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LES BICARBONATES DE SODIUM DANS L'ARRET CARDIAQUE EXTRAHOSPITALIER : ANALYSE RETROSPECTIVE SUR UNE COHORTE FRANCAISE ET NORD-AMERICAINE.

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ABREVIATIONS

ACR :	Arrêt cardiaque
RCP :	Réanimation cardio-pulmonaire
RACS :	Retour de la circulation spontanée
BS :	Bicarbonate de sodium

OHCA :	Out-of-hospital cardiac arrest
CPR :	Cardiopulmonary resuscitation
ROSC :	Return of spontaneous circulation
SB :	Sodium bicarbonate

INTRODUCTION

Avec une incidence de 75,3 cas pour 100 000 habitants par an, l'arrêt cardiaque (ACR) extrahospitalier est une cause majeure de mortalité mais également de morbidité y compris chez des sujets jeunes (*Luc G et al.* Anaesth crit care 2018). Les objectifs de la prise en charge sont de rétablir rapidement la perfusion cardiaque et cérébrale par la réanimation cardio-pulmonaire (RCP), d'obtenir le retour de la circulation spontanée (RACS) et d'obtenir un résultat neurologique favorable. Pour aider à atteindre ces objectifs, les recommandations publiées par *l'International Liaison Committee On Resuscitation* (ILCOR) sont largement diffusées et appliquées au niveau international. La dernière version des directives de l'ILCOR recommande l'administration de médicaments uniquement dans des conditions spécifiques (*Truhlář A et al.* Resuscitation 2015).

Il existe une association statistique forte entre, la profondeur de l'acidose métabolique à l'admission en soins intensifs après un arrêt cardiaque extrahospitalier et la mortalité en soins intensifs (*Jamme M et al.* Ann Intensive Care 2018). La profondeur de cette acidose est dépendante du rythme cardiaque initial et du délai entre le collapsus et le RACS. Pendant plusieurs années, les directives de l'ILCOR ont préconisé une perfusion de bicarbonate de sodium (BS) en cas d’arrêt cardiaque prolongé. Ces recommandations étaient fondées sur des études expérimentales animales et sur de petites études de cohorte montrant l’intérêt du BS pendant un arrêt cardiaque (*Aufderheide T et al.* Am J Emerg Med 1992). Cependant, en raison des inquiétudes concernant de potentiels effets indésirables du BS et de l'absence de preuves cliniques convaincantes de ses bénéfices chez l’homme, les indications du BS se sont restreintes ces dernières années. Les recommandations plus récentes de l'ILCOR (2020) préconisent un bolus de 1 mL/kg de BS uniquement pour les patients présentant un élargissement du QRS, une hyperkaliémie ou un surdosage en antidépresseurs tricycliques (recommandation de classe IIb, niveau de preuve C).

Cependant, l'utilisation du BS varie considérablement d'un pays à l'autre. Ainsi, il est couramment utilisé en Amérique du Nord mais moins fréquemment en Europe. Cette hétérogénéité dans la pratique est probablement liée à l'organisation des soins préhospitaliers mais également et surtout aux résultats contradictoires de plusieurs études récentes : certaines ont montré une amélioration de la survie ou de l'augmentation de la proportion de patients avec un RACS (*Vukmir RB et al.* Am J Emerg Med. 2006), tandis que d'autres n'ont trouvé aucun bénéfice *(Ahn S et al.* J Thorac Dis. 2018 *; Kawano T et al.* Resuscitation. 2017*).* Aucun essai contrôlé randomisé de grande envergure n'a évalué les avantages potentiels de l'administration de bicarbonate de sodium chez les patients victimes d'un arrêt cardiaque extrahospitalier.

Notre objectif ici était d'évaluer l'association entre l'utilisation préhospitalière du BS et le devenir neurologique après un arrêt cardiaque extrahospitalier, afin de disposer d'éléments pour conduire un essai randomisé contrôlé.

Nous avons utilisé deux grandes bases de données, l'une en France (registre RéAC) et l'autre en Amérique du Nord (essai ROC-CCC).

- Les données Françaises concernaient la période allant de juillet 2011 à mars 2018 du registre national français des arrêts cardiaques (RéAC). Celui-ci inclut tous les arrêts cardiaques extrahospitaliers pris en charge par les équipes médicalisées en France en dehors de la région Ile de France. Les patients inclus dans l'essai étaient âgés de 18 ans ou plus et présentaient un ACR non traumatique. Nous n'avons pas inclus les patients de moins de 18 ans, les patients présentant un ACR traumatique, ayant une durée de « no-flow » (temps entre l'effondrement et le début de la RCP) supérieure à 20 minutes, une suspicion d'hyperkaliémie, une directive anticipée écrite de ne pas réanimer, un RACS avant l'arrivée des premiers secours, ou des données manquantes sur le résultat principal.

- L'essai ROC-CCC a recruté des patients de juin 2011 à mai 2015 (*Nichol G et al.* N Engl J Med. 2015). Cet essai randomisé a comparé des compressions thoraciques en continu avec une ventilation en pression positive à des compressions intermittentes, interrompues pour des ventilations en pression positive selon un ratio de 30 compressions pour 2 insufflations. Les patients inclus dans l'essai étaient âgés de 18 ans ou plus et avaient un ACR non traumatique. Les patients n'ont pas été inclus si un intervenant médical d'urgence avait été témoin de l'arrêt, s'il y avait une directive préalable écrite de ne pas réanimer ou s'il manquait des données sur le pronostic neurologique.

Le critère de jugement principal était le devenir neurologique au 30ème jour dans la cohorte française évalué à l'aide de la catégorie de performance cérébrale (CPC), et le devenir neurologique à la sortie de l'hôpital dans l'ensemble de données nord-américain, évalué par l'échelle de Rankin modifiée (mRS). Le pronostic a été classé comme bon si le score CPC ≤2 ou le score mRS≤ 3. Le critère de jugement secondaire pour les deux cohortes était la survie à la sortie de l'hôpital.

Nous avons ajusté les facteurs de confusion potentiels en effectuant une analyse du score de propension avec une pondération inverse de la probabilité de traitement.

Sur les 54 807 patients de la cohorte française, 1234 (2,2%) ont reçu du bicarbonate de sodium. Après appariement par score de propension, la perfusion de bicarbonate de sodium n'était pas associée à un meilleur devenir neurologique au 30ème jour (odds ratio ajusté [aOR], **0,912** ; intervalle de confiance à 95 % [95%CI], [0,501-1,655]).

Dans la cohorte nord-américaine, sur les 23 711 patients inclus, 4902 (20,6 %) ont reçu du BS. Dans l'analyse appariée par score de propension, la perfusion de BS était associée à un moins bon devenir neurologique à la sortie de l'hôpital (aOR, **0,45** ; intervalle de confiance à 95 % [95%CI], [0,34-0,58]).

L'interprétation de ces résultats est :

- Concernant les patients, dans les deux cohortes, ceux ayant reçu des BS présentaient les caractéristiques considérées auparavant par l'ILCOR comme justifiant un traitement par BS, telles qu'une RCP prolongée ou un support en vasopresseurs. Ces patients étaient plus susceptibles de présenter une acidose marquée en raison d'un bas débit prolongé et étaient donc plus susceptibles de répondre favorablement au traitement par BS. Bien que les données suggèrent que le BS était administré aux patients les plus susceptibles d'en bénéficier, nous n'avons trouvé aucune différence significative entre les groupes dans la cohorte française et une différence significative en défaveur du BS dans la cohorte nord-américaine.

- Les différences de résultats entre les deux cohortes peuvent avoir plusieurs explications. Premièrement, les résultats ont été déterminés 30 jours après l'ACR dans l'ensemble de données français et à la sortie de l'hôpital dans l'ensemble de données nord-américain. Une autre différence notable est l'absence d'ajustement dans l'étude nord-américaine de certains facteurs de confusion, notamment l'intoxication médicamenteuse, l'insuffisance rénale chronique et les durées de No Flow et de Low Flow. Des différences de résultats sont probablement apparues également dans la sélection des populations étudiées. Enfin, la divergence peut également être liée aux différences d'organisation des soins d'urgence entre les États-Unis et la France, notamment la présence d'un médecin dans les équipes mobiles d'urgence en France mais pas aux États-Unis.

- Le manque d'efficacité du BS dans l'amélioration de la survie et du devenir neurologique chez les patients victimes d'un ACR extrahospitalier peut s'expliquer de plusieurs façons. D'une part, l'acidose métabolique semblerait n'avoir aucun impact sur la récupération neurologique chez les patients sortant vivant de l'hôpital (*Jamme M et al.* Ann Intensive Care 2018). D'autre part, parce que l'acidose lactique induite par le bas débit cardiaque avec anoxie cellulaire n'est que le reflet indirect de la durée de l'anoxie cérébrale. Sa correction pourrait n'intervenir que trop tardivement pour observer un effet et donc ne pas limiter la durée d'anoxie cérébrale.

- Nos résultats avec l'ensemble des données nord-américaines sont conformes à ceux d'une étude prospective avec appariement par score de propension. Celle-ci a montré des résultats neurologiques et une survie plus mauvaise dans le groupe ayant reçu le bicarbonate de sodium (*Kawano T et al.* Resuscitation. 2017).

- Dans les études cliniques sur l'acidose métabolique, l'administration de BS n'a pas réduit la mortalité chez les patients non sélectionnés. Les explications possibles incluent une acidose intracellulaire paradoxale, la diminution du tonus vasomoteur et la diminution du calcium ionisé plasmatique induits par l'administration de BS. Le BS a également un effet inotrope négatif sur le myocarde ischémique. Il produit un décalage vers la gauche de la courbe de dissociation de l'oxygène, inhibant davantage la libération d'oxygène dans les tissus. En réagissant avec les acides métaboliques, le BS produit du CO_2 qui se diffuse facilement à travers les membranes cellulaires et la barrière hémato-encéphalique. Une augmentation de la PCO_2 dans le liquide céphalo-rachidien provoque une acidose et un œdème cérébral. Une augmentation de la production de CO_2 est également responsable d'une diminution du tonus vasculaire cérébral. Ainsi, les différences dans les modalités d'oxygénation des voies aériennes peuvent contribuer aux différents résultats des ensembles de données français et nord-américains.

Nous avons observé que chez les patients victimes d'un ACR extrahospitalier non traumatique, l'administration pré-hospitalière de bicarbonate de sodium n'était pas associée à une amélioration du pronostic neurologique dans une cohorte française et était associée à de plus mauvais devenir neurologique dans une large cohorte nord-américaine.

Malgré le grand nombre de patients inclus dans l'ensemble de données appariées, la puissance statistique était quelque peu limitée en raison du faible nombre de survivants et de patients présentant de bons résultats neurologiques. La réalisation d'une étude contrôlée randomisée de grande envergure, avec des patients sélectionnés, permettrait de répondre définitivement à la place des BS au cours de l'arrêt cardiaque extrahospitalier.

Nous manquions également d'informations sur les doses et le moment des perfusions de BS. La durée de perfusion et la concentration de bicarbonate modifiant la vitesse de correction de l'acidose, ainsi que le timing d'administration du BS pourraient influencer le résultat et devraient être étudiés dans d'autres essais. Un modèle d'analyse en risque compétitif prenant en compte le RACS et l'arrêt de la réanimation cardiopulmonaire permettrait d'évaluer l'efficacité du BS.

Enfin, un tiers des patients victimes d'un ACR extrahospitalier meurent d'un choc post-arrêt dans les 72 heures suivant l'admission en réanimation. Il existe une association entre la gravité de l'acidose métabolique à l'admission en réanimation après un arrêt cardiaque extrahospitalier et la mortalité. La réalisation d'un essai en réanimation sur l'utilisation des bicarbonates de sodium dans le choc post-ressuscitation notamment chez les patients avec une acidose sévère et une instabilité hémodynamique devrait être évaluée dans de futures études.

Article :

Sodium Bicarbonate for Out-of-Hospital Cardiac Arrest: Insights from French and North-American Datasets

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ABSTRACT

Background: No large randomized controlled trial has assessed the potential benefits of sodium bicarbonate administration in patients with out-of-hospital cardiac arrest (OHCA). Current guidelines on this point are based on old and discordant data. Our objective here was to evaluate the potential benefits of sodium bicarbonate infusion during prolonged OHCA.

Methods: We used two large datasets, one from France (RéAC Registry) and the other from North-America (ROC-CCC trial). We adjusted for potential confounders by performing a propensity score analysis with inverse probability-of-treatment weighting.

Results: Of the 54 807 patients in the French dataset, 1234 (2.2%) received sodium bicarbonate. After propensity score matching, sodium bicarbonate infusion was not associated with better neurological outcomes on day 30 (adjusted odds ratio [aOR], 0.912; 95% confidence interval [95%CI], 0.501-1.655). In the North-American dataset, of the 23,711 patients included, 4902 (20.6%) received SB. In the propensity-score matched analysis, SB infusion was associated with poorer neurological outcomes at hospital discharge (aOR, 0.45; 95%CI, 0.34-0.58).

Conclusion: In patients with OHCA, pre-hospital SB administration was not associated with neurological outcomes in the French dataset and was associated with worse neurological outcomes in the North-American dataset. The use of SB in patients with OHCA must be reserved, in accordance with the latest international guidelines, for patients with absolute indications such as hyperkaliemia and/or ventricular arrythmias with QRS widening.

INTRODUCTION

With an incidence of 75.3 cases per 100,000 population per year, out-of-hospital cardiac arrest (OHCA) carries a high risk of major neurological morbidity and mortality (1). The treatment goals are to promptly restore cardiac and cerebral perfusion by cardiopulmonary resuscitation (CPR), achieve the return of spontaneous circulation (ROSC), and obtain a favorable neurological outcome. To help reach these goals, guidelines issued by the International Liaison Committee On Resuscitation (ILCOR) are widely disseminated and applied internationally. The latest version of the ILCOR guidelines recommends the administration of specific drugs under specific conditions (2).

There is a strong association between the severity of metabolic acidosis at ICU admission after OHCA and mortality in critical care. Metabolic acidosis strongly determined by the initial cardiac rhythm and the time from collapse to ROSC (3). For several years, the ILCOR guidelines advocated an infusion of sodium bicarbonate (SB) in the event of prolonged OHCA. This guideline was based on experimental animal studies and on small cohort studies showing benefits of SB during OHCA (4,5). This practice changed over the years, however, due to concerns about adverse effects of SB and to the lack of convincing clinical evidence of benefits (6,7). The 2005 ILCOR guidelines reserve SB for specific situations (8), and the most recent ILCOR guidelines (2020) recommend a bolus of 1 mL/kg SB only for patients who have QRS widening and severe cardiotoxicity, hyperkalemia, or tricyclic antidepressant overdosage (Class IIb recommendation, level of evidence C) (9).

However, the use of SB varies widely across countries. SB is used commonly in North-America (10) but significantly less often in Europe (11). This heterogeneity is probably related to the conflicting results of several recent studies: some showed improved survival (12) or an increase in the proportion of patients with ROSC (13–15), while others found no benefits (16–18).

Our objective here was to evaluate associations between the prehospital use of SB and the neurological outcomes after OHCA. We used datasets from countries with different prehospital protocols, one from France where the first responders include a physician and the other from North America where the first responders are paramedics.

METHODS

This manuscript complies with the STROBE guidelines (19).

Study Design

French dataset

We used data entered into the French National OHCA Registry (RéAC) from July 2011 to March 2018. RéAC includes all OHCAs managed by mobile intensive care units (MICUs) in France and has been described elsewhere (20–24). An MICU team consists at the minimum of an ambulance driver, a nurse, and a senior emergency physician, who have the skills and equipment to provide advanced life support on-scene. A detailed description of the emergency medical system in France has been published previously (25). The RéAC data entry form meets the requirements of the French Emergency Medical Service organization and is structured according to the Utstein style (26). The 30-day follow-up is the responsibility of the local RéAC investigator. Receiving department physicians generally transmit the discharge letter with the neurological outcome to the local RéAC investigator or they directly fill out the 30-day follow-up form on the RéAC database.

North-American dataset

We used the data from the ROC-CCC trial that enrolled patients from June 2011 to May 2015 (27). This randomized controlled trial compared continuous compressions with positive-pressure ventilation to compressions that were interrupted for positive pressure ventilations at a ratio of 30 compressions to two ventilations. The primary outcome was survival to hospital discharge.

In North-America, the management of cardiac arrest relies on a two-tiered system involving mobile emergency units and fire departments. The basic life support tier consists of firefighters or police officers and emergency medical technicians who can apply automated external defibrillators and initiate or pursue CPR maneuvers (including chest compressions). The advanced life support (ALS) tier consists of emergency medical service (EMS) personnel who are skilled in rescue techniques (endotracheal intubation or supra-glottic device insertion, intravenous line placement, and drug administration) but are not physicians (28).

Ethics

The study of the French dataset was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS) and the French National Data Protection Authority (CNIL, authorization #910946). In compliance with French law about registry studies, patient consent was not required (29).

The North-American dataset study was approved by the ethics committee of the French Society of Critical Care (FICS/SRLF) (#19-60) and by the National Heart, Lung, and Blood Institute (www.biolincc.nhlbi.nih.gov).

Patient selection

French dataset

The RéAC registry collects data on all cases of OHCA in adults and children. For this study, we did not include patients younger than 18 years, patients with traumatic OHCA, a no-flow duration (time between collapse and CPR initiation) above 20 minutes, suspected hyperkalemia, a written advance directive to not resuscitate, ROSC before first responder arrival, or missing data on the main outcome.

North-American dataset

Patients included in the trial were 18 years of age or older and had non-trauma-related OHCA. Patients were not included if an emergency medical responder witnessed the arrest, there was a written advance directive to not resuscitate, or data were missing about the neurological prognosis.

Outcomes

The primary outcome was the neurological outcome on day 30 in the French dataset and at hospital discharge in the North-American dataset. The neurological status was evaluated using the Cerebral Performance Category (CPC) in the French dataset and the modified Rankin scale (mRS) in the North-American dataset. The prognosis was classified as good if CPC ≤2 or mRS≤ 3 and as poor otherwise (30).

The secondary outcome for both datasets was survival at hospital discharge.

Data collection

The data were collected from July 2011 to March 2018 for the French dataset and from June 2011 to May 2015 for the North American dataset. According to the Utstein style (26), the following variables were collected in both datasets: age, gender, occurrence at home, witnessed status, initial cardiac rhythm, cumulative epinephrine dose used during resuscitation, times from collapse to first chest compression (no-flow duration) and from first chest compression to ROSC (low-flow duration) in the French dataset or time from collapse to ROSC in the North American dataset, post-resuscitation shock (defined as a need for vasopressors [epinephrine or norepinephrine] for >6 hours despite adequate fluid loading), survival, and neurological outcome on day 30 for the French dataset or at discharge for the North-American dataset. For the French dataset, we also recorded a history of chronic renal failure and cases of drug poisoning (as markers for specific indications for SB use).

Statistics

The patients were dichotomized based on prehospital administration of SB. Continuous variables were described as mean±SD if normally distributed and as median [interquartile range] otherwise. Categorical variables were described as patient count and percentage. Normality was assessed using the Shapiro-Wilk test and by visually checking the distribution (histogram) of each variable.

As prehospital SB administration was not randomly assigned, we performed a propensity score analysis to mitigate the potential effects of selection bias and unmeasured confounders (31). As recommended by Brookhart *et al.* (32), only co-variables potentially related to the judging criteria were used to build the propensity score, irrespective of whether they were related to SB administration. The selected variables were age, in three categories (18-49 years, 50-79 years, and ≥80 years); gender; location of the intervention; CPR delivered by witnesses (yes or no); no-flow duration dichotomized according to median value (<8 min or ≥8 min) and low-flow duration dichotomized according to median value (<28 min or ≥28 min) for the French dataset and time to ROSC (<20 min or ≥20 min) for the North American dataset; initial shockable rhythm (yes or no); cumulative amount of epinephrine administered according to median value (<5 mg or ≥5 mg); and administration of vasopressors (yes or no). As a history of chronic renal failure or drug poisoning was not collected in the North American trial, these variables could not be included in the propensity score for that dataset.

The balance of selected covariables between the two treatment groups was assessed based on the standardized mean difference (SMD). We considered that an SMD<10% indicated a negligible imbalance in the distribution of the covariable in question between groups (31). The propensity score for SB administration was built using multivariable logistic regression, taking into account the above-listed co-variables. The presence of a sufficient common support area for matching was assessed graphically. Then, 1:1 propensity score matching was performed using the nearest neighbor method. The impact of SB administration on the neurological prognosis and survival was finally estimated by computing the adjusted odds ratios (aORs) with their 95% confidence intervals (95%CIs). The statistical analyses were performed using R version 3.5.1 (http://www.r-project.org). $P<0.05$ was considered significant.

RESULTS

French dataset

Figure 1 is the patient flowchart. From July 2011 to March 2018, 54,807 patients with OHCA meeting our selection criteria were recorded in the registry. Among them, 1234 (2.2%) received SB. As shown in Table 1, the two groups had statistically significant differences for many parameters. The only parameter that differed significantly between the two groups for one dataset but not the other was male sex, which was significantly more common in the SB group in the French dataset but was not different between groups in the North American dataset.

After elimination of patients with missing data about the co-variables of interest, 450 patients given SB were kept for the propensity score analysis. The distribution of the propensity scores in the two groups showed considerable overlap, allowing matching of all SB-treated individuals without missing data on the covariates of interest (eFigure 1). Thus, each patient given SB was matched to a patient who did not receive SB. None of the co-variates of interest were balanced in either treatment group, except for drug poisoning (Figure 2). After matching, the balance between the different covariates was considered satisfactory on the basis of the SMDs (Figure 2).

The analysis of the matched data demonstrated that the aOR of having a favorable neurological outcome on day 30 in patients who received SB versus those who did not was 0.912 (95%CI, 0.501-1.655). The aOR of 30-day survival was 0.894 (0.52-1.53).

North-American dataset

Figure 1 is the patient flow chart. From June 2011 to May 2015, of the 23,711 patients with non-traumatic OHCA who were included, 4902 (20.7%) received SB.

Table 2 reports the baseline characteristics. Again, many parameters differed significantly between the two treatment groups.

None of the covariates of interest were balanced in either treatment group (eFigure 2). After elimination of patients with missing data about the co-variables of interest, 1238 patients given SB were kept for the propensity score analysis. Each patient was matched to a patient who did not receive SB. The SMD for each baseline covariate was within 10% (Figure 3).

SB administration was significantly associated with a poorer neurological outcome at hospital discharge (aOR, 0.45; 95%CI, 0.34-0.58) and with a lower probability of survival (aOR, 0.59; 95%CI, 0.47-0.73).

The SB and no-SB groups in the two datasets were very similar for most of the parameters, so that there is no clear evidence of a difference in the indications for SB.

DISCUSSION

In our study, we examined 54,807 patients in France and 23,711 in North-America who experienced non-traumatic OHCA. The use of SB was not significantly associated with the neurological outcome or survival of patients in the French dataset. On the other hand, in the North-American dataset, SB administration during resuscitation was associated with a poorer neurological prognosis and decreased survival at hospital discharge.

In both datasets, patients who received SB had the characteristics considered formerly by the ILCOR as warranting SB treatment, such as prolonged CPR or a need for vasopressor infusion. These patients were more likely to have marked acidosis due to a long low-flow time and were therefore more likely to respond favorably to SB therapy (33). The proportion of patients given SB was surprisingly high in the North-American dataset (20.6% vs. 2.2% in the French dataset) suggesting that SB treatment may be more severely restricted in France to patients with characteristics indicating a high likelihood of beneficial effects. Moreover, the propensity score for the French dataset included drug poisoning (but not specifically tricyclic antidepressants poisoning) and chronic renal failure potentially responsible for hyperkalemia. Although the data suggest that SB was reserved for patients most likely to benefit, we found no significant difference between treatment groups in the French dataset and an association of SB treatment with poorer outcomes in the North-American dataset.

The differences in results between the two datasets may have several explanations. First, the outcomes were determined 30 days after OHCA in the French dataset and at hospital discharge in the North-American dataset. A more notable difference is the lack of adjustment in the North-American study for certain confounding factors including drug poisoning, chronic renal failure, and no-flow and low-flow durations. Differences probably occurred also in the selection of the study populations. Finally, the discrepancy may also be linked to the differences in emergency care organization between the United States and France, particularly the presence of a physician in mobile emergency teams in France but not in the United States.

OHCA alters the body's homeostasis by causing acid-base, metabolic, electrolyte, and hydration disturbances whose severity increases with the duration of tissue anoxia. Prolonged resuscitation is responsible for mixed acidosis. The introduction of mechanical ventilation completely corrects the respiratory component upon hospital arrival (22), resulting in significant lactic acidosis (34). Metabolic acidosis strongly determined by the initial cardiac rhythm and the time from collapse to ROSC (3).

The lack of efficacy of SB in improving survival and neurological outcomes in patients with OHCA may be explained by incomplete correction of the lactic acidosis induced by the low cardiac output with cellular anoxia, which is an indirect reflection of cerebral anoxia. Moreover, metabolic acidosis appears to have no impact on neurological recovery in patients discharged alive (3). Our results with the North American dataset are in line with those of a prospective study with propensity score matching, which showed worse neurological outcomes and survival in the group given SB (17). Interestingly, the use of epinephrine during resuscitation for OHCA is also being challenged based on a randomized placebo-controlled trial (PARAMEDIC2) showing better 30-day survival with epinephrine but no difference in the proportion of patients with a favorable outcome, as many survivors had severe neurological impairments (35). However, other interventions targeting a hemodynamic improvement may provide better neurological outcomes (36,37).

In clinical studies of metabolic acidosis, SB administration did not reduce mortality in unselected patients (38,39). Possible explanations include the exacerbation of intracellular acidosis, decreased vasomotor tone, and decreased plasma ionized calcium induced by SB administration. SB also has a negative inotropic effect on the ischemic myocardium. It produces a leftward shift in the oxygen dissociation curve, further inhibiting oxygen release to tissues (40,41). Upon reacting with metabolic acids, SB produces CO_2 that diffuses readily across cell membranes and the blood-brain barrier. A PCO_2 increase in the cerebrospinal fluid causes acidosis and cerebral edema (42). An increase in CO_2 production is also responsible for a decrease in cerebral vascular tone (43). Thus, differences in airway oxygenation modalities may contribute to the different results in the French and North-American datasets.

The limitations of our study must be acknowledged. First, despite the large number of patients included in the matched dataset, statistical power was limited somewhat due to the low number of survivors and of patients with good neurological outcomes. Second, we lacked information on the doses and timing of the SB infusions. For instance, SB may have been used too late to produce benefits. In both datasets, SB was mainly used in patients with cardiac arrest whose prognosis was therefore already poor. In an ICU study, the time needed to recover from severe acidemia, rather than the initial pH value, was an independent risk factor for mortality (44). Third, no-flow and low-flow durations are informative but cannot be used to accurately estimate the severity of acidosis, which can vary from one situation to another. Fourth, we were not able to evaluate same timeframe for neurological prognosis as outcome after hospital discharge was not available in North-American dataset. Last, we did not adjust for in-hospital interventions such as targeted temperature management (45) or coronary artery procedures (46,47). It is important to remember that within 72 hours after admission, 35% of patients with OHCA die from post-arrest shock (48). It might be interesting to conduct further studies of the place for SB in the management of critically ill patients with severe acidosis.

CONCLUSION

In patients with OHCA, the use of SB during the prehospital management was not associated with the neurological outcome or survival in a French dataset and was associated with worse neurological outcomes and survival in a North-American dataset. The use of SB in patients with OHCA must be reserved for patients with hyperkalemia, ventricular arrhythmias with QRS widening, and other absolute indications according to the latest ILCOR guidelines.

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FIGURE LEGENDS

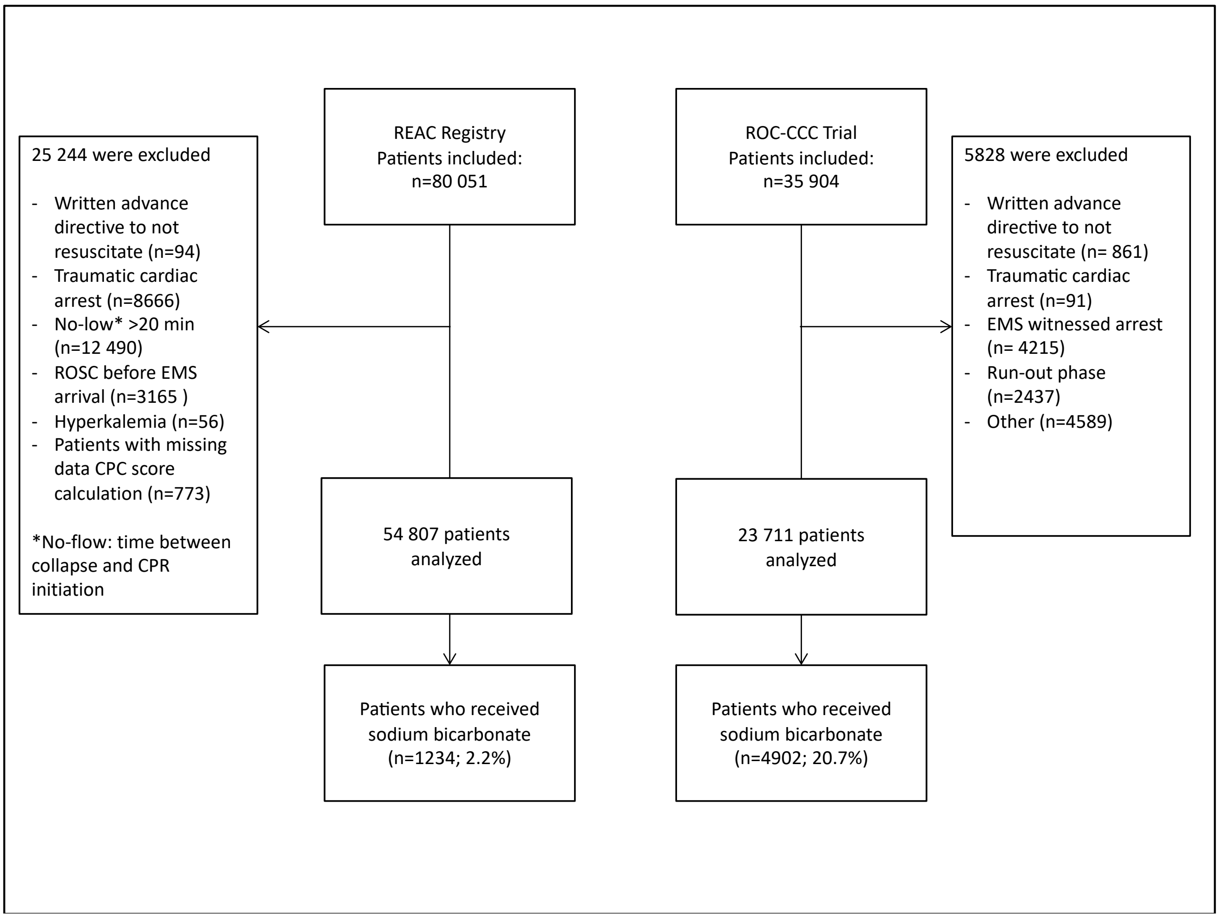

Figure 1. Flowchart

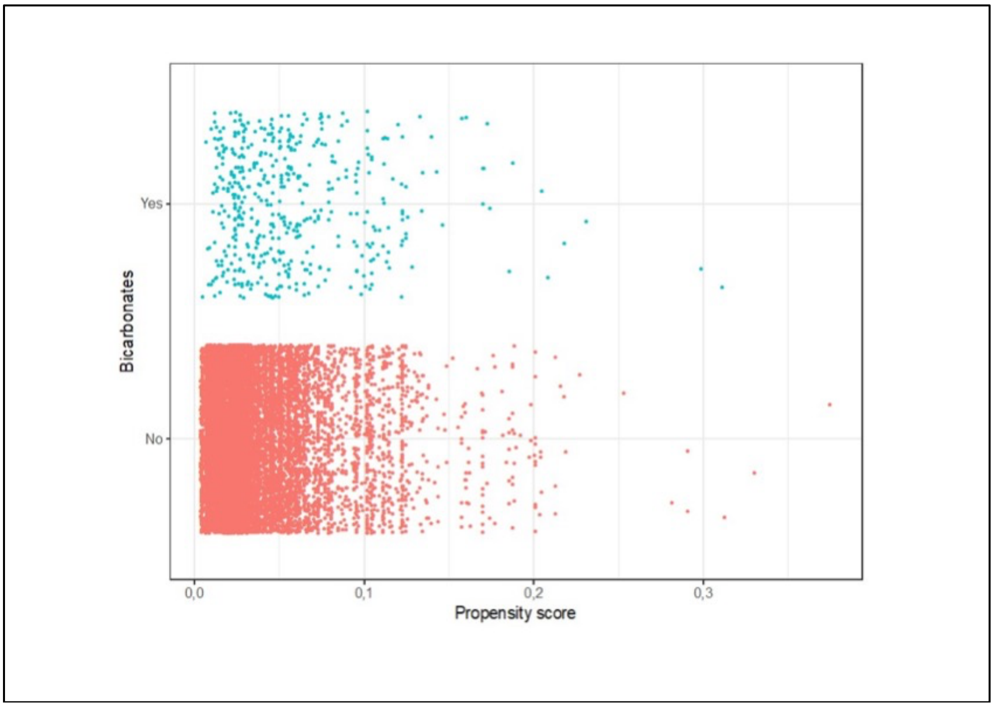

Figure 2. Overlaps Réac

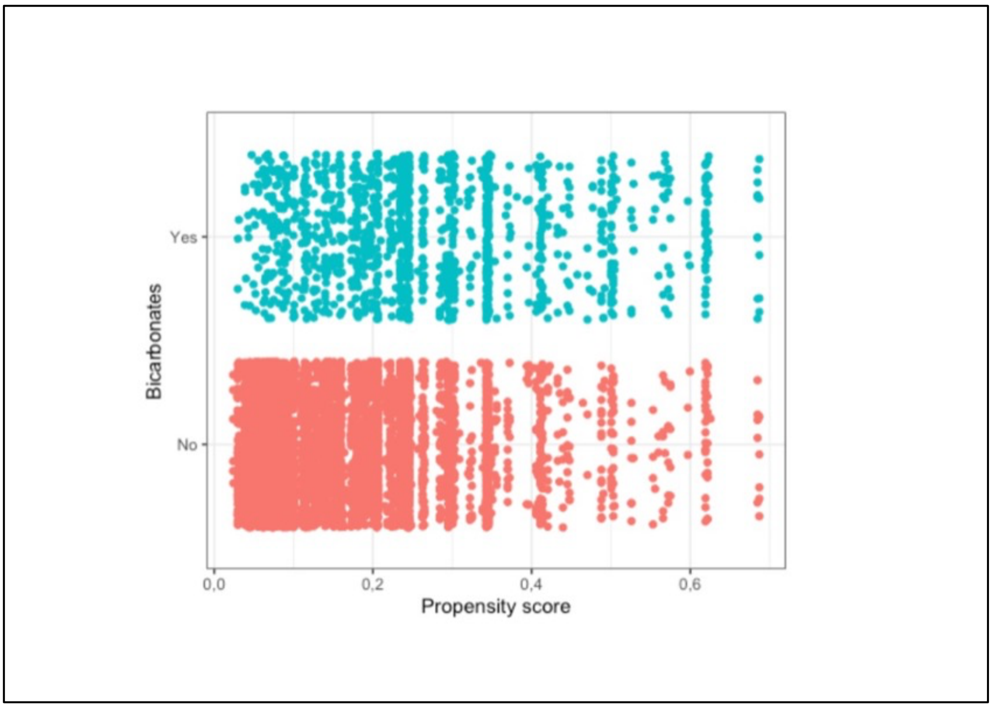

Figure 3. Overlaps ROC-CCC

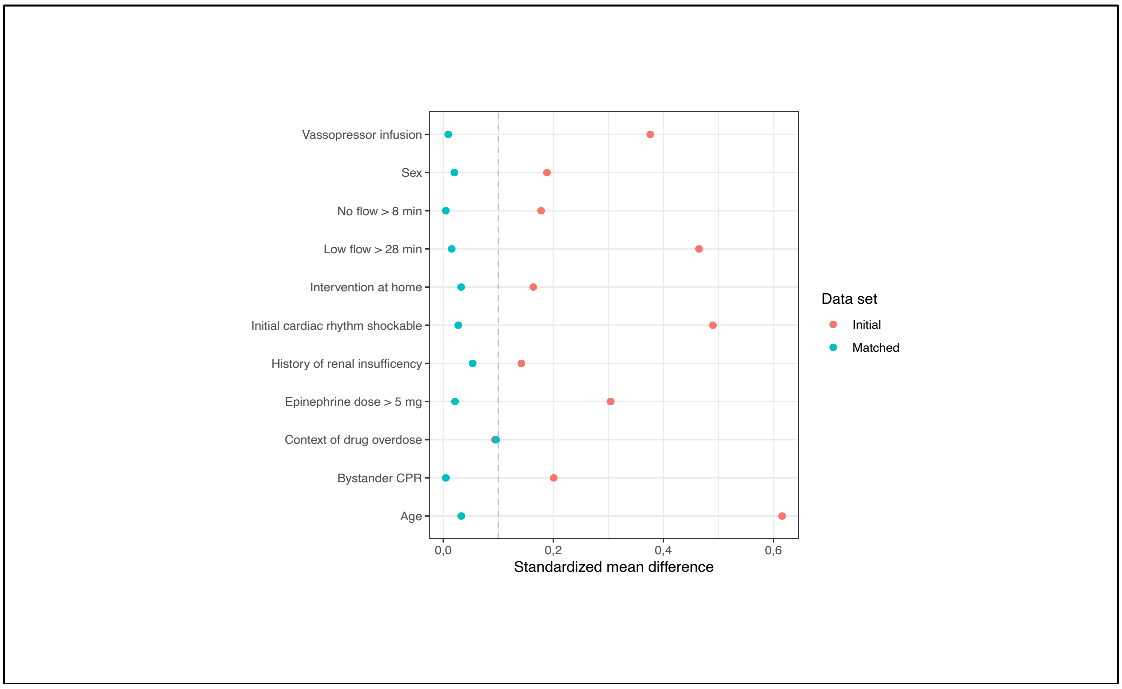

Figure 4. SMD Réac

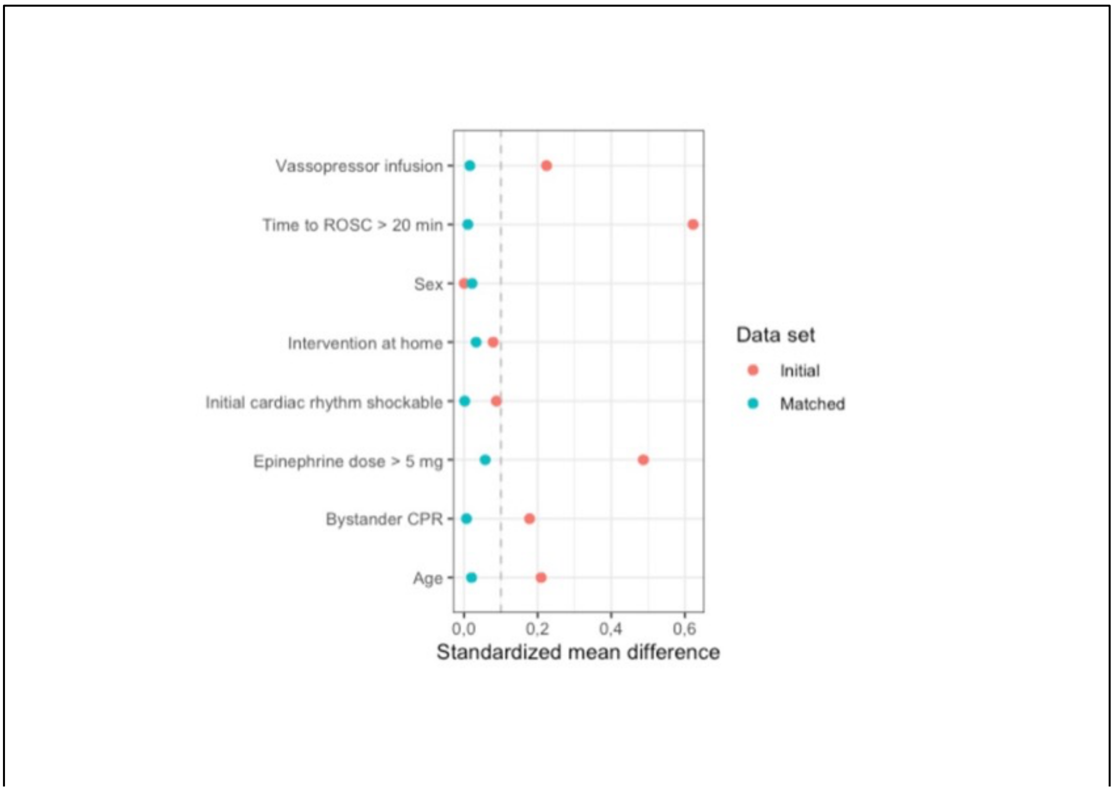

Figure 5. SMD ROC-CCC

n (%) unless otherwise specified	**Bicarbonate group** (n=1234)	**Control group** (n=53 573)	P value
Charactéristics			
Age, mean±SD	60±16	70±16	<0.001
Male sex	905 (73.3)	34 599(64.6)	<0.001
History of kidney failure	57 (4.6)	1111 (2.1)	<0.001
Drug poisoning	34 (2.8)	759 (1.4)	<0.001
Intervention at home	834 (67.6)	38 608 (72.1)	<0.001
Bystander CPR	696 (56.4)	24 138 (45.1)	<0.001
No flow >8 min	503 (40.8)	26 356 (49.2)	<0.001
Low flow >28 min	894 (72.4)	28 214 (52.7)	<0.001
Initial shockable rhythm	475 (38.5)	9196 (17.2)	<0.001
Epinephrine dose >5 mg	180 (14.6)	14986 (28.0)	<0.001
Vasopressor infusion	410 (33.2)	5442 (10.2)	<0.001
Outcome			
Survival to day 30	63 (5.1)	1659 (3.1)	<0.001
Favorable outcome on day 30	46 (3.7)	305 (2.4)	0.004

Table 1. REAC dataset: Baseline characteristics of the groups that did and did not receive sodium bicarbonate. CPR, cardiopulmonary resuscitation.

The analysis of the matched data demonstrated that the aOR of having a favorable neurological outcome on day 30 in patients who received SB versus those who did not was 0.912 (95%CI, 0.501-1.655). The aOR of 30-day survival was 0.894 (0.52-1.53).

n (%) unless otherwise specified	**Bicarbonate group** (n=1234)	**Control group** (n=53 573)	P value
Charactéristics			
Age, mean±SD	64±17	67±16	<0.001
Male sex	3136 (64%)	12 025 (64%)	0.97
Intervention at home	4295 (88%)	15 948 (85%)	<0.001
Bystander CPR	2617 (53%)	8371 (44%)	<0.001
Time to ROSC	28 ±10	22±9	<0.001
Initial shockable rhythm	963 (20%)	4374 (23%)	<0.001
Epinephrine dose, mean±SD	5±3	3±2	<0.001
Vasopressor infusion	1497 (30%)	4864 (26%)	<0.001
Admission to hospital	1020 (21%)	4837 (26%)	<0.001
Outcome			
Survival to hospital discharge	171 (3%)	2028 (11%)	<0.001
Favorable outcome at hospital discharge	97 (2%)	1630 (<1%)	<0.001

Table 2. ROC-CCC dataset: Baseline characteristics of the groups that did and did not receive sodium bicarbonate

SB administration was significantly associated with a poorer neurological outcome at hospital discharge (aOR, 0.45; 95%CI, 0.34-0.58) and with a lower probability of survival (aOR, 0.59; 95%CI, 0.47-0.73).

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Titre de Thèse : Bicarbonates for out-of-hospital cardiac arrest: insights from a French and a North-American dataset

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RESUME (10 lignes)

Contexte : Aucun grand essai contrôlé randomisé n'a évalué les avantages potentiels de l'administration de bicarbonate de sodium chez les patients victimes d'un arrêt cardiaque extrahospitalier. Les directives actuelles sur ce point sont basées sur des données anciennes et discordantes. Notre objectif ici était d'évaluer les avantages potentiels de l'infusion de bicarbonate de sodium pendant un arrêt cardiaque prolongé.

Méthodes : Nous avons utilisé deux grandes cohortes de données, l'un en France (registre RéAC) et l'autre en Amérique du Nord (essai ROC-CCC). Nous avons ajusté les facteurs de confusion potentiels en effectuant une analyse du score de propension avec une pondération inverse de la probabilité de traitement.

Résultats : Sur les 54 807 patients de la base de données française, 1234 (2,2%) ont reçu du bicarbonate de sodium. Après appariement par score de propension, la perfusion de bicarbonate de sodium n'était pas associée à de meilleurs résultats neurologiques au 30e jour (odds ratio ajusté [aOR], 0,912 ; intervalle de confiance à 95 % [95%CI], 0,501-1,655). Dans l'ensemble de données nord-américain, sur les 23 711 patients inclus, 4902 (20,6 %) ont reçu un SB. Dans l'analyse appariée par score de propension, la perfusion de SB était associée à de moins bons résultats neurologiques à la sortie de l'hôpital (aOR, 0,45 ; 95%CI, 0,34-0,58).

Conclusion : Chez les patients victimes d'un arrêt cardiaque extra hospitalier, l'administration pré-hospitalière de bicarbonate de sodium ne modifiait pas le résultat neurologique dans l'ensemble des données françaises et était associée à de plus mauvais résultats neurologiques dans l'ensemble des données nord-américaines. L'utilisation du bicarbonate de sodium chez les patients victimes d'un arrêt cardiaque extra hospitalier doit être réservée, conformément aux dernières directives internationales, aux patients présentant des indications absolues telles que l'hyperkaliémie et/ou des arythmies ventriculaires avec élargissement du QRS.

MOTS-CLES

BICARBONATE DE SODIUM ; ARRET CARDIAQUE.