Toxin-induced cardiac arrest: frequency, causative agents, management and hospital outcome

Les arrêts cardiaques d'origine toxique : Fréquence et pronostic

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RÉSUMÉ

Background : Cardiac arrest (CA) is a public health problem, with various etiologies and a fatal issue in 90-95% of cases. Toxin-induced cardiac arrests (TICA) are poorly described. Scarcity of national data prompted us to carry-out this study.
Aim : To determine TICA frequency in a Tunisian reference center in toxicology and its hospital prognosis, and to describe its clinical and therapeutic aspects
Methods : Data were collected retrospectively over an 8-years period. We included patients admitted for post-CA care with highly suspected or confirmed TICA. Clinical and toxicological data were recorded.
Results : We recorded 21 cases of TICA, which represented 48.8% of CA. A single toxic agent was incriminated in 90% of cases. Main causative agents identified in our series were pesticides and betablockers: chloralosed (n = 6), carbamate inhibitor of cholinesterase (n = 5), acebutolol (n = 4) and organophosphate (n = 2). One case of opiates and cocaine poisoning was reported. Median duration of «no flow» was 0 minutes. Mean duration of «low flow» was 13.74±9.15 minutes. An initial shockable rhythm was noted only in three patients. Mortality rate was 76% (16/21). Four of the five survivors had a Cerebral Performance Category Scale (CPC) 1, only one patient survived with a CPC 3. Factors associated with mortality were : the duration of «low flow» (p=0.02) and APACHE II score (p=0.014). APACHE II≥29 was the only independent factor (OR=2.0, 95%CI [1.07;3.71]).
Conclusion : TICA were most frequently provoked by pesticides, mortality was high and was independently predicted by APACHE II score.
Keywords: cardiac arrest, toxic, epidemiology, prognosis

SUMMARY

Introduction : L'arrêt cardiaque (AC) a de nombreuses étiologies et constituent un problème de santé publique, avec une issue fatale dans 90-95% des cas. Les arrêts cardiaques d'origine toxique (ACOT) sont peu décrits dans la littérature et les données nationales sont rares.
Objectifs : Déterminer la fréquence des ACOT dans un centre de référence en toxicologie en Tunisie et en évaluer le pronostic à court terme, et décrire ses aspects cliniques et thérapeutiques.
Méthodes : Le recueil des données était rétrospectif sur une période de huit ans. Ont été inclus les patients admis pour réanimation post-AC avec une origine toxique fortement suspectée ou confirmée. Les données cliniques et toxicologiques ont été enregistrées.
Résultats : Le nombre d'ACOT était de 21, ce qui a représenté 48.8% des AC. Un agent toxique unique a été incriminé dans 90% des cas. Les principaux toxiques identifiés étaient les pesticides et les bétabloquants : le chloralose (n=6), les carbamates inhibiteurs de l'acétylcholinestérase (n=5), l'acébutolol (n=4) et les esters d'organophosphorés (n=2). Un cas d'intoxications aux opiacés et à la cocaïne a été noté. La durée médiane du «no flow» était de 0 minute. La durée moyenne du «low flow» était de 13,74±9,15 minutes. Un rythme choquable a été noté, seulement, chez trois patients. La mortalité était de 76% (16/21). Quatre parmi les cinq survivants avaient un Cerebral Performnace Category Scale (CPC) à 1, un seul patient a survécu avec un CPC 3. Les facteurs liés à la mortalité, était la durée du «low flow» (p à 0,02) et le score APACHE II (p=0,014). Seul un score APACHE II ≥ 29 était un facteur indépendant prédictif de mortalité dans les ACOT (OR=2.0, IC 95% [1.07;3.71]).
Conclusion : Les agents des ACOT les plus fréquents étaient les pesticides. La mortalité était élevée et prédite par le score APACHEII.
Mots clés : arrêt cardiaque, toxique, épidémiologie, pronostic

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INTRODUCTION

Cardiac arrest (CA) is a major public health problem, since it is associated with high mortality, the survival rate is 5% (1, 2) to 10% (3). Almost 50% of survivors will have neurological sequelae hindering resumption of a normal social life (4, 5).

Etiologies of CA are numerous. Toxin-induced cardiac arrests (TICA) are poorly described. A better prognosis has been suggested in the literature with a survival rate up to 26% (6). Scarcity of national data prompted us to carry out this study which aimed to determine the frequency of this type of CA in a Tunisian teaching toxicological intensive care unit (ICU), and to evaluate its prognosis.

METHODS

We carried out a retrospective, monocentric and descriptive study.

Study population

We included all adult patients (≥18 years) admitted between January 2008 and December 2015 for medical care after a CA with successful cardiopulmonary resuscitation (CPR) and highly suspected or confirmed toxic etiology regardless of the location of CA occurrence in an extra hospital or an emergency department.

We did not include patients who presented for a nontoxic CA, patients who presented a CA during their hospital stay as well as pediatric population.

According to the in-hospital outcome, the study population was divided into 2 groups: survivors and deceased patients.

Diagnosis criteria

Toxic etiology was considered highly suspected either when it was reported by relatives or in the presence of a toxidrome evoking the use of toxic substances which identification by specific tests was not technically possible: betablockers (toxidrome after CPR: bradycardia, bradyarrhythmia, large QRS and bronchospasm) and paraphenylenediamine (toxidrome after CPR : head and neck edema, hard muscles, rhabdomyolysis).

It was considered confirmed when a toxicological test was positive.

All patients admitted for medical care after resuscitated nontoxic CA were otherwise identified. This is was not the case for patients who presented a CA during their stay in the ICU.

Definitions

We defined:

-No flow duration as the delay between occurrence of CA and the start of CPR, during this period heart output is zero.

-Low flow duration as the period during which CPR is performed.

Data Collection and parameters of patient evaluation

We recorded demographic, clinical, biological and toxicological data. They were subdivided chronologically into 3 groups; data concerning the occurrence of CA and its conditions, data at arrival to hospital and data during the hospital stay. We applied 2 prognostic scores to assess the disease severity at the admission; Acute Physiology and Chronic Health Evaluation (APACHE II) score (7). And the Simplified Acute Physiology Score (SAPS II) (8). Acute respiratory distress syndrome diagnostic was considered according to Berlin definition (ARDS) (9). The neurological evaluation during ICU stay was based on: Brain stem reflexes and pupillary diameter. Neurological outcome in survivors was evaluated by the cerebral performance category score (CPC) (10). Diagnosis of brain death has not been confirmed by complementary examinations (electroencephalography, angiography).

Statistics

Data were analysed using SPSS software (Version 23.0. Armonk, NY: IBM Corp.), absolute frequencies or percentages were reported for qualitative variables. Means ± standard deviation (SD) for variables with a normal distribution, and if more appropriate, medians and extreme values or [Interquartile range (IQR)], were reported for quantitative ones. Qualitative variables were compared using Pearson's Chi-square and quantitative variables were compared using U-Mann-Whitney test. To identify independent factors associated to letality we used a regression linear model and calculated the adjusted Odds ratio (OR) of identified factors. Statistical significance was considered when $p<0.05$ for all tests.

RESULTS

We recorded 21 patients with TICA over the 8-years study period from a total number of 43 patients admitted to the ICU after a CA, so the proportion of TICA was 48.8%.

Population characteristics

The median age was 24 years with extremes of 19 and 68 years. Females were more frequent with a Sex ratio of 6/15. None of the patients had a history of cardiovascular disease, only one patient had a history of TICA secondary to cocaine overdose. Two patients had psychiatric disease history.

Circumstances of occurrence

TICA occurred at home in 4 patients, during transport in 7 patients and in emergency department (ED) in 10 patients. A witness was present in all cases, he was doctor in 12 cases (57%) or a relative in 9 cases (43%). Intoxication was non accidental, and a suicide attempt was reported by relatives in all cases.

Causative toxic agents

Sixteen patients had a toxic test. One or more toxic agents were identified in all patients who had testing. Toxic tests have not been requested in cases of intoxications with betablockers and paraphenylenediamine. Most patients (n=20) used a single toxic agent while only one patient presented with multi-drug intoxication (table 1). Two patients used another drug concomitantly to the toxic agent: promethazine with Lannate in one case and acetaminophen with chloralose and in the other. One patient had an intoxication with acepromazine a veterinary anxiolytic drug and one patient had an intoxication with paraphenylenediamine which is commercialized for cosmetic purpose.

Table 1. Involved drugs in toxic cardiac arrest

Toxic agent	Number of cases
Chloralose	6
Lannate	5
Acebutolol	4
Organophosphates	2
Acepromazine	1
Benzodiazepine	1
Paraphenylenediamine	1
Opiates, cocaïne, methamphetamine, carbamate, phenothiazine, amitriptyline, imipramine	1

Immediate assistance

“No-flow” duration was noted for 17 patients. Its median was 0 minutes [0-12.5 minutes] with a maximum of 30 minutes. Average duration of “low flow” was 13.74 ± 9.15 minutes.

Electrocardiographic data during CA was recorded in only 4 cases. It consisted in a pulseless ventricular tachycardia (VT) in 2 patients (one was intoxicated with both Lannate and Promethazine and the other by chloralose), ventricular fibrillation (VF) in one case (Acebutolol), and pulseless electrical activity in one case (chloralosed).

Patients with VT or VF received an electrical shock. Adrenaline was administered during CPR, which was applied in almost all patients 20/21 (95%). Average dose was 3 ± 3 mg (maximum dose 9 mg). None of our patients received amiodarone. Semi-molar bicarbonate was administered to 8 patients; it was indicated for a membrane-stabilizing effect due to a beta-blocker poisoning and for prolonged CA in the other cases. Glucagon was used at the dose of 1 mg in a case of beta-blocker poisoning. Isuprenaline was administered to a patient who had beta-blocker poisoning and had a 2nd degree atrioventricular block at recovery from CA.

Medical data and management in the intensive care unit

All patients were already mechanically ventilated intubated at admission, they were all ventilated according to controlled volume mode. The SAPS II average score was 57.7 ± 16.3. Median APACHE II score was 29 [19.5-35,3]. One patient fulfilled criteria of ARDS, his PaO_2/FiO_2 ratio was 68 mmHg. At admission, 10 out of 21 patients (62%) were in shock; a cardiogenic shock in 8 patients (47%) which required adrenaline maintenance doses (median 4 mg [2-32.5 mg]), a vasodilatory shock in one patient intoxicated by chloralosed who received a continuous noradrenaline infusion and a hypovolemic shock, after taking Lannate in one patient who also received a noradrenaline infusion. Lactate average level was 9.19 ± 4.97 mmol/L.

Six patients had acute renal failure. Fourteen patients had hepatic cytolysis. Hyperglycemia was noted in 6 cases and rhabdomyolysis in ten cases.

All patients were sedated and mechanically ventilated for at least the first 24 hours. Median duration of mechanical ventilation was 1 day [1-59]. Brain stem reflexes at admission were abolished in 17 patients (80.9%). Pupillary

status was miosis (n=11), mydriasis (n=7) or medium position (n=3). Hypocapnia was noted in 10 patients with an average arterial blood gas carbon dioxide (CO_2) level of 27.8 ± 8 mmHg. Hypercapnia was noted in 5 patients (23.5%) with an average blood CO_2 level of 63 ± 7mmHg. Normocapnia was targeted by acting on ventilatory parameters. A blood oxygen saturation> 92% was targeted for all patients. Goal was achieved in all cases except for the patient with ARDS.

Therapeutic hypothermia at 36°C was applied only one patient. All others were normothermic.

Seven patients received atropine as a pathophysiological treatment of acute intoxication with cholinesterase inhibitors at the mean cumulative dose of 41.5 ± 17 mg. Isuprenaline was maintained for patient having atrio-ventricular block. Insulin therapy was necessary to maintain euglycemia in 12 patients. Natremia was maintained normal in all patients by balanced daily intake and repeated biological controls.

Non-fatal in-hospital complications

Median duration of hospital stay was 2 days [1; 38], during which the following complications were recorded:

Nine patients developed *aspiration pneumonia*. Only one was bacteriologically documented with isolation of a methicillin-sensitive Staphylococcus aureus.

Four patients developed *ventilator associated pneumonia*, two of which presented two episodes. In total, six episodes were recorded. Main involved germs were noted in table 2.

Five patients presented a *septic shock* secondary to a pulmonary infection in 2 of them and without definite source in the others due to multiple suspected primitive infections (lung and bedsore) and/or non-conclusive bacteriological results.

Eight patients experienced *seizures*. Seizures occurred beyond the first 48 hours for all of them (Table 3). Six patients had a cerebral imaging. Cerebral computed tomography in five patients did not show abnormalities for four of them and revealed a cerebellar herniation for one. Magnetic resonance imaging was performed in two patients; it revealed an ischemic occipital-temporal lesion in one patient and was normal in the other.

During their ICU stay, 2 patients presented stage 2 and 3 *bedsores*.

Table 2. Identified germs in ventilator associated pneumonia

Germs	Number of episodes	Antibiotic Sensitivity
Acinetobacter baumanii	2	Cabapenemase
Klebsielle pneumoniae	2	Sensitive (n=1) -ESBL* (n=1)
Proteus mirabilis	1	Sensitive
Stenotrophomonas maltophilia	1	Sensitive

*ESBL: enlarged spectrum betalactamase

Table 3. Frequency of seizures occurrence according to toxic substances

Toxic	Number of cases of seizure
Lannate	3
Chloralose	1
Organophosphate	1
Acebutolol	1
Acepromazine	1
Opiates, cocaine, methamphetamine, carbamate, phenothiazine, amitriptyline, imipramine	1

Lethality and its associated factors

Lethality rate in our series was 76% (16/21). Four of the five survivors recovered ad integrum (CPC scale at 1) while one patient maintained severe neurological sequelae with a deep sensorimotor deficiency (CPC 3). The common point between survivors was a “no flow” estimated at zero minutes. Cardiac rhythm during CA was not recorded in any of these patients and none of them received an electric shock.

Survivors and deceased groups were comparable concerning demographic characteristics, circumstances of occurrence of CA, the incriminated toxic agent, the duration of “no flow”. Two factors were associated with lethality, namely the duration of “low flow” with a lower in group of survivors: 4.5 ± 4.2 versus 15.89 ± 10,8 minutes (p = 0.02), and APACHE II score whose median was significantly higher in group of deceased patients: 32 [22.5;

3] versus 18 [14.5; 26] (p = 0.014) (table 4). APACHE II score ≥ 29 was an independent factor predictive of TICA mortality (OR =2, IC 95% [1.07;3.71]).

Table 4 : Comparison of Characteristics in Survivors and deceased groups

Characteristic	Survivors (n=5)	Deceased (n=16)	p
Age (years), median [IQR]	24 [22-26]	23[18-41]	0.905
Gender			
-Female (number)	5	10	0.105
Witness	5	16	1
No flow (minutes), median [IQR]	0	5 [0-17.5]	0.75
Low Flow (minutes), mean±SD	4.5 ± 4.2	15.89 ± 10.8	0.02
Epinephrine (mg), mean±SD	1 ± 1.73	4 ± 3.28	0.19
IGS II, mean±SD	46.4 ± 10	62.08 ± 16	0.065
APACHE II, mean±SD	18 [14.5 ; 26]	32 [22.5 ; 3]	0.014
Nature of toxic (number)			0.64
Lannate	2	3	
Organophosphate	0	2	
Chloralose	2	4	
Bétablockers	1	3	
Acepromazine	0	1	
Benzodiazepine	0	1	
Paraphenylenediamine	0	1	
Opiates, cocaïne, methamphetamine, carbamate, phenothiazine, amitriptyline, imipramine.	0	1	

DISCUSSION

In this retrospective study in a reference center we recorded 21 cases of TICA over an 8-years period, representing 48.8% of all patients admitted for medical care after a CA. Females were more represented (sex ratio 6/15). All intoxications were self-deliberated, a single toxic agent was used in 95% of cases. However, 2 patients ingested other drugs without direct cardiovascular toxic effect and a case of multiple intoxication with up to 7 toxic agents was observed. Main toxic agents identified in our series were pesticides; among them chloralosed in 6 patients, carbamate inhibitor of cholinesterase in 5 and organophosphate in 2, followed by betablockers (4 cases). One case of Opiates' and cocaine poisoning was observed in a drug-abuse patient. Eight patients were in shock when admitted to the ICU, infectious complications and seizures were common during the hospital stay. The lethality was high; 76% and among the 5 survivors, 4 were CPC 1 and one patient had severe neurological sequelae (CPC 3). Even if we did not observe a statistically significant difference, the common point in all survivors was a no-flow duration= 0. Low-flow duration was significantly lower in survivors' group (p = 0.02); APACHE II ≥ 29 was the only independent predictor of lethality (OR =2, IC 95% [1.07;3.71]).

Epidemiological data

A retrospective American study, conducted in a teaching center of cardiac resuscitation, reported a 12% proportion of TICAs among resuscitated CA (11). In this study, mean age was 47 ± 13.6 years, higher than mean age of our population, and men were more involved than females. A French prospective multicenter study (12) found that TICA accounted for 2-4% of pre-hospital CA and the median age was 46 [35-58], which was lower than median age in non-toxic CAs (71 [58-82]), a male predominance was also found in this registry. The much higher proportion of TICAs in our study was explained by the specialized character of our center (reference center in toxicology in Tunisia).

Initial management

According to Wissenberg et al (13), the presence of a witness improved survival rate. In a German study (14), duration of "no-flow" was reduced when a witness was present and after training the paramedics staff for resuscitation of intra-hospital CAs (11). Median "no-flow" duration according to the official French electronic registry (12) was 9 minutes [1-15], it was longer than that found in our study (0 minutes [0; 12.5]), this result could be explained by the presence of a witness in all our cases who was a doctor in more than half of them (57%).

Median duration of "low flow" was 21 minutes [10-33] according to French electronic registry (12). In our study, average duration of "low flow" was 13.74 ± 9.15 minutes. It was significantly lower in survivors' group: 4.5 ± 4.2 minutes versus 15.89 ± 10.8 minutes in deceased group (p= 0.02). Probably this parameter: low-flow duration was itself influenced by no-flow duration.

Causative Toxic agents

An American study found that the main toxic agents involved were : cocaine, benzodiazepines and opiates (11). French studies (15-17), reported benzodiazepines, tricyclic antidepressants and serotonin reuptake inhibitors as main involved agents. Pesticides were frequently involved in developing countries (12), they were by far the more frequent toxic agents incriminated in our series followed by beta-blockers. We noted only one case of opioid and cocaine poisoning, and we reported two rarely described toxic agents, namely acepromazine and paraphenylenediamine. Acepromazine is used exclusively in veterinary medicine as anxiolytic (18, 19). Its toxicity in humans was poorly described (20). It caused inhibition of central nervous system with respiratory depression and hypotension, it had no cardiac toxicity in humans. Considering the clinical findings, the presumed mechanism of CA in our case was also respiratory depression, and vasoplegia. Paraphenylenediamine is used in a cosmetic purpose for its tinctorial properties and was more frequently used for suicidal purposes in developing countries (21). Its ingestion induced a serious intoxication: cervical, facial and tongue edema inducing an asphyxia syndrome, with a rhabdomyolysis and acute renal failure (22). Heart muscle could also be affected leading to toxic myocarditis (23, 24). In our case, mechanism of CA was airway obstruction by a local edema.

Management of TICAs considering their specificities

TICAs are often associated with a non-shockable rhythm (11, 12). Modisett et al. who reported that only 38% of TICAs had an electrical shock (11). In our study, rhythm during CA was noted in only 19% of cases (4/21). Only three patients had had an electrical shock.

Toxicodynamics and toxicokinetics principles, led us to consider some specific measures in resuscitation of TICA (25):

- Antidotes if available (e.g. digoxin, acetylcholinesterase inhibitors)

- Sodium bicarbonate for drugs with membrane-stabilizing effect like tricyclic antidepressants, betablockers and chloroquine.

- High doses of insulin and glucose for betablockers and calcium channel blockers. Glucagon has also been prescribed in such cases but currently it is less used.

- Calcium in calcium channel blocker poisoning

- Lipid emulsions for lipophilic substances at a dose of 1.5 ml/kg bolus of a 20% lipid emulsion followed by a continuous infusion of 0.25-0.5ml/kg/min.

But clinical effectiveness of these treatments is still debated and based on low levels of evidence, in fact, conducting randomized clinical trials is difficult, given rarity of these cases (25). In our series, semi-molar bicarbonate was administered in one patient who presented a membrane stabilizing effect secondary to beta-blocker poisoning. Glucagon was also used at the dose of 1 mg in one patient with acebutolol poisoning. One patient received isuprenaline for a conductive disorder. Atropine was used at recovery in cases of acetylcholinesterase inhibitors. Effect of these specific treatments on prognosis could not be assessed because of their limited use in our series (n = 3). Therapeutic hypothermia was applied in one patient,

Other specific treatments were proposed in the literature especially hemodialysis, cardiac pacing, and extracorporeal membrane oxygenation type circulatory assistance (11, 12). In fact, TICA patients could represent good candidates for extracorporeal membrane oxygenation due to reversibility of their state. Circulatory assistance allowed survival of 80% of 25 cases of intoxication with antiarrhythmics and other cardiotoxic substances (26). Unfortunately, these techniques, remain insufficiently used even in developed countries (12).

Patients outcome

Some studies suggested that TICAs had a better vital and neurologic prognosis compared to CA secondary to other etiologies (25, 27). Authors found that even after prolonged resuscitation, TICA patients survived with a completely normal neurological state (28, 29). This could be explained by The low median age in this population who usually did not have pre-existing co-morbidities, it can also be explained by neuroprotective effect of certain toxic substances involved in TICAs (benzodiazepines, barbiturates) (25).Thus it has been suggested to prolong CPR even up to four hours, and to use circulatory assistance until toxic elimination (25).

In our study, lethality was 76% (16/21), low flow ($p = 0.02$) and APACHE II score ($p = 0.014$) were associated to lethality. This high mortality rate could be explained by the harmfulness of involved molecules (pesticides, betablockers) and limited use of specific therapies and lack of circulatory assistance use.

Limits of the study

Retrospective character and the limited number of cases did not allow us an exhaustive and reliable conclusion about the predictors of mortality in this population. Our objectives were, however, mainly descriptive.

CONCLUSION

TICA is poorly described in literature. Some studies suggest that it is had better prognosis given the particularity of involved population and the potential reversibility of their state (27).

In our study, we found that prognosis of TICAs was overall poor. Specific management measures described in the literature are not supported by enough evidence levels and were of limited availability and use in our series. These measures remain to develop ideally along with prospective multicentric randomized trials to better assess their security and usefulness. It is also important to not omit the important role of healthcare professionals and also every potential witness (so the large population) and the necessity to improve in them the awareness about this problem and mastering of resuscitation techniques.

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