Défaillance hépatique aux soins intensifs et techniques de suppléance : Etat de l'Art

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UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

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pharmacologie, soins intensifs et urgences

Service des soins intensifs

Thèse préparée sous la direction du Professeur Karim Bendjelid

Défaillance hépatique aux soins intensifs et techniques de suppléance : Etat de l'Art

Thèse

présentée à la Faculté de Médecine

de l'Université de Genève

pour obtenir le grade de Docteur en médecine

par

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de

Espagne

Thèse n° 11054

Genève

2021

UNIVERSITÉ
DE GENÈVE
FACULTÉ DE MÉDECINE
Secrétariat des étudiants

DOCTORAT EN MEDECINE

Thèse de :

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originaire d'Espagne

Intitulée :

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Omnium rerum principia parva sunt

Marcus Tullius Cicero

La conclusion de cette thèse n'aurait pas été possible sans le soutien de deux personnes :
mon directeur de thèse, le Professeur Karim Bendjelid,
et mon épouse, Laura Porto Pena.

Mes remerciements les plus sincères à tous les deux.

Présentation

L'essentiel de cette thèse se base sur deux publications originales dans des journaux à politique éditoriale et diffusion internationale :

García Martínez JJ, Bendjelid K**.** Artificial liver support systems: what is new over the last decade?. Annals of Intensive Care. 2018;8(1):109.

García Martínez JJ, Mollard F, Baud FJ, Bendjelid K**.** Intoxication with Calcium Channel Blockers and Other Highly Protein-Bound Drugs: Why Use MARS? Two Clinical Case Reports. Journal of Clinical Toxicology. 2018;08(03)

Je déclare n'avoir aucun conflit d'intérêt, ni financier ni personnel, en lien avec le contenu de cette thèse.

Je déclare n'avoir reçu aucun financement pour la rédaction de cette thèse

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RESUME

Le foie est un organe complexe qui assure des fonctions essentielles et sa défaillance entraine un risque vital majeur. Au vu des options thérapeutiques limitées, certains dispositifs de suppléance hépatique ont été développés comme thérapie de soutien jusqu'à la transplantation du foie (bridge-to-transplant) ou sa récupération fonctionnelle (bridge-to-recovery). Ces techniques sont basées sur le concept de dialyse à l'albumine et la possibilité d'éliminer les toxines accumulées dans la défaillance hépatique et incriminées dans sa physiopathologie, y compris celles fortement liées aux protéines.

La présente thèse est basée sur deux publications originales qui examinent l'utilisation clinique de ces techniques de suppléance hépatique. Tout d'abord, nous rapportons une étude des cas où ces dispositifs ont été utilisées pour traiter des intoxications à drogues à forte liaison aux protéines avec une excellente réponse clinique, témoignant de la probable efficacité de ces techniques épuratives. Deuxièmement, nous avons conduite une revue approfondie de la littérature publiée à ce sujet afin de déterminer la plus-value clinique de ces dispositifs.

Les études publiées à ce jour ont prouvé la capacité de ces techniques de suppléance à remplacer, au moins partiellement, la fonction de détoxication du foie. Par ailleurs, la correction de divers marqueurs d'homéostasie a été démontrée, avec le plus souvent un bénéfice associé en termes de conditions hémodynamiques et/ou neurologiques. Cependant, il n'est pas encore avéré si l'utilisation de la suppléance hépatique artificielle améliore la survie, étant donné un niveau de preuves encore insuffisant si on évoque les essais randomisés contrôlés. En outre, des alternatives doivent encore être trouvées pour compenser les fonctions de régulation et de synthèse du foie, les organes bioartificiels étant un espoir à cet égard.

En attendant la mise en place de nouveaux essais cliniques suffisamment robustes pour aborder les questions cliniques d'ordre pronostic, l'utilisation de la suppléance hépatique artificielle ne peut être recommandée que comme thérapie de sauvetage de défaillances réfractaires à tout autre traitement.

ETAT DE LA QUESTION

Selon les statistiques de l'Organisation Mondial de la Santé, plus de deux millions de personnes décèdent chaque année dans le monde des suites d'une cirrhose hépatique ou d'un cancer du foie. Et si les étiologies les plus courantes de la cirrhose restent les hépatites virales B et C et la consommation d'alcool, nous assistons à une augmentation d'autres étiologies, telles que la maladie stéatosique non-alcoolique du foie, liée à la prévalence croissante du syndrome dit métabolique et des facteurs de risque qui lui sont associés. Les hépatites aiguës virales ont été elles-mêmes responsables de plus de 150000 décès dans le monde en 2016[1].

Une proportion significative des décès associés aux maladies hépatiques survient dans le contexte d'une défaillance hépatique aigue (*Acute Liver Failure* ou ALF, acronyme anglais couramment utilisé dans la littérature internationale et qui sera également utilisé, *post haec*, dans ce texte) ou d'une défaillance hépatique aigue sur chronique (*Acute on chronic liver failure* ou AoCLF). Les deux pathologies sont grevées d'une forte mortalité. La moitié des patients qui développent une ALF finissent par décéder, malgré l'augmentation constante des transplantations hépatiques dans le monde. En ce qui concerne l'AoCLF, des études récentes montrent qu'un tiers des patients hospitalisés pour une cirrhose avec une complication aiguë développent une AoCLF, et leur mortalité augmente de façon très significative (1). A titre d'exemple, la mortalité due au syndrome de détresse respiratoire aigüe atteint 90% chez les patients présentant une cirrhose sévère (Child-Pugh C).

Dans ce contexte et compte tenu de la pénurie d'organes pour transplantation, des efforts ont été faits pour trouver des alternatives thérapeutiques pour les patients en attente d'un nouvel organe (bridge-to-transplant) ou qui ne sont pas candidats à une transplantation mais qui ont des possibilités de récupération (bridge-to-recovery).
Plusieurs systèmes de suppléance hépatique ont été développés au cours des 30 dernières années, basés principalement sur le concept de la « dialyse à l'albumine ». Bien que de nombreuses études cliniques aient démontré un bénéfice en termes hémodynamiques ou neurologiques, une amélioration de la survie avec l'application de ces systèmes de suppléance chez les patients souffrant d'une défaillance hépatique n'a pas encore été clairement démontrée.

Au vu de la forte prévalence des maladies hépatiques dans le monde et de l'incidence croissante de la défaillance hépatique (ALF ou AoCLF) avec l'augmentation de la mortalité qui en résulte, la suppléance hépatique extracorporelle sera probablement un domaine de recherche majeur dans les années à venir.

[1] Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

DISCUSSION

I. PHYSIOPATHOLOGIE HEPATIQUE : QUELQUES NOTIONS IMPORTANTS

Le foie est l'un des organes dites « nobles » qui assure des fonctions fondamentales de régulation énergétique et homéostatique, de synthèse et de détoxification.

Il joue un rôle central dans le métabolisme des carbohydrates, l'équilibre énergétique et le stockage de glycose. Il contribue à assurer les besoins énergétiques des organes vitaux en contrôlant la glycogenèse, la glycogénolyse, la glycolyse et la gluconéogenèse, principalement par la régulation des enzymes glucose-6-phosphatase et de son homologue glycolytique, la glucokinase, ainsi que de la protéine de transport GLUT 2 (2).

La production d'acides biliaires par le foie à partir du cholestérol intervient dans l'absorption des lipides et des vitamines liposolubles et contribue à moduler la flore intestinale, participant à la régulation de l'homéostasie immunitaire (3). La dysbiose, ou déséquilibre dans la composition du microbiote intestinal, joue probablement un rôle central dans la pathophysiologie des maladies du foie (4, 5). D'autre part, l'équilibre entre les différents types d'acides biliaires sera également altéré dans les maladies hépatiques, comme cela a été démontré chez les patients cirrhotiques, avec une augmentation des niveaux d'acides biliaires primaires (cholique et chénodésoxycholique) par rapport aux acides biliaires secondaires (désoxycholique et lithocholique) (6). Il existe donc un lien entre le microbiote intestinal, les différents types d'acides biliaires et la défaillance hépatique et ses complications, comme l'encéphalopathie hépatique (4), pour laquelle plusieurs études animales ont démontré les effets des acides biliaires sur la perméabilité de la barrière hémato-encéphalique, la neuroinflamation et le dysfonctionnement neuronale (7, 8). L'accumulation de sels biliaires a également été identifiée comme un facteur susceptible de contribuer de façon directe aux lésions hépatiques (9) en raison d'un effet potentiellement toxique sur les hépatocytes et les cholangiocytes par le biais d'un processus inflammatoire avec des lésions mitochondriales (10).

Il a une fonction majeure de synthèse protéinique : des milliers de protéines différentes y sont synthétisées, allant des protéines constitutives telles que l'albumine ou la transferrine aux protéines de phase aiguë (par exemple la protéine C réactive ou le fibrinogène). Beaucoup de ces protéines sont de synthèse hépatique exclusive et ont des demi-vies très courtes, comme les facteurs de la coagulation. La participation du foie à l'équilibre hémostatique est cruciale et la perte de cet équilibre est l'un des facteurs les plus importants de morbidité et de mortalité dans la maladie hépatique.

Le foie est également un élément clé dans la détoxification des diverses substances endogènes et exogènes. Un exemple paradigmatique est le cycle de l'ammoniaque (NH_4OH), libéré par la flore bactérienne intestinale à partir de la dégradation de la glutamine apportée par les protéines alimentaires, transporté par la circulation portale et dégradé en urée par le foie pour être éliminé par les reins. La perte de cette fonction de détoxification, et le shunt de sang portal très riche en ammonium (NH_4^+) vers la circulation systémique, est suspecté depuis longtemps comme étant à

la base (avec d'autres mécanismes, notamment inflammatoires) de la dysfonction neuronale et le développement de l'encéphalopathie hépatique dans la défaillance hépatique (11). Mais le foie participe également à la neutralisation de nombreux autres produits toxiques provenant de l'environnement, ingérés comme médications ou générés par l'organisme, essentiellement par la voie du cytochrome P450 (phase I) puis par de processus multiples tels que la glucurono-conjugaison (bilirubine), la sulfatation (acides biliaires), l'acétylation ou la combinaison avec le glutathion ou la glycine (phase II) (12). Certains de ses produits sont impliquées dans la physiopathologie de la défaillance hépatique et ses complications. Il joue finalement un rôle d'autorégulation systémique tan sur le plan immunitaire qu'hémodynamique, sa défaillance entraînant une atteinte multiorganique sévère.

D'un point de vue histopathologique, la défaillance hépatique aigue ou ALF se caractérise par une nécrose, qui peut être initialement centrolobulaire (comme dans les cas de l'intoxication à l'acétaminophène ou des atteintes ischémique ou hypoxique du foie) ou diffuse et hautement inflammatoire (typiquement dans la plupart des hépatites virales ou médicamenteuses). Dans les cas les plus sévères le résultat final sera une nécrose massive avec une perte extensive des hépatocytes, un effondrement de la structure de soutien réticulaire du foie, une congestion des vaisseaux sinusoïdaux et une réaction ductulaire péri-portale importante (13). Une réponse régénérative va se déclencher par différentes voies d'activation, selon le type et l'ampleur de l'agression, par prolifération ou hyperplasie des hépatocytes, la participation des cellules progénitrices à ce processus étant encore débattue (14).

Dans l'AoCLF, l'histopathologie est moins décrite. Elle semble être plus hétérogène et liée à la pathologie hépatique sous-jacente, mais avec la présence également de nécrose hépatique à différents dégrées (15). Cette nécrose hépatique est responsable à terme de la perte des différentes fonctions du foie et finalement du développement d'une défaillance multiple d'organe **(figure 1)**.

La perte de la fonction de synthèse protéique conduit à une déplétion des facteurs pro et anticoagulants et à une situation d'équilibre instable entre la diathèse hémorragique (thrombocytopénie et déficit de facteurs de la coagulation, facteur VIII excepté) et l'état procoagulant (déficit en antithrombine III, protéine C et S, plasminogène et ADMATS 13, hyperproduction de factor VIII) (16).

L'absence de sécrétion adéquate de sels biliaires dans le duodénum entraîne une modification de la flore bactérienne commensale, comme on l'a observée chez les patients cirrhotiques ou déjà démontrée après une obstruction des voies biliaires lors d'expériences sur des animaux. Cette dysbiose de la flore intestinale contribuera au tableau de réponse inflammatoire systémique observé dans la défaillance hépatique avancée (*vide infra*).

Le défaut de clairance des toxines endogènes entraîne l'accumulation de l'ammonium et d'acides aminés (tryptophane ou glutamine) qui sont impliqués dans le développement de l'encéphalopathie hépatique, bien que cette pathologie ait des explications plus complexes (17). L'accumulation d'endotoxines semble également jouer un rôle direct dans le développement de l'atteinte rénal associée à la défaillance hépatique en combinaison avec l'état de vasoplégie splanchnique et systémique.

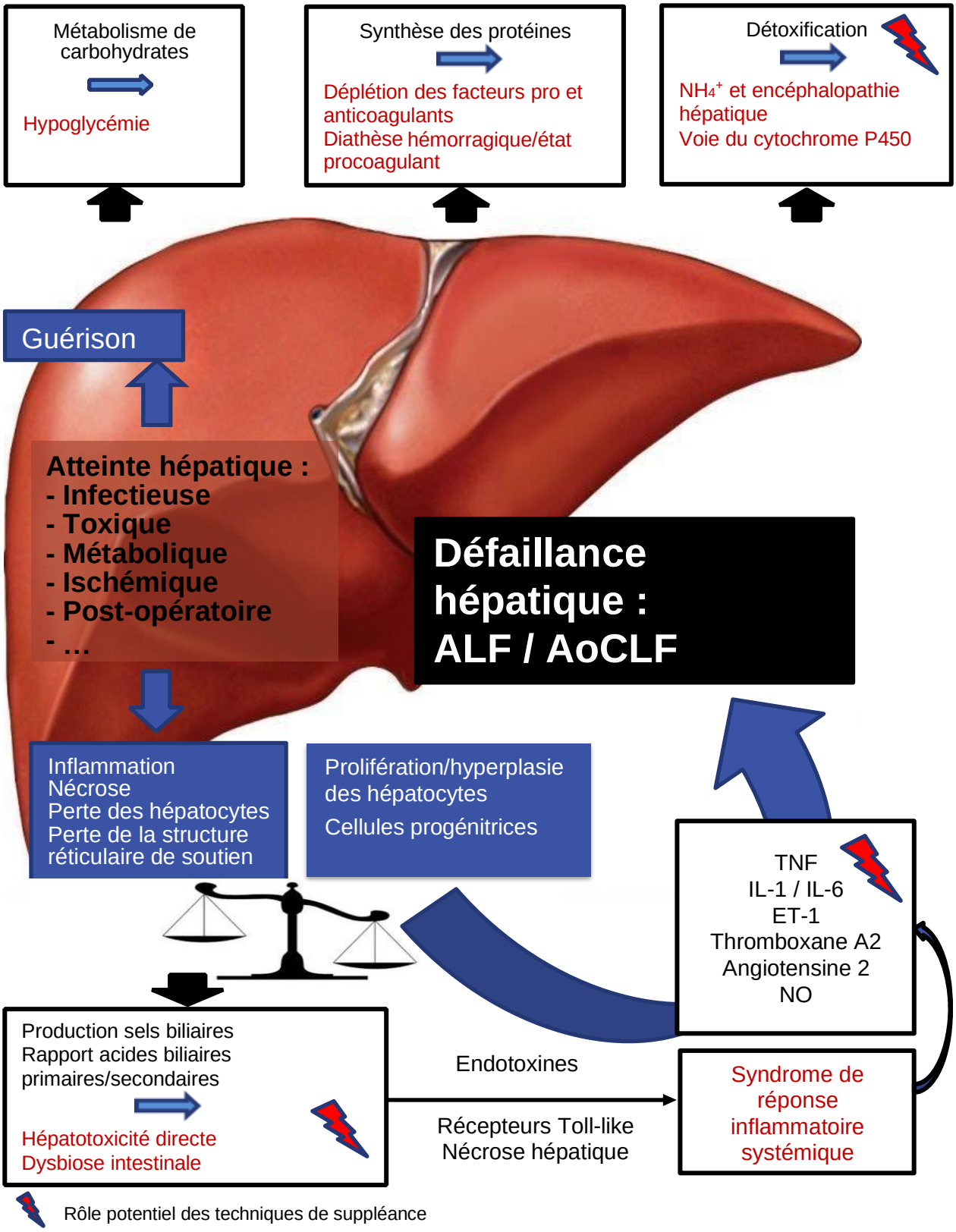

Figure 1. Physiopathologie de la défaillance hépatique et dispositifs de suppléance.

Le passage d'endotoxines de l'intestin vers la circulation portal et systémique, dans un contexte d'hypertension portal avec circulation collatérale et dysfonctionnement du filtre hépatique, contribue à l'activation de neutrophiles et l'installation d'un tableau de réponse inflammatoire systémique (18).

La nécrose hépatique et l'activation de récepteurs « Toll-like » entraînent la libération de cytokines proinflammatoires, les facteurs de nécrose tumorale (TNF) et les interleukines IL-1 et IL-6 étant les plus importants. La stimulation du stress oxydatif et la libération de substances vasoactives telles que l'endothéline-1 (ET-1), le thromboxane A2 ou l'angiotensine 2 participent aux lésions hépatiques et conduisent à terme, tout comme la dérégulation de la synthèse de monoxyde d'azote (NO), à une vasodilatation avec hypotension systémique et collapse hémodynamique (19, 20).

La possibilité de remplacer l'activité de détoxification du foie et d'éliminer les substances impliquées dans sa défaillance, et dans la progression vers les différentes insuffisances d'organe, est à la base des techniques de suppléance hépatique développées ces dernières années.

II. SUPPLEANCE ARTIFICIELLE DU FOIE : LE CONCEPT

Depuis les années 1990, plusieurs systèmes de suppléance hépatique ont été développés sur la base du concept de dialyse à l'albumine. Ces systèmes auraient la capacité d'éliminer les toxines accumulées dans la défaillance hépatique, y compris celles fortement liées aux protéines. Ces systèmes pourraient également moduler l'équilibre des cytokines pro et anti-inflammatoires et affecter les niveaux circulants d'oxyde nitrique (21, 22), entravant la progression vers une défaillance multiple d'organe systémique.

Les substances potentiellement éliminées sont nombreuses et leurs rôles divers : bilirubine ou protoporphyrine conjuguée ou non conjuguée, acides biliaires, phénols, acides gras à chaîne courte et moyenne, aminoacides (tels que le tryptophane ou la glutamine) ou composés organiques hétérocycliques. Ces dispositifs peuvent également éliminer des substances hydrosolubles, telles que l'ammoniaque, la créatinine ou l'urée, ainsi que des protéines à bas poids moléculaire comme certaines cytokines, par un processus de dialyse standard.

Les techniques de suppléance hépatique actuellement disponibles reposent sur l'utilisation d'un dialysat enrichi en albumine, ce qui permet l'épuration de toxines à forte affinité pour les protéines. La méthode est basée sur deux principes: l'affinité de liaison aux protéines et le mouvement d'un soluté selon un gradient de concentration (23).
L'albumine ajoutée au dialysat se lie à la toxine libre qui traverse la membrane du dialyseur en raison du gradient de concentration entre le sang et le dialysat. Dès que la toxine se lie à l'albumine du côté du dialysat, le gradient de concentration de toxine libre est rétabli, et une plus grande quantité de toxine du côté du sang se dissocie de l'albumine plasmatique, traverse la membrane du dispositif et se lie ensuite à l'albumine du côté du dialysat. Le dialysat est alors évacué (dans les engins plus simples) et les toxines sont éliminées du système. L'élimination des toxines se fait donc par le processus de diffusion et dépend de la concentration en toxines libres (qui est principalement affectée par le rapport molaire entre la toxine et l'albumine).

La concentration d'albumine dans le dialysat joue probablement un rôle majeur dans la capacité de désintoxication de ces techniques. *Drexler et al.* (24) ont évalué in vitro l'impact de la concentration d'albumine dans le dialysat sur la capacité d'éliminer les molécules ayant une forte affinité pour les protéines. Ils sont mis en évidence une corrélation entre cette concentration et la capacité de clairance de ces systèmes.
Dans une étude in vitro utilisant un modèle d'hémodialyse continue, *Churchwell et al.* (25) ont également montré que la clairance des différentes drogues avec forte fixation protéique était principalement influencée par la concentration d'albumine dans le dialysat et le type de dialyseur utilisé. Ils ont comparé les effets de différents flux sanguins, des flux de dialysat, des concentrations d'albumine dans le dialysat (concentrations d'albumine de 0, 2,5 et 5 %) et des dialyseurs sur l'élimination de la carbamazépine, de la phénytoïne et de l'acide valproïque ajoutés à du sang bovin. Les taux d'extraction les plus élevés ont été obtenus en utilisant une combinaison d'un dialysat d'albumine à 5 % et d'un dialyseur en polysulfone (surface de 1,5 m2).

Le dispositif de suppléance hépatique le plus largement utilisé et le plus connu est le Molecular Adsorbent Recirculating System (MARS®), développé à l'origine par *Stange et al.* (26) et disponible pour un usage clinique depuis 1998. Il est composé d'un circuit sanguin, d'un circuit d'albumine (typiquement une solution d'albumine humaine à 20%) et d'un circuit "rénal" classique **(figure 2)**. Le sang est dialysé à travers une membrane de polysulfone imprégnée d'albumine (MARS® Flux 2.1 : surface effective 2,1 m2, épaisseur 100 nm et cutoff moléculaire 50 kDa), de sorte que les toxines hydrophobes liées à l'albumine sont libérées à travers la membrane et sont ensuite collectées par l'albumine dans le dialysat. Les toxines sont éliminées en passant par les colonnes d'adsorption, qui contiennent du charbon activé et une résine échangeuse d'anions (diaMARS® AC250 et diaMARS® IE250). L'albumine est ainsi régénérée et est capable d'accepter de nouvelles toxines lorsqu'elle repasse la membrane. En outre, le circuit d'albumine lui-même est dialysé selon une méthode d'épuration extrarénal conventionnel (diaFLUX® 1.4), qui diminue la charge de toxines hydrosolubles.

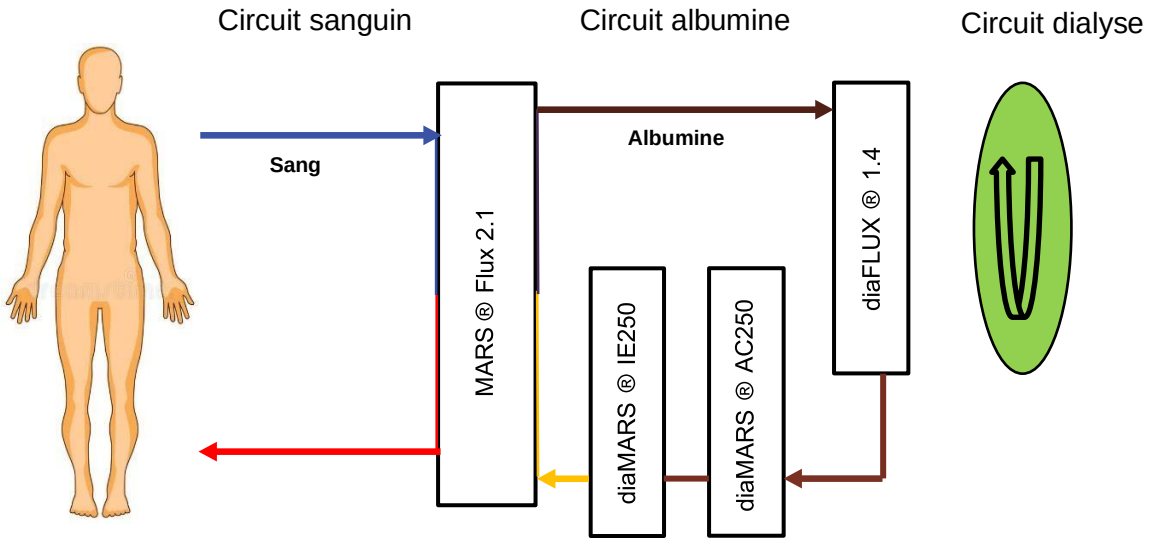

Figure 2. Vue schématique du dispositif MARS® (Molecular Adsorbent Recirculating System).

Plus simple que le MARS, le Single-Pass Albumin Dialysis (SPAD) est également utilisé depuis la fin des années 1990 (27). Il peut être appliqué dans toute unité de soins intensifs utilisant un

circuit d'épuration extrarénale continue standard. Aucune colonne ou circuit adsorbant supplémentaire n'est nécessaire. Le sang du patient est dialysé à travers un hémodiafiltre à haut flux utilisant un dialysat contenant de l'albumine. Après être passé dans le dialyseur, le dialysat est rejeté (contrairement au système MARS, où le dialysat d'albumine est régénéré), et les toxines sont donc éliminées du système. De grandes quantités d'albumine sont consommées avec le SPAD, ce qui rend ce traitement très coûteux.

Le troisième système utilisé dans la pratique clinique est le Fractionated Plasma Separation and Adsorption System (FPSA, Prometheus®), qui a été décrit pour la première fois par *Falkenhagen et al.* (28). Alors que le MARS utilise une solution d'albumine exogène, la machine Prometheus permet à la propre albumine du patient d'entrer dans le premier circuit en utilisant le filtre AlbuFlow® AF 01 (membrane de polysulfone, surface effective 1,0 m2, cutoff moléculaire 250 kDa). L'albumine est réactivée à l'aide d'un adsorbeur à résine neutre (Prometh® 01) et d'une colonne échangeuse d'anions (Prometh® 02) puis remise en circulation. Le sang entre ensuite dans un second circuit où il est traité par hémodialyse classique à haut flux avant d'être renvoyé au patient **(figure 3).**

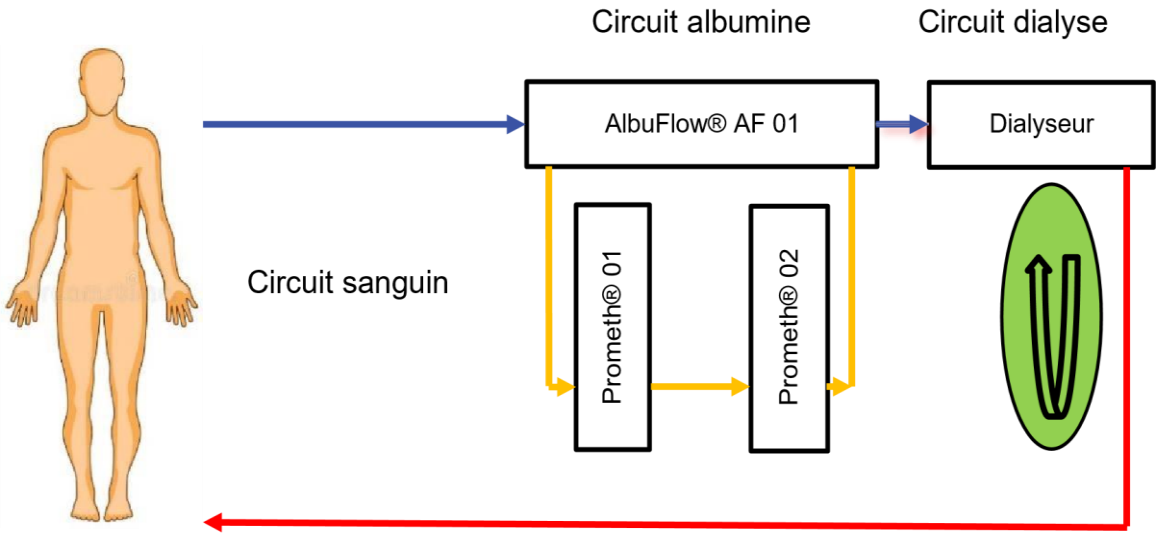

Figure 3. Vue schématique du dispositif Prometheus® (Fractionated Plasma Separation and Adsorption System)

D'autres modèles ont été conçus ces dernières années, tels que le MARS dit de haute puissance, développé par *Marangoni et al.* (29), qui utilise une double unité d'adsorption dans le circuit d'albumine du système MARS classique (une paire des colonnes contenant du charbon activé et une autre paire avec une résine échangeuse d'ions, montées en parallèle).
En 2013, un nouveau prototype de dispositif de suppléance hépatique, dénommé ADVOS (ADVanced Organ Support) a été présenté par *Al-Chalabi et al.* (30). Ce système comprend un circuit sanguin extracorporel, un circuit d'hémodialyse contenant de dialysat avec une concentration d'albumine de 2 à 4 % et un troisième circuit dans lequel le dialysat d'albumine est divisé en deux parties. Avant d'atteindre des filtres cationiques et anioniques, chaque partie subit une modification de la valeur du pH par l'ajout d'acide ou de base et est soumise à un changement de température, ce qui entraîne la libération des toxines liées à l'albumine. Les dialysats qui en résultent et qui contiennent de l'albumine exempte de toxines, sont à nouveau combinés pour

atteindre le pH souhaité avant d'entrer à nouveau dans l'hémodialyseur. Ce dispositif a été testé sur un modèle animal par la même équipe de *Al-Chalabi et al.* (31) et dans un essai clinique non contrôlé par *Huber et al.* (32).

III. L'ÉLIMINATION DES TOXINES ENDOGÈNES ET EXOGÈNES : EST-CE VRAIMENT LE CAS ?

La capacité des dispositifs de suppléance hépatique à éliminer différentes molécules a été étudiée in vitro et in vivo dans des modèles animaux et humaines.

Au début des années 2000, *Sen et al.* (33) ont démontré la capacité du MARS à éliminer efficacement certains médicaments liés à l'albumine et à d'autres protéines sur un modèle animal (des porcs présentant une insuffisance hépatique aiguë provoquée). Les chercheurs ont utilisé du midazolam (principalement lié à l'albumine) et du fentanyl (essentiellement lié à l'alpha-1-glycoprotéine acide) pour maintenir les animaux sous sédation pendant la thérapie MARS et ont mesuré la clairance de ces médicaments par le dispositif (à noter que la partie d'hémodiafiltration standard du système a été désactivée pour l'expérience). Ils ont démontré que cette technique était non seulement efficace pour extraire le midazolam (principalement épuré du dialysat dans la colonne de charbon activé), mais aussi le fentanyl, qui serait dissocié de l'alpha-1-glycoprotéine acide dans le plasma et, sous forme libre, se lierait à l'albumine de la membrane et du dialysat et serait ainsi éliminé. Cette expérience confirme la capacité du MARS à éliminer non seulement les toxines liées à l'albumine, mais aussi celles liées à d'autres protéines plasmatiques. Ces données soutiennent également l'hypothèse selon laquelle les toxines sont éliminées sous leur forme libre, avec un rééquilibrage constant des composants libres et liés aux protéines plasmatiques.

Le système le mieux étudié chez l'homme jusqu'à présent est le MARS. *Novelli et al.* (34) ont montré une diminution significative des taux de bilirubine, d'ammonium, de lactate et de créatinine en 116 patients traités par MARS. Une diminution des niveaux plasmatiques d'acides aminés aromatiques (tryptophane, tyrosine et phénylalanine) et d'autres acides aminés neuroactifs (méthionine, glutamine, glutamate, histidine et taurine) a également été démontrée par *Koivusalo et al.* (35) avec un effet favorable sur le profil plasmatique des acides aminés chez les patients atteints d'encéphalopathie hépatique (Fischer's ratio). Récemment, *Quintero Bernabeu et al.* (36) ont obtenu des résultats comparables en termes de clairance de toxines (ammonium, créatinine, bilirubine, acides biliaires) dans une population pédiatrique souffrant d'ALF et en attente d'un organe.

Des résultats similaires ont été obtenus avec l'utilisation du SPAD. En 2004, *Sauer et al.* (37) ont comparé les capacités de détoxification in vitro du SPAD et du MARS pour les molécules hydrosolubles et celles liées aux protéines (bilirubine et acides biliaires) et ont démontré que les performances des deux techniques étaient similaires et que toutes deux étaient supérieures à l'hémodiafiltration veno-veineuse continue standard (CVVHD). Ces résultats n'ont été que partiellement confirmés in vivo, mais les études cliniques sont limitées par le fait que la concentration optimale d'albumine dans le dialysat et le débit optimale de celui-ci ne sont pas encore clairement établis.

En ce qui concerne le FPSA, *Grodzicki eI al.* (38) ont démontré des diminutions significatives de l'ammonium, de la bilirubine, de l'aspartate aminotransférase, de l'alanine aminotransférase, de l'urée et de la créatinine avec l'utilisation du FPSA chez des patients souffrant d'ALF. *Rifai et al.* (39) ont montré comme une seule séance de FPSA diminuait les niveaux de divers acides aminés chez des patients souffrant d'une défaillance hépatique. Certains des acides aminés éliminés (tels que la glutamine, la phénylalanine, la tyrosine et le tryptophane) ont été directement impliqués dans le développement de l'encéphalopathie hépatique.

Concernant la régulation et l'élimination des cytokines, un nombre significatif d'études ont démontré l'élimination des cytokines proinflammatoires par le MARS. En 2003, *Guo et al.* (21) ont démontré une élimination significative du NO et de certaines cytokines telles que le TNF-α, l'IL-6, l'IL-8 et l'interféron de type II (INF-ɣ) chez des patients en défaillance hépatique sévère, ce qui a été associée également à une amélioration des paramètres cliniques. *Novelli et al.* (22) ont aussi montré une diminution dans les niveaux d'interleukines proinflammatoires (IL-1, TNF, non significatif pour l'IL-6) chez des patients souffrant d'AoCLF traités par MARS par rapport au traitement standard. Dans leur étude, les niveaux d'IL-10, cytokine avec activité anti-inflammatoire, sont restés stables dans les deux groupes tout au long de la période d'observation. Alors que d'autres études ont été moins concluants, l'utilisation d'un système MARS avec des membranes à pores plus larges semble pouvoir améliorer considérablement l'élimination de cytokines (40).

D'autres dispositifs, en particulier le Prometheus, ont également démontré la capacité à réguler les niveaux des cytokines. Ainsi, *Rocen et al.* (41) ont montré une diminution significative de certaines cytokines et des concentrations de marqueurs inflammatoires lors de séances de FPSA chez onze patients atteints d'ALF d'étiologies différentes (dont neuf ont finalement été transplantés).

- ***Epuration lors d'intoxications médicamenteuses : un exemple représentatif***

En partant de l'hypothèse que les dispositifs de suppléance hépatique sont efficaces pour éliminer les toxines à forte affinité aux protéines et sur la base des expériences décrites précédemment dans la littérature, le système MARS a été utilisé pour traiter deux patients avec intoxication sévère aux anticalciques (amlodipine) hospitalisés dans le Service de soins intensifs des Hôpitaux Universitaires de Genève. Les cas cliniques ont été publiés dans le *Journal of Clinical Toxicology* en juillet 2018 **(Annexe 1)**.

L'amlodipine est un inhibiteur des canaux calciques ayant un volume de distribution élevé et une demi-vie d'élimination de 30-50 heures. Elle présente une liaison aux protéines de l'ordre de 98% (42), entravant son élimination par les méthodes de dialyse standard. L'utilisation de la dialyse à l'albumine, principalement le MARS, a été décrite dans des intoxications sévères par diverses drogues : des antiépileptiques tels que la carbamazépine, la lamotrigine, la phénytoïne et l'acide valproïque ; des antihypertenseurs comme le diltiazem, le vérapamil et l'amlodipine ou encore d'autre molécules comme la théophylline ou le lopéramide (43-45). Dans une majorité de ces cas cliniques les auteurs ont montré une élimination plus rapide de ces médicaments fortement liés aux protéines grâce à l'application de cette technique et, dans tous les cas, une amélioration de l'état clinique du patient.

Nous avons utilisé le MARS dans deux cas d'intoxication massive et volontaire à l'amlodipine (l'un d'entre eux associé également à l'ingestion d'olmésartan médoxomil). Les deux patients présentaient un état de choc vasoplégique profond avec besoin de hautes doses des drogues constrictrices et une absence de réponse aux traitements classiquement utilisés pour l'intoxication aux anticalciques ou pour la vasoplégie réfractaire. Dans les deux cas cliniques la première séance de MARS a permis une réduction drastique du soutien vasopresseur, indiquant probablement une réversion rapide de la vasoplégie induite par l'amlodipine.

Notre première hypothèse pour expliquer les résultats obtenus avec l'utilisation du MARS est une accélération de la clairance des drogues, dans ce cas l'amlodipine, comme l'ont déjà démontré d'autres auteurs pour des drogues à forte fixation protéique. Cependant, dans le cas clinique publié par *Gérard et al.* (43), très similaire au nôtre, les auteurs ont constaté que la quantité d'amlodipine effectivement éliminée par le MARS n'était pas très significative. Plus récemment, *Pinto et al.*(46) ont également rapporté l'utilisation du MARS dans un cas pédiatrique d'intoxication grave à l'amlodipine où, malgré une réponse hémodynamique favorable, les auteurs ont constaté une diminution non linéaire des taux plasmatiques d'amlodipine qui n'était que partiellement corrélée avec les séances de MARS. Il est important de noter que le patient a également bénéficié d'une circulation extracorporelle (ECMO), ce qui peut avoir influencé les volumes de distribution du médicament.

La seconde hypothèse est basée sur la capacité du MARS à éliminer le monoxyde d'azote (NO). Les effets vasodilatateurs du NO et sa participation aux tonus vasculaire sont connus depuis des années (47). Des études expérimentales ont montré une augmentation de la biodisponibilité du NO avec les dihydropyridines. L'amlodipine, en particulier, augmenterait la libération de NO et diminuerait sa dégradation (48-50). Le MARS aurait participé à l'élimination du NO, probablement sous sa principale forme complexe circulante, S-nitroso albumine (51), ce qui expliquerait la stabilisation rapide obtenue chez ces patients.

La capacité à éliminer les toxines liées aux protéines et à diminuer le NO circulant, qui est probablement à l'origine de l'effet hémodynamique observé dans ces cas cliniques, pourrait également jouer un rôle clé dans le traitement de la défaillance hépatique. Cette hypothèse renforcerait l'explication physiopathologique soutenant l'utilisation de différentes techniques de dialyse à l'albumine dans ce contexte.

IV. ET D'UN POINT DE VUE CLINIQUE : Y A-T-IL UN AVANTAGE ?

Dans les premières années qui ont suivi le développement des différents dispositifs de suppléance hépatique, plusieurs auteurs ont tenté de démontrer les avantages cliniques de son utilisation chez les patients atteints d'ALF ou d'AoCLF. Cependant, la plupart de ces études étaient non contrôlées et ne portaient que sur un petit nombre de patients. Les conclusions des premières études contrôlées randomisées publiées sont également limitées par la grande hétérogénéité des patients inclus et l'absence de définitions claires de la pathologie et de son spectre de gravité. Malgré cela, l'intérêt pour ces techniques n'a pas faibli et elles ont continué à être utilisées dans des nombreuses institutions à travers le monde. La littérature scientifique n'a cessé de s'enrichir avec de nouveaux essais cliniques qui cherchent à démontrer l'utilité de ces dispositifs dans une maladie en constante augmentation et associée à une mortalité élevée.

En novembre 2018, nous avons publié une revue narrative dans le journal médical *Annals of Intensive Care* qui recense les progrès réalisés et les nouvelles données apparus sur les systèmes de suppléance hépatique au cours de la dernière décennie, ainsi que les perspectives d'avenir pour ces dispositifs **(Annexe 2)**.

Le dispositif le plus étudié à ce jour est le MARS, avec plus d'une vingtaine d'études cliniques publiées ces dernières années, dont certains essais randomisés contrôlés et des meta-analyses.

L'étude avec le plus haut niveau de preuves a été conduite par *Saliba et al.* (52) en 2013. Il s'agit d'une étude randomisée contrôlée et multicentrique portant sur 102 patients atteints d'ALF et ne présentant aucune contre-indication absolue à une transplantation hépatique. Les patients ont été randomisés pour recevoir soit un traitement conventionnel seul (*standard medical treatment*, SMT), soit un traitement conventionnel en combinaison avec le MARS. L'étude n'a pas montré de différence significative entre les deux groupes en ce qui concerne la survie globale à 6 mois ou la survie sans transplantation à 6 mois et 1 an. Toutefois, ces résultats décevants doivent être interprétés avec prudence étant donné le grand nombre de patients inclus dans l'étude qui purent être transplantés et le court délai entre la randomisation et la transplantation. En effet, 14 des 53 patients du groupe MARS ont été exclus parce qu'ils n'ont finalement pas reçu de traitement MARS ou n'ont bénéficié que d'une courte séance, un organe pour transplantation étant rapidement disponible. Soixante-six patients (64,7 %) ont subi une transplantation, dont 75 % dans les 24 heures suivant leur inscription sur la liste d'attente. Les résultats auraient été certainement différents dans une situation où moins d'organes étaient disponibles pour transplantation. Il convient également de noter que les patients présentant une contre-indication absolue à la transplantation ont été exclus de l'essai. Il n'est donc pas possible de savoir si l'utilisation du MARS dans cette population pourrait être utile et si ces patients pourraient particulièrement bénéficier de cette technique (traitement de dernière ligne).

Bañares et al. (53) ont publié en 2013 un autre essai randomisé contrôlée et multicentrique incluant 153 patients souffrant de AoCLF : l'essai RELIEF. Cet essai a également comparé traitement conventionnel versus traitement conventionnel associé avec MARS et n'a pas démontré un avantage en termes de survie avec l'utilisation de MARS, que ce soit dans la population générale incluse où dans des sous-groupes prédéfinis. Cependant, l'utilisation de la suppléance par MARS semble améliorer certaines dysfonctions d'organes, notamment l'encéphalopathie hépatique. Il convient de souligner que certains des critères d'exclusion de l'étude (plaquettes < 50.000/mm3, rapport international normalisé (INR) > 2,3 ou instabilité hémodynamique) auraient écarté les patients les plus graves et peut-être les plus susceptibles de bénéficier de la technique. Les auteurs se sont également interrogés sur la pertinence de la fréquence ou de la dose des séances MARS utilisées, ce qui aurait pu influencer les résultats finaux de l'étude. A cet égard, le même groupe a publié en 2019 une méta-analyse utilisant des données individuelles de patients atteints d'AoCLF et précédemment inclus dans quatre études randomisés contrôlées comparant MARS versus SMT (54). Cette méta-analyse a montré une amélioration statistiquement significative de la survie dans le sous-groupe de patients ayant reçu 5 séances MARS ou plus par rapport aux patients ayant reçu un traitement moins intense ou un traitement conventionnel seul. Dans cette étude, en utilisant un modèle de régression de Cox, le nombre de sessions MARS a été associé à la survie de manière indépendante.

Récemment, *Gerth et al.* (55) ont publié une étude rétrospective, contrôlée et non randomisée, portant sur 101 patients souffrant d'AoCLF. Les patients inclus dans l'étude ont été classés en fonction de leurs défaillances d'organes selon les critères du *Chronic Liver Failure Consortium*,

CLIF-C (56). L'étude a démontré une réduction significative de la mortalité dans le groupe MARS par rapport au groupe ayant reçu un traitement médical standard à jour 7 (0% contre 18,5%, $p < 0,01$) et à jour 14 (6,4% contre 27,8%, $p < 0,05$). Cet effet bénéfique disparaît à jour 21, ce qui pourrait s'expliquer par l'interruption précoce du traitement (la thérapie MARS était arrêtée si la bilirubine diminuait de plus de 30% par rapport aux valeurs de base ou en l'absence de tout changement après trois séances consécutives). Ainsi, les patients n'ont bénéficié en moyenne que de trois séances par patient. La mortalité à 14 jours a été particulièrement réduite chez les patients présentant deux défaillances d'organes ou plus (9,5% dans le groupe MARS contre 50% dans le groupe SMT, $p < 0,01$). Les auteurs ont également effectué une analyse secondaire des données de l'essai RELIEF (53) en utilisant les critères de classification CLIF-C et ont montré un bénéfice avec le MARS pour la mortalité à 14 jours dans le sous-groupe de patients présentant une défaillance de deux organes ou plus, bien que statistiquement non significative.

Plusieurs études non randomisées, dont beaucoup sont rétrospectives et pour la plupart non contrôlés, ont été publiées au cours de la dernière décennie, montrant des résultats mitigés en termes de survie avec l'utilisation du MARS. Toutefois, dans la plupart de cas, l'utilisation du MARS présente des avantages dans des aspects cliniques spécifiques, tels que l'encéphalopathie hépatique ou l'hémodynamique.

Il existe également deux meta-analyses récemment publiées (57, 58), qui incluent des patients souffrant d'ALF et d'AoCLF et qui ont montré une amélioration de l'encéphalopathie hépatique avec MARS mais pas de bénéfice significatif en termes de survie. D'autre part, deux revues systématiques avec des meta-analyses indépendantes pour les patients souffrant d'ALF ou d'AoCLF ont montré un bénéfice en termes de survie, mais uniquement pour les patients atteints d'ALF. Celle de *Stutchfield et al.* (59) inclue également dans son analyse des essais utilisant des dispositifs bioartificiels. En revanche, la revue systématique publiée par *He et al.* (60) ne prend en considération que les essais cliniques utilisant le MARS. Les auteurs ont comparé la survie chez des patients non transplantés avec ALF et ont constaté que le traitement MARS réduisait significativement la mortalité par rapport au SMT ($RR = 0,61$, $p < 0,05$). Malgré des critères d'inclusion variables, du petit nombre total de patients et de la faible qualité de certaines des études incluses, les résultats sont cohérents d'une étude à l'autre et suggèrent que le MARS pourrait être un outil précieux dans le sous-groupe des patients atteints d'ALF qui sont gravement malades.

Le MARS a aussi été utilisé dans des pathologies hépatiques autres que l'ALF ou l'AoCLF, comme la dysfonction hépatique post-hépatectomie (61, 62), le prurit cholestatique sévère ou le syndrome hépatorénal. Les résultats sont disparates, avec une réduction du supporte aminergique dans certaines études.

En ce qui concerne le Fractionated Plasma Separation and Adsorption System (FPSA, Prometheus®), seul un nombre limité d'essais cliniques ont été publiés ces dernières années. Le plus importante est l'étude HELIOS, publié en 2012 par *Kribben et al.* (63). Cet essai multicentrique et randomisé contrôlé, comparant le Prometheus au SMT chez 145 patients atteints d'AoCLF, n'a pas montré une amélioration de la survie avec l'utilisation du Prometheus à 28 et 90 jours. Le recrutement des patients dans l'étude a été interrompu après analyse provisoire par futilité. Il est toutefois important de noter que la probabilité de survie des patients atteints d'une maladie hépatique sévère (Model for End-Stage Liver Disease - MELD > 30) était plus élevée avec Prometheus qu'avec le SMT uniquement (résultat statistiquement significatif).

D’autres études publiées montrent des avantages hémodynamiques ou sur l’encéphalopathie, mais il s'agit de petites études sans groupe contrôle pour la plupart.

Pour finir, bien que plusieurs études aient démontré in vivo et in vitro la capacité de détoxification de la Single-Pass Albumin Dialysis (SPAD), et qu’une étude récente ait montré des résultats cliniques encourageantes avec son utilisation dans le contexte d’AoCLF (64), la seule étude randomisée contrôlée publiée à ce jour, qui compare l’influence sur des paramètres cliniques et paracliniques entre MARS et SAPD, a donné des résultats décevants (65).

V. PERSPECTIVES

La défaillance hépatique est associée à une mortalité élevée, et ce malgré une prise en charge médicale optimale. Et bien que l’activité de transplantation hépatique soit globalement en augmentation, de nombreux patients continuent à décéder en attendant un organe. Il semble donc essentiel de pouvoir développer des techniques de soutient hépatique qui puissent servir de « pont » vers un traitement ou une guérison définitifs.

Plusieurs dispositifs de suppléance hépatique ont été mis au point au cours de deux dernières décennies, mais il n’est pas encore certain que leur utilisation entraîne une amélioration de la survie des patients, étant donné l'absence de résultats solides issus d'essais randomisés contrôlés. Cela est dû à plusieurs facteurs, notamment au fait que les patients souffrant d’une défaillance hépatique constituent une population hétérogène avec une multimorbidité importante et développent souvent une défaillance concomitante d’autres organes. A cet égard, cette multimorbidité d’ordre systémique, avec multitudes de « *cross talk* » inter-organes, rend difficile l’établissement d’une médecine basée sur les preuves pour la fonction d’un organe noble à la physiologie complexe. En outre, il n'y a pas de recommandations précises sur les aspects pratiques (timing, dose, choix de patients…) dans l’application de ces systèmes de suppléance hépatique. Les perspectives d'avenir de ces dispositifs doivent, donc, être fondées à la fois sur des études cliniques à but pragmatique dans un cadre compassionnel, et sur la réalisation d'essais cliniques suffisamment robustes qui abordent ces questions cliniques cruciales. De nouvelles indications, telles que la défaillance hépatique post-hépatectomie, devraient également être explorées davantage. Finalement, pour les fonctions de régulation et de synthèse du foie, des alternatives valables doivent encore être trouvées, étant donné que les systèmes bioartificiels sont toujours confrontés à plusieurs problèmes de développement et à des coûts de production très élevés.

Dans l'intervalle, et en l'absence d'autres options pour soutenir cet organe vital aux fonctions variées et complexes, il semble légitime d’utiliser ces dispositifs de suppléance hépatique comme thérapie compassionnelle de "sauvetage", et ce malgré l’absence à l’heure actuelle de niveau de preuve acceptable démontrant un bénéfice sans équivoque.

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ANNEXES

ANNEXE 1

Journal of Clinical Toxicology
ISSN: 2161-0495

Martínez et al., J Clin Toxicol 2018, 8:3
DOI: 10.4172/2161-0495.1000388

Case Report Open Access

Intoxication with Calcium Channel Blockers and Other Highly Protein-Bound Drugs: Why Use MARS? Two Clinical Case Reports

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Received date: July 13, 2018; **Accepted date:** July 18, 2018; **Published date:** July 24, 2018

Abstract

Overdose with calcium channel blockers is often a life-threating condition that is frequently exacerbated by the availability of extended-release preparations with slow drug clearances. In the annual report of the American Association of Poison Control Centers, calcium channel inhibitor overdose is one of the most deadly poisonings. In addition, calcium channel blockers are highly bound to proteins, making them difficult to remove using standard dialysis techniques. We describe two cases of amlodipine overdose that presented with profound circulatory shock and were treated with the Molecular Adsorbent Recirculating System™ (MARS™). In this regard, the authors reviewed other cases reported in the literature to discuss the rationale for using albumin dialysis techniques in the setting of highly protein-bound drug intoxication.

Keywords: MARS; Albumin dialysis; Highly protein-bound drugs; Intoxication; Overdose

Introduction

Intentional or unintentional poisoning with legal drugs is a worldwide problem. In the USA, cardiovascular drugs are one of the substance categories most frequently involved in poisoning and the second most common cause of death among pharmaceutical drugs, just behind analgesics. In 2016, amlodipine, a calcium channel blocker (CCB), ranked third among the pharmaceutical drugs most frequently implicated in fatal poisonings in the USA according to the National Poison Data System [1].

CCB overdoses can lead to severe depression of the cardiovascular system, impeding cardiac contraction and heart electrical conduction and producing arterial vasodilatation and deep hypotension. The resulting cardiogenic and vasoplegic shock state is poorly responsive to inotropic and vasopressive drugs or other supportive therapies. Other therapeutic options, such as calcium salts and glucagon administration and the so-called hyperinsulinemia-euglycemia therapy, and lipid emulsion, have been proposed.

In this context, the rationale of enhancing drug clearance may become the cornerstone of treatment, especially for amlodipine, which has a much longer elimination half-life. However, the fact that the drugs are highly protein-bound makes it difficult to remove them from blood with standard dialysis. The use of the Molecular Adsorbent Recirculating System™ (MARS™) or another type of albumin dialysis technique is rationally interesting for this field, and there are some cases that have been published in recent years that showed a faster removal of the drug and marked improvement in patient clinical status [2].

In the present paper, the authors present two cases of amlodipine intoxication treated with MARS. We reviewed the literature and discussed the rational for its use. Written informed consent for data analysis and publication of these two clinical reports was not required by our local IRB, as the reports are observational without any impact on existing diagnostic or therapeutic strategies.

Case Report No. 1

A male patient in his twenties, without significant prior disease, was admitted to the intensive care unit (ICU) 8 hours after ingestion of a large number of multiple pharmaceutical drugs. The patient ingested 840 mg of amlodipine (as amlodipine besilate) and 3360 mg of olmesartan medoxomil in a combined standard formulation. He also self-reported 14 g of acetylsalicylic acid (but salicylate plasma concentration was <1.1 mmol/L), 14 g of paracetamol (but the acetaminophen plasma concentration at admission was outside of the toxic range), 82 mg of acenocoumarol and less significant amounts of other drugs. The patient was conscious, hemodynamically stable and able to confirm the ingestion at the time of admission to the emergency department (ED), approximately 6 hours post-ingestion. His clinical condition deteriorated rapidly over the next two hours with deep hypotension about 7 hours after ingestion that was poorly responsive to high doses of vasopressor drugs, and progressive deterioration in consciousness led to orotracheal intubation and mechanical ventilation 8 hours post-ingestion. Vasodilatory shock was confirmed by transpulmonary thermodilution with a high cardiac

output (>10 L/min) and low systemic vascular resistances (<500 dyn·s·cm^{-5}). The patient presented with acute renal injury (AKIN 2) on admission and developed respiratory failure in the first hours following intubation. The patient received intravenous calcium (gluconate and chloride), continuous infusion of hyperinsulinemia-euglycemia therapy and a single dose of intravenous lipid emulsion (500 mL of Lipofundin MCT LCT, 20%™, ~6.5 mL/kg) 15 hours post-ingestion. He remained deeply in shock, despite adequate volume resuscitation and high doses of norepinephrine (up to 1.5 µg/kg/min) associated with terlipressin (1 mg every 6 hours). Low-dose corticosteroids (50 mg of hydrocortisone every 6 hours) and a single dose of 100 mg of methylene blue (~1.5 mg/kg) were administered in the context of refractory vasoplegia without improvement.

The first MARS session was conducted 8 hours after admission to the ICU (16 hours post-ingestion), with a rapid improvement in hemodynamic condition (Figure 1), which allowed for a drastic reduction in vasopressor drugs in the following hours. The MARS device consisted of a standard dialysis machine (PrismaFlex™ system; Baxter International Inc.) and an additional device for running and monitoring a closed-loop albumin circuit (MARS™ Monitor 1TC and X-MARS™ Treatment Kit; Baxter International Inc.). The MARS circuit was primed with 600 ml of 20% human serum albumin and was driven at the same rate as blood flow, between 80 ml/min and 150 ml/min (depending on hemodynamics). Continuous renal replacement therapy (CRRT) was used with standard prescriptions with a dialysate flow rate of 1500 mL/h and Prismasol 4™ (K^+ 4 mmol/L) was used as hemodialysis solution. Anticoagulation was carried out with unfractionated heparin. The MARS session lasted 5 hours. Two more MARS sessions were performed on day 2 and day 3 with similar parameters and duration. Table 1 shows total serum protein and albumin values during MARS therapy.

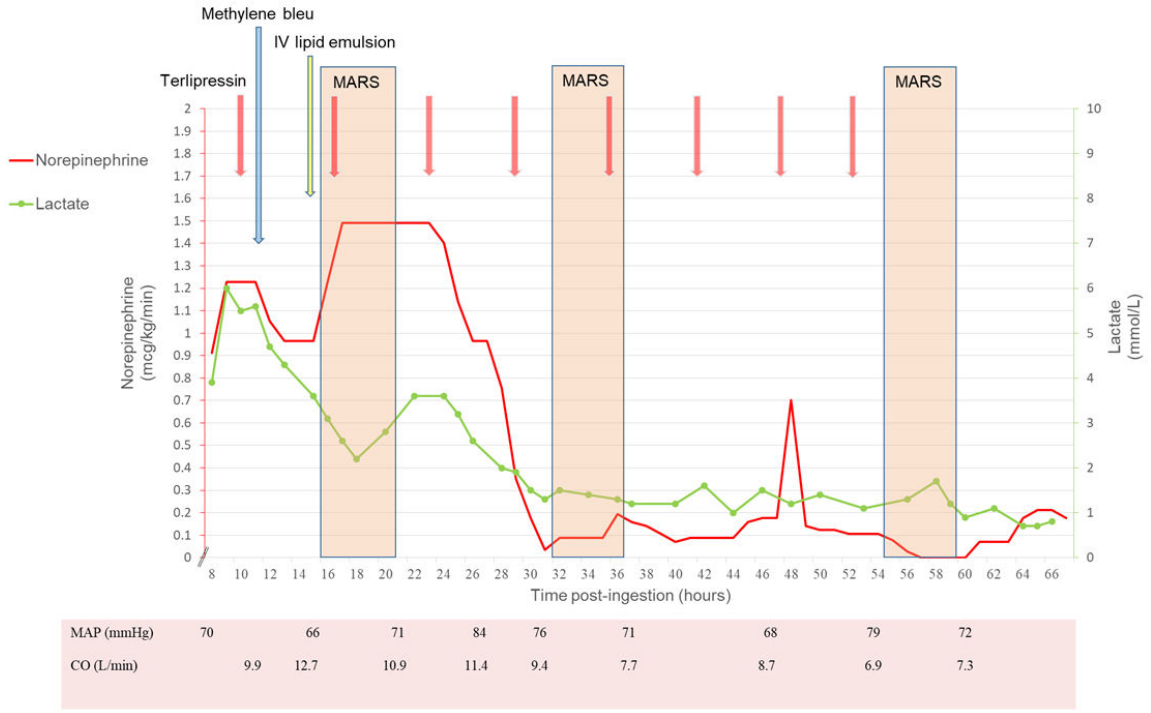

Figure 1: Graphic showing the time course of vasopressor drugs and lactate during MARS sessions in case report no. 1 (MAP: Mean arterial pressure; CO: Cardiac output).

The ICU stay was complicated on day 4 by a primary ARDS (with *Haemophilus influenzae* and *Streptococcus pneumoniae* found in a pulmonary specimen), which required prone position ventilation. The course was favorable with adequate antibiotic treatment. Norepinephrine was stopped definitively on day 9, and the patient was weaned from the ventilator on day 10. He was discharged from the ICU on day 11 without any sequelae.

Case Report No. 2

A man in his fifties with a medical history of hypertension and type 2 diabetes was admitted to the ED approximately 24 hours after ingesting nearly 1000 mg of amlodipine. In the ED, the patient complained of nonspecific chest and abdominal pain, vomiting and oliguria. He had a slight bradycardia (junctional rhythm) and severe hypotension associated with a lactic acidosis. He presented with renal insufficiency, AKIN III, and a slight cytolysis without hepatic failure. In the ED, the patient was given fluids, vasopressor drugs and intravenous calcium gluconate without improvement and was admitted to the ICU 26 hours post-ingestion. A Swan-Ganz catheter was inserted, which showed a vasoplegic shock with a normal cardiac index, low pulmonary artery occlusion pressure and systemic vascular resistance estimated at 500 dyn·s·cm^{-5}. Hemodynamic status worsened in the first hours following ICU admission with the need for very high doses of vasopressive drugs, up to 2.1 µg/kg/min of norepinephrine at

35 hours post-ingestion. Anuria and severe lactic acidosis persisted (maximum lactate 9.6 mmol/L).

Time post ICU admission (hours)	Albumin (g/L)	Total protein (g/L)
H0	38	58
H5	36	55
H19	34	54
H43	31	52
H67	26	50

Table 1: Total serum protein and albumin values during MARS therapy in case report no. 1.

The decision to start MARS therapy within 8 hours of ICU admission (34 hours post-ingestion), was based on our successful experience in the first case report. The MARS technique used was the same as previously described. The MARS circuit was driven at 130 ml/minute. Dialysate flow was kept at 1100 mL/h. The first session lasted 7 hours and allowed a drastic reduction in arterial lactate and even a temporary stop of vasopressor drugs at 40 hours post-ingestion (Figure 2). Two more MARS sessions were subsequently performed on day 3 and day 4 (with the same parameters, and durations of 7 and 5 hours, respectively) without any significant changes in hemodynamic status; however, the doses of vasopressor drugs were already lower. Of note, standard dialysis was continued between the MARS sessions. For the MARS sessions, anticoagulation was carried out with unfractionated heparin, while regional citrate anticoagulation was used when CRRT was performed alone. Total serum protein and albumin values during MARS therapy are shown in Table 2.

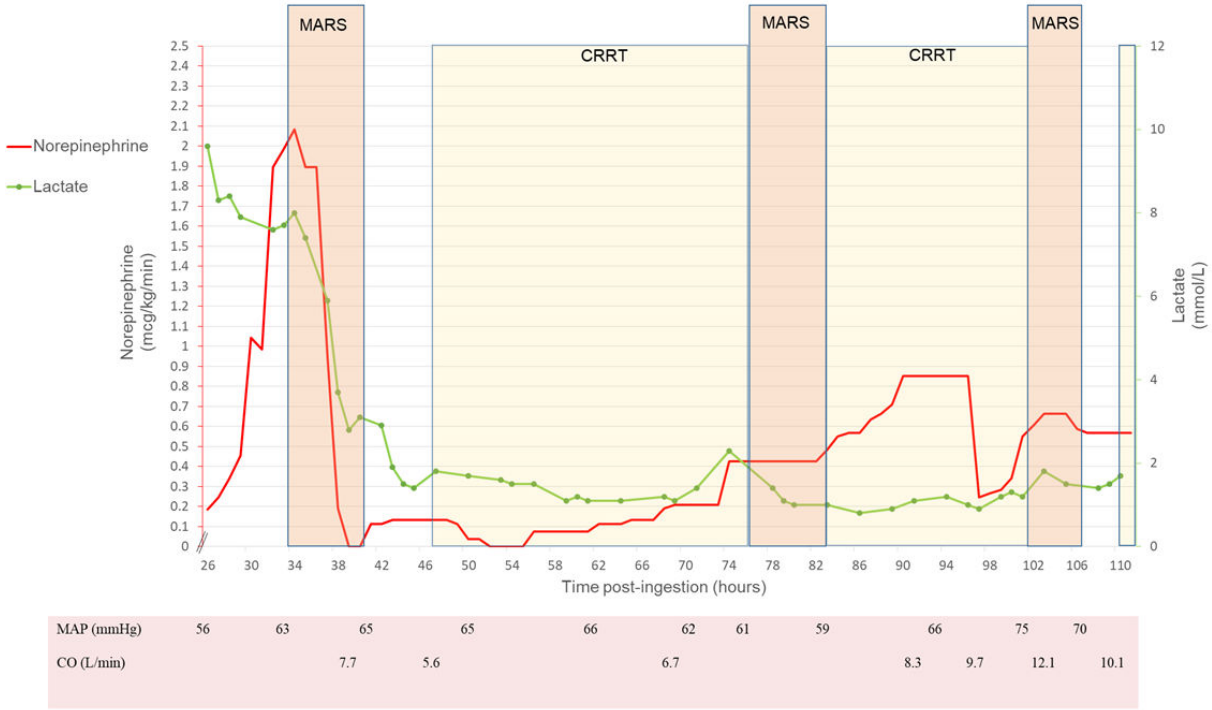

Figure 2: Graphic showing the time course of vasopressor drugs and lactate during MARS sessions in case report no. 2 (MAP: Mean arterial pressure; CO: Cardiac output).

On day 3, the patient developed respiratory failure that required invasive mechanical ventilation. He was diagnosed with aspiration pneumonia, which progressed favorably with the proper antibiotic treatment. The final evolution was satisfactory, and the patient was weaned from mechanical ventilation and vasopressor drugs on day 6. He was discharged to the ward on day 7 without sequelae.

Discussion

The present paper displays two clinical cases of severe intoxication with CCB drugs treated in a multidisciplinary intensive care unit. Most precisely, two intoxications with high doses of amlodipine, a low-clearance, long-acting 1,4-dihydropyridine calcium channel blocker. Like other CCB drugs, amlodipine directly inhibits voltage-gated, L-type calcium channel opening and calcium influx into myocardial and vascular smooth muscle cells, preventing calcium-dependent myocyte contraction and sinoatrial node depolarization. In myocardial tissue, CCBs' actions result in negative inotropy, chronotropy and dromotropy. By acting on vascular smooth muscle, anticalcic drugs prevent arterial contraction and reduce systemic afterload and arterial blood pressure. The CCBs also inhibit calcium L-type channels in pancreatic islet cells, reducing insulin secretion leading to a secondary hyperglycemia and decreasing myocardial glucose use.

Dihydropyridines, such as amlodipine, act preferentially on the peripheral vasculature, inducing systemic hypotension.

Time post ICU admission (hours)	Albumin (g/L)	Total protein (g/L)
H0	41	74
H4	42	72
H16		60
H19	35	63
H45		67
H69	35	67
H93		63

Table 2: Total serum protein and albumin values during MARS therapy in case report no. 2.

Amlodipine has some distinctive pharmacokinetic characteristics that are not seen with other CCB drugs, probably due to its high degree of ionization. A high volume of distribution and low clearance give amlodipine a slow rate of elimination (elimination half-life of 30-50 hours) compared to other CCB. It has high oral bioavailability (60%-80%) with a linear disposition relationship. Amlodipine is a highly bound drug with protein-binding in the range of 98% [3], mostly to albumin. In cases of overdose, the main toxic effect is refractory hypotension due to vasodilation, which presents similarly to distributive shock. This hypotension responds slightly to fluids and vasopressor drugs and results in hypoperfusion, tissue ischemia, lactic acidosis and multi-organ failure. Impaired cardiac glycolytic metabolism and contractility also contribute to the shock state but less frequently than with other CCB. The action in the pancreatic beta cells also has adverse consequences by reducing insulin release. The initial management of amlodipine overdose (like CCB intoxication in general) involves standard care with respiratory and hemodynamic assessment and stabilization. Intravenous calcium and glucagon administration are classically considered as the first-line therapy; however, there is insufficient, and sometimes conflicting, evidence to formally recommend their use. Hyperinsulinemia-euglycemia therapy has also been described in numerous CCB toxicity case reports and is used to counteract the hypoinsulinemic state and its detrimental effects on cardiac metabolism and function. The use of intravenous lipid emulsion can also be found anecdotally in the literature. Extracorporeal life support has been used to treat refractory cardiogenic shock and cardiac arrest induced by drug overdose, particularly by cardiovascular drugs, with poor results in CCB intoxications [4].

In view of the poor response to standard therapies and the long duration of action of amlodipine, the attempt to accelerate the elimination of amlodipine and other CCBs (often proposed in delayed-release formulations) becomes particularly important in a toxic situation. Classically, invasive techniques, such as intermittent hemodialysis (IHD) and hemofiltration (IHF), have been used to eliminate specific life-threatening toxins. These techniques are useful for drugs or metabolites that are water soluble, have a low volume of distribution, low plasma protein binding and ideally low molecular weight. However, improvements in dialyzers over the past three decades have allowed larger molecules and protein-bound substances to be removed (especially if there is a constant substrate of free drug in the plasma). The continuous renal replacement therapies (CRRT) performed in the intensive care unit have the same principles as intermittent techniques, but blood and effluent flows are normally lower, conditioning a lower clearance over time. Continuous techniques could prevent post-treatment rebound, but conventional dialysis should be preferred if rapid toxin removal is required.

For many years, there was enthusiasm for using hemoperfusion (HP) in the field of intoxication. Consisting of the passage of blood through an absorptive-containing cartridge (typically charcoal or resins), hemoperfusion allows the elimination of larger molecules than IHD or IHF, as molecular size does not appear to have a major influence on clearance by HP, except when the molecular weight exceeds 5000 Da. Furthermore, HP seemed to be more effective in removing highly protein-bound drugs, especially with resin columns; some studies using an adsorbent cartridge showed extraction ratios that consistently exceeded 80% when the proportion of protein-bound poison was less than 90% [5]. However, as stated above, the advent of new high-flux, high-efficiency dialysis filters and the use of larger catheters and higher dialysate and blood flows have drastically reduced these advantages compared to IHD or IHF. If we add up the complications related to the nonspecific adsorption of biological components, and the fact that hemodialysis is also renal replacement therapy, correcting the electrolyte and acid-base abnormalities that may be present during any intoxication, we can explain why the use of HP consistently decreased in many countries in this setting. Nonetheless, HP is still widely used for poisoned patients in some parts of the word. The use of other techniques, such as sustained low-efficiency dialysis, therapeutic plasma exchange or exchange transfusion, is anecdotal [6].

In the case of intoxication with highly protein-bound drugs, such as amlodipine, the use of some form of albumin dialysis technique seems strongly rational. The simplest system is called single-pass albumin dialysis (SPAD), which uses a standard CRRT where blood is dialyzed against an albumin-containing dialysate. This technique is based on two basic thermodynamic principles: protein-binding affinity and solute movement along a concentration gradient [7]. The elimination of toxins thus takes place through the diffusion process and depends on the free toxin concentration (mainly affected by the molar ratio of toxin to albumin). The albumin added to the dialysate binds the free toxin that crosses the dialyzer membrane due to the concentration gradient from the blood to the dialysate side. As soon as the toxin binds to albumin on the dialysate side, the concentration gradient is restored, and more blood-side toxin disassociates from albumin, crosses the membrane into the dialysate and then binds to the albumin on the dialysate-side. The dialysate is then discharged, and the toxins are removed from the system. In an *in vitro*, continuous hemodialysis model, Churchwell et al. [8] showed that drug clearance was mainly influenced by the concentration of albumin in the dialysate and the type of hemodialyzer used. They compared the effects of various blood flows, dialysate flows, dialysate albumin concentrations (0%, 2.5%, and 5% albumin concentrations) and dialyzers on the clearance of several highly protein-bound drugs. They demonstrated that the highest extraction ratios were achieved using the combination of 5% albumin dialysate and the larger polysulfone dialyzer (surface area 1.5 m^2). The importance of albumin concentration in the dialysate has also been confirmed by other researchers [9].

In the last two decades, new techniques have been developed in the field of extracorporeal liver assistance, mainly based on the principle of

albumin dialysis and the combination of filtration and adsorption. The most widely published system is the Molecular Adsorbent Recirculating System (MARS), developed by Stange et al. [10], which is composed of a blood circuit, an albumin circuit, and a classic 'renal' circuit. Following the same principles described above, blood is dialyzed through an albumin impregnated high-flux dialysis membrane (surface area of 2.1 m^2, membrane thickness of 100 nm and molecular cut-off of approximately 50 kDa) in such a way that albumin-bound toxins are released through the membrane and subsequently collected by albumin in the dialysate. Subsequently, the toxins are cleared when passing the absorber columns that contain activated charcoal and anion exchange resin, and albumin is regenerated and able to accept new toxins when it passes the membrane again. Additionally, the albumin circuit itself is dialyzed in the CRRT method, diminishing the load of water-soluble toxins.

Sen et al. [11] published a paper showing the ability of MARS to efficiently eliminate albumin-bound and other protein-bound drugs. The authors conducted an animal study using pigs in which acute liver failure was induced. The researchers used midazolam (mainly albumin-bound) and fentanyl (essentially alpha-1-acid glycoprotein bound) to keep the animals sedated during MARS therapy and measured the clearance of these drugs through MARS dialysis (note that the hemodiafiltration part of the system was disabled for the experiment). They demonstrated that this technique of albumin dialysis not only effectively extracted midazolam (mostly removed from the dialysate at the charcoal column site), but, surprisingly, also extracted fentanyl (which was found in the dialysate, mainly linked to albumin). Therefore, MARS could efficiently remove not only albumin-bound drugs but also those bound to other proteins. However, few attempts to use these techniques in the context of protein-bound drug intoxication have been described in the literature, despite the fact that MARS was approved by the U.S. Food and Drug Administration (FDA) for the treatment of drug overdoses and poisonings.

In this regard, we performed a search for relevant articles in PubMed and Web of Science with the search terms of Intoxication OR poisoning OR overdose AND MARS OR Prometheus OR liver dialysis OR hepatic dialysis OR extracorporeal hepatic assistance OR extracorporeal hepatic support OR albumin dialysis. The filter settings used were "English language" and "French language" and the "humans" filter. We set the range of "January 1, 2000" custom dates. Bibliographies of recovered articles were reviewed to identify any other relevant articles. We found only 11 papers reporting the use of MARS or some form of albumin dialysis to treat drug intoxication with the aim of accelerating drug elimination. The drugs reported were predominantly antiepileptic drugs: carbamazepine [12,13], lamotrigine [14], phenytoin [15], phenobarbital [16] and valproic acid [17]. There were 4 papers reporting the use of albumin dialysis or MARS to treat intoxication by different antihypertensive drugs: diltiazem [18,19], verapamil and bisoprolol [20] and amlodipine/valsartan [21]. One case report described the use of MARS for theophylline poisoning [22]. In these different studies, the authors showed a quicker elimination of these highly protein-bound drugs with MARS and a faster than expected improvement in the patient's clinical condition, which presented these techniques as promising tools.

In the specific field of CCB intoxications, Pichon et al. [20] described three cases of diltiazem and verapamil (in combination with bisoprolol) overdose that presented in circulatory failure with deep hypotension and cardiac dysfunction (inotropic and chronotropic) that was unresponsive to high doses of catecholamines and all other standard care, including the recommended antidotes. The patients had renal failure and severe lactic acidosis. In this paper, a single 4 to 6 hours session with MARS for each patient enhanced elimination of the drug and, most notably, allowed a drastic decrease in adrenergic support and reversed shock state, demonstrated by the expeditious normalization of lactate.

Gérard et al. [21] published a case report describing an overdose with amlodipine and valsartan, pretty similar to our first case but with half the dose of amlodipine and a much less comparable dose of an angiotensin II receptor blocker. Both patients presented in refractory shock with extremely low systemic vascular resistances (with a preserved cardiac index) and evolved into multiple organ failure. The authors applied two 16 hours MARS sessions and observed a rapid improvement in hemodynamic conditions, which enabled the weaning of catecholamine support. Astonishingly, the amount of amlodipine effectively removed by dialysis appeared not to be relevant. The authors pointed out the ability of MARS to remove nitric oxide (NO) as an alternative explanation for the hemodynamic stability achieved.

In the two clinical cases presented in this paper, the doses of amlodipine that patients confessed to taking were among the highest in the literature. In a recently published case report on poisoning with a similar dose of amlodipine, the patient developed refractory hypotension and, finally, cardiac arrest that was recuperated by ECMO. However, the patient was ultimately pronounced brain dead. Any depuration technique was attempted [23]. In both of the current cases, the patients presented in deep circulatory failure, requiring extremely high catecholamine support, associated with severe lactic acidosis. Both patients benefited from invasive hemodynamic monitoring that confirmed vasodilatory shock and received adjuvant treatment for vasoplegia. The culprit drug was amlodipine for both patients with an association with the angiotensin II receptor blocker, olmesartan medoxomil, in our first case. Different therapeutic options for CCB intoxications were tried without significant improvement in hemodynamic status. Nevertheless, the first MARS therapy session allowed a drastic reduction in vasopressor support in both patients and improved the organ failure.

The first hypothesis to explain the spectacular results achieved with the use of MARS is the acceleration in drug clearance, which has already been demonstrated by other authors. As stated above, the ability of MARS to efficiently remove protein-bound drugs has been proven in *in vitro* and *in vivo* studies. In our two clinical cases, MARS probably enhanced amlodipine clearance, which fundamentally contributed to the observed hemodynamic improvement. It should be noted that our first case required high doses of sedation, up to 60 mg per hour of midazolam combined with 300 μg per hour of fentanyl, both highly protein-bound drugs. They were also probably effectively eliminated by MARS, as demonstrated by Sen et al. [11]. The second hypothesis is the role of MARS in NO removal. Experimental studies have shown an increase in NO bioavailability with dihydropyridines. In particular, amlodipine may increase the release of NO, which is responsible for specific anti-inflammatory and antioxidative effects, and decrease its degradation [24-26]. The vasodilatory effect of NO is well known, and some studies have shown the ability of MARS to remove it [27-29], probably in its main circulating complex form, S-nitroso-serum albumin [30]. MARS could have also participated in the rapid stabilization achieved in our patients in this way.

Regarding limitations, the plasma concentrations of amlodipine were not measured in either patient of the presented reports, as the

specific test is not routinely available in our hospital. This also prevented the monitoring of plasma concentrations during MARS therapy. Plasma drug concentration as a predictor of outcome has been shown for some drugs, such as verapamil [31]. However, both patients confessed at the time of admission to taking the described amounts of drugs and reconfirmed their intake before being discharged from the ICU [32]. We should also note that there is no specific protocol in our hospital for MARS use in the field of drug intoxication. We used the standard protocol that applies when using MARS in the context of liver failure. The number and duration of MARS sessions were defined by the patient's clinical evolution, other cases described in the scientific literature and some technical limitations (availability of trained personnel to perform the procedure).

Conclusion

The usefulness of MARS in the case of highly protein-bound drug intoxication is clinically demonstrated in these two life-threatening CCB poisoning situations. MARS certainly enhanced the elimination of the drugs, as already described in the literature. In the case of amlodipine poisoning, the elimination of the potent vasodilator, NO, may also play a role. Further research is needed to correctly determine the advantages of MARS, or other albumin-based dialysis devices, over standard techniques in this setting. The most appropriate parameters for the use of the technique should also be established.

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ANNEXE 2

García Martínez and Bendjelid
Ann. Intensive Care (2018) 8:109
https://doi.org/10.1186/s13613-018-0453-z

Annals of Intensive Care

REVIEW

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Artificial liver support systems: what is new over the last decade?

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Abstract

The liver is a complex organ that performs vital functions of synthesis, heat production, detoxification and regulation; its failure carries a highly critical risk. At the end of the last century, some artificial liver devices began to develop with the aim of being used as supportive therapy until liver transplantation (bridge-to-transplant) or liver regeneration (bridge-to-recovery). The well-recognized devices are the Molecular Adsorbent Recirculating System™ (MARS™), the Single-Pass Albumin Dialysis system and the Fractionated Plasma Separation and Adsorption system (Prometheus™). In the following years, experimental works and early clinical applications were reported, and to date, many thousands of patients have already been treated with these devices. The ability of artificial liver support systems to replace the liver detoxification function, at least partially, has been proven, and the correction of various biochemical parameters has been demonstrated. However, the complex tasks of regulation and synthesis must be addressed through the use of bioartificial systems, which still face several developmental problems and very high production costs. Moreover, clinical data on improved survival are conflicting. This paper reviews the progress achieved and new data published on artificial liver support systems over the past decade and the prospects for these devices.

Keywords: Acute liver failure, Acute on chronic liver failure, Artificial liver support, Albumin dialysis, MARS, Prometheus, SPAD, FPSA

Background

In 2016, liver diseases were responsible for more than one million deaths worldwide, and the trend has been clearly increasing in the last 10 years [1]. Some of these deaths occur in the context of liver failure, in the form of either acute liver failure (ALF) or acute on chronic liver failure (AoCLF). In ALF, the adult mortality is approximately 50%, despite the increase in the number of patients receiving liver transplants. Regarding AoCLF, some recent studies show that one-third of patients hospitalized for cirrhosis with an acute complication develop AoCLF, and their mortality thus increases dramatically [2]. In this context and given the shortage of organs for transplantation, efforts already have been developed to find therapeutic alternatives for patients who are waiting for a new organ (bridge-to-transplant) or who are not candidates for transplantation but for whom recovery is considered possible (bridge-to-recovery).

From the 1990s and onwards, several systems based on the concept of albumin dialysis have been developed, the best-known being the following: the Molecular Adsorbent Recirculating System™ (MARS™), the Single-Pass Albumin Dialysis system (SPAD) and the Fractionated Plasma Separation and Adsorption system–FPSA (Prometheus™). These systems are based on the concept of albumin dialysis and therefore on the capacity to remove the albumin-bound toxins that accumulate in liver failure. These toxins are thought to be responsible for brain failure resulting from hepatic encephalopathy (HE), renal failure due to hepatorenal syndrome, cardiovascular failure and/or an immunodepression state. These devices can also remove water-soluble substances, such as ammonia, creatinine or urea and smaller proteins such as some cytokines, by standard dialysis.

Some of the substances removed by the different artificial hepatic support systems include conjugate or unconjugated bilirubin or protoporphyrin, bile acids, glycoside

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derivatives, phenols, short- and medium-chain fatty acids, such as octanoate, or heterocyclic organic compounds. Removal of cytokines and other recognized inducers of HE, such as ammonia or amino acids (e.g. tryptophan or glutamine), may be a valuable tool for this major complication of liver failure [3]. Some preclinical and clinical investigations also report the removal of plasmatic nitric oxide (NO) and some pro-inflammatory and anti-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin-6 or interleukin-10 [4, 5], even though the final balance in the setting of ALF or AoCLF and its contribution to multiorgan failure are still unknown.

In the early years following the development of the different liver devices, some clinical trials demonstrated haemodynamic and neurological benefits in their use in patients with ALF and in those with AoCLF, but many of these studies were uncontrolled and included very few patients. Some randomized controlled trials showed an improvement in survival, but the small sample size, high heterogeneity of the included patients and high variability in disease severity prevented definitive conclusions from being reached [6, 7]. However, artificial liver devices have continued to be used in many hospitals, and new experimental and clinical studies on them have been published over the past decade. In the present review, the authors emphasize new data published in this field and discuss the future of these devices.

Methods and materials

We conducted research for relevant articles through PubMed (National Institutes of Health) and Web of Science published after 1 January 2008. The filter settings used were "English language" and "French language" and the "humans" filter. The bibliographies of the recovered articles were reviewed to identify any other relevant papers. We included randomized controlled studies preferentially, but we also discussed uncontrolled studies when the statistical comparison versus baseline was provided. We also comment on other relevant literatures.

Molecular Adsorbent Recirculating System (MARS)

The Molecular Adsorbent Recirculating System (MARS) was originally developed by Stange et al. [8]. The technique has been available for broad clinical use since 1998. The system is composed of a blood circuit, an albumin circuit and a classic "renal" circuit. Blood is dialyzed through an albumin-impregnated high-flux dialysis membrane in such a way that hydrophobic albumin-bound toxins are released through the membrane and subsequently collected by albumin in the dialyzate. The method is based on two basic thermodynamic principles: protein-binding affinity and solute movement along a concentration gradient [9]. The elimination of toxins thus takes place through the diffusion process and depends on the free toxin concentration (which is mainly affected by the molar ratio of toxin to albumin). Toxins are cleared when passing the adsorber columns that contain activated charcoal and anion-exchange resin, and albumin is regenerated and able to accept new toxins when it passes the membrane again. Additionally, the albumin circuit itself is dialyzed in the CRRT (continuous renal replacement therapy) method, diminishing the load of water-soluble toxins.

MARS is the most widely published artificial liver support system. In the first few years following its introduction to the market, several animal and in vitro experiments and clinical studies demonstrated its capacity to remove various albumin-bound and water-soluble metabolites that accumulate in liver failure and are implicated in some of its major complications, such as HE [3, 10].

Another point of interest has been the ability of MARS to eliminate cytokines and modulate the inflammatory response involved in liver failure. Cytokines have been implicated in the development of HE, vasodilation, systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF). These proteins are believed to mediate hepatic inflammation, cholestasis and liver cell necrosis and apoptosis [11, 12]. From a theoretical standpoint, the removal of some pro-inflammatory cytokines may counteract some clinical complications of liver failure related to the inflammatory and hyperdynamic state. However, anti-inflammatory cytokines would also be removed, and the final imbalance and its contribution to multiorgan failure in the setting of ALF or AoCLF are still unknown. Old and new works show a significant elimination of some pro-inflammatory cytokines, such as TNF-α, interleukin-6 and interleukin-1 β, and anti-inflammatory cytokines, such as interleukin-10, by the MARS device [4, 5, 13]. However, other studies failed to demonstrate an effective change in the plasma cytokine concentration in patients with liver failure, perhaps due to the high rate of production in this setting [14, 15]. In 2013, Donati et al. [16] published the results of 269 MARS treatments that showed no effect on cytokine plasma levels but a significant increase in hepatic growth factor levels (a humoral hepatotrophic factor that enhances liver regeneration). Interestingly, Dominik et al. [17] demonstrated, in an in vitro study, that the removal of some cytokines could be drastically improved by using MARS with larger pore membranes, which could contribute to optimizing the cytokine plasma profile of patients. We must also consider the removal of plasmatic NO, which plays a central role in the multifactorial phenomenon of splanchnic and systemic vasodilatation and the hyperdynamic state

associated with liver failure. In conclusion, the precise roles of different cytokines in the pathophysiology of liver failure and the influence of MARS on cytokine plasmatic profiles have not yet been fully elucidated over the last years. This represents undoubtedly a very interesting line of research for the future.

In recent years, some authors have been interested in other active biological substances that can also be removed by MARS. Gay et al. [18] explored the proteins dialyzed and then absorbed in the anion-exchange resin cartridge of MARS in patients with cholestasis and pruritus and found some biological relevant proteins, such as secreted Ly6/uPAR-related protein-1 (SLURP1) or defensin human neutrophil peptide–1 (HNP-1), which are involved in the inflammatory and defensive processes. In contrast, MARS does not appear to influence the plasma levels of other molecules with known immunomodulatory effects, such as neutrophil gelatinase-associated lipocalin (NGAL) or the chemokines monocyte chemoattractant protein-1 (MCP-2) and macrophage inflammatory protein-3 alpha (MIP-3α), according to some published studies [19, 20].

In vitro and in vivo studies have explored the elimination of some antibiotics by MARS, showing, for example, a significant removal of the low protein-bound antibiotics moxifloxacin and meropenem [21]. Similar results have been found with piperacillin/tazobactam. Surprisingly, one case report showed minimal removal of the highly protein-bound immunosuppressive drug tacrolimus [22]. Special attention should be paid to the dose adjustment and monitoring of some critical drugs during MARS sessions, and additional pharmacokinetic studies are required.

The optimal anticoagulation regimen during MARS has also been discussed. This is an important issue considering the difficult haemostasis balance in patients suffering from hepatic failure, who are at high risk of haemorrhagic and thrombotic phenomena. The best-known and most used method is unfractionated heparin, but there are some concerns regarding haemorrhagic risk and heparin-induced thrombocytopenia. Some studies have explored the use of continuous extracorporeal systems without anticoagulation and have found a comparable circuit lifespan [23]. In this sense, the anticoagulant-free approach may be a valid option in patients at high risk of bleeding. Local anticoagulation with citrate may also become a good option if close metabolic monitoring is exercised, and some studies have shown that it is safe and that it guarantees a longer treatment time, preventing filter loss [24, 25]. However, its widespread use cannot be recommended at this stage. In most clinical trials, unfractionated heparin was the anticoagulant of choice, but some studies have used local citrate anticoagulation, especially trials with FPSA [26, 27], with no reported adverse effects. The use of prostacyclin can be found anecdotally in the literature.

From a technical point of view, several questions have been raised about the stability of the binding properties of albumin after passing the adsorber columns or about the influence and clinical relevance of some stabilizers (such as octanoate) used in commercial albumin preparations [28, 29]. Nevertheless, there are no definitive conclusions, and these issues should be the subject of further study in the future.

With respect to clinical outcomes, several studies were published in the first years following MARS commercial availability, mostly of a retrospective and an uncontrolled nature. Most of them demonstrated benefits in terms of encephalopathy, and some showed improvement in the haemodynamic parameters. The few randomized controlled trials (RCT) assessing survival presented conflicting results [30–32]. These trials included few patients suffering from AoCLF, which was defined in a variable way according to each study. No well-conducted RCTs were published during this period in the field of ALF.

In the last decade, new studies have been performed to help understand the potential clinical benefits of using MARS. Nevertheless, patient series remain limited, definitions and inclusion criteria are strongly variable, and randomized controlled trials are scarce. We have divided recent studies found in the literature according to whether target patients suffer exclusively from ALF or AoCLF or whether both group of patients are included together (mostly in meta-analysis studies). We also report some clinical studies that point to other medical indications for MARS (miscellaneous).

MARS for acute liver failure

Several studies on the use of MARS in the field of ALF have been published in the last decade. These studies are summarized in Table 1.

Unfortunately, only one trial, which was presented by Saliba et al. [33], was controlled and randomized. This trial included 102 patients with ALF and without an absolute contraindication for liver transplantation. Patients were recruited from 16 liver transplantation centres across France (mostly from three centres). The trial could be rated as fair, as it scored 3 on the Oxford quality scoring system [34]. We cannot consider it to be good (scores 4–5) because the trial was not blinded. Patients received conventional treatment alone or conventional treatment combined with MARS and were stratified according to whether or not the ALF was paracetamol induced. The study failed to prove a significant difference in the overall 6-month survival and in the 6-month transplant-free survival and 1-year survival. Additionally, there

Table 1 Studies with clinical endpoints for ALF using MARS

Study	Years	Design	Patients number	Outcomes	Comments	LOE
Kantola et al. [35]	2008	Controlled, non-randomized MARS + SMT vs. SMT	159	No improvement in 28-day and 6-month survivals	Trend to improved survival in unknown aetiology subgroup Likely improvement in HE	2
Novelli et al. [45]	2008	Uncontrolled, prospective	6	Neurological and haemodynamic improvements*	Paediatric population PELD and SOFA improvement**	3
Novelli et al. [46]	2009	Uncontrolled, retrospective	45	Number of MARS treatments associated with survival*	No improvement with MARS is a predictive factor of a fatal outcome and the need for a transplant	3
Camus et al. [47]	2009	Uncontrolled, retrospective	18	Clinical improvement MARS therapy associated with withdrawal from the emergency transplantation list*	Clinical improvement compared to a control group obtained from a national register*	3
Saliba et al. [33]	2013	Controlled, randomized, multicentre MARS + SMT vs. SMT	102	No improvement in 6-month, 6-month transplantation-free and 1-year survivals	High transplant rate and short waiting time until transplant Similar adverse effects	1
Lexmond et al. [36]	2015	Controlled, non-randomized MARS + SMT vs. SMT	20	No improvement in survival	Patients in MARS group were sicker Patients in MARS group received more thrombocyte transfusion* Paediatric population	2
Gerth et al. [37]	2017	Controlled, non-randomized MARS + SMT vs. SMT	73	No improvement in 28-day survival	Patients with graft dysfunction included No differences in outcomes between subgroups Biochemical improvement**	2
Hanish et al. [48]	2017	Uncontrolled, retrospective	27	Improvement in encephalopathy and in the APACHE II score**	Biochemical improvement*	3
Quintero Bernabeu et al. [49]	2018	Uncontrolled, retrospective	11	Haemodynamic improvement*	Paediatric population No significant adverse effects	3

LOE level of evidence, determined using the strength of recommendation taxonomy (SORT) criteria [50], *SMT* standard medical therapy, *HE* hepatic encephalopathy, *PELD* paediatric end-stage liver disease, *SOFA* sequential organ failure assessment, *APACHE II* Acute Physiology and Chronic Health Evaluation II

*$p < 0.01$

**$p < 0.05$

was no significant improvement in encephalopathy with the MARS therapy, unlike most other published works. It is noted that the 6-month transplant-free survival was greater among the patients with paracetamol-induced ALF than that of the others (38% vs. 13%, respectively, $p < 0.01$). These disappointing results must be interpreted carefully, as the high transplantation rate and the short delay from randomization to liver transplantation in the study preclude definitive conclusions. Indeed, 14 of the 53 patients in the MARS group initially eligible for analysis were ultimately excluded because they did not receive MARS or they only received a short session of it because an organ was readily available. Sixty-six patients (64.7%) underwent transplantation, of whom 75% did so within the first 24 h following a wait-list registration. As patients with contraindication to liver transplantation were excluded from the trial, we cannot indicate whether the use of MARS might be helpful in this population and whether these patients could especially benefit from this technique (last-line treatment).

Some non-randomized controlled studies were also published, the largest being the work of Kantola et al. [35], which included 113 prospectively collected patients who received MARS and a retrospectively collected historic control group of 46 patients with whom they were compared. There was no significant difference in the 28-day and 6-month survival rates between the two groups. The native liver recovery rate of the MARS group was higher than that of the control group (49% vs. 17%, respectively, $p < 0.01$), and the transplant-free survival was also higher (66% vs. 40%, $p < 0.05$). However, the trial design and the predominantly toxic aetiology of ALF in the MARS group greatly hampered the interpretation of these results. In the most homogenous subgroup of patients with ALF of an unknown aetiology, there was a trend towards a better survival, but this was without statistical significance. The MARS patients in the other subgroups had a significantly lower model for end-stage liver disease (MELD) score compared to that of the control group, which also precludes definitive conclusions.

Two other controlled trials recently published failed to prove a survival improvement with MARS. As these are non-randomized studies, inclusion in the intervention group depended, to a large extent, on the treating physician, which is a major bias. In the work of Lexmond et al. [36], MARS treatment was reserved for the most severe patients, and these patients had a significantly higher HE grade (3.4 vs. 2, respectively, $p < 0.01$) and PELD (Paediatric End-Stage Liver Disease)/MELD score (47 vs. 38, $p < 0.05$) than those in the other group. In the study published by Gerth et al. [37], the whole cohort was composed of mildly ill patients (HE grade ≤ 1 and no vasopressor drugs). Some uncontrolled studies show haemodynamic and neurological improvements but include few patients and are of limited quality.

MARS for acute on chronic liver failure

Trials published in the setting of AoCLF are summarized in Table 2. Only one correctly randomized controlled trial assessing survival and other clinical outcomes in this setting has been published in recent years: the RELIEF trial by Bañares et al. [38]. This relatively large multicentric trial, which scored 3 on the Oxford quality scoring system [34], failed to demonstrate a survival benefit with MARS use in both the general population included and in all of the predefined subgroups. The study showed a trend of improvement in HE in the MARS group compared to that of the control group, but this was without statistical significance. It should be pointed out that some of the exclusion criteria (platelets < 50.000/mm3, international normalized ratio > 2.3 or haemodynamic instability) could have ruled out the more severe patients. The authors also discuss the appropriateness of the schedule or dosage of the MARS sessions chosen.

In a different way, a work presented by Hessel et al. [39], which was primarily designed to explore the cost-effectiveness of MARS in patients with AoCLF, showed that the cumulative survival probability at 3 years was higher in the MARS group (logrank $p < 0.05$). However, the randomization in the study was rather unclear, and the follow-up was too long to interpret the true influence of the technique on mortality.

Recently, Gerth et al. [40] published a retrospective, controlled, non-randomized study that included 101 patients with AoCLF graded according to the new Chronic Liver Failure Consortium (CLIF-C) criteria [41]. The study showed a significant reduction in early mortality in the MARS group compared to that of the standard medical therapy (SMT) group on day 7 (0% vs. 18.5%, respectively, $p < 0.01$) and day 14 (6.4% vs. 27.8%, $p < 0.05$). This effect disappeared at day 21, which could be explained by the interruption of therapy (in the MARS group, extracorporeal therapy was performed almost daily, with a median of three sessions per patient). The 14-day mortality was especially reduced among patients with two or more organ failures (9.5% in MARS group vs. 50% in SMT group, $p < 0.01$). Furthermore, in Kaplan–Meier estimates of the 28-day survival rate in this subgroup of patients, MARS was associated with improvement (logrank $p < 0.05$). Similarly, the authors performed a secondary analysis of the RELIEF trial data (36) using the CLIF-C criteria and showed a benefit from MARS in regard to the 14-day mortality in the subgroup of patients with two or more organ failures, but this was without statistical significance. Despite its limitations, this study suggests the necessity for further

Table 2 Studies with clinical endpoints for AoCLF using MARS

Study	Years	Design	Patients number	Outcomes	Comments	LOE
Hessel et al. [39]	2010	Controlled, randomized MARS + SMT vs. SMT	149	3-year survival improvement*	Acceptable cost-outcome ratio (measured by cost per LYG and costs per QALY)	2
					Inadequate randomization	
Novelli et al. [51]	2010	Controlled, non-randomized MARS vs. SMT	20	MELD improvement**	Delta MELD predict survival	2
Bañares et al. [38]	2013	Controlled, randomized, multicentre MARS + SMT vs. SMT	156	No improvement in 28-day and 90-day transplant-free survivals	No differences in 28-day transplant-free survival in subgroups: MELD > 20, HRS at admission, severe HE, and progressive hyperbilirubinemia	1
Gerth et al. [40]	2017	Controlled, non-randomized MARS + SMT vs. SMT	101	Improvement in 7-day** and 14-day*** transplant-free survivals	No differences in 21-day and 28-day transplant-free survivals	2
					Improvement in estimate 28-day transplant-free survival rate in subgroup of patients with two or more organs failure (CLIF-ACLF grade ≥ 2)*	

LOE level of evidence, determined using the strength of recommendation taxonomy (SORT) criteria [50], *SMT* standard medical therapy, *LYG* life years gained, *QALY* quality-adjusted life years, *MELD* model for end-stage liver disease, *HRS* hepatorenal syndrome, *HE* hepatic encephalopathy, *CLIF-ACLF* chronic liver failure-acute-on-chronic liver failure

*logrank $p < 0.05$

**$p < 0.01$

***$p < 0.05$

trials targeting those more severe patients suffering from AoCLF, who may especially benefit from the technique.

In addition, a meta-analysis published by Shen et al. [42] in 2016, which enrolled studies that included patients with AoCLF, showed a significative reduction in mortality with the use of artificial liver support systems. However, this meta-analysis included several non-randomized trials, and some of the studies used restrictive inclusion criteria and techniques other than MARS in the intervention group. The largest RCT used plasma exchange as liver support and included only patients with HBV-associated AoCLF [43]. These encouraging results must therefore be interpreted with caution.

Trials in the setting of AoCLF are conditioned by the absence of a worldwide recognized definition of AoCLF, which makes the selection of patients for these studies quite variable [44]. In this regard, the acceptance and use of an international definition can be a key step in optimizing future research.

MARS for acute liver failure and acute on chronic liver failure combined

The few published trials that included ALF and AoCLF patients together are uncontrolled and retrospective. Notwithstanding, several systematic reviews and meta-analyses including RCTs published over the last 20 years have been presented recently. These studies included patients with ALF and AoCLF, and they are summarized in Table 3.

The meta-analysis published by Vaid et al. [52] in 2012 and the one published by Tsipotis et al. [53] in 2015 included quite similar trials. However, the work of Tsipotis included only RCT trials and was published 3 years later, allowing the authors to include the larger study by Saliba et al. [33] and complete data from the study by Bañares et al. [38], which had already been included in the meta-analysis by Vaid but which was reported as only a scientific abstract at the time. Both meta-analyses showed an improvement in hepatic encephalopathy with MARS (OR = 3.0, $p < 0.01$ in the Vaid study; RR = 1.5, $p < 0.01$ in the Tsipotis study). Disappointingly, neither meta-analysis showed a significant effect of MARS on mortality. Tsipotis also included some trials using Prometheus in its meta-analysis, such as the RCT published by Kribben et al. [26], which were meta-analyzed separately and combined with MARS trials with the same result.

Two systematic reviews, one published by Stutchfield et al. [54] in 2011 and the other by Guo-Lin He et al. [55] in 2015, conducted a separate meta-analysis for trials involving patients with ALF or AoCLF. In both studies, extracorporeal liver support significantly reduced

Table 3 Studies with clinical endpoints for ALF and AoCLF combined using MARS

Study	Years	Design	Patients number	Outcomes	Comments	LOE
Rusu et al. [59]	2009	Uncontrolled, retrospective	27	Improvement in HE in ALF**	Haemodynamic improvement in patients with liver failure post-transplantation**	3
				No clinical improvement in AoCLF		
Stutchfield et al. [54]	2011	Systematic review	8 RCT	ELS improved survival in ALF**	Independent meta-analysis for trials including patients with ALF or AoCLF	2
				No statistically significant reduction in mortality in AoCLF	3 trials using bioartificial devices included	
Vaid et al. [52]	2012	Meta-analysis	9 RCT 1 NRS	Improvement in HE*	No significant differences in subgroups (by age or MARS number sessions)	2
				No statistically significant reduction in overall mortality	Safety data no meta-analyzed	
Cisneros-Garza et al. [60]	2014	Uncontrolled, retrospective	70	Improvement in HE*	Patients with cholestasis disease were included. MARS associated with improved itching	3
Tsipotis et al. [53]	2015	Meta-analysis	10 RCT	Improvement in HE*	No significant differences in subgroups (by number of sessions or type of albumin dialysis technique)	2
				No statistically significant reduction in overall mortality	3 trials used Prometheus	
Guo-Lin He et al. [55]	2015	Systematic review	10 RCT	Reduction in mortality in ALF**	Independent meta-analysis for trials including patients with ALF or AoCLF	
				No statistically significant reduction in mortality in AoCLF	Very few patients with ALF included	2

LOE level of evidence, determined using the strength of recommendation taxonomy (SORT) criteria [50], *HE* hepatic encephalopathy, *RCT* randomized controlled trial, *ELS* extracorporeal liver support, *NRS* non-randomized controlled study

*$p < 0.01$

**$p < 0.05$

mortality in patients with ALF compared to SMT, and no beneficial effect on survival in AoCLF was found. However, the study of Stutchfield et al. included trials using bioartificial devices, precluding any specific conclusion for MARS.

In the systematic review by Guo-Lin He et al., only trials using MARS in the intervention group were included. In the meta-analysis of the four RCTs that involved patients with ALF, the authors compared the survival in the non-transplanted patients and found that MARS therapy significantly reduced mortality compared to SMT (RR = 0.61, $p < 0.05$). This result can be confounding because very few patients were included. Furthermore, the inclusion criteria are quite different over the studies with two trials exclusively involving patients with liver failure secondary to cardiogenic shock. With the exception of the Saliba study [33], the other RCTs did not report on follow-up or allocation data, and scored low on the CONSORT score analysis [56]. One study did not have survival as a primary outcome. Nevertheless, the results are consistent across studies ($p = 0.52$; $I^2 = 0\%$) and suggest that MARS may be a valuable tool in the subgroup of patients with ALF who are critically ill.

Another meta-analysis published by Zheng et al. [57] in 2013 found a mortality benefit of artificial liver support systems over SMT in patients with liver failure. However, the study did not focus on albumin dialysis and included earlier studies using transfusion, haemoperfusion, haemofiltration and other outdated devices, such as the Bio-Logic-DT system.

In this regard, and in order to identify the patients who could most benefit from MARS therapy, Kantola et al. [58] analyzed 188 patients treated with MARS, most of whom suffered from ALF or AoCLF (some patients with graft failure and other liver injuries were also included). In this prospective observational study, the authors identified the aetiology of liver disease as the main factor in the survival and recovery without transplantation, with the non-transplanted patients with AoCLF having the highest mortality and probably benefitting minimally from the MARS treatment. The 1-year survival rates of all of the transplanted patients in the study were very high (91% for the ALF patients), which the authors attributed to the clinical and biochemical improvements achieved with MARS. The grade of encephalopathy prior to MARS treatment and coagulation factors levels were identified as prognostic factors in ALF.

At this time, larger RCTs with well-defined inclusion criteria are still required to confirm the benefits of MARS and to be able to widely recommend its use. In the case of ALF, which is often a life-threatening condition, the use of MARS as a bridge-to-transplant to gain time or, eventually, as a bridge-to-recovery, is warranted.

Miscellaneous

Table 4 summarizes recently published trials in which MARS was used in clinical indications other than for ALF or AoCLF. At least one ongoing RCT was identified on the US-based clinical trials registration website (Molecular Adsorbent Recirculating System (MARS®) in Hypoxic Hepatitis, clinicaltrials.gov: NCT01690845). The current status of this trial is unknown.

Single-Pass Albumin Dialysis (SPAD)

Single-Pass Albumin Dialysis was described as an alternative to more sophisticated devices, such as MARS, in the late 1990s [65]. It is the simplest artificial liver device and can be applied in any intensive care unit employing a standard CRRT. No additional adsorbent columns or circuits are required. The patient's blood is dialyzed through a high-flux hollow-fibre haemodiafilter using an albumin-containing dialyzate. After passing through the dialyzer, the dialyzate is discarded (in contrast to the MARS system, in which the albumin dialyzate is regenerated), and the toxins are thus removed from the system. High amounts of albumin are consumed with SPAD, making this treatment substantially expensive.

In 2004, Sauer et al. [66] published one of the first papers comparing the in vitro detoxification capacities of SPAD and MARS for water-soluble and protein-bound compounds (bilirubin and bile acids) and demonstrated that the performances of the two were similar and that both were superior to standard continuous venovenous haemodiafiltration (CVVHD). The authors used a 4.4% albumin dialyzate solution.

These results were partially confirmed in vivo by Kortgen et al. [67], who compared the detoxification capacity of the two techniques in patients with liver failure.

Table 4 Studies using MARS in clinical indications other than for ALF or AoCLF

Study	Years	Design	Patients number	Clinical indication	Outcomes	LOE
Wong et al. [61]	2009	Uncontrolled, prospective	6	Type 1 HRS refractory to vasoconstrictor therapy	No improvement in haemodynamics	3
					No improvement in GFR; temporary improvement of creatinine during MARS**	
					Reduction in NO levels**	
Schaefer et al. [62]	2012	Uncontrolled, retrospective	3	Severe cholestatic pruritus	Paediatric patients	3
					Significant decrease in NRS score*	
					135 MARS sessions in total, during 4, 8 and 13 months prior liver transplantation	
Lavayssière et al. [63]	2013	Uncontrolled, retrospective	32	Type 1 HRS	No improvement in renal function	3
					In patients receiving norepinephrine, significant dose reductions**	
Gilg et al. [64]	2018	Uncontrolled, prospective	10	Post-hepatectomy liver failure	No improvement in MELD	3
					No major complications reported	

LOE level of evidence, determined using the strength of recommendation taxonomy (SORT) criteria [50], *HRS* hepatorenal syndrome, *GFR* glomerular filtration rate, *NO* nitric oxide, *NRS score* numeric rating scale, NRS 0: no pruritus, NRS 10: maximal pruritus, *MELD* model for end-stage liver disease

*$p < 0.01$

**$p < 0.05$

They showed a significant decrease in the serum bilirubin level with both treatments. However, only with MARS did the creatinine and urea levels significantly decrease. There were no significant differences in the other biochemical, haemodynamic or clinical values. The study was retrospective and non-randomized, and there were far fewer patients in the SPAD arm than there were in the MARS arm. The authors performed SPAD with a 5% albumin dialyzate solution and a low dialyzate flow rate (700 mL/h), which probably influenced the results.

The determination of the optimal albumin concentration in the dialyzate solution or that of the most efficient dialyzate flow rate when carrying out SPAD was already addressed by Churchwell et al. [68] in 2009. They compared the effect of various blood flow rates, dialyzate flow rates, dialyzate albumin concentrations (0%, 2.5% and 5%) and dialyzers on the clearance of some highly protein-bound drugs (valproic acid and carbamazepine). The authors demonstrated that the highest extraction ratios were achieved using the combination of 5% albumin dialyzate and a larger polysulfone dialyzer (surface area 1.5 m^2). Two years later, Benyoub et al. [69] showed significant reductions in the bilirubin and bile acid levels in patients suffering from ALF or AoCLF from using SPAD with a 3.2% albumin dialyzate and a 1000 mL/h dialyzate flow rate. More recently, Schmuck et al. [70] found, in an in vitro model, an optimal detoxification efficiency for albumin-bound substances (bilirubin and bile acids) with a 3% albumin concentration and a dialyzate flow rate of 1000 mL/h. They used SPAD with conventional CVVHD and a high-flux polysulfone haemodiafilter.

With respect to clinical data on SPAD, only a few case reports were published in the early years, and there are currently no published studies that focus on demonstrating the clinical benefits of SPAD versus standard medical therapy (SMT) in ALF or AoCLF. Two retrospective uncontrolled studies reviewing data from patients with liver failure treated with SPAD as rescue therapy were identified. One included paediatric patients with ALF of different aetiologies [71], and the other included adults patients with severe liver dysfunction in a context of alcoholic liver disease who were treated with SPAD or Prometheus [72]. Neither of these studies allow us to draw conclusions about the clinical usefulness of SPAD, and they only show us its relative ease of use and the absence of unexpected complications from its use.

The only randomized study using SPAD was recently published by Sponholz et al. [73]. This is a randomized, controlled crossover study comparing the detoxification capacity and influence on clinical and paraclinical parameters of SPAD (4% albumin dialyzate solution; 700 mL/h dialysis flow rate) and MARS (20% albumin flow rate equal to the blood flow rate, 2000 mL/h dialysis flow rate). The authors found similar reductions in the total plasma bilirubin levels, without significant differences between the two devices. The reductions in the total bile acids and γ-glutamyl transferase levels in the SPAD arm were non-significant. The creatinine and urea levels were not significantly reduced with SPAD compared to those of MARS. In contrast to other studies, neither MARS nor SPAD induced a reduction in the systemic cytokine levels. Moreover, the patients treated with SPAD presented some metabolic derangements such as increasing lactate levels or decreasing calcium levels, which are probably explained by the preferential use of citrate anti-coagulation with a low dialysis flow rate. The effects of MARS and SPAD on the clinical parameters (HE and haemodynamic status) were small and equivalent.

Currently, SPAD may be an easy-to-use alternative to MARS, but the optimal albumin dialyzate concentration, dialyzate flow rate and treatment regimen are not yet fully established. A new randomized crossover trial comparing MARS and SPAD (with the change in the plasma levels of total bilirubin as the primary endpoint, and with tolerance, change in bile acid levels, change in conjugate bilirubin levels, pulsatility index of the middle cerebral artery and HE score as the secondary endpoints) is underway. The recruitment phase of the study has actually completed (clinicaltrials.gov: NCT02310542).

Fractionated Plasma Separation and Adsorption–FPSA (Prometheus)

The FPSA method was first described by Falkenhagen et al. [74]. While MARS uses an exogenous albumin solution, the available Prometheus machine allows for the patient's own albumin to enter the first circuit using the AlbuFlow® filter (molecular cut-off of 250 kDa). Albumin is reactivated and returned to circulation using a neutral resin adsorber (Prometh® 01) and an anion-exchange column (Prometh® 02). The blood then enters a second circuit where it is treated by conventional high-flux haemodialysis before being returned to the patient.

In the first 10 years after its appearance on the market, some studies demonstrated the in vitro and in vivo efficacy of Prometheus in clearing ammonia, bilirubin or bile acids, showing that it performs even better than MARS does [75].

These results have been confirmed in recent years. In 2009, Grodzicki el al. [76] showed significant decreases in serum ammonia, bilirubin, aspartate aminotransferase, alanine aminotransferase, urea and creatinine with the use of FPSA in patients suffering from ALF. Rifai et al. [77] demonstrated a decrease in almost all twenty-six of the amino acids measured in nine patients with liver failure (eight of them with an HE grade of 2 or more) with a single FPSA session. Some of the amino acids cleared

(such as glutamine, phenylalanine, tyrosine and tryptophan) have been directly implicated in the development of HE, suggesting that FPSA may improve this serious condition associated with liver failure. In another study involving patients with ALF monitored by cerebral microdialysis, the authors found the same trend in the removal of aromatic amino acids (especially phenylalanine) from the arterial blood after a single FPSA session, but it was surprisingly without a significant change in the concentrations measured in the microdialyzate [78]. It should be noted, in this regard, that one of the inclusion criteria was a high risk of intracranial hypertension, but the patients did not need to have clinical encephalopathy. On the same topic, we found an interesting paper published by Ryska et al. [79] that described the influence of Prometheus therapy on the evolution of intracranial pressure (ICP) in a well-conducted experimental model of ALF in pigs. The authors showed a significant reduction in the ICP in the group treated with FPSA compared to that of the control group (24 mmHg vs. 29.8 mmHg, respectively, 12 h after liver devascularization, $p < 0.05$) again indicating the probable usefulness of Prometheus in HE.

On the removal of cytokines and other molecules involved in the development and evolution of liver failure, Rocen et al. [80] measured the concentrations of cytokines, inflammatory markers (C-reactive protein and procalcitonin) and liver regeneration markers, such as hepatocyte growth factor (HGF) and α1 fetoprotein, during FPSA sessions in eleven patients with ALF of different aetiologies (nine of whom were finally transplanted). The authors showed a significant decrease in most cytokines and inflammatory marker concentrations with Prometheus, which contrasts the results of previous research [81]. Nevertheless, no clinical improvement, except for improvement of encephalopathy, was demonstrated. Surprisingly, the HGF concentration increased significantly, which could favour hepatic regeneration. As with MARS, the ability of Prometheus to influence the cytokine profile and the final clinical outcome of this action are still unclear and require further research.

Few clinical studies evaluating the survival or other clinical outcomes with Prometheus were published in the 2000s. A randomized controlled trial published during this period by Laleman et al. [81] compared SMT with MARS and Prometheus in patients presenting AoCLF, and only MARS showed benefits in some of the included haemodynamic variables, such as mean arterial pressure, stroke volume or systemic resistances. Survival was not assessed in this study. Dethloff et al. [82] showed the same tendency to improve mean arterial pressure only with MARS treatment in a randomized controlled study comparing MARS, Prometheus and conventional haemodialysis in patients with decompensated cirrhosis. These different actions on haemodynamics of MARS and Prometheus have no obvious explanation. As described above, MARS and Prometheus may influence cytokine and inflammatory molecules concentrations, thus inducing haemodynamic changes, but the final balance for both is unknown. Several studies have demonstrated a reduction in NO levels with MARS [4, 81], which is probably removed in its main circulating complexed form, S-nitroso-serum albumin [83], but the use of Prometheus probably also influences NO levels [84]. In addition, most of the clinical trials published so far using MARS or Prometheus in AoCLF did not use haemodynamic outcomes and description of haemodynamic changes with treatment was often not included. It should also be noted that haemodynamically unstable patients were systematically excluded in these studies.

Over the last few years, only a limited number of studies have used clinical endpoints (Table 5). The most important was the HELIOS study, which was published in 2012 by Kribben et al. [26]. This is a multicentric randomized controlled trial comparing Prometheus with SMT in 145 patients with AoCLF, and the primary endpoint was the probabilities of survival at 28 days and 90 days (irrespective of liver transplantation). This RCT scored 3 on the Oxford quality scoring system. This trial failed to prove a survival benefit with Prometheus in the overall patient population, and the patient recruitment was interrupted after the interim analysis (90 patients) due to futility (204 patients were initially planned for inclusion in the study). It is important to note that in the overall population the probability of survival was slightly higher in the Prometheus group compared to the SMT group (90-day survival probability: 47% vs. 38%) but without statistical significance.

Among the predefined subgroups analyzed, the survival probability of patients with more severe liver disease (MELD > 30) treated with Prometheus was significantly higher than that of the patients treated with SMT alone (90-day survival probability: 48% vs. 9%, respectively, logrank $p < 0.05$). In the subgroups of patients with less sever disease (MELD < 20 and MELD 20–30), differences in survival are not statistically significant. This may indicate the usefulness of Prometheus when applied to more severe patients, but this conclusion is strongly limited by the small size of the subgroups.

Some other studies, although quite heterogeneous, have been published in recent years. Sentürk el al. [27] compared the biochemical and clinical parameters during FPSA in patients with ALF and AoCLF, demonstrating a significant improvement in the biochemical parameters and in HE. Survival was not assessed in this study. Komardina et al. [85] described haemodynamic

Table 5 Studies with clinical endpoints using Prometheus

Study	Years	Design	Patients number	Liver disease	Outcomes	LOE
Sentürk et al. [27]	2010	Uncontrolled, prospective	27	ALF AoCLF	Biochemical improvement Improvement in HE*	3
Kribben et al. [26]	2012	Randomized, controlled, multicentric Prometheus + SMT vs SMT	145	AoCLF	No improvement in 28-day and 90-day survivals, except in subgroup with MELD > 30 Similar adverse effects	1
Bergis et al. [86]	2012	Controlled, non-randomized, multicentric	20	Amanitas phalloides intoxication and liver dysfunction	No statistically significance difference in survivals	2
Komardina et al. [85]	2017	Uncontrolled, prospective	39	Ischaemic ALF	Haemodynamic and biochemical improvements**	3

LOE level of evidence, determined using the strength of recommendation taxonomy (SORT) criteria [50], *HE* hepatic encephalopathy, *SMT* standard medical therapy, *MLED* model for end-stage liver disease

*$p < 0.05$

**$p < 0.01$

and biochemical improvements with Prometheus in patients with ischaemic ALF (complication after cardiac surgery), but no change in the survival was shown. Surprisingly, the overall mortality was very high in the study (only 9 of the 39 patients included were alive at day 28).

Other devices

Some new artificial devices, or modifications to currently used systems, have been developed in the past few years.

Marangoni et al. [87] presented the so-called high-efficiency MARS by inserting a double adsorption unit (double columns containing charcoal and another pair with ion-exchange resin, mounted in parallel) into the albumin circuit. The authors compared the detoxification capacity of their system with that of the "classical" MARS in four patients with liver failure and showed that the "improved" MARS was notably more effective in removing bilirubin and bile acids.

An hybrid extracorporeal protocol was presented by Akcan Arikan et al. [88], which combined high-flux CRRT for hyperammonaemia, therapeutic plasma exchange for coagulopathy and MARS for hepatic encephalopathy. They presented this protocol in a retrospective observational study that included fifteen paediatric patients with ALF or AoCLF, who were supported with this therapy and showed improvement in HE.

In 2017, one experimental study by Al-Chalabi et al. [89] using an animal model of ALF in pigs and one uncontrolled clinical trial by Huber et al. [90] including 14 patients with liver failure were published, both of which used a new device called ADVOS (ADVanced Organ Support). The laboratory prototype of ADVOS was first presented in 2013 [91] and included an extracorporeal blood circuit, a dialyzate circuit containing standard dialyzate with a 2–4% albumin concentration and a third circuit where the albumin dialyzate was divided into two parts. Before reaching the cation and anion filters, each part undergoes a change in the pH value by the addition of acid or base and is subjected to a temperature change, resulting in a release of albumin-bound toxins. The resulting dialyzates containing toxin-free albumin join with each other in order to reach the desired pH before entering the haemodialyzer again. In the animal study mentioned above, all of the animals treated by ADVOS survived (5 out of 10), whereas the pigs treated with SMT died in the 10-h observation period ($p < 0.01$). Significant haemodynamic and biochemical improvements were demonstrated with ADVOS. A significant decrease in the bilirubin level was also demonstrated in the clinical trial published by Huber et al. [90]. No further clinical studies on this promising technique have been published so far.

Some modifications of the techniques described above, such as plasma diafiltration and some protocols already used several years ago to treat liver failure, such as plasma exchange or therapeutic apheresis using a bilirubin adsorbent column, are also found anecdotally in the literature [43, 92, 93].

Conclusion

Severe liver failure is associated with high mortality, as many patients die despite undergoing optimal medical treatment. Even if liver transplantation has emerged as an essential therapy, many patients with this disease will unfortunately die while waiting for a hepatic transplant. Consequently, there is a clear need for a liver support system to provide a "bridge" to a final treatment. Over the last two decades, several artificial liver support systems with promised advances were

introduced. However, whether such improvements could be translated into survival benefit is still uncertain, given the scarcity of available results of RCTs. The present reality is probably related to several factors, including the involvement of several interconnected organs and the fact that liver failure patients constitute a heterogeneous population with severe multimorbidity [94]. Moreover, there is no precise recommendation on the effective timing of the initiation of artificial liver support systems. In this regard, the future prospects of artificial liver support systems should rely on the completion of adequately powered RCTs addressing these crucial clinical issues and endpoints. New indications for this organ support, such as post-hepatectomy liver failure, should also be explored. In the meantime, and in the absence of alternative options to support this vital organ, it is difficult to criticize the cautious use of these secured artificial liver devices as "salvage" therapy in patients suffering from ALF or severe AoCLF.

Abbreviations
MARS: Molecular Adsorbent Recirculating System; SPAD: Single-Pass Albumin Dialysis; ALF: acute liver failure; AoCLF: acute on chronic liver failure; HE: hepatic encephalopathy; NO: nitric oxide; TNF-α: tumour necrosis factor alpha; CRRT: continuous renal replacement therapy; RCT: randomized controlled trial; PELD: paediatric end-stage liver disease; MELD: model for end-stage liver disease; CLIF-C: Chronic Liver Failure Consortium; SMT: standard medical therapy; OR: odds ratio; RR: risk ratio; CVVHD: continuous venovenous haemodiafiltration; ICP: intracranial pressure; HGF: hepatocyte growth factor; ADVOS: advanced organ support.

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Authors' contributions
JJGM drafted the majority of the manuscript. KB contributed to manuscript drafting and revised critically the manuscript. All authors read and approved the final manuscript.

Acknowledgements
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Not applicable.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Funding
No funding was obtained for the creation of this review.

Publisher's Note

Received: 5 July 2018 Accepted: 7 November 2018
Published online: 15 November 2018

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