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Clinical paper

Early recurrent arrhythmias after out-of-hospital cardiac arrest associated with obstructive coronary artery disease: Analysis of the PROCAT registry

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Abstract

Objective: After out-of-hospital cardiac arrest (OHCA) associated with obstructive coronary artery disease (CAD), the risk of recurrence during the early period is unclear and the indication for anti-arrhythmic treatment is debated. We assessed the incidence and predisposing factors for severe cardiac arrhythmias in this population.

Design: Retrospective study in a cardiac arrest center.

Settings: The primary endpoint was the occurrence of major cardiac arrhythmias from hospital admission to intensive care unit (ICU) discharge in patients admitted after an OHCA associated with obstructive CAD. A major arrhythmia was defined as any arrhythmic event (auricular or ventricular) associated with cardiac arrest recurrence and/or severe arterial hypotension. Secondary outcomes were time from ICU admission to arrhythmia occurrence and all-cause in-ICU mortality. Risk factors for recurrence of a major arrhythmia were assessed using multivariate analysis.

Patients: We included all consecutive OHCA patients resuscitated from ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) as initial rhythm associated with obstructive CAD, and who had a successful primary percutaneous coronary intervention.

Intervention: None.

Measurements and main results: Among 256 patients, a major arrhythmia occurred in 29 (11.3%), within the first 24 h in 79.3% of cases and were mostly VF (44.8%). Mortality rate was significantly increased in patients with major arrhythmia recurrence (69% vs 41%; p = 0.006). Factor significantly associated with recurrence of severe arrhythmia was male gender (OR 0.32 [0.12–0.92]; p = 0.034). Treatment with prophylactic anti-arrhythmic in the ICU was not associated with a change in the risk of recurrence (OR 0.85 [0.21–3.65], p = 0.82).

Abbreviations: AA, anti-arrhythmic; ACS, acute coronary syndrome; AMI, acute myocardial infarction; BLS, basic life support; CA, cardiac arrest; CAD, coronary artery disease; ECG, electrocardiographic; ICU, intensive care unit; LVEF, left ventricular ejection fraction; OHCA, out of hospital cardiac arrest; OR, odds ratio; PCI, percutaneous coronary intervention; PROCAT, Parisian region out of hospital cardiac arrest; ROSC, return of spontaneous circulation; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

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Conclusion: An early recurrence of major arrhythmia was observed in more than 10% of post-cardiac arrest patients. These events happened mostly within the first 24 h. The interest of prophylactic anti-arrhythmic treatment remains to be evaluated in this population.
Keywords: Cardiac arrest, Acute coronary syndrome, Arrhythmia recurrence, Prophylaxis anti arrhythmic treatment

Introduction

Sudden cardiac death is an important public health issue, with an estimated incidence attributable to ventricular fibrillation (VF) among adults in Europe of 14 per 100,000 person years.[1] Although survival is higher in these VF patients as compared with other causes of cardiac arrest (CA), many of these patients will die during the post-resuscitation period.[2]

While early recurrence of VF after return of spontaneous circulation (ROSC) and during transportation is frequent[3] and is subjected to international recommendations,[4] data regarding incidence and management of recurrent arrhythmia in the next hours and days are scarce. It is unknown if early coronary reperfusion in CA due to an acute coronary syndrome (ACS) is sufficient to prevent from recurrence of arrhythmia. Contrary to acute myocardial infarction (AMI), in which this has been extensively evaluated,[5,6] indication for prophylactic anti-arrhythmic (AA) treatments during the post-resuscitation period is unclear.

In the present study, we hypothesized that arrhythmia recurrences might be a frequent event and that it would be useful to identify risk factors. Therefore, we aimed to evaluate the incidence of in-ICU severe arrhythmia in patients resuscitated from a VF or pulseless ventricular tachycardia (VT) associated with obstructive coronary artery disease (CAD) and who were treated with early percutaneous coronary intervention (PCI). We also aimed to identify risk factors for developing arrhythmia during the post-resuscitation period.

Materials and methods

Study setting

We performed a single center study between January 2007 and December 2016 in the 24-bed medical ICU at Cochin University Hospital (Paris, France). We included all consecutive patients with an initial VF/VT associated with obstructive CAD and who were successfully treated with early percutaneous coronary intervention (PCI). Patients with reperfusion failure and patients who died before ICU admission were not included in the analysis.

Patients' data were prospectively entered in the PROCAT (Parisian Region Out of Hospital Cardiac ArresT) electronic registry database that was previously described,[7] according to Utstein style.[8] The following information was recorded prospectively for each patient: demographic data, clinical parameters, cardiac arrest location, initial cardiac rhythm, time from collapse to basic life support (BLS) and time from BLS to sustainable return of spontaneous circulation (ROSC), BLS provided by witness, CPR management, coronary angiogram data, temperature management over the first 48 h, use of prophylactic anti-arrhythmic (AA) treatments, need for epinephrine or dobutamine, occurrence and type of severe arrhythmia and ICU mortality.

The Cochin CA registry (PROCAT) was approved by our local ethics committee (Commission d'Ethique de la Société de Réanimation de Langue Française ; and Comite Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé #CNIL_91239, #CCTIRS_12-336, #CE_SRLF_11–353). According to French law, our institutional review board waived the need for written informed consent.

Post cardiac arrest management

As part of our local policy,[9] immediate coronary angiogram was considered in all patients with a possible cardiac cause of arrest, regardless to electrocardiographic changes. After resuscitation, patients were admitted directly to the catheterization laboratory, before intensive care admission, and a PCI was attempted if a significant acute coronary lesion possibly responsible for the cardiac arrest was identified. A coronary lesion was considered as a culprit lesion if unstable and resulting in more than a 50% reduction in luminal diameter by visual estimation.[7] Patients with a TIMI 3 score flow were considered to have a successful revascularization, as compared with all other patients with a TIMI score flow rated 0, 1 or 2.[10] Targeted temperature management using external cooling and targeting 33 °C was started as soon as possible and was maintained during 24 h. At time of ICU admission, the decision to introduce any prophylactic AA treatment was left to the discretion of the physician in charge. Post-resuscitation shock was defined as the need for continuous epinephrine, norepinephrine or dobutamine infusion to maintain mean arterial pressure above 60 mmHg for more than 6 h despite adequate fluid loading.

Outcome assessment

The primary endpoint was the occurrence of major arrhythmia during the ICU stay. Arrhythmia could be either auricular or ventricular but had to provoke either a cardiac arrest recurrence or a severe arterial hypotension requiring catecholamine introduction (or an increase if previously used). In addition, a sensitivity analysis was performed by restricting the primary outcome to severe ventricular arrhythmia recurrences (VF, pulseless VT).

Secondary outcomes were time from ICU admission to arrhythmia occurrence, clinical consequence, all causes mortality and managemen of this arrhythmia.

Statistics

Descriptive statistics were reported as median (with interquartile range) and frequency (percentage) for continuous and categorical variables respectively. Characteristics of the 2 subgroups (with and without major arrhythmia occurrence) were compared using the Chi-square test or the Fisher's exact test.

Variables associated with the occurrence of a major arrhythmia with a p-value < 0.20 in the univariate test were included in the multivariate analysis. The logistic regression predicting the occurrence of a major arrhythmia integrates the following variables: age, sex, arterial hypertension, smoking, place of the CA, number of defibrillation attempts, administration of prophylactic AA drugs and

initial lactate value. In a sensitivity analysis, we re-runed the model restricting the endpoint to severe ventricular arrhythmias.

All statistical tests were two-sided using a type I error of 0.05. Analyses were performed using STATA/SE 14.2 (college station, TX, USA).

Results

Between January 2007 and December 2016, 392 consecutive patients had an immediate coronary angiogram performed as soon as possible after an OHCA with an initially shockable rhythm. Among them, 256 patients (65.3%) with significant acute coronary lesion were treated with successful PCI and were then transported in the ICU. Patients with no significant coronary artery lesion, patients with an ACS not revascularized and patients who died before ICU admission were not retained in the analysis (Fig. 1).

Patients

Baseline characteristics of the whole population are described in Table 1. Patients were mostly male with a median age of 59 y.o. Cardiac arrest was witnessed in 97% of cases and bystanders provided CPR in 72%. An automated external defibrillation delivered at least two shocks in 117 (46%) patients and 104 (41%) patients received amiodarone during the CPR sequence. Only 40% of patients had an ST-segment elevation on post-resuscitation ECG and a quarter of them had a triple-vessel coronary disease (Table 2). More than 90% of the patients had a successful PCI, as assessed by a TIMI 3 score (Thrombolysis In Myocardial Infarction [10]) flow. Therapeutic hypothermia was performed in 90% of patients over the first 24 h. A post-resuscitation shock occurred in 133 patients (52%). There were significantly more patients with a low left ventricular dysfunction (LVEF < 50%) in the major arrhythmia recurrence group as compared with controls (83% vs 64%; p = 0.03).

Prevalence and characteristics of major arrhythmia recurrence

A major arrhythmia was observed in 29 (11.3%) patients. As compared with controls, there were significantly more smoking patients (70% versus 89%; p = 0.04, respectively) and cardiac arrest occurred less frequently in a public place in the major arrhythmia group (51% versus 24%; p = 0.006). During the first 48 h in ICU, there was no significant difference regarding the median lowest temperature between the two groups. Regarding the management of the post-resuscitation shock, dobutamine and/or epinephrine were used in the same proportion of patients in the 2 groups (55% vs 66%, p = 0.33).

In the whole population, all cause ICU mortality was 44.5% (n = 114) and 3 patients (1%) died of a major arrhythmia recurrence. Mortality was significantly higher in the major arrhythmia recurrence group (69% vs 41%; p = 0.006).

In the group of patients with recurrence of a major arrhythmia, this arrhythmia was a VF in 13 (44.8%) patients, a non-perfusing VT in 10 (34.5%), an atrial fibrillation in 4 (13.8%) and a polymorphic VT in 2 (6.8%). Median time from ICU admission to major arrhythmia occurrence was 16 h (0.33–336). In 79.3% of cases, major arrhythmia occurred within the first 24 h after the ROSC. Regarding potential causes of arrhythmia, a stent thrombosis was confirmed in 4 cases (13.8%) and hypokalemia in 2 cases (6.9%). Apart from the initial ACS, no additional cause of arrhythmia was identified in the other patients.

Prophylactic anti-arrhythmic treatment

In the whole population, 36 (14%) patients received a prophylactic AA treatment at admission in the ICU (which was amiodarone in all

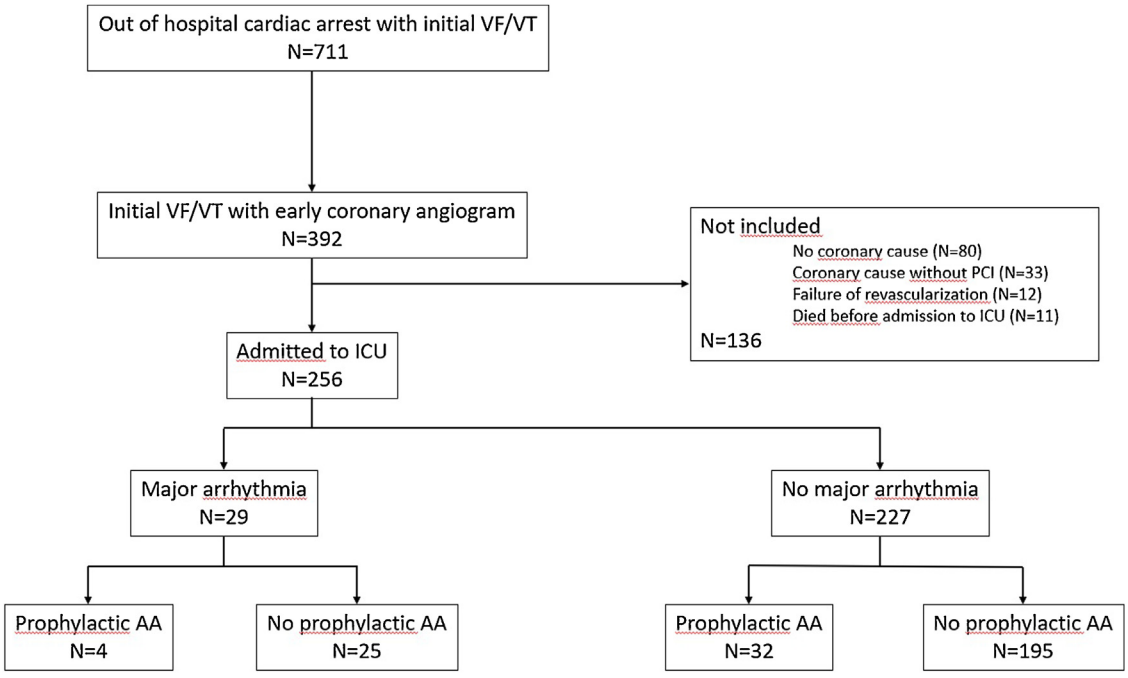

Fig. 1 – Flow chart.

***Abbreviations*: VF: ventricular fibrillation, VT: ventricular fibrillation, ACS: acute coronary syndrome, ICU: intensive care unit, AA: anti arrhythmic.**

Table 1 – Baseline characteristics.

	Overall N = 256	No major arrhythmia N = 227	Major arrhythmia N = 29	p-Value
Age >59 years; n(%)	130 (51)	114 (50)	16(55)	0.62
Male gender; n(%)	205 (80)	185 (82)	20 (69)	0.14
Hypertension; n(%)	96 (39)	81 (37)	15 (53)	0.09
Diabetes; n(%)	39 (16)	35 (16)	4 (14)	1
Dyslipidemia; n(%)	83 (34)	74 (34)	9 (32)	0.85
Smoking; n(%)	170 (72)	146 (70)	24 (89)	0.04
Coronary disease; n(%)	35(14)	32 (14)	3 (11)	0.78
Public place; n(%)	124 (48)	117 (51)	7 (24)	0.006
Witnessed CA; n(%)	246 (97)	218 (97)	28 (97)	1
Bystander CPR; n(%)	180 (72)	158 (71)	22 (76)	0.62
Number of defibrillation>2; n(%)	117 (46)	101 (45)	16 (57)	0.23
Time between collapse and ROSC > 20 min; n(%)	117 (48)	102 (47)	15 (56)	0.40
Epinephrine>1 mg during CPR; n(%)	106 (43)	90 (41)	16 (59)	0.08
Amiodarone during CPR; n(%)	104 (41)	87 (39)	17 (59)	0.07
Prophylactic AA treatment in the ICU; n(%)	36 (14)	32 (14)	4 (14)	1
Lactate>3.65 mmol/L; n(%)	111(65)	94 (48)	17 (65)	0.14
Post-resuscitation hemodynamic shock; n(%)	133 (52)	116 (51)	17 (59)	0.56
Dobutamine and/or epinephrine in ICU; n(%)	144 (56)	125 (55)	19 (66)	0.33
Lowest temperature during first 24 h; average °C (SD)	32.71 (1.23)	32.75 (1.17)	32.35 (1.64)	0.12
Mortality rate (all cause); n(%)	114 (45)	94 (41)	20 (69)	0.006

Abbreviations: CA = cardiac arrest; CPR = cardio-pulmonary resuscitation; AA = anti-arrhythmic; ICU = intensive care unit; ECG = electrocardiogram; PCI = percutaneous coronary intervention; LVEF = left ventricular ejection fraction.

Table 2 – Characteristics of ECG and coronary angiogram.

	Overall N = 256	No major arrhythmia N = 227	Major arrhythmia N = 29	p-Value
ST-segment elevation on post-resuscitation ECG; n (%)	100 (39)	85 (37)	15 (52)	0.15
Coronary artery lesions; n (%)				0.20
One-vessel disease	115 (45)	105 (46)	10 (34)	
Double-vessel disease	78 (30)	70 (31)	8 (28)	
Triple-vessel disease	63 (25)	52 (23)	11 (38)	
TIMI score; n (%)				0.048
TIMI 3	233 (91)	209 (92)	24 (83)	
TIMI 2	20 (8)	15 (7)	5 (17)	
LVEF at ICU admission; n (%)				0.03
<50%	170 (66)	146 (64)	24 (83)	
≥50%	69 (27)	66 (29)	3 (10)	

Abbreviations: ECG = electrocardiography; TIMI = thrombolysis in myocardial infarction; LVEF = left ventricular ejection fraction; ICU = intensive care unit.

cases), with no significant difference between the 2 groups (4/29 in the major arrhythmia group vs 32/227 in controls; p = 1) (Table 1).

Management of recurrent arrhythmia

For management of recurrent severe arrhythmia, 17 of 29 (58.6%) patients received at least one defibrillation. Other therapies administered were amiodarone, magnesium bolus, lidocaine and potassium infusion for 16 (55.2%), 8 (27.6%), 3 (10.3%) and 3 (10.3%) patients respectively.

Risk factors of major arrhythmia

In multivariate analysis, factor significantly associated with recurrence of severe arrhythmia was male gender (OR 0.32 [0.12–0.92]; p = 0.034) (Table 3). Prophylactic AA treatment was not associated with a lesser risk of arrhythmia recurrence (OR 0.85 (0.21–3.65), p = 0.82). These results were not modified by performing a sensitivity analysis using only serious ventricular arrhythmia recurrences as the primary endpoint (Supplemental Table 1).

Discussion

The present study aimed to evaluate the prevalence and risk factors associated with major arrhythmia recurrence in patients resuscitated from a cardiac arrest associated with obstructive CAD. An early recurrence of major arrhythmia was observed in more than 10% of post-cardiac arrest patients. These events happened mostly within the first 24 h.

The cause of ventricular arrhythmia during and after acute myocardial ischemia is incompletely understood but is supposed to result from both ischemia-induced electrophysiological changes and genetic factors.[11] Early coronary revascularization may decrease the incidence of recurrent arrhythmia due to ischemic lesions, but persistent ischemia-reperfusion injuries may increase the risk.

Table 3 – Factors associated with major arrhythmia (auricular or ventricular) recurrence in multivariate analysis.

	OR	[95% Conf.	Interval]	p-Value
Age >59 years	2.27	0.81	6.37	0.12
Male gender	0.32	0.12	0.92	0.034
Number of defibrillation attempts >2	1.57	0.54	4.53	0.4
Epinephrine>1 mg during CPR	1.12	0.35	3.56	0.85
Amiodarone during CPR	2.19	0.74	6.15	0.16
Prophylactic AA treatment in the ICU	0.85	0.21	3.65	0.82
Lactate>3.65 mmol/L	1.41	0.45	4.39	0.56
LVEF ≥ 50% at admission	0.42	0.11	1.43	0.19
TIMI score 3	0.59	0.16	2.14	0.42

Abbreviations: CPR = cardio-pulmonary resuscitation; AA = anti-arrhythmic; ICU = intensive care unit; LVEF = left ventricular ejection fraction; TIMI = thrombolysis in myocardial infarction.

Moreover, reperfusion by percutaneous coronary intervention can be incomplete[10] or can leave distal ischemic lesions not accessible to angioplasty (no reflow).[12] In cardiac arrest patients, very early recurrence of VF during advanced life support is a well-known event. During pre-hospital care, just after resuscitation, around 75% of patients with VF as initial rhythm will develop at least one recurrence of VF (3,13). It has been shown that these re-fibrillation events are negatively associated with survival[13] and neurological recovery.[14] However, data regarding rhythmic complications that may occur later, during the ICU stay, are scarce. Incidence of rhythmic complications has mostly been studied in patients who presented an ACS without CA. For example, Ohlow et al [15] reported an incidence of malignant ventricular arrhythmia (VF or non-perfusing VT) of 4.7% in patients hospitalized for STEMI. In this cohort, 99% of the patients had undergone a successful PCI. Examining the timing, 60% of these malignant ventricular events occurred within the first 24 h and 92% within the first 48 h after hospital admission. On the other hand, in a 293 non-STEMI cohort with successful revascularization, no patient presented serious arrhythmia recurrence (VF, VT, asystole).[16] The results of our study suggest a clinically significant incidence of 11.3% of arrhythmia recurrences in our population of successfully revascularized patients. This incidence is higher than what is commonly reported in patients with of acute myocardial infarction.[15,17] This is plausible result since our patients have already presented a severe arrhythmia and a cardiac arrest and are therefore more likely to be at risk of recurrence. In addition, we decided that it was clinically relevant to consider atrial fibrillation requiring catecholamine as a severe arrhythmia. On the other hand, this incidence is quite low as compared with the immediate post-cardiac arrest period and transportation,[3] suggesting that the risk decreased over time. Another explanation is the potential benefit of coronary revascularization, as previously discussed.

We also found that 80% of major arrhythmia events occurred within the first 24 h after ICU admission. This result is consistent with previous studies examining patients with acute myocardial infarction.[15] This timing suggests that future prospective trials aiming to test the potential prophylactic benefit of AA should be done during the first hours of post cardiac arrest care. Importantly, among the 29 patients who had a major arrhythmia recurrence, only 4 had an obvious cause (stent thrombosis in all cases) for which a prophylactic AA treatment would possibly have no effect.

We have collected data on left ventricular systolic function at the admission because it is known that a low left ventricular dysfunction is associated with an increased risk for ventricular fibrillation in ischemic heart disease.[18] Our results are consistent since there was a greater proportion of patients with left ventricular dysfunction at admission in the major arrhythmia recurrence group. However, we did not show any association between left ventricular dysfunction and recurrence of major arrhythmia.

Dumas and al. showed that successful immediate percutaneous intervention was associated with improved hospital survival in patient with OHCA with no obvious extra-cardiac cause of arrest (7). In our study, there was a higher proportion of partial revascularization in the major arrhythmia group but no association between the degree of revascularization and the recurrence of arrhythmia was found in the multivariate analysis. However, the number of patients with a partially successful revascularization was too small to draw any firm conclusion.

No AA treatment has shown any effective prophylactic effect in patients resuscitated after CA. Some studies have highlighted the benefice of amiodarone or lidocaine in the prevention of rhythm disorder after acute myocardial infarction, but outside the context of cardiac arrest.[19–25] Only β blockers are associated with a decrease of mortality after AMI, not only because of their anti-arrhythmic effect.[26] In the specific context of post-cardiac arrest care, only one retrospective study evaluated the benefice of prophylactic lidocaine treatment after a successful defibrillation in a large cohort of patients included between 1992 and 2008.[27] In this study, the prevalence of re-arrests due to shockable arrhythmias was 21.8%. This high incidence may be explained by the fact that patients were included just after the first ROSC, before hospital admission, and especially before coronary revascularization. Regarding prophylactic anti arrhythmic treatment, Kudenchuk et al. reported a lower incidence of recurrent cardiac arrest resulting from shockable arrhythmias in prophylactic lidocaine group as compared with placebo (22.8% vs 38.5%, $p < 0.0001$). Nevertheless there is no firm recommendation about prophylactic use of antiarrhythmic drugs after ROSC in this population.[4] In brief, our results did not suggest a benefit in giving AA during the first days after a resuscitated VF, but our study was underpowered and further prospective research is required to explore this aspect.

The other clinically relevant result is the large difference in mortality rate between the two groups. Patients with major arrhythmia recurrence disorders had a significantly higher mortality rate than the expected mortality following a resuscitated CA with initial shockable rhythm.[28] This mortality rate was nearly 70% and reflects the severity of these patients. This is probably not solely due to the recurrence of major arrhythmia, since this recurrence is possibly a marker of severity associated with a more pejorative prognosis.

We acknowledge several limitations. First, some factors potentially responsible of major arrhythmia recurrence may have been missed. For example, patients who died from a new arrhythmia did not all have a new angiography to detect a potential stent thrombosis. The other confounding factor is the targeted temperature control since therapeutic hypothermia was performed in 90% of patients, a treatment that may provoke arrhythmia in this setting.[29] However, this bias was limited as the average of the minimum temperature during cooling was comparable between groups. In addition, the absence of a statistical link between major arrhythmia recurrence and the administration of prophylactic AA treatment is probably unreliable as this study was not designed to address this issue. The decision of AA treatment may simply reflect a higher perceived severity, based on arrhythmia recurrences during transportation or coronary angiogram. The small size of the prophylactic AA group leads to a lack of significant statistical power precluding any firm conclusion. Moreover, the purely descriptive design and the low number of patients who received prophylaxis preclude from any definitive conclusion regarding AA effect. Finally, the present study was performed in specific population of OHCA patients and results cannot be extrapolated to other populations. Indeed, in order to obtain a homogeneous population, we included only successful revascularization patients and we didn't use any control patients. As a consequence, our study is mainly descriptive and we cannot draw any firm conclusion regarding a protective effect of revascularization against early arrhythmic recurrences.

To conclude, recurrence of major arrhythmia is a frequent complication during the post resuscitation period, occurring mostly during the first 24 h. Even if we did not find any association between prophylactic anti-arrhythmic treatment and risk of major arrhythmia recurrence, further research is required to clarify this point.'

Disclosures

The authors have reported that they have no relationships relevant to the contents of this manuscript to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.05.034.

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