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Emergency Percutaneous Coronary Intervention in Post–Cardiac Arrest Patients Without ST-Segment Elevation Pattern

Insights From the PROCAT II Registry

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ABSTRACT

OBJECTIVES In a large cohort of out-of-hospital cardiac arrest (OHCA) patients without ST-segment elevation (STE), the study assessed the relationship between the use of an early invasive strategy and patient outcome.

BACKGROUND Emergent coronary angiogram (CAG) and reperfusion are currently a standard of care in patients resuscitated from an OHCA with ST-segment elevation (STE). However, using a similar invasive strategy is still debated in patients without STE.

METHODS In the absence of an obvious extracardiac cause, for many years our practice has had to perform an emergent CAG in all OHCA patients (STE and no STE) at admission, followed by percutaneous coronary intervention (PCI) when required. All patients' characteristics are prospectively collected in the PROCAT (Parisian Registry Out-of-Hospital Cardiac Arrest) database. Focusing on non-STE patients and using logistical regression, we investigated the association between early PCI and favorable outcome (cerebral performance category 1 to 2 at discharge) and we searched predictive factors for PCI requirement.

RESULTS During the study period (2004 to 2013), we investigated 958 OHCA patients with an emergent CAG. Among them 695 of 958 (73%), mostly male (76%), and average 60 years of age had no evidence of STE on the post-resuscitation electrocardiography. A PCI was deemed necessary in 199 of 695 (29%). A favorable outcome was observed in 87 of 200 (43%) in patients with PCI compared with 164 of 495 (33%) in patients without PCI ($p = 0.02$). After adjustment, PCI was associated with a better outcome (adjusted odds ratio: 1.80 [95% confidence interval: 1.09 to 2.97]; $p = 0.02$). The other predictive factors of favorable outcome were a shorter resuscitation length (<20 min), an initial shockable rhythm, and a lower dose of epinephrine during resuscitation ($p < 0.001$). An initial shockable rhythm (adjusted odds ratio: 2.83 [95% confidence interval: 1.84 to 4.36]; $p < 0.001$) was the sole independent indicator for PCI requirement.

CONCLUSIONS A culprit coronary lesion requiring PCI was found in nearly one-third of OHCA patients without STE. In these patients, emergent PCI was associated with a nearly 2-fold increase in the rate of favorable outcome. These findings support the use of an invasive strategy in these patients, particularly in those resuscitated from a shockable rhythm. (J Am Coll Cardiol Intv 2016;9:1011–8) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAG = coronary angiography

CI = confidence interval

CPC = cerebral performance category

ECG = electrocardiography

ICU = intensive care unit

OHCA = out-of-hospital cardiac arrest

OR = odds ratio

PCI = percutaneous coronary intervention

ROSC = return of spontaneous circulation

STE = ST-segment elevation

Current guidelines of the International Liaison Committee on Resuscitation highlight the need for a comprehensive etiological research, focused on reversible causes of out-of-hospital cardiac arrest (OHCA) (1). When return of spontaneous circulation (ROSC) is obtained, finding and treating the cause of the arrest can prevent relapse and subsequent clinical deterioration. Acute coronary syndrome (ACS) is considered a frequent cause of OHCA, and emergent percutaneous coronary intervention (PCI) is associated with improved hospital survival in OHCA patients with ACS (2,3). Recent guidelines therefore recommend that resuscitated patients of presumed coronary cause should undergo emergent coronary angiography (CAG) with subsequent PCI if indicated (4).

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In OHCA patients with ST-segment elevation (STE) on the post-ROSC electrocardiography (ECG), this invasive strategy is widely and routinely applied because an acute coronary occlusion is most often the cause of the arrest and because an early coronary revascularization is associated with a significant clinical benefit. However, patients without evidence of STE on post-ROSC ECG represent the vast majority, ranging from one-quarter to nearly two-thirds of resuscitated OHCA patients. Previous studies have reported variable rates of acute coronary occlusion in this group of patients, ranging between 21% and 53% (5–8). We previously found at least 1 significant coronary lesion requiring PCI in only 26% of patients without STE, as compared with 74 % in patients with STE (3). Whether it is useful to use an immediate invasive strategy in non-STE patients resuscitated from OHCA is debated, as it is associated with multiple logistical and organizational challenges, and because the benefit of emergent PCI on outcome is still debatable in these patients (9,10).

Using the PROCAT (Parisian Registry Out-of-Hospital Cardiac Arrest) registry, we assessed the influence of emergent PCI on outcome in patients without STE on post-resuscitation ECG. In addition, we aimed to identify the characteristics of patients who would mostly benefit from this invasive strategy.

METHODS

STUDY SETTING AND POPULATION. In Paris (France), management of OHCA involves mobile emergency units and fire departments. They cover a population of approximately 6.5 million during the day. Upon witnessed call and in suspected cases of sudden cardiac arrest, the closest emergency unit is dispatched on the scene. Out-of-hospital resuscitation is delivered by an emergency team, which includes at least 1 trained physician in emergency medicine according to the European guidelines (11). Patients in whom ROSC is achieved are then referred to a cardiac arrest center with an intensive care unit (ICU) and coronary intervention facilities available 24 h a day, 7 days a week. According to the Utstein template (12), resuscitated patients with obvious extracardiac causes, such as respiratory failure, brain stroke, metabolic disorder, hemorrhage, or any other noncardiac causes, are explored and treated according to standard critical care procedures. In the absence of an obvious extracardiac cause, patients are admitted directly to the cardiac catheterization laboratory at hospital admission, regardless of clinical and ECG findings. An immediate CAG and a left ventricular angiography are performed using standard techniques. If indicated, a PCI is attempted. After the procedure, patients are admitted to the ICU for supportive treatment including targeted temperature management (13).

DATA ANALYSIS. Patients' data were prospectively entered in the PROCAT electronic registry database that was previously described (3). All eligible cases entered in the database between January 2004 and December 2013 were included in the present analysis. OHCA data were collected according to the Utstein recommendations (12) and included age (according to its median), sex, cardiovascular risk factors (e.g., hypertension, diabetes mellitus, current smoking), location of cardiac arrest, and initial cardiac rhythm (presence of ventricular fibrillation or ventricular tachycardia). The delay between the onset of OHCA and ROSC estimated by the emergency medical service team and the cumulated initial epinephrine dose were classified according to their medians. The post-ROSC ECG pattern, the use of therapeutic hypothermia and occurrence of a post-cardiac arrest shock, previously defined (14), were also noted. Coronary angiographic data were prospectively entered in the database. A coronary lesion resulting in more than a 70% reduction in luminal diameter by visual estimation was considered clinically significant. Considering angiographic aspects, a PCI was attempted if there was an acute coronary artery occlusion or if there was an unstable lesion that could be considered as the cause of cardiac arrest. At the end of the procedure, PCI was deemed successful if it resulted in residual stenosis of <50% with Thrombolysis In Myocardial Infarction flow grade 3.

STUDY POPULATION AND OUTCOME. All consecutive patients with sustained ROSC without any obvious extracardiac cause and in the absence of STE on the post-ROSC ECG were included for analyses. An STE was defined as an elevation of 1 mm or more in 2 contiguous leads in standard leads and 2 mm or more in precordial leads. All other aspects were considered non-STE patterns. The primary outcome was the best level on the cerebral performance category (CPC) scale observed at hospital discharge by the physician in charge, considering CPC 1 or 2 as a good outcome (15).

STATISTICAL ANALYSIS. Descriptive statistics were summarized as proportions for categorical variables and mean ± SD for continuous variables. The associations between categorical variables were assessed using a chi-square test (or Fisher exact test when appropriate) and continuous variables compared with Student *t* test.

We investigated the association between successful PCI and good neurological outcome using logistical regression including all the potential confounders (age, sex, cardiovascular factors, initial rhythm, location, witnessed status and bystander cardiopulmonary resuscitation, resuscitation length, epinephrine dosage, targeted temperature management, post-arrest shock). Additionally we performed a multivariable analysis identifying predictive factors for successful PCI performance, incorporating early and reliable parameters (age, sex, initial rhythm, resuscitation length, location and use of epinephrine). To refine the analysis in different categories of patients, we selected the variables found as significant in univariate assessment (age, sex, initial rhythm).

Because the study period covers a decade, sensitivity analyses were performed including the year of inclusion of the patients in the PROCAT registry. All variables of interest were exhaustively and carefully reviewed, in order to minimize potential bias. Furthermore, a supplemental analysis using multiple imputations (by 10 imputations multivariable normal regression) was also performed (16).

Odds ratios (ORs) are presented with 95% confidence interval (CI). A p value <0.05 was considered statistically significant. All calculations were performed using STATA 12-1/SE software (Stata Corp., College Station, Texas).

RESULTS

During the study period, 1,430 patients were admitted to the ICU after OHCA. Among these patients, 472 of 1,430 (33%) presented an obvious extracardiac cause (sepsis, neurological, respiratory, trauma, asphyxia, hemorrhage, or other), a STE was observed on the post-resuscitation ECG in 251 of 1,430 (18%), and 12 of 1,430 cases had no available post-ROSC ECG. Finally 695 patients with no obvious extracardiac cause and without STE were investigated with a systematic and emergent CAG at hospital admission and were included in the analysis.

Among these patients, 66% were men (528 of 695), with a mean of 60 ± 13.7 years of age. An initial shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) was noted in 62% of patients (431 of 695). Cardiac arrest occurred at home in 63% of patients (440 of 695), was witnessed in 90% of patients (611 of 677) and bystander cardiopulmonary resuscitation was performed in 51% of patients (342 of 674). The median interval delay from cardiac arrest to ROSC was 20 min (interquartile range: 14 to 32 min) (Table 1).

On post-resuscitation ECG, 39% of patients presented with nonspecific repolarization abnormalities (negative T waves and ST-segment depression), 26% presented with conduction disturbances, 20% had a normal ECG pattern, and 15% presented with other patterns (supraventricular tachycardia, atrial fibrillation).

The emergent CAG identified at least 1 significant lesion in 403 of 695 patients (58%). A culprit coronary lesion deemed responsible for the cardiac arrest was identified and treated by PCI in 199 of 695 patients (29%). The culprit lesions for cardiac arrest were localized on the left anterior descending (n = 93), left main (n = 13), circumflex (n = 44), and right coronary arteries (n = 51).

The overall favorable outcome rate at discharge was 251 of 695 patients (36%) (Table 2). Patients treated

TABLE 1 Baseline Characteristics of the Studied Overall Population (n = 695)

Age, yrs	60.1 ± 13.7
Male	528 (76)
Diabetes mellitus	131 (21)
Hypertension	291 (46)
Current smoker	268 (46)
Initial shockable rhythm	431 (62)
Public location of CA	255 (37)
Witnessed CA	611 (90)
Resuscitation length <20 min	292 (46)
Bystander CPR	354 (53)
Epinephrine >2 mg	302 (45)
Post-resuscitation shock	437 (63)
TTM	616 (89)
CPC 1 or 2 at discharge	251 (36)

Values are mean ± SD or n (%).

CA = cardiac arrest; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; TTM = targeted temperature management.

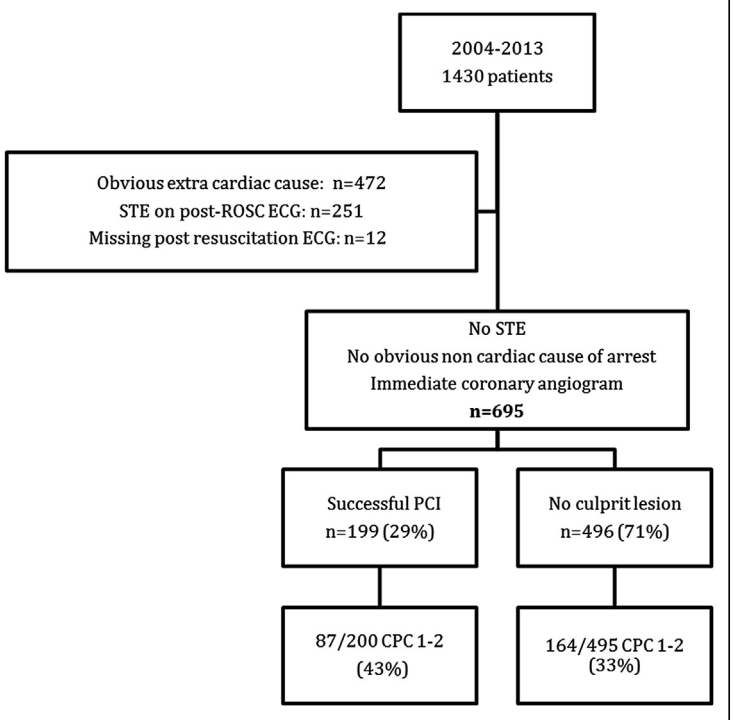
TABLE 2 Predictive Factors of Good Neurological Outcome At Discharge (Multivariable Analysis)

	OR	95% CI	p Value
Age (for each additional year)	0.97	0.95–0.99	0.002
Male	1.18	0.68–2.06	0.55
Diabetes mellitus	1.64	0.89–3.0	0.11
Hypertension	1.03	0.62–1.69	0.92
Current smoker	1.21	0.75–1.94	0.46
Public location of CA	1.27	0.78–2.07	0.34
Witnessed CA	3.43	0.89–13.26	0.07
Bystander CPR	1.35	0.85–2.15	0.20
Initial shockable rhythm	3.40	1.95–5.91	<0.001
Resuscitation length <20 min	3.15	1.94–5.10	<0.001
Epinephrine >2 mg	0.27	0.16–0.46	<0.001
TTM	0.93	0.41–2.07	0.85
Post-CA shock	0.58	0.36–0.92	0.02
Successful PCI	1.80	1.09–2.97	0.02

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

with successful PCI had a better outcome in 85 of 199 patients (43%) compared to 166 of 496 patients (33%) in whom the CAG was not followed by emergent PCI (p = 0.02) (Figure 1). After adjustment for potential confounders, emergent successful PCI was independently associated with a better outcome (adjusted OR: 1.80 [95% CI: 1.09 to 2.97]; p = 0.02) (Table 2). This association remained stable even after adjusting on the year of inclusion (adjusted OR: 1.80 [95% CI: 1.09 to 2.99]). After multiple imputations for missing data PCI was associated with a better outcome of adjusted OR (1.52 [95% CI: 1.0 to 2.29]). Besides a shorter resuscitation length (<20 min), an initial shockable rhythm and a low dose of epinephrine were also significantly associated with a better outcome (p < 0.001).

FIGURE 1 Flowchart of Studied Population



CPC = cerebral performance category; ECG = electrocardiography; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation; STE = ST-segment elevation.

Table 3 summarizes the different baseline characteristics of patients with or without a successful PCI. Male sex, smoking, and initial shockable rhythm were significantly associated with PCI (p < 0.05). In patients >50 years of age, 166 of 549 patients (30.2%) presented a culprit coronary lesion compared to 33 of 146 patients (22.6%) <50 years of age (p = 0.07). After adjustment for early potential confounders, an initial shockable rhythm remained the sole predictive factor for successful PCI with an adjusted OR of 2.83 (95% CI: 1.84 to 4.36) (Table 4). In the whole cohort, 164 of 528 of male patients (31%) had PCI compared to 35 of 167 of female patients (21%; p = 0.01); 150 of 431 (35%) initial shockable rhythm patients had PCI compared to 49 of 264 (18.6%) nonshockable rhythm patients (p < 0.001). Among the latter, 125 of 264 patients (47%) who presented an initial nonshockable rhythm had finally at least 1 significant lesion diagnosed during the procedure (Table 4).

When focusing on subgroups of patients, we noted that male patients >50 years of age with an initial shockable rhythm required PCI in nearly 40% of cases. In contrast, only 13% of women older than 50 years of age resuscitated from a nonshockable rhythm required emergent PCI (Figure 2).

DISCUSSION

In this large cohort study, in which a systematic and immediate CAG was performed in all patients, "ad hoc" PCI was performed in nearly one-third of the population. This emergent invasive strategy was significantly and independently associated with an improved hospital outcome. A shorter resuscitation length (<20 min), an initial shockable rhythm, and a lower dose of epinephrine were also significantly associated with a better outcome. A shockable rhythm at emergency medical service presentation was the strongest predictor of the presence of an acute coronary lesion requiring early PCI. Focusing on subgroups, male patients of >50 years of age with an initial shockable rhythm seem to benefit most from this invasive strategy, with a rate of culprit coronary lesion

of 40%. In this subgroup, when PCI was performed, the rate of favorable outcome was high (48.1%).

One important challenge in post-cardiac arrest invasive strategy remains the appropriate selection of candidates. To decrease the risk of inappropriate invasive procedures, an ideal strategy should restrict early CAG to OHCA patients with the highest probability of recent coronary occlusion requiring PCI (i.e., those with a definite ACS). Unfortunately eliminating the diagnosis of ACS after OHCA is difficult. In contrast to the usual presentation of ACS in non-cardiac arrest patients, both clinical symptoms (e.g., chest pain or dyspnea) and ECG findings suggesting myocardial ischemia are difficult to assess and lack sensitivity to rule out an acute coronary artery occlusion as the cause of OHCA. Several studies suggested that the incidence of acute coronary occlusion is high even when STE is not present on the post resuscitation ECG. Spaulding et al. (2) reported culprit coronary occlusions in 39% of patients without STE and chest pain. These findings were confirmed in several observational studies, which reported a high prevalence of recent coronary occlusion even in the absence of typical ischemic changes on the post-ROSC ECG, ranging from 25% to 57% (17–19). Our group reported at least 1 significant coronary lesion requiring PCI in 26% of patients without acute ischemic ECG changes (3). In more recent published reports, sensibility and specificity of STE on post-ROSC ECG were 88% and 69% to 84%, respectively (20,21). More recently, Hollenbeck et al. (6) conducted a retrospective observational study of a prospective cohort of 754 consecutive comatose patients following cardiac arrest. A total of 269 (35.7%) patients had cardiac arrest due to a ventricular arrhythmia without STE. Cardiac catheterization was performed in 122 (45.4%) comatose patients (early cardiac catheterization). Acute coronary occlusion was noted in 26.6% of patients treated with early cardiac catheterization compared to 29.3% of patients treated with late cardiac catheterization ($p = 0.38$). Patients managed with early CAG were more likely to survive to hospital discharge compared to those not treated with cardiac catheterization (65.6% vs. 48.6%; $p = 0.02$). In a multivariate analysis, early cardiac catheterization was independently associated with a significant reduction in the risk of death (OR: 0.35 [95% CI: 0.18 to 0.70]; $p < 0.01$). The relatively low number of patients and the selection criteria were important limitations. In our study we demonstrated that an immediate invasive strategy routinely applied in a large cohort is associated with a clinical benefit regarding outcome. This lack of negative predictive value of post resuscitation ECG in the absence of STE could be due in part to the global myocardial ischemia-reperfusion, and also to electrolyte and acid-base abnormalities that are very common in the post-ROSC period. On the whole, the poor predictive value of ECG for acute coronary lesions in resuscitated OHCA patients with a high prevalence of coronary artery disease emphasizes the use of systematic acute CAG as part of a standard post-cardiac arrest protocol.

Biomarkers of ischemic myocardial injury could be an alternative to discriminate between coronary and noncoronary causes. It has been hypothesized that an early measurement of cardiac enzymes could be an adjunct to pre-established risk factors to detect OHCA patients most susceptible to have a recent coronary occlusion, but this strategy is disappointing. Although Grubb et al. (22) reported good diagnostic values of creatine kinase-myocardial band fraction with very high cutoffs, several subsequent studies

TABLE 3 Baseline and Angiographic Characteristics According to PCI

	Successful PCI (n = 199)	No Culprit Lesion (n = 496)	p Value
Age, yrs	61.4 ± 12.2	59.7 ± 14.2	0.06
Male	164 (82)	364 (73)	0.01
Diabetes mellitus	46 (25)	85 (19)	0.06
Hypertension	89 (49)	202 (44)	0.22
Current smoker	94 (58)	174 (41)	<0.001
Initial shockable rhythm	150 (75)	281 (57)	<0.001
Public location of CA	79 (40)	176 (35)	0.30
Witnessed CA	180 (93)	431 (89)	0.20
Resuscitation length <20 min	90 (48)	202 (45)	0.49
Bystander CPR	110 (57)	244 (51)	0.13
Epinephrine >2 mg	82 (43)	220 (46)	0.50
Post-resuscitation shock	133 (67)	304 (61)	0.17
TTM	178 (89)	438 (88)	0.67
At least 1 significant lesion (70% stenosis)	*198 (99)*	*205 (41)*	<0.001
Occluded lesion (100% stenosis)	*90 (45)*	*105 (21)*	<0.001
CPC 1 or 2 at discharge	85 (43)	166 (33)	0.02

Values are mean ± SD or n (%). These above values are italicized since these variables concerned only the findings of coronary angiogram.

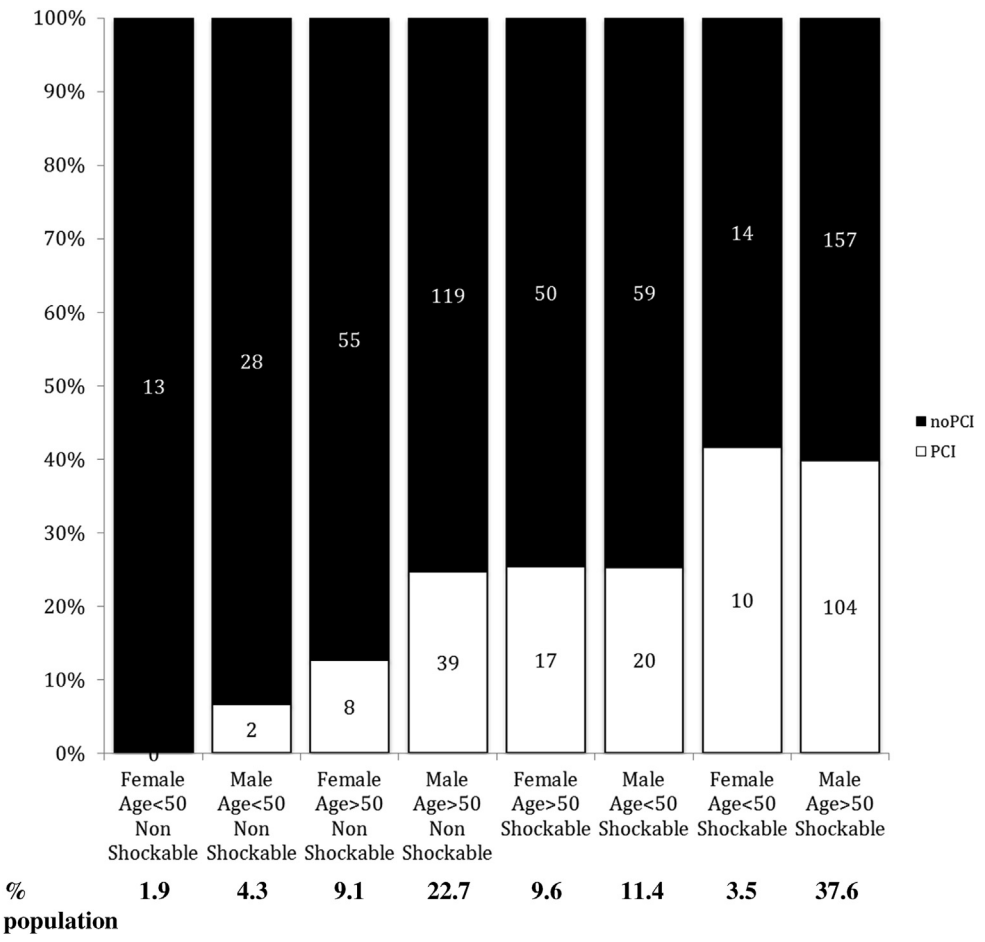
PCI = percutaneous coronary intervention; all other abbreviations as in Table 1.

TABLE 4 Pre-Hospital Predictive Factors for Successful PCI

	OR	95% CI	p Value
Age (per-yr increase)	1.01	1.0-1.03	0.08
Sex	1.39	0.88-2.20	0.16
Public location	1.03	0.69-1.52	0.89
Witnessed CA	1.04	0.48-2.24	0.93
Bystander CPR	1.04	0.71-1.52	0.84
Initial shockable rhythm	2.83	1.84-4.36	<0.001
Resuscitation length <20 min	1.08	0.72-1.61	0.71
Epinephrine >2 mg	1.00	0.68-1.48	0.98

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

FIGURE 2 Proportion and Number of Patients in Whom a PCI Was Deemed Necessary in Different Subgroups According to Sex, Age, and Cardiac Rhythm at EMS Presentation



Proportion and number of patients in whom a percutaneous coronary intervention (PCI) was deemed necessary in different subgroups according to sex, age, and cardiac rhythm at emergency medical service presentation. EMS = emergency medical services.

have been at variance with this study (23,24). The use of different cutoff values to discriminate groups of patients render comparisons between studies difficult. Recently, the additional value of high sensitivity troponin was evaluated in OHCA patients (24). The predictive values were also disappointing. We do not routinely use cardiac biomarkers to guide our strategy for invasive strategy, which is why we did not include this variable in the present analysis.

On the whole, clinical, ECG, and biological tools to assess coronary ischemia are clearly less efficient in this setting. They lack sensitivity and specificity to predict an acute coronary artery occlusion as the cause of OHCA. Taken together, our findings support the use of an invasive strategy in all OHCA patients without an obvious noncardiac cause of arrest. This is supported by a recent meta-analysis that included all ECG patterns, and reported a significant benefit of an invasive strategy for survival (25). Moreover we identified a large group of patients, which can be identified early with simple and reliable factors (e.g., age, sex, rhythm), who may mostly benefit from this invasive strategy. The high prevalence of obstructive coronary artery disease in ventricular tachycardia/ventricular fibrillation cardiac arrest has been previously described (26). In centers where a systematic invasive approach at admission cannot be performed, patients could be triaged for emergent angiogram using these factors. Finally it can also be argued that even a negative CAG would provide useful diagnostic information because the absence of a culprit lesion is an important finding, which will prompt searching for alternative causes of cardiac arrest.

Our management strategy of OHCA includes an emergent CAG at admission in all survivors of OHCA with no obvious noncardiac cause of arrest, even if there is no STE on the post-ROSC ECG. Recently, a statement from the European Association for Percutaneous Cardiovascular Interventions/Stent for Life groups suggested immediate cardiac arrest in survivors of OHCA with STE and a short (<2 h) "emergency room stop" in survivors without STE to perform diagnostic procedures such as brain and thorax CT scan and an echocardiogram. If no extracardiac cause of arrest is found, a cardiac arrest is recommended and should be performed <2 h after admission (9). This is an interesting strategy that should be further evaluated.

The present study is obviously limited by its nonrandomized and retrospective design, precluding any conclusion regarding a causal relationship. Data coming from ongoing randomized trials are needed (NCT02309151). This current study aimed to assess the role of PCI when emergent and systematic CAG is performed. As a result, in our strategy all the procedures were performed at hospital admission. Unfortunately, due to the design of the study we cannot provide comparative information between early and delayed strategy. Additionally our findings are drawn from a single center and may not be applicable in all communities, though this single-center design is associated with a strong homogeneity in all other aspects of management. Finally, we used the CPC at hospital discharge as main endpoint although recent International Liaison Committee on Resuscitation guidelines encouraged the use of 90-day survival. However, the CPC hospital discharge score is known to be a good surrogate indicator for long-term survival in post-cardiac arrest patients (27).

CONCLUSIONS

Our findings show that an emergent PCI is associated with a better outcome in patients without STE on the post-ROSC ECG after OHCA. Older men (older than 50 years of age) resuscitated from an initially shockable rhythm mostly benefitted from this strategy. In the absence of randomized trials, the present results support the use of an emergent invasive strategy in this specific population and may help to select the best candidates.

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PERSPECTIVES

WHAT IS KNOWN? Emergent CAG and reperfusion are currently a standard of care in patients resuscitated from an OHCA with STE.

WHAT IS NEW? Whether it is useful to use an immediate invasive strategy in non-STE patients resuscitated from OHCA is debated, because it is associated with multiple logistical and organizational challenges, and also because the benefit of emergent PCI on outcome is still debatable in these patients. An emergent PCI is independently associated with a better outcome in patients without STE on the post-resuscitation ECG after OHCA. Older men (>50 years of age) resuscitated from an initially shockable rhythm mostly benefitted from this strategy.

WHAT IS NEXT? In the absence of randomized trials, the present results support the use of an emergent invasive strategy in this specific population and may help to select the best candidates.

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