Incidence, Risk Factors and Outcomes of New Onset Supraventricular Arrhythmias in African American Patients with Severe Sepsis

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Purpose: New onset supraventricular arrhythmias (SVA) are commonly reported in mixed intensive care settings. We sought to determine the incidence, risk factors and outcomes of new onset SVA in African American (AA) patients with severe sepsis admitted to medical intensive care unit (MICU).

Methods: Patients admitted to MICU between January 2012 through December 2012 were studied. Patients with a previous history of arrhythmia or with new onset of ventricular arrhythmia were excluded. Data on risk factors, critical care interventions and outcomes were obtained.

Results: One hundred and thirty-one patients were identified. New onset SVA occurred in 34 (26%) patients. Of those 34, 20 (59%) had atrial fibrillation (AF), 6 (18%) had atrial flutter and 8 (24%) had other forms of SVA. Compared with patients without SVA, patients with new onset SVA were older (69 ± 12 yrs vs 59 ± 13 yrs, P=.003), had congestive heart failure (47% vs 24%, P=.015) and dyslipidemia (41% vs 15%, P=.002). Additionally, they had a higher mean mortality prediction model (MPM II) score (65 ± 25 vs 49 ± 26, P=.001) and an increased incidence of respiratory failure (85% vs 55%, P=.001). Hospital mortality in patients with new onset SVA was 18 (53%) vs 30 (31%); P=.024; however, in a multivariate analysis, new onset SVA was associated with non-significantly increased odds (OR 2.58, 95% CI 0.86-8.05) for in-hospital mortality.

Conclusion: New onset SVA was prevalent in AA patients with severe sepsis and occurred more frequently with advanced age, increased severity of illness, congestive heart failure, and acute respiratory failure; it was associated with higher unadjusted in hospital mortality. However, after multiple adjustments, new onset SVA did not remain an independent predictor of mortality. *Ethn Dis*.2016;26(2):205-212; doi:10.18865/ed.26.2.205

Keywords: Supraventricular Arrhythmia; Atrial Fibrillation; Severe Sepsis; Critical Care; Length of Stay; Mortality

Introduction

New onset supraventricular arrhythmias (SVA), most commonly atrial fibrillation(AF), have been reported to occur frequently in critically ill patients.[1-4] Previous studies in a mixed medical/surgical intensive care unit (ICU) population reported new onset SVA incidences, AF in particular, in 4%-23% of critically ill patients.[1,5-9] Patients who develop a new onset SVA had longer ICU and hospital stays and increased mortality rates.[2,5,7,10,11] However, such data from medical ICU stays among African American patients are limited.

Severe sepsis, defined as infection complicated by acute organ dysfunction, occurs more frequently and leads to more deaths in Black than non-Black patients.[12-15] These racial disparities in severe sepsis incidence and mortality rates were largest among younger adults.[12,14] The higher severe sepsis rate among Blacks was thought to be due to both a higher infection rate and a higher risk of developing acute organ dysfunction[12] and due to factors such as poor baseline health and premorbid conditions.[13,14,16] However, the racial disparities in infection and severe sepsis incidence and mortality rates persisted after adjusting for preexisting chronic illness and source of infection[13,17] suggesting other factors such as genetic susceptibility, insurance status, lifestyle and socioeconomic factors and class might also play a role.[16,17]

Although new onset SVA appears to be relatively common in patients with severe sepsis and the severe sepsis rate is higher among Blacks, data are sparse as to its incidence and associated risk factors

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and effects in African American patients with severe sepsis admitted to medical ICU. Therefore, in this study, we aimed to describe the incidence of new onset SVA, risk factors associated with its development and associated adverse outcomes among African American patients with severe sepsis.

Methods

A retrospective study on patients admitted to an inner-city, 16-bed adult medical ICU between January and December 2012 was performed. The institutional research review board of Howard University Hospital approved this study; the requirement of informed consent was waived because of the nature of the study. A manual review of charts, utilizing the guidelines from *Definitions for Sepsis and Organ Failure and* guidelines for the use of *Innovative Therapies in Sepsis,*[18] identified 139 medical ICU patients who self-identified as African American and had a primary diagnosis of severe sepsis.

Patients with a previous history of chronic or paroxysmal atrial fibrillation/flutter (AF), ventricular arrhythmia or a length of stay <24 hours were excluded from the study. Out of the total 139 patients, 2 (1%) had ventricular arrhythmias and 6 (4%) had a history of AF prior to being admitted to the ICU; these patients were excluded,

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Table 1. Characteristics of patients with and without new onset supraventricular arrhythmias

Characteristics	SVA, n = 34	No SVA, n = 97	P
Age, yr, mean (SD)	68.8 (12.4)	59.1 (13.3)	.003
Male, n (%)	16 (47.1)	47 (48.5)	.889
Female, n (%)	18 (52.9)	50 (51.6)	
BMI kg/ m^2, mean (SD)	24.6 (8.0)	28.0 (10.0)	.082
MPM II Score	65 (25)	49 (26)	.001
Lactic acid mg/dl, mean (SD)	3.9 (5.8)	3.1 (3.5)	.540
Bilirubin, total mg/dl mean (SD)	1.9 (2.6)	1.7 (1.9)	.745
Total protein g/dl, mean (SD)	5.2 (1.0)	5.6 (1.0)	.067
Albumin g/dl, mean (SD)	1.8 (0.5)	2.2 (0.7)	.013
Platelets x10^9/L, mean (SD)	147.7 (93.7)	165.2 (109.6)	.409
INR, mean (SD)	1.9 (1.0)	1.6 (0.8)	.184
TSH, mean (SD)	2.7(9.3)	1.7(8.3)	.570
CHF, n (%)	16 (47.1)	24 (24.7)	.015
IHD, n (%)	8 (23.5)	15 (15.5)	.288
HCVD, n (%)	16 (47.1)	46 (47.4)	.971
COPD, n (%)	6 (17.7)	13 (13.4)	.545
OSA, n (%)	3(8.8)	5(5.2)	.427
PH, n (%)	6 (17.7)	10 (10.3)	.261
Asthma, n (%)	2 (5.9)	11 (11.3)	.513
Cerebrovascular disease, n (%)	14 (41.2)	26 (26.8)	.117
Hypothyroidism n (%)	4(11.8)	5(5.2)	.237
Hyperthyroidism n (%)	1(2.9)	3(3.1)	1.000
CKD, n (%)	8 (23.5)	22 (22.7)	.919
DM, n (%)	15 (44.1)	38 (39.2)	.613
HTN, n (%)	27 (79.4)	67 (69.1)	.249
Malignancy, n (%)	7 (20.6)	18 (18.6)	.795
HIV, n (%)	2 (5.9)	16 (16.5)	.155
Hyperlipidemia, n (%)	14 (41.2)	15 (15.5)	.002
Organ Failure			
Circulatory failure, n (%)	23 (67.7)	71 (73.2)	.536
Respiratory failure, n (%)	29 (85.3)	53 (54.6)	.001
Renal failure, n (%)	23 (67.7)	72 (74.2)	.460
Hematologic failure, n (%)	16 (47.1)	40 (41.2)	.555
Neurologic failure, n (%)	6 (17.7)	15 (15.46)	.795
Hepatic failure, n (%)	2 (5.9)	14 (14.4)	.237

BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; INR, international normalization ratio; HCVD, hypertensive cardiovascular disease; MPM, mortality prediction model; OSA, obstructive sleep apnea; PH, pulmonary hypertension; SVA, supraventricular arrhythmia.

leaving 131 patients for further analysis. The patients were classified into two groups: having new onset SVA, including new onset AF, and without SVA. The identification of new onset SVA was made from reviewing ICU electrocardiograms (EKGs). The EKGs were examined to determine the type of SVA (eg, atrial fibrillation/flutter, multifocal atrial tachycardia).

Demographic characteristics, comorbidities, laboratory data within 24 hours of ICU admission were extracted from the medical records for both groups of severe sepsis patients (new onset SVA and no SVA) and are summarized in Table 1. The Mortality Prediction Model II (MPM II) score,[19] an index of severity of illness, was determined from the values obtained within 24 hours of ICU admission. The length of days on mechanical ventilation, ICU and hospital length of stay, number of failed organs and in-hospital mortality were compared among the three groups.

Statistical Analysis

We used descriptive statistics to assess patient baseline clinical and demographic factors associated with new onset SVA. Categorical variables were evaluated for statistical significance using the chi-square or Fisher's exact test where appropriate. We performed a t-test to compare for parametric categorical variables to assess significance for any differences in means among patients with or without new onset SVA; Wilcoxon's rank-sum test was applied for comparisons of non-normal continuously distributed data. The association between SVA and a number of outcomes was assessed: number of patients requiring mechanical ventilation; ventilation days; hospital length of stay; ICU length of stay; and number of organs failed. We evaluated the independence of the relationship between mortality and SVA categories using logistic regression analysis.

Univariate analysis was performed to assess potential confounders for the association between SVA and mortality. Variables that were significantly associated with mortality and SVA were included in a multivariable stepwise logistic regression analysis to examine the association between SVA and mortality and variables are presented as odds ratios and confidence intervals. *P* values <.05 were considered statistically significant and confidence intervals (CI) were calculated at the 95% level. Data analysis was conducted using the Statistical Analysis System software 9.3 (SAS Institute, Cary, NC) and Statistical Analysis and Graphics (NCSS 9.0.7, Kaysville, UT). Sensitivity analysis was performed using patients with AF instead of SVA. Results were essentially the same as shown below.

Results

New onset SVA occurred in 34 (26%) and 97 (74%) patients had no SVA. Among the patients who had SVA's, 20 (59%) had atrial fibrillation (15% of the total studied population), 6 (18%) had atrial flutter and 8 (24%) had multifocal atrial tachycardia. Compared with patients without SVA, patients who developed new onset SVA were older (69 ± 12 vs 59 ± 13 yrs, *P*=.003), had history of congestive heart failure (47% vs 24%, *P*=.015) and dyslipidemia (41% vs 15%, *P*=.002). Additionally, the patients with new onset SVA had higher MPM II score (65 ± 25 vs 49 ± 26, *P*=.001), lower mean albumin (1.8 ± .5 vs 2.2 ± .7gm/dL, *P*=.013) and an increased incidence of respiratory failure (85% vs 55%, *P*=.001) compared with patients without SVA (Table 1). Results of the multivariable analysis for factors associated with new onset SVA with severe sepsis are shown in Table 2. Body mass indexes (BMI), history of heart failure, hyperlipidemia and albumin level were associated with increased risk of new onset SVA.

Outcome measures by new onset SVA status are shown in Table 3. Patients with new onset SVA had higher

Table 2. Multivariate logistic regression analysis for new onset supraventricular arrhythmia predictors

Characteristic	Odds Ratio	CIs
BMI	.94	(.88-.99)
Albumin	.26	(.11-.63)
CHF	3.84	(1.45-10.15)
Hyperlipidemia	10.04	(3.10-32.51)

BMI, body mass index; CHF, congestive heart failure; SVA, supraventricular arrhythmia.

unadjusted in-hospital mortality compared with patients without SVA (53% vs 31%; *P*=.024). Compared with patients without SVA, patients with new onset SVA were also more likely to need a mechanical ventilation (77% vs 53%; *P*=.015). There was a trend for a longer hospital length of stay in patients with new onset SVA; however, the mean ICU length of stay was similar between the two groups.

Logistic regression analysis showed that malignancy (OR 11.98, 2.15-66.77), mechanical ventilation (OR 23.86, 4.18-136.38) and numbers of organs failed (OR 3.14, 1.90-5.18) were all independent predictors of mortality but new onset SVA (OR 2.59, 0.83-8.05) was not significantly associated with mortality independent of comorbidity and severity indicators (Table 4).

Table 3. Outcomes of patients with severe sepsis with and without new onset supraventricular arrhythmia

Characteristics	SVA, n = 34	No SVA, n = 97	P
In-hospital mortality, n (%)	18 (52.9)	30(30.9)	.024
Mechanical ventilation, n (%)	26 (76.5)	51 (52.6)	.015
Ventilation days, mean (SD)	8.64 (7.0)	7.31 (8.6)	.505
Hospital LOS, mean (SD)	17.09 (12.8)	12.78 (10.8)	.058
ICU LOS, mean (SD)	9.62 (7.8)	8.03 (9.6)	.387
Number of organs failed, mean (SD)	3.09 (1.1)	2.93 (1.4)	.542

ICU, intensive care unit; LOS, length of stay; SVA, supraventricular arrhythmia.

Discussion

The results of our study confirm a number of clinically relevant findings of previous studies in a series of inner-city African American patients. First, the study shows new onset SVA frequently occurs during severe sepsis in African American patients admitted to medical ICU. In our study, new onset SVA developed in 26%, with AF (15%) being the most common SVA. In addition, we identified demographic and clinical factors associated with new onset SVA during severe sepsis. The variables associated with the development of new onset SVA included older age, comorbidities, such as history of congestive heart failure, and acute factors, such as increased severity of illness (higher MPM II score), respiratory failure, and the use of mechanical ventilation. Importantly, patients with new onset SVA during severe sepsis had increased risk for in-hospital mortality in a univariate analysis, but new onset SVA was not significantly associated with mortality independent of comorbidity and severity indicators (OR 2.58, CI.83-8.05). However, our sample was too small to establish whether new onset SVA was an independent predictor of mortality.

Prior studies[1,4,6,8] demonstrate severe sepsis to be strongly associated with new onset AF and worse outcomes. However, most of the previous studies related to new onset SVA/AF incidence and outcomes in critical illness come from a heterogeneous population of mixed medical, surgical and trauma patients.[4,6-8,10,20-23] Moreover, unlike previous studies, our study examined a cohort of African American medical ICU patients and importantly excluded surgical, trauma and postcardiotomy patients with severe sepsis.

Not all previous studies reported the incidences of new onset SVA/AF for the various sepsis stages separately and the reported incidences vary widely. Kuipers and collegues in their recent review reported that the weighted mean incidence of new onset AF was 8% (range 0-14%), 10% (4%-23%) and 23% (6%-46%) in patients with sepsis, severe sepsis and septic

Table 4. Multivariate analysis for in-hospital mortality predictors

Characteristics	Odds Ratio	CIs
SVA	2.59	(.83-8.05)
Malignancy	11.98	(2.15-66.77)
Mechanical ventilation	23.86	(4.18-136.38)
Number of organs failed	3.14	(1.90-5.18)

SVA, supraventricular arrhythmia
Logistic regression analysis showed that malignancy (OR 11.98, 2.15-66.77), mechanical ventilation (OR 23.86, 4.18-136.38) and numbers of organs failed (OR 3.14, 1.90-5.18) were all independent predictors of mortality but new onset SVA (OR 2.59, 0.83-8.05) was not significantly associated with mortality independent of comorbidity and severity indicators.

shock respectively.[24] Studies from a surgical and trauma ICU reported a combined incidence of new onset AF for patients with either sepsis or severe sepsis as a mean of 5%, with a range 3%-10%,[10,20,23] and two studies in mixed ICU reported an incidence for patients with sepsis of unspecified severity (mean 28%; range 23%- 50%).[6,8] Salman and colleagues reported incidence of new onset AF of 23% in mixed surgical and medical patients with severe sepsis.[4] In contrast, a single large study that was not formally restricted to the ICU setting only, and that used ICD-9-CM codes to detect episodes of new onset AF, reported an incidence of 5% in hospitalized patients with severe sepsis and 6% in patients with septic shock.[5] Our finding of 26% new onset SVA, including 15% new onset AF, suggests that there may be a higher incidence of new onset SVA in African Americans patients with severe sepsis. The higher incidence of new onset SVA in our study may be due to the fact that African Americans have increased severity and rate of severe sepsis[13] with more comorbidity compared with previous studies of White patients,[10,12] and insurance status, lifestyle and socioeconomic factors might also play a role.[16,17] Differences in study methods and case selection may also explain the wide variation in results among various studies.

It is not entirely clear why patients with severe sepsis have an increased incidence of new onset SVA. Severe sepsis is characterized by a systemic release of pro-inflammatory cytokines, high levels of circulating stress hormones and autonomic and acute organ dysfunction.[25,26] In addition, hypoxemia, intravascular volume shifts and cardiovascular compromise will frequently lead to hypotension and elevated lactate levels.[27,28] All of these factors may lead to the development of new onset SVA. Sepsis is associated with significant myocardial dysfunction. Myocardial depression was previously considered a preterminal event; it is now clear that cardiac dysfunction is present in most patients with severe sepsis and septic shock.[29] New onset SVA may be one manifestation of this phenomenon.

The variables associated with the development of new onset SVA included older age, comorbidities, such as history of congestive heart failure, and acute factors, such as increased severity of illness (higher MPM II score), respiratory failure, and the use of mechanical ventilation.

Markers of illness severity such as MPM II score as well as critical care intervention such as use of mechanical ventilation were associated with an increased risk of AF in our study. These findings give support for the general notion that new onset SVA/AF may be triggered by high levels of circulating pro-inflammatory cytokines, catecholaminergic stress, electrolyte imbalances, and a disrupted volume status during severe sepsis. In addition, known risk factors for chronic AF in the general population, such as older age, comorbidities (eg, heart failure and dyslipidemia)[1,4,30,31] have all been associated with new onset SVA during severe sepsis in this study. However, in contrast to reported associations in the general population, new onset SVA or AF was not higher with comorbidities such as hypertension, ischemic heart disease, diabetes, and COPD in our study.[30,32,33] Similarly, two previous studies paradoxically reported that diabetes mellitus was associated with a decreased risk of AF onset[5,34] indicating acute factors, rather than preexisting cardiovascular comorbid conditions, are associated with increased risk for newly diagnosed AF during sepsis. This suggests that mechanisms of newly diagnosed SVA/AF during severe sepsis may differ from the general population of patients with AF.

We found new onset SVA was associated with 22% increase in the unadjusted risk for in-hospital mortality as compared with those without SVA. However, on multivariate analysis the association was attenuated. Similar to our finding, previous studies reported worse outcomes in patients with new onset AF in a univariate analysis[4,5,7,10]

but only few studies showed independent associations with mortality.[4,5] Yet, in both of these studies, residual confounding cannot be excluded as the number of covariates collected were limited. This raises the question as to whether or not new onset SVA functions as a marker for increased illness severity and poor prognosis (eg, new onset SVA represents an additional "organ dysfunction") or directly contributes to mortality (eg, through refractory hypotension, stroke, or heart failure) that warrants further investigation. Additional morbidity and mortality following the development of AF in patients with sepsis may be explained by the decrease in cardiac output and blood pressure that occurs in most patients due to reduced left ventricular filling. This is particularly the case in the presence of rapid ventricular response rates. The resulting hemodynamic compromise may impair the recovery of organ function in patients with severe sepsis or shock. Nonetheless, the development of AF is associated with a sudden reduction in cardiac output and rise in filling pressures and it is, therefore, possible that increased mortality is due to the adverse consequences of AF on cardiac function.[35] In addition, chronic AF is associated with thromboembolic complications, and it is plausible that some of these risks also affect critically ill patients with an acute episode of AF.[36]

Study Limitation

Our study has several limitations. Being a retrospective chart review of 131 cases, it lacks power for multivariate analyses of SVA and has limited generalizability to African American patients in MICU settings. Other limitations include possible confounding by variables not measured or controlled for (eg, electrolyte imbalances, presence of central venous catheter). Further, we cannot determine causality between new onset SVA and mortality in our retrospective analysis. A larger prospective study design would be required to determine whether SVA is associated with hospital mortality independent of comorbidity and severity of sepsis in African Americans. It still remains uncertain whether new onset SVA in patients with sepsis is merely a marker for severity of disease or whether it truly impacts outcome. Further research is warranted to demonstrate these independent associations with morbidity and mortality.

Conclusions

The findings of our study of African American patients with severe sepsis in a medical ICU are consistent with previous findings that new onset SVA, including AF, is a common occurrence in critically ill patients with severe sepsis. Some multivariable analyses suggested that it is independently associated with poor outcome, but others have not; whether this relation is truly causal remains difficult to establish. In view of these findings, there is a need for high quality, prospective studies. Reliable identification of patients with sepsis who are prone to the development of new onset SVA with increased mortality may allow for early pharmacological interventions to prevent this complication.

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Lewis, Ngwa, Gillum, Thomas, Davis, Poddar, Adams, Thomas, Jr, Mehari; Acquisition of data: Lewis, Ngwa, Mehari; Data analysis and interpretation: Lewis, Ngwa, Gillum, Mehari; Manuscript draft: Lewis, Ngwa, Gillum, Thomas, Davis, Poddar, Adams, Thomas, Jr, Mehari; Statistical expertise: Lewis, Ngwa, Gillum, Mehari; Administrative: Lewis, Ngwa, Gillum, Thomas, Poddar, Adams, Thomas, Jr, Mehari; Supervision: Gillum, Mehari

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