Clinical paper

Immediate versus early coronary angiography with targeted temperature management in out-of-hospital cardiac arrest survivors without ST-segment elevation: A propensity score-matched analysis from a multicenter registry

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Abstract

Aim: The optimal coronary angiography (CAG) timing in out-of-hospital cardiac arrest (OHCA) survivors without ST-segment elevation (STE) for good neurologic outcome remains unknown. This study aimed to evaluate whether immediate versus early CAG impacts neurological outcomes of OHCA survivors without STE.

Methods: This multicenter retrospective observational registry-based study was conducted at the emergency department (ED) of 8 Korean tertiary care hospitals. Data of adult non-traumatic OHCA patients with no obvious extra-cardiac cause, without STE, who were treated with targeted temperature management (TTM), and in whom CAG was performed within 24 h after return of spontaneous circulation between 2010 and 2015 were extracted. Patients in the immediate ($\leq$2 h) and early (2–24 h) CAG groups were propensity score matched. The primary endpoint was 1-month good neurological outcomes.

Results: Among 346 patients with TTM and CAG, 119 who underwent CAG after 24 h were excluded, leaving 112 and 115 in the immediate and early CAG groups, respectively. Median time to CAG was 120.0 (70.0–224.0) minutes; 97 (42.7%) patients had significant coronary artery stenosis. Good

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neurological outcome was higher in the early versus immediate CAG group (50.4% vs. 31.3%, P = 0.003), but no significant intergroup difference persisted after matching. CAG timing was not associated with good neurological outcomes (odds ratio, 1.917; 95% confidence interval, 0.954–3.852; P = 0.07).

Conclusions: Coronary artery stenosis was found in 42.7% of TTM-treated non-STE OHCA patients with CAG within 24 h, but there was no clear neurological benefit of immediate versus early CAG.

Keywords: Out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, Coronary angiography, Percutaneous coronary intervention, Outcome

Introduction

Despite recent advances in post-resuscitation care for survivors of cardiac arrest, the overall outcomes of out-of-hospital cardiac arrest (OHCA) remain poor.[1] In addition to targeted temperature management (TTM), a mainstay of the post-resuscitation care, current guidelines emphasized the role of emergent coronary angiography (CAG) and percutaneous coronary intervention (PCI) for OHCA survivors with ST-segment elevation (STE) on a post-resuscitation electrocardiogram (ECG) after the return of spontaneous circulation (ROSC).[2–5] The 2017 European Society of Cardiology and 2014 US guidelines for STE myocardial infarction assign a class I (level of evidence B) recommendation for immediate CAG for OHCA survivors with STE,[6,7] controversy persists for those without STE.[8–10]

Some recent observational studies demonstrated an association between early CAG and better outcomes in OHCA survivors without STE.[9,11–13] However, the inherent biases of observational studies and heterogeneous definition of "early" or immediate CAG from 2 h to 72 h limited the value of their findings.[14,15] Also, the potential risks of adverse events due to CAG such as requiring mobilization at a time of haemodynamic instability, exposure to contrast, and delays in appropriate diagnoses of other possible causes of cardiac arrest and incorrect therapeutic decisions may be increased with routine immediate CAG.[8,10,16,17] Thus, the optimal timing of CAG, i.e. the immediate CAG strategy, performing CAG within 2 h after ROSC, versus early CAG strategy, performing CAG between 2 h and up to 24 h after optimal medical therapy and evaluation, has not yet been settled. The objective of this study was to evaluate whether the immediate CAG strategy would impact the 1-month neurological performance and survival of OHCA survivors without STE compared to the early CAG strategy.

Methods

Study design and patients

This multicenter, retrospective, observational, registry-based study was conducted at the emergency department (ED) of 8 tertiary care university-affiliated teaching hospitals in Korea. Data were extracted from OHCA registries containing prospectively collected data of consecutive patients with OHCA since January 2010.[17] The Institutional Review Board of the University of Ulsan College of Medicine reviewed and approved the study protocol (No. 2016-1038). Informed consent was waived due to the retrospective nature of the study. The OHCA registry enrolled adult (≥18 years) non-traumatic OHCA survivors treated with TTM.

We included patients with no obvious extracardiac cause of OHCA such as hanging, drowning, asphyxia, and poisoning; no evidence of STE myocardial infarction or new-onset left bundle branch block on post-resuscitation ECG; treated with TTM due to unconsciousness after ROSC; and CAG performed within 24 h after ROSC between January 2010 and December 2015. Patients whose post-resuscitation ECG was lost were excluded. Immediate CAG was defined as CAG performed within 2 h after ROSC or ED presentation,[4,18] whereas early CAG was defined as CAG performed between 2 and 24 h.[19] Throughout the study period, CAG timing was determined by an interventional cardiologist. The decision for subsequent PCI or medical treatment was based on the interventional cardiologist's judgment and the angiographic findings.

Management and data collection

During the study period, all OHCA patients received cardiopulmonary resuscitation and post-resuscitation care, including TTM and coronary reperfusion, according to the then-current advanced cardiac life support guidelines.[20,21] TTM was performed for all unconscious patients using cooling devices such as the Blanketrol II (Cincinnati Subzero Products, Cincinnati, OH, USA), Arctic Sun Energy Transfer Pad (Medivance Corp., Louisville, CO, USA), or an endovascular cooling device (Thermoguard; ZOLL Medical Corporation, Chelmsford, MA, USA). The target temperature (33 °C or 36 °C) was maintained for 24 h. After 24 h, patients were rewarmed at a rate of 0.25 °C/h following maintained normothermia until 72 h from ROSC. The temperature was monitored using an esophageal or rectal temperature probe. We used propofol, benzodiazepine, and opioids for sedation and analgesia. If necessary, a neuromuscular blocking agent was administered to control shivering. All patients received standard intensive care according to institutional protocols.

Demographic and clinical data, including age, sex, previous medical history, resuscitation profiles such as the presence of a witness on collapse, initial documented rhythm, duration of resuscitation, and interventions at the ED were obtained. Initial electrocardiographic and coronary angiographic findings as well as interval from ED presentation to CAG were retrieved from the patients' electronic medical records.[17] Neurological performance assessed by Cerebral Performance Category score and survival at 1 month were also obtained. Among the patients who received early CAG (<24 h after presentation), those who underwent CAG within 2 h were compared to those who underwent CAG at 2–24 h. The primary endpoint was a good neurological outcome at 1 month defined as a Cerebral Performance Category score of 1–2, while the secondary outcome was 1-month survival.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range). Categorical variables are expressed as number (percentage). Comparisons of demographic and clinical characteristics between the immediate and early CAG groups were performed using Student's t-test or the Mann–Whitney U

test for continuous variables and the Chi-square test for categorical variables.

To reduce the effect of treatment selection bias and potential confounding factors inherent in an observational study, we adjusted for differences in the patients' baseline characteristics using propensity score matching. The propensity scores were estimated without regard to outcomes through a multiple logistic regression analysis. A full non-parsimonious model was developed that included all variables shown in Table 1. The discrimination and calibration abilities of each propensity score model were assessed using the C-statistic and the Hosmer–Lemeshow statistic.[22] Propensity score-matched pairs were created by matching between patients in the immediate and early CAG groups on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score. Using the matched set, we examined the similarities between the immediate and early CAG groups by calculating standardized differences for each of the baseline variables listed in Table 1. The C-statistic of the propensity score model was 0.760, while the P value of the Hosmer–Lemeshow statistics was 0.247. In this crude model, good neurological outcomes and 1-month survival were compared using the logistic regression model. In the propensity-matched analysis, good neurological outcomes and 1-month survival were compared using the conditional logistic regression model for matched pairs data. All reported P values are two-sided, and P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 517 non-traumatic OHCA survivors who received CAG and TTM were admitted during the study period; of them, 171 were excluded due to STE on their post-resuscitation ECG (n = 147) or ECG loss (n = 24) (Fig. 1). Of the remaining 346 patients, 119 were excluded because they underwent CAG after 24 h. Thus, 227 patients were ultimately included in the study. Patients were categorized into the immediate CAG (n = 112, 49.3%) or early CAG (n = 115, 50.7%) groups. Using propensity score matching, each group included 73 of 146 patients and compared for neurological and survival outcomes.

The demographic and clinical characteristics of the patients before and after propensity score matching are summarized in Table 1 and e-Table 1, respectively. Despite no difference in past cardiac diseases such as acute myocardial infarction and coronary artery disease, the immediate group showed higher rates of non-cardiac diseases including diabetes mellitus and chronic kidney disease. Patients in the immediate CAG group had a higher rate of witnessed arrest (75.0% vs. 62.6%, P = 0.04) and received more extracorporeal life support in the ED (18.8% vs. 2.6%; P < 0.001).

The coronary angiographic findings are presented in Table 2. The median interval from ROSC to CAG was 120.0 (interquartile range, 70.0–224.0) minutes, and 97 of 227 (42.7%) had at least one significant coronary artery stenosis episode; of the 97 episodes, 49 (21.6%) required subsequent PCI. The rate of subsequent PCI was not significantly different between the immediate and early CAG groups [n = 28 (25.0%) vs. n = 21 (18.3%), respectively; P = 0.22].

Fig. 2 compares the outcomes at 1 month before and after propensity score matching. The 1-month survival and good neurological outcome rates before matching were significantly higher in the early CAG group than in the immediate CAG group. In contrast, the 1-month survival and good neurological outcome rates after matching did not significantly differ between the two groups. Likewise, early CAG was associated with 1-month good neurological outcomes (odds ratio (OR), 2.238; 95% confidence interval (CI), 1.309–3.872; P = 0.004) as well as 1-month survival (OR, 2.272; 95% CI, 1.289–4.063; P = 0.005) compared to immediate CAG (Table 3). After

Table 1 – Demographic and electrocardiographic characteristics of patients with out-of-hospital cardiac arrest without ST-segment elevation according to coronary angiography timing.

Characteristic	Total patients (n = 227)	Immediate group (<2 h) (n = 112)	Early group (2–24 h) (n = 115)	P Value
Demographics				
Age, years	57.24 ± 13.34	57.25 ± 13.31	57.23 ± 13.43	0.99
Male	170 (74.9%)	85 (75.9%)	85 (73.9%)	0.73
Previous medical history				
Hypertension	89 (39.2%)	44 (39.3%)	45 (39.1%)	0.98
Diabetes mellitus	54 (23.8%)	33 (29.5%)	21 (18.3%)	0.05
Acute myocardial infarction	14 (6.2%)	6 (5.4%)	8 (7.0%)	0.62
Coronary artery disease	24 (10.6%)	12 (10.7%)	12 (10.4%)	0.95
Congestive heart failure	11 (4.9%)	6 (5.4%)	5 (4.4%)	0.72
Chronic kidney disease	14 (6.2%)	11 (9.8%)	3 (2.6%)	0.02
Arrest characteristics				
Witnessed	156 (68.7%)	84 (75.0%)	72 (62.6%)	0.04
Bystander CPR	115 (50.7%)	57 (50.9%)	58 (50.4%)	0.95
Initial shockable rhythm	104 (45.8%)	49 (43.8%)	55 (47.8%)	0.54
Time from collapse to ROSC, min	32.4 ± 16.33	34.0 ± 17.24	30.8 ± 15.27	0.14
Interventions before CAG				
Vasopressor use	151 (66.5%)	81 (72.3%)	70 (60.9%)	0.07
Extracorporeal life support	24 (10.6%)	21 (18.8%)	3 (2.6%)	<0.001

Values are expressed as mean ± standard deviation or n (%) as appropriate.
CAG = coronary angiography, CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation.
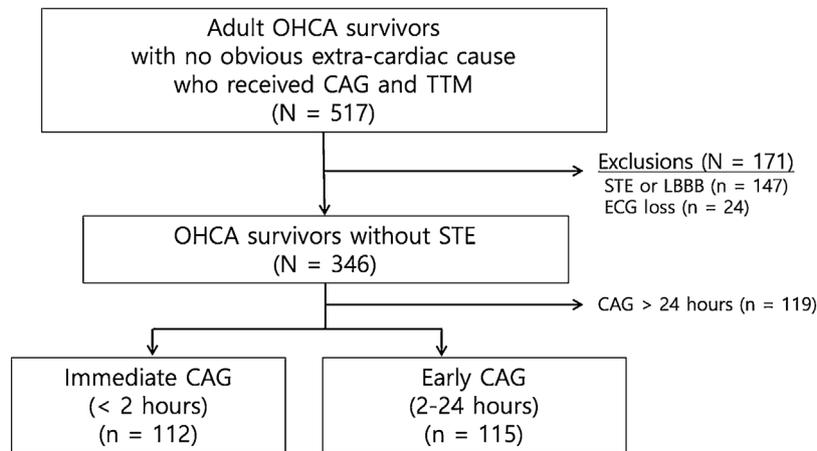
Fig. 1 – Flowchart of patient selection process.
CAG, coronary angiography; ECG, electrocardiogram; LBBB, left bundle branch block; OHCA, out-of-hospital cardiac arrest; STE, ST-segment elevation; TTM, targeted temperature management.

Table 2 – Coronary angiography findings and revascularization of patients with out-of-hospital cardiac arrest without ST-segment elevation according to coronary angiography timing.

Variable	Total patients (n = 227)	Immediate group (< 2 h) (n = 112)	Early group (2–24 h) (n = 115)	P-Value
Interval from ROSC to CAG, min	120.0 (70.0–224.0)	70.0 (55.0–94.8)	223.0 (160.0–300.0)	<0.001
Significant coronary stenosis	97 (42.7%)	54 (48.2%)	43 (37.4%)	0.10
1 vessel	38/97 (39.2%)	17/54 (31.5%)	21/43 (48.8%)	0.22
2 vessels	25/97 (25.8%)	16/54 (29.6%)	9/43 (20.9%)	
3 vessels or left main artery disease	34/97 (35.1%)	21/54 (38.9%)	13/43 (30.2%)	
Subsequent percutaneous coronary intervention	49 (21.6%)	28 (25.0%)	21 (18.3%)	0.22

Values are expressed as *n* (%) or median with interquartile range.
CAG = coronary angiography, ROSC = return of spontaneous circulation.

propensity score matching, CAG timing was not independently associated with 1-month survival or good neurological outcomes on the logistic regression model of the matched groups (1-month good neurological outcome: OR, 1.917, 95% CI, 0.954–3.852, P = 0.07; 1-month survival: OR, 1.600, 95% CI, 0.726–3.526, P = 0.24, respectively).

Additionally, we categorized the patients who were treated with subsequent PCI into immediate (<2 h, n = 23) and early (2–24 h, n = 26) PCI groups. The demographic and clinical characteristics did not differ between two groups except the rate of extracorporeal life support in the ED (43.5% of immediate PCI group vs. 3.8% of early PCI group; P = 0.001) (e-Table 2). The 1-month survival and good neurological outcome rates did not show significant differences between two groups (e-Table 3).

Discussion

In this multicenter registry-based study, among the OHCA survivors without STE who received CAG within 24 h regardless of the initial documented rhythm, we found no significant difference in 1-month

good neurological outcomes or survival between early CAG and immediate CAG after propensity score matching.

In our study, 97 (42.7%) resuscitated patients without STE had at least 1 significant coronary lesion, of whom 49 (21.6%) were required subsequent PCI. The overall prevalence of PCI in our study is comparable to those of other studies of OHCA. Jentzer et al. analyzed 599 OHCA subjects from a prospective two-center registry and reported that 26.4% of patients without STE underwent PCI,[23] and Dumas et al. reported that about 25% of patients without STE underwent successful PCI.[24] In another study, among 524 cardiac arrest survivors without STE who received CAG, 157 (30.0%) were treated with PCI.[9] In a recent meta-analysis of 23 articles, 38.7% of OHCA survivors without STE in the early CAG group received revascularization such as PCI (34.6%) and coronary artery bypass grafting (4.1%).[25] Based on the previous study results and our results, around one third of OHCA survivors without STE will have an occluded coronary artery and undergo successful PCI, which suggests that not all OHCA survivors without STE should proceed to CAG. There are important non-cardiac or other cardiac causes for which PCI is not expected to improve survival.[26] Furthermore, immediate angiography is clearly associated with potential risks in OHCA survivors in whom
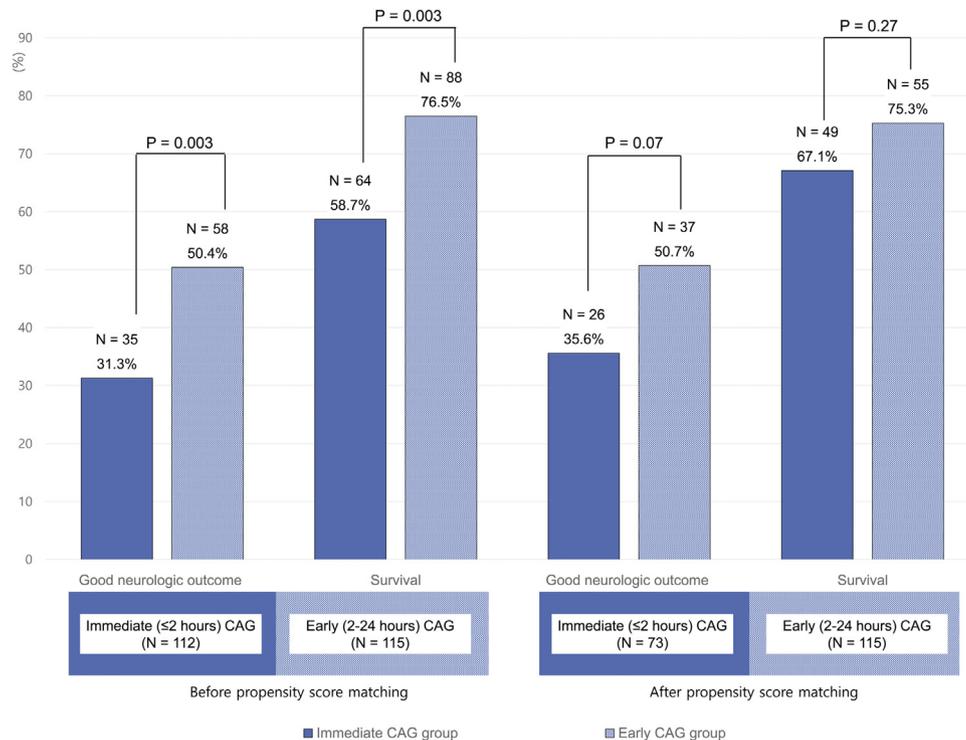
Fig. 2 – Good neurologic outcome and survival at 1 month outcomes of patients with out-of-hospital cardiac arrest without ST-segment elevation according to coronary angiography timing.
CAG, coronary angiography.

Table 3 – Odds ratios of the early versus immediate coronary angiography group of good neurological outcome and survival at 1 month.

Outcome	Model	Number	Odds ratio	95% confidence interval	P Value
Good neurological outcome	Crude	227	2.238	1.309–3.872	0.004
	Propensity score matching	146	1.917	0.954–3.852	0.07
Survival	Crude	227	2.272	1.289–4.063	0.005
	Propensity score matching	146	1.600	0.726–3.526	0.24

the coronary anatomy is not responsible.[10] Unnecessary mobilization at a time of important monitoring and exposure to contrast may affect renal function, vascular injury risk, and bleeding risk from adjunctive medication.[27] Thus, identifying patients who will benefit the most from PCI would assist in targeting resources.

Timing for angiography remains under debate. Current guidelines for the management of non-ST-segment elevation (NSTE) acute coronary syndromes recommend immediate CAG within 2 h for haemodynamically unstable patients and early CAG within 24 h for patients who are haemodynamically stable but at high risk for NSTE myocardial infarction (Class I).[4] The European Association for Percutaneous Cardiovascular Interventions and Stent for Life recommend angiography within 2 h in NSTE sudden cardiac arrest patients without obvious non-cardiac cause,[18] but the level of evidence is low. The clinical characteristics of OHCA survivors are different from those with NSTE acute coronary syndrome given the growing weight of evidence demonstrating significantly higher survival in OHCA patients undergoing early CAG within 24 h than delayed or no CAG. However,

how early it should be provided remains unclear. Some investigators found no benefit from CAG within the first 6 h compared to within 24 h,[13,28] and a recent study using the Swedish CAG registry of 4308 sudden cardiac arrest patients found no clear benefit of early CAG,[29] while research from the Netherlands reported that early (<3 h) CAG compared to non-early CAG was not associated with reduced 30-day mortality in OHCA patients.[30] In line with recent reports and trends, our study showed that good neurological outcome and survival rates at 1 month did not differ between immediate (<2 h) and early (2–24 h) CAG groups in OHCA survivors without STE, who received CAG within 24 h treated with TTM. These results imply that until the results of ongoing randomized trials are available,[31–33] the benefit of immediate CAG in patients without STE will remain controversial. However, Dumas et al. recently demonstrated that successful immediate PCI was associated with a nearly 2-fold increase in the rate of favorable outcome using the data of the PROCAT (Parisian Registry Out-of-Hospital Cardiac Arrest) registry, a cohort data of OHCA survivors with immediate CAG.[34] That study also found that men over 50 years old with shockable initial rhythm

were more likely to have culprit coronary lesion required immediate PCI.[34] Immediate CAG may be reasonable in selected patients with suspected culprit lesions rather than all resuscitated patients without STE.

Our study has several strengths and limitations. First, among OHCA survivors with TTM, we only included those in whom CAG was performed within 24 h, which could reduce survivorship bias. Although early prognostication in OHCA patients is challenging, physicians tend to avoid invasive treatment when patients are expected very poor outcome, particularly those after prolonged resuscitation or those with old age. Second, this multicenter study used good neurological outcomes at 1 month as the primary endpoint, which may be more clinically significant. Third, all of the study patients were treated with TTM according to the current guidelines. Owing to the observational nature of our study, we are able to report an independent association but not a causal relationship between CAG timing and outcomes. We also performed a propensity score matching analysis to achieve intergroup balance. However, despite the propensity score matching, the intergroup differences were still possible due to other blinded variables which could affect the prognosis as well as the decision of CAG timing. Additionally, although the attending physician made the clinical decisions according to the guidelines, post-resuscitation care could be a potential confounding factor. We did not adjust for coronary angiographic findings or PCI use rate, which may have affected the outcome. However, the coronary angiographic findings and PCI use rate were not significantly different between two groups, and those findings cannot be predicted before CAG.

Conclusions

Immediate CAG after resuscitation versus early CAG in OHCA patients without STE who were treated with TTM was not associated with 1-month survival or good neurological outcomes in our propensity score-matched cohort. Further randomized clinical trials are warranted to define the guidelines for recommending optimal CAG timing and selecting patients most likely to benefit from immediate CAG among OHCA survivors without STE.

Conflicts of interest

None.

Funding source

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.12.011.

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