VIA MEDICA

ORIGINAL AND CLINICAL ARTICLES

Anaesthesiology Intensive Therapy
2015, vol. 47, no 4, 309–314
ISSN 1642–5758
10.5603/AIT.a2015.0040
www.ait.viamedica.pl

Epidemiology of new-onset paroxysmal atrial fibrillation in the General Intensive Care Unit population and after discharge from ICU. A retrospective epidemiological study

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Abstract

Background: Evidence of various cardiac arrhythmias in septic patients has been demonstrated by multiple clinical reports and observations. Most cardiac arrhythmias in sepsis are new-onset and may be related to sepsis-induced myocardial dysfunction. We propose to investigate and analyze data of new-onset paroxysmal atrial fibrillation (AF) in a critically ill septic population.

Methods: This is a retrospective epidemiologic study. We collected clinical data from two hundred septic patients who developed a new episode of atrial fibrillation during their hospitalization in General Intensive Care Unit (GICU) between January 2007 and June 2013.

Results: Of these 200 septic patients, 81 septic patients developed a new episode of AF and included in the present study. Thirty-seven patients had no past medical history of atrial fibrillation (AF) or antiarrhythmic therapy (new episode of atrial fibrillation, Group 1) and 44 had previously known episodes of atrial fibrillation and were prescribed antiarrhythmic therapy at home (Group 2). Group 2 patients had longer duration of recurrent episodes of atrial fibrillation compared to patients in Group 1 (11.07 ± 8.7 vs. 7.4 ± 6.1 days; $P = 0.013$). The overall ICU and in-hospital mortality rate was similar in both study groups. There was no significant difference in new stroke and pulmonary embolism (PE) between both study groups ($P > 0.05$).

Conclusion: In the present study we demonstrated no difference in morbidity and mortality rate in-ICU and after discharge between septic patients who had previous AF episodes and patients who had no previous past medical history of any cardiac arrhythmias.

Key words: cardiac arrhythmias, new-onset atrial fibrillation; intensive care, sepsis

Anaesthesiology Intensive Therapy 2015, vol. 47, no 4, 309–314

Sepsis is one of the most important causes of morbidity and mortality in critically ill patients worldwide [1–3]. Progressive cardiovascular deterioration plays a central role in the pathogenesis of sepsis [4–7]. Evidence of various cardiac arrhythmias in septic patients has been demonstrated by multiple clinical reports and observations [8–11]. Most cardiac arrhythmias in sepsis are new-onset and may be related to sepsis-induced myocardial dysfunction, autonomic dysfunction and, most likely also, by impairment and involvement of the cardiac conduction system [9–13]. However, abnormalities of the cardiac conduction system in sepsis have not been well described so far [6]. Both sepsis-induced myocardial dysfunction and sepsis-induced cardiac arrhythmias are related to high intensive care unit (ICU) mortality and increased risk of acute stroke [11, 14, 15]. Subsequently, optimal management with the goal of restoring normal cardiac rhythm and function (antiarrhythmic drugs, inotropic agents, mechanical ventilation etc.) is needed.

The clinical significance of recurrent acute atrial fibrillation (AF) in septic patients with preexisting cardiac comor-

bidities, which can be complicated and triggered by severe systemic inflammatory reaction [9–11] is poorly understood. Some authors [16] have shown a higher frequency of recurrent AF episodes in patients with preexisting cardiac arrhythmias than in patients with unknown past cardiac history during sepsis. One might argue that the prognostic impact of previously known cardiac arrhythmias, as a sign of chronic underlying cardiovascular disease, is worst in the septic population. However, no studies focusing on septic patients' outcome after recurrent AFs with underlying cardiac disease have been done yet.

We investigate and analyzed data and clinical outcome of new-onset paroxysmal atrial fibrillation in a critically ill septic population with unknown (Group 1) and preexisting medical history of atrial fibrillation (Group 2), treated with antiarrhythmic therapy while hospitalized in our General ICU (GICU) and after the discharge from hospital during the last 6 years.

METHODS

The Human Research and Ethics Committee at Soroka Medical Center in Beer-Sheva, Israel approved this study (RN: SOR-0043-14). We collected clinical data from all cases of septic patients who developed a new episode of atrial fibrillation during their hospitalization in General Intensive Care Unit, Soroka Medical Center between January 2007 and June 2013. In this study, all clinical data was extracted from the MetaVision® Clinical Information System for ICUs (*i*MD*soft*®, Israel) and the *OFEK* Electronic Data system (in-hospital medical record electronic system). This is an observational, retrospective study performed in a university teaching hospital.

INCLUSION CRITERIA

All critically ill septic persons who developed an episode of paroxysmal atrial fibrillation during the ICU stay and had documented sinus rhythm before admission to the ICU.

EXCLUSION CRITERIA

Critically ill septic patients who had persistent episodes of paroxysmal atrial fibrillation and patients who had stayed in the ICU less than 48 hours were excluded from the present study.

VARIABLES, MEASURES, PRIMARY AND SECONDARY OUTCOME

Data collected includes the demographic data, cause of sepsis on admission, APACHE-II (Acute Physiology and Chronic Health Evaluation II) and SOFA (The Sequential Organ Failure Assessment score) scores, patients' cardiac comorbidities (myocardial infarction (MI) in the past, chronic AF, cardiomyopathy) and length of ICU stay, epidemiologic data of new episode of atrial fibrillation (total duration of arrhythmia, time of incident, type of antiarrhythmic therapy); and laboratory data (phosphate, calcium, magnesium, potassium, glucose blood levels; urea, creatinine blood levels; hemoglobin, platelets, white blood cell count, pH arterial blood, results of microbiological studies). All laboratory data was collected during the new and recurrent AF episode within ICU stay. Moreover, in-ICU and in-hospital mortality rates were collected. The primary outcome endpoint of the present study was the ICU mortality rate while secondary outcomes were complications of new arrhythmic episode (incidence of new stroke (CVA) and pulmonary embolism (PE)) during and after ICU stay.

STATISTICAL ANALYSIS

Data summaries were performed using SPSS v. 17 (SPSS, Chicago, USA). Data collected in this study were summarized using frequency tables, summary statistics, confidence intervals, and *P*-values as appropriate. For continuous variables with non- normal distribution, comparisons were evaluated for significance with the use of the Wilcoxon rank-sum test. For categorical variables, proportions were compared using Fisher's exact test or $\chi 2$ as appropriate. Continuous variables were analyzed with a Student's *t*-test or the Wilcoxon rank sum test, depending on the validity of the normality assumption. A two-tailed P-value < 0.05 was considered to be significant.

RESULTS

In total, 200 septic critically ill patients were hospitalized in the GICU over the above-mentioned six-year period. Of these, 81 septic patients with an atrial fibrillation episode were included in the present study (Table 1). Thirty-seven patients had no past medical history of atrial fibrillation or antiarrhythmic therapy (new episode of atrial fibrillation, Group 1, see Table 1) and 44 had previously known episodes of atrial fibrillation and were prescribed antiarrhythmic therapy at home (recurrent episode of atrial fibrillation, Group 2, Table 1). Demographic data showed an older age of Group 2 patients, $P = 0.04$; Table 1). There was a higher incidence of line and wound sepsis in Group 1 patients compared to a higher incidence of intrabdominal sepsis in Group 2 ($P < 0.05$,Table 2). There was no significant difference in length of ICU and hospital stay, APACHE II and SOFA scores and continuous renal replacement therapy (CRRT) requirements.

The overall ICU and in-hospital mortality rate was similar in both study groups (Table 1). Group 2 patients had longer duration of recurrent episodes of atrial fibrillation compared to patients in Group 1 (11.07 ± 8.7 vs. 7.4 ± 6.1 days; $P = 0.013$, Table 2). Subsequently, the duration of antiarrhythmic therapy during hospital stay and at home after an arrhythmic episode was significantly longer in Group 2 critically

Table 1. Demographic data (mean, median ± SD, %) and clinical outcome endpoints study group patients

	Group 1 (n = 37)	Group 2[a] (n = 44)	*P*-value
Age (mean ± SD)	73.6 ± 13.9	79.8 ± 7.9	0.045
Gender (male)			
(n/total, %)	25/37 (67%)	27/44 (61%)	NS
Diagnosis on admission (%)			
Intra-abdominal sepsis			
(n, %)	11/37 (29.7%)	21/44 (47%)	0.045
VAP/CAP (n, %) 11/37	(29.7%)	12/44 (27.2%)	NS
Urosepsis (n, %)	3/37 (8%)	3/44 (6.8%)	NS
Catheter-related			
sepsis (n, %)	4/37 (10.8%)	2/44 (4.5%)	0.034
Wound infection			
(n, %)	4/37 (10.8%)	2/44 (4.5%)	0.04
Endocarditis (n, %)	2/37 (5.4%)	2/44 (4.5%)	NS
Cholangitis (n, %)	2/37 (5.4%)	2/44 (4.5%)	NS
Length of ICU stay			
(day, median ± SD)	20.7 ± 20.6	18.6 ± 14.7	0.68
Length of hospital stay			
(day, median ± SD)	27.3 ± 18.9	30.3 ± 18.3	0.34
APACHE II score			
(units)	26.8 ± 6.7	26.9 ± 5.5	0.93
SOFA score			
(units)	9.8 ± 2.4	8.8 ± 1.8	0.051
CRRT			
(n, %)	6/37 (16.2%)	6/44 (13.6%)	NS
In-ICU mortality rate			
(n, %)	14/37 (37%)	17/44 (38%)	NS
In-hospital mortality			
after discharge from ICU			
(n, %)	5/23 (21%)	6/26 (23%)	NS

[a]Group 2 patients had preexisting cardiac disease: previously known coronary artery disease (old MIs) (n = 20), idiopathic cardiomyopathy (n = 5) and chronic atrial fibrillation only (n = 19). Also patients with coronary artery disease and idiopathic cardiomyopathy had well-documented episodes of AF in the past. NS — non significant, other abbreviations explained in text

ill patients ($P < 0.05$, see Table 2). Group 2 patients were more likely to receive anticoagulation therapy during their hospital stay, and at home, than Group 1 ($P < 0.05$, Table 2). However, there was no significant difference in new stroke and pulmonary embolism (PE) between both study groups ($P < 0.05$, Table 2).

There were no significant differences in laboratory data between both study groups during the new and recurrent AF episodes in the ICU stay (see Table 3).

DISCUSSION

Atrial fibrillation (AF) is one of the most widespread cardiac arrhythmias in the critically ill septic population [14–19]. AF in septic patients is very poorly characterized compared to the dysfunction of other major organs [20–24] and is believed to be multifactorial [25–29]. A number of previously published studies have shown a strong clinical relationship between severity of the illness (sepsis), episodes of new acute atrial fibrillation and worst clinical outcome [30–32]. Even more, it has been shown that new atrial fibrillation in the septic ICU population is associated with an increased risk of acute stroke and prolonged ICU duration [14, 15, 30–32].

Our data did not find a significant difference in clinical outcome (in-ICU and in-hospital mortality; new embolic events (CVA or PE)) in septic patients with new onset AF episodes with no past medical history of atrial fibrillation or antiarrhythmic therapy and septic persons who had previ-

Table 2. Duration, treatment and clinical outcome of new onset (Group 1) and recurrent (Group 2) episodes of atrial fibrillation during the ICU stay of both study groups

	Group 1 (n = 37)	Group 2 (n = 44)	*P*-value
«ICU arrhythmia day» (day, mean ± SD)	5.4 ± 7.7	3.2 ± 4.5	0.22
Duration of arrhythmia (day, mean ± SD)	7.4 ± 6.1	11.07 ± 8.7	0.013
New CVA (n, %)	1/37 (1%)	0/44	NS
New PE (n, %)	0/37	1/44 (1%)	NS
Antiarrhythmic therapy during hospital stay after ICU dischargec (n, %)[#]	8/32 (25%)	16/38 (42.1%)	0.02
Antiarrhythmic therapy at home after hospital dischargec (n, %)[#]	4/32 (12.5%)	13/38 (34.2%)	0.04
Proarrhythmic therapy during ICU stayb (n, %)	24/37 (64.8%)	23/44(52.2%)	NS
Anticoagulation therapy during hospital stay (n, %)[#a]	1/32 (3.1%)	5/38 (13.1%)	0.025
Anticoagulation therapy at home (n, %)[#a]	2/32 (6.25%)	6/38 (15.7%)	0.02

[#]from percent of patients who has been discharged at home with antiarrhythmic therapy recommendations; [a]Anticoagulation therapy (as a preventive treatment for potential risk of new CVA and PE events) included during hospital stay Low Molecular Weight Heparin (LMWH) and warfarin at home; [b]Proarrhythmic therapy included use of inotropic (dopamine, dobutamine, epinephrine) and vasopressors (norepinephrine) agents; [c]Antiarrhythmic therapy during ICU stay included amiodarone and beta-blocker group; antiarrhythmic therapy at home included both beta-blocker and calcium-channel blockers group. NS — non significant, other abbreviations explained in text

ously known episodes of atrial fibrillation and prescribed antiarrhythmic therapy at home. Moreover, some patients also had preexisting coronary artery disease and idiopathic cardiomyopathy history (Group 2). These findings correlated well with previously published data. Thus, Walkey *et al.* [16, 33] demonstrated that only a small number of risk factors (right heart catheterization, diagnosis of endocarditis and past coronary artery bypass graft surgery) are associated with an increased risk of new atrial fibrillation episodes in septic ICU patients. Other cardiovascular comorbidities (heart failure, hypertension, previous myocardial dysfunction, valve disease) had no correlation with new AF episodes.

Kanji *et al.* [34] documented the clinical follow up of 139 patients with new onset AF and 186 patients with preexisting AF in a mixed ICU population. Pharmacological and electrical rhythm conversions were more successful in new-onset AF patients in comparison to the preexisting AF population [34]. The mortality rate in-ICU and after discharge from the intensive care unit was similar for both groups (22–27% and 32–38% respectively). Our data supported their findings, but considered only the septic population of the ICU. In our study, the mortality rate in-ICU and after discharge was 37% and 21% for patients with new onset AF compared to 38% and 23% for septic patients with preexisting AF. We found significantly longer duration of antiarrhythmic therapy in hospital and at home for patients with preexisting AF than with new onset AF. Appropriate recommendations of anticoagulation therapy for elderly septic patients with new onset AF still remain indeterminate [35]. In the same study, Kanji *et al.* [34] found similar rates of therapeutic anticoagulation for new onset and preexisting AF (16% and 19% respectively). In our study septic patients with preexisting AF had at least a twice-as-high rate of an-

Table 3. Laboratory data[a] of study group of patients during the new and recurrent episode of atrial fibrillation within the ICU stay (mean ± SD or median (IQR)

	Group 1 (n = 37)	Group 2 (n = 44)	*P*-value
Phosphorus blood level (mmol L^{-1})	4.1 ± 1.52	3.5 ± 1.01	0.11
Serum calcium serum (mmol L^{-1})	1.02 ± 0.1	1.06 ± 0.09	0.053
Serum magnesium (mmol L^{-1})	2.2 ± 0.3	2.1 ± 0.45	0.38
Serum potassium (mEql L^{-1})	4.02 ± 0.67	4.07 ± 0.54	0.67
Serum glucose (mg dL^{-1})	161.3 ± 88.1	151.8 ± 7.3	0.54
Serum creatinine (mg dL^{-1})	1.62 ± 1.03	1.23 ± 0.91	0.07
Serum urea (mg dL^{-1})	90.08 ± 47.1	73.2 ± 39.5	0.08
pH arterial blood	7.32 ± 0.1	7.3 ± 0.1	0.53
Haemoglobin (g dL^{-1})	9.9 ± 2.1	9.6 ± 1.9	0.5
WBC (G L^{-1})	13 (2–37)	11 (2–59)	0.75
PLT (G L^{-1})	188,8 ± 83,4	225,1 ± 191,0	0.2

[a]All laboratory data was collected during the new AF episode within the ICU stay. Note: no significant electrolyte disturbances were found in both study groups during the AF episode

ticoagulation therapy at home compared to the new onset AF group (15.7% vs. 6.25%). A large part of septic patients in the present study did not receive anticoagulation therapy during their hospital stay and at home because of a high risk of potential complications and contraindications (high risk of bleeding, coagulopathy, recurrent surgery, chronic renal failure etc.).

Our study had a number of limitations. This is a retrospective study. We could not provide retrospectively consistent data of some medical records and it might explain possible selection bias in both study groups. Another limitation of our study is the request for long-term clinical follow up after discharge from the hospital. The small sample size is further limitation of our study, which significantly restricts our conclusions regarding patients' clinical outcome. It may be argued that a large prospective, multicenter study is warranted for a precise clinical analysis of patients' morbidity and mortality after new episodes of AF during the ICU stay and the effectiveness of antiarrhythmic therapy in the prevention of new stroke/PE episodes at home.

CONCLUSION

In the present study we demonstrated no difference in morbidity and mortality rates in-ICU and after discharge between septic patients who had previous AF episodes and patients who had no previous past medical history of any cardiac arrhythmias. We propose that a large multicenter prospective study would help clarify clinical outcomes and the long-term therapeutic management requirements of antiarrhythmic and anticoagulation therapy of critically ill septic patients with new AF episodes.

ACKNOWLEDGEMENTS

1. The authors declare no financial disclosure.
2. The authors declare no conflict of interest.

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Received: 6.12.2014
Accepted: 2.04.2015