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Association of ventricular arrhythmia and in-hospital mortality in stroke patients in Florida: A nonconcurrent prospective study

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A nonconcurrent prospective study

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Abstract

Stroke remains one of the leading causes of death in the United States. Current evidence identified electrocardiographic abnormalities and cardiac arrhythmias in 50% of patients with an acute stroke. The purpose of this study was to assess whether the presence of ventricular arrhythmia (VA) in adult patients hospitalized in Florida with acute stroke increased the risk of in-hospital mortality.

Secondary data analysis of 215,150 patients with ischemic and hemorrhagic stroke hospitalized in the state of Florida collected by the Florida Agency for Healthcare Administration from 2008 to 2012. The main outcome for this study was in-hospital mortality. The main exposure of this study was defined as the presence of VA. VA included the ICD-9 CM codes: paroxysmal ventricular tachycardia (427.1), ventricular fibrillation (427.41), ventricular flutter (427.42), ventricular fibrillation and flutter (427.4), and other – includes premature ventricular beats, contractions, or systoles (427.69). Differences in demographic and clinical characteristics and hospital outcomes were assessed between patients who developed versus did not develop VA during hospitalization (χ^2 and t tests). Binary logistic regression was used to estimate unadjusted and adjusted odds ratios and 95% confidence intervals (CIs) between VA and in-hospital mortality.

VA was associated with an increased risk of in-hospital mortality after adjusting for all covariates (odds ratio [OR]: 1.75; 95% CI: 1.6–1.2). There was an increased in-hospital mortality in women compared to men (OR: 1.1; 95% CI: 1.1–1.14), age greater than 85 years (OR: 3.9, 95% CI: 3.5–4.3), African Americans compared to Whites (OR: 1.1; 95% CI: 1.04–1.2), diagnosis of congestive heart failure (OR: 2.1; 95% CI: 2.0–2.3), and atrial arrhythmias (OR: 2.1, 95% CI: 2.0–2.2). Patients with hemorrhagic stroke had increased odds of in-hospital mortality (OR: 9.0; 95% CI: 8.6–9.4) compared to ischemic stroke.

Identifying VAs in stroke patients may help in better target at risk populations for closer cardiac monitoring during hospitalization. The impact of implementing methods of quick assessment could potentially reduce VA associated sudden cardiac death.

Abbreviations: AA = atrial arrhythmias, AHCA = Agency for Health Care Administration, ANS = autonomic nervous system, CHF = coronary heart failure, CI = confidence interval, CVD = cerebrovascular disease, DM = diabetes mellitus, ECG = electrocardiogram, HTN = hypertension, ICD = international classification of diseases, OR = odds ratio, PVC = premature ventricular contraction, US = United States, VA = ventricular arrhythmia.

Keywords: Florida, in-hospital mortality, stroke, ventricular arrhythmia

1. Introduction

According to the World Health Organization, 15 million people worldwide suffer a stroke annually.[1] Of these, nearly 6 million die and another 5 million are left permanently disabled, placing a burden on family and community. Stroke remains one of the leading causes of death in the United States (US) with around 129,000 events each year.[2] The highest death rates from stroke in the US occur in the Southeast region where the state of Florida is located. Florida has one of most diverse minority populations in the US including African Americans and Hispanics, and in 2013 reported 8142 strokes.[3] Disparities in acute stroke diagnosis, management, and care, along with secondary prevention exist for African Americans, but are less well documented in the rapidly growing Hispanic population.[3]

Early experimentation was conducted using rat models by Oppenheimer et al.[4] This study showed connections between the insula, autonomic changes, and cardiac arrhythmias. Significant dysrhythmias on electrocardiogram (ECG) were documented after stimulation of the anterior cortex, similar to those observed after an ischemic stroke. In contrast to the control group, the majority of the experimental individuals experienced various dysrhythmias such as p-wave alterations, progressive QRS complex widening, and premature ventricular complexes. These findings led to the identification of cortical sites that control central and peripheral cardiac autonomic changes in relation to ventricular arrhythmia (VA) in patients after a stroke.[4] Another

study by Koppikar et al assessed the effects after an acute stroke particularly within the first 24 hours.[5] They showed that 14% of patients had nonsustained ventricular tachycardia while 36% presented ventricular ectopic beats.

Serious cardiac events are common in the acute period after stroke. Early observations identified electrocardiographic (ECG) abnormalities and cardiac arrhythmias in 50% of patients with an acute stroke.[6] Patients at highest risk are identifiable and may benefit from more aggressive strategies to improve survival.[7] There is ample research with regard to atrial arrhythmias (AA) as an independent risk factor for stroke but few studies have explored the association of VAs and cerebrovascular disease (CVD). One of the most serious cardiac consequences after a stroke is an increased risk of VA, which can increase the risk of sudden death.[8,9] The proposed mechanism by which VA may occur following stroke involves autonomic imbalance modulated by direct injury to neurogenic structures and enhanced by catecholamine surge leading to myocardial damage and arrhythmogenesis.[10] Experimental and clinical data have also suggested that strokes involving the insular cortex play a direct role in autonomic dysregulation and the development of VA in the acute period following stroke. However, very few studies have been performed that specifically look at in-hospital mortality of stroke patients with VAs, particularly in the state of Florida which has a very diverse patient demographic.

The main aim of this study was to assess whether the presence of VA in stroke patients increase the risk of in-hospital mortality in Florida from 2008 to 2012.

2. Methods

A secondary analysis of data collected from 2008 to 2012 as part of the Florida Agency for Health Care Administration (AHCA) registry was conducted using a nonconcurrent, population-based, cohort design.

The database comprised information from 319,492 adult patients with the diagnosis of acute stroke from all hospitals within the state of Florida. Stroke was defined according to following international classification of diseases (ICD)-9 codes: cerebrovascular accident ischemic (434.91), cerebrovascular accident embolic (434.11), intracerebral hemorrhage (431), other or unspecified intracerebral hemorrhage (432.9), occlusion of cerebral arteries (434), occlusion and stenosis of the precerebral arteries (433), acute but ill-defined CVD (436), and other generalized ischemic CVD (437.1).

Children, defined as under the age of 18, and patients having the diagnosis of transient ischemic attack (ICD-9 Code), acute ill-defined CVD, late CVD effects, other ill-defined CVD, subarachnoid hemorrhage (SAH), transient cerebral ischemia, and unspecified intracranial hemorrhage as the primary diagnosis were excluded from the study.

The main outcome for this study was in-hospital mortality. The main exposure of this study was defined as the presence of VA. VA included the ICD-9 CM codes: paroxysmal ventricular tachycardia (427.1), ventricular fibrillation (427.41), ventricular flutter (427.42), ventricular fibrillation and flutter (427.4), and other – includes premature ventricular beats, contractions, or systoles (427.69). The presence of ventricular dysrhythmias was ascertained for this study if reported by the hospital to the AHCA registry during the current admission. Potential confounders included gender, age, race, ethnicity, principal payer, and type of stroke, coronary artery disease (CAD), hypertension (HTN), AA,

congestive heart failure (CHF), diabetes mellitus (DM), tobacco use, and obesity. Gender was divided into 2 groups: male and female. Age was divided into 5 groups: 18 to 54, 55 to 64, 65 to 74, 75 to 84, and 85+ years-of-age. Race was divided into 3 groups: White, Black, and other (native American, Alaska native, Asian, Pacific Islander, Native Hawaiian, Other, and Unknown). Ethnicity was divided into 2 groups: Hispanic and Non-Hispanic. Principal payer or insurance type was divided into 5 groups: Medicare, Medicaid, other government (TriCare or Other Federal Government, VA, other state/local government), private/other (which included Commercial Health Insurance, Worker's Compensation, other, and commercial liability coverage), and no insurance (which included self-pay and nonpayment). Type of stroke was divided into 2 groups: ischemic and hemorrhagic. Both ischemic and hemorrhagic strokes were effect modifiers and additional stratification was completed. CAD, HTN, AA (atrial fibrillation and atrial flutter), CHF, DM, tobacco use, and obesity were divided into groups denoting the presence or absence of the respective comorbidity. The effect modifier was the type of stroke (ischemic or hemorrhagic) as defined by the database.

2.1. Statistical analysis

IBM Statistical Package for the Social Sciences v21 was used to conduct all analyses. Exploratory analysis was carried out by examining frequency distribution. Chi-square test was used to test bivariate associations between potential confounders and the exposures and outcome, respectively. Binary logistic regression was used to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) between VA and in-hospital mortality. A P-value of less than 0.05 was considered statistically significant.

2.2. Ethical considerations

Ethical approval was waived since the analysis was considered nonhuman subjects research by the Florida International University Health Science Institutional Review Board.

3. Results

The total number of patients in the database was 333,367, but 854 people were younger than 18 years and an additional 117,363 records in the registry corresponded to transient ischemic attack, acute ill-defined CVD, late CVD effects, other ill-defined CVD, subarachnoid hemorrhage (SAH), transient cerebral ischemia, and unspecified intracranial hemorrhage leaving an eligible population of 215,150 patients who were included in the analysis. Overall in-hospital mortality was 5% and overall frequency of VAs was 2%.

Table 1 shows the baseline characteristics of Florida stroke patients according to presence of VA during 2008 and 2012. Patients with VA tended to be male, older (>75 years old), black, insured by Medicare, obese, and tended to have CAD, CHF, DM, and AA (P-values < .05). The patients who did not have VA tended to be tobacco users and hypertensive. No statistically significant difference in type of stroke or ethnicity was observed between patients with and without VA.

Table 2 shows the unadjusted and adjusted association of in-hospital mortality among Florida stroke patients (2008–2012). The baseline characteristics of stroke patients according to in-hospital mortality showed a significantly higher proportion of

Table 1

Baseline characteristics of Florida stroke patients according to presence of ventricular arrhythmia during 2008 and 2012.

	Ventricular arrhythmia			
	No **n, %**	**Yes** **n, %**	**Total** **n, %**	**P**
	(n = 208,826)	(n = 4395)	(n = 213,221)	
Sex				<.001
Male	106,054 (50.8)	2778 (63.2)	108,832	
Female	102,772 (49.2)	1617 (36.8)	104,389	
Age group, y				<.001
<55	24,947 (11.9)	362 (8.2)	25,309	
55–64	35,205 (16.9)	629 (14.3)	35,834	
65–74	52,108 (25.0)	1070 (24.3)	53,178	
75–84	60,271 (28.9)	1456 (33.1)	61,727	
85+	36,295 (17.4)	878 (20.0)	37,173	
Race				<.001
White	164,729 (79.5)	3405 (78.0)	168,134	
Black	32,970 (15.9)	802 (18.4)	33,772	
Other	9581 (4.6)	160 (3.7)	9741	
Ethnicity				.398
Hispanic	53,259 (26.0)	1099 (25.5)	54,358	
Non-Hispanic	151,364 (74.0)	3218 (74.5)	154,582	
Insurance				<.001
Medicare	148,312 (71.0)	3365 (76.6)	151,677	
Medicaid	13,233 (6.3)	284 (6.5)	13,517	
Other gov/VA	4329 (2.1)	70 (1.6)	4339	
No insurance	12,685 (6.1)	191 (4.3)	12,876	
Private	30,236 (14.5)	554 (12.6)	30,790	
Type of stroke				.505
Ischemic	188,407 (90.2)	3952 (89.9)	192,359	
Hemorrhagic	20,419 (9.8)	443 (10.1)	20,862	
Coronary artery disease	66,032 (31.6)	2018 (45.9)	68,050	<.001
Congestive heart failure	88,298 (42.3)	3212 (73.1)	91,510	<.001
Hypertension	146,390 (70.1)	2855 (65.0)	149,215	<.001
Atrial arrhythmias	42,400 (20.3)	1532 (34.9)	43,932	<.001
Diabetes mellitus	72,664 (34.8)	1648 (37.5)	74,312	<.001
Tobacco use	33,589 (16.1)	647 (14.7)	34,236	<.001
Obesity	18,951 (9.1)	487 (11.1)	19,438	<.001

VA = ventricular arrhythmia.

death in patients with VA than patients without VA. All potential confounders were significantly associated with in-hospital mortality. The unadjusted and adjusted OR for the association between VA and in-hospital mortality showed patients with VA had almost twice the odds of in-hospital mortality compared to patients without VA (OR: 1.89, 95% CI: 1.69–2.10). After adjustment, there was a 1.75 (95% CI: 1.56–1.97) higher odds of in-hospital mortality for patients with VA compared to patients without VA, while holding all other variables constant. In the adjusted model, females had a 10% increased odds of in-hospital mortality compared with men. As age increased the adjusted odds of in-hospital mortality increased. African Americans had a 10% increased adjusted odds of in-hospital mortality compared to the reference group (White) while the "Other race" category had no significant difference in odds of in-hospital mortality. Hispanics had a 10% increased odds of in-hospital mortality compared to the non-Hispanic patient group. Patients with CAD were not significantly different than patients without CAD in terms of in-hospital mortality. CHF increased odds of in-hospital mortality by 2.12 (95% CI: 1.97–2.28). Patients with a hemorrhagic stroke had 9 times greater odds of in-hospital mortality compared to patients with an ischemic stroke.

Table 3 shows the adjusted association of type of stroke and in-hospital mortality among Florida stroke patients (2008–2012).

After stratifying by type of stroke we found that ischemic stroke patients with VA have a 74% increased odds of in-hospital mortality compared to those without VA. Hemorrhagic stroke patients with VA had a 31% higher odds of in-hospital mortality compared to those without VA.

4. Discussion

Our study showed that there was a 75% increased odds of in-hospital mortality in stroke patients who had VA when compared to patients without VA after controlling for various factors.

There are 2 main pathophysiological mechanisms that may explain ventricular arrhythmogenesis following strokes. The first hypothesis suggests that there may be damage to the central structures that have direct control over the autonomic nervous system (ANS).[11] This damage results in sympathetic amplification or parasympathetic inhibition of the ANS, with subsequent ECG changes, without permanent myocardial damage. The 2nd hypothesis proposes an imbalance between sympathetic and parasympathetic reflex controls, leading to an augmented sympathetic discharge.[12] These changes have been noted to occur slowly unlike the 1st mechanism, they can cause myocytolysis that creates the setting for VA observed after stroke.

Table 2

Unadjusted and adjusted association of in-hospital mortality among Florida stroke patients (2008–2012).

	Unadjusted OR* (95% CI†)	Adjusted OR (95% CI)
Ventricular arrhythmia	1.89 (1.69–2.10)	1.75 (1.56–1.97)
Sex		
Male	Ref‡	Ref
Female	1.12 (1.10–1.19)	1.09 (1.05–1.14)
Age group, y		
<55	Ref	Ref
55–64	0.86 (0.80–93)	1.10 (1.01–1.20)
65–74	0.82 (0.80–0.88)	2.05 (1.86–2.25)
75–84	1.21 (1.13–1.30)	2.94 (2.68–3.23)
85+	1.69 (1.57–1.81)	3.88 (3.52–4.28)
Race		
White	Ref	Ref
Black	1.07 (1.01–1.13)	1.11 (1.04–1.18)
Other	1.14 (1.04–1.25)	1.00 (0.90–1.12)
Ethnicity		
Hispanic	Ref	Ref
Non-Hispanic	0.84 (0.88–1.06)	1.09 (1.03–1.14)
Insurance		
Private	Ref	Ref
Medicare	0.78 (0.74–0.82)	0.41 (0.38–0.44)
Medicaid	0.97 (0.88–1.06)	0.91 (0.82–1.00)
Other gov/VA	2.26 (2.04–2.51)	1.98 (1.76–2.23)
No insurance	0.85 (0.77–0.93)	1.01 (0.91–1.12)
Type of stroke		
Ischemic	Ref	Ref
Hemorrhagic	9.07 (8.70–9.46)	8.96 (8.57–9.37)
Coronary artery disease	0.90 (0.86–0.94)	0.97 (0.92–1.01)
Congestive heart failure	1.79 (1.72–1.86)	2.12 (1.97–2.28)
Hypertension	0.72 (0.69–0.75)	0.70 (0.67–0.74)
Atrial arrhythmias	1.33 (1.29–1.39)	2.13 (2.04–2.22)
Diabetes mellitus	0.81 (0.77–0.84)	0.92 (0.88–0.96)
Tobacco use	1.33 (1.28–1.39)	0.8 (0.7–0.8)
Obesity	0.69 (0.64–0.75)	0.75 (0.69–0.82)

CI = confidence interval, OR = odds ratio, VA = ventricular arrhythmia.
* Odds ratio.
† Confidence interval.
‡ Reference group.

Table 3

Adjusted association of type of stroke and in-hospital mortality among Florida stroke patients from 2008 to 2012.

	Type of stroke	
	Hemorrhagic Adjusted OR* (95% CI†)	Ischemic Adjusted OR (95% CI)
Ventricular arrhythmia	1.31 (1.05–1.63)	1.76 (1.54–2.01)
Sex		
Male	Ref‡	Ref
Female	1.10 (1.03–1.18)	1.07 (1.01–1.13)
Age group, y		
<55	Ref	Ref
55–64	1.07 (0.95–1.21)	1.08 (0.95–1.23)
65–74	1.29 (1.12–1.49)	2.22 (1.94–2.54)
75–84	1.48 (1.29–1.71)	3.01 (2.63–3.44)
85+	1.28 (1.10–1.49)	4.12 (3.59–4.73)
Race		
White	Ref	Ref
Black	0.96 (0.87–1.05)	1.25 (1.15–1.36)
Other	0.80 (0.67–0.96)	1.11 (0.96–1.28)
Ethnicity		
Non-Hispanic	Ref	Ref
Hispanic	0.95 (0.88–1.03)	1.19 (1.12–1.27)
Insurance		
Private	Ref	Ref
Medicare	0.79 (0.70–0.89)	0.28 (0.26–0.31)
Medicaid	1.06 (0.91–1.22)	0.81 (0.71–0.92)
Other gov/VA	1.58 (1.29–1.94)	2.11 (1.83–2.43)
No insurance	1.12 (0.97–1.30)	0.88 (0.76–1.02)
Coronary artery disease	1.08 (0.99–1.17)	0.88 (0.83–0.93)
Congestive heart failure	0.76 (0.71–0.81)	2.41 (2.26–2.56)
Hypertension	0.81 (0.75–0.87)	0.68 (0.64–0.72)
Atrial arrhythmias	1.34 (1.23–1.46)	2.13 (2.01–2.27)
Diabetes mellitus	0.98 (0.91–1.06)	0.89 (0.83–0.94)
Tobacco use	0.78 (0.69–0.88)	0.65 (0.59–0.72)
Obesity	0.77 (0.67–0.89)	0.74 (0.66–0.82)

CI = confidence interval, OR = odds ratio, VA = ventricular arrhythmia.
* Odds ratio.
† Confidence interval.
‡ Reference group.

Several case studies using animal models have shown there may be an anatomical link in the brain that is associated with development of VA. There is evidence to suggest that the limbic system, specifically the amygdala and insular cortex, may be involved in central control of the ANS.[13] Strokes involving the right insula decrease basal sympathetic tone and may result in parasympathetic hyperactivity. Insular lesions are usually part of a larger infarct supplied by the middle cerebral artery. Due to this, most studies on humans have not isolated insular infarcts to determine the impact of lateralization on autonomic function. Thus, it is possible that infarcts in this location may be contributing to the increased incidence of VA (2%) in our population.

After initial data analysis we realized that type of stroke could be an effect modifier, so we decided to stratify by type of stroke and observed there was a difference in in-hospital mortality between patients with VA and hemorrhagic stroke versus ischemic stroke and saw that type of stroke was an effect modifier. After stratifying by type of stroke we found that ischemic stroke patients with VA had higher odds of in-hospital mortality compared to those without VA. Hemorrhagic stroke patients with VA had a higher risk of in-hospital mortality compared to those without VA. We contribute this pattern to the more malignant nature of hemorrhagic strokes. It is plausible that hemorrhagic stroke patients were underreported in the database due to these patients expiring prior to reaching the hospital. Similarly, depending on stroke severity, hemorrhagic stroke patients may be less likely to be diagnosed with VA prior to succumbing to their disease. Finally, in the VAs group, the presence of a higher frequency of ischemic heart disease, heart failure, and AA may be partially explained by alterations in central sympathetic regulation expressed as a chronically elevated sympathetic nerve activity.[14,15]

Our findings are in line with previous studies and confirms the malignant sequelae of VA in stroke patients and supports the notion that development of VA in stroke patients infers increased mortality. Patients with hemorrhagic stroke had 9 times greater odds of in-hospital mortality compared to patients with an ischemic stroke. It has been reported in the literature that anywhere from 10% to 20% of all strokes are hemorrhagic whereas the ischemic subtype accounts for 80% to 90%. In our study, hemorrhagic stroke accounted for 10% of all events. A Danish study compared hemorrhagic versus ischemic stroke on the basis of stroke severity, mortality, and cardiovascular risk

factors.[16] Their results were in line with our reporting that the hemorrhagic subtype comprised 10% of all strokes. They concluded that strokes are generally more severe in patients with hemorrhagic stroke and that hemorrhagic stroke was associated with a considerable increase in mortality. Our study did not exclusively look at factors favoring ischemic versus hemorrhagic strokes but more attention should be given in the future to this topic as well as risk stratification and identifying risk factors for VA after a stroke. If we can identify certain risk factors that predispose to VA after stroke, clinicians can incorporate preventative measures.

The observed overall in-hospital mortality of 5% is relatively low in comparison with other studies such as the aforementioned study from Denmark where they reported a 49% overall mortality for hemorrhagic stroke and 26% overall mortality for ischemic stroke; however, their study included follow-up data whereas our study was limited to in-hospital events.[14] Our 5% overall in-hospital mortality rate more closely reflects the 7-day unadjusted case fatality rates for ischemic (1.8%) and hemor-rhagic stroke (13.2%) reported by Graham et al.[14] This highlights an area of potential future research in which stroke patients with VA receive extensive follow-up. In addition, it is important to mention that while ventricular tachycardia, fibrillation, and flutter certainly carry high risks of cardiovascular death, premature ventricular contractions (PVCs) are less likely to confer direct patient in-hospital mortality. In our study, 0.8% (n=1788) of the patients had PVCs (ICD-9 codes 427.60, 427.61, 427.69); however, there was no significant association between PVCs and mortality ($P=.107$).

In our study, we found a 2% overall prevalence of VA. Our overall frequency of VA in stroke patients is lower than reported by some previous studies. Koppikar et al[5] reported electrocar-diographic abnormalities and cardiac arrhythmias in up to 50% of patients with an acute stroke. This discrepancy in frequency could be accounted for by our more selective definition of VA. We only included paroxysmal ventricular tachycardia, ventricular fibrillation, ventricular tachycardia, premature ventricular beats, contractions, and systoles, whereas other studies were more liberal in their definition of arrhythmia and included AA and diagnoses such as long QT syndrome and torsades de pointe. Few if any previous studies have exclusively studied overall frequency of VA in stroke patients. Moreover, the increasing progression of CVD as a whole may also explain the differences in age groups.

The strengths of this study include the generalizability of the population-based study design that included all patients hospitalized with stroke during the study years from a well-characterized Floridian population.

The limitation of this study includes the lack of case validation. The Florida AHCA requests hospital reports based on the ICD-9 discharge diagnosis, which are not necessarily validated by a neurologist or by imaging studies under a standardized criteria.

We did not have information on the severity of the stroke or the availability of a stroke team. In addition, because we could not determine whether in-hospital treatment approaches were prescribed either before or after the acute stroke, we did not adjust for receipt of in-hospital medications in the multivariate-adjusted regression models. Finally, we did not examine the roles of other risk factors for stroke, such as cigarette smoking, or control for HTN and diabetes.

In conclusion, future research should utilize a prospective cohort design to better elicit causality. Nevertheless, 2% of all stroke patients developing deadly VA is alarming and precau-tionary measures should aim to promote prevention, early detection and management with emphasis on continuous cardiac monitoring, drug therapy, and/or electrolyte correction as guided by the clinical scenario. The impact of implementing methods of quick assessment could potentially reduce VA associated sudden cardiac death.

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