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Does Coronary Vasospasm Show a Better Prognosis in Out of Hospital Cardiac Arrest: Data from the Korean Cardiac Arrest Research Consortium (KoCARC) Registry

ABSTRACT

Background: Previous cohort studies focused on relative risk stratification among patients diagnosed with vasospastic angina, and it is unknown how much vasospasm accounts for the cause of out-of-hospital cardiac arrest, and whether prognosis differs.

Methods: From a registry data collected from 65 hospitals in Korea, 863 subjects who survived hospital cardiac arrest were evaluated. The patients with insignificant coronary lesion, vasospasm, and obstructive lesion were each grouped as group I, group II, and group III, respectively. The primary and secondary outcomes were survival to hospital discharge and good neurological function at discharge defined as cerebral performance index 1.

Results: At hospital discharge, 529 subjects (61.3%) survived. There was no significant difference in survival according to coronary angiographic findings (P = .133 and P = .357, group II and group III compared to group I), but the neurological outcome was significantly better in groups II and III (P = .046 and P = .022, groups II and III compared to group I). Two multivariate models were evaluated to adjust traditional risk factors and cardiac biomarkers. The presence of coronary artery vasospasm did not affect survival to hospital discharge (P = 0.060 and P = .162 for both models), but neurological function was significantly better (OR: 1.965, 95% CI: 1.048-3.684, P = .035, and OR: 1.706, 95% CI: 1.012-2.878, P = .045 for vasospasm, models I and II, respectively).

Conclusions: Coronary vasospasm does not show better survival to hospital discharge, but shows better neurological outcomes. Aggressive coronary angiography and intensive medical treatment for adequate control of vasospasm should be emphasized to prevent and manage fatal events.

Keywords: KoCARC; cardiac arrest; vasospasm; outcome

INTRODUCTION

Vasospastic angina, or variant angina, is a unique type of coronary artery disease, induced by dynamic obstruction of epicardial coronary arteries due to transient vasospasm.[1] First recognized decades ago, studies have suggested various mechanisms to explain the transient vasospasm, such as abnormal response to autonomic nervous system,[2-4] endothelial dysfunction,[3,5] abnormal reaction of vascular smooth muscles,[5,6] or magnesium deficiency.[7,8] Genetic inheritance has also been suggested as one of the mechanisms,[9] and still unresolved, it is known to be more popular in Asians, especially in Japan and Korea, than other ethnics.[10] Previous cohort studies of vasospastic angina has shown that not all vasospastic angina show the same prognosis, with 8.6% presenting as aborted sudden cardiac death (ASCD).[11] Vasospastic angina responding to vasodilator therapy commonly shows a good prognosis, but medically refractory subjects can show unfavorable events such as life-threatening arrhythmia and eventually sudden cardiac arrest.[12-14] Vasospastic angina with ASCD showed worse prognosis compared to those without ASCD, with higher incidence of in-hospital death and higher rate of additional

ORIGINAL INVESTIGATION

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cardiac arrest, ventricular tachyarrhythmia and myocardial infarction after discharge.[11]

The out-of-hospital cardiac arrest (OHCA) has become major public health concern in Korea and worldwide,[15] and with a comprehensive concept of active surveillance by medical emergency team or rapid response team, most of second and tertiary hospitals are making an effort to improve the survival rate and neurological outcome. The coronary artery disease has been highlighted as the major etiology of OHCA, and thus, the post cardiac arrest care includes consideration of coronary angiography in patients after return of spontaneous circulation.[16,17] Studies mostly focus on OHCA resulted by obstructive coronary artery disease, but as we have mentioned above, coronary vasospasm can also result in OHCA, which has not been evaluated in depth. Most of the previous cohort studies of vasospastic angina focused on relative risk stratification within patients diagnosed as vasospastic angina. Yet, it is unknown how much vasospasm accounts for the cause of sudden cardiac arrest in OHCA, and whether different cardiac causes show different prognosis in terms of survival at hospital discharge and neurological outcome.

Thus in this study, we aimed to evaluate the significance and prognosis of vasospasm in patients with OHCA, and compared the outcome with OHCA due to other causes including obstructive coronary artery disease and insignificant coronary lesions.

METHODS

Study Subjects

The data of study subjects were obtained from the database of The Korean Cardiac Arrest Research Consortium (KoCARC) registry.[18] The KoCARC is a collaborative research network of 65 secondary or tertiary hospitals in Korea. It was organized in 2014, including 7 research committees which are Epidemiology and Preventive Research Committee, Community Resuscitation Research Committee, Emergency Medical Service (EMS) Resuscitation Research Committee, Hospital Resuscitation Research Committee, Hypothermia and Post-resuscitation Care Research Committee, Cardiac Care Resuscitation Committee and Pediatric Resuscitation Research Committee. All patients with OHCA who were transported to participating hospitals were enrolled in the KoCARC registry since October 2015. The subjects with terminal illness documented by medical records, under hospice care, in pregnancy, with pre-documented "Do Not Resuscitate" card, and with definite non-cardiac cause were excluded.

Between October 2015 and June 2018, a total of 9521 patients were registered. Of 2915 subjects who survived, 1,116 patients had records of coronary angiography before discharge. Excluding those who had coronary angiography after more than 3 days of return of spontaneous circulation, only those who had coronary angiography within 3 days of OHCA were included for analysis, and total number of study subjects was 863 (Figure 1).

Ethics Statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (number 1401-090-5550). The informed consent was waived by the IRB. All authors had access to the study data and had reviewed and approved the final manuscript.

Measurements

The demographic information and traditional risk factors of atherosclerosis including hypertension, diabetes mellitus, hypercholesterolemia, smoking history, and family history of coronary artery disease were acquired. Hypertension was defined as previously diagnosed hypertension or the use of antihypertensive medication. Diabetes mellitus was defined as prior history of diabetes mellitus or taking an oral hypoglycemic agent. Hypercholesterolemia was defined as a previous diagnosis of hypercholesterolemia or the use of a lipid-lowering agent. For smoking, regular smoking habit within the past 12 months was inquired. Data regarding initial resuscitation by lay rescuer and EMS were also obtained, with an initial electrocardiogram (ECG) when available. Initial ECG was reviewed and categorized as shockable rhythm for ventricular fibrillation and tachycardia and non-shockable rhythm for asystole and pulseless electrical activity.

The blood tests included complete blood cell counts, cholesterol profile, glucose levels, renal function, and creatinine

HIGHLIGHTS

- Coronary vasospasm does not affect survival outcome defined as survival to hospital discharge.
- The patients with coronary vasospasm show better neurological outcomes compared to patients with insignificant stenosis, even with known cardiovascular risk factors adjusted.
- Aggressive coronary angiography and intensive medical treatment for adequate control of vasospasm should be emphasized to prevent and manage fatal events.

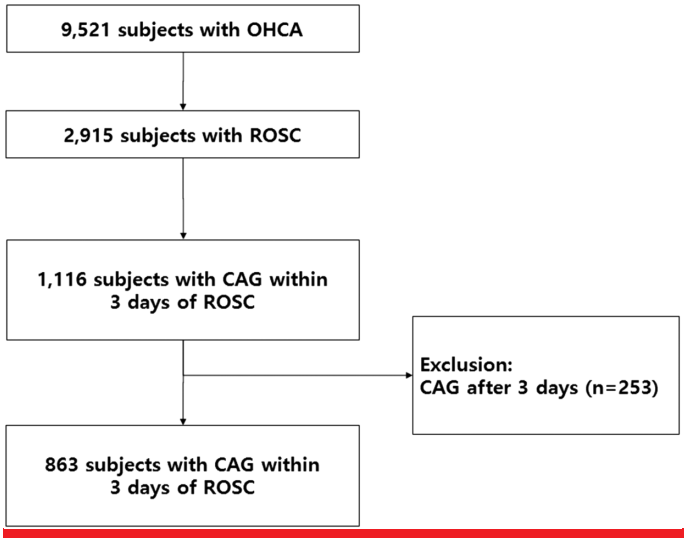

Figure 1. Inclusion criteria of study subjects.

kinase MB (CK-MB) as cardiac biomarkers. CK-MB was categorized into quartiles for statistical analysis, with lowest to highest quartiles marked as Q1-Q4 serially.

The reports of coronary angiography were all reviewed and patients were grouped into 3 different groups according to the angiographic finding. The subjects without any significant coronary lesion were defined as group I, the subjects with vasospasm were grouped as group II, and those with significant stenosis as culprit lesion were categorized as group III. The patients with coronary angiographic (CAG) findings showing severe vasospasm and consequently coronary artery obstruction due to spasm and relief of obstruction with intracoronary nitroglycerin, and without no other obstructive culprit lesion were defined as vasospastic angina.

The primary outcome was survival to hospital discharge. The secondary outcome was functional ability in neurological function based on cerebral performance category (CPC) scoring system at discharge. Cerebral performance category was assessed mainly based on electronic medical records, and a good neurological outcome was defined as a CPC score 1 (normal). Cerebral performance category 2 with mild or moderate functional impairment but still independent, CPC 3 with conscious with severe disability and dependence, CPC 4 with coma or vegetative state, and CPC 5 which indicates death were also assessed. Cerebral performance categories 2 to CPC 5 were defined as the poor neurological outcome in this study.

Statistical Analysis

The continuous variables were presented as mean ± standard deviation, and categorical variables were described using numbers and percentages. For comparison between different groups, analysis of variances (one-way analysis of variance) test and independent sample *t*-test were used. The categorical variables were compared using Pearson's chi-square test. To analyze the significant parameters that affect outcome, univariate logistic regression analysis was applied, and using multivariate logistic regression, possible confounders were adjusted in different models. The statistical analysis was performed using SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). All statistical tests were 2-sided and *P*-value of <.05 was considered significant.

RESULTS

Baseline Characteristics of Study Population

The coronary angiographic findings were reviewed in 863 subjects who survived OHCA and had coronary angiography within 3 days of arrest. Overall results showed 271 (31.4%) subjects without any significant coronary lesion, 119 (13.8%) subjects had vasospasm, and 473 (54.8%) subjects had significant coronary artery stenosis as culprit lesion. As shown in Table 1, the mean age of study subjects differed within 3 groups, with significantly older age in group III ($P < .001$). In group II patients with vasospasm-related OHCA, male gender was more common (73.8% vs. 87.4%, $P = .003$ in group I vs. group II), but prevalence of hypertension, diabetes mellitus, and dyslipidemia did not show significant difference compared to group I ($P = .239$, $P = .890$, and $P = .137$, accordingly). Smokers were significantly more common in group II, which is also a well-known risk factor of vasospasm (21.8% vs. 36.1%, $P = .005$ of current smokers in group I vs. group II). In group III patients with obstructive culprit lesions, significantly greater number of patients were male gender (73.8% vs. 86.7%, $P = .000$ in group I vs. group III) and had history of hypertension and diabetes mellitus compared to group I (35.2% vs. 53.1%, $P = .000$ and 22.2% vs. 31.5% $P = .011$ for hypertension and diabetes mellitus in group I vs. III accordingly). Neither the prevalence of hypercholesterolemia nor smoking history showed difference between groups I and III ($P = .875$ and $P = .461$ for hypertension and smoking history, respectively).

In group II greater number of patients were current smokers compared to group III ($P = .034$ in group II vs. III), less had hypertension ($P = .043$) and diabetes mellitus ($P = .035$). The gender ($P = 1.000$), hypercholesterolemia ($P = .157$) and witnessed arrest ($P = .786$) did not show significant difference between groups II and III.

The EMS data did not show significant difference in number of witnessed arrest among the 3 groups ($P = .108$). Bystander Cardiopulmonary resuscitation (CPR) was performed in 60.2% of the total study subjects, and initial basic life support by bystander did not show significant difference among the 3 groups. Initial ECG taken by EMS showed a significant difference among the 3 groups ($P = .034$), with a greater number of shockable rhythm in group III compared to group I (65.2% vs. 74.2%, $P = .015$, in group I vs. III).

The laboratory data showed no significant difference in hemoglobin, platelet counts, albumin, renal function, and glucose levels (Table 1). Total cholesterol was significantly higher in group III compared to group I (148 ± 40 vs. 160 ± 49, $P = .010$ in group I vs. group III).

The initial and peak cardiac enzyme levels were measured using CK-MB, and both were evaluated in quartiles for analysis. The initial CK-MB did not differ within the 3 groups ($P = .647$), and also when groups II and III were compared to group I ($P = .709$ and $P = .453$ in group II vs. Groups I and III vs. group I, respectively). The peak values for CK-MB showed significant difference within the 3 groups ($P = .000$), with significantly higher level of peak CK-MB in groups II and III compared to group I ($P = .020$ and $P = .000$ in groups II and III vs. group I, respectively).

Among 863 study subjects, 529 subjects (61.3%) survived to hospital discharge. The survival to hospital discharge did not show significant difference within the 3 groups (Figure 2). A total of 158 subjects (58.3%), 79 subjects (66.4%) and 292 subjects (61.7%) survived to hospital discharge in groups I, II, and III respectively ($P = .307$). When groups II and III were each compared with group I, there was still no difference in survival to hospital discharge ($P = .144$ and $P = .391$ in group II vs. groups I and III vs. group I, respectively).

The neurological function was assessed in all patients at hospital discharge as shown in Table 1. The neurological

Table 1. Baseline Characteristics According to Coronary Angiographic Finding

Parameters	Insignificant Coronary Lesion (Group I) n = 271	Coronary Vasospasm (Group II) n = 119	Obstructive Coronary Lesion (Group III) n = 473	*P*
Demographic parameters				
Age (years)	56 ± 15	56 ± 12	61 ± 12¶††	<.001
Male gender, n (%)	200 (73.8%)	104 (87.4%)¶	410 (86.7%)¶	<.001
Comorbidity				
Hypertension, n (%)	89 (35.2%)	46 (38.7%)	238 (53.1%)¶	<.001
Diabetes mellitus, n (%)	56 (22.2%)	23 (19.3%)	140 (31.5%)¶	.035
Hypercholesterolemia, n (%)	16 (6.7%)	12 (10.1%)	30 (7.1%)	.741
Smoking history, n (%)				.031
Current smoker	59 (21.8%)	43 (36.1%)¶	133 (28.1%)††	
Ex-smoker	35 (12.9%)	15 (12.6%)	64 (13.5%)	
Never smoker	98 (36.2%)	28 (23.5%)	173 (36.6%)	
Unknown	79 (29.2%)	33 (27.7%)	102 (21.6%)	
Witnessed arrest	205 (76.5%)	97 (83.6%)	386 (82.3%)	.108
Initial electrocardiogram by emergency team, n (%)				.034
Shockable rhythm	165 (65.2%)	77 (67.5%)	333 (74.2%)¶	
Non-shockable rhythm	88 (34.8%)	37 (32.5%)	116 (25.8%)	
Laboratory parameters				
Hemoglobin (g/dL)	13.5 ± 2.5	14.0 ± 1.8	13.5 ± 2.4††	.151
Platelet (×10^3/μL)	211 ± 74	210 ± 61	212 ± 79	.962
Blood urea nitrogen (mg/dL)	21 ± 20	19 ± 9	22 ± 12††	.281
Creatinine (mg/dL)	3.6 ± 20.4	7.0 ± 31.9	2.8 ± 10.4	.192
Albumin (g/dL)	3.6 ± 0.6	3.7 ± 0.5	3.7 ± 0.8	.174
Glucose (mg/dL)	294 ± 133	280 ± 86	284 ± 123	.551
HbA1C (%)	6.1 ± 1.5	6.0 ± 0.9	6.7 ± 1.8¶††	.061
Total cholesterol (mg/dL)	148 ± 40	154 ± 44	160 ± 49¶	.048
Triglyceride (mg/dL)	177 ± 138	142 ± 67	146 ± 81	.259
High-density lipoprotein cholesterol (mg/dL)	43 ± 14	47 ± 14	40 ± 12††	.084
Low-density lipoprotein cholesterol (mg/dL)	114 ± 148	98 ± 43	123 ± 111	.761
Initial creatinine kinase-MB				.647
Q1	69 (25.7%)	31 (26.1%)	98 (21.0%)	
Q2	72 (26.9%)	30 (25.2%)	127 (27.2%)	
Q3	66 (24.6%)	25 (21.0%)	119 (25.5%)	
Q4	61 (22.8%)	33 (27.7%)	123 (26.3%)	
Peak creatinine kinase-MB				<.001
Q1	69 (32.2%)	22 (22.2%)¶	62 (16.4%)¶	
Q2	83 (38.8%)	31 (31.3%)	119 (31.5%)	
Q3	31 (14.5%)	20 (20.2%)	58 (15.3%)	
Q4	31 (14.5%)	26 (26.3%)	139 (36.8%)	
Neurological evaluation at hospital discharge				
CPC 1	108 (39.9%)	61 (51.3%)¶	230 (48.6%)¶	<.001
CPC 2	13 (4.8%)	4 (3.4%)	31 (6.6%)	
CPC 3	6 (2.2%)	4 (3.4%)	14 (3.0%)	
CPC 4	23 (8.5%)	10 (8.4%)	16 (3.4%)	
CPC 5	121 (44.7%)	40 (33.6%)	182 (38.4%)	

¶*P* < .05 compared to normal
††*P* < .05 spasm versus significant stenosis
CPC, cerebral performance category; HbA1C, glycated hemoglobin; Q, quartile.

assessment showed significant difference within groups at hospital discharge (*P* = .000). Group II showed significantly better neurological status at hospital discharge compared to group I (39.9% vs. 51.3% *P* = .046 for CPC 1 at hospital discharge, group I vs. group II). Group III also showed better neurological function at hospital discharge compared to group I (39.9% vs. 48.6%, *P* = .022 for CPC 1 at hospital discharge, group I vs. group III).

Correlation of Various Parameters in Association with Survival to Hospital Discharge

Age older than 65 years old and presence of comorbidities including hypertension and diabetes mellitus were associated with poor outcome defined as survival at hospital discharge (OR: 0.358, 95% CI: 0.269-0.478, *P* = .000 for age ≥65, OR: 0.666, 95% CI: 0.500-0.886, *P* = .005 for hypertension, OR: 0.377, 95% CI: 0.274-0.518, *P* = .000 for diabetes mellitus, Table 2). Witnessed OHCA showed a better survival (OR: 1.711, 95% CI: 1.215-2.410, *P* = .002). The patients with initially shockable rhythm showed better survival outcome (OR: 5.319, 95% CI: 3.843-7.361, *P* = .000). The highest quartile of CK-MB at both baseline and peak was associated with poor survival at discharge (OR: 0.322, 95% CI: 0.213-0.487, *P* = .000, OR: 0.193, 95% CI: 0.117-0.319, *P* = .000 for Q4 vs. Q1 in baseline and peak CK-MB, respectively). The survival to hospital discharge did not show difference according to coronary angiographic findings (*P* = .133 and *P* = .357, groups II and III compare to group I).

Significant Parameters of Good Neurological Outcome at Hospital Discharge

CPC 1 was defined as good neurological outcome in this study. As shown in Table 2, the parameters associated with good neurological outcome at hospital discharge were witnessed arrest and initially shockable ECG rhythm (OR: 2.248, 95% CI: 1.565-3.230, *P* = .000 and OR: 5.779, 95% CI: 4.008-8.334, *P* = .000 for witnessed arrest and initial shockable rhythm on ECG). Age older than 65 years old, presence of diabetes mellitus, and glycated hemoglobin (HbA1C) ≥7% were associated with poor neurological outcome (OR: 0.335, 95% CI: 0.249-0.451, *P* = .000, for age≥65, OR: 0.375, 95% CI: 0.269-0.522, *P* = .000, for diabetes mellitus, OR: 0.265, 95% CI: 0.104-0.673, *P* = .005 for HbA1C≥7%). Higher levels of CK-MB both at baseline and peak showed poor neurological outcome (OR: 0.284, 95% CI: 0.189-0.426, *P* = .000, OR: 0.216, 95% CI: 0.137-0.341, *P* = .000, for Q4 vs. Q1 in baseline and peak CK-MB, respectively). Groups II and III patients showed a better neurological outcome at hospital discharge, compared to group I (OR: 1.587, 95% CI: 1.028-2.450, *P* = .037. OR: 1.429, 95% CI: 1.055-1.934, *P* = .021 for groups II and III respectively, Figure 3).

Adjusted Risk Factors for Survival and Neurological Outcome

Multivariate models were evaluated to adjust possible confounders including traditional cardio-metabolic risk factors and cardiac biomarker. Model I included age≥65, gender, smoking and peak CK-MB, and model II included age≥65, gender, hypertension, diabetes mellitus, and initial ECG for adjustment as covariates.

The presence of coronary artery vasospasm did not affect survival to hospital discharge, even after adjustment (*P* = .060 and *P* = .162 for models I and II, Table 3). However, multivariate analysis for good neurological outcomes at hospital discharge showed that patients with vasospasm or obstructive lesion had significantly better neurological function even after adjusting the confounding variables (OR 1.965, 95% CI 1.048-3.684, *P* = .035 for vasospasm and OR 2.566, 95% CI 1.620-4.064, *P* = .000 for obstructive coronary artery lesions, Model I). With additional risk factors for atherosclerosis adjusted, vasospasm showed a significant association with good neurological function at hospital discharge (OR 1.706, 95% CI 1.012-2.878, *P* = .045, Model II).

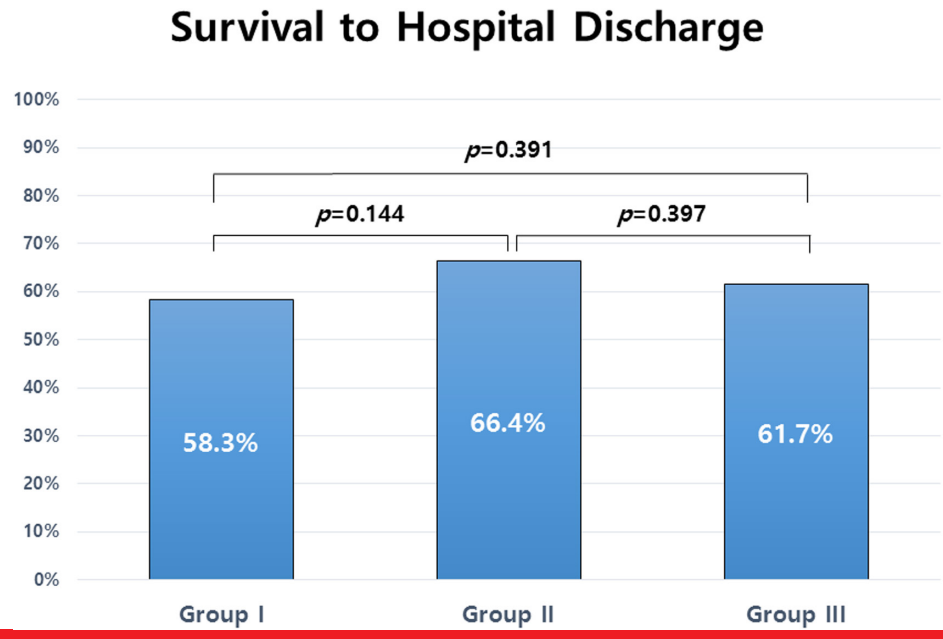

Figure 2. Primary outcome analysis: survival to hospital discharge according to coronary angiographic findings.

Table 2. Univariate Analysis for Association with Outcomes at Hospital Discharge

Variables	Survival			Good Neurological Function		
	OR	95% CI	*P*	OR	95% CI	*P*
Age ≥65	0.358	0.269-0.478	<.001	0.335	0.249-0.451	<.001
Male gender	1.198	0.837-1.714	.324	1.213	0.849-1.733	.288
Hypertension	0.666	0.500-0.886	.005	0.785	0.595-1.035	.087
Diabetes mellitus	0.377	0.274-0.518	<.001	0.375	0.269-0.522	<.001
Dyslipidemia	0.749	0.436-1.288	.296	1.079	0.632-1.844	.780
Smoking			.473			
Never-smoker	Ref			Ref		
Ex-smoker	1.145	0.732-1.791	.554	1.036	0.672-1.596	.873
Current smoker	1.246	0.872-1.778	.227	1.308	0.929-1.842	.124
Witnessed arrest	1.711	1.215-2.410	.002	2.248	1.565-3.230	<.001
Initially shockable rhythm from EMS data	5.319	3.843-7.361	<.001	5.779	4.008-8.334	<.001
Targeted temperature management	0.995	0.742-1.332	.971	0.843	0.633-1.123	.242
Hemoglobin (g/dL)	1.351	1.251-1.460	<.001	1.421	1.308-1.543	<.001
Platelet ($\times 10^3/\mu L$)	1.011	1.009-1.014	<.001	1.010	1.007-1.012	<.001
Albumin (g/dL)	4.005	2.870-5.588	<.001	4.332	3.051-6.151	<.001
Fasting glucose ≥126 mg/dL	0.583	0.244-1.393	.225	0.378	0.164-0.871	.022
HbA1C ≥7%	0.161	0.065-0.401	<.001	0.265	0.104-0.673	.005
Total cholesterol ≥200 mg/dL	1.807	1.005-3.251	.048	2.173	1.266-3.730	.005
Triglyceride ≥150 mg/dL	0.523	0.255-1.074	.078	0.700	0.356-1.375	.300
HDL cholesterol ≥45 mg/dL	2.033	0.959-4.308	.064	1.440	0.729-2.845	.294
LDL cholesterol ≥130 mg/dL	1.354	0.543-3.374	.516	1.731	0.734-4.080	.210
Blood urea nitrogen (mg/dL)	0.969	0.955-0.984	<.001	0.976	0.962-0.991	.001
Creatinine (mg/dL)	0.999	0.989-1.008	.776	0.994	0.983-1.005	.252
Initial creatinine kinase-MB						
Q1	Ref			Ref		
Q2	0.627	0.413-0.949	.027	0.461	0.312-0.680	<.001
Q3	0.556	0.365-0.847	.006	0.521	0.351-0.774	.001
Q4	0.322	0.213-0.487	<.001	0.284	0.189-0.426	<.001
Peak creatinine kinase-MB						
Q1	Ref			Ref		
Q2	0.604	0.364-1.004	.052	0.517	0.335-0.797	.003
Q3	0.400	0.226-0.710	.002	0.353	0.211-0.590	<.001
Q4	0.193	0.117-0.319	<.001	0.216	0.137-0.341	<.001
Coronary angiography finding						
Normal or insignificant	Ref			Ref		
Vasospasm	1.412	0.900-2.216	.133	1.587	1.028-2.450	.037
Significant stenosis	1.154	0.851-1.564	.357	1.429	1.055-1.934	.021

CK-MB, creatinine kinase-MB; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; Q, quartile.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the significance of coronary vasospasm-related OHCA in survival and neurological outcome in the real world. In this study we present a novel finding showing the incidence and related outcomes of vasospasm in OHCA: 1) coronary vasospasm does not affect survival outcome defined as survival to hospital discharge, and 2) patients with coronary vasospasm show better neurological outcome compared to patients with insignificant stenosis.

The most common cause of cardiogenic OHCA is acute coronary syndrome. It has been reported that 70% of ASCD taken to immediate coronary angiography had clinically significant coronary artery disease, 50% of whom had an acutely occluded vessel.[19,20] Kern et al reported the importance of coronary angiography in OHCA survivors, both in patients

Table 3. Multivariate Models for Outcome Analysis

	Model I		Model II	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Survival to hospital discharge				
Patients with vasospasm	1.918 (0.972-3.784)	.060	1.474 (0.855-2.540)	.162
Patients with obstructive coronary lesion	2.232 (1.384-3.598)	.001	1.214 (0.833-1.770)	.313
Good neurological function at hospital discharge				
Patients with vasospasm	1.965 (1.048-3.684)	.035	1.706 (1.012-2.878)	.045
Patients with obstructive coronary lesion	2.566 (1.620-4.064)	<.001	1.482 (1.022-2.151)	.038

Model I: adjusted parameters were age≥65, gender, smoking and peak CK-MB in quartile.
Model II: adjusted parameters were age ≥65, gender, hypertension, diabetes mellitus, initial electrocardiogram.

with ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction,[19] and suggested immediate coronary angiography regardless of ST segment elevation when suspicious. The survival was similar for those with and without ST segment elevation myocardial infarction among all patients who underwent immediate coronary angiography, whereas it was equally poor in those who did not undergo coronary angiography. Thus, the importance of aggressive post-cardiac arrest care including targeted temperature management and coronary artery reperfusion was highlighted in Kern's study. In contrast to Kern's study, our result did not show survival difference, neither in vasospasm-related arrest nor obstructive coronary artery disease-related arrest. The study population and evaluated measures were different in our study, which may explain the conflicting results. Kern's study population consisted of comatose post-cardiac arrest patients and excluded patients with responsive or alert mental status, whereas we evaluated all subjects with ASCD. Whereas Kern's study compared patients with and without ST segment elevation focusing on obstructive lesions, we evaluated and compared overall angiographic findings including vasospasm and obstructive lesions.

Vasospastic angina is characterized by "reversible" obstruction of the epicardial coronary artery and subsequent chest pain with 'transient' ST segment elevation on ECG.[21] In patients who respond well to vasodilators, a favorable prognosis has been reported.[13] However, recent data show that not all vasospastic angina show a good prognosis, and from many cohort studies, researchers have tried to stratify the relative risks of patients with vasospastic angina.[10,11,22-24] Vasospasm has been suggested as a cause of vulnerable plaque rupture, leading to myocardial infarction. What is commonly agreed upon nowadays is that within the spectrum of this unique disease, vasospastic angina with ASCD shows higher rates of cardiac death compared to non-ASCD, and history of ASCD is an important risk factor of adverse events in patients with vasospasm. Yet, as mentioned above, the incidence and associated parameters of vasospasm in patients who present as OHCA had not been studied much previously. It was unknown how much share vasospasm takes in OHCA, and whether prognosis shows a difference in vasospasm with ASCD.

There has been a western registry data from France,[25] collecting community-based multicenter data of OHCA in Paris

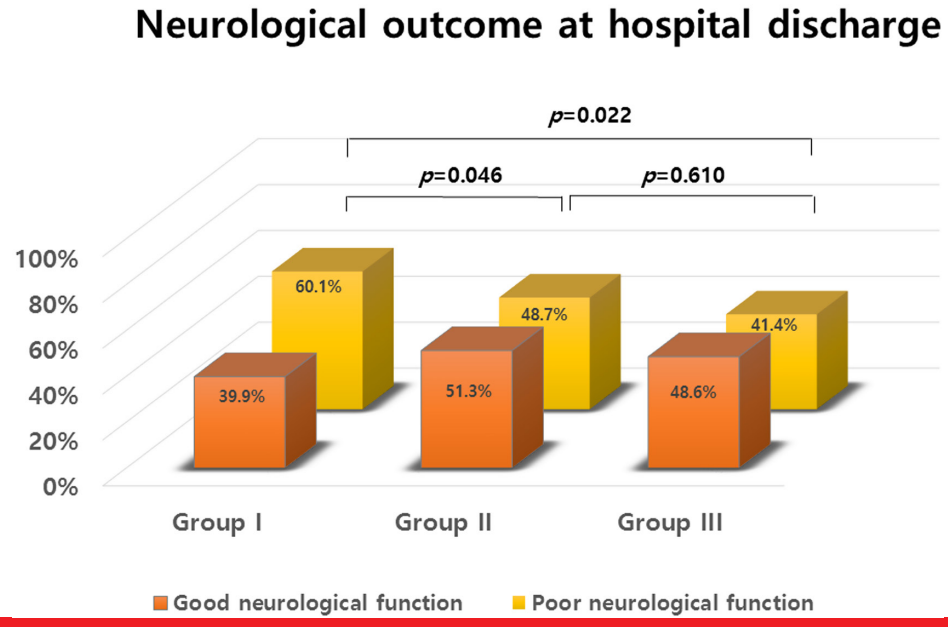

Figure 3. Secondary outcome analysis: neurological function at hospital discharge according to coronary angiographic findings.

and suburbs since 2011. The Paris Sudden Death Expertise Center (Paris-SDEC) registry reviewed and evaluated etiologies of all OHCA, and from initial evaluation using ECG, echocardiogram, and coronary angiography, reported 525 coronary artery disease from 717 survivors of sudden cardiac arrest, of which 24 (3.3%) was vasospasm-related cardiac arrest. From the result, we have shown that 13.8% of study subjects had vasospasm as a cardiogenic cause of OHCA in Korea, which is about 4 times more common than that reported from the Paris-SDEC registry. Considering that vasospasm is much more common in Asians[12,26] and tends to be underdiagnosed, the proportion of vasospasm-related OHCA is expected to be much greater in Korea than that in the western world and also from what has been reported. Previous cohorts of vasospastic angina from Korea[11] and Japan[27] each have reported 8.6% (598 out of 6972 diagnosed vasospastic angina) and 2.5% (35 out of 1429 vasospastic angina) of documented vasospastic angina patients presenting with ASCD respectively. These are the numbers who have survived cardiac arrest, and the numbers would be even greater if we include those who had OHCA but failed to survive. Interestingly, despite no survival difference, patients with vasospasm showed significantly better neurological outcomes at hospital discharge, the importance of which cannot be depreciated or emphasized less.

In some patients, coronary artery vasospasm may be lethal at first presentation, and in others who survived after OHCA, vasospasm may still be life-threatening despite intensive vasodilator therapies. A study has shown that 13.7% of vasospastic angina suffer from intractable spasm with a young age onset who had higher portion of smokers.[28] The intractable vasospasm is very difficult to manage but still extremely important. Larger doses of vasodilators, combination of different classes, and co-administration of other medications such as magnesium,[29] antioxidants,[30-32] statins[33,34] and estrogens[35] have also been suggested as treatment options in refractory vasospasm. In vasospastic angina with ASCD, implantable cardioverter defibrillator has shown beneficial effect, which can be considered as another treatment option, together with maximal medical treatment.[22]

Considering that patients with ASCD due to vasospasm are high-risk subjects for major adverse cardiac events and that patients with intractable vasospasm are also at high risk of fatal arrhythmia, early coronary angiography in OHCA without definite non-cardiac cause of arrest and aggressive medical management should be stressed.

Study Limitations

Although clinical registry data is considered as a gold standard of observational studies, it still has many limitations. Since the registry included multiple centers, there is always a concern in collecting data properly and accurately, with clinically appropriate variables and without coding inaccuracies by administrative. The KoCARC registry emphasizes on regular education and feedback for maintaining data accuracy and quality control, to all researchers and principal investigators of each participating hospitals, to minimize the human error. As is other registry datas, KoCARC registry data does not represent the overall population, although it is the biggest registry data of OHCA in Korea. A more detailed description and data from cardiovascular exams may give us even more valuable results in studying OHCA, which may be expected in near future. Another limitation is that we cannot give a long-term prognosis for the study subjects. We do not have enough follow-up data on these arrest survivors to evaluate their prognosis. Follow-up data for prognosis of ASCD with prescribed medications can give us an in-depth understanding of vasospasm, and eventually improve outcomes and help suggest treatment guidelines for intractable vasospasm.

CONCLUSION

The survivors from OHCA induced by coronary artery vasospasm did not show difference in survival to hospital discharge, but showed significantly better neurological performance at discharge, compared to survivors with insignificant coronary lesions. Vasospasm does not always show a good prognosis, and should be effectively and aggressively controlled when diagnosed. Possible underdiagnosis or misdiagnosis should also be considered, and since vasospasm is much more common in Korea, vasospastic angina or vasospasm-related cardiac events should be considered as a differential diagnosis of OHCA. Also, in patients with OHCA, aggressive coronary angiography for diagnosis and treatment should be emphasized.

Ethics Committee Approval: The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (number: 1401-090-5550).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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