selon les recommandations. A la suite de cette période, les cochons ont été déclarés morts si aucune reprise de circulation spontanée n'a été observée. Le groupe ECLS a bénéficié du support par l'assistance circulatoire.

Cette étude a montré que l'ECLS améliore la survie dans ce modèle d'AC réfractaire proche de l'AC réfractaire humain(153–157), résultat expliqué par la capacité de l'ECLS de générer un débit circulatoire suffisant pour assurer la perfusion systémique d'organes, y compris la perfusion cardiaque. Cette stratégie a permis une reprise d'une circulation spontanée chez tous les cochons traités par ECLS.

Le deuxième résultat important de cette étude est l'absence d'amélioration de la survie par

l'utilisation de l'adrénaline. L'adrénaline permet par son effet vasoconstricteur et inotrope positif d'améliorer la perfusion systémique en cas de reprise d'une circulation spontanée. Dans une étude randomisée chez l'homme, l'adrénaline a permis d'améliorer la reprise d'une circulation spontanée sans améliorer la survie(58). Notre étude suggère que son utilisation dans l'AC réfractaire dû à une fibrillation ventriculaire n'améliore pas la survie, et permet de formuler l'hypothèse que l'adrénaline n'est pas indispensable à la réanimation cardiopulmonaire de ces patients. Ce résultat pourrait être expliqué par l'effet de l'adrénaline sur l'augmentation de la consommation d'énergie au niveau tissulaire et la production excessive d'acide lactique qui pourrait avoir un effet délétère dans les réanimations cardiopulmonaires prolongées. Les résultats de cette étude expérimentale sont à confirmer par des études randomisées en clinique humaine.

5 Canulation percutanée en salle de coronarographie pour la mise en place d'assistance circulatoire chez les patients en arrêt cardiaque réfractaire – travail observationnel

5.1 Introduction

Si la décision de mettre en place une assistance circulatoire en urgence est prise devant la présence d'un AC réfractaire(129,130,132,135,142–144), les options de canulation des vaisseaux fémoraux sont la canulation chirurgicale(132,135,144,160) et la canulation percutanée(130,134,137,138,161,162). La plupart des études françaises(132,135,144,160) ont utilisé la technique chirurgicale qui permet d'exposer par dissection, la veine et l'artère fémorales et d'introduire les canules veineuse et artérielle par la technique de Seldinger sous contrôle de la vue. Cette technique est précise mais nécessite la présence d'un chirurgien vasculaire ou d'un médecin réanimateur ou urgentiste ayant suivi une formation chirurgicale spécifique(132,163). La canulation percutanée est réalisée par la technique de Seldinger sans dissection chirurgicale, et présente la difficulté du cathétérisme artériel et veineux fémoral chez des patients sous massage cardiaque qui ne présentent pas de pouls artériel. Une étude française utilisant la canulation percutanée avec ponctions vasculaires selon des repères anatomiques(159), a rapporté des taux de réussite de 75% chez les patients en AC réfractaire sous massage cardiaque, suggérant que cette technique nécessite une amélioration. Plus récemment, la ponction vasculaire guidée par échographie doppler a été utilisée dans plusieurs études avec des taux de succès de canulation jusqu'à 100%(134,137,138).

Dans notre centre, nous avons réalisé initialement les ponctions vasculaires pour canulation percutanée selon les repères anatomiques, mais depuis Novembre 2015, cette procédure a été réalisée sous contrôle échographique et en utilisant également des guides rigides, différents de ceux fournis par les fabricants des canules. Ces guides rigides présentent moins de risque d'être pliés lors de l'introduction des canules et pourraient rendre ainsi la procédure plus rapide. Nous avons donc

réalisé une étude observationnelle rétrospective, comparant la faisabilité et les délais de canulation dans la première période (ponctions fémorales selon des repères anatomiques et des guides standard) avec la deuxième période (ponctions écho-guidées et des guides rigides), chez les patients en AC réfractaire, dans notre centre.

5.2 Percutaneous extracorporeal life support in the catheterization laboratory for refractory cardiac arrest in a center without on-site cardiovascular surgery

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Abstract

Background

Cardiac arrest (CA) without return of spontaneous circulation can be treated with veno-arterial extracorporeal membrane oxygenator (vaECMO) as last resort life-saving therapy, implemented by surgical or percutaneous technique. Since surgeons are not always available for such procedures, we performed a study assessing feasibility and time for vaECMO percutaneous cannulation in the catheterization laboratory in patients with refractory CA.

Methods

Single-centre retrospective study in a University hospital in Paris without on-site cardiovascular surgery, including patients aged >18 receiving vaECMO for out- or in-hospital refractory CA (defined as >15 minutes of arrest despite advanced life support) between 2010 and 2016. Cannulation was performed in the catheterization laboratory by trained interventional cardiologists. Cannulation time in the first study period using anatomic landmarks vessel puncture and conventional wires was compared with the second period cannulation time, using ultrasound guided vessel puncture and stiff wires. Data are expressed as medians (interquartile range) and percentages, and compared using Mann-Whitney test and Fischer's exact test.

Results

Forty five patients were included, age 56 (49-62), 34 in the first period. Shockable initial rhythm occurred in 28 (62%) patients, 25 (56%) had acute myocardial infarction. Out-of-hospital refractory CA occurred in 27 (60%) cases. Time from out-of-hospital refractory CA to admission was 100 (80-118) minutes.

Cannulation was successful in 41 (91%) patients. Cannulation time was 14 (10-21) minutes overall, 17 (12-26) in the first period and 8 (6-12) minutes in the second period ($p=0.0005$). Three patients survived, overall survival to discharge was 7%.

Conclusion

In patients receiving vaECMO for refractory CA, rapid percutaneous cannulation is feasible in the catheterization laboratory using ultrasound guidance and stiff wires in a centre without on-site vascular surgery.

Introduction

Out-of-hospital cardiac arrest (CA) is associated with high mortality when return of spontaneous circulation is achieved after resuscitation measures(1,2), and a much more severe prognosis when the out-of-hospital CA is refractory and no return of spontaneous circulation occurs despite well-performed advanced life support(3–5). When appropriate resuscitation does not restore spontaneous circulatory function, patients are declared deceased unless life-saving measures such as veno-arterial extracorporeal membrane oxygenator (vaECMO) devices are used(6).

VaECMO devices are supplanting circulatory and pulmonary function and are connected to the patient through arterial and venous cannulae inserted in refractory CA patients in the femoral vessels under cardiopulmonary resuscitation(6,7).

The insertion of the vaECMO cannulae can be performed by the surgical technique using femoral dissection(3–5,8,9) or by the percutaneous technique in the catheterization laboratory under fluoroscopic guidance(10–14).

Since 2005, in our center, vaECMO support is implemented in refractory CA patients using surgical cannulation performed by medical doctors who underwent training by vascular surgeons in this technique(4), but more recently, refractory CA patients receive cannulation for vaECMO support by the percutaneous technique, performed by interventional cardiologists. The puncture of the femoral vessels was initially performed in our centre using anatomic landmarks, and the insertion of the cannulae was performed by the Seldinger technique using conventional wires provided by the manufacturers of the cannulae. More recently, we used ultrasound-guided puncture of the femoral vessels and stiff wires in an attempt to improve cannulation delays. Several studies evaluated the results of the vaECMO inserted by the percutaneous technique with variable success rates(10–14), but no precise analysis of strategies improving cannulation delays were performed.

We therefore performed a retrospective study analyzing the feasibility and time interval required for percutaneous cannulation for vaECMO in refractory cardiac arrest patients in the two strategies.

Our hypothesis was that cannulation using ultrasound guidance and stiff wires may be faster than anatomic landmark cannulation using standard wires.

Methods

This single-centre retrospective study was performed in Lariboisière University Hospital in Paris. The ethics committee of our institution approved the study and informed consent from the patients or the next of kin was not required. The study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association.

Patients

Patients were included in the present analysis if they presented with refractory CA of presumed cardiac cause and vaECMO support was attempted by the percutaneous technique. The inclusion period was between March 2010 and October 2016.

We excluded patients who had stable return of spontaneous circulation at cannulation, patients who had cardiac arrest of non-cardiac etiology such as poisoning, hypothermia, septic or hemorrhagic shock etc. In general, patients in our centre are eligible to receive vaECMO if they don't present with unfavorable prognostic criteria according to data in the literature such as major comorbidities, lactate concentration >16 mmol/L, end-tidal CO₂ <10 mmHg on admission, time interval from the collapse of the patient to the beginning of cardiopulmonary resuscitation >5 minutes(4,15). However, given the retrospective nature of the study no strict criteria were pre-established.

Patients were identified after analyzing the hospital database containing the medical records of all hospitalized patients.

VaECMO assistance device, cannulation technique and rationale for the two-period analysis

In our centre, the circulatory assistance device used is Maquet Rotaflow[®] pump, (Hirrlingen, Germany) using Rotaflow Maquet BE-PLS circuit (Rastatt, Germany). Cannulation was performed preferably in the in the right femoral vessels using venous 21, 23 or 25 French BE-PVL cannulae and arterial 15, 17 or 19 French BE-PAL cannulae (Maquet, Rastatt, Germany), using the Seldinger

technique.

Cannulation was initially performed using anatomic landmarks for the puncture of the femoral vessels and the conventional wires included by the manufacturer in the cannulae kits until November 2015 (first period). Starting December 2015, the puncture of the vessels was performed under ultrasound guidance (second period) and cannulae were inserted over stiff wires, Amplatz Super Stiff™, Boston Scientific, Marlborough, MA, USA. Ultrasound-guided puncture was introduced because during some anatomic landmark procedures, the artery and/or vein were difficult to wire, thus prolonging the procedure and potentially exposing to more cannulation failure. Stiff wires were introduced to avoid wire bending during cannulae insertion, and thus avoid prolonging further the cannulation procedure. This decision was made following several cannulations in the first period during which wires bent and required changing, thus prolonging cannulation time.

After predilatation, the cannulae were inserted in the corresponding vessel over the wire, then the wire was withdrawn and the cannulae were rinsed with saline, clamped and connected to the ECMO circuit.

Cannulation time was defined as time interval before the first puncture of the patient's skin and the end of the insertion of the cannulae.

After initiation of vaECMO support, distal perfusion of the cannulated femoral artery was insured by an antegrade 4F catheter. After the ECMO initiation, coronary angiogram was performed using the standard technique preferably by radial access and angioplasty was performed if indicated as previously described(16,17).

Management of the patients

Management of the OHCA patients in Paris has been previously described(16,17). Briefly, ambulances provided with resuscitation material (intubation, ventilation, intravenous access and catecholamines) and staffed by physicians are dispatched to the cardiac arrest site. The ambulances

may be preceded by firefighters who are able to provide basic life support, defibrillation and oxygen until the arrival of the medical personnel. When no return of spontaneous circulation was achieved despite well-performed advanced life support, the medical staff on site made the decision to transport the patient to the hospital for vaECMO. The hospital staff admitting the patients did not interfere with this decision. The time spent on site by the emergency medical team was at the discretion of the physician in charge. Patients were transported to the hospital under chest compressions using a LUCAS[®] device and mechanical ventilation.

On admission to the hospital, patients were received in the catheterization laboratory by two interventional cardiologists and two intensive care doctors. If the decision to perform vaECMO support was made according to the aforementioned criteria, cannulation as described was performed, and the circulatory assistance was begun as soon as possible.

After insertion, the vaECMO cannulae were connected to the circuit and the pump was started at >3000 rotations/min in order to achieve an output of at least 3.0 L/min. The oxygen fraction in the oxygenator was between 100% and 60% and the initial sweep was between 3 and 4 L/min according to the physician in charge.

After the vaECMO support initiation, the invasive arterial pressure was monitored and the intravenous infusion of norepinephrine was titrated to obtain mean arterial pressure higher than 65 mmHg.

Subsequently, patients were transferred to the medical intensive care unit where they received standard care ensuring appropriate temperature control at 33° C, ventilation to normalize oxygen and CO₂ arterial partial pressure(18), transfusion to maintain hemoglobin to at least 7 g/dl as well as normalization of glucose and electrolytes, and treatment of occurring infections.

Survival was assessed using the Cerebral performance Category score(19).

Statistical analysis

Numerical variables are expressed as medians and interquartile range (IQR) and categorical variables as percentages. Comparisons between numerical variables were performed using Mann-

Whitney test and categorical variables using Fisher's exact test. Statistical analysis was performed using MedCalc®, version 11.0.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Forty five patients were included in the analysis during the study period from 2010 to 2016. In the first period of the study from 2010 to November 2015, 34 patients were included (76%) and 11 (24%) patients were included in the second period. The flow chart of the patients is represented in Figure 1. Eighteen patients had in-hospital refractory CA. The overall characteristics of the patients and of the CA are shown in table 1.

Cannulation data

All patients received percutaneous cannulation while in refractory cardiac arrest under cardiopulmonary resuscitation. Different time intervals were recorded, including time from CA to vaECMO support, time spent on site by the emergency medical staff, time required for transfer to the hospital, and are expressed in Table 2. The rate of success of the implantation of vaECMO was 91% overall, due to four failures to cannulate, all in the first period, three due to the impossibility to insert the venous cannula and one the arterial cannula over the wire into the vessels. Cannulation success rate in the first period was 88% and in the second period 100% ($p=0.56$)

Cannulation time was 14 (10-21) min in the overall population, significantly longer 17 (12-26) min in the first period (data known in $n=22$ patients) versus 8 (6-12) min in the second period (data known in $n=8$ patients), $p=0.0005$. The time required for surgical cannulation in patients in similar circumstances in our centre was 15 (14-20) minutes, longer than percutaneous cannulation time in the second period ($p=0.01$). Distal femoral perfusion catheter insertion in the cannulated femoral artery was successful in all patients. It was not attempted in 3 patients due to optimal antegrade perfusion documented by doppler analysis.

Coronary angiogram showed acute myocardial infarction in 25 patients (56%), 92% of the

attempted angioplasty procedures were successful.

Outcome

Overall survival to hospital discharge was 7% (3 survivors), 1 in the first period (3%) and 2 (18%) in the second period. Among patients with out-of hospital cardiac arrest 2 survived (7%), while among the 12 in-hospital cardiac arrest patients 1 survived (6%). All survivors were CPC 1 and were discharged from the hospital after 23, 56 and 79 days, their individual characteristics are shown in Table 3. Besides the 3 survivors, another patient was decannulated and weaned from the respirator but died later in the hospital of complications of vegetative state.

All survivors had shockable initial rhythm, survival of the patients in the shockable rhythm group was 11% versus 0% in non-shockable initial rhythm patients ($p=0.54$).

Hospital stay of deceased patients was 1 (1-1) day, 6 patients met the criteria for brain death and among them 2 were referred for organ donation. Multi organ failure associated with refractory shock and impossibility to maintain ECMO output despite massive fluid repletion was present in 24 (57%) of the 42 deceased patients at the time of death.

Bleeding at the cannulation site requiring transfusion occurred in 9 (20%) patients. No surgical procedure was required for the bleeding at the site of cannulation. No acute ischemia of the leg related to the cannulated femoral artery was observed and no infections of the cannulated site occurred.

In one of the survivors, a short dissection of the common femoral artery on 2 cm length required femoro-femoral bypass at decannulation without further complications. In another survivor, a hematoma unrelated to the vaECMO but to the coronary angiogram introducer located in the contralateral femoral artery required repeat transfusions and two surgical interventions prolonging hospitalization to 79 days.

Discussion

The most important finding in our study was that cannulation time was significantly shorter in the second period of the study, when cannulation was performed using ultrasound-guided femoral vessel puncture and stiff wires. In addition, our study confirms the high incidence of coronary artery disease in the population of refractory cardiac arrest patients(14) and the null survival of the patients with asystole as initial rhythm, as found by previous studies(5,14).

This study is the first comparison of the two percutaneous cannulation strategies in refractory CA patients. One of the difficulties of cannulation is represented by the puncture of the femoral vessels in the absence of a palpable pulse which decreases the rate of success or prolongs cannulation time. Our study shows that ultrasound guidance and use of stiff wires significantly shortened the cannulation time which is a clinically significant parameter, as time to vaECMO support is a significant prognostic factor in this population according to previous data(11). Moreover, ultrasound guidance also allows for the selection of the most appropriate femoral vessels (right or left) in case of severe atherosclerosis and allows to select the vessels with the most appropriate anatomical situation as previously suggested(14,20). Time interval required for cannulation especially in our second period compares favorably to the surgical implantation time in our centre, but a very short vaECMO initiation time of only 5 minutes was reported in a recent percutaneous cannulation study, suggesting this time interval could be shortened even further(14).

The high rate of success and the short cannulation time especially in the second period is a significant finding showing the technique is improving, and shorter cannulation time and less failure to cannulate may encourage a more widespread use of the technique in other catheterization laboratories. More generalized, rapid and reliable percutaneous cannulation and vaECMO support could be a major advance not only in the management refractory CA patients but also in refractory cardiogenic shock in the catheterization laboratory associated with acute myocardial infarction and/or severe coronary heart disease(21,22).

The high success rate of the percutaneous technique in our study and in other studies in the

literature(13,14) is in favor of the feasibility of the ECMO support, even in the absence of a cardiovascular surgeon team on site, especially in the catheterization laboratory which allows for fluoroscopy confirmation of the placement of the wires and cannulae in the correct position.

Cannulation failure was reported in up to 25% in the percutaneous technique in refractory OHCA patients(10) and in 1,5% in the surgical technique(4), but cannulation success was also reported in 100 % studies in percutaneous(13,14) as well as surgical technique(8). Our data shows an encouraging success rate of 91% that may be improved by the use of ultrasound guidance and stiff wires.

Despite good results reported by recent studies(13,14), the use of vaECMO in refractory CA patients remains limited to relatively small number of centres. Factors limiting the more widespread use of vaECMO are the very poor survival of refractory CA patients and the lack of randomized trials in this setting, the high cost and the relatively complex logistics and difficulties in cannulation. The overall rate of survival in the present study is relatively low although in line with other French studies showing survival of 1.6-8.8%(3–5). Other groups reported survival rates between 33% and 53% probably due to a much shorter duration between the collapse of the patient and the admission to the hospital(11,13,14,23). Indeed, recent studies showed a much better survival, up to 53% if the time interval from CA to hospital admission are minimized and the ECMO is inserted in a short time interval thus decreasing the time from CA to vaECMO support to approximately 50 minutes(11,13,14). Survival in our cohort is much lower and this may be attributed to the very long delay from CA to vaECMO support in our patients which is approximately 110 minutes, accounted for in out-of-hospital patients mainly by the pre-hospital phase which in our population lasted 95 minutes. Therefore, even though cannulation time can be shortened using a more refined technical approach, this was not sufficient to improve mortality and efforts should be made to shorten the time interval from CA to hospital admission.

Our data confirms the extremely poor survival of patients with non-shockable initial rhythm which is 0% in our study as in a recent French study(5) suggesting that asystole as initial rhythm and/or at

cannulation, may be considered a contraindication to vaECMO in out-of-hospital CA patients without toxic or hypothermia etiology. Moreover, this data supports patient selection criteria in some recent studies considering non-shockable initial rhythms as an exclusion criterion(13,14). Since all patients in our study had coronary angiogram in order to diagnose and treat a suspected acute coronary syndrome, we were able to show that our population had a very high prevalence of significant coronary artery disease and acute coronary syndrome, as suggested by previous data(14).

Limitations

Our study compared two techniques of cannulation but it was not randomized, and the number of included patients was relatively small. Since patients in the two groups were included in two consecutive periods, the reduction of cannulation time may have been influenced not only by the change in the technique but also by the “learning curve”. Unfortunately, its role in the reduction of cannulation delays is difficult to quantify. Unfortunately, cannulation delays are missing in some cases, due to the difficulties of recording precisely time intervals in the emergency situation of refractory CA. Our study confirmed the poor survival in this setting compared to more recent data, but given the limited number of survivors, no statistical comparisons in search of prognostic factors of survival could be performed.

Finally, our data showed a shorter cannulation time in the second period, but it could not assess the impact of cannulation delays on survival due to its limited sample size and the reduced number of survivors, therefore future larger studies are needed to address this issue.

In conclusion, our study shows that percutaneous cannulation time for vaECMO support in refractory CA patients can be achieved rapidly when using ultrasound guidance and stiff wires encouraging the use of percutaneous cannulation techniques, but overall survival remains low and future efforts are required to reduce delays to vaECMO support, improve patient selection and overall outcome in this population.

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Table 1 Characteristics of the patients and of the cardiac arrest at baseline and on admission

	Overall population n=45	First period n=34	Second period n=11	p
Age (years)	56 (49-62)	56 (50-66)	52 (24-60)	0.14
Male gender	37 (82)	28 (82)	9 (82)	1.0
Body weight (kg)	80 (73-93)	85 (79-97)	75 (65-84)	0.051
Risk factors (n=40)				
Tobacco smoking	20 (44)	17 (50)	3 (27)	0.16
Diabetes	5 (11)	5 (15)	0 (0)	0.29
Hypertension	17 (38)	13 (38)	4 (36)	0.72
Hypercholesterolemia	15 (33)	14 (41)	1 (9)	0.01
Out-of-hospital arrest	27 (60)	18 (53)	9 (82)	0.16
Witnessed arrest	42 (93)	32 (94)	10 (91)	0.44
Witness performing cardiopulmonary resuscitation	36 (80)	26 (76)	10 (91)	0.66
Initial rhythm (n=43)				
Shockable initial rhythm	28 (62)	20 (59)	8 (73)	1.0
Ventricular fibrillation	26 (58)	18 (53)	8 (73)	0.48
Ventricular tachycardia	2 (4)	2 (6)	0 (0)	1.0
Non-shockable initial rhythm	15 (33)	12 (35)	3 (27)	1.0
Asystole	10 (22)	8 (24)	2 (18)	1.0
Pulseless electrical activity	5 (11)	4 (12)	1 (9)	1.0
Number of electric shocks	3 (1-7)	3 (1-7)	4 (1-7)	0.80
No flow (n=32)	1 (0-5)	1 (0-4)	1 (1-6)	0.42
Low flow (n=42)	95 (70-122)	85 (70-120)	115 (79-138)	0.18
Initial lactate	15 (10-17)	15 (11-17)	16 (9-17)	0.85
Initial arterial pH	7.0 (6.8-7.1)	7.0 (6.8-7.1)	6.9 (6.8-7.3)	0.88
Initial creatinine	128 (100-146)	130 (103-144)	120 (97-146)	0.49

Numerical data are expressed as medians (interquartile range) and categorical data as numbers (percentages of the total population).

Table 2 Time intervals to vaECMO support and outcome of the patients

	Overall population n=45	First period n=34	Second period n=11	p
Time spent on site by emergency medical personnel (out-of hospital arrest) (n=20)	52 (46-66)	50 (45-59)	56 (50-72)	0.46
Time required for hospital transfer (out-of hospital arrest) (n=18)	13 (8-18)	11 (5-17)	12 (10-18)	0.45
Time from out-of-hospital arrest to hospital (n=20)	100 (80-118)	95 (75-113)	115 (102-124)	0.08
Cannulation time (n=30)	14 (10-21)	17 (12-26)	8 (6-12)	0.0005
Time from hospital arrival to vaECMO support (n=27)	41 (35-51)	45 (38-54)	35 (29-36)	0.025
Time from arrest to vaECMO support (n=36)	106 (72-132)	101 (71-124)	116 (82-141)	0.34
Successfully implanted vaECMO	41 (91)	30 (88)	11 (100)	0.56
Acute myocardial infarction	25 (56)	20 (59)	5 (45)	0.5
Survival to discharge	3 (7)	1 (3)	2 (18)	0.14

Numerical data are expressed as medians (interquartile range) and categorical data as numbers

(percentages of the total population).

Table 3 Characteristics of the three survivors

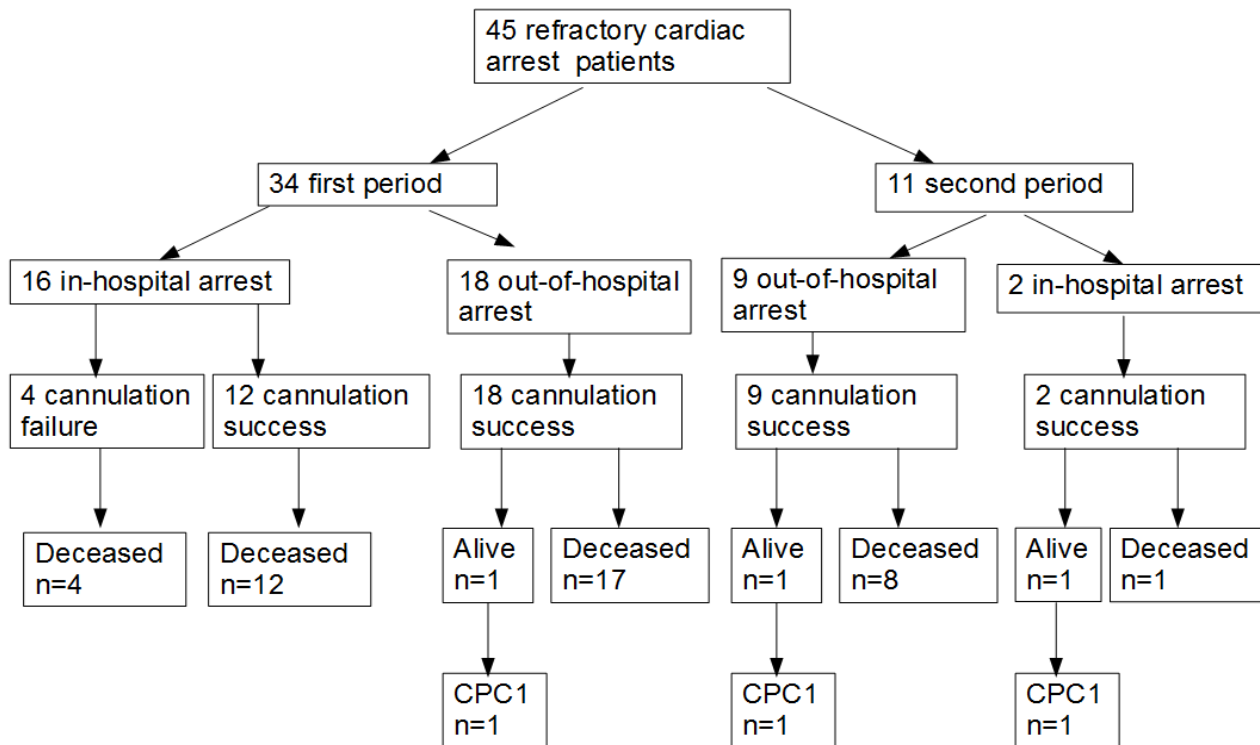
	Survivor 1	Survivor 2	Survivor 3
Age (years)	60	21	61
Out-of hospital arrest	1	1	0
No-flow (minutes)	1	4	0.5
Low-flow (minutes)	86	105	55
Time from arrest to vaECMO support (minutes)	86	109	56
Time spent on site by the emergency team (minutes)	38	35	NA
Cannulation time (minutes)	-	5	11
Initial lactate concentration (mmol/L)	11	12	8
ETCO ₂ at cannulation (mmHg)	-	26	32
Cause of cardiac arrest	AMI	HCM	AMI
Left ventricular ejection fraction at discharge	42%	65%	50%
Cerebral performance score at discharge	1	1	1
Day of hospital discharge	56	23	79

VaECMO-veno-arterial extracorporeal membrane oxygenator; NA-not attributed; “-” - missing

data; ETCO₂ – end-tidal CO₂; AMI – acute myocardial infarction; HCM – hypertrophic

cardiomyopathy. See text for definitions of no-flow and low-flow.

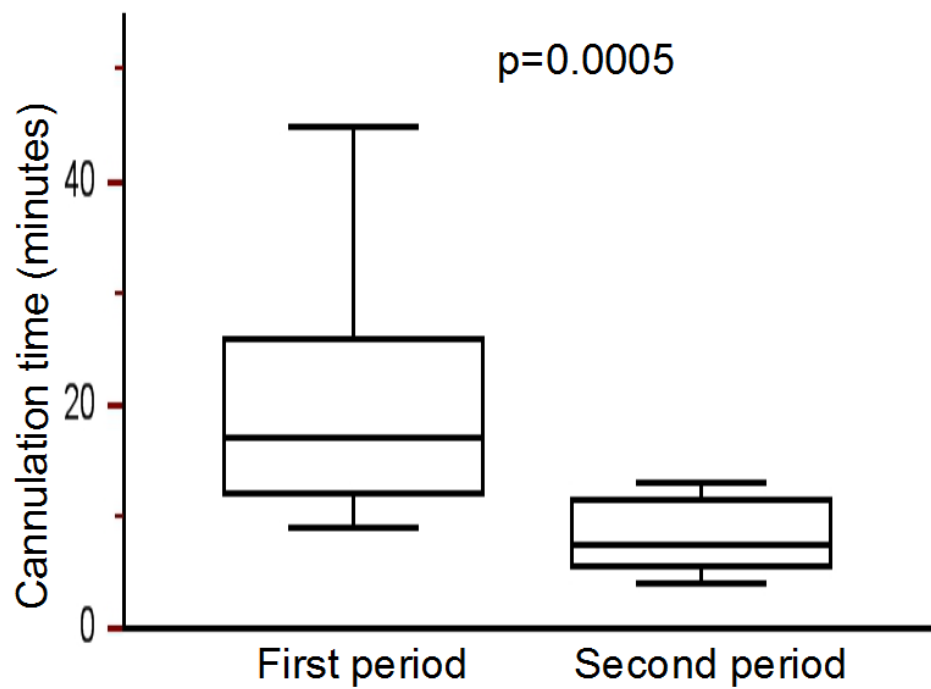
Figure 1 Flow chart of the included patients



CPC - cerebral performance category

Figure 2

Cannulation time from puncture to cannulae insertion in the two periods of the study, before and after the use of stiff wires and ultrasound guidance



The first period is defined by femoral vessel puncture based on anatomic landmarks and the use of regular wires. The second period is defined by ultrasound-guided femoral vessel puncture and the use of stiff wires. Cannulation time is expressed in minutes. See text for further explanations.

5.3 Discussion

Cette étude a montré que la canulation percutanée est plus rapide lorsque la ponction vasculaire est réalisée sous contrôle échographique et l'introduction des canules est réalisée à l'aide de guides rigides. Cette étude a également confirmé l'absence de survie des patients qui ont présenté un AC avec un rythme non choquable, donnée mise en évidence par une étude française récente(135).

La durée de canulation a été d'environ 8 minutes et le taux de succès en utilisant cette méthode a été de 100%, par rapport à 88% dans la première période, sans différence significative de succès entre les deux techniques. Même si la différence entre les deux périodes en termes de succès de canulation n'a pas été significative, une amélioration du taux de succès par le repérage échographique et l'utilisation de guides rigides ne peut pas être exclue, car le nombre de patients inclus dans la deuxième période est relativement restreint (11 patients). Cette étude permet donc d'envisager la canulation percutanée comme une solution permettant de mettre en place rapidement une assistance circulatoire type ECLS chez les patients présentant un AC réfractaire en absence d'un chirurgien vasculaire sur place. Le repérage échographique, l'utilisation de guides rigides et la possibilité de vérifier la bonne position des guides par fluoroscopie avant l'insertion des canules sont des facteurs qui permettent de réaliser avec plus de sécurité la canulation des vaisseaux en salle de coronarographie. Cette procédure permet donc de rendre plus généralisable le support hémodynamique par ECLS à des laboratoires de cardiologie interventionnelle dans des centres non dotés de chirurgie vasculaire, dans des conditions d'urgence en cas d'AC réfractaire extra-hospitalier(134,137,138) ou intra-hospitalier(140,141), ou en état de choc cardiogénique réfractaire au traitement bien conduit par catécholamines(102,164).

Cette étude est actuellement en cours de préparation pour soumission à la revue Eurointervention.

6 Facteurs identifiant le risque de décès par insuffisance circulatoire après un arrêt cardiaque récupéré – travail observationnel

6.1 Introduction

Après un AC réanimé avec succès, l'insuffisance circulatoire est responsable de 23% à 35% des décès(7,74), malgré le traitement par catécholamines bien conduit. Le décès survient avant de pouvoir réaliser une évaluation neurologique des patients, dont une partie présente potentiellement un état neurologique compatible avec la survie. Cette insuffisance circulatoire qui persiste ou récidive, peut se manifester par des récidives d'AC, ou par la diminution de la perfusion d'organes et l'apparition progressive d'une insuffisance rénale, hépatique, l'apparition de troubles de la coagulation et finalement d'une insuffisance multiple d'organes(10). L'insuffisance circulatoire peut également aggraver les lésions neuronales par un débit cérébral faible. Chez ces patients, le fait d'assurer une pression artérielle et un débit circulatoire adaptés, pourrait éviter les effets délétères de l'hypoperfusion d'organes. Ceci pourrait diminuer le risque de décès de cause circulatoire, assurer une meilleure perfusion cérébrale, et permettre d'évaluer sur le plan neurologique les patients après la levée du contrôle thermique et de la sédation(73). Cette amélioration de la fonction circulatoire peut être réalisée avec des moyens d'assistance circulatoire, notamment l'Impella®, assistance ventriculaire gauche, et par l'ECLS, assistance cardiaque droite et gauche et pulmonaire. Comme ces moyens d'assistance présentent des effets adverses liés à leur implantation et à leur fonctionnement, il est difficile de concevoir leur utilisation chez tous les patients présentant un état de choc après réanimation cardiopulmonaire, des critères de sélection étant nécessaires pour identifier les patients qui pourraient en bénéficier avec un rapport bénéfice-risque favorable.

Pour répondre à la nécessité de critères de sélection des patients, nous avons réalisé une étude

observationnelle concernant les facteurs prédictifs de décès de cause circulatoire après un AC. Une partie des patients a été incluse dans une cohorte rétrospective permettant de déterminer ces facteurs sous forme d'un score issu d'une analyse multivariée. Une autre partie des patients a été incluse dans une cohorte prospective permettant de vérifier les performances de ces critères. Cette analyse a été faite sur des paramètres cliniques et biologiques mesurés à l'arrivée des patients à l'hôpital pour pouvoir prendre le plus rapidement la décision de l'assistance circulatoire et éviter ainsi l'aggravation des patients par l'hypoperfusion d'organes prolongée.

6.2 Can mortality due to circulatory failure in comatose out-of-hospital cardiac arrest patients be predicted on admission? A study in a retrospective derivation cohort validated in a prospective cohort



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Can mortality due to circulatory failure in comatose out-of-hospital cardiac arrest patients be predicted on admission? A study in a retrospective derivation cohort validated in a prospective cohort[☆]



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ABSTRACT

Purpose: Circulatory failure (CF) influences management of out-of-hospital cardiac arrest (OHCA) patients and the decision of circulatory assistance. We performed a study to identify on hospital admission patients at risk for CF-related death.

Materials and methods: This is a single-center study including OHCA patients without obvious extracardiac cause and sustained return of spontaneous circulation, in a retrospective derivation (RC) and prospective validation cohort (PC). Univariate/multivariate logistic regression was used in the RC to determine a score predicting CF-related death (due to re-arrest or persistent shock despite adequate fluid and catecholamine treatment). The score was validated in the PC.

Results: We included 207 patients in the RC and 96 in the PC. Circulatory failure occurred in 59% of RC and 63% of PC patients ($P = .70$); 35% in both cohorts died of CF. In multivariate regression, correlates of CF-related death making up the logistic score were arterial pH ($P < .0001$) and shock requiring catecholamines on admission ($P = .0045$). In the PC, for a logistic score cut-off of 0.5, sensitivity for CF-related death was 50%; specificity, 92%. Patients with shock and arterial pH less than or equal to 7.11 had a CF-related death probability greater than 0.5.

Conclusion: A logistic score based on arterial pH and shock requiring catecholamines on admission can predict CF-related death in OHCA patients.

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1. Introduction

Despite continuous efforts to improve outcome [1,2], many patients resuscitated from out-of hospital cardiac arrest (OHCA) die due to prehospital or inhospital re-arrest, due to the onset of shock during the first days of hospitalization, and later due to the complications of postanoxic brain injury [3]. Neurologic failure and circulatory failure (CF) are the most frequent modes of death of OHCA patients [3] after

resuscitation, and efforts should be made to improve circulatory and neurologic status to improve survival.

Circulatory failure is frequently present during the postresuscitation phase due to a high incidence of acute myocardial infarction (AMI) [2,4] and myocardial dysfunction and/or vasodilation caused by the postresuscitation syndrome [5]. The presence of CF is associated with increased mortality [6,7], but little data exist regarding patients in whom CF is the direct cause of death after resuscitation from OHCA. This is an important issue because the optimization of catecholamine therapy and the use of circulatory assistance devices may improve circulatory function and prognosis. In some patients, circulatory assist devices may allow for cardiac function improvement in reversible conditions such as revascularized AMI [8] or myocarditis. Even when CF is not fatal in the first hours after resuscitation, it may lead to multiple

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organ failure by inducing and/or worsening vital organ ischemia [9–11]; therefore, CF may represent an important therapeutic target.

Several predictors including blood pressure, lactate concentration, and the type and rate of infusion of catecholamines were reported as criteria for assessing severity of the CF [6,7]. Moreover, several studies attempted to predict death in OHCA patients by identifying prognostic factors and creating prognostic scores on admission or in the first days after the OHCA [12,13]. However, these studies attempted to predict inhospital death irrespective of the system failure that induced it (neurologic, circulatory, or other) and the question remains as to which patients will die of CF despite appropriate catecholamine treatment. Reversal of CF is more effective if initiated early during the hospital stay to avoid multiple-organ failure (MOF) [10,11], and these patients should be identified as early as possible. We therefore performed a study to determine on admission to the hospital the predictors of death due to CF in patients resuscitated from an OHCA. The study used a retrospective derivation cohort to determine a logistic score predictive of death due to CF and a prospective cohort to validate the results.

2. Materials and methods

This single-center observational study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The national French Ethics Committee approved the study (CE 11-330). According to the ethics committee recommendations, no signed informed consent was required from the patients or the next of kin. According to the French law, in the prospective cohort, information was provided to patients when conscious or the next of kin if patients remained unconscious. Patients were excluded if they or their next of kin refused participation in the study.

We screened all patients aged at least 18 years old admitted to our center for OHCA between January 2002 and October 2011. Patients were included irrespective of the initial rhythm of the OHCA. We excluded patients without sustained return of spontaneous circulation (ROSC), patients in whom the cardiac arrest occurred in the hospital or was obviously due to a noncardiac cause (including obvious hypoxemia, trauma, hemorrhagic or septic shock, drowning, hypothermia, and drug poisoning), and patients in whom the mode of death in the intensive care unit (ICU) could not be determined.

Inclusions were performed from 2002 to 2008 in the retrospective cohort and from 2009 to 2011 in the prospective cohort.

2.1. Management of the patients

The emergency medical system in Paris, France, has been previously described [14]. Resuscitation in the prehospital phase includes defibrillation, mechanical ventilation, venous access, and catecholamine treatment according to guidelines [15]. After effective resuscitation in the prehospital setting, the emergency team continues mechanical ventilation, sedation, and hemodynamic optimization using fluid repletion and/or catecholamine treatment. Blood pressure is measured noninvasively.

Presence of shock was defined in our study by the presence of systolic blood pressure less than 90 mm Hg despite at least 30 mL/kg fluid repletion [10]. Dobutamine, noradrenaline, or adrenaline is used in the prehospital phase according to the physician in charge to restore systolic blood pressure to greater than 90 mm Hg and mean blood pressure to greater than 65 mm Hg [15]. In the prehospital setting, adrenaline is the preferred drug especially in case of severe hypotension [10,15]. Out-of-hospital cardiac arrest patients with ROSC without an obvious noncardiac cause of arrest are transported to the cardiac catheterization laboratory for routine coronary angiogram and angioplasty if indicated. Patients with CF may receive intraaortic balloon pump (IABP) in the catheterization laboratory especially if AMI is present or an Impella assistance device according to the physician in charge.

In the ICU, ventilation is performed using the volume-controlled mode with tidal volumes of 6 to 8 mL/kg to achieve plateau pressure less than 30 cm H₂O. Positive end-expiratory pressure is initially set to 5 cm H₂O and is subsequently modified together with the inspired oxygen fraction to achieve an arterial O₂ partial pressure of 70 to 120 mm Hg. Respiratory rate is adjusted to achieve an arterial CO₂ partial pressure of 36 to 42 mm Hg [16].

Circulatory function in the ICU is monitored using an intraarterial catheter for continuous blood pressure monitoring as well as PiCCO, Vigileo, or echocardiography according to the physician in charge. If hypotension less than 90 mm Hg persists despite fluid repletion, catecholamine treatment is initiated [17]. In the inhospital phase, dobutamine is preferred in case of low cardiac output or low left ventricular ejection fraction, and noradrenaline is preferred in case of decreased systemic vascular resistance. The target mean arterial pressure is greater than or equal to 65 mm Hg, and the target systolic blood pressure is greater than or equal to 90 mm Hg. In case of CF requiring increasingly high catecholamine infusion rates in the ICU, patients may be treated with venoarterial extracorporeal life support (ECLS) according to age, comorbidities, and physiological status. Venoarterial ECLS is inserted by surgical technique in the ICU [18].

Therapeutic hypothermia (TH) is performed for all OHCA patients with ventricular fibrillation as initial rhythm but also nonshockable rhythms according to recommendations [15]. Therapeutic hypothermia is usually initiated on admission to the hospital using 30 to 50 mL/kg cold saline and then maintained for 12 to 24 hours using external (ice and cooling blankets) or endovascular methods for target temperature of 32°C to 34°C [15]. During the rewarming phase, the core temperature is increased by maximum 0.5°C/h. Standard care is continued subsequently until discharge from the hospital or death.

2.2. Studied parameters and predictors of death due to CF

Clinical and biological characteristics of the patients and usual parameters of the OHCA were recorded. Blood gas, arterial pH, blood lactate, and serum creatinine concentrations are routinely measured on admission in our center.

No flow was defined as the time interval between the patient's collapse and the beginning of cardiopulmonary resuscitation; and low flow, as the time interval between the beginning of cardiopulmonary resuscitation and the ROSC. Sustained ROSC was defined as spontaneous circulation with palpable pulse for at least 20 consecutive minutes [19]. Data were recorded according to "Utstein style"–recommended guidelines for uniform reporting of data from OHCA [19].

The type and rate of catecholamine infusion on admission were recorded, and an inotropic score (IS) adjusted to body weight was calculated according to the catecholamine infusion rate as follows: IS ($\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$) = dopamine + dobutamine + 15 × milrinone + 100 × adrenaline + 100 × noradrenaline + 100 × isoproterenol [6,20].

We considered survivors to hospital discharge patients who had a cerebral performance category (CPC) less than or equal to 3 [21].

2.3. Analysis of the mode of death in the ICU

Death from CF was considered death from a persistent shock state despite adequate fluid repletion and catecholamine treatment or due to recurring cardiac arrest [3].

Patients without a circulatory cause of death and in whom brain death or persistent deep coma due to postanoxic injury or persistent myoclonic status was documented were considered deceased due to neurologic causes [3].

Patients who died due to miscellaneous causes (sepsis, aortic dissection, acute hemorrhage, tension pneumothorax, etc) were considered deceased due to other causes.

Multiple-organ failure associated with CF was diagnosed if one of the following organ dysfunctions was present before death based on the

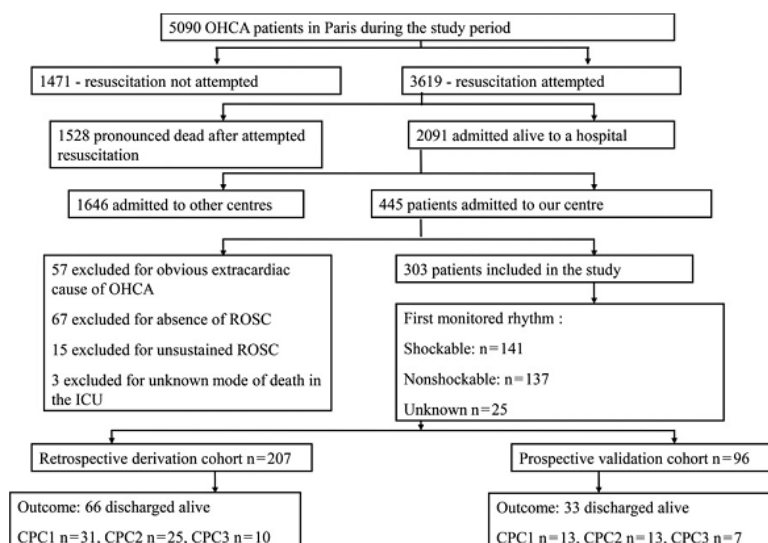


Fig. 1. Flow chart of the patients included in the study. VF indicates ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

sequential organ failure assessment [9]: hypoxemia (PaO_2 /fraction of inspired oxygen ratio less than 200 mm Hg with positive end-expiratory pressure of at least 5 cm H_2O), platelet count less than 50 G/L, bilirubin greater than 6 mg/dL, creatinine greater than 3.5 mg/dL, or oliguria (urine output 500 mL/d).

2.4. Statistical analysis

Continuous variables were expressed as median (25–75 interquartile range [IQR]) and were compared using the 2-tailed Mann-Whitney U test. Categorical variables were reported as frequencies and percentages

and compared using the χ^2 test. A statistical difference with $P < .05$ was considered significant.

Univariate logistic regression was used in the retrospective cohort to identify variables that were correlated with death due to CF. Variables with $P < .1$ on univariate analysis were introduced into a stepwise multivariate logistic regression model to select independent variables correlated with this endpoint and determine a logistic score.

The score was subsequently validated in the prospective cohort by determining its diagnostic characteristics for the prediction of death due to CF for a 0.5 cutoff of calculated probability of death due to CF. The area under the receiver operating characteristic curve was also determined.

Table 1
General characteristics of the patients on admission

	Retrospective cohort, n = 207	Prospective cohort, n = 96	P
Age, y, median (IQR)	56 (48–67)	57 (48–69)	.95
Male sex, n (%)	170 (82%)	73 (76%)	.28
Body weight, kg, median (IQR) (known in 295) ^a	80 (70–90)	80 (70–90)	.64
Risk factors (known in 288)			
Hypertension, n (%)	71 (34%)	29 (30%)	.52
Hypercholesterolemia, n (%)	43 (21%)	13 (14%)	.16
Diabetes, n (%)	33 (16%)	13 (14%)	.11
Active smoking, n (%)	78 (38%)	32 (33%)	.47
History of coronary artery disease, n (%) (known in 290)	37 (18%)	19 (20%)	.81
Glasgow Coma Scale, median (IQR)	3 (3–3)	3 (3–3)	.24
Endotracheal intubation, n (%)	207 (100%)	95 (99%)	.95
Systolic blood pressure, median (IQR) (mm Hg)	126 (97–150)	130 (107–159)	.23
Diastolic blood pressure, median (IQR) (mm Hg)	73 (60–88)	74 (60–88)	.96
Heart rate, beats/min, median (IQR)	98 (78–114)	110 (71–120)	.84
Lactate concentration on admission, mmol/L, median (IQR) (known in 286)	5 (2–9)	6 (3–10)	.10
Arterial pH, median (IQR) (known in 292)	7.23 (7.12–7.33)	7.24 (7.12–7.35)	.92
Cardiac arrest in a public place, n (%)	124 (60%)	45 (47%)	.03
Initial rhythm (known in 286)			
Shockable, n (%)	104 (50%)	37 (39%)	.21
Nonshockable, n (%)	90 (43%)	47 (49%)	.15
Duration of no flow, min, median (IQR) (known in 251)	4 (0–10)	4 (1–10)	.65
Duration of low flow, min, median (IQR) (known in 249)	20 (10–30)	15 (10–30)	.42
Left ventricular ejection fraction on admission (known in 162)	45 (30–55)	45 (30–55)	.39

Data are on admission to the hospital.

^a When parameters are not known in all patients, the number of known cases is specified in parenthesis.

Table 2
Catecholamine treatment on admission, mechanical circulatory support, and mode of death in the ICU

	Derivation cohort, n = 207	Validation cohort, n = 96	P
CF on admission, n (%)	123 (59%)	60 (63%)	.70
No. of patients on adrenaline ^a infusion, n (%)	94 (45%)	45 (47%)	.91
Adrenaline infusion rate, ^b mg/h, median (IQR)	2 (1–4)	2 (1–3)	.26
No. of patients on noradrenaline ^a infusion, n (%)	8 (4%)	9 (9%)	.09
Noradrenaline infusion rate, ^b mg/h, median (IQR)	1.8 (1–4.3)	2 (1–4)	.96
No. of patients on dobutamine ^a infusion, n (%)	23 (11%)	17 (18%)	.16
Dobutamine infusion rate, ^b $\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$ median (IQR)	10 (5–10)	8 (5–11)	.67
Intraaortic balloon pump, n (%)	27 (13%)	16 (17%)	.28
ECLS, n (%)	6 (3%)	5 (5%)	.33
Impella, n (%)	1 (0.5)	1 (1%)	NC
Survivors, n (%)	66 (33%)	33 (34%)	.80
Death due to CF, n (%)	72 (35%)	34 (35%)	.92
Death due to neurologic failure, n (%)	60 (29%)	28 (29%)	.92
Death due to miscellaneous causes, n (%)	9 (4%)	1 (1%)	NC

NC indicates not calculated due to the small number of patients; CF, circulatory failure; ECLS, extracorporeal life support. Data were known in all patients.

^a Thirteen patients received on admission 2 of the 3 catecholamines at the same time.

^b The numbers represent the median rates in patients in whom the drug was administered.

Statistical analysis was performed using MedCalc, version 11.0.1.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Characteristics of the patients

Among the 388 OHCA patients with ROSC admitted to our center during the study period, 303 were included (Fig. 1), 207 in the retrospective cohort and 96 in the prospective cohort. No patient (after regaining consciousness) or next of kin refused inclusion in the study.

The characteristics of the patients at baseline and on admission are shown in Table 1. Fifty-nine percent of the patients in the retrospective cohort and 63% in the prospective cohort required intravenous catecholamine infusion on admission (Table 2). No patients were treated with isoproterenol, dopamine, or milrinone. Left ventricular ejection fraction was only available in 162 patients on admission; there were no differences in left ventricular ejection fraction between the retrospective and prospective cohorts.

The causes of cardiac arrest were AMI in 66 patients (32%) in the retrospective cohort and 27 (28%) in the prospective cohort ($P = .6$), ischemic heart disease with significant stenosis but without AMI in 38 patients (18%) in the retrospective cohort and 17 patients (18%) in the prospective cohort ($P = .8$), hypoxemia in 20 patients (10%) in the retrospective cohort and 19 patients (20%) in the prospective cohort ($P =$

.024), and other causes (rhythm disturbance, neurologic disease, electrolyte disturbances, aortic dissection, etc) in 66 patients (32%) in the retrospective and 30 (32%) in the prospective cohort. In 17 patients (8%) in the retrospective and 3 patients (3%) in the prospective cohort ($P = .04$), the cause of OHCA remained undetermined. The threshold of TH was reached in 165 patients (80%) in the retrospective cohort and 91 (95%) in the prospective cohort ($P = .0006$).

3.2. Survival and mode of death in the ICU

Sixty-six patients (32%) survived to hospital discharge in the retrospective cohort; and 33 (34%), in the prospective cohort ($P = .80$). According to the CPC classification, in the retrospective cohort, 31 survivors (15%) were CPC 1, 25 (12%) were CPC 2, and 10 (5%) were CPC 3. In the prospective cohort, 13 patients (13.5%) were CPC 1, 13 (13.5%) were CPC 2, and 7 (7%) were CPC 3 ($P > .05$ for all CPC categories).

Seventy-two patients (35%) died of CF in the retrospective cohort and 34 (35%) in the prospective cohort ($P = .98$). Fifty eight patients (28%) in the retrospective cohort and 29 patients (30%) in the prospective cohort died of CF associated to MOF ($P = .9$). No differences were found in the use of mechanical circulatory assistance devices between the 2 cohorts (Table 2). Among patients with intraaortic balloon pump, 15 (35%) survived, whereas among the 11 patients with ECLS, 2 (18%) survived.

Table 3
Univariate and multivariate logistic regression in the derivation cohort—correlation to death by CF

Variable	β Coefficient	SE for β	Odds ratio	χ^2	P
Univariate regression					
Systolic blood pressure	−0.017	0.007	0.98 (0.97–0.99)	6.2	.019
Diastolic blood pressure	−0.042	0.014	0.96 (0.93–0.98)	11.0	.0033
Initial lactate concentration	0.198	0.037	1.212 (1.123–1.302)	34.5	<.0001
Arterial pH	−7.416	31/12/82	0.0006 (0.0001–0.0074)	49.2	<.0001
Bicarbonate concentration	−0.091	0.032	0.921 (0.869–0.977)	9.5	.0046
Paco ₂	0.034	0.009	1.034 (1.015–1.053)	15.4	.0003
Creatinine	0.011	0.003	1.011 (1.005–1.017)	18.2	.0002
Shockable initial rhythm	−1.070	0.31	0.343 (0.185–0.635)	12.1	.0007
Nonshockable initial rhythm	1.054	0.311	2.87 (1.60–5.47)	12.4	.0007
Low flow	0.041	0.011	1.035 (1.014–1.058)	14.1	.0005
Presence of shock	1.616	0.352	5.035 (2.528–10.028)	24.8	<.0001
Left ventricular ejection fraction	−0.137	0.0598	0.872 (0.776–0.981)	10.9	.022
Inotropic score	0.009	0.003	1.010 (1.003–1.016)	12.4	.0023
Multivariate regression					
Presence of shock	1.28	0.45	3.59 (1.49–8.68)	^a	.0045
Initial arterial pH	−6.29	1.30	0.0019 (0.0001–0.0236)	^a	<.0001

In univariate analysis, only parameters significantly correlated to the end point are shown.

^a The χ^2 of the multivariate model is 57, the area under the curve is 0.812 (confidence interval, 0.750–0.865), and the constant of the logistic regression equation is 43.5. The P for the overall model fit is less than .0001.

Table 4
Diagnostic characteristics of the logistic score in the retrospective and prospective cohorts

	Sensitivity	Specificity	PPV	NPV	AUC
Logistic score >0.5 retrospective cohort	51 (38–63)	92 (87–96)	77 (62–86)	79 (71–85)	0.812 (0.750–0.865)
Logistic score >0.5 prospective cohort	50 (32–68)	92 (82–97)	76 (53–92)	78 (66–87)	0.818 (0.724–0.890)

PPV indicates positive predictive value; NPV, negative predictive value; AUC, area under the curve.

There were no differences in the rates of death due to CF or neurologic failure in the 2 cohorts (Table 2).

3.3. Correlates of death due to CF and validation of the logistic score

Parameters associated with death due to CF in univariate and multivariate regression are shown in Table 3. In multivariate regression, only arterial pH and CF requiring catecholamines on admission were independently associated with this end point. The area under the curve of the model was 0.812 (0.750–0.865) (Table 3).

The equation of the logistic regression found in the retrospective cohort model was $\text{logit}(p) = 43.5 + 1.28 \times [\text{presence of shock requiring catecholamine infusion}] - 6.29 \times [\text{arterial pH}]$, and the probability of death due to CF (logistic score) was $P = 1/(1 + e^{-\text{logit}(p)})$. The variable “presence of shock requiring catecholamine infusion” was attributed the value 1 in case of shock and 0 in case of the absence of shock requiring catecholamines on admission.

In the prospective cohort, the cutoff 0.5 for the logistic score yielded a sensitivity of 50% and a specificity of 92% for the prediction of death due to CF, and the area under the curve of the model was 0.818 (0.724–0.890) (Table 4). Data on the observed percentage of patients who died due to CF in the group of patients with a low (logistic $P < .5$) vs high (logistic $P > .5$) risk of death due to CF as estimated by the logistic score in each cohort are provided in Fig. 2. In the prospective cohort, among patients with a logistic score less than 0.5, only 22% of the patients died of CF. Among the patients with a logistic score greater than 0.5, 80% died of CF.

4. Discussion

In this study including severely ill OHCA patients, the main finding is that a logistic score based on 2 variables—arterial pH and the presence of shock requiring catecholamine infusion on admission to the

hospital—can be used to identify patients with a particularly poor prognosis who die of CF despite catecholamine treatment.

This study attempted to identify on admission to the hospital patients who were at high risk for death due to CF. We chose to identify these patients on admission instead of later during the hospital stay because additional therapy such as mechanical circulatory assistance is available at admission, and to prevent irreversible organ failure, it should be used as early as possible [22]. Circulatory assistance devices are used in refractory cardiac arrest [23,24] and in refractory cardiogenic shock [10], but in OHCA patients with ROSC and CF, the indications for these devices are less clear and no precise guidelines exist to date [15]. The results of the present study and the logistic score determined in our population may be a first step in the identification of OHCA patients with ROSC who may require mechanical circulatory improvement to improve organ failure and prognosis.

According to the logistic score, in a patient presenting with shock on admission and an arterial pH less than or equal to 7.11, the probability of death due to CF is greater than 0.5. It is noteworthy that although the sensitivity of the logistic score is relatively low, the specificity is very high in both retrospective and prospective cohorts (>90%), and the positive and negative predictive values are greater than 75%.

This score is a first attempt to identify patients in whom circulatory function fails to maintain adequate organ perfusion despite catecholamine treatment, leading to MOF, refractory shock, or re-arrest and eventually death. Its purpose is to contribute to the decision of implementing circulatory assistance in OHCA patients with ROSC and CF, which is often difficult, especially because it requires to be made in an emergency setting and no specific recommendations exist to date. Beside circulatory parameters, this decision takes into account multiple clinical data such as age, comorbidities [10], characteristics of the cardiac arrest [1], and our score could be used as one of the parameters influencing this complex decision. However, we are aware that although this score identifies some of the patients at high risk for death due to CF, it remains unclear if improvement of the circulatory function might improve survival in this severely ill population.

Several studies analyzed prognostic factors in OHCA patients and constructed scores predictive of survival [12,25–27]. However, these studies focused on overall survival and final neurologic outcome and did not attempt to predict death due to an organ or system failure such as CF. We therefore consider the present data to be complementary to other prognostic scores as it aims to help in selecting patients who develop persistent CF despite catecholamine treatment and may help in making a therapeutic decision.

Prognostic biochemical parameters such as arterial pH, blood gas, lactate, and creatinine concentrations are generally not available immediately on admission but can be obtained rapidly in an emergency setting; therefore, we considered that they could be included in the present analysis. Lactate concentration on admission and creatinine concentration on admission are robust predictors of overall death [10,12,15], which were significant in univariate analysis in our study. However, when introduced in the multivariate analysis, they were not independently associated with CF-related death. This was probably due to their interdependence with the arterial pH, which is one of the 2 parameters independently associated with CF-related death, together with the presence of CF requiring catecholamine treatment on admission. Several studies found that lactate concentration and pH after OHCA were correlated with overall mortality in univariate or multivariate analysis [7,12,14]. Indeed, creatinine and lactate concentration

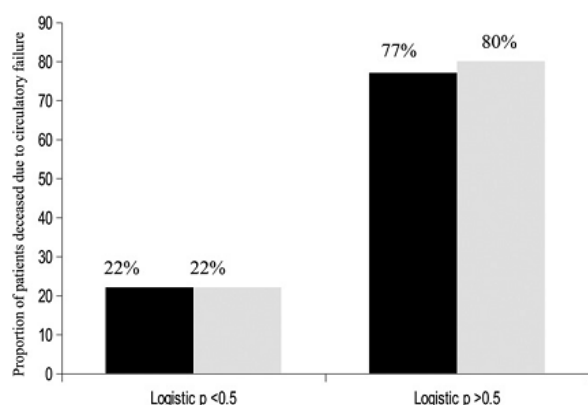


Fig. 2. Observed proportion of death due to circulatory failure in the retrospective and prospective cohort in patients with a probability of death due to circulatory failure less than 0.5 and greater than 0.5 as estimated by the logistic score. Results in the retrospective cohort are represented in black and in the prospective cohort in gray. Patients with an estimated probability of death due to circulatory failure less than 0.5 by the logistic score are shown on the left. Patients with an estimated probability of death due to circulatory failure greater than 0.5 by the logistic score are shown on the right. Numbers above the columns represent the percentage of patients who died due to CF in each group.

were independent predictors in multivariate analysis in a multicenter study of OHCA patients that determined an overall survival score on admission [12], a strong prognostic tool that predicted death accurately but did not suggest specific therapeutic interventions.

The IS, another prognostic parameter, is a fast and easy to collect prognostic factor that may estimate the degree of CF on admission, before the logistic score can be obtained [6]. However, catecholamine infusion may vary according to the physician in charge and does not always reflect the hemodynamic status of the patient, which may explain why it was not found significant in multivariate analysis.

Blood pressure, a major predictor of poor prognosis after resuscitation [28,29], and duration of no flow and low flow did not perform well in the prediction of death due to CF, but this may be related to the initiation of catecholamine treatment in patients with CF leading to normal blood pressure on admission in many patients despite the presence of shock, whereas the durations of no flow and low flow may be subject to errors of estimation in the emergency setting. Bray et al [30] focused on the association between survival and systolic blood pressure on arrival at the hospital and found that systolic blood pressure less than 90 mm Hg was associated with worse prognosis in OHCA patients with shockable initial rhythm, but similar to our data, systolic blood pressure was not significantly associated with survival after adjusting for other predictors.

Our study was performed in a university hospital and included severely ill patients who had a high incidence of CF and were comatose after the OHCA. Survival to discharge was similar in the 2 cohorts and to other OHCA studies [2,12]. The most frequent cause of OHCA was AMI, as previously found in several studies [2,31]. Interestingly, despite a high prevalence of cardiogenic shock in OHCA patients [32], AMI was not associated with death due to CF in univariate or multivariate regression. This is probably due to the rapid revascularization of patients with AMI and also the presence of cardiogenic shock in some patients without AMI, due to chronic heart disease or postresuscitation myocardial stunning. Indeed, low cardiac output and low left ventricular ejection fraction were observed in more than 50% of the patients especially in the first 24 hours after resuscitation, independently of the underlying cardiac disease in a study investigating circulatory function in this setting [33].

Our patients were treated with hypothermia (32°C–34°C target) and some of them with IABP despite data showing that therapeutic hypothermia 32°–34°C did not confer any clinical benefit when compared to 36°C temperature target [34] and that IABP did not improve outcome in patients with cardiogenic shock [35], as these data were published after the inclusion period in our study.

Patients in our study benefited from a modern management including prehospital advanced life support with mechanical ventilation and catecholamine treatment, TH, coronary angiogram for diagnostic and/or therapeutic purposes, and intensive care treatment including TH as advised by recent recommendations [10,15]. We therefore consider it relevant to contemporary medical practice and its results applicable to cardiac arrest populations in other centers or countries.

4.1. Limitations

The number of patients included in each cohort is small compared to multicenter studies [29,36] but comparable to other single-center studies [1,3,28], thus remaining relevant for the everyday practice.

The logistic score was determined using several clinical and biological parameters, and although the specificity is as high as 92%, the sensitivity of the score is low, 50%, suggesting it may be improved in the future.

Despite the focus on the circulatory function of the study, the ejection fraction of the left ventricle was only available on admission in 53% of the patients. This is due to the emergency context in which echocardiograms are not always available and left ventricular function is not consistently measured during coronary angiograms. Although this

parameter was not associated with CF in univariate regression, future studies are needed to determine its prognostic value in this setting.

Some parameters were not available in a small proportion of our patients, such as arterial pH in 3.6% and lactate concentration in 5.6% (Table 1), but this was due to difficulties related to the emergency setting and laboratory technical problems.

The initial rhythm of the OHCA and the durations of no flow and low flow remained undetermined in up to 18% of our patients, a relatively high percentage, but also reported in other retrospective studies [37]. This can be explained by the difficulty of collecting data in an emergency situation, by the emergency system physicians as well as by hospital physicians.

Certain differences were found between the retrospective and prospective cohorts: in the retrospective cohorts, more OHCA took place in public places and target temperature for hypothermia was reached in more patients in the prospective than in retrospective cohort. This may be due to a more effective induction of TH in the later part compared to the beginning of the study, due to more aggressive implementation of TH and use of more effective cooling methods in the recent period according to guidelines. However, although these differences may induce some bias in our results, this is unlikely to have a major influence, especially in the light of recent data regarding the similar clinical benefit of TH vs 36°C target temperature [34]. Despite the aforementioned differences in the 2 cohorts, the predictive values of the logistic score are very similar in the retrospective and prospective cohorts, which may be considered a strength of our study rather than a weakness.

Because this is a single-center study and many other centers in Paris are in charge of OHCA patients, many OHCA cases occurring in Paris were not included in our study because they were addressed to other hospitals as shown in Fig. 1. However, more than 75% of OHCA patients with ROSC addressed to our center were included in the present analysis according to the inclusion criteria.

Out-of-hospital cardiac arrest patients present with a high incidence of CF beginning rapidly after resuscitation, persisting 24 hours or more and characterized by low cardiac output [33] and cardiogenic shock [32]. Our score identifies a population with high risk of CF and death, and it may be taken into account in the clinical process of selecting patients for circulatory assistance. However, to date, no data showed an improvement in survival by assist devices in these patients, and it remains to be established whether rapid improvement of the circulatory function might improve outcome. Future studies are necessary to explore this hypothesis.

5. Conclusion

In OHCA patients, a logistic score based on arterial pH and the presence of shock requiring catecholamine infusion on admission could be used to predict death due to CF. These results may help in identifying patients who have a high rate of death due to CF and in whom therapies improving circulatory function may influence outcome.

Conflicts of interest

The authors declare that they have no conflicts of interest related to this work.

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6.3 Discussion

Nos résultats montrent que deux critères très faciles à évaluer à l'admission à l'hôpital identifient avec une sensibilité modeste d'environ 50% mais une spécificité élevée de plus de 90% et une valeur prédictive positive dans notre population de 77% (Tableau 4 du manuscrit), les patients qui décéderont d'insuffisance circulatoire au cours de l'hospitalisation. Ces deux critères sont, la présence d'un état de choc nécessitant l'administration de catécholamines, et un pH artériel inférieur à 7,11. Les patients de notre étude qui ont présenté ces deux critères, sont décédés en proportion d'environ 80% d'insuffisance circulatoire pendant l'hospitalisation (Figure 2 du manuscrit). Les patients présentant ces deux critères à l'admission peuvent donc être considérés comme étant des candidats potentiels à une assistance circulatoire.

Le travail soumis initialement a incorporé une analyse des caractéristiques diagnostiques de facteurs pronostiques significatifs en analyse univariée. Parmi les paramètres analysés, la concentration de lactates plasmatiques à l'arrivée avait montré une valeur intéressante avec une aire sous la courbe ROC proche de 0,8 et une sensibilité de 78% et spécificité de 76% pour la valeur seuil de 5,7 mmol/L, valeur montrant une activation importante du métabolisme anaérobie due à l'hypoperfusion systémique.

Récemment, une étude française a publié des résultats concernant des patients présentant un état de choc cardiogénique après un AC, ayant bénéficié d'une assistance circulatoire type ECLS(102), mais cette étude ne permet pas d'identifier les critères de sélection précis et le moment idéal pour débiter le traitement par ECLS. Néanmoins, elle montre que la survie des patients est meilleure lorsque le score SOFA (Sequential Organ Failure Assessment)(165) est inférieur à 14 et l'INR est inférieur à 2,4.

Notre travail a montré également, que les patients qui décèdent de cause circulatoire, sont, dans nos cohortes, plus nombreux que ceux décrits initialement dans la littérature(7), la proportion étant d'environ 35%, similaire à une étude française récente(74). Ce pourcentage montre la dimension

relativement importante du problème de l'insuffisance circulatoire menant au décès, les facteurs pronostiques retrouvés ici permettant d'identifier les patients les plus à risque, et d'adapter la prise en charge.

Malgré l'identification d'une population à très haut risque de décès de cause circulatoire dans notre étude, les patients qui ne présentent pas les deux critères retrouvés ici, ont un risque de décès de cause circulatoire non négligeable, d'environ 20% (Figure 2 du manuscrit), ce qui suggère que nos critères de sélection doivent être améliorés dans l'avenir. Néanmoins, ce travail permet pour la première fois, d'évaluer dès l'arrivée à l'hôpital, le risque de survenue d'un décès par insuffisance circulatoire, en vue d'adapter précocement la prise en charge et envisager la possibilité d'une assistance circulatoire.

7 Amélioration de la fonction ventriculaire gauche sous assistance circulatoire à flux pulsatile synchronisé avec le rythme cardiaque – travail expérimental

7.1 Introduction

L'assistance circulatoire de type ECLS peut assurer un débit sanguin jusqu'à 5 L/min et une oxygénation sanguine permettant la survie du patient, mais elle n'est pas dépourvue d'effets indésirables. Le flux sanguin généré par l'ECLS est éjecté par la canule artérielle au niveau d'une des artères iliaques. Ce flux est dirigé vers le cœur, il est opposé au sens de circulation physiologique du sang dans l'aorte, et s'oppose à l'éjection du ventricule gauche. Plus le débit de l'ECLS est important, plus l'augmentation de la postcharge du ventricule gauche est importante et sa fraction d'éjection diminue, comme l'a montré une étude expérimentale récente(145). Ce flux rétrograde a pour effet sur un ventricule gauche à faible contractilité, une diminution du volume d'éjection systolique(143) et une augmentation de la postcharge qui peuvent également générer un œdème pulmonaire parfois très important. Celui-ci peut nécessiter des moyens supplémentaires pour diminuer la pression intraventriculaire et la pression capillaire pulmonaire comme la mise en place d'un ballon de contre pulsion, la mise en place d'une assistance par Impella® ou la réalisation d'une atrio-septostomie de décharge(147–149).

Nous avons évalué dans une étude expérimentale l'effet de la diminution du débit de l'ECLS pendant la systole cardiaque, sur ces deux paramètres d'intérêt majeur: la fraction d'éjection du ventricule gauche et la pression capillaire pulmonaire. Cette diminution du débit de l'ECLS lors de la systole cardiaque a été obtenue à l'aide d'un dispositif qui transforme le flux continu de l'ECLS en flux pulsatile. Son effet a été évalué par la mesure de la fraction d'éjection du ventricule gauche et de la pression capillaire pulmonaire, dans un modèle expérimental d'AC par fibrillation ventriculaire chez le cochon.

7.2 Synchronized pulsatile flow with low systolic output from veno-arterial extracorporeal membrane oxygenator improves myocardial recovery after experimental cardiac arrest in pigs

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Abstract

Background: Circulatory failure following cardiac arrest (CA) requires catecholamine support and occasionally veno-arterial extracorporeal membrane oxygenator (vaECMO). VaECMO-generated blood flow is continuous and retrograde, increasing afterload.

Purpose: To assess the benefit of a device generating a pulsatile vaECMO flow synchronized with the heart rhythm lowering systolic vaECMO output, on the left ventricular ejection fraction (LVEF) and pulmonary capillary pressure (Pcap) after CA.

Material and methods: Experimental randomized study in pigs comparing standard non-pulsatile vaECMO (control) with pulsatile synchronized vaECMO (study) group using a pulsatility generating device.

After sedation and intubation, ventricular fibrillation was induced by pacing. After 10-min ventricular fibrillation, cardiopulmonary resuscitation was performed for 20 min then vaECMO, defibrillation and 0.15 µg/kg/min intravenous epinephrine infusion were initiated. Hemodynamics, Pcap, LVEF by echocardiography and angiography were measured at baseline and every 30 min after the vaECMO start until vaECMO and epinephrine were stopped (at 120 min), and 30 min later.

Results: Baseline hemodynamics did not differ between groups. At 120 min after vaECMO initiation, LVEF by echocardiography and angiography was significantly higher in the study than control group 55±19% versus 34±13% (p=0.042), 50±16% versus 33±12% (p=0.043) respectively. Pcap decreased from baseline by 4.2±8.6 mmHg in the study group but increased by 5.6±5.9 mmHg in the control group (p=0.043). Thirty min later, LVEF remained higher in the study group 44±7% versus 26±11% (p=0.008) while Pcap did not differ.

Conclusion: A synchronized pulsatile device decreasing systolic output from vaECMO improved LVEF and Pcap in a pig model of cardiac arrest and resuscitation.

Keywords: cardiac arrest, synchronized pulsatile ECMO, left ventricular ejection fraction, pulmonary capillary pressure.

Circulatory failure is often present after resuscitated cardiac arrest^{1,2} and is one of the factors leading to multiorgan failure and death^{3,4}. One possible treatment of severe circulatory failure including refractory cardiac arrest is veno-arterial extracorporeal membrane oxygenator (vaECMO). Although survival in refractory cardiac arrest patients was extremely low in previous studies⁵⁻⁷, a recent study from the University of Minnesota showed that survival rate of 50% is an obtainable goal⁸. VaECMO is providing the necessary hemodynamic support and respiratory gas exchange support for the hearts to recover, but as most patients have significant acute and/or chronic coronary pathology, cardiac recovery takes at least 3-5 days⁸. While this is happening, vaECMO flow is increasing cardiac afterload as shown by previous data⁹⁻¹¹ and it may impede functional recovery since these patients have very significant troponin elevations, far more than would be expected from the coronary events alone⁸. In an effort to decrease afterload for recovering patients, intraaortic balloon pump¹² and Impella[®] device^{9,13} have been used in different institutions but robust experimental or clinical data to guide treatment strategies are lacking.

Our team has recently developed a device that could be added to the ECMO circuit to generate a synchronized pulsatile flow and decrease vaECMO output during the heart systole. This is achieved by briefly compressing a part of the circuit using pressurized gas and transforming the continuous ECMO flow into a pulsatile flow synchronized with the heart systole. The device inflates at the initiation of the QRS complex and deflates during the diastolic period. Consequently, cardiac contraction faces less afterload.

We therefore hypothesized that implementation of artificial pulsatile vaECMO support would facilitate left ventricular systolic function recovery and decrease left ventricular filling pressure in

an established porcine model of cardiac arrest and resuscitation supported by vaECMO.

Material and methods

This experimental study was carried out within the ethical guidelines established by the National Institute of Health, the French Ministry of Agriculture and the European Union Legislation. The protocol was approved by the local ethics committee for animal experimentation of the National Institute of Agronomic Research.

The device used to generate pulsatile flow and decrease systolic output from vaECMO

This device is composed of an outer rigid plastic tube inside which a second compressible silicone tube is placed (Figure 1). The device is interposed into the ECMO circuit, just upstream of the arterial cannula, and has a backflow prevention valve to mitigate to and fro flow in the ECMO circuit. Oxygenated blood flows inside the inner tube and is injected by the vaECMO into the iliac artery. In the space between the outer and inner tube, helium flows in pulses reaching a predefined pressure in order to compress the inner tube and limit the ECMO flow entering the common iliac artery during systole. The helium pulses are controlled by a specially designed console receiving input from the animal's surface electrocardiogram. The console increases helium pressure compressing the inner tube during systole and decompresses the inner tube during diastole effectively timing the helium pulses opposite to the intraaortic balloon pump. Tracings of blood pressure in the ascending aorta recorded through a pressure wire in a pig receiving pulsatile and then non-pulsatile vaECMO flow are shown in Figure 2.

Preparation and instrumentation of the animals

Fourteen female pigs were sedated, intubated and ventilated using a Narcomed 6000[®] respirator

(Telford, PA, USA). Sedation was initially performed with intramuscular 10 mg/kg ketamine and 4 mg/kg xylazine intravenously and was subsequently continued with Isoflurane 1-1.5% administered by the respirator through the tracheal tube. After intubation animals were ventilated with 25% oxygen, 6 ml/kg tidal volume and 15/min respiratory rate.

Right femoral vessels cannulation was performed using venous 21 French (BE-PVL) and arterial 15 French (BE-PAL) ECMO cannulae (Maquet, Rastatt, Germany), using the Seldinger technique. Cannulae were connected to a Maquet BE-PLS circuit (Rastatt, Germany), and a Maquet Rotaflow[®] pump, (Hirrlingen, Germany).

In the left femoral vein a 7-French sheath was placed, together with a Swan-Ganz catheter that was advanced into the right or left inferior branch of the pulmonary artery to measure the Pcap. The position of the Swan-Ganz catheter was verified by fluoroscopy and injection of contrast media to insure optimal placement and arterial occlusion when the balloon of the catheter was inflated.

In the left femoral artery a 5-French sheath was inserted and a 5-French pigtail PIG 155 catheter (Boston Scientific, Baja California, Mexico), was placed in the left ventricle for left ventricular ejection fraction (LVEF) measurement by angiography.

In the right carotid artery, we placed a 5-French sheath to measure arterial pressure. In the right jugular vein, a 6-French sheath was placed for the insertion of a transvenous pacing catheter (Bard Electrophysiology, Lowell, Ma, USA) into the right ventricle. This catheter was used to trigger ventricular fibrillation. In the left jugular vein a central venous catheter was placed for epinephrine and fluid administration.

Blood pressures were recorded using PXVMP260 pressure transducers, Edwards Lifesciences, Irvine, CA, USA.

Experimental protocol

The experimental protocol is detailed in Figure 3. Female mini pigs were randomly included in two groups: standard vaECMO group (control) and pulsatile flow vaECMO group.

After general anesthesia and intubation, instrumentation was performed as described above. Vascular repletion was administered at 15 ml/kg per hour using 0.9% saline. Baseline measurements were performed before induction of ventricular fibrillation. Ventricular fibrillation was induced by stimulating the right ventricle at a frequency of 300/min¹⁴.

After ventricular fibrillation, ventilation and vascular repletion were discontinued and the animal remained in cardiac arrest for 10 minutes. After 10 minutes of cardiac arrest, basic life support was started, ventilation was restored (6 ml/kg tidal volume, 10/min respiratory rate) and chest compressions initiated at a frequency of 100/min¹⁵. Chest compressions were performed using a LUCAS device (Jolife, Lund, Sweden) according to recommendations, with the animal kept on its back and epinephrine 15 µg/kg¹⁶ was administered every 5 min¹⁵. After 20 min of chest compressions, the vaECMO pump was turned on at a fixed rotation frequency of 3000/min, 25% inspired oxygen fraction and 3L/min sweep. Simultaneously, epinephrine continuous infusion was initiated at 0.1 µg/kg/min in all pigs irrespective of the blood pressure to mimic human resuscitation requiring intravenous catecholamines. Heparin 70 IU/kg was administered at the beginning of the venous and arterial cannulae insertion and every hour thereafter to prevent thrombosis. There were no pre-established target vaECMO output and blood pressure, these parameters were analyzed and compared between groups as outcome variables.

Defibrillation was performed using 200 J external electric shocks and was repeated if necessary every approximately two minutes until sustained return of spontaneous circulation was achieved.

Immediately after defibrillation, LVEF was measured by angiography. Subsequently, measurements were performed 30, 60, 90 and 120 min after the start of the vaECMO (T30, T60, T90 and T120

respectively).

At the end of 120 min of vaECMO, epinephrine and vaECMO were stopped and the animals were kept alive another 30 min at the end of which LVEF and Pcap were measured again.

Studied parameters

We measured arterial pressure, heart rate, central venous pressure (at baseline in the right atrium), pulmonary capillary pressure using the Swan-Ganz catheter, LVEF using the angiographic method and the echocardiographic method using the Teicholz method in the parasternal long axis view, and the output of the vaECMO as displayed by the device. Systolic volume was calculated by angiography and cardiac output was calculated as systolic volume multiplied by the heart rate. Coronary perfusion pressure was calculated as diastolic pressure minus pulmonary capillary wedge pressure¹⁷. Pressures and heart rate values were averaged over 10 seconds. These parameters were measured at baseline before induction of the ventricular fibrillation, and 30, 60, 90 and 120 min after the beginning of the ECMO and 30 min after the vaECMO and epinephrine cessation.

During the 20 min of basic life support, blood pressure was measured to account for differences between groups that may have influenced the results.

In addition, the influence of the pulsatile device on the vaECMO output was also studied ex vivo. The venous cannula of the vaECMO circuit was placed in a water reservoir and the arterial cannula ejected water in a recipient for 60 seconds with the vaECMO rotation frequency kept at 3000 rotations/min. The output of the pulsatile vaECMO and non-pulsatile vaECMO during the one minute period was subsequently measured and compared.

Statistical analysis

In order to show a significant difference between the two groups in the recovery of the LVEF, for a

alpha-type error of 5% and a beta-type error of 10% a difference in LVEF between groups of at least 15% at the end of the study, assuming a standard deviation of 10%, seven pigs were required in each group.

Numerical variables were expressed as means $\pm$ standard deviation, and categorical variables as percentages. Changes in the variables of interest (LVEF and Pcap) during different time points of the protocol were also calculated as $\text{Value}_t - \text{Value}_{\text{baseline}}$ where Value_t is the value of the variable at a given time point, $\text{Value}_{\text{baseline}}$ is the value of the variable at baseline. Comparisons between numerical variables were performed using independent Student t-test. P-values inferior to 0.05 were considered significant.

Results

Fourteen pigs were included in the study. Since one control pig died of hemorrhage immediately after the end of the cardiopulmonary resuscitation, only six pigs were finally analyzed in the control group and seven in the pulsatile ECMO group. Body weight in the control group was 47 ± 6 kg and 51 ± 5 kg in the study group ($p=0.19$).

Hemodynamic parameters, LVEF by angiography and echocardiography and Pcap were similar at baseline in the two groups (Table 1). Mean arterial pressure was similar during the CPR, 30 ± 8 mmHg in the control group versus 29 ± 8 mmHg in the pulsatile ECMO group as was the coronary perfusion pressure 11 ± 4 mmHg versus 10 ± 5 mmHg respectively. Table 2 shows hemodynamic parameters at different time points during the protocol. Arterial pressure and ECMO output did not differ between groups at any time point during the study (Table 1 and Table 2).

Immediately after the cardiac arrest, LVEF by angiography decreased to very low values, $<10\%$ in both groups. After ECMO and epinephrine treatment, LVEF by echography and angiography improved progressively in both groups (Figure 4).

At the end of the 120 min of ECMO and epinephrine treatment, LVEF was significantly higher in the pulsatile ECMO group compared to the control group, $55\pm 19\%$ versus $34\pm 13\%$ by echocardiography ($p=0.042$) and $50\pm 16\%$ versus $33\pm 12\%$ by angiography ($p=0.043$, Table 2). Stroke volume tended to improve in the pulsatile group 17 ± 5 mL versus 24 ± 7 mL, $p=0.056$ (Table 2). Changes from baseline showed better LVEF recovery in the pulsatile ECMO group compared to the control group at T120 ($p<0.04$) data not shown.

Pcap at T120 was 10 ± 6 mmHg in the control group and 7 ± 7 mmHg (Figure 5) in the pulsatile ECMO group ($p=0.42$, Table 2). Changes from baseline in Pcap showed significant differences in favor of the pulsatile ECMO group, at T120. Pcap in the pulsatile ECMO group decreased by 4.2 ± 8.6 mmHg while in the control group it increased by 5.6 ± 5.9 mmHg ($p=0.043$, Figure 5). Due to a technical dysfunction, Pcap was not available in one of the control animals.

Thirty minutes after stopping the vaECMO and epinephrine, LVEF in the control group was $26\pm 11\%$, significantly higher in the pulsatile ECMO group, $44\pm 7\%$ ($p=0.008$, Table 3). No difference in Pcap was observed at this time point (Table 3).

Under *ex-vivo* experimental conditions using water as circulating fluid, the non-pulsatile vaECMO had an output of 4.8 L/min and the pulsatile vaECMO had an output of 4.6 L/min in 60 seconds, corresponding to a small decrease in vaECMO output of 4.2% due to the pulsatile device.

Discussion:

In a pig model of vaECMO-resuscitated cardiac arrest with patent coronary arteries, we showed that LVEF was significantly improved two hours after the beginning of the vaECMO treatment using a device able to lower output from the vaECMO during heart systole by generating pulsatile flow synchronized with the cardiac cycle. Moreover, LVEF improvement by the pulsatile vaECMO was accompanied by a favorable change from baseline in Pcap in the study group compared to the control group.

The better LVEF recovery in the pulsatile ECMO group suggests that synchronized pulsatile flow may play a role in the attempt to improve LVEF after a prolonged cardiac arrest, usually accompanied by extensive myocardial damage⁸. A faster recovery of the LVEF may shorten the period of ECMO assistance favoring weaning, which may have a clinically significant impact since vascular ischemic complications increase with time. Our hypothesis to explain the improvement in the LVEF recovery by the device generating pulsatile ECMO flow is a decrease in left ventricle afterload during the systole. It is confirmed by several studies that the vaECMO generates a retrograde flow that is directed towards the heart and thus opposes physiological flow from the left ventricle to the aorta increasing afterload^{10,11}. The ECMO flow decreases the LVEF and increases its workload as recently documented in an experimental study in pigs undergoing ECMO treatment for cardiogenic shock¹⁰. The device used here limited this phenomenon and may have achieved an effect similar to lowering afterload in chronic cardiac failure patients treated with angiotensin-converting enzyme inhibitors¹⁸ which is a major therapeutic effect decreasing myocardial energy consumption and improving LVEF.

Synchronized pulsatile ECMO assistance was associated with favorable Pcap changes from baseline in the pulsatile ECMO group compared to controls and this could prove clinically significant in the

population of ECMO patients who require left ventricular unloading especially when pulmonary edema is present. In these patients additional devices such as Impella or intraaortic balloon pump are therapeutic options^{12,13} and pulsatile synchronized flow could diminish or avoid the need for such interventions.

In animal models, pulsatile flow generated by centrally implemented left ventricular assist devices was shown beneficial, improving end-organ function in relation to enhanced cardiac output, lowered left atrial pressure and increased mean aortic pressure¹⁹. However, several studies in humans performed in cardiac surgery patients did not find a benefit of pulsatile non-synchronized pulsatile central circulatory assistance^{20–25}. Unlike these studies, the device used in our protocol transforms the continuous flow of the vaECMO into a pulsatile flow synchronized with the cardiac cycle, offering a major advantage to the concept studied here.

In an experimental model in swines featuring a pulsatile electrocardiogram-synchronized vaECMO device, Wang et al showed better renal perfusion and increased diuresis after a 24-hour period of ECG-synchronized pulsatile compared to non-pulsatile vaECMO²⁶. However, no cardiac arrest was induced in this model and data regarding the effects on LVEF and Pcap were not available. Our results are now showing that after cardiac arrest, pulsatile vaECMO is also associated with an improvement in LVEF two hours after vaECMO initiation, a result that persisted 30 min after the vaECMO was stopped.

Interestingly, the vaECMO output measured *in vivo* did not significantly decrease in the pulsatile vaECMO-treated pigs, and only a mild decrease was evidenced in the pulsatile flow vaECMO in the *ex vivo* experiment under conditions of low liquid viscosity (water), optimal preload and low afterload. This relatively small difference *ex-vivo* may be due to a rebound flow effect during decompression of the vaECMO circuit in the diastole, compensating for the decrease in flow during

the compression period.

No experimental data were published regarding the effect of synchronized pulsatile flow on Pcap in the setting of cardiac arrest treated with vaECMO, but a previous *in silico* simulation study suggested that pulsatility could decrease left atrium pressure and Pcap²⁷, supporting the possible benefit of the pulsatile device to limit the risk of pulmonary edema. We did document a more favorable change from baseline in the pulsatile vaECMO group but we did not observe a significant difference between the two groups in the absolute Pcap values measured 120 min after vaECMO initiation. This may be due to an underpowered analysis (Pcap known in 5 pigs in the control versus 7 in the study group) and a large standard deviation in Pcap measurements. Despite this important variability, our study did show significant differences in the Pcap changes from baseline in favor of the pulsatile vaECMO group, a result that could be clinically significant and should be further explored.

Our study has several original aspects. Although previous studies used pulsatile devices, the experimental design of previous pulsatile circulatory assistance and their chosen endpoints differed from ours. Circulatory assistance was previously provided mostly by central devices and therefore, increased afterload from vaECMO-generated retrograde flow was not an issue. In contrast to our study, pulsatility was generally not synchronized with cardiac systole, which is a major advantage of the device used here. We believe the present study provides new insights into circulatory function in synchronized pulsatile vaECMO and its potential to improve hemodynamics after cardiac arrest.

The present study was designed as a proof-of-concept study regarding the effect of afterload decrease during systole on LVEF and Pcap. It was not designed to reproduce as closely as possible the specific clinical situation of the cardiac arrest, and this explains the relatively short duration of cardiopulmonary resuscitation and the absence of experimental myocardial infarction in the present protocol. To minimize inter-individual variability in LVEF, Pcap and vaECMO output, we

administered fixed fluid volumes and epinephrine doses and we maintained constant the ECMO pump rotation speed.

Several limitations are also present in our study. The increase in LVEF observed in pigs may not be easily demonstrable in humans that have significant coronary artery disease in the majority of the cases. In this pilot study, we did not measure myocardial biomarkers to assess the degree of myocardial injury in each group and did not use pressure-volume measurements due to technical issues pertaining to our laboratory. These could be assessed in a future more detailed and longer vaECMO assistance protocol comprising an experimental myocardial infarction.

In the literature, a benefit from pulsatile flow in experimental settings was observed as a decrease in the production of free radicals and inflammation in vessel walls²⁸. Our study was not designed to assess these beneficial effects which could not be confirmed or excluded. Additionally, thromboembolic side-effects were documented in patients treated with pulsatile assistance devices different from vaECMO, especially related to thrombosis of the blood chamber after several days of assistance²⁹. However, due to the short vaECMO treatment in our study, this complication could not be evaluated.

Our study included animals with "healthy" hearts and artificially-induced cardiac arrest which does not reproduce the exact conditions of human cardiac arrest, usually associated with myocardial infarction or chronic ischemic and non-ischemic heart disease^{30,31}. Our model investigated the issue of myocardial stunning after cardiac arrest¹⁴ avoiding the more complex models including experimental myocardial infarction to avoid difficulties in measuring LVEF due to regional wall motion abnormalities and individual variability in infarct size between pigs.

In conclusion, based on our pig model of ECMO-resuscitated cardiac arrest, we showed significant improvement in LVEF and favorable changes from baseline in Pcap when using a

synchronized pulsatile flow decreasing afterload using a specially made device. Future studies are needed to explore the benefits of such a device in other experimental models and if confirmed, to investigate its potential benefits in human circulatory assistance.

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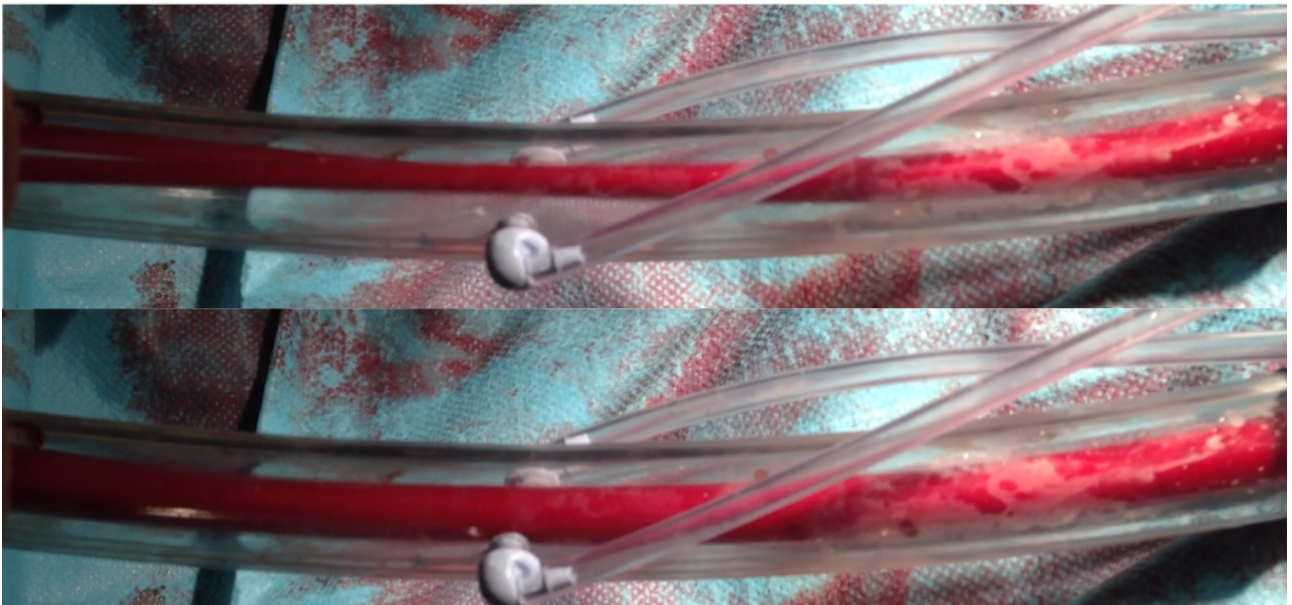
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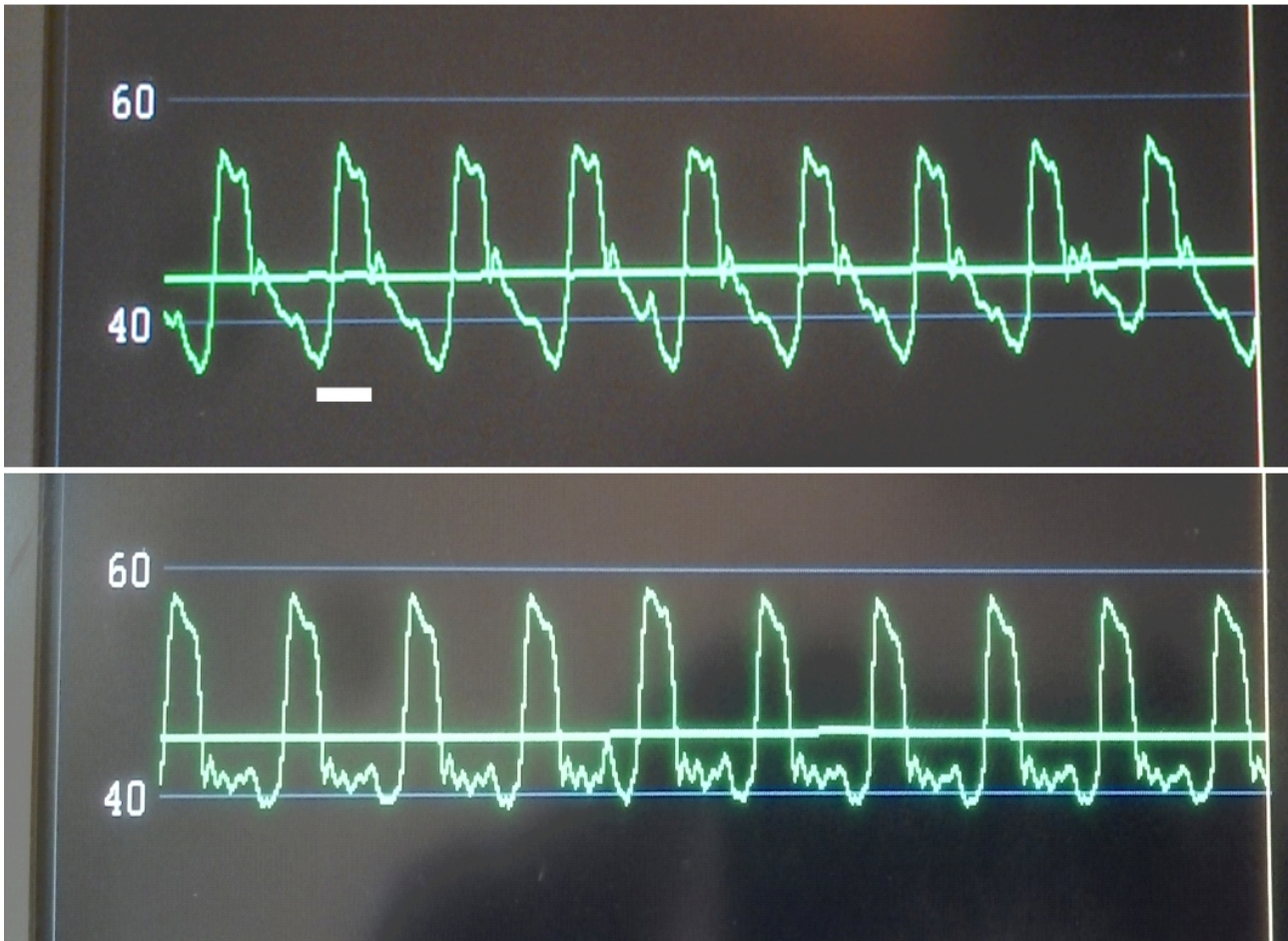
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Figure 1 The device used to generate pulsatile flow and lower output from vaECMO during the systole



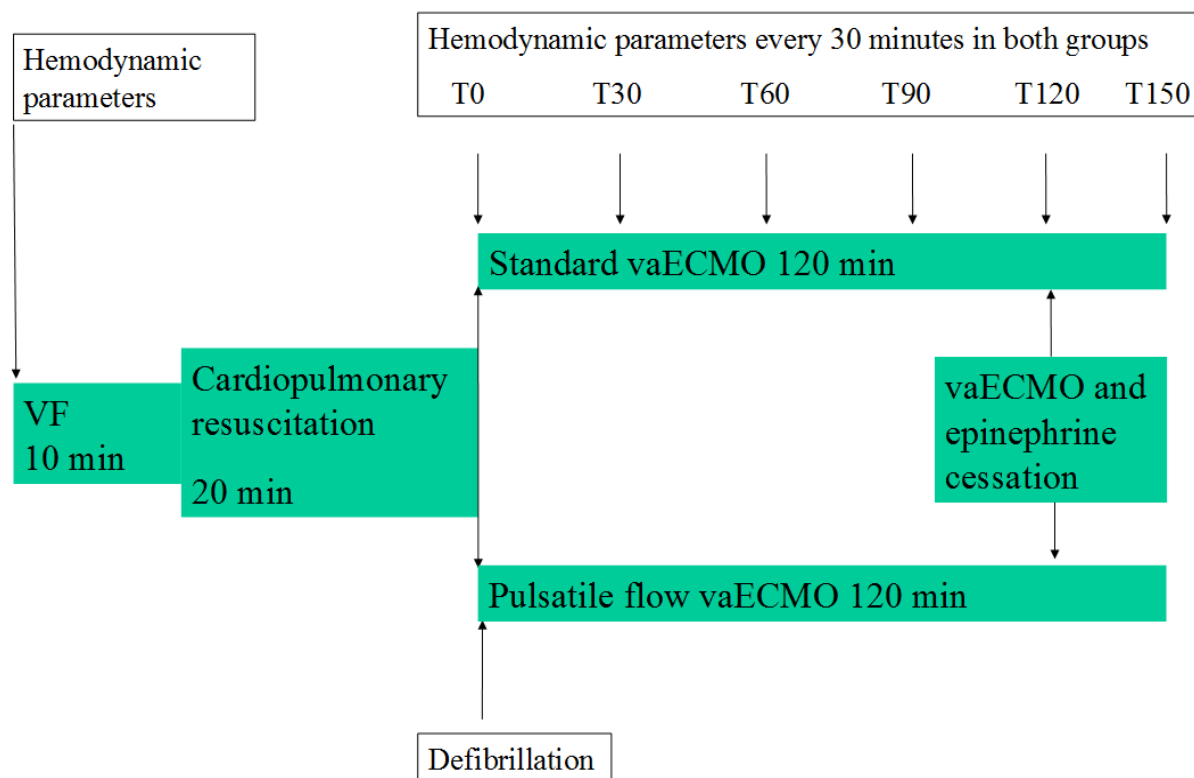
The device consists of an outer rigid tube and an inner compressible tube. In the space between the two tubes helium is injected during the heart systole compressing the inner tube and reducing the output of the veno-arterial extracorporeal membrane oxygenator. The top image shows the inner tube compressed during the systole and the bottom image the inner tube decompressed during the diastole.

Figure 2 Blood pressure in the proximal left anterior descending artery during pulsatile and non-pulsatile ECMO



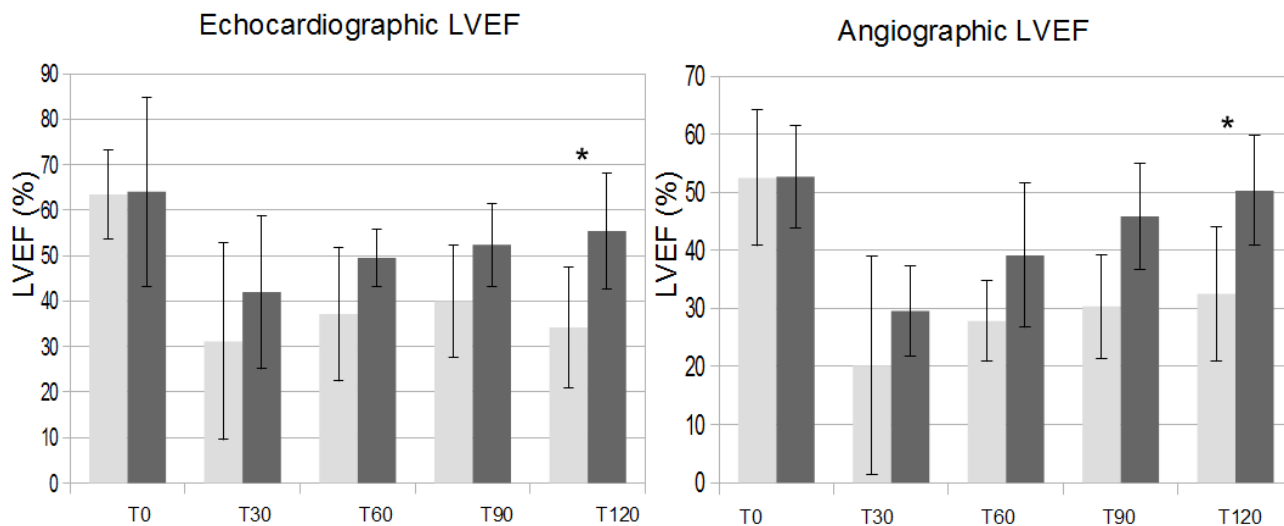
The upper panels represents blood pressure in the proximal left anterior descendant artery measured using a pressure wire with the pulsatile vaECMO device on and pulsatile vaECMO flow. The lower panel is showing the same pressure with the device off and continuous vaECMO flow. The pulsatile flow trace shows a dicrotic notch and a slightly higher pulse pressure. The white bar on the second cardiac cycle of the pulsatile trace represents the period of reduction of the vaECMO output by the pulsatile device.

Figure 3 Experimental protocol



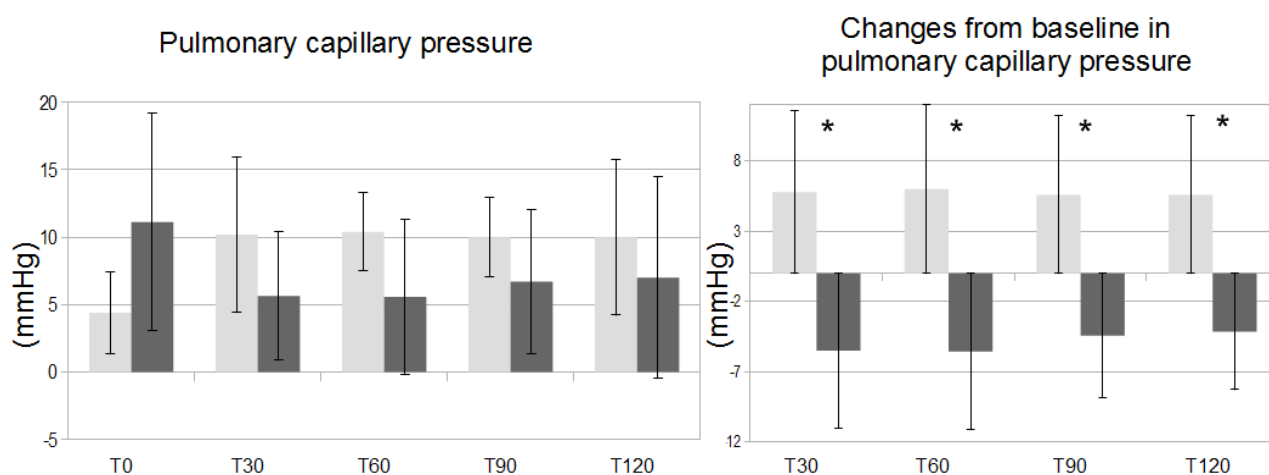
Measured hemodynamic parameters included arterial blood pressure, central venous pressure, pulmonary capillary pressure, left ventricular ejection fraction. VF-ventricular fibrillation, vaECMO-venoarterial extracorporeal membrane oxygenation T0, T30, T60, T90, T120, T150 – measurement timepoints (30-150 minutes) from the vaECMO onset until the end of the protocol.

Figure 4 Left ventricular ejection fraction measured by echocardiography (left) and angiography (right) at different measurement times



T0 - baseline, T30, T60, T90, T120 – 30, 60, 90, 120 minutes after the end of the cardiopulmonary resuscitation and the beginning of the extracorporeal membrane oxygenator (ECMO). Non-pulsatile ECMO (control) animals are shown in light gray and pulsatile ECMO animals in dark gray. LVEF: left ventricular ejection fraction, expressed in percentages. * $p < 0.05$. Bars represent standard deviations

Figure 5 Pulmonary capillary pressure (Left) and changes from baseline (Right) at different measurement times



T0, baseline; T30, T60, T90, T120, 30, 60, 90, 120 min after the end of the cardiopulmonary resuscitation and the beginning of the venoarterial extracorporeal membrane oxygenator (vaECMO). Non-pulsatile vaECMO (control) pigs are shown in light grey and pulsatile vaECMO pigs in dark gray; LVEF, left ventricular ejection fraction; * $p < 0.05$. Bars represent standard deviations. Pressures are expressed in mmHg.

Table 1 Characteristics of the animals at baseline

Characteristic	Control group	Pulsatile vaECMO group	p
Body weight (kg)	47±6	51±5	0.168
SBP (mmHg)	89±20	86±23	0.95
DBP (mmHg)	58±13	59±21	0.96
MBP (mmHg)	73±15	72±22	0.928
Heart rate	118±24	102±34	0.349
CVP (mmHg)	5±3	6±4	0.658
Pcap (mmHg)	4±3	11±8	0.13
Coronary perfusion pressure (mmHg)	68±14	67±21	0.922
LVEF (%) (angiography)	53±12	53±9	0.97
LVEF (%) (echocardiography)	64±10	64±19	0.95
Stroke volume (mL)	25±7	25±7	0.95
Cardiac output (mL/min)	3.1±1.5	2.6±1.2	0.59

SBP-systolic blood pressure, DBP-diastolic blood pressure, MBP-mean blood pressure, CVP-central venous pressure, Pcap-pulmonary capillary pressure, LVEF-left ventricular ejection fraction, CPR-cardiopulmonary resuscitation.

Table 2 Hemodynamic parameters during vaECMO treatment

Parameter*	Control group	Pulsatile vaECMO group	p
SBP T30 (mmHg)	92±31	94±32	0.92
SBP T120 (mmHg)	105±31	114±24	0.57
DBP T30 (mmHg)	68±15	52±34	0.297
DBP T120 (mmHg)	76±22	71±22	0.677
MBP T30 (mmHg)	79±21	71±30	0.62
MBP T120 (mmHg)	88±25	87±24	0.958
Heart rate (beats/min)T30	127±14	114±26	0.331
Heart rate (beats/min)T120	149±9	144±25	0.630
Pcap T30 (mmHg)	10±6	6±5	0.161
Pcap T120 (mmHg)	10±6	7±7	0.42
LVEF angio T30 (%)	20±19	30±24	0.46
LVEF angio T120 (%)	33±12	50±16	0.043
LVEF echo T30 (%)	31±22	42±23	0.40
LVEF echo T120 (%)	34±13	55±19	0.042
Stroke volume T30 (mL)	9±9	14±9	0.34
Stroke volume T120 (mL)	17±5	24±7	0.056
Cardiac output T30 (L/min)	1.1±1.1	1.5±1.1	0.55
Cardiac output T120 (L/min)	2.5±0.6	3.4±1.2	0.14
Coronary perfusion pressure T30 (mmHg)	74±22	68±31	0.694
Coronary perfusion pressure T120 (mmHg)	83±24	83±26	0.985
vaECMO output T30 (L/min)	2.2±0.39	2.0±0.56	0.47
vaECMO output T120 (L/min)	1.82±0.53	1.80±0.53	0.96

* - data at T60 and T90 are not shown, similar values without significant differences were found at these timepoints in all parameters. SBP-systolic blood pressure, DBP-diastolic blood pressure, MBP-mean blood pressure, Pcap-pulmonary capillary pressure, LVEF-left ventricular ejection fraction.

Table 3 Hemodynamic measurements 30 minutes after the end of the vaECMO and epinephrine infusion (T150)

	Control group	Pulsatile vaECMO group	p
Heart rate (beats/min)	159±8	152±22	0.479
Central venous pressure (mmHg)	5±5	5±4	0.942
LVEF (angiography)	26±11	44±7	0.008
SBP (mmHg)	81±23	72±15	0.434
DBP (mmHg)	42±8	38±13	0.539
MBP (mmHg)	57±11	51±15	0.469
Pcap (mmHg)	3±5	7±10	0.679
Coronary perfusion pressure (mmHg)	52±13	49±17	0.748
Stroke volume (mL)	13±5	18±2	0.09
Cardiac output (L/min)	2.0±0.9	2.6±0.5	0.20

LVEF-left ventricular ejection fraction, SBP-systolic blood pressure, DBP-diastolic blood pressure, MBP-mean blood pressure, Pcap-pulmonary capillary pressure.

7.3 Discussion

Cette étude réalisée sur un modèle expérimental d'AC chez le cochon a montré que la diminution du débit de l'ECLS pendant la systole permet l'amélioration de la fraction d'éjection du ventricule gauche, et permet une évolution plus favorable de la pression capillaire pulmonaire par rapport à une assistance circulatoire type ECLS à flux continu.

L'utilisation d'un dispositif spécial permettant de diminuer le flux rétrograde de l'ECLS lors de la systole a permis dans cette étude de récupérer après 120 minutes d'assistance circulatoire, une fraction d'éjection du ventricule gauche de $55\% \pm 19\%$ chez les animaux traités avec l'ECLS pulsatile à flux systolique diminuée, alors que dans le groupe contrôle la fraction d'éjection a été de $34 \pm 13\%$ ($p=0.042$). Des valeurs similaires ont été observées quand les mesures ont été réalisées par angiographie du ventricule gauche. Ce résultat est significatif de point de vue statistique et présente une importance clinique par le fait qu'une amélioration plus rapide de la fonction ventriculaire gauche pourrait permettre un sevrage plus rapide de l'ECLS. Nos résultats sont concordants avec une étude expérimentale réalisée dans le cadre du choc cardiogénique chez des cochons, qui a montré que l'augmentation importante du débit de l'ECLS diminue la fonction ventriculaire gauche(145). Cet effet est probablement dû à l'augmentation de la postcharge ventriculaire gauche par l'ECLS selon les données de la littérature(145,146).

Le deuxième résultat important de cette étude est la variation favorable par rapport à la valeur de base, de la pression capillaire pulmonaire dans le groupe ECLS pulsée comparé au groupe contrôle. La différence significative à 120 minutes d'ECLS de la variation de la pression capillaire pulmonaire entre le groupe contrôle et le groupe ECLS pulsée, montre que la diminution du débit systolique de l'ECLS influence favorablement la pression capillaire pulmonaire et pourrait

représenter une solution thérapeutique pour l'œdème pulmonaire, ou pourrait prévenir son apparition.

Ces résultats ont été obtenus dans des conditions expérimentales chez des cochons avec des cœurs antérieurement sains, et leur validité en cas d'infarctus du myocarde ou autre cardiopathie associée, reste à évaluer.

Le dispositif responsable de la diminution de la postcharge, réalise une compression intermittente du circuit de l'ECLS, uniquement lors de la systole, à l'aide d'un gaz comprimé (hélium). Cette compression intermittente n'a pas diminué de façon significative le débit de l'ECLS, ces résultats étant encourageants pour de futures études sur des modèles animaux plus proches de l'AC humain, associé souvent à une cardiopathie ischémique et/ou à un infarctus aigu du myocarde.

Cette étude a été soumise pour publication à la revue Artificial Organs et est actuellement en cours de reviewing.

8 Amélioration de la circulation cérébrale lors de l'hypothermie thérapeutique par le contrôle de la pression artérielle en gaz carbonique – travail observationnel

8.1 Introduction

Après la réanimation cardiopulmonaire, les patients comateux bénéficient d'une intubation et d'une ventilation mécanique, de même que d'un contrôle thermique avec une température cible entre 32 et 36°C(73). Cet intervalle de 32° à 36°C permet de réaliser un contrôle thermique soit dans la zone d'hypothermie modérée entre 32° et 34°C, soit entre 34° et 36°C. Lorsque la température des patients est inférieure à 37°C, la pression partielle artérielle en CO₂ peut être mesurée de deux façons, selon la température. La mesure en stratégie alpha-stat réalise la mesure de pression partielle en CO₂ à la température standard de 37°, indépendamment de la température réelle du patient, alors que la stratégie pH-stat mesure la pression partielle en CO₂ à la température réelle du patient. A des températures du patient proches de 37°C, la différence entre les deux stratégies est très faible, mais à des températures proches de 32°C ou 33°C, la différence entre les deux mesures peut être importante, jusqu'à 5 à 7 mmHg. Cette différence est significative cliniquement, car le gaz carbonique influence la circulation cérébrale qui est très sensible à la pression partielle en gaz carbonique(153,166). Une pression en CO₂ élevée, induit une vasodilatation cérébrale, augmente le débit cérébral et peut augmenter la pression intracrânienne, alors qu'une pression diminuée en CO₂ diminue la pression intracrânienne et induit une vasoconstriction cérébrale qui peut prédisposer à une ischémie cérébrale. Après un AC, la pression artérielle en CO₂ doit être maintenue entre les

limites normales(73,167), mais les recommandations ne spécifient pas dans quelle stratégie la pression partielle en CO₂ doit être mesurée, la normalité ne pouvant pas être acquise à la fois dans les deux stratégies, notamment à des températures de 32 à 34°C. Chez les patients réanimés après un AC, la stratégie de mesure et la normalisation de la pression en gaz carbonique est très importante pour éviter d'aggraver les lésions neurologiques installées lors de l'AC. Nous avons réalisé une étude en crossover chez des patients post AC, permettant de comparer les effets sur la circulation cérébrale des deux stratégies de normalisation de la pression artérielle en gaz carbonique, à la température théorique de 37°C (alpha-stat), ou à la température réelle du patient (pH-stat).

8.2 Influence of alpha-stat and pH-stat blood gas management strategies on cerebral blood flow and oxygenation in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest: a crossover study

Influence of α -Stat and pH-Stat Blood Gas Management Strategies on Cerebral Blood Flow and Oxygenation in Patients Treated With Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest: A Crossover Study*

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Objectives: In patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest, two blood gas management strategies are used regarding the $Paco_2$ target: α -stat or pH-stat. We aimed to compare the effects of these strategies on cerebral blood flow and oxygenation.

*See also p. 1950.

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This study was performed at the Intensive Care Unit Department of Lariboisière University Hospital, Paris, France.

Drs. Voicu and Deye contributed equally to this work and are cofirst authors of this article.

Dr. Vigué lectured for Laboratoire français du Fractionnement et de Biotechnologie (LFB) and Octapharma. Dr. Vigué and his institution consulted for LFB and received grant support from Thermofischer. Dr. Mebazaa consulted for Bayer, Cardiorientis, and Vifor and lectured for Alere, Edwards, Novartis, and Orion. Dr. Baud received support for article research from the Ministère Français de la Santé. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Design: Prospective observational single-center crossover study.

Setting: ICU of University hospital.

Patients: Twenty-one therapeutic hypothermia-treated patients after out-of-hospital cardiac arrest more than 18 years old without history of cerebrovascular disease were included.

Interventions: Cerebral perfusion and oxygenation variables were compared in α -stat ($Paco_2$ measured at 37°C) versus pH-stat ($Paco_2$ measured at 32–34°C), both strategies maintaining physiological $Paco_2$ values: 4.8–5.6 kPa (36–42 torr).

Measurements and Main Results: Bilateral transcranial middle cerebral artery flow velocities using Doppler and jugular vein oxygen saturation were measured in both strategies 18 hours (14–23 hr) after the return of spontaneous circulation. Pulsatility and resistance indexes and cerebral oxygen extraction were calculated. Data are expressed as median (interquartile range 25–75) in α -stat versus pH-stat. No differences were found in temperature, arterial blood pressure, and oxygenation between α -stat and pH-stat. Significant differences were found in minute ventilation ($p = 0.006$), temperature-corrected $Paco_2$ (4.4 kPa [4.1–4.6 kPa] vs 5.1 kPa [5.0–5.3 kPa], $p = 0.0001$), and temperature-uncorrected $Paco_2$ ($p = 0.0001$). No differences were found in cerebral blood velocities and pulsatility and resistance indexes in the overall population. Significant differences were found in jugular vein oxygen saturation (83.2% [79.2–87.6%] vs 86.7% [83.2–88.2%], $p = 0.009$) and cerebral oxygen extraction (15% [11–20%] vs 12% [10–16%], $p = 0.01$), respectively. In survivors, diastolic blood velocities were 25 cm/s (19–30 cm/s) versus 29 cm/s (23–35 cm/s) ($p = 0.004$), pulsatility index was 1.10 (0.97–1.18) versus 0.94 (0.89–1.05) ($p = 0.027$), jugular vein oxygen saturation was 79.2 (71.1–81.8) versus 83.3% (76.6–87.8) ($p = 0.033$), respectively. However, similar results were not found in nonsurvivors.

Conclusions: In therapeutic hypothermia-treated patients after out-of-hospital cardiac arrest at physiological PaCO_2 , α -stat strategy increases jugular vein blood desaturation and cerebral oxygen extraction compared with pH-stat strategy and decreases cerebral blood flow velocities in survivors. (*Crit Care Med* 2014; 42:1849–1861)

Key Words: blood gases; carbon dioxide; cardiac arrest; cerebral blood flow; cerebral oxygen extraction; therapeutic hypothermia

In out-of-hospital cardiac arrest (OHCA) patients, neurological injury is a major cause of mortality (1). Cerebral perfusion depends on PaCO_2 , hypocapnia leading to cerebral vasoconstriction and ischemia while hypercapnia may lead to cerebral vasodilation, and increased intracranial pressure (2, 3). Therefore, ensuring physiological PaCO_2 in OHCA patients seems important to prevent worsening of the neurological status (1, 4–6). Therapeutic hypothermia (TH) is the major therapeutic measure improving prognosis and neurological outcome after OHCA (1). Hypothermia may lead to dyscarbia especially in this situation (7, 8). Normocapnia in hypothermic patients can be achieved based on two different blood gas management strategies, α -stat and pH-stat (9). In the α -stat strategy, mechanical ventilation is set to achieve physiological PaCO_2 measured at 37°C, unadjusted to the patient's temperature, whereas in the pH-stat strategy, ventilation is set to achieve physiological PaCO_2 measured at the patient's actual temperature. The latter strategy leads to a relative hypoventilation compared with the α -stat strategy. The effect of PaCO_2 on cerebral perfusion and oxygenation has been assessed by several methods, including the cerebral blood flow (CBF) velocities and pulsatility index (PI) measured by transcranial Doppler technique and internal jugular vein oxygen saturation (Sjvo_2) (9–11). Randomized trials showing improved survival in OHCA patients managed with TH used temperature-corrected CO_2 measurements (pH-stat management) (12) or a management strategy that was not specified (13). Several experimental randomized trials in deeply hypothermic pigs showed that pH-stat strategy is associated with an improved cerebral oxygenation, less abnormalities in cerebral metabolism, and even better short-term neurological outcome compared with α -stat management (14–16). Several randomized trials performed in profoundly hypothermic patients (28–32°C) undergoing cardiopulmonary bypass showed that pH-stat management may offer the advantage of less episodes of internal jugular vein oxygen desaturation and better regional cerebral oxygen saturation, compared with α -stat management (9, 17), but raised the question of “luxury cerebral perfusion” (18). Ensuring a higher Sjvo_2 may influence outcome since low Sjvo_2 was associated with poorer prognosis after head injury (19), but the influence of the pH-stat versus α -stat strategy on outcome is still debated since α -stat strategy seems associated with better cerebral autoregulation (9, 20, 21). The increased CBF in pH-stat strategy may predispose to embolic ischemic events during heart surgery although this was not confirmed in an experimental study (14).

In patients with stroke undergoing TH, pH-stat strategy was not only associated with an increased CBF but also associated with an increased intracranial pressure at day 3 (22).

A study performed in eight OHCA patients managed with pH-stat strategy ventilated to CO_2 tensions considered as “lower and upper threshold normocapnia” (4.3 and 6.0 kPa, respectively) showed that “lower threshold normocapnia” resulted in lower Sjvo_2 and CBF mean velocities, suggesting an increased risk of cerebral ischemia (11). To date, no study including OHCA patients treated with TH and ventilated with strictly physiological PaCO_2 according to α -stat versus pH-stat strategies has been performed. Furthermore, no recommendations exist regarding the blood gas management strategy indicated in OHCA patients during TH (1) in spite of the potential influence on outcome of the PaCO_2 management (4, 5).

We therefore performed a prospective physiological study comparing the effects of two different management strategies, α -stat and pH-stat, maintaining strictly physiological PaCO_2 on CBF using as main evaluation criterion the CBF velocities, and as secondary evaluation criterion the cerebral oxygenation. We hypothesized that one of these strategies could offer a more appropriate cerebral perfusion and/or oxygenation.

MATERIALS AND METHODS

This observational single-center prospective crossover study included patients 18 years old or older resuscitated from OHCA, with stable return of spontaneous circulation (ROSC) and treated with TH. We excluded patients with in-hospital cardiac arrest, unsustained ROSC (defined as impossibility to maintain ROSC with palpable pulse for > 20 min) (23), known previous history of ischemic or hemorrhagic cerebrovascular disease, unstable hemodynamic conditions (defined as blood pressure variations requiring inotrope/vasopressor infusion changes or fluid repletion in the last hour before the beginning of the protocol), unstable TH during the maintenance phase, neurological etiology of the OHCA, acute respiratory distress syndrome, and patients with deficient temporal bone transcranial Doppler window.

This study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The Ethics Committee of our institution (CERB GHU Nord) approved our study (Institutional Review Board of Paris North Hospital No. IRB00006477) and surviving patients or their next of kin if necessary gave written informed consent.

Patient Management

Prehospital resuscitation of the patients was performed according to guidelines as described elsewhere (24). Resuscitation intervals were defined as no flow (time from collapse to first cardiopulmonary resuscitation) and low flow (time from first cardiopulmonary resuscitation to ROSC). TH in our department is performed in patients resuscitated from an OHCA with ventricular fibrillation as initial rhythm but also after other initial rhythms such as asystole or pulseless electrical activity (25). During TH, sedation was performed with continuous infusion of midazolam 5–15 mg/hr and sufentanyl

5–20 µg/hr. Neuromuscular blockade was induced using atracurium 0.5–1 mg/kg/hr to favor cooling and prevent shivering according to the train of four monitoring (26).

TH was initiated as soon as possible by administration of cold saline at 4°C followed by application of ice packs and cooling blankets or endovascular methods for a target temperature of 32–34°C as recommended (1). All measurements were performed during a stable maintenance phase of TH. Core temperature was measured using esophageal or urinary Foley catheters with thermistor probe (Tyco Healthcare, France).

Circulatory function was monitored by radial or femoral arterial catheter with systolic blood pressure maintained greater than or equal to 90 mm Hg and mean arterial pressure (MAP) greater than or equal to 65 mm Hg. Hypotension was, if necessary, treated with dobutamine and norepinephrine or epinephrine titrated to the targeted blood pressure according to the cardiac output monitored using echocardiogram, Vigileo (Edwards Lifesciences, Irvine, CA) or PiCCO plus (Pulsion Medical Systems, Munich, Germany), according to the physician in charge. Fluid management was left at the discretion of the attending physician.

Study Protocol

After inclusion in the study, a 4F catheter was inserted in the right or left internal jugular vein and advanced until resistance was encountered, then withdrawn until blood could be aspirated (9). Its correct position was verified with a lateral skull radiograph and it was used for internal jugular blood sampling.

Ventilation was performed according to the α -stat and pH-stat strategies in order to target physiological PaCO_2 . Normal CO_2 blood gas pressure varies across different studies, 33–47 torr (4.4–6.3 kPa) (9) or 34–41 torr (4.5–5.5 kPa) (10). The target “physiological” range of CO_2 tension in our study was considered as greater than or equal to 36 torr (4.8 kPa) and less than or equal to 42 torr (5.6 kPa). According to the α -stat strategy, minute ventilation (V_e) was adapted to target an arterial PaCO_2 within physiological limits considered in this study and measured at 37°C. Ventilation according to pH-stat strategy targeted the same physiological PaCO_2 measured at the actual temperature of the patient, that is, “temperature-corrected.” In our ICU, ventilation is set in volume-controlled mode using either α -stat or pH-stat strategy according to the physician in charge. If a patient was correctly ventilated in one strategy (i.e., in the physiological PaCO_2 range), the first set of measurements was performed and V_e was secondarily modified to target the opposite strategy for the second set of measurements 60 minutes later (Fig. 1). The choice of the first strategy of blood gas management was not randomized in order to minimize the number of PaCO_2 changes per patient. Ventilation settings were modified using the gradient between PaCO_2 and end-tidal CO_2 (EtCO_2) to adapt V_e by changing the respiratory rate and/or the tidal volume.

All measurements were performed during a stable hemodynamic phase. No fluid depletion or repletion was administered, and no adjustments in the FiO_2 were made between the measurements.

Since cerebral autoregulation may be impaired in some patients, especially those with a dismal neurological prognosis (27), variables in our study were also analyzed separately in survivors and nonsurvivors.

Measured Variables

During each strategy, arterial blood gases, pH, arterial blood lactate, serum sodium, glucose, jugular vein lactate concentrations, and Sjvo_2 were collected (Fig. 1). Bilateral transcranial Doppler velocities were measured simultaneously and represented the main evaluation criterion of the study.

During the two strategies, transcranial color-coded Doppler was performed by the same physician blinded to the ventilation strategies and the blood gas results, using a Vivid-i device and a 1.5–2.5 MHz matrix ultrasound transducer (GE Medical Systems Phoenix, AZ). Middle cerebral artery was

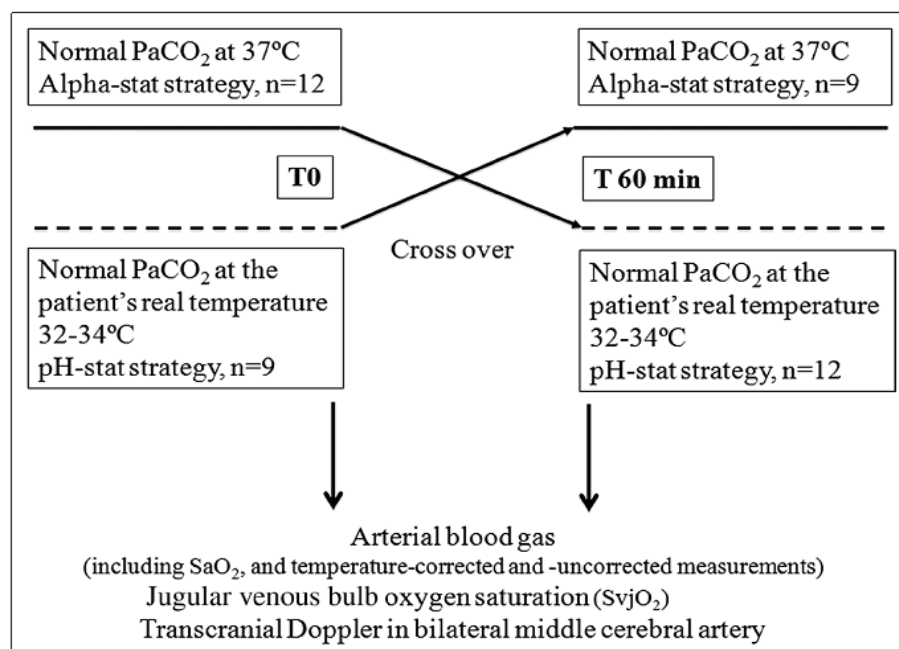


Figure 1. Study design. Ventilation targeting physiological PaCO_2 values was performed in the initial phase according to the physician in charge either in α -stat or in pH strategy. After the initial transcranial Doppler and arterial (SaO_2) and jugular venous bulb oxygen saturation (Sjvo_2) measurements, the opposite ventilation strategy was adopted. One hour later, the second set of measurements was performed. Twelve patients were initially ventilated in α -stat and nine patients in pH-stat strategy. Arterial CO_2 tension was maintained in each strategy in the physiological range: 4.8–5.6 kPa.

examined bilaterally through the temporal bone window at a 45–55 mm depth according to the standard technique (28).

Systolic (V_s), diastolic (V_d), and mean (V_m) middle cerebral artery blood flow velocities were recorded and analyzed bilaterally. PI was calculated as $(V_s - V_d)/V_m$. Resistance index (RI) was calculated as $(V_s - V_d)/V_s$ (29).

In order to rule out technical problems in the cerebral blood velocities measurement due to intraobserver variability, a comparison of velocities recorded on the right versus left side was performed in all patients.

Blood gas samples from the jugular vein and the arterial catheter were immediately analyzed using a point-of-care automate (RapidLab 1265 Bayer Health Care, France). EtCO_2 was measured using a portable capnograph (Oridion Microcap, Oridion Medical Systems, Jerusalem, Israel). Arterial and jugular vein oxygen content (mL/dL) were calculated using blood hemoglobin concentration (Hb), oxygen saturation (So_2), and blood oxygen tension (Po_2) as $[\text{Hb} (\text{g/dL}) \times 1.34 \times \text{So}_2 (\%) / 100] + \text{Po}_2 (\text{torr}) \times 0.003$ (30). Arteriojugular oxygen content difference (AJD_{O_2}) was calculated as the difference in oxygen content between arterial and jugular vein blood. Cerebral oxygen extraction (CEO_2) was defined as the difference between the arterial and jugular venous bulb oxygen content divided by the arterial oxygen content (31).

All clinical variables including ventilation and hemodynamic variables were recorded. Neurological outcome was assessed according to the Cerebral Performance Category (CPC) score until hospital discharge (32). Data were recorded according to the Utstein-style recommendations for reporting resuscitation outcomes (23).

Statistical Analysis

Based on the results by Bisschops et al (10) who found an SD of 9.5 cm/s in Doppler CBF velocities in OHCA patients and by Pynnönen et al (11) who found an average increase of 10–20% in mean velocity flow in upper threshold versus lower threshold hypercapnia, and considering an α coefficient of 0.05 and a statistical power of 0.90, the sample size for this study was estimated at 43, corresponding to 21 or 22 patients in a crossover study. Continuous variables were expressed as medians (interquartile range 25–75) and compared using the two-tailed Wilcoxon test for paired samples and two-tailed Mann-Whitney test for independent samples. Categorical variables were expressed as percentages and compared using Fisher exact test. Differences were considered significant if p is less than 0.05. The results for general clinical and biological variables were expressed in the first versus the second set of measurements according to CONSolidated Standards of Reporting Trials statement for reporting trials. Statistical analysis was performed using MedCalc, version 11.0.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Patients' General Characteristics

Among the 25 patients screened from April 2011 to August 2012, four (15%) had unsuitable transtemporal Doppler window and were excluded. The general characteristics of the 21

patients included are shown in Table 1. Glasgow coma scale at admission was 3 (3–3). Nine patients (43%) survived to hospital discharge. Median duration of the ICU stay was 7 days (5–9 d), and the duration of hospitalization was 8 days (6–12 d). On hospital discharge, three survivors (14%) were CPC 1, four (19%) were CPC 2, and two (10%) were CPC 3. All 12 non-survivors died of severe postanoxic encephalopathy or brain death. Nine patients (43%) were first ventilated using pH-stat strategy and 12 patients (57%) using α -stat strategy (Fig. 1). No fluid repletion was required during the protocol.

α -Stat and pH-Stat Comparisons in the Overall Population

The general clinical and biological variables in the first versus the second set of measurements are shown in Table 2. The time interval between ROSC and the first set of measurements was 18 hours (14–23 hr). The second set of measurements was performed 73 minutes (49–87 min) after the first set, and only three patients had the second set of measurements greater than

TABLE 1. General Characteristics of the Patients at Baseline and at Admission ($n = 21$)

Variable	Value
Age, yr	55 [46–63]
Male sex (%)	17 (81)
Risk factors (%)	
Hypertension	3 (14)
Hypercholesterolemia	1 (5)
Diabetes	1 (5)
Active smoking	8 (38)
History of coronary heart disease	3 (14)
Bystander CPR (%)	11 (52)
No flow (time from collapse to first CPR), min	3 [1–12]
Low flow (time from first CPR to return of spontaneous circulation), min	20 [11–29]
Initial rhythm (%)	
Ventricular fibrillation	12 (57)
Asystole	8 (38)
Pulseless electrical activity	1 (5)
Cause of out-of-hospital cardiac arrest (%)	
Acute myocardial infarction	9 (43)
Hypoxemia	4 (19)
Chronic ischemic heart disease	3 (14)
Miscellaneous	5 (24)

CPR = cardiopulmonary resuscitation.

Results are expressed as median [interquartile range 25–75] or number (percentages).

TABLE 2. General Clinical and Biological Variables in the First Versus the Second Set of Measurements in the Overall Population ($n = 21$)

Variable	First Measurement	Second Measurement
Core temperature (°C)	33.3 [32.3–33.6]	33.2 [33.0–33.8]
Systolic arterial blood pressure (mm Hg)	117 [108–126]	117 [110–136]
Diastolic arterial blood pressure (mm Hg)	58 [50–65]	58 [51–64]
Heart rate (beats/min)	79 [65–94]	80 [64–98]
Patients on catecholamines, n (%)	12 (57)	12 (57)
Epinephrine infusion rate ^a (mg/hr)	1.0	0.95
Norepinephrine infusion rate ^b (mg/hr)	1.3 [0.8–3.2]	1.2 [0.8–3.6]
Dobutamine infusion rate ^c (μg/kg/min)	9 [6–12]	9 [6–12]
Serum glucose concentration (mmol/L)	6.6 [5.5–8.3]	6.6 [5.2–7.9]
Serum sodium concentration (mmol/L)	140 [139–144]	141 [139–143]
Arterial lactate concentration (mmol/L)	1.45 [0.96–5.01]	1.59 [0.85–3.81]
Jugular vein lactate concentration (mmol/L)	1.87 [1.10–5.56]	1.84 [0.98–3.81]

^a $n = 2$.^b $n = 10$.^c $n = 8$.

Results are expressed as median [interquartile range 25–75] unless otherwise specified. According to CONSolidated Standards of Reporting Trials statement for reporting trials, results are expressed in the first versus the second set of measurements and p values (although > 0.1 for all variables) are not provided.

100 minutes after the first one (149, 192, and 270 min, respectively). Conversely, only two patients had the second set of measurements less than 45 minutes after the first one (43 and 39 min). In three patients, due to the technical problems, the internal jugular vein saturation was not available.

No significant differences were found in CBF velocities, PI, and RI between the two strategies in the overall population (Table 3 and Fig. 2). SjvO₂ was significantly lower in the α -stat versus the pH-stat strategy, whereas AJD_{O₂} was significantly higher as well as CEO₂ (Table 3 and Fig. 3). No significant differences were observed between right and left side CBF velocities measured by Doppler ($p > 0.1$) in both strategies.

According to the study protocol, significant differences were found in the ventilation variables: Ve, respiratory rate, and tidal volume, which were higher in the α -stat strategy, leading to significant differences in PaCO₂ and arterial pH (Table 3). No significant differences were found in catecholamines infusion rate, sedative drug infusion, circulatory variables, and lactate, glucose, and sodium concentrations between the two strategies. There was no difference between PaCO₂ at 37°C (normocapnia in α -stat) and PaCO₂ at 33°C (normocapnia in pH-stat): 5.2 kPa (5.0–5.5 kPa) versus 5.1 kPa (5.0–5.3 kPa), respectively ($P=0.85$).

Comparison of α -Stat Strategy Versus pH-Stat Strategy in Survivors

According to the study protocol, significant differences were found in PaCO₂ and arterial pH in α -stat versus pH-stat strategy (Table 4). No significant differences were found in catecholamine infusion rate, circulatory variables, and arterial

lactate, glucose, and sodium concentrations between the two strategies.

Diastolic CBF velocities were significantly lower in α -stat versus pH-stat, and mean and systolic velocities tended to be lower. PI and RI were higher in α -stat versus pH-stat. SjvO₂ was significantly lower in α -stat versus pH-stat, whereas AJD_{O₂} and CEO₂ were higher in α -stat versus pH-stat (Table 4 and Figs. 2 and 3).

Comparison of α -Stat Strategy Versus pH-Stat Strategy in Nonsurvivors

Significant differences found in PaCO₂ and arterial pH in α -stat versus pH-stat strategy (Table 4), without significant differences in catecholamine infusion rate, circulatory variables, and arterial lactate, glucose, and sodium concentrations. No significant differences were found between the two strategies in Doppler velocities or cerebral oxygenation variables (Table 4). Contrary to findings in survivors, PI and RI were similar or tended to be lower in α -stat versus pH-stat strategy.

Comparison of Survivors Versus Nonsurvivors

No-flow duration (but not low-flow duration), creatinine, lactate concentrations, and S100B protein values were lower in survivors ($n = 9$) versus nonsurvivors ($n = 12$), whereas arterial pH tended to be higher in survivors (Table 5).

Right Vs, Vd, and Vm in α -stat were higher in nonsurvivors than in survivors (66 cm/s [54–70 cm/s] vs 123 cm/s [76–155 cm/s], $p = 0.01$; 48 cm/s [25–65 cm/s] vs 25 cm/s [19–30 cm/s], $p = 0.04$; and 73 cm/s [43–99 cm/s] vs 37 cm/s [31–44 cm/s], $p = 0.027$, respectively). Similar results were obtained in pH-stat and in the left hemisphere.

TABLE 3. Cerebral Blood Flow, Blood Gas, and Ventilation Variables in α -Stat Versus pH-Stat Strategies in the Overall Population

Variable	α -Stat	pH-Stat	<i>p</i>
Right systolic cerebral blood flow velocity (cm/s)*	73 [62–139]	87 [70–130]	0.84
Right mean cerebral blood flow velocity (cm/s)*	44 [32–84]	48 [36–72]	0.88
Right diastolic cerebral blood flow velocity (cm/s)*	30 [20–50]	35 [25–48]	0.62
Right pulsatility index*	1.08 [0.93–1.17]	1.00 [0.86–1.19]	0.85
Right resistance index*	0.63 [0.57–0.66]	0.60 [0.55–0.66]	0.82
Jugular vein oxygen saturation (%)	83.2 [79.2–87.6]	86.7 [83.2–88.2]	0.009
Arteriojugular oxygen content difference (mL/dL)	2.70 [2.29–3.34]	2.21 [1.75–2.93]	0.01
Cerebral oxygen extraction (%)	17 [12–21]	13 [11–16]	0.01
Arteriojugular lactate difference concentration (mmol/L)*	−0.06 [−0.17 to 0.05]	−0.04 [−0.22 to 0.01]	0.94
Jugular vein lactate concentration (mmol/L)	1.84 [1.10–4.99]	2.56 [1.47–7.06]	0.43
pH _{art} (T°-uncorrected)	7.32 [7.22–7.37]	7.26 [7.21–7.32]	0.0001
pH _{art} (T°-corrected)	7.38 [7.26–7.42]	7.30 [7.27–7.38]	0.0001
Pao ₂ (T°-uncorrected, kPa)	15.3 [14.4–16.9]	15.3 [12.7–17.3]	0.64
Pao ₂ (T°-corrected, kPa)	12.4 [11.3–14.0]	12.3 [10.5–14.3]	0.63
Paco ₂ (T°-uncorrected, kPa)	5.2 [5.0–5.5]	6.1 [5.8–6.4]	0.0001
Paco ₂ (T°-corrected, kPa)	4.4 [4.3–4.6]	5.1 [5.0–5.3]	0.0001
Arterial oxygen saturation (%)	97.9 [97.8–98.3]	97.7 [96.8–98.5]	0.61
Minute ventilation (L/min)	7.1 [6.3–9.4]	6.4 [4.7–7.3]	0.0005
Tidal volume (mL)	475 [402–510]	450 [387–483]	0.006
Respiratory rate (breaths/min)	17 [14–23]	14 [12–17]	0.0003
Positive end-expiratory pressure (cm H ₂ O)	5 [5–7]	5 [5–6]	0.11

pH_{art} = arterial pH, T° = core temperature.

*Similar nonsignificant results were observed for arterial lactate concentration, systolic blood pressure, mean blood pressure, diastolic blood pressure, heart rate, catecholamines, T°, and Doppler velocities in the left hemisphere.

Results are expressed as median [interquartile range 25–75].

In α -stat strategy, Sjvo₂ was lower in survivors versus non-survivors, whereas AJD_{O₂} was higher (Table 5 and Fig. 4). CEo₂ was higher in survivors versus nonsurvivors in both strategies. None of the other blood gas and Doppler variables including PI and RI were significantly different. No differences were observed in catecholamine infusion rate or sedative drug infusion between survivors and nonsurvivors in either strategy.

DISCUSSION

The most important finding in this study maintaining a physiological Paco₂ target is that Sjvo₂ was significantly lower in α -stat management compared with pH-stat strategy, whereas AJD_{O₂} and CEo₂ were significantly higher in the included OHCA patients, while no differences were found in CBF Doppler variables in the overall population. The second important finding is that CBF velocities and Sjvo₂ decreased, whereas PIs and RIs, ADJ_{O₂}, and CEo₂ increased in α -stat compared with pH-stat strategy in survivors, but not in nonsurvivors.

Transcranial Doppler Data

Transcranial Doppler measurements in our patients showed that most of the diastolic velocities were within normal range 21–77 cm/s according to a previous study including 182 normal subjects (33). PI was slightly higher in our patients compared with normal subjects (1.08 ± 0.30 vs 0.70 ± 0.10, respectively) (34), probably due to changes in the cerebrovascular flow in TH-treated OHCA patients, as previously suggested (10). Furthermore, PI measured in our patients was in agreement with a recent study that found a median PI of 1.23 (0.94–1.45), relatively stable during a 100-hour period monitored in 10 OHCA patients treated with TH (35).

Significant changes in CBF variables were found in some studies showing that the reactivity to Paco₂ of the cerebral circulation in OHCA patients is preserved (10, 36). In the study by Buunk et al (36) performed before the hypothermia era, hypercapnia was associated with significant increase in CBF velocities and decrease in PI. However, in this study, Paco₂ was maintained between 3 and 4 kPa in the

TABLE 4. Cerebral Doppler and Cerebral Oxygenation Variables in α -Stat Versus pH-Stat in Survivors and Nonsurvivors

Variable	α -Stat	pH-Stat	<i>p</i>
Survivors (<i>n</i> = 9)			
pH _{art} (<i>T</i> ^c -corrected)	7.42 [7.38–7.43]	7.36 [7.33–7.38]	0.004
Pao ₂ (<i>T</i> ^c -corrected, kPa)	11.6 [11.2–15.2]	13.8 [10.5–15.6]	0.57
Paco ₂ (<i>T</i> ^c -corrected, kPa)	4.4 [4.3–4.5]	4.9 [4.8–5.5]	0.004
Vs right (cm/s)	66 [54–70]	73 [60–78]	0.25
Vm right (cm/s)	37 [31–44]	41 [34–46]	0.074
Vd right (cm/s)	25 [19–30]	29 [23–35]	0.004
PI right	1.10 [0.97–1.18]	0.94 [0.89–1.05]	0.027
RI right	0.63 [0.59–0.66]	0.58 [0.56–0.62]	0.028
Vs left (cm/s)	75 [63–80]	75 [72–87]	0.039
Vm left (cm/s)	43 [38–46]	48 [43–56]	0.02
Vd left (cm/s)	29 [24–32]	34 [30–37]	0.004
PI left	1.04 [0.87–1.2]	0.89 [0.79–1.21]	0.039
RI left	0.61 [0.55–0.68]	0.56 [0.52–0.67]	0.039
Sjvo ₂ (%)	79.2 [71.1–81.8]	83.3 [76.6–87.8]	0.033
AJD _{O₂} (mL/dL)	3.34 [2.81–5.22]	2.99 [1.89–3.68]	0.047
CEo ₂ (%)	21 [17–29]	16 [13–21]	0.031
Nonsurvivors (<i>n</i> = 12)			
pH _{art} (<i>T</i> ^c -corrected)	7.31 [7.17–7.39]	7.28 [7.16–7.31]	0.014
Pao ₂ (<i>T</i> ^c -corrected, kPa)	12.4 [11.3–13.7]	12.0 [10.4–13.7]	0.97
Paco ₂ (<i>T</i> ^c -corrected, kPa)	4.5 [4.3–4.8]	5.2 [5.1–5.3]	0.0005
Vs right (cm/s)	123 [76–155]	115 [83–138]	0.62
Vm right (cm/s)	73 [43–99]	68 [47–77]	0.42
Vd right (cm/s)	48 [25–65]	44 [27–53]	0.18
PI right	1.04 [0.82–1.18]	1.09 [0.84–1.28]	0.09
RI right	0.62 [0.53–0.66]	0.63 [0.54–0.69]	0.13
Vs left (cm/s)	128 [71–142]	106 [99–138]	0.97
Vm left (cm/s)	72 [43–92]	60 [49–91]	0.47
Vd left (cm/s)	45 [29–65]	37 [27–59]	0.23
PI left	0.96 [0.74–1.22]	1.13 [0.98–1.35]	0.034
RI left	0.59 [0.50–0.67]	0.64 [0.59–0.71]	0.034
Sjvo ₂ (%)	85.8 [83.9–89.2]	87.3 [85.6–88.4]	0.24
AJD _{O₂} (mL/dL)	2.38 [1.85–2.77]	2.02 [1.68–2.51]	0.28
CEo ₂ (%)	13 [10–16]	12 [10–13]	0.32

pH_{art} = arterial pH, *T*^c = core temperature, Vs = systolic cerebral blood flow velocity, Vm = mean cerebral blood flow velocity, Vd = diastolic cerebral blood flow velocity, PI = pulsatility index, RI = resistance index, Sjvo₂ = jugular vein oxygen saturation, AJD_{O₂} = arteriojugular oxygen content difference, CEo₂ = cerebral oxygen extraction.

No significant differences were observed for the following variables: core temperature, systolic blood pressure, diastolic blood pressure, and mean blood pressure, heart rate, catecholamine infusion rate, and arteriojugular lactate difference. Results are expressed as median [interquartile range 25–75].

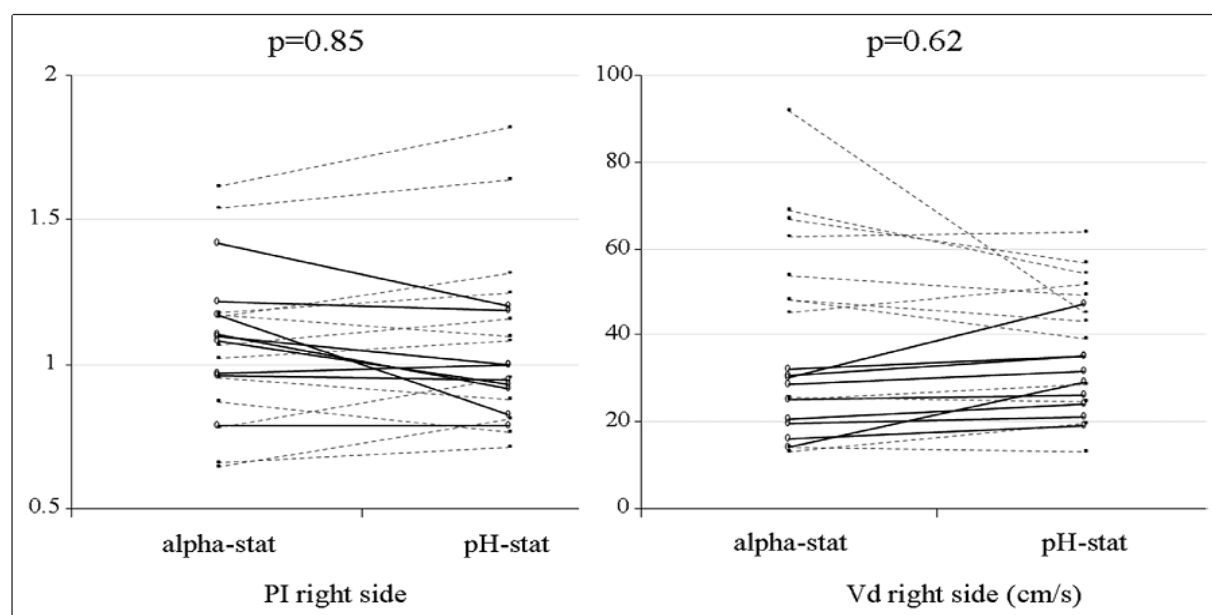


Figure 2. Individual changes of main Doppler variables in the right hemisphere in α -stat versus pH-stat strategy ($n = 21$). Survivors are shown in *thick black lines* and nonsurvivors in *dashed gray lines* (see text and Table 4 for significant differences found in survivors). PI = pulsatility index, Vd = diastolic cerebral blood velocity.

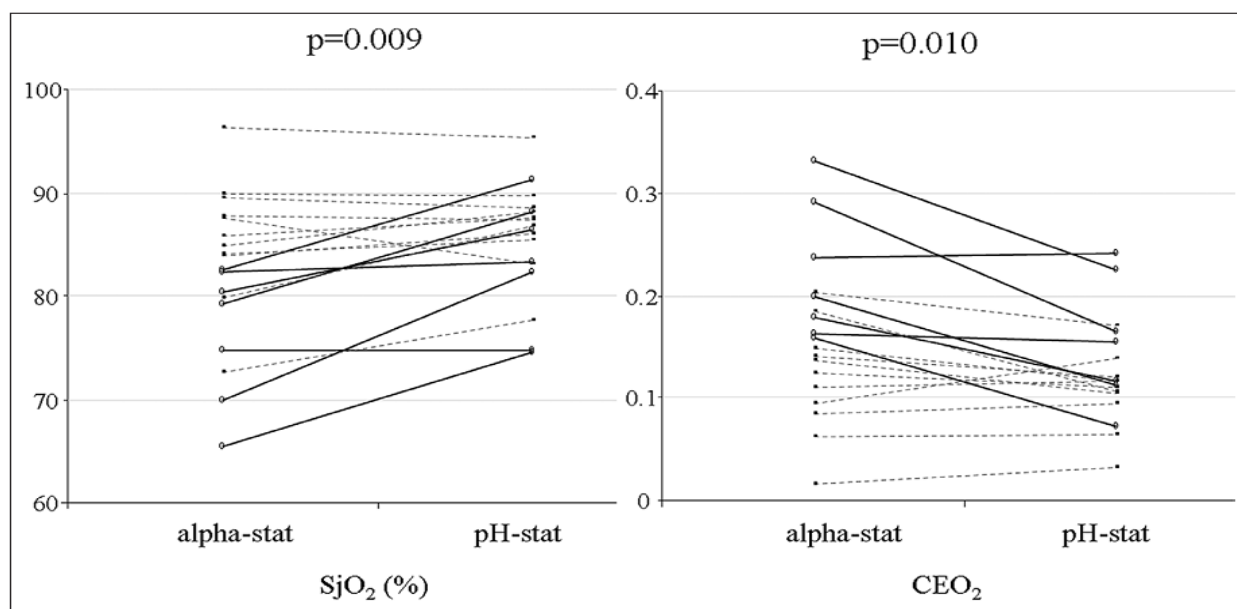


Figure 3. Individual changes of cerebral oxygenation variables in α -stat versus pH-stat strategy ($n = 18$). Survivors are shown in *thick black lines* and nonsurvivors in *dashed gray lines* (see text and Table 4 for significant differences found in survivors). SjvO₂ = jugular vein oxygen saturation, CEO₂ = cerebral oxygen extraction.

TABLE 5. Clinical and Biological Variables in Survivors Versus Nonsurvivors

Variable	Survivors (n = 9)	Nonsurvivors (n = 12)	p
Heart rate (beats/min), α -stat	64 [49–96]	86 [73–95]	0.09
No-flow (time from collapse to first CPR) duration (min)	2 [1–3]	11 [4–15]	0.01
Low-flow (time from first CPR to ROSC) (min)	13 [11–28]	26 [18–30]	0.18
Time to ROSC (min)	15 [13–31]	34 [25–40]	0.004
Ventricular fibrillation as initial rhythm, n (%)	9 (100)	3 (25)	0.001
Asystole as initial rhythm, n (%)	0 (0)	8 (66.7)	0.005
Left ventricular ejection fraction (%)	40 [34–48]	50 [40–65]	0.04
Hemoglobin concentration	12.9 [11.6–13.6]	13.6 [12.3–14.9]	0.26
Lactate _{art} , α -stat (mmol/L)	0.76 [0.66–1.93]	2.64 [1.55–6.29]	0.009
Lactate _{art} , pH-stat (mmol/L)	0.85 [0.66–1.68]	2.64 [1.55–6.29]	0.006
pH _{art} (T° -uncorrected), α -stat	7.37 [7.33–7.37]	7.26 [7.12–7.33]	0.056
pH _{art} (T° -uncorrected), pH-stat	7.31 [7.27–7.33]	7.24 [7.10–7.25]	0.03
pH _{art} (T° -corrected), α -stat	7.42 [7.38–7.43]	7.31 [7.17–7.39]	0.056
pH _{art} (T° -corrected), pH-stat	7.36 [7.33–7.38]	7.28 [7.16–7.31]	0.047
Sjvo ₂ , α -stat (%)	79.2 [71.1–81.8]	85.8 [83.9–89.2]	0.004
Sjvo ₂ , pH-stat (%)	83.3 [76.6–87.8]	87.3 [85.0–88.7]	0.21
AJD _{O₂} , α -stat (mL/dL)	3.34 [2.81–5.22]	2.39 [1.86–2.77]	0.008
AJD _{O₂} , pH-stat (mL/dL)	2.99 [1.89–3.68]	2.02 [1.68–2.51]	0.13
CEo ₂ , α -stat (%)	21 [17–29]	13 [10–16]	0.001
CEo ₂ , pH-stat (%)	16 [13–22]	12 [10–13]	0.03
Patients on catecholamines, n (%)	5 (56)	7 (58)	1.00
Norepinephrine infusion rate (mg/hr)	0.8 [0.78–3.35] ^a	1.8 [0.73–3.3] ^a	0.8
Dobutamine infusion rate (μ g/kg/min)	5 ^b	10 [8–11] ^a	0.6
Creatinine (μ mol/L)	48 (42–61)	83 (65–128)	0.03
Neuronal-specific enolase (ng/L)	31 (21–41)	37 (26–85)	0.12
S100B protein (μ g/L)	0.131 (0.094–0.152)	0.588 (0.292–0.924)	0.0002

CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation, lactate_{art} = arterial lactate, pH_{art} = arterial pH, T° = temperature, Sjvo₂ = jugular vein oxygen saturation, AJD_{O₂} = arteriojugular oxygen content difference, CEo₂ = cerebral oxygen extraction.

^an = 5.

^bn = 3. Interquartiles were not calculated due to the small sample size.

No significant differences were observed between survivors and nonsurvivors for the following variables in either strategy: bystander CPR, core temperature, systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, minute ventilation, tidal volume, respiratory rate, positive end-expiratory pressure, catecholamine infusion rate, blood glucose, arteriojugular lactate difference, pulsatility index, and resistance index ($p > 0.10$).

Results are expressed as median [interquartile range 25–75] unless otherwise specified.

hyperventilation strategy and between 5 and 6 kPa in the hypoventilation strategy corresponding to 2 kPa of difference in PaCO₂ between the two strategies, much higher than in our patients. Therefore, the absence of significant difference in CBF velocities, PI, and RI in the two strategies in the overall population of our study may be partly explained by the relatively small difference in PaCO₂.

Studies assessing cerebral flow and oxygenation variables while targeting two different PaCO₂ levels showed that

ventilation-associated hypercapnia increases cerebral flow velocities while ventilation-associated hypocapnia decreases flow velocities, but this did not occur in the overall population in our study (9, 10). However, in our survivors, pH-stat management was associated with a modest but significant increase in Vd and an increase or tendency to increase in Vm and Vs compared with α -stat management. Furthermore, PI and RI decreased during the pH-stat strategy in survivors, these findings being in accordance with previous data on the

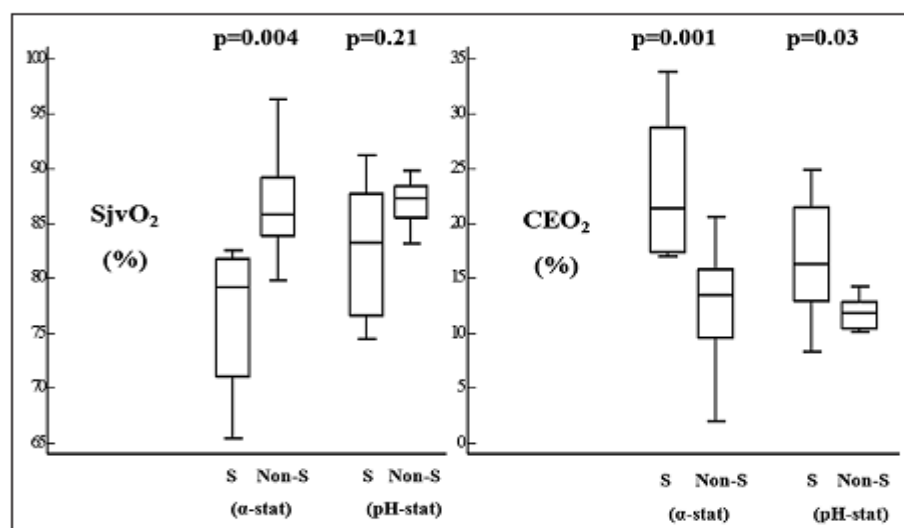


Figure 4. Cerebral oxygenation variables in survivors versus nonsurvivors in α -stat and pH-stat strategies. SjvO₂ = jugular vein oxygen saturation, CEO₂ = cerebral oxygen extraction, S = survivors, Non-S = nonsurvivors.

physiologic response to relative hypercapnia found in OHCA studies (36).

The reason for the absence of change in CBF velocities or even paradoxical changes in PI and RI in nonsurvivors remains unclear, but may be related to their critical physiological state. Indeed, two out of the 12 nonsurvivors progressed rapidly to brain death due to the initial extremely severe ischemic damages, and the rest died of severe anoxic injuries. These patients had lower arterial pH and higher creatinine, lactate, and S100B protein concentrations (Table 5). Furthermore, eight out of the 12 nonsurvivors had no-flow duration greater than or equal to 10 minutes and nine had low-flow duration greater than or equal to 20 minutes corresponding to prolonged durations of resuscitation. Due to their critical state, some of these patients may have lost the physiological response to CO₂, making differences in CBF velocities between α -stat and pH-stat strategies unapparent. Indeed, it has been shown that similar to our data, patients with intracranial hemorrhage and unfavorable prognosis have a significantly impaired reactivity to CO₂ (27). Another study found that in eight out of 18 of the cardiac arrest patients, cerebral autoregulation in response to MAP variation was significantly impaired (37). Similar results were found in a study of deeply hypothermic cardiac bypass patients showing impaired CBF regulation in 34% of the patients during hypothermia and in 53% during rewarming (38).

Doppler CBF velocities after OHCA are variable in time and may differ in survivors and nonsurvivors, but these findings are not constant in the literature (31, 39). Similar CBF velocities were found in survivors and nonsurvivors during the first 2 days after the OHCA (31), whereas higher CBF velocities were found in survivors 72 hours after the OHCA (31, 39). In our patients, CBF velocities, especially Vm, were higher in nonsurvivors than in survivors, which may be related to the

impaired autoregulation of CBF in some of these patients (27, 37, 38). Furthermore, nonsurvivors tended to have higher heart rate than survivors especially in α -stat strategy (64 vs 86/min, $p = 0.09$), which may have also influenced CBF velocities.

SjvO₂, ADJ_{O₂}, and CEO₂ Data

SjvO₂ demonstrated an interesting prognostic value in patients suffering from head injury in whom jugular vein blood desaturation is associated with worse prognosis (19). Similarly, very high or very low SjvO₂ values after head injury were associated with an unfavorable prognosis (40).

In our patients, the difference in SjvO₂ between α -stat and pH-stat strategies was significant but relatively modest. However, this was expected since the difference in PaCO₂ was also modest compared with other studies (11, 36) and since hypothermia decreases CEO₂ (31). SjvO₂ was significantly higher in pH-stat compared with α -stat strategy, similar to the results in a previous study by Hoover et al (9). This study showed that during more profound hypothermia (28–32°C) used in cardiopulmonary bypass and during the rewarming phase, SjvO₂ decreased in some patients to less than 50% in α -stat but not in pH-stat strategy. Before the use of TH, hyperventilation was associated with cerebral ischemia after cardiac arrest, with a significant increase in arteriojugular lactate difference and decrease in SjvO₂, whereas hypoventilation was associated with a significant increase in SjvO₂ (36). More recently, a study using exclusively pH-stat strategy found that ventilation at lower threshold normocapnia (4.3 kPa) was associated with a decrease in SjvO₂ compared with upper threshold normocapnia (6.0 kPa) and considered normocapnia in pH-stat strategy to be a safer approach (11).

Interestingly, the analysis of cerebral oxygenation variables after separating survivors and nonsurvivors showed that significant differences between α -stat and pH-stat strategies do exist in SjvO₂, ADJ_{O₂}, and CEO₂ in survivors but not in nonsurvivors. The reasons for the absence of changes of these variables in nonsurvivors may be related to the possibly impaired autoregulation and decrease in CO₂ reactivity as suggested in previous studies and discussed above (27).

α -Stat Versus pH-Stat Management

None of our patients had SjvO₂ lower than 69.9%, which may suggest that both strategies are safe as long as physiological PaCO₂ is achieved in spite of SjvO₂ being higher in pH-stat strategy.

However, since in pH-stat strategy SjvO₂ was higher than in α -stat strategy, the pH-stat strategy may prevent jugular vein

blood desaturation in OHCA patients in hypothermia and be considered a more secure management strategy. This result is consistent with the studies by Pynnönen et al (11) who found less jugular vein blood desaturation in upper threshold CO_2 in pH-stat strategy and Hoover et al (9) who found less jugular vein desaturation in pH-stat than in α -stat strategy in cardiac bypass patients. Similarly, CEo_2 was lower in pH-stat as this strategy may increase CBF and lead to less cerebral ischemia. However, pH-stat strategy may induce in patients with cerebrovascular disease a “cerebral steal phenomenon” diverting blood flow from areas with arterial stenosis toward zones with normal cerebral arteries, thus increasing the risk of focal ischemia (41). A deleterious effect of the pH-stat strategy may also be an increase in intracranial pressure but this seems to occur later, after the first 48 hours of hospital stay in TH-treated ischemic stroke patients (22), and was not found in OHCA patients ventilated at upper versus lower threshold normocapnia in pH-stat (11). A review of α -stat versus pH-stat management in cardiac surgery patients showed that pH-stat strategy may be associated with better intraoperative and postoperative outcome in pediatric patients, whereas in adults, three studies found no difference between the two management strategies and three other studies found better results with α -stat strategy (20).

In our patients as in other studies, α -stat strategy was associated with lower jugular vein blood saturation, but it may better preserve CBF autoregulation. Henriksen et al (42) showed that α -stat management allowed for better CBF autoregulation compared with pH-stat management in deeply hypothermic cardiac bypass patients. The α -stat management may allow for CBF autoregulation in a larger range of MAP, offering more protection against cerebral ischemia (41), and may be easier to implement than pH-stat management (43).

Since both strategies have certain physiological benefits, it may be hypothesized that each strategy may be preferred according to the physiological status of the patient. However, the clinical relevance of the pros and cons of the α -stat and pH-stat strategies are difficult to appreciate in the absence of a large trial directly comparing the clinical outcomes related to these strategies.

Previous studies that tested the effect of CO_2 -induced changes on cerebral perfusion either increased then decreased minute ventilation by 20% (10) or modified ventilation to obtain upper and lower threshold normocapnia (11). Our study provides new physiological insight as it targets strictly physiological Paco_2 in two different management strategies established by the literature in hypothermic patients.

Limitations

Several issues limit the interpretation of our data. During the 24-hour period of hypothermia, only two measurements were performed and therefore our study cannot point out differences that may occur in α -stat versus pH-stat strategy during the entire hypothermia period. However, the results of a protocol comprising several measurements at different times may be more difficult to interpret due to the possible need for

fluid repletion, catecholamine infusion rates, and ventilation changes from one time frame to another. Furthermore, in this crossover study, multiple measurements, although possible, may have required several changes in ventilation strategy rendering the protocol more complex and increasing the risk of dyscarbia during multiple crossovers.

The time interval between the first and the second set of measurements was not identical in all patients, three having a prolonged interval and two a short interval. It may be argued that this may have influenced the reactivity to CO_2 and induced heterogeneity in the results. However, CO_2 reactivity is a phenomenon that occurs in a time scale of a few seconds; therefore, it is unlikely that the results of the Doppler measurements were significantly influenced by these time intervals (44).

The transcranial Doppler technique we used did not include a head holder and Doppler angle corrections were not performed; therefore, intraobserver variability may be higher than in other studies due to variations in the insonation angle. However, the variability of the transcranial Doppler technique measuring cerebral flow velocities is also acknowledged in other studies (45). This difficulty was partly overcome by recording the PI and RI which are independent of the insonation angle.

In the present study, we did not perform other measurements such as near-infrared spectroscopy, sidestream dark-field microcirculation imaging, or cerebral microdialysis, which may provide information about the systemic and cerebral circulation and metabolism (11, 46). However, cerebral metabolism was assessed indirectly in our study by the arteriojugular lactate difference that was not significantly different between the two strategies. In our patients, the intracranial pressure measurement was not performed, and the effect of the two strategies on this variable could not be evaluated; therefore, cerebral perfusion pressure could not be correlated with CBF velocities. Such measurements were performed in a previous study that did not find significant differences between intracranial pressure in OHCA patients ventilated with lower threshold and upper threshold normocapnia (11).

The size of this study was estimated by the data in the literature in studies with a related topic but with different methods and Paco_2 targets, and therefore, our sample size may have been underestimated. However, this is an exploratory study and precise sample size estimations are difficult to perform. Consequently, the potential prognostic value of cerebral perfusion and oxygenation variables measurements needs to be further investigated. As dyscarbia and especially hypocapnia were recently found as prognostic factors in the postcardiac arrest management (4, 5), larger studies may be needed to point out whether a benefit in terms of prognosis and neurological outcome can be achieved by using pH-stat strategy over α -stat management.

CONCLUSIONS

Our study shows that in patients treated with TH after OHCA and ventilated to achieve physiological Paco_2 , the α -stat strategy is associated with a slight but significant increase in jugular vein blood oxygen desaturation and higher CEo_2 compared

with pH-stat strategy. In survivors, similar significant changes were found in oxygenation variables and also in CBF velocities which were lower in α -stat compared with pH-stat. Conversely, all these changes were not found in nonsurvivors. However, whether targeting normocapnia in α -stat or in pH-stat strategy may influence outcome in these patients remains to be determined in further studies.

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8.3 Discussion

Cette étude observationnelle a exploré la relation physiologique entre la pression partielle en gaz carbonique et la circulation cérébrale après un AC. Elle a montré que plusieurs paramètres de la circulation cérébrale s'améliorent lorsque la pression en gaz carbonique est normalisée à la température réelle du patient en stratégie pH-stat. L'effet de cette stratégie est l'augmentation des vitesses de circulation sanguine mesurées par doppler transcrânien au niveau de l'artère cérébrale moyenne(101,104), surtout chez les patients qui ont présenté un bon pronostic, les survivants. Les patients qui sont finalement décédés n'ont pas présenté cette augmentation significative des vitesses de circulation sanguine au niveau de l'artère cérébrale moyenne, témoignant d'une altération majeure de leur réactivité au gaz carbonique(164), en rapport probablement avec les lésions graves d'anoxie cérébrale. Une perte de réactivité au CO₂ similaire, a été décrite dans un autre contexte clinique, chez des patients avec un pronostic défavorable après une hémorragie intracrânienne(169). Un des paramètres permettant d'évaluer l'adéquation entre la demande en oxygène du tissu cérébral et l'apport en oxygène, est la saturation en oxygène du sang aspiré au niveau de la partie initiale de la veine jugulaire interne, le bulbe jugulaire(170,171). Dans notre étude, ce paramètre a été plus favorable dans la stratégie pH-stat, 87%, par rapport à la stratégie alpha-stat, 83% (p=0,009). Ce résultat permet de favoriser la stratégie pH-stat dans la pratique courante chez les patients à risque de perfusion cérébrale insuffisante(172), car l'apport adéquat en oxygène au tissu cérébral est essentiel pour éviter l'aggravation des lésions cérébrales(173). Cette amélioration de la saturation du sang veineux jugulaire interne n'a pas été observée chez les patients avec un pronostic défavorable, probablement en raison de la perte de réactivité au CO₂. Cette stratégie favorise une pression artérielle du CO₂ plus élevée, et pourrait être associée avec une augmentation de la pression intracrânienne ce qui est un effet non souhaité dans le contexte de l'AC. Néanmoins, cet effet

semble peu probable, car une étude ayant mesuré ce paramètre, n'a pas montré d'augmentation significative des pressions intracrâniennes pour des valeurs de la pression en gaz carbonique similaires à notre travail(107).

Notre étude a montré une amélioration de la saturation jugulaire en oxygène et des vitesses de circulation sanguine artérielle de l'artère cérébrale moyenne par la stratégie pH-stat, qui pourrait être la stratégie préférée de normalisation de la pression partielle artérielle en gaz carbonique, notamment chez les patients à risque de perfusion cérébrale insuffisante. Néanmoins, il reste à déterminer si cette optimisation de la circulation cérébrale améliore la performance cérébrale des patients.

9 Discussion et perspectives

Les travaux présentés ici suggèrent des possibilités d'amélioration de la fonction circulatoire à différentes étapes de la prise en charge de l'AC. Pendant la réanimation cardiopulmonaire prolongée dans le cas de l'AC réfractaire, entre la 10^e et 45^e minute de réanimation cardiopulmonaire, nos données expérimentales ont montré que l'utilisation de bolus d'adrénaline intraveineux selon les recommandations n'a pas amélioré la survie. Ce résultat confirme les données retrouvées en clinique humaine dans des études rétrospectives(60,61) et prospectives(58) n'ayant pas montré d'amélioration de la survie avec bonne performance neurologique chez les patients traités avec des bolus d'adrénaline. Nos données suggèrent qu'une évaluation spécifique de l'effet de l'adrénaline dans le traitement de l'AC réfractaire est nécessaire pour optimiser le traitement dans cette population.

Lorsque les manœuvres de réanimation cardiopulmonaire ne permettent pas de rétablir une circulation spontanée efficace, l'utilisation de l'ECLS est actuellement discutée en clinique humaine selon les résultats obtenus par des études observationnelles montrant une efficacité inconstante. Le travail réalisé ici, apporte un premier argument expérimental montrant une amélioration de la survie lorsque l'ECLS est utilisée précocement, après 45 minutes de réanimation cardiopulmonaire dans un modèle expérimental d'AC réfractaire proche de la clinique humaine. Ce résultat est en faveur d'un effet bénéfique de l'ECLS dans l'AC réfractaire et conforte sur le plan expérimental les données humaines qui ont montré une tendance à l'amélioration de la survie à partir de séries rétrospectives(129,130). Des études randomisées chez l'homme sont en cours.

La mise en place des canules chez les patients en AC réfractaire en vue du support hémodynamique par l'ECLS est réalisée dans la plupart des études françaises par voie chirurgicale. Une des études

présentées dans cette thèse montre que l'utilisation d'un repérage échographique pour la ponction des vaisseaux fémoraux et l'utilisation de guides rigides permettent de réaliser la canulation en environ 8 minutes, permettant un support hémodynamique rapide. Ces deux éléments techniques permettent de raccourcir la durée de canulation, par rapport à la canulation sans repérage échographique et avec les guides souples fournis par le fabricant. Cette étude est une première comparaison entre ces deux stratégies.

Si lors des efforts de réanimation cardiopulmonaire, la reprise d'une circulation spontanée est obtenue, les patients ne sont pas à l'abri de l'apparition d'une insuffisance circulatoire conduisant au décès. Un de nos travaux a permis d'identifier dès l'arrivée à l'hôpital les patients à très haut risque de développer une insuffisance circulatoire réfractaire au traitement par les catécholamines. Les critères retrouvés dans ce travail représentent un premier pas dans l'identification des patients qui potentiellement bénéficieront d'une optimisation circulatoire par des moyens d'assistance mécanique après une reprise d'une circulation spontanée. Pour éviter l'apparition de l'insuffisance multiple d'organes qui est en général irréversible dans cette population, les patients doivent être identifiés le plus précocement possible, dès l'arrivée à l'hôpital, comme dans notre travail, ou dans les premières heures après l'hospitalisation(102). Notre étude a montré que la présence d'un état de choc nécessitant l'administration de catécholamines et un pH artériel $<7,11$, permettent de discriminer une population à haut risque, d'environ 80%, de décès de cause circulatoire.

Les effets bénéfiques de l'ECLS sur le débit circulatoire systémique sont dus au débit sanguin généré par le dispositif, qui supplée ou se rajoute au débit cardiaque spontané. Ce débit sanguin généré par l'ECLS est dirigé de façon « non physiologique » vers le cœur, et présente le risque d'augmentation de la postcharge du ventricule gauche. Un des travaux expérimentaux réalisés ici, a montré un effet bénéfique de la réduction du flux de l'ECLS pendant la systole cardiaque, sur la récupération de la fonction systolique du ventricule gauche. Cette réduction du flux de l'ECLS lors

de la systole cardiaque transforme le flux continu de l'ECLS en flux pulsatile, synchrone avec l'activité cardiaque, et son effet sur la fonction systolique ventriculaire gauche a été évalué pour la première fois dans cette étude. Le fait de réduire le débit de l'ECLS pendant la systole cardiaque expose à la diminution du débit de l'ECLS, mais cette réduction a été très faible. La diminution de la postcharge s'est avérée bénéfique pour la récupération de la fonction ventriculaire gauche et également pour l'évolution des pressions capillaires pulmonaires par rapport à l'ECLS standard, avec deux implications cliniques significatives possibles: un sevrage plus précoce de l'ECLS, et une réduction du risque d'œdème pulmonaire sous ECLS. Ces effets sont à confirmer par d'autres études expérimentales sur des modèles animaux plus complexes, comprenant un infarctus aigu du myocarde et dans l'avenir, ce principe pourrait être évalué en clinique humaine dans le but d'améliorer la fonction ventriculaire gauche et raccourcir les délais de sevrage de l'ECLS.

L'amélioration de la fonction circulatoire systémique permet une perfusion de l'ensemble des organes, mais la perfusion cérébrale présente des mécanismes spécifiques d'autorégulation, et une bonne perfusion systémique ne garantit pas nécessairement une bonne perfusion cérébrale. Une des raisons est l'interdépendance entre la pression artérielle partielle en gaz carbonique et les résistances vasculaires cérébrales. Pour une perfusion cérébrale optimale, la pression partielle en gaz carbonique doit être maintenue dans les limites normales y compris en hypothermie, un moyen thérapeutique utilisé dans la prise en charge de l'AC. En hypothermie, la pression partielle en gaz carbonique peut être normalisée à la température théorique de 37° indépendamment de la température réelle du patient, (stratégie alpha-stat), ou à la température réelle du patient (stratégie pH-stat), la stratégie la plus avantageuse n'étant pas bien définie. Le dernier travail présenté ici a montré que la normalisation de la pression en gaz carbonique en stratégie pH-stat permet une augmentation des vitesses de circulation sanguine cérébrale, et délivre probablement plus d'oxygène au tissu cérébral. Notre étude a montré que cette stratégie pourrait être préférée chez des patients à

risque d'un apport d'oxygène cérébral insuffisant.

Le présent travail suggère donc des moyens d'amélioration circulatoire systémique et cérébrale à plusieurs étapes de la prise en charge de patients ayant présenté un AC, à commencer par la période de réanimation cardiopulmonaire en cas d'AC réfractaire, en cas d'insuffisance circulatoire à risque de devenir réfractaire au traitement par catécholamines, et pendant la période de stabilité hémodynamique pour optimiser la circulation cérébrale. Les principes retrouvés dans les travaux présentés ici, appliqués seuls ou ensemble à différentes étapes du traitement, offrent la perspective d'une amélioration de la prise en charge des patients ayant présenté un AC.

10 Conclusion

Le présent travail montre que l'amélioration de la fonction circulatoire peut être obtenue à plusieurs étapes de la prise en charge de l'arrêt cardiaque. L'assistance circulatoire apporte un bénéfice sur la mortalité dans la prise en charge de l'arrêt cardiaque réfractaire expérimental, et peut être mise en place rapidement par voie percutanée chez les patients, alors que les bolus répétés d'adrénaline n'apportent pas de bénéfice sur la mortalité dans un modèle expérimental d'arrêt cardiaque réfractaire. Notre travail a retrouvé des critères pronostiques identifiant les patients qui, après un arrêt cardiaque, présentent une reprise d'une circulation spontanée mais sont à haut risque d'insuffisance circulatoire réfractaire au traitement par les catécholamines. La stabilisation de la fonction circulatoire par l'assistance circulatoire de type ECLS peut être suivie par une meilleure récupération de la fonction ventriculaire gauche en diminuant, par un dispositif pulsatile, le débit de l'assistance circulatoire lors de la systole cardiaque. L'optimisation de la circulation cérébrale nécessite en plus de l'optimisation de la circulation systémique, le contrôle de l'interaction entre la pression en gaz carbonique et le débit sanguin cérébral, amélioré par une gestion de la pression en gaz carbonique en stratégie pH-stat, qui mesure la pression en gaz carbonique à la température réelle du patient. L'ensemble de ces résultats, pouvant être appliqués à différentes étapes de la prise en charge d'un patient présentant un arrêt cardiaque, pourraient permettre l'amélioration du pronostic des patients.

11 Annexes

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Clinical paper

Value of post-resuscitation electrocardiogram in the diagnosis of acute myocardial infarction in out-of-hospital cardiac arrest patients[☆]

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ABSTRACT

Background: Diagnosis of acute myocardial infarction (AMI) in out-of-hospital cardiac arrest (OHCA) patients is important because immediate coronary angiography with coronary angioplasty could improve outcome in this setting. However, the value of acute post-resuscitation electrocardiographic (ECG) data for the detection of AMI is debatable.

Methods: We assessed the diagnostic characteristics of post-resuscitation ECG changes in a retrospective single centre study evaluating several ECG criteria of selection of patients undergoing AMI, in order to improve sensitivity, even at the expense of specificity. Immediate post resuscitation coronary angiogram was performed in all patients. AMI was defined angiographically using coronary flow and plaque morphology criteria.

Results: We included 165 consecutive patients aged 56 (IQR 48–67) with sustained return of spontaneous circulation after OHCA between 2002 and 2008. 84 patients had shockable, 73 non-shockable and 8 unknown initial rhythm; 36% of the patients had an AMI. ST-segment elevation predicted AMI with 88% sensitivity and 84% specificity. The criterion including ST-segment elevation and/or depression had 95% sensitivity and 62% specificity. The combined criterion including ST-segment elevation and/or depression, and/or non-specific wide QRS complex and/or left bundle branch block provided a sensitivity and negative predictive value of 100%, a specificity of 46% and a positive predictive value of 52%.

Conclusion: In patients with OHCA without obvious non-cardiac causes, selection for coronary angiogram based on the combined criterion would detect all AMI and avoid the performance of the procedure in 30% of the patients, in whom coronary angiogram did not have a therapeutic role.

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1. Introduction

Sudden out-of-hospital cardiac arrest (OHCA) is a severe condition with a poor survival, estimated at 33% in 1990¹ and 38% in 1997² in patients who were admitted to the hospital. Recent data

from large studies estimate mortality rate between 58% and 86% at one month after admission to the hospital in 3,853 OHCA patients,³ and 71% in 24,132 patients admitted to intensive care units (ICU) after in-hospital or OHCA.⁴

It has been suggested that acute myocardial infarction (AMI) is one of the main causes of OHCA, and two studies showed that coronary angioplasty significantly improved survival rate in this setting.^{2,5} Even if the role of coronary angioplasty in OHCA is still under debate,^{6–9} making the diagnosis and treating an ongoing AMI as early as possible after OHCA would appear crucial.

One of the main criteria for AMI diagnosis in non-cardiac arrest patients is ST-elevation on electrocardiogram (ECG),¹⁰ but in

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patients resuscitated from OHCA, ECG changes may be difficult to interpret due to false positive and false negative results.^{2,5} Indeed, acute ischemia–reperfusion syndrome after return of spontaneous circulation (ROSC) may cause myocardial injury, leading to significant ECG changes even in the absence of AMI.^{11,12} Therefore, it has been suggested that ST-elevation on ECG was not contributive.^{2,5} Conversely, ST-elevation had good positive (PPV) and negative (NPV) predictive values for AMI diagnosis in another study.⁶

Even though the diagnostic value of the ST-elevation is uncertain in the OHCA setting, we hypothesised that ECG changes may still be useful as a triage method for establishing the indication for emergency coronary angiogram (ECA). We performed a study aiming to identify ECG criteria that improve selection for ECA of the patients undergoing AMI. The need for triage is justified by the fact that not all OHCA patients benefit from the ECA^{7,8} and by the limited availability and the cost of the technique. We therefore analysed different ECG criteria of patient selection, including several ECG changes in addition to ST-elevation, such as ST-depression or wide QRS complex, which are known to occur during AMI.¹³

2. Methods

In Paris, France, the mobile emergency medical system is based in five hospitals in the city. One centre dispatches ambulances carrying resuscitation equipment and physicians trained in emergency medicine. The ambulances reach the scene in approximately 18 min, and are generally preceded by fire-fighters trained in basic life support, who reach the OHCA scene in approximately 8.5 min.¹⁴ Patients effectively resuscitated are transferred to hospitals. In our centre, all OHCA patients with stable ROSC and without obvious non-cardiac causes of OHCA are admitted directly to the catheterisation laboratory for routine ECA.

2.1. Study design and patients

This single-centre retrospective study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The Ethics Committee of our institution approved the study and no informed consent was required from the patients or the next of kin.

All consecutive patients aged ≥ 18 years resuscitated from an OHCA and admitted to our centre between January 2002 and June 2008 were screened for inclusion. Patients with an obvious non-cardiac cause of OHCA, without sustained ROSC or without available ECG traces post-ROSC were excluded. Sustained ROSC was defined as spontaneous circulation with palpable pulse for at least 20 min.¹⁵ No flow was defined as the time between witnessed collapse and the beginning of cardiopulmonary resuscitation (CPR) and low flow as the time between the beginning of CPR and the ROSC. The initial rhythm of the OHCA was considered the heart rhythm present when a monitor or defibrillator was attached to the patient after the collapse.¹⁵

On arrival at the hospital, an ECA with angioplasty if indicated was performed in all patients through femoral or radial artery approach. Hypothermia was usually initiated in the catheterism laboratory using IV infusion of cold saline.

After the ECA, patients were transferred to the ICU for standard management and optimal hypothermia. Patients discharged with a cerebral performance category (CPC)¹⁶ of 1 or 2 were counted as survivors with favorable neurological outcome, and patients with CPC3 as survivors with unfavorable neurological outcome.

2.2. ECG analysis

The reference ECG used for analysis was the first interpretable 12-lead ECG obtained after sustained ROSC. The reference ECG

were retrospectively analysed by two experienced observers independently of the ECA and disagreement was arbitrated by a third party.

Recorded ECG changes were ST-elevation, ST-depression, presence of left (LBBB) and right (RBBB) bundle branch block and non-specific wide QRS complex. ST-elevation was considered significant if present in ≥ 2 contiguous ECG leads with an amplitude ≥ 2 mV for men and 0.15 mV for women in V2 or V3, and ≥ 0.1 mV in the rest of the leads.¹⁷ ST-depression was considered significant if ≥ 0.1 mV in ≥ 2 contiguous leads.¹⁸ LBBB was defined as QRS duration > 120 ms with QS or rS pattern in V1 and broad R waves in lead I, V5 and V6.¹⁹ ST-elevation or depression and LBBB were analysed because they represent major criteria of acute cardiac ischemia diagnosis.¹⁷ RBBB was defined as QRS duration ≥ 120 ms with rSR' complex in V1 and V2 and S wave in lead I and V5 or V6¹⁹ and was analysed because it is a conduction disturbance occurring in large AMI.²⁰

Non-specific wide QRS complex was defined as QRS duration ≥ 120 ms without LBBB or RBBB morphology. It was analysed as a component of selection criteria for ECA because abnormal resting repolarisation following wide QRS prevents accurate interpretation of ECG changes related to ischemia,²¹ and AMI may be present in these patients. Moreover, myocardial ischemia is associated with slowing of ventricular conduction in vitro²² and can increase QRS duration to up to 160 ms in patients without bundle branch block.²³

2.3. Angiographic analysis and AMI diagnosis

ECA were retrospectively analysed by two independent experienced observers and disagreement was arbitrated by a third party. Coronary flow was assessed according to the TIMI classification.²⁴ AMI was angiographically defined by the presence of lesions suggestive of ruptured plaques (Ambrose type II)²⁵ with evidence of fresh thrombus in a main coronary artery¹⁷ with TIMI 1 or 0 flow. This definition has been previously used,^{2,6} and cardiac arrest with evidence of fresh thrombus are part of the criteria for universal definition of myocardial infarction by the European Society of Cardiology.¹⁷ To avoid misdiagnosing chronic occlusions as AMI, the occlusion had to be easily crossed by an angioplasty guide wire² and troponin concentration was required to increase during the hospital stay⁶ to ≥ 4 ng/ml.²⁶ Coronary angioplasty was considered successful if residual stenosis was $< 50\%$ with TIMI 3 flow.²⁷ All coronary stenoses with a diameter reduction $\geq 50\%$ were considered significant. To avoid side effects of the contrast agents, angioventriculographies were not routinely obtained.

2.4. Statistical analysis

Continuous variables were expressed as median (interquartile range—IQR 25–75) and compared using the Wilcoxon test. Categorical variables were reported as frequencies and percentages and were compared using the Chi-square test and if not applicable, Fisher's exact test. Univariate logistic regressions were used to identify variables that best explained the presence of AMI. Clinically significant variables with a $p < 0.1$ on univariate analysis were introduced into a stepwise multivariate model to select independent variables of this endpoint.

3. Results

3.1. Patient characteristics

The selection of the included population and the final outcome are shown in Fig. 1. Most patients were men aged 56

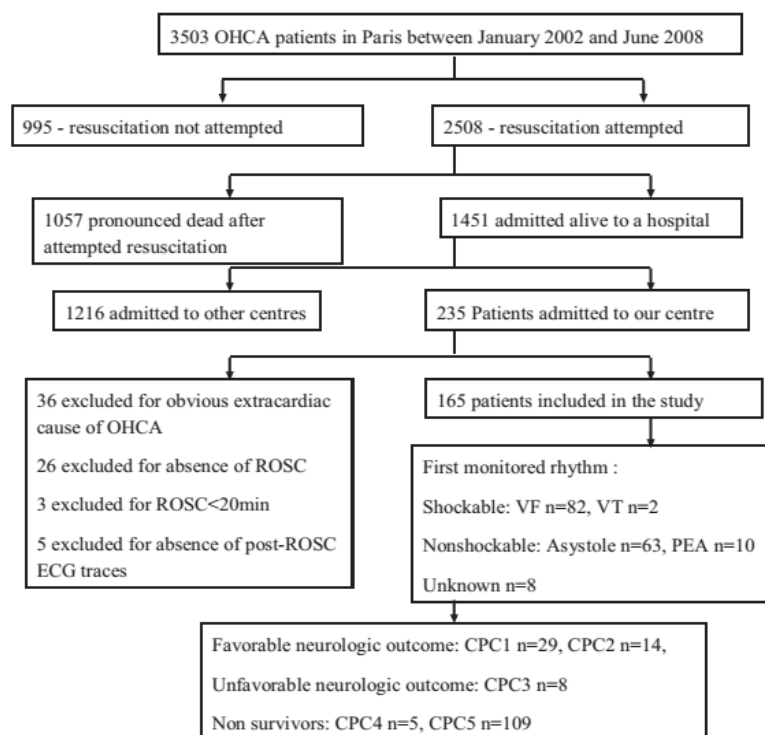


Fig. 1. Flow chart of the OHCA patients included in the study. OHCA = out of hospital cardiac arrest; ROSC = return of spontaneous circulation; ECG = electrocardiogram; VF = ventricular fibrillation; VT = ventricular tachycardia; PEA = pulseless electrical activity; CPC = cerebral performance category.

(48–67) y.o., and 18% had previous history of coronary artery disease. Most OHCA occurred in public places (60%). The median no flow and low flow were 3 and 20 min respectively. The initial rhythm was ventricular fibrillation (VF) in 50% of the patients (Table 1).

OHCA was caused in 36% of the cases by AMI, in 23% by ischemic heart disease without AMI (chronic coronary occlusion, ischemic dilated cardiomyopathy), in 6% by rhythm disturbance due to non-

ischemic cardiomyopathy, and in 5% by idiopathic VF. In 18% of the patients OHCA was due to hypoxia, pulmonary embolism, electrolyte disturbances, aortic dissection etc., and in 12% the cause remained unidentified.

3.2. Coronary angiogram analysis and AMI

Of the 165 patients, 27% had normal ECA, 14% had non-significant coronary stenosis, and 59% had ≥ 1 significant stenosis. Angiographic AMI was found in 60 (36%) patients. In all 60, troponin I concentration was above threshold (4 ng/ml): 74.5 (27–157) ng/ml. Among AMI patients, the left anterior descending artery (LAD) was involved in 52%, the right coronary artery (RCA) in 35% and the circumflex artery (Cx) in 8%. Lateral or diagonal arteries were each involved in 5% of the patients and the left main coronary artery in 6%. In 11% of the patients two arteries were simultaneously involved.

Emergency angioplasty was attempted in 87% of the patients with AMI and 94% of the attempts were successful. Patients with a small diameter of the involved artery or presence of abundant intracoronary thrombi were treated with antiplatelet and anticoagulant agents before a second angiogram.

3.3. Management of the patients and outcome

Patients were managed in the ICU after the ECA with mechanical ventilation (99%) and inotropic support (52%). Therapeutic hypothermia was performed in 76% of the patients, never in the pre-hospital phase. Fifty one patients (31%) survived to hospital discharge (CPC1–3) (Fig. 1).

Table 1
Clinical characteristics of the included population.

Variables	N (%)
Age (years), median (IQR), n = 165	56 (48–67)
Male sex	131 (79)
Risk factors	
Hypertension	53 (32)
Hypercholesterolemia	34 (21)
Diabetes	28 (17)
Active smoking	66 (40)
Unknown	11 (7)
History of coronary artery disease	29 (18)
Unknown	4 (2)
Place of cardiac arrest	
Public place	99 (60)
Home	56 (34)
Unknown	10 (6)
Initial rhythm	
Ventricular fibrillation	82 (50)
Ventricular tachycardia	2 (1)
Asystole	63 (38)
Pulseless electrical activity	10 (6)
Unknown	8 (5)
Duration of no flow, median (IQR), n = 127	3 (0–10)
Unknown	38 (23)
Duration of low flow, median (IQR), n = 130	20 (10–30)
Unknown	35 (21)

Table 2
ECG changes in patients with and without AMI.

ECG changes	Patients with AMI <i>n</i> (%) <i>n</i> = 60	Patients without AMI <i>n</i> (%) <i>n</i> = 105	<i>p</i> value
ST-segment elevation	53 (88)	17 (16)	<0.001
ST-segment depression without ST-segment elevation	4 (7)	22 (21)	0.015
LBBB	2 (3)	10 (9)	0.2
Nonspecific wide QRS complex	1 (2)	7 (7)	0.3
RBBB without other significant changes	0 (0)	8 (8)	0.03
Patients without significant ECG changes	0 (0)	41 (39)	<0.001

ECG = electrocardiography; AMI = acute myocardial infarction; LBBB = left bundle branch block; RBB = right bundle branch block.

3.4. ECG data

Among the 60 patients with AMI, 88% had ST-elevation (Table 2); 45% in the anterior leads, 38% in the inferior leads and 22% in the lateral leads (17% of the patients with AMI had ST-elevation in 2 territories). Reciprocal changes (ST-depression ≥ 1 mm in leads reciprocal to those showing ST-elevation) were present in 11% (18 patients): in 22% of the patients with AMI (13 patients) and in 5% of the patients without AMI (5 patients).

Seven patients (12% of the patients with AMI) had AMI without ST-elevation: 4 had ST-depression, 2 had LBBB, 1 had non-specific wide QRS (the culprit artery in this patient was the left main coronary). Eight patients had RBBB without significant ST segment changes but none had AMI.

None of the patients with non-specific wide QRS presented with significant hyperkalaemia or antiarrhythmic drug overdose. However, the precise potassium concentration at the moment of the reference ECG could not be obtained.

Among all patients, 13 (8%) had supraventricular arrhythmia (atrial fibrillation) on the reference ECG.

3.5. Correlates of AMI

In univariate logistic regression the correlates of AMI were: male gender—OR = 4.2, CI = 1.5–11.5 ($p = 0.005$), ST-elevation—OR = 39.3, CI = 15.2–100.7 ($p < 0.001$), initial VF—OR = 7.4, CI = 3.4–16 ($p < 0.001$), age (per 10 years increment) OR = 7.7, CI = 3.5–17.2 ($p < 0.001$), initial asystole—OR = 0.17, CI = 0.08–0.39 ($p < 0.001$). These variables were introduced into a multivariate logistic regression and the independent correlates of AMI found were ST-elevation—OR = 29.6, CI = 10.8–81.08 ($p < 0.001$) and the presence of VF as initial rhythm—OR = 5.7, CI = 2.1–15.8 ($p < 0.001$).

3.6. Combined ECG data

In order to improve selection of patients with AMI, 3 ECG criteria in addition to ST-elevation were defined: ST-elevation and/or depression, the combined criterion comprising ST-elevation and/or depression and/or LBBB and/or non-specific wide QRS and the extended criterion comprising ST-elevation and/or depression and/or LBBB and/or non-specific wide QRS and/or RBBB. To evaluate the performance of the criteria, we measured the sensitivity, specificity, PPV, NPV and accuracy for the detection of patients with angiography-diagnosed AMI. ST-elevation predicted AMI with

a sensitivity of 88% and a specificity of 84%, while the ST-elevation and/or depression criterion showed a sensitivity of 95% and a specificity of 62%. The combined criterion had a sensitivity of 100% and a specificity of 46% and the extended criterion a sensitivity of 100% and a specificity of 39% (Table 3).

4. Discussion

In this series of 165 patients, the most important finding is the 100% sensitivity of the combined/extended ECG criteria for the selection of patients with AMI. This is the first evaluation of such ECG criteria in patients resuscitated from an OHCA. Few studies evaluated the characteristics of the ECG for the diagnosis of AMI in the setting of OHCA, due to the difficulties in the diagnosis of AMI by other methods.^{26,28}

AMI was found in 36% of our patients, being the most frequent cause of OHCA, ranging from 37.5% to 70%^{6,29–31} in other studies. Other causes of OHCA are similar to published data: arrhythmia triggered by myocardial scar,²⁹ primary rhythm disturbances,³⁰ non-ischemic cardiomyopathy,³² and rarely, non-cardiac causes.⁶ The presence of VF as initial rhythm was strongly associated with AMI in our population and in previous studies.³⁰

The advantage of our study is the use of ECA as the gold standard for AMI definition, as ECA was performed immediately after resuscitation in all patients, irrespective of the ECG changes. The sensitivity of ST-elevation for AMI diagnosis in our population (88%) is similar to other studies which included patients with AMI not complicated by cardiac arrest. In 418 patients angiographically diagnosed with AMI, the sensitivity of ST-elevation was 85% if LAD and RCA were occluded, and 46% for Cx occlusion.³³ In our population, Cx-lateral artery occlusion occurred only in 13% of the cases, explaining the high sensitivity of ST-elevation.

The specificity of ST-elevation for AMI diagnosis in our patients was 84%, lower than usually found in non-cardiac arrest patients—92% in a study including 755 patients.³⁴ This may be explained by the differences in the AMI definition, but also by the presence of false positive cases due to ischemia–reperfusion injury occurring in the OHCA.⁹

4.1. The combined/extended criteria

A report including non-cardiac arrest patients compared the diagnostic value of ST-elevation with that of a criterion of ST-elevation or depression,³⁵ using contrast enhanced MRI as the

Table 3
Characteristics of the combination of different ECG criteria for the selection of OHCA patients with AMI.

	Sensitivity (%) (CI)	Specificity (%) (CI)	PPV (%) (CI)	NPV (%) (CI)	Accuracy (%) (CI)
ST-elevation (<i>n</i> = 70)	88 (77–95)	84 (75–90)	76 (64–85)	92 (85–97)	85 (79–90)
ST-elevation and/or depression (<i>n</i> = 96)	95 (86–99)	62 (52–72)	59 (49–69)	96 (87–99)	74 (67–81)
Combined criterion ^a (<i>n</i> = 116)	100 (94–100)	46 (36–56)	52 (42–61)	100 (92–100)	66 (58–73)
Extended criterion ^b (<i>n</i> = 124)	100 (94–100)	39 (30–49)	48 (39–58)	100 (91–100)	61 (52–69)

PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval.

^a The combined criterion includes ST-elevation and/or depression, and/or left bundle branch block and/or non-specific wide QRS complex.

^b The extended criterion includes ST-elevation and/or depression, and/or left bundle branch block and/or non-specific wide QRS complex and/or right bundle branch block.

gold standard for AMI diagnosis. ST-elevation had a sensitivity of 50% and a specificity of 97%, while the criterion of ST-elevation or depression had a sensitivity of 84% and a specificity of 94%. Even though angiographic data were not available, this study indicates that combined ECG criteria might improve the diagnostic value of the ECG.

Interestingly, ST-depression, LBBB, RBBB and non-specific wide QRS in our study occurred more frequently in patients without AMI than in patients with AMI, which was not the case for ST-elevation. This shows that in the OHCA setting, ST-elevation is more likely triggered by acute coronary occlusion, while other changes are more frequently induced by other types of myocardial injury. Nevertheless, 12% of the patients with AMI had as only ECG abnormalities ST-depression or LBBB or non-specific wide QRS, justifying the inclusion of these changes into our selection criteria, thus increasing sensitivity and NPV to 100% at the expense of a diminished accuracy. Even though none of the patients with RBBB had AMI in our series, we cannot exclude that in rare cases of AMI RBBB may be the only ECG change.

The finding of 100% sensitivity for ECG criteria may seem surprising since non-OHCA patients with AMI may present with normal ECG findings^{18,36} especially if the Cx-lateral artery is occluded,^{18,36} which in our study represents only a minority of the culprit arteries. These patients presenting with AMI and normal ECG traces have a good prognosis and generally do not suffer cardiac arrest.³⁶

If the combined criterion had been used to select patients for ECA in our population, 116 (70%) patients would have undergone the procedure, and AMI would have been diagnosed in 60 of them (52% of 116). Consequently, ECA could have been avoided in 49 patients (30% of 165) and in 41 patients (25% of 165) if the extended criterion had been used. In these patients ECA did not have a therapeutic role: only 10 patients of the 49 had significant coronary stenosis, none had AMI, and angioplasty and intraaortic balloon pump were not indicated. In their case, ECA may have delayed diagnosis and treatment of the underlying cause of the OHCA and the initiation of the neuroprotective measures,³⁷ making selection for ECA seem worthwhile.

This selection may be made using ECG criteria, but there is lack of consensus about the ECG diagnostic parameters in OHCA. A study including 77 OHCA patients³⁸ found a sensitivity identical to our study for the ST-elevation on 12-lead post-ROSC ECG using a different definition of AMI. In 3 studies, ECA was performed immediately after resuscitation, and the diagnostic characteristics of the ST-elevation were evaluated: PPV ranged from 63% to 83% and NPV from 74% to 84%.^{2,5,6} In our study, these parameters were 76% and 92% respectively. Whether these differences are due to chance or differences in the included patients, the general tendency is towards ST-elevation not being an optimum criterion for AMI diagnosis in OHCA patients. The combined/extended criteria could be used in the patients' selection for ECA if future studies confirm their value.

4.2. Limitations

Our single-centre study took place in a Teaching Hospital in Paris, and therefore it reflects the management of patients in our centre. Due to our ECA facilities, we cannot exclude that selected patients were dispatched to our centre. Our study can nevertheless be considered representative in that ECA were performed using standard procedures and ECG interpretations were made using criteria established in the literature.

Unfortunately ECG changes in the leads V7–9 and Vr3–6 were unavailable because in the emergency setting of OHCA, these were only recorded in a minority of the patients. Emergency echocardiography was not performed in our patients before ECA, but by

assessing wall motion abnormalities, this technique could improve the selection criteria and could be evaluated in future studies.

We included a smaller number of patients than studies devoted to the diagnostic values of the ECG in non-OHCA patients,³³ but as many or more than studies dealing with OHCA patients.^{2,7,8,39} Owing to the small number of patients with ECG changes other than ST-elevation, no conclusion can be definitively drawn concerning the prevalence of these changes in patients with/without AMI, and the statistical significance of these differences is difficult to evaluate due to small sample sizes. These changes are rare^{20,23,30} and large studies may be needed to estimate their prevalence.

5. Conclusion

In OHCA, without obvious non cardiac cause, due to its excellent sensitivity, the combined/extended ECG criteria comprising the presence of ST-elevation and/or depression and/or LBBB and/or non-specific wide QRS and/or RBBB are easily applicable and could help in identifying patients who may benefit from ECA. Future studies are needed to confirm their value.

Conflict of interest statement

None.

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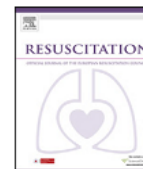
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Clinical paper

Role of cardiac troponin in the diagnosis of acute myocardial infarction in comatose patients resuscitated from out-of-hospital cardiac arrest[☆]

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ABSTRACT

Background: Troponin is a major diagnostic criterion of acute myocardial infarction (AMI) but in out-of-hospital cardiac arrest (OHCA) patients, its diagnostic value may be altered by cardiopulmonary resuscitation.

Methods: Single-centre study assessing the diagnostic characteristics of troponin for AMI diagnosis in consecutive patients resuscitated from OHCA between 2002 and 2008 with coronary angiogram (CA) performed on admission. Patients with obvious non-cardiac cause of OHCA, unsustained or absent return of spontaneous circulation were excluded. AMI was defined on CA by the presence of acute occlusion or critical stenosis with intracoronary fresh thrombus easily crossed by an angioplasty wire. Troponin concentration was recorded once on admission and once 6–12 h after the OHCA.

Results: A total of 163 patients aged 56 (median) years (interquartile range (IQR) 48–65) was included, all comatose. Most prevalent initial OHCA rhythms were ventricular fibrillation (49%) and asystole (41%). AMI was diagnosed on coronary angiogram in 37% of the patients.

Median troponin concentration on admission was 1.7 (0.3–10) ng ml⁻¹ and sensitivity for AMI diagnosis was 72% and specificity 75% for a 2.5 ng ml⁻¹ cut-off. A combined criterion comprising ST elevation and troponin >2.5 ng ml⁻¹ had a sensitivity of 93% and specificity of 64%.

Six to twelve hours after the OHCA, median troponin concentration was 7.6 ng ml⁻¹ (1.4–47.5), sensitivity was 84% and specificity 84% for a 14.5 ng ml⁻¹ cut-off.

Conclusion: Troponin I has a good diagnostic value for AMI diagnosis in OHCA patients. In combination with ST elevation, troponin I on admission achieves a very high sensitivity.

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Out-of-hospital cardiac arrest (OHCA) is a condition with a dismal prognosis despite continuous efforts to improve outcome. The most frequent cause of OHCA without an obvious non-cardiac cause is acute myocardial infarction (AMI)¹ and one of the procedures

improving survival in this setting is coronary angioplasty.^{2,3} Therefore, the diagnosis of AMI appears to be an important step in the management of these patients.

Electrocardiographic (ECG) data are the mainstay of the diagnosis of AMI in patients not suffering cardiac arrest, but in OHCA the diagnostic value of ECG data is still open to discussion.^{2–5} A reliable method of AMI diagnosis is immediate coronary angiogram (CA) after OHCA,^{2–4} but this is not available in all centres in the emergency setting and it may delay the diagnosis and management of other causes of the OHCA.

Cardiac troponins are widely available and highly sensitive biochemical markers of acute ischaemia⁶ and might be of great help

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in AMI diagnosis. However, their diagnostic characteristics are less well defined in this setting and may be difficult to interpret.^{7,8} Studies assessing the diagnostic value of troponin in OHCA patients without obvious non-cardiac cause showed that at hospital admission troponin was not useful for AMI diagnosis⁸ but 12 h after admission and at peak value during the hospital stay, it had good diagnostic value.^{7,8} A major limitation in these studies was that the method used for the diagnosis of AMI was not the same in all patients,^{7,8} the diagnosis was occasionally uncertain⁷ and coronary angiographic data were not available.

Therefore, we performed a study aiming to evaluate the diagnostic characteristics of cardiac troponin measured at hospital admission and in the interval 6–12 h after the OHCA, using a unique, angiographic definition of AMI, based on the CA performed immediately after resuscitation.

1. Methods

This study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The ethics committee of our institution approved the study and no informed consent was required from the patients or the next of kin.

It is a retrospective single-centre study for which we screened all patients >18 years old admitted after successful resuscitation from an OHCA between January 2002 and June 2008. Sustained return of spontaneous circulation (ROSC), CA and troponin assessment on admission were required for inclusion. Sustained ROSC was defined as the presence of circulatory function with palpable pulse for at least 20 consecutive minutes.⁹ We excluded patients with an obvious non-cardiac cause of OHCA.

1.1. Management and angiographic analysis

Pre-hospital management of the patients in France has been previously described.^{3,5} After resuscitation according to guidelines,^{10,11} patients are transferred in our centre directly to the catheterisation laboratory for routine CA performed through femoral or radial access using standard techniques.

CA was retrospectively analysed by two independent observers. Coronary artery stenoses $\geq 50\%$ of the lumen diameter were considered significant. Coronary artery flow was assessed according to thrombolysis in myocardial infarction (TIMI) classification.¹²

AMI was defined angiographically by the presence of lesions suggestive of ruptured plaques (Ambrose type II)¹³ with evidence of fresh thrombus in a main coronary artery¹⁴ with TIMI 0 or 1 flow, or TIMI 2 or 3 flow with critical stenosis and presence of thrombus (spontaneous reperfusion), easily crossed by an angioplasty wire.³ This definition is in accordance with the universal definition of myocardial infarction¹⁴ and previous studies.^{3,5,15}

Therapeutic hypothermia was usually initiated in the catheterisation laboratory by cold saline infusion. After the CA with angioplasty, if indicated, patients were transferred to the intensive care unit (ICU).

1.2. Troponin concentration assessment

Blood samples were drawn in the catheterisation laboratory after establishing arterial access for the CA. Blood was collected in sterile 3 ml BD Vacutainer® PST™ II tubes containing lithium heparinate.

All assessments were of troponin I and were performed by the hospital laboratory using immunoassay techniques by Abbott Laboratories, AxSYM® Troponin-I ADV from 2002 to 2004 (99th

percentile normal concentration $<0.4 \text{ ng ml}^{-1}$) and ARCHITECT STAT Troponin-I® from 2005 to 2008 (99th percentile normal concentration $<0.04 \text{ ng ml}^{-1}$). The analytical sensitivity of the tests is 0.3 ng ml^{-1} and 0.01 ng ml^{-1} , respectively, and the cut-offs for AMI diagnosis are 1.9 ng ml^{-1} and 0.3 ng ml^{-1} , respectively (manufacturer stated). The reference limit at which the coefficient of variation (CV) is $<10\%$ is 0.03 ng ml^{-1} for ARCHITECT STAT® (manufacturer stated). For AxSYM®, the CV was $<9.6\%$ for concentrations $\geq 1.29 \text{ ng ml}^{-1}$.¹⁶ The upper limit of assessment of undiluted samples for both techniques is 50 ng ml^{-1} . These techniques may suffer interference from heterophile antibodies and rheumatoid factor, responsible for false positive/negative cases.¹⁷

Troponin concentrations measured by the two techniques were analysed separately and together as they are very well correlated (correlation coefficient of the two techniques = 0.98).¹⁷

We recorded troponin concentrations twice after the OHCA:

- on admission to the hospital for all patients (Ta), as in the study by Mullner et al.⁸
- 6–12 h after the OHCA (T6–12) because in AMI patients the best sensitivity for troponin is achieved after 6 h⁶ and the artery reopening can be beneficial in the first 12 h after the AMI.¹⁸

The interval between the OHCA and the assessment of troponin was calculated using the time of the OHCA in the patients' medical record and the time of assessment recorded by the laboratory.

1.3. Other parameters

We recorded baseline clinical characteristics, the initial rhythm of the OHCA⁹ and the durations of no-flow and low-flow intervals. No-flow was defined as the time interval between the patient's collapse and the beginning of chest compressions, and low-flow as the time between the beginning of chest compressions and the ROSC. Shock on admission was defined as hypotension requiring treatment with catecholamines. The presence of ST elevation was interpreted according to recommendations¹⁴ on the first ECG trace obtained after sustained ROSC.

Neurological outcome was evaluated using cerebral performance category (CPC) score.¹⁹ Data were recorded according to the Utstein-style recommendations for reporting resuscitation outcomes.⁹

1.4. Statistical analysis

Continuous variables were expressed as medians (IQR) and compared using the two-tailed Mann–Whitney test. Categorical variables were reported as frequencies and percentages and were compared using the chi-square test and, if not applicable, Fisher's exact test. For AMI diagnosis, sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and accuracy were calculated according to standard definitions and expressed as percentages (95% confidence interval (CI)). Diagnostic characteristics of troponin were evaluated using the manufacturer's cut-off and also the cut-offs of maximum accuracy obtained after the receiver operator characteristic (ROC) curve analysis. Univariate analysis was performed to determine correlates of troponin at Ta above the ROC curve-suggested cut-off. Significant variables were introduced into a stepwise multivariable logistic regression to determine the independent correlates of this parameter.

Significant correlates of troponin were also searched for in univariate regression.

Statistical analysis was performed using MedCalc®, version 11.0.1.0 (MedCalc Software, Mariakerke, Belgium).

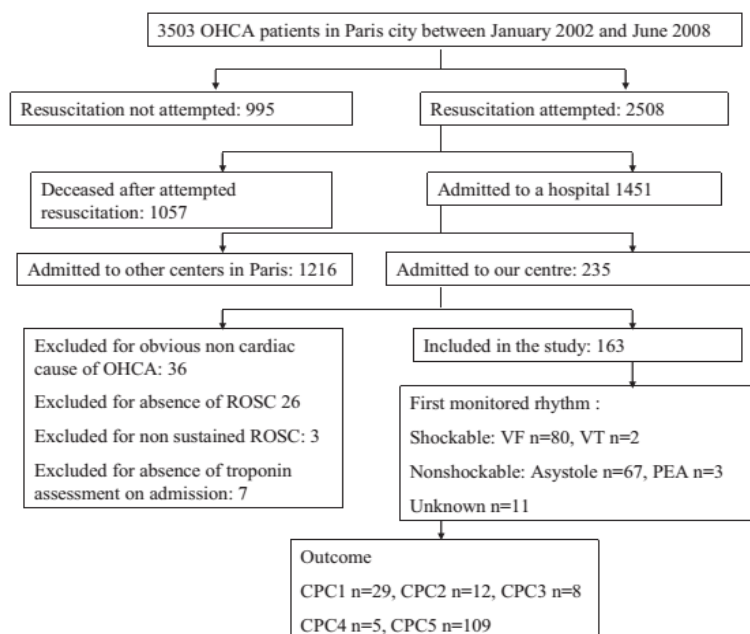


Fig. 1. OHCA in Paris, the screening according to the inclusion criteria and outcome of the patients included in the study OHCA: out-of-hospital cardiac arrest. ROSC: return of spontaneous circulation. VF: ventricular fibrillation. PEA: pulseless electrical activity. CPC: cerebral performance category.

2. Results

During the study period, 1451 OHCA patients were admitted to a hospital in Paris city. Among the 235 patients admitted to our centre, 163 were included, all comatose on admission (Fig. 1). Characteristics of the patients and the OHCA are shown in Tables 1 and 2. None of the patients had a history of positive rheumatoid factor or treatment with heterophile antibodies.

CA showed angiographically defined AMI in 37% of the patients, of whom 62% had TIMI 0 and 38% had TIMI 1 flow. Angioplasty was successful in 94%. Only 82% of the patients with AMI had ST elevation on the first ECG trace after sustained ROSC, diagnostic sensitivity of 82% (70–90), specificity 84% (75–90), PPV 74% (62–84), NPV 89% (82–94) and accuracy 83% (75–89).

Other OHCA causes were ischaemic heart disease without AMI – 17%, hypoxemia – 9%, non-ischaemic cardiomyopathy – 6%

and primary rhythm disturbance (Brugada or long QT syndrome, idiopathic ventricular fibrillation (VF)) – 4% of the patients. Miscellaneous causes were found in 19%: pulmonary embolism, electrolyte disturbances, neurologic disorders and aortic dissection. The OHCA cause remained undetermined in 8% of the patients.

2.1. Management and outcome

In the pre-hospital phase, 66% of the patients required three (1–5) external electric shocks. Adrenaline (epinephrine) boluses were administered in 86%, median total dose 3 mg (2–5), 99% required mechanical ventilation and 52% presented with shock on admission. None of the patients received pre-hospital therapeutic hypothermia, and 65% received hypothermia in the ICU.

Of all patients, 18% died during the first day of hospitalisation and 30% survived to hospital discharge after an ICU and hospital

Table 1
Characteristics of the patients at baseline and on admission.

Characteristic	All n = 163	With AMI n = 60	Without AMI n = 103	p-Value
Age, years median (IQR)	56 (48–65)	50 (45–61)	60 (51–70)	0.0003
Men, n (%)	130 (80%)	55 (92%)	75 (73%)	0.007
Risk factors, n (%)				
Hypertension	54 (34%)	15 (25%)	39 (38%)	0.09
Hypercholesterolemia	36 (22%)	15 (25%)	21 (20%)	0.73
Diabetes	28 (17%)	3 (5%)	25 (24%)	0.002
Active smoking	65 (40%)	30 (50%)	35 (34%)	0.09
Unknown risk factors	7 (4%)	1 (2%)	6 (6%)	NC
History of coronary artery disease n (%)	30 (18%)	11 (18%)	19 (18.5)	0.9
Unknown, n (%)	4 (2%)	0 (0%)	4 (4%)	NC
Adrenaline or noradrenaline rate of infusion on admission ^a (mg/h)	2 (1–4)	1 (0.6–3.5)	2 (1–4)	0.17
Dobutamine on admission ^b (μg/kg min)	10 (7–13)	10 (6–10)	10 (5–20)	0.5
Lactate concentration on admission (mmol/l)	4.6 (2.5–9)	4.3 (2.5–6)	5.8 (2–9)	0.049

NC: not calculated.

^a 72 patients were treated with adrenaline or noradrenaline.

^b 13 patients were treated with dobutamine.

Table 2
Characteristics of the OHCA and troponin concentration on admission and 6–12 h after the OHCA.

Characteristics	All n = 163	With AMI n = 60	Without AMI n = 103	p-Value
Place of OHCA, n (%)				
OHCA in public place	104 (64%)	43 (72%)	61 (59%)	0.15
OHCA at home	56 (34%)	16 (27%)	40 (39%)	0.15
Undetermined	3 (2%)	1 (1%)	2 (2%)	NC
Initial rhythm n (%)				
Ventricular fibrillation	80 (49%)	45 (75%)	35 (34%)	>0.0001
Ventricular tachycardia	2 (1%)	0 (0%)	2 (2%)	NC
Asystole	67 (41%)	10 (17%)	57 (55%)	<0.0001
Pulseless electrical activity	3 (2%)	0 (0%)	3 (3%)	NC
Unknown	11 (7%)	5 (8%)	6 (6%)	NC
Number of electric shocks, median (IQR)	1 (0–4)	3 (1–7)	1 (0–2)	<0.0001
Duration of no-flow, min, median (IQR)	3 (0–9)	4.5 (0–9)	3 (0–9)	0.7
Unknown, n (%)	37 (23%)	16 (27%)	21 (20%)	NC
Duration of low-flow, min, median (IQR)	20 (10–30)	22 (10–32)	20 (10–30)	0.1
Unknown, n (%)	44 (27%)	13 (22%)	31 (30%)	NC
GCS 3 on admission	143 (88%)	53 (88%)	90 (87%)	0.16
GCS 4–7 on admission	20 (12%)	7 (12%)	13 (13%)	0.2
Mechanical ventilation required	162 (99%)	60 (100%)	102 (99%)	0.98
Troponin concentration on admission, ng ml ⁻¹	1.7 (0.3–10)	7 (2–44)	0.5 (0.2–2.5)	<0.0001
Troponin concentration 6–12 h after the OHCA ^a , ng ml ⁻¹	7.6 (1.4–47.5)	54 (19–121)	2.6 (0.3–9)	0.008

NC: not calculated due to reduced patient number or expressing missing data; GCS: Glasgow Coma Scale OHCA: out-of-hospital cardiac arrest.

^a Troponin concentration 6–12 h after the OHCA was available in 127 patients, 45 patients with AMI and 82 patients without AMI.

stay of eight (6–13) and 20 (15–40) days, respectively. Their CPC is shown in Fig. 1.

2.2. Troponin concentration and diagnostic characteristics

Troponin concentrations and diagnostic characteristics are shown in Tables 2 and 3.

Troponin concentration at Ta was available for all patients. The interval from the OHCA to Ta was 209 (158–267) min, similar between patients with and without AMI ($p = 0.5$).

Troponin at Ta was above the manufacturer's AMI cut-off in 112 patients. When the manufacturer's AMI cut-off was used for diagnosis, sensitivity was 95%, specificity 47% and accuracy 64%.

After ROC curve analysis at Ta we found a cut-off of 2.5 ng ml⁻¹, with 72% sensitivity and 75% specificity for AMI diagnosis, for maximum accuracy of 74%.

When troponin concentrations obtained by each assessment method were analysed separately, the cut-offs were very similar, 2.4 ng ml⁻¹ for AxSYM[®] and 3 ng ml⁻¹ for ARCHITECT STAT[®] on admission (Fig. 2).

When the diagnostic criterion at Ta was a combination of troponin >2.5 ng ml⁻¹ or ST elevation, sensitivity was 93% (83–98), specificity 64% (54–73), PPV 60% (50–70), NPV 94% (86–98) and accuracy 75% (66–82).

Troponin concentration at T6–12 was available in 127 patients. The interval from the OHCA to T6–12 was 9.5 h (7–11.5) similar

between patients with and without AMI ($p = 0.4$). The maximum accuracy cut-off was 14.5 ng ml⁻¹ (Table 3).

2.3. Troponin concentration on admission in patients with normal CA

In the 43 patients with normal CA, troponin at Ta was 0.6 ng ml⁻¹ (0.07–5.5) and 15 had concentrations >2.5 ng ml⁻¹. Troponin concentration was as high as 23 ng ml⁻¹ 30 min after the OHCA and 48 ng ml⁻¹ 220 min after the OHCA. The causes of OHCA in these 15 patients were rhythm disturbances (idiopathic or due to dilated cardiomyopathy), pulmonary embolism, hypoxia, poisoning, cerebral haemorrhage and unknown in two patients.

2.4. Correlates of troponin

None of the variables – age, lactate concentration on admission, rate of catecholamines infusion on admission, no-flow and low-flow – were correlated with troponin on admission in univariate linear/non-linear regression ($R^2 \leq 0.5$).

In univariate logistic regression, significant correlates of troponin at Ta > 2.5 ng ml⁻¹ are shown in Table 4.

In stepwise multivariable logistic regression, independent correlates of troponin at Ta > 2.5 ng ml⁻¹ were ST elevation OR = 9.8 (95%CI 3.6–27), $p < 0.0001$ and low-flow OR = 1.05 (1.01–1.08), area under the curve (AUC) = 0.83 (95%CI 0.74–0.9), $p < 0.0001$.

Table 3
Diagnostic characteristics of troponin at Ta and T6–12 according to the manufacturer's cut-off and suggested by ROC curve analysis.

Timing of assessment	Troponin cut-off (ng ml ⁻¹)	Se (CI)	Sp (CI)	PPV (CI)	NPV (CI)	Ac (CI)	AUC (CI)
Ta	Manufacturer recommended	95% (86–99)	47% (47–58)	51% (41–60)	94% (84–99)	64% (54–71)	NC
	2.5 ng ml ^{-1a}	72% (59–83)	75% (66–84)	64% (51–75)	82% (73–89)	74% (66–81)	0.8 (0.73–0.86)
T6–12	Manufacturer recommended	100% (92–100)	31% (21–43)	46% (36–56)	100% (86–100)	57% (49–65)	NC
	14.5 ng ml ^{-1a}	84% (71–94)	84% (74–91)	75% (60–86)	91% (82–96)	84% (75–90)	0.9 (0.84–0.95)

^a The 2.5 and 14.5 are the cut-offs of maximum accuracy suggested by the ROC curves at Ta and T6–12. Ta-troponin concentration on admission. T6–12-troponin concentration 6–12 h after the out-of-hospital cardiac arrest. Se – sensitivity, Sp – specificity, PPV – positive predictive value, NPV – negative predictive value, Ac – accuracy, CI – 95% confidence interval, AUC – area under the ROC curve. NC – not calculated, since ROC curves were only constructed in the case of cut-offs of maximum accuracy.

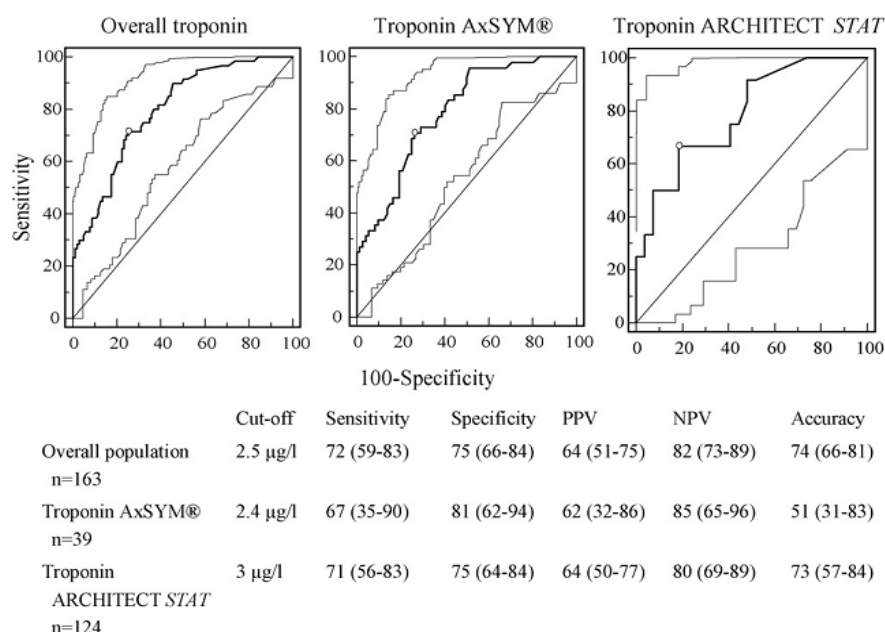


Fig. 2. ROC curves for acute myocardial infarction diagnosis and diagnostic characteristics. Troponin concentration measured by Troponin AxSYM® technique and ARCHITECT STAT were analysed together (overall population), and separately (Troponin AxSYM® and Troponin ARCHITECT STAT). The cut-offs and detailed diagnostic characteristics and confidence intervals are also represented. The markers on the ROC curves represent the point of maximum accuracy corresponding to the cut-off of maximum accuracy for AMI diagnosis.

Table 4
Correlates of troponin > 2.5 ng ml⁻¹ on admission in univariate logistic regression.

Variables	OR (95%CI)	p-Value
AMI	8 (3.9–16)	<0.0001
ST-elevation	5.1 (2.6–10.1)	<0.0001
Ventricular fibrillation	3 (1.6–6)	0.01
Tobacco smoking	2.3 (1.2–4.4)	0.01
Single vessel disease	2.1 (1.03–4.3)	0.04
Number of electric shocks	1.7 (1.05–1.3)	0.003
Low-flow	1.05 (1.02–1.08)	0.002
Age	0.96 (0.94–0.99)	0.004
Asystole	0.3 (0.16–0.6)	0.0008
Diabetes	0.3 (0.1–0.8)	0.01

AMI – acute myocardial infarction.

In a model not adjusting for ST elevation, significant variables were AMI, OR = 9.4 (3.5–25), $p < 0.0001$, tobacco smoking, OR = 3.3 (1.2–9.1), $p = 0.02$ and low-flow OR = 1.04 (1.003–1.08), $p = 0.03$, AUC = 0.83 (0.75–0.9), $p < 0.0001$.

3. Discussion

In this study in which the method of reference for AMI diagnosis was the CA on admission, the most important finding is that in OHCA patients without obvious non-cardiac cause, troponin can be useful for the AMI diagnosis alone or in combination with ST elevation. We evaluated the diagnostic characteristics of troponin on admission and 6–12 h after the OHCA because early diagnosis and treatment in patients with AMI may improve survival,^{2,3} while coronary reperfusion after a diagnosis of AMI made more than 12 h after the onset of artery occlusion does not improve outcome.¹⁸ Thus, by diagnosing AMI while artery reopening is still beneficial, our results can influence the management of the patients.

Our data show that AMI diagnosis can be made using the manufacturer's cut-offs with very high sensitivity and NPV, but low specificity and accuracy due to numerous false positive cases.

To improve these last parameters we used the ROC curve analysis to find cut-off concentrations of maximum accuracy, and we obtained a diagnostic performance at Ta comparable to another study⁸ which found a Youden index of 0.36 versus 0.47 in our patients. The cut-offs we obtained are higher than those suggested by the manufacturer, especially at T6–12. This is consistent with previous studies,^{7,8} which found very different cut-offs for AMI diagnosis: 4 ng ml⁻¹ for troponin at peak concentration during hospitalisation and 0.6 ng ml⁻¹ 12 h after admission, probably due to differences in the severity of the patients, and possibly between the time from the OHCA to the troponin assessment. Unlike the afore-mentioned studies, we provided information on the time intervals between the OHCA and the troponin assessments. Even though these may be in some cases overestimated by up to 30 min (the delay of transportation of the blood samples was not always accounted for), they make our results interpretable in everyday practice.

Interestingly, the strongest correlate of troponin at Ta above the AMI cut-off in multivariable analysis was not the presence of AMI, but the presence of ST elevation which is a marker of myocardial injury. The injury may be not only due to an acute coronary occlusion²⁰ but also due to ischaemia due to diffuse hypoperfusion possibly aggravated by chronic stenoses, or to myocardial injury during chest compressions²¹ explaining another important finding in our study, the correlation in multivariable analysis between low-flow and troponin concentration above cut-off.

The non-ischaemic myocardial injury during chest compressions and the ischaemia and reperfusion syndrome²² may explain the high troponin concentrations very early after the OHCA even in patients with normal CA, which is another important finding in our study. Other causes (myocarditis and transient coronary spasm)

could be suspected only in four patients with normal CA and troponin above cut-off: two patients with unknown causes of OHCA and two who suffered VF considered 'idiopathic'.

At T6–12, diagnostic characteristics of troponin were better than at Ta, but lower than in a study⁷ assessing troponin at peak during hospitalisation: sensitivity 84% versus 95% and specificity 84% versus 88%. However, in 21% of the patients in this report,⁷ the diagnosis of AMI was equivocal by ECG criteria, and they were excluded from the analysis, probably accounting for the high diagnostic value. AMI diagnosis using ECG criteria after OHCA may be difficult,^{2,3,5} and the advantage in our study is that all patients underwent CA immediately on admission, allowing for angiographic diagnosis of AMI. However, troponin concentration at T6–12 in patients with angiographic AMI was most certainly influenced in our study by the angioplasty and, in their case, the concentration at T6–12 does not reflect the natural 'rise and/or fall'¹⁴ of troponin. Angioplasty may precipitate a rapid increase or diminish the release of troponin and, therefore, in AMI patients not undergoing angioplasty, the concentration and the cut-off of troponin at T6–12 may be different. Also, all our AMI patients had culprit arteries with TIMI 0–1 flow and our results may be different in patients presenting with spontaneous reperfusion of the culprit artery (TIMI 2–3).

Interestingly, on admission, the use of a composite diagnostic criterion ST elevation or troponin $>2.5 \text{ ng ml}^{-1}$ may improve diagnostic sensitivity compared with ST elevation or troponin concentration alone, allowing for a better detection of AMI patients. This combination could be used as a diagnostic tool if future studies confirm its value.

It has been suggested that hypothermia may decrease myocardial injury after AMI,²³ but in our study, no differences occurred in troponin concentrations between hypothermia and non-hypothermia patients at Ta, T6–12 or at peak concentration during hospitalisation ($p > 0.2$, data not shown). However, since hypothermia was not randomised for, no certain conclusion can be drawn about its effect.

The causes of OHCA in our population are similar to other studies: AMI in 37.5–51%^{1,4} of the patients, ischaemic heart disease without AMI in up to 34%⁴ and non-ischaemic cardiomyopathy in up to 11%.⁴ Our population had high prevalence of shock and high lactate concentration on admission, and even though may be considered heterogeneous, it represents a 'real-life' cohort of OHCA patients, making our results applicable in everyday practice. The survival in our patients is similar to studies including patients without selected initial rhythm^{3,24} and, as expected, lower than in studies including only patients with initial shockable rhythm.²⁵

3.1. Limitations

Since this is a retrospective study, troponin concentration at T6–12 was not available in all patients mainly because 18% expired during the first day. Nevertheless, troponin at Ta was recorded in all patients and our study provides data on a number of patients larger than in similar studies.^{7,8,20}

Troponin assessment was performed using two different methods by the same manufacturer. However, our results remain valid because the cut-offs obtained are above the thresholds of recommended CV $< 10\%$ for both methods, the two methods are very well correlated¹⁷ and also the cut-offs are very similar when assessments by the two methods are analysed separately (Fig. 2).

Also, our study did not include a multimarker approach using creatine kinase (CK)/CKMB or myoglobin, but these were shown to be less sensitive and specific and influenced by the external electric shocks²⁶ or circulatory shock.²⁷ Therefore, an improvement of the diagnostic characteristics by their use seems less likely.

Troponin assessment by the hospital laboratory may be too long in the setting of OHCA, and a bedside test may be more valuable due to its rapid results. Such tests were not available in our population but could be the object of future evaluations.

Certain parameters remained undetermined in up to 27% of our patients (low-flow), but this occurred in a similar range in other retrospective studies,²⁸ and is difficult to avoid.

Finally, the diagnostic sensitivity of troponin may be improved by highly sensitive troponin assays,^{29,30} which could be evaluated in future studies. However, the Abbott ARCHITECT Troponin test used in our study was one of the four sensitive troponin tests that showed very good diagnostic value (AUC = 0.96) in one of these studies³⁰ and thus our results remain valid.

4. Conclusion

Using an angiographic definition of AMI, our study showed that cardiac troponin assessment may be useful for the AMI diagnosis after OHCA. When combined with ST elevation, troponin on admission achieves very good sensitivity. Troponin on admission may reach high concentrations even in patients with normal CA and is correlated with the duration of chest compressions during the resuscitation. Troponin 6–12 h after the OHCA is a good diagnostic criterion with an excellent NPV when using the manufacturer's cut-off, but these findings should be interpreted cautiously due to the influence of the primary angioplasty on the troponin release in our population.

Conflict of interest statement

None.

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Favourable 5-year postdischarge survival of comatose patients resuscitated from out-of-hospital cardiac arrest, managed with immediate coronary angiogram on admission

Georgios Sideris^{1,2,3,*}, Sebastian Voicu^{1,2,3,*}, Demetris Yannopoulos⁴, Jean-Guillaume Dillinger^{1,2,3}, Julien Adjedj^{1,3}, Nicolas Deye^{1,2,3}, Papa Gueye^{1,3,5}, Stéphane Manzo-Silberman^{1,2,3}, Isabelle Malissin^{1,2,3}, Damien Logeart^{1,2,3}, Nikos Magkoutis¹, Dragos D Capan⁶, Siham Makhouloufi⁷, Bruno Megarbane^{1,3,8}, Benoit Vivien^{5,9,10}, Alain Cohen-Solal^{1,2,3}, Didier Payen^{1,3,5}, Frédéric J Baud^{1,3,8} and Patrick Henry^{1,2,3}

Abstract

Aims: On-admission coronary angiogram (CA) with angioplasty (percutaneous coronary intervention, PCI) may improve survival in patients resuscitated from out-of-hospital cardiac arrest (OHCA), but long-term survival data are scarce. We assessed long-term survival in OHCA patients managed with on-admission CA and PCI if indicated and compared survival rates in patients with/without acute coronary syndrome (ACS).

Methods: Retrospective single-centre study including patients aged ≥ 18 years resuscitated from an OHCA without noncardiac cause, with sustained return of spontaneous circulation, undergoing on-admission CA with PCI if indicated. ACS was diagnosed angiographically. Survival was recorded at hospital discharge and at 5-year follow up. Survival probability was estimated by Kaplan–Meier survival curves.

Results: A total of 300 comatose patients aged 56 years (IQR 48–67 years) were included, 36% with ST-segment elevation. All had on-admission CA; 31% had ACS. PCI was attempted in 91% of ACS patients and was successful in 93%. Hypothermia was performed in 84%. Survival to discharge was 32.3%. After discharge, 5-year survival was $81.7 \pm 5.4\%$. Survival from admission to 5 years was $26.2 \pm 2.8\%$. ACS patients had better survival to discharge (40.8%) compared with non-ACS patients (28.5%, $p=0.047$). After discharge, 5-year survival was $92.2 \pm 5.4\%$ for patients with ACS and $73.4 \pm 8.6\%$ without ACS (hazard ratio, HR, 2.7, 95% CI 0.8–8.9, $p=0.1$). Survival from admission to 5 years was $37.4 \pm 5.2\%$ for ACS patients, $20.7 \pm 3.0\%$ for non-ACS patients (HR 1.5, 95% CI 1.12–2.0, $p=0.0067$).

Conclusions: OHCA patients undergoing on-admission CA had a very favourable postdischarge survival. Patients with OHCA due to ACS had better survival to discharge at 5-year follow up than patients with OHCA due to other causes.

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Acute coronary syndrome, coronary angiography, heart arrest, long-term survival

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Introduction

Management of out-of-hospital cardiac arrest (OHCA) is complex, challenging, and continuously evolving, but overall survival remains poor, and most patients die due to neurological or circulatory failure. Despite low in-hospital survival of OHCA patients, long-term survival after hospital discharge is good¹ and varies according to the population studied and the therapeutic interventions.²

Acute coronary artery occlusion is the main cause of OHCA³ and data from nonrandomized studies suggest that immediate coronary angiogram (CA) on admission may be a useful diagnostic and therapeutic procedure.^{3–8} According to recent guidelines CA is recommended in OHCA patients with ST-elevation myocardial infarction and should be considered in patients with high suspicion of ongoing infarction.⁹ Although no randomized studies exist to date, CA is performed immediately on admission in several centres.^{3,4,6–8,10,11}

Survival to hospital discharge of patients managed with immediate on-admission CA and angioplasty (percutaneous coronary intervention, PCI), if indicated, is well documented,^{3–5} but there is little data on long-term survival. Even though several studies found higher long-term survival in OHCA of cardiac origin compared to noncardiac origin,^{12,13} data on patients with angiographically defined acute coronary syndrome (ACS) compared with those without ACS are scarce. This is an important issue since the benefit of CA with PCI occurs especially in this population.

In our centre, routine CA with PCI is performed on admission to the hospital before transfer to the intensive care unit (ICU), for all OHCA patients without an obvious noncardiac cause. The main purpose of the present study was to assess the long-term survival of the patients managed with this strategy. The secondary purpose was to evaluate long-term survival of patients with ACS compared with patients without ACS.

Methods

This study was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The ethics committee of our institution approved the study and no informed consent was required from the patients or the next of kin.

The prehospital management of the patients in Paris, France has been previously described.¹⁴ After successful resuscitation according to guidelines,¹⁵ patients are

transferred to our centre directly to the catheterization laboratory for routine CA on admission.

Population

We included in this retrospective single-centre study all comatose patients admitted for OHCA between January 2002 and August 2011, ≥ 18 years old (no upper age limit) with sustained return of spontaneous circulation¹⁶ (ROSC), regardless of the initial OHCA rhythm and electrocardiogram (ECG) changes. In order to avoid the inclusion of a heterogeneous population, we excluded patients with in-hospital cardiac arrest or obvious noncardiac cause (e.g. trauma, drowning, poisoning, drug overdose, hypovolaemic shock, accidental hypothermia, electrocution). We also excluded patients with Glasgow Coma Scale (GCS) >7 on admission, patients with refractory OHCA (absence of ROSC despite resuscitation attempts until hospital admission), or unsustained ROSC (impossibility to maintain circulation with palpable pulse and systolic blood pressure >80 mmHg for >20 min).¹⁶

Patient management on admission and CA

On admission to the catheterization laboratory, cardiologists performed CA and PCI if indicated and ICU doctors managed ventilation and circulatory function and initiated/continued therapeutic hypothermia using cold intravenous saline (4°C)¹⁷ with target temperature of 32–34°C. Therapeutic hypothermia was maintained during 24 hours and was performed in all patients including those with asystole or pulseless electrical activity as initial rhythm.¹⁷

CA was performed through femoral or radial access using standard technique. PCI was attempted if a culprit lesion considered responsible for the OHCA was found. Coronary artery flow was assessed according to Thrombolysis in Myocardial Infarction (TIMI) classification.¹⁸ Coronary stenoses were considered significant if $\geq 50\%$.^{3,5,10}

ACS was defined angiographically in accordance with previous data¹¹ by the presence of a main coronary artery occlusion (TIMI 0 or 1)¹⁸ easily crossed by an angioplasty wire³ or lesions with TIMI 2 or 3 flow¹⁹ suggestive of ruptured plaques (Ambrose type II)²⁰ with evidence of fresh thrombus.¹⁸

PCI was considered successful if postangioplasty blood flow was TIMI 3 and residual stenosis was $<50\%$. CA were retrospectively analysed by two independent experienced observers.

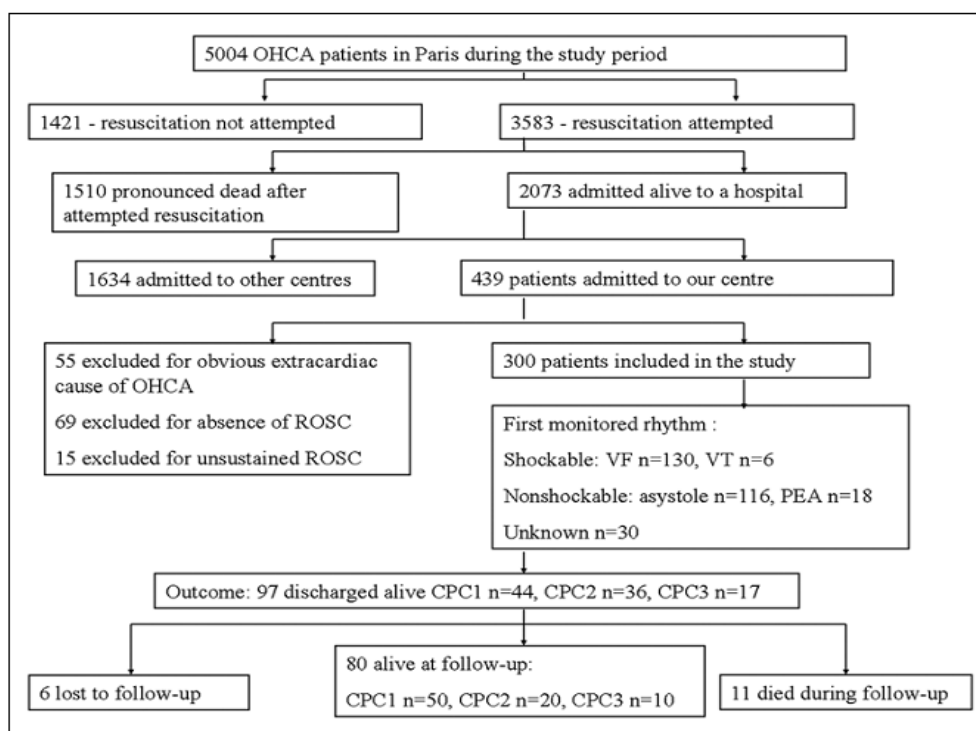


Figure 1. Flow chart and outcome of the included population in the city of Paris (population approximately 2.25 million people). CPC, cerebral performance category; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

If CA did not provide the aetiology of the OHCA, a CT-scan pulmonary angiography and brain CT-scan were performed before ICU admission.²¹

Data collection

Studied variables included clinical characteristics, biochemical parameters, and resuscitation intervals: no flow and low flow. We considered no flow as the interval between the patient's collapse and the beginning of chest compressions and low flow the interval between the beginning of chest compressions and ROSC. The initial rhythm of the OHCA was considered the first ECG trace available after the OHCA, before ROSC. The neurological status was assessed using the Cerebral Performance Category score (CPC).^{16,22}

Survival for three time frames was determined: (i) in-hospital survival was defined as survival from admission to hospital discharge; (ii) postdischarge survival was defined as survival from hospital discharge to long-term follow up; and (iii) long-term overall survival was defined as survival from admission to long-term follow up.

Statistical analysis

Continuous variables were described as median (interquartile range, IQR) and compared using the two-tailed

Mann–Whitney U-test. Categorical variables were reported as frequencies and percentages and compared using the chi-squared test and if not applicable, Fisher's exact test. A statistical difference with $p < 0.05$ was considered significant.

Survival was assessed using Kaplan–Meier survival curves. To establish correlations with survival, clinically significant parameters were introduced into a Cox proportional hazards univariate regression. Factors found significant in univariate regression were introduced into Cox proportional hazards multivariate regression. Statistical analysis was performed using MedCalc version 11.0.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Between January 2002 and June 2011, 439 OHCA patients were admitted to our institution, and 300 were included (Figure 1). The general characteristics of the patients and the OHCA are given in Tables 1 and 2. All patients were comatose on admission, intubated, and mechanically ventilated.

Angiographic data

CA was performed in all patients on admission. There were 93 patients (31%) who had ACS (Table 3). Only 80% of the

Table 1. Characteristics of the patients at baseline and on admission.

Characteristic	Overall (n=300)	In-hospital survivors (n=97)	Nonsurvivors (n=203)	p-value
Age (years)	56 (48–67)	50 (45–63)	59 (49–67)	0.001
Male	237 (79)	81 (83.5)	156 (77)	0.23
Risk factors (n=285)				
Hypertension	99 (33%)	38 (39)	61 (30)	0.30
Hypercholesterolaemia	57 (19)	21 (22)	36 (18)	0.715
Diabetes	47 (16)	9 (9)	38 (19)	0.102
Active smoking	111 (37)	48 (49)	63 (31)	0.013
History of coronary artery disease	55 (18)	14 (14)	41 (20)	0.22
SBP (mmHg)	128 (100–150)	131 (110–160)	124 (96–151)	0.062
DBP (mmHg)	73 (60–88)	79 (68–91)	70 (59–86)	0.05
Patients receiving catecholamines	179 (60)	40 (41)	139 (68)	<0.0001
GCS	3 (3–3)	3 (3–3)	3 (3–3)	0.18
ST-elevation (n=284)	109 (36)	41 (42)	68 (33.5)	0.25
Peak TnI ($\mu\text{g/l}$)	10.2 (2.3–65.0)	9.5 (6.6–18.6)	11.5 (4.9–34.2)	0.98
Lactate (mmol/l)	5.4 (2.5–9.2)	2.8 (2.1–3.2)	7.0 (4.0–11.7)	<0.0001
Therapeutic hypothermia	256 (84)	96 (99)	160 (79)	0.0008
Time from collapse to hypothermia initiation (min)	116 (92–148)	112 (89–145)	120 (95–154)	0.27
LVEF on admission (%; n=158)	40 (30–50)	40 (30–50)	45 (24–55)	0.30

Values are median (IQR) or n (%).

DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TnI, cardiac troponin I.

Table 2. Characteristics of OHCA patients.

Characteristic	Overall (n=300)	In-hospital survivors (n=97)	Nonsurvivors (n=203)	p-value
OHCA in public place	170 (57)	65 (67)	105 (52)	0.042
Initial rhythm (n=270)				
Ventricular fibrillation	130 (43)	67 (69)	63 (31)	<0.0001
Ventricular tachycardia*	6 (2)	3 (3)	3 (1)	NC
Asystole	116 (39)	11 (11)	105 (52)	<0.0001
Pulseless electrical activity	18 (6)	7 (7)	11 (5)	0.73
Duration of no flow (min; n=243)	4 (0–10)	2.5 (0–5)	5 (1–10)	0.0031
Duration of low flow (min; n=245)	20 (10–30)	10 (6–21)	22 (12–30)	<0.0001

Values are median (IQR) or n (%).

*One patient had torsade de pointe, one had polymorphic ventricular tachycardia, and four had monomorphic ventricular tachycardia.

NC, not calculated due to the reduced number of patients; OHCA, out-of-hospital cardiac arrest. See text for definition of no flow and low flow.

patients with ACS had ST-elevation on the post-ROSC ECG. Troponin was increased in all patients with ACS (Table 4). The time interval from OHCA to CA was 132 min (104–176 min) and from OHCA to PCI 143 min (124–193 min).

PCI was attempted in 91% of the ACS patients and was successful in 93% (Table 3). Initial PCI was not attempted in 4.5% due to the presence of coronary spasm (successfully treated with intracoronary nitrates) and in 4.5% due to abundant intracoronary thrombi with TIMI 3 flow. These patients were treated with antiplatelet and anticoagulant agents before subsequent angioplasty.

Causes of OHCA

The most frequent cause of OHCA was ACS in 93 patients (31%, of whom four patients had coronary artery spasm), followed by rhythm disturbances due to chronic ischaemic heart disease in 54 patients (18%). The cause was hypoxia in 39 (13%) and pulmonary embolism in 7 (2%) patients. Long QT, Brugada syndrome, or idiopathic ventricular fibrillation (VF) occurred in 24 (8%) patients and nonischaemic dilated cardiomyopathy in 11 (4%) patients. Miscellaneous conditions (e.g. electrolyte disturbances, neurological conditions, aortic dissection, complete heart block, ruptured aneurysm,

Table 3. Angiographic data.

Characteristic	Overall (n=300)	In-hospital survivors (n=97)	Nonsurvivors (n=203)	p-value
ACS	93 (31)	38 (39)	55 (27)	0.047
One-vessel disease	74 (25)	30 (31)	44 (22)	0.11
Two-vessel disease	41 (14)	15 (15.5)	26 (13)	0.66
Three-vessel disease	51 (17)	20 (21)	31 (15)	0.32
Left main disease	9 (3)	3 (3)	7 (3)	0.84
At least one chronic total occlusion	37 (12)	13 (13)	24 (12)	0.55
Nonsignificant stenosis	46 (15)	7 (7)	39 (19)	0.0115
Normal coronary angiogram	88 (29)	25 (26)	63 (31)	0.42
Attempted angioplasty	85 (28)	36 (37)	49 (24)	0.56
Successful angioplasty	79 (26)	34 (35)	45 (22)	0.59

Values are n (%).

ACS, acute coronary syndrome which was defined angiographically by the presence of a main coronary artery occlusion (TIMI 0 or 1) easily crossed by an angioplasty wire or lesions with TIMI 2 or 3 flow suggestive of ruptured plaques (Ambrose type II) with evidence of fresh thrombus.

Table 4. Significantly different parameters in patients with ACS vs. patients without ACS.

Characteristic	Patients with ACS (n=93)	Patients without ACS (n=207)	p-value
Survivors	38 (40.8)	59 (28.5)	0.047
Age (years)	52 (46–61)	59 (49–70)	0.0046
Risk factors			
Hypertension	29 (23)	70 (34)	0.021
Diabetes	7 (8)	40 (19)	0.0018
Active smoking	49 (53)	62 (30)	0.0002
ST-elevation (n=284)	74 (80)	35 (17)	<0.0001
Peak TnI (µg/l)	59 (46–102)	3.5 (1–14)	<0.0001
OHCA in public place	61 (66)	109 (53)	0.035
Initial rhythm			
Ventricular fibrillation	66 (71)	64 (31)	<0.0001
Asystole	13 (14)	93 (45)	<0.0001
PEA	1 (1)	17 (8)	0.036
No. of electric shocks	3 (1–5)	0 (0–1)	<0.0001
Duration of low flow (min)	22 (11–40)	19 (10–29)	0.017

Values are median (IQR) or n (%). Comparisons were performed for all recorded characteristics; only significantly different characteristics are shown.

ACS, acute coronary syndrome; Tn I, cardiac troponin I; OHCA, out-of hospital cardiac arrest; PEA, pulseless electrical activity. See text for definition of low flow.

poisoning initially not suspected) were found in 45 (15%) patients. The cause of OHCA remained undetermined in 27 (9%) patients.

In-hospital management

Inotropic support was necessary on admission in 60% of the patients. Among ACS patients, 44 (46%) received an intra-aortic balloon pump. Extracorporeal life support was inserted in the ICU in 10 (3.3%) patients (two (2%) in ACS and eight (3.9%) in non-ACS patients). Left ventricular assistance by Impella 2.5 was inserted in the catheterization laboratory in two ACS patients.

Therapeutic hypothermia was more frequently performed in survivors (Table 1) since 43 nonsurvivors died rapidly after admission before reaching target temperature.

An implantable cardiac defibrillator (ICD) was inserted in 21 survivors (22%): all non-ACS patients – six with chronic ischaemic heart disease and myocardial scars, six with dilated cardiomyopathy, and nine with long QT, Brugada syndrome, or idiopathic VF. No deaths were recorded in these patients during follow up. Among the 38 non-ACS survivors without ICD, a reversible OHCA cause was detected in 25. Two patients refused the ICD, and in four it was not implanted due to poor outcome (CPC3). One patient already had an ICD, two patients were transferred to other centres,

Table 5. Factors associated with survival in univariate and multivariate Cox-proportional hazards survival analysis.

Variable	Beta coefficient±SE	chi-squared	p-value
Univariate regression			
Age	0.0178±0.0048	13.749	0.0002
Asystole	0.939±0.1408	43.549	<0.0001
Successful angioplasty	-0.4686±0.1916	6.365	0.0140
ACS	-0.3997±0.1551	7.030	0.0090
Diabetes	0.3891±0.1814	4.324	0.0320
Therapeutic hypothermia	0.9047±0.1888	18.945	<0.0001
Shock on admission	0.7556±0.1484	27.631	<0.0001
Lactate concentration on admission	0.1520±0.01483	91.784	<0.0001
OHCA in public place	-0.3154±0.1416	4.885	0.0259
OHCA at home	0.2958±0.1417	4.287	0.0369
Duration of low flow	0.0158±0.0039	13.856	0.0002
Duration of no flow	0.0177±0.0082	3.913	0.0310
Diastolic blood pressure	-0.0118±0.0050	5.697	0.0173
Arterial pH on admission	-3.4441±0.4240	57.718	<0.0001
VF as initial rhythm	-0.9635±0.1517	42.929	<0.0001
Initial troponin	0.0009±0.0004	3.796	0.0162
Multivariate regression			
Initial pH	-1.4929±0.5469	— ^a	0.0063
VF as initial rhythm	-0.4837±0.2001	— ^a	0.0157
Initial lactate	0.1072±0.0204	— ^a	<0.0001
Age	0.0167±0.0055	— ^a	0.0027

In univariate regression, all recorded characteristics were tested but only factors with $p < 0.05$ are shown.

^aIn multivariate analysis, chi-squared applies to the model ($\chi^2 = 116.45$, $p < 0.0001$) and therefore no chi-squared is expressed for individual variables.

ACS, acute coronary syndrome; OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation. See text for definition of no flow and low flow.

Table 6. Survival in the overall population and in ACS and non-ACS patients.

	Overall (n=300)	Patients with ACS (n=93)	Patients without ACS (n=207)	p-value
In-hospital survival	97 (32)	38 (40.8)	59 (207)	0.047
Postdischarge survival (%) ^a	81.7±5.4	92.2±5.4	73.4±8.6	0.1
Long-term overall survival (%) ^a	26.2±2.8	37.4±5.2	20.7±3.0	0.0067

Values are n (%) or mean±SD.

ACS, acute coronary syndrome.

^aExpressed as probability according to Kaplan–Meier survival curve.

and four had ischaemic heart disease with normal electro-physiological study after complete revascularization.

At discharge, all patients with significant coronary artery disease received long-term aspirin, statin therapy, and beta-blockers unless contraindicated. Dual antiplatelet therapy was administered in all ACS patients.

In-hospital, postdischarge, and long-term overall survival

Survival is described in Table 6. There were 97 patients (32%) who were discharged alive from the hospital and 80 (82.5%) were alive at follow up (11 died, six were lost to follow up). Median follow up was 46 months (22–64 months). For the entire population, the probability of

postdischarge survival was 81.7±5.4% and of long-term overall survival was 26.2±2.8% (Table 6).

CPC at discharge was 1 in 44 patients, 2 in 36 patients, and 3 in 17 patients. At long-term follow up, 11 patients died, 15 improved their CPC from 2 to 1, and four improved their CPC from 3 to 2. Thus, 70/97 (72%) patients had good neurological status at long-term follow up: 50 were CPC1, 20 CPC2, and only 10 were CPC3 (Figure 1).

Among patients deceased during follow up, the cause of death was pneumonia in two, severe sepsis in two, metastatic cancer in one, and respiratory failure in one patient. Diastolic heart failure was the cause of death in one patient and cardiogenic shock following ACS due to a coronary lesion different from the initial ACS in another patient. In three patients, the cause of death remained undetermined.

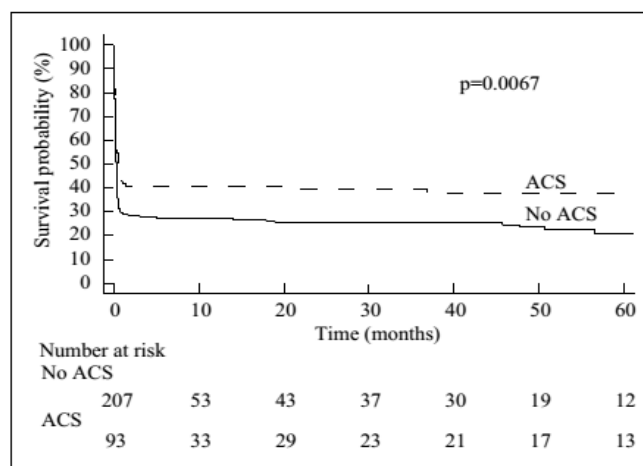


Figure 2. Probability of long-term overall survival of ACS patients vs. non-ACS patients according to Kaplan–Meier survival analysis.

The probability of long-term overall survival in ACS patients (dashed line) was $37.4 \pm 5.2\%$ and in non-ACS patients (solid line) was $20.7 \pm 3.0\%$ (hazard ratio 1.5, 95% CI 1.12–2.0; $p=0.0067$. ACS, acute coronary syndrome.

Four patients required repeat revascularization: two in lesions not related to the initial ACS and four for in-stent restenosis.

Survival in patients with ACS vs. patients without ACS

Patients with ACS had better in-hospital survival than patients without ACS ($p=0.047$; Table 6). Despite a tendency in favour of the ACS group, probability of postdischarge survival was not different in the two groups (Table 6). The probability of long-term overall survival in patients with ACS was significantly higher than in patients without ACS (hazard ratio 1.5, 95% CI 1.12–2.0, $p=0.0067$ according to the Kaplan–Meier survival curve; Figure 2).

All recorded characteristics were compared between patients with and without ACS. Characteristics showing significant differences between the two groups are provided in Table 4. The left ventricular ejection fraction at discharge in ACS patients did not differ from non-ACS patients (50%, IQR 42–60 vs. 50%, IQR 37–55%, $p=0.4$). Among the 58 non-ACS survivors, 31 had cardiomyopathy (22 ischaemic heart disease, and nine dilated cardiomyopathy), with left ventricular ejection fraction of 45% (IQR 29–51%).

Univariate and multivariate survival analysis

The factors significantly associated with long-term overall survival in univariate regression are expressed in Table 5. In multivariate regression, four variables were associated with prognosis: presence of VF, age, initial lactate concentration, and initial arterial pH (Table 5).

Discussion

The present study is the first to report 5-year probability of survival in a population of resuscitated OHCA patients regardless of the presenting rhythm and presence of ST-elevation on post-ROSC ECG who were managed with an early invasive strategy including routine CA on admission to the hospital and PCI if indicated. The most important findings are that postdischarge survival was high (81.7%) in the entire OHCA population and that in-hospital survival and, especially, long-term overall survival in patients with OHCA caused by ACS were significantly higher than in patients without ACS.

Patients included in our study had an in-hospital survival of only 32 %, relatively lower than other studies – 38%,³ 40%,⁵ 54%⁴ – but this was due to the severity of our population. Indeed, 197 patients (66%) had at least one very poor prognostic factor: either asystole or pulseless electrical activity as initial rhythm and/or very long resuscitation duration with no flow >5 min and/or low flow >30 min, which may account for the relatively high mortality.

Favourable postdischarge survival in the overall population

Survival for patients with OHCA varies widely across the studies according to the population included. Garot et al.²³ reported a 54% 6-month survival in a selected population (OHCA with VF and presumed ST-elevation myocardial infarction referred for primary PCI), but longer follow-up data were not available. A study of 200 OHCA patients with VF as initial rhythm (47% with ACS), reported 79% 60-month postdischarge survival, similar to our data. However, CA was not performed routinely and only 24% of

these patients had a myocardial revascularization attempt (by PCI or coronary surgery) during hospitalization.¹

Postdischarge survival in our patients seems higher than in OHCA studies before hypothermia and CA were introduced. Indeed, Engdahl et al.² found in 430 OHCA patients with 86% VF as initial rhythm, a 60-month postdischarge survival of only 48%. This difference may be due to therapeutic hypothermia and possibly to CA with revascularization in our patients, but also to long-term medical treatment using beta-blockers and lipid-lowering drugs.^{2,9}

A recent study analysed outcome according to the use of CA and PCI and showed improved survival in patients undergoing this procedure.²⁴ In this cohort, 60-month postdischarge survival was 78.7% in patients receiving PCI, compared to 92.7% in our study, a difference that may be explained by therapeutic hypothermia used in 99% of the survivors in our population vs. only 26%.²⁴ Indeed, 9.1% of the patients in this study²⁴ received PCI and therapeutic hypothermia, and the 60-month survival (88.6%) was comparable to our patients. However, the moment of the coronary angiogram in this population was less well defined and was not performed routinely on admission.

Long-term follow up in our population showed not only a good survival, but also an improvement of CPC status, consistent with previous data²⁵ suggesting that neurological improvement continues after hospital discharge.^{25,26}

Favourable prognosis in ACS patients

In the setting of the OHCA the diagnosis of ACS without the use of CA is complex, due to the limited diagnostic value of the ECG changes^{3,14} and troponin elevation.¹¹ In the absence of CA, ACS cases and severe coronary heart disease may remain undetected and without appropriate treatment. In our population, immediate routine CA avoided this limitation.

Before the era of emergency revascularization, OHCA studies suggested that survival was better in patients with ACS.^{27,28} A more recent report²⁹ showed better 3-year survival of OHCA patients with ST-elevation ACS, but CA was not performed on a routine basis and details on the selection of patients for PCI are not provided.

Even though in our population the presence of ACS was not independently associated with prognosis in multivariate analysis, the better survival of ACS patients emphasizes the importance of CA with PCI in the initial management of resuscitated OHCA patients. Only four very strong prognostic factors (presence of VF as initial rhythm, age, initial lactate concentration, and initial arterial pH) found in many OHCA studies^{3,14,23} were independently associated with prognosis in multivariate regression. Even though successful PCI is not one of them, due to the design of our study, no definite conclusion can be drawn on the influence of PCI on survival, and randomized trials are warranted to evaluate this issue.⁷

Interestingly, the favourable postdischarge prognosis of ACS patients was similar to that recorded in recent ACS

studies without OHCA. In a study comparing thrombolysis vs. PCI,³⁰ 5-year probability of survival in the PCI group was 87%, similar to 92.2% in our population. This favourable postdischarge survival may be explained by the good neurological status at discharge in our patients and the preserved left ventricular function. The median value of left ventricular ejection fraction was 50% in ACS patients, suggesting that the overall management including CA with PCI may have a role in preserving cardiac function.

Prognosis of non-ACS patients also compared favourably to previous studies. In a single-centre study including 123 non-ACS OHCA patients, 3-year survival was 19.5%,²⁹ compared to 25.6% in our study. This difference may be due to the routine use of hypothermia in our centre. Thus, despite the severity of our population, postdischarge survival remained favourable, suggesting that an early invasive initial management strategy as the one applied in this study, including CA with PCI on admission, hypothermia, medical management according to guidelines,^{9,17} and use of ICD leads to good long-term neurological survival in most survivors.

Limitations

Our study has several limitations. The study was performed in a single centre highly specialized in OHCA care and therefore the results may not be obtained in other settings.

In our study, 69% of the patients did not have an ACS and may be argued that CA induced a delay in the induction of hypothermia, in the diagnosis of OHCA causes and increased the risk of contrast media-induced nephropathy. However, a benefit may be expected from the knowledge of the coronary status in the subsequent management including optimization of haemodynamic function using catecholamines, antiplatelet treatment, and the subsequent diagnostic algorithm.²¹

In survivors, hypothermia was performed more frequently but this occurred due to the death of some nonsurvivors before reaching target temperature.

Intra-aortic balloon pumps were used more frequently in ACS than non-ACS patients, but this was performed according to previous recommendations.⁹ The use of other circulatory assist devices was performed in less than 5% of the patients and their influence on survival in ACS vs. non-ACS patients was probably less significant.

Conclusion

Our study showed that, despite significant in-hospital mortality in these severely ill comatose patients resuscitated after OHCA and managed with CA on admission, postdischarge prognosis remains favourable for up to 5 years. Moreover, long-term overall survival was better in ACS patients than in patients without ACS. This type of early invasive in-hospital management seems effective, complementing modern out-of-hospital resuscitation measures and should be further evaluated.

Conflict of interest

The authors declare that there is no conflict of interest.

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