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Clinical paper

Mechanism and extent of myocardial injury associated with out-of-hospital cardiac arrest☆

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Abstract

Aim: We investigated the mechanism and extent of myocardial injury associated with out-of-hospital cardiac arrest (OHCA).

Methods: 159 consecutive patients undergoing immediate coronary angiography after OHCA were included and divided into groups with acute culprit lesion (A), stable obstructive coronary disease (B) and non-obstructive or absent coronary disease (C). Post-resuscitation electrocardiogram (ECG) and serial measurements of high sensitivity cardiac troponin I (cTnI) were compared.

Results: ST-elevation myocardial infarction (STEMI) was documented in 65% in group A, 26% in group B, and 11% in group C ($p < 0.001$). cTnI, which was 0.88 ng/mL, 0.44 ng/mL and 0.19 ng/mL in groups A, B and C on admission ($p < 0.001$), increased to a maximum of 63.96 ng/mL, 10.00 ng/mL and 2.35 ng/mL, respectively ($p < 0.001$). Within the group A, cTnI was significantly larger in patients with acute occlusion than in patients with spontaneous reperfusion at initial angiography. Within groups B and C, peak cTnI correlated with duration of resuscitation, number of defibrillations and cumulative adrenaline (epinephrine) dose. If admission cTnI exceeded 0.46 ng/mL and STEMI was present in ECG, sensitivity for detection of acute culprit lesion was 88% and specificity 54%.

Conclusions: Significant myocardial injury associated with OHCA occurs in the presence of acute culprit lesion while extent of myocardial injury in stable or absent coronary disease is significantly smaller and correlates with the duration and intensity of cardiac resuscitation. Admission cTnI, although combined with post-resuscitation ECG, have insufficient accuracy to securely predict presence of acute culprit lesion.

Keywords: Myocardial injury, Out-of-hospital cardiac arrest, Cardiac biomarkers

Introduction

Sudden out-of-hospital cardiac arrest (OHCA) remains the leading cause of death in developed countries with an annual incidence ranging from 36 to 81 events per 100,000 inhabitants.[1] Numerous studies have demonstrated that significant coronary artery disease, either stable or with the presence of acute culprit lesion, may be found in more than 70% of patients after reestablishment of spontaneous circulation (ROSC).[2,3] Following hospital admission, acute myocardial injury, documented by ischemic electrocardiographic changes and increase in cardiac biomarkers, especially cardiac troponin, is typically observed.[4–6] Post-resuscitation concentration of cardiac troponin, however, varies significantly from patient to patient indicating different extent and mechanism of acute myocardial injury. In the present study, we thought to better understand the underlying pathophysiology and therefore related anatomic features obtained by immediate coronary angiography, early post-resuscitation 12-lead electrocardiogram (ECG) and serial measurements of high sensitivity cardiac troponin in patients with OHCA following ROSC.

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Methods

The study was conducted at the University Medical Centre Ljubljana. The research protocol has been approved by the National ethics committee (No. 30/08/14) and study complied with Declaration of Helsinki.

Consecutive patients with OHCA of presumed cardiac origin and ROSC on the field undergoing immediate coronary angiography from January 1, 2013 through March 31, 2018 were screened. Immediate percutaneous coronary intervention (PCI) was performed according to Consensus document issued by European association for percutaneous cardiovascular interventions (EAPCI) and Stent for life (SFL) initiative in 2014.[7] All patients underwent contemporary intensive care including hemodynamic support, mechanical ventilation, target temperature management (32–34 °C), antimicrobial therapy and renal replacement therapy.[8]

Coronary angiograms were reviewed by an experienced interventional cardiologist who was blinded to 12-lead ECG and cardiac troponin measurements. Patients were divided into the 3 groups. Group A included patients who had an obvious acute lesion defined as irregular eccentric coronary stenosis with a narrow neck, acute angles or craters which were thought to represent disrupted plaque with or without the presence of coronary thrombus.[9–11] Coronary flow was assessed by Thrombolysis in Myocardial Infarction (TIMI) classification.[12] Coronary artery occlusion was defined as TIMI grade 0 or 1 flow, and was considered acute if there was evidence of thrombus at the site of occlusion or if regular guidewire could have been easily passed through the occluded segment. Group B included patients with stable obstructive coronary disease (>70% diameter stenosis in a major epicardial vessel) without the presence of an acute culprit lesion. Group C included patients with stable non-obstructive coronary disease (<70% diameter stenosis) or angiographic absence of coronary artery disease.

Post-resuscitation 12-lead ECG was recorded after ROSC and before coronary angiography. All ECG recordings were reviewed by a single experienced acute cardiac care cardiologist blinded to angiographic findings and cardiac troponin measurements.

Peak and serial sampling of cardiac troponin were selected to estimate the size of acute myocardial injury because it has been validated against cardiac magnetic resonance and provided a good estimation of infarct size.[13] We used cardiac troponin I (cTnI) (Siemens ADVIA Centaur TnI-Ultra Assay, Siemens, New Jersey), which was measured at hospital admission and 3, 6, 12 18, 24, 36 and 48 h later. Assay total imprecision is 10% at 0.03 ng/mL and 99th percentile reference value is 0.04 ng/mL.

Left ventricular ejection fraction was measured after admission to the cardiac intensive care unit using bedside echocardiography.

Exclusion criteria were delay of more than 3 h from OHCA to the first cTnI measurement, missed cTnI measurements on admission and at 3 and 6 h, documented subacute myocardial infarction (MI) prior to OHCA, acute myocarditis documented by cardiac magnetic resonance, cocaine toxicity and stent thrombosis within the 48 h after the index PCI.

Numerical variables are presented as mean ± standard deviation or median with 25th and 75th percentile. Categorical variables are presented as proportions in percentages. For overall comparison between the groups, one-way analysis of variance or Kruskal–Wallis H test was used according to the data distribution. For comparison of categorical variables, Fischer's exact test and Chi-square test were used. For multiple comparisons, a Holm's sequential Bonferroni adjustment was made. An optimal value of admission cTnI was determined based on the best sum of sensitivity and specificity. A p value of <0.05 was considered as statistically significant.

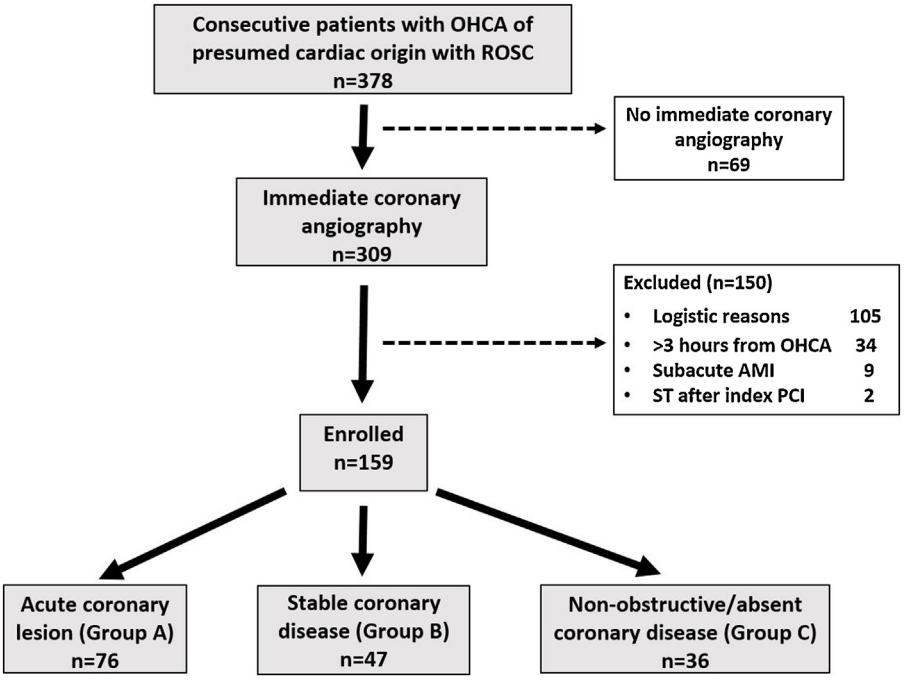

Fig. 1 – Study chart. OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; AMI = acute myocardial infarction; ST = stent thrombosis; PCI = percutaneous coronary intervention.

Results

Between January 1, 2013 and March 31, 2018, among 378 consecutive patients with OHCA and ROSC on the field, 309 (82%) underwent immediate coronary angiography (Fig. 1). The reasons for not performing immediate coronary angiography were non-shockable rhythm without ST elevation (n = 20), already documented non-ischemic cardiomiopathy (n = 14), advanced age/significant comorbidities (n = 12), enrolment into competing study (n = 8), prolonged prehospital resuscitation with remote likelihood of neurological recovery (n = 7), death before coronary angiography (n = 5) and decision of the attending physician (n = 3). Following immediate coronary angiography, 150 patients were excluded due to logistic reasons related to missed initial cTnI measurements (n = 105) or due to one of the other exclusion criteria. Accordingly, 159 patients were ultimately enrolled into the study. Seventy six patients (48%) had acute culprit lesion (Group A), 47 (30%) presented with stable obstructive coronary disease (Group B) and 36 (22%) had no significant or absent coronary disease (Group C).

Patients in group B were older, had more hypertension, history of myocardial infarction and previous percutaneous or surgical revascularization (Table 1). There was no significant difference in the prehospital features of OHCA and initial resuscitation between the groups. Except for immediate PCI, which was performed in 98.7% in group A, 44.7% in group B and obviously in none of the patients in group C ($p < 0.001$), there was no significant difference in post-resuscitation treatment. Patients in group C had lower arterial lactate and better left ventricular ejection fraction on admission. There was no significant difference in hospital survival and survival with good neurological outcome.

Average delay from collapse to coronary angiography was 153 + 68 min. Acute culprit lesion in group A was predominantly located on the left anterior descending artery (46.1%) and majority of these patients (67%) presented with TIMI 0–1 flow. Patients in group A had less often multi-vessel coronary disease (51% versus 75%;

Table 1 – Patients, features of out-of-hospital cardiac arrest (OHCA) and post-resuscitation phase.

	All patients n = 159	Group A n = 76	Group B n = 47	Group C n = 36	p
Patient characteristics					
Age, years	62 ± 12	60 ± 13[b]	66 ± 10	61 ± 13	0.03
Men	135 (84.9%)	63 (82.9%)	43 (91.5%)	29 (80.6%)	0.31
Hypertension	94 (59.1%)	3 (46.1%)[b]	36 (76.6%)	23 (63.9%)	0.004
Hypercholesterolemia	45 (28.3%)	20 (26.3%)	16 (34.0%)	9 (25.0%)	0.59
Diabetes	22 (13.8%)	7 (9.2%)	10 (21.3%)	5 (13.9%)	0.18
Current smoking	49 (30.8%)	29 (38.2%)	13 (27.7%)	7 (19.4%)	0.05
Previous MI	23 (14.5%)	6 (7.9%)[b]	12 (25.5%)	5 (13.9%)	0.03
Previous PCI	14 (8.8%)	4 (5.3%)	8 (17.0%)	2 (5.6%)	0.09
Previous CABG	6 (3.8%)	0 (0%)[b]	5 (10.6%)	1 (2.8%)	0.006
OHCA features					
Witnessed OHCA	144 (90.6%)	71 (93.4%)	41 (87.2%)	32 (88.9%)	0.46
Bystander-initiated BLS	94 (59.1%)	42 (55.3%)	27 (57.4%)	25 (69.4%)	0.47
Time from arrest to ACLS, minutes[a]	7 (5–10)	7 (4–10)	7 (5–10)	7 (5–11)	0.70
Initial shockable rhythm	141 (88.7%)	66 (86.8%)	43 (91.5%)	32 (88.9%)	0.55
Total number of defibrillations[a]	3 (1–5)	3 (2–5)	2.5 (1–5)	2 (1–5)	0.77
Cumulative adrenaline dose, mg[a]	2 (0–4)	2 (0–5)	2 (0–4)	1 (0–3)	0.13
Time from ACLS to ROSC, minutes[a]	13 (7–21)	13.5 (8–30)	15.0 (6–20)	11.5 (7–20)	0.63
Post-resuscitation phase					
PCI	96 (60.3%)	75 (98.7%)[b]	21 (44.7%)[c]	0 (0%)	<0.001
IABP	21 (13.2%)	15 (19.7%)	4 (8.5%)	2 (5.6%)	0.06
Therapeutic hypothermia	149 (93.7%)	71 (93.4%)	46 (97.9%)	32 (88.9%)	0.39
Admission arterial lactate, mmol/L[a]	4.3 (2.3–9.2)	5.5 (3.2-10.9)[d]	4.0 (1.9–7.8)	3.4 (1.9–6.5)	0.01
LVEF<40% on admission	68 (42.8%)	29 (38.2%)[d]	15 (31.9%)[c]	24 (66.7%)	0.01
eGFR < 50 mL/min/1.73 m^2 <48 h	40 (25.2%)	22 (28.9%)	11 (23.4%)	6 (19.4%)	0.56
Hospital outcome					
Survival	97 (61%)	49 (64.5%)	23 (48.9%)	25 (69.4%)	0.09
Survival with CPC $^1/_2$	89 (56%)	43 (56.6%)	22 (46.8%)	24 (66.7%)	0.46

ACLS = advanced cardiac life support; BLS = basic life support; CABG = coronary artery bypass grafting; CPC1/2=cerebral performance category indicating good neurological outcome; eGFR = estimated glomerular filtration rate; Group A = acute coronary lesion; Group B = stable obstructive coronary disease; Group C = non-obstructive/absent coronary disease; IABP = intra-aortic balloon counter-pulsation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation.

[a] Median and 25th/75th interquartile range.

[b] $p < 0.05$ group A versus group B.

[c] $p < 0.05$ group B versus group C.

[d] $p < 0.05$ group A versus group C.

Table 2 – Electrocrdiographic features, coronary anatomy and cTnI concentration in patients with out-of-hospital cardiac arrest (OHCA).

	All patients n = 159	Group A n = 76	Group B n = 47	Group C n = 36	p
Post-resuscitation ECG					<0.001
STEMI	65 (40.9%)	49 (64.5%)	12 (25.5%)	4 (11.1%)	
Ischemic ST-T changes	33 (20.8%)	13 (17.1%)	16 (34.0%)	4 (11.1%)	
Bundle branch block	30 (18.9%)	8 (10.5%)	10 (21.3%)	12 (33.3%)	
Nonspecific changes	16 (10.1%)	3 (3.9%)	6 (12.8%)	7 (19.4%)	
Normal	15 (9.4%)	3 (3.9%)	3 (6.4%)	9 (25.0%)	
Coronary angiography					
Time from OHCA, minutes	153 ± 68	142 ± 55	151 ± 47	176 ± 101	0.17
Extent of obstructive coronary disease					<0.001
One vessel	49 (30.8%)	37 (48.7%)	12 (25.5%)	0 (0%)	
Two vessel	39 (24.5%)	24 (31.6%)	15 (31.9%)	0 (0%)	
Three vessel	35 (22.0%)	15 (19.7%)	20 (42.6%)	0 (0%)	
Presence of ≥1 CTO	27 (17.0%)	6 (7.9%)[b]	21 (44.7%)	0 (0%)	<0.001
Acute culprit lesion	76 (47.8%)	76 (100%)	–	–	
LM	10 (6.3%)	10 (13.2%)	–	–	
LAD	35 (22.0%)	35 (46.1%)	–	–	
LCX	16 (10.1%)	16 (21.1%)	–	–	
RCA	15 (9.4%)	15 (19.7%)	–	–	
Culprit TIMI flow 0–1	51 (32.1%)	51 (67.1%)	–	–	
OHCA to 1st cTnI, minutes[a]	99 (66-145)	100 (66–137)	92 (67–153)	99 (63–136)	0.84
Admission cTnI (ng/mL)[a]	0.45 (0.16–2.25)	0.88 (0.25–3.01)[d]	0.44 (0.13–2.51)	0.19 (0.09–0.66)	<0.001
Maximal cTnI (ng/mL)[a]	23.51 (3.50–68.30)	63.96 (29.05–128.18)[b,d]	10.00 (3.30–25.34)[c]	2.35 (0.84–7.57)	<0.001
cTnI AUC[a]	552.4 (80.7–2072.8)	1988.0 (874.1–4436.0)[b,d]	265.6 (83.6–710.5)[c]	53.7 (18.0–129.3)	<0.001

AUC = area under curve; cTnI = cardiac Troponin I; CTO = chronic total occlusion; ECG = 12-lead electrocardiogram; Group A = acute coronary lesion; Group B = stable obstructive coronary disease; Group C = non-obstructive/absent coronary disease; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main coronary artery; OHCA = out-of-hospital cardiac arrest; RCA = right coronary artery; STEMI = ST elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

[a] Median and 25th/75th interquartile range.

[b] $p < 0.05$ group A versus group B.

[c] $p < 0.05$ group B versus group C.

[d] $p < 0.05$ group A versus group C.

p = 0.001) and chronic total occlusion (8% versus 45%; $p < 0.001$) than patients in group B.

ST-elevation myocardial infarction (STEMI) was documented in 65% in group A, in 26% in B, and only in 11% of patients in group C ($p < 0.001$) (Table 2). Other electrocardiographic patterns were also significantly different between the groups. Ischemic STT changes were most often observed in group B (34%) and bundle branch block in groups C (33.3%) and B (21.3%) which was the case also for non-specific ECG changes. Normal ECG was the most frequent finding in the group C (25%).

Admission TnI, which was obtained in average 99 min after OHCA, was significantly different between the groups with the highest concentration in group A (Table 2). During subsequent hours, cTnI increased to a maximum of 63.96 ng/mL in group A and remained significantly lower in groups B and C (Fig. 2). Also area under curve (AUC), which was 1988.0 ng/mL/h in group A, was significantly larger than in other two groups (Table 2). Median delay from OHCA to peak cTnI was 13.5 h in group A, 9.5 h in group B and 8.5 h in group C (p = 0.102). Within the group A, cTnI was significantly greater in the presence of acute occlusion (TIMI 0–1) at initial coronary angiography than in patients with spontaneous reperfusion (TIMI 2–3) (Fig. 3).

In patients with stable coronary disease (groups B and C), peak cTnI linearly correlated with the time from collapse to ROSC (r = 0.35; p = 0.001), number of defibrillation attempts (r = 0.36; p = 0.002) and cumulative adrenaline (epinephrine) dose (r = 0.24; p = 0.04) but not with arterial lactate concentration on hospital admission (r = 0.12; p = 0.33).

If admission cTnI exceeded 0.46 ng/mL, sensitivity for prediction of acute coronary lesion was 64%, specificity 60%, positive predictive value 60% and negative predictive value 64%. If admission cTnI was combined with signs of STEMI in the early post-resuscitation ECG, sensitivity increased to 88%, specificity decreased to 54%, positive predictive value increased to 64% and negative predictive value increased to 83%.

We further compared coronary anatomy and cTnI between patients with STEMI and without STEMI in post-resuscitation ECG. (Table 1 Supplementary data). Acute culprit lesion, which was more often apparent in STEMI (75.4% versus 28.7%), was associated with larger myocardial injury which, however, did not compromise the hospital outcome. Using univariate analysis, only admission cTnI (OR 1.307; CI 1.046–1.633; p = 0.018) and lactate (OR 1.137; CI 1.02–1.267; p = 0.021) predicted the presence of acute coronary lesion (Table 2 Supplementary data).

Discussion

Our study demonstrated that acute myocardial injury associated with resuscitated OHCA has heterogeneous mechanisms and

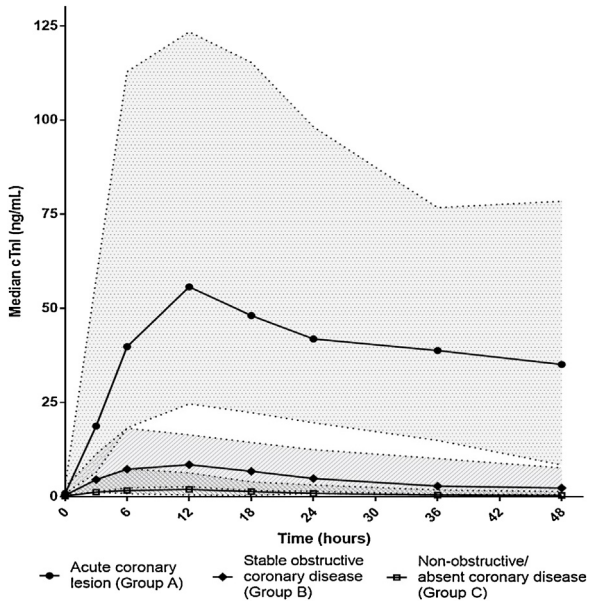

Fig. 2 – Time course of cardiac troponin I (cTnI) concentration according to coronary anatomy in groups A, B and C. Median values (thick line) and 25th and 75th quartiles (dotted lines) are shown.

varies significantly in terms of size. Acute culprit lesion, which is present in nearly 50% of patients and obviously triggers OHCA, is associated with the largest myocardial injury, particularly if the infarct-related coronary artery is still occluded at the time of initial coronary angiography. According to recently published "Fourth universal definition of myocardial infarction", such post-resuscitation myocardial injury may be regarded as type 1 myocardial infarction (MI).[14] However, we demonstrated that acute myocardial injury, although significantly smaller, occurs also in the absence of acute culprit lesion and may be regarded as type 2 MI.[14,15] In these patients, cause-effect relationship between OHCA and coronary disease is less certain. Possible mechanisms include transient ischemia caused by plaque thrombosis - spontaneous reperfusion, coronary spasm or decrease in perfusion pressure across the tight lesion or collaterals in case of sudden drop in arterial pressure.[7,16] On the other hand, coronary artery disease may also be only an "innocent bystander" without direct cause-effect relationship to OHCA. As expected, myocardial injury was significantly larger in patients with stable obstructive disease then in patients with non-obstructive/absent coronary disease. Although statistically significant, this difference is not likely to be clinically relevant. From pathophysiological point of view, such post-resuscitation myocardial injury may be best explained by global myocardial ischemia during cardiac arrest which is likely to be intensified by resuscitation interventions such as defibrillations[17] and repeated adrenaline boluses.[18] Indeed, in the absence of acute culprit lesion, we were able to demonstrate weak but significant positive linear correlation with duration of cardiac arrest, number of defibrillations and cumulative dose of adrenaline. This is in agreement with some studies[19,20] and in contrast with others.[6,21,22]

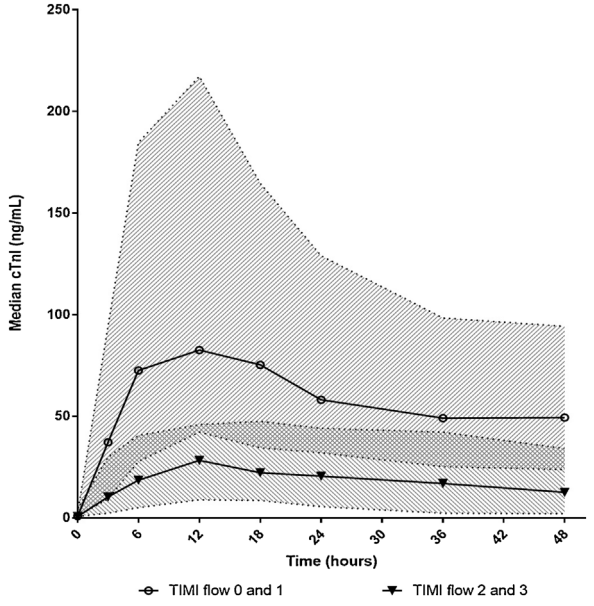

Fig. 3 – Time course of cardiac troponin I (cTnI) concentration according to TIMI (Thrombolysis in Myocardial Infarction) flow at initial coronary angiography in patients with the presence of acute culprit lesion (Group A). Median values (thick line) and 25th and 75th quartiles (dotted lines) are shown.

From practical point of view, the key question for a physician admitting a patient with resuscitated OHCA is weather acute culprit lesion amenable to PCI, is present. Such information, available already on admission, would trigger immediate coronary angiography.[7,23] Although cTnI was significantly greater in patients with acute culprit lesion, values exceeded ninety-ninth percentile of healthy population (>0.04 ng/L) were documented in almost all patients regardless of the coronary anatomy. With a cut off value of 0.46 ng/L, we would miss 36% patients with acute culprit lesion and take to the catheterization laboratory 40% of patients with stable or no coronary disease. If presence of STEMI in early post-resuscitation ECG is combined with admission cTnI, we would still miss 12% of patients with acute culprit lesion and take even more patients (45%) unnecessarily to the catheterization laboratory. Also the difference in admission arterial lactate concentration obtained by univariate analysis was too small to guide for decision-making for immediate coronary angiography.

Accordingly, at the present time, we are still not able to accurately select the best candidates for immediate coronary angiography which is in accordance with previous studies.[4,5,24–26] On the other hand, there was no significant difference in neurologically intact survival between the three study groups. This may represent a treatment benefit of immediate PCI in group A with acute culprit lesion resulting in better survival than expected. Alternatively, immediate angiography with PCI may not contribute to favourable outcome in comatose survivors of OHCA who mainly die due to lack of neurological recovery. Hopefully, several ongoing randomized trials performed predominantly in patients without STEMI in post-resuscitation ECG, will at least in part answer this important clinical dilemma. Moreover, we also do not know if coronary angiography/PCI should be done immediately as opposed to on the index hospitalization. This is a very important distinction since the complexities and risks of immediate angiography are very different from delayed intervention within next 24–48 h or when (if) the patient wakes up from post-resuscitation coma.

Study strengths and limitations

The strengths of our study are prospective design together with short and consistent time interval from OHCA to coronary angiography and initial cTnI measurement which was not a case in previous studies.[4,21,24] We could also obtain 12-lead ECG before coronary angiography in all patients. Unfortunately, almost 50% of patients undergoing immediate coronary angiography were excluded mainly because initial cTnI measurements were missed. Nevertheless, we believe that exclusion was a random event and our study sample is representative of OHCA patients with presumed coronary origin. We are also well aware of limitations of coronary angiography in the diagnosis of unstable coronary plaque and thrombus but more sensitive tools such as optical coherence tomography (OCT) were not routinely available in our catheterization laboratory. Moreover, cTnI assay used in our institution does not strictly met all high sensitivity criteria which may lead to suboptimal early diagnostic accuracy.[27–29]

Conclusion

OHCA with acute culprit lesion, present in nearly 50% of patients, is associated with the largest myocardial injury particularly if the infarct-related coronary artery is still occluded at hospital admission (Type 1 MI). Acute myocardial injury, although significantly smaller and clinically probably less relevant, occurs also in the absence of acute culprit lesion and is larger in patients with stable obstructive disease then in patients with non-obstructive or absent coronary disease (Type 2 MI). This myocardial injury is best explained by global myocardial ischemia during cardiac arrest which is intensified by resuscitation interventions such as defibrillation and repeated adrenaline boluses. Admission cTnI although combined with post-resuscitation 12-lead ECG is insufficient to accurately select the patients with acute culprit lesion which are the best candidates for immediate coronary angiography.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.026.

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