Research Article

Interventional Cardiology

Immediate coronary intervention in comatose survivors of out-of-hospital cardiac arrest: Outcomes from two tertiary, 24/7 primary percutaneous coronary intervention centres in UK

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Background: There is a relative lack of data regarding the outcomes of comatose patients who present to the cath lab intubated and ventilated.

Aim of the study: To analyse patient- and procedural-related variables at the time of emergency percutaneous coronary intervention (PCI) in patients who arrive in the cath lab intubated and ventilated and establish their relation to 30-day mortality.

Setting: Two regional tertiary cardiac centres, the University Hospital of Wales in Cardiff and Morriston Cardiac Centre in Swansea.

Methods: We included all consecutive patients between 01/03/2007 and 31/03/2014 who had PCI to a native coronary artery while being intubated and ventilated, and we documented their clinical and interventional features using the cath lab databases of the 2 institutions. We correlated these features with survival status at 30 days.

Results: We included 133 patients (71% M), mean age 63.7 years (61.7-65.8; 95% confidence interval - CI) who had primary PCI for ST-segment elevation myocardial infarction (STEMI) (62%), PCI for unstable angina (UA)/ Non-STEMI (NSTEMI) (31%) or rescue PCI (8%). Mortality was 37% at 30 days, with most deaths occurring during the first week after PCI. The following features correlated with mortality (p values): History of myocardial infarction (MI) (0.026); age (0.021), cardiogenic shock (0.007), reduced pre-procedural Thrombolysis in myocardial infarction (TIMI) flow in the culprit artery (0.020), number of coronary arteries with stenosis >70% (0.03), incomplete revascularisation (0.01). In multi-variate analysis only cardiogenic shock (p=0.008; OR 4.552), incomplete revascularisation (p<0.001; OR 7.554) and <TIMI3 flow in the infarct-relate artery (IRA) (p<0.011, odds ratio – OR - 9.788) remained consistently and strongly associated with mortality.

Conclusion: PCI in comatose patients has a high, but not prohibitive, 30-day mortality, clustered mainly in the first post-procedural week. Cardiogenic shock, incomplete revascularisation and reduced post-procedural TIMI flow in the infarcted related artery are associated with death.

Keywords: Coronary intervention ▪ Comatose survivors ▪ Cardiopulmonary resuscitation

Introduction

The increasing availability of bystander cardiopulmonary resuscitation (CPR) and of primary percutaneous coronary intervention (PPCI) in economically-advanced countries means that an increasing number of patients are brought to catheter labs following successful resuscitation from a cardiac arrest.

In a recent meta-analysis, the prevalence of an acute coronary artery lesion was 80% in out of hospital cardiac arrest (OOHCA) patients without an obvious non-cardiac aetiology [1], but there is little clarity regarding the correct policy in OOHCA survivors whose post-arrest electrocardiogram (ECG) does not show evidence of STEMI, as most published studies focus on STEMI and PPCI. Concerns about futility of PCI, in the context of potentially irreversible hypoxic brain damage, often underpin the decision to manage such patients conservatively. We set out to investigate outcomes of PCI in comatose survivors of OOHCA in our practice.

Aims of the Study

The primary research aim was to describe 30-day mortality in our study population, and to identify patient, peri and intra-procedural characteristics associated with mortality. Assessing the clinical and procedural features associated with outcomes for patients admitted to the catheter labs intubated and ventilated from two cardiac tertiary Centre's in Wales, UK, in an effort to contribute to the body of data about this topic.

Methods

Centres

The University Hospital of Wales is a teaching hospital in Cardiff, Wales, United Kingdom,with a catchment area of approximately 1.8 million people. The catheter labs performs approximately 2200 PCI/year (of which 1700 are PCI and 500 are PPCI), and 24/7 PPCI has been performed since 2012. Morriston Cardiac Centre (MCC) is the teaching, tertiary cardiac institution in West Wales, UK, with a catchment population of approximately 1.2 million people. It performs 1200 PCI/year (approx. 375 of which are primary PCI), and the PPCI programme started in 2010.

Patients

We queried the dedicated interventional databases in the two interventional centres, retaining for analysis all patients that were intubated and mechanically ventilated at the time of PCI to a native coronary artery, between 01/03/2007 and 31/03/2014. We included consecutive all-comers, and the only inclusion criteria for patients who had presented intubated and ventilated to the cath lab were availability of a cath lab database entry and of an outcome regarding survival status at 30 days after PCI.

For specific variables we tested various thresholds in an attempt to tease out any relevant associations (e.g. 50% or 70% stenosis severity, TIMI III flow *vs.* all other degrees of flow, or TIMI III and II *vs* all others etc.). Finally, we explored a number of general questions relating to procedural efficiency. The statistical methodology is detailed in the supplementary file. Statistical analysis was conducted using SPSS, version 22 (SPSS Inc., 233 S. Wacker, Chicago, IL). Since our outcome measure (30-day mortality) is binary and most tests included multiple variables, we measured the impact of all variables using Logistic Regression (LR).

Results

Overview

We identified 133 consecutive patients who had PCI while intubated, during the study period. The majority of the sample were male (71%) and ages ranged from 35 to 89 years, with a mean age of 63.7 years (SD 61.7-65.8; 95% CI). A fifth (20%) had a history of MI and approximately 16% were diabetic. Table 1 shows patient and procedural characteristics.

Indications for PCI were STEMI undergoing PPCI (62%), followed by UA/NSTEMI (31%) with a small proportion (8%) undergoing rescue PCI. Three quarters (73%) were emergency procedures with urgent and salvage procedures comprising around 13-14% each. Cardiogenic shock (BP<100mm Hg and either mechanical circulatory support or on-going pharmacological or intra-aortic balloon pump inotropic support) was present in 55% of patients.

Two-thirds (76%) of procedural results were designated as 'Excellent' and a further 16% as 'Good', leaving around 8% roughly equally split between 'No Change', 'Poor' and 'Failed'; an 'Excellent' or 'Good' result were considered 'Successful'.

The overall mortality rate at censoring was 43%, with 37% mortality at 30 days. Of the 49 patients who

Table 1: Baseline characteristics of the study group.

Clinical Features		
Age (years)	Mean (SD)	63.7 (11.8)
Male	n/N (%)	94/133 (71%)
Previous MI	n/N (%)	22/112 (20%)
Previous CABG	n/N (%)	4/130 (3%)
Previous PCI	n/N (%)	10/128 (8%)
Diabetic	n/N (%)	19/120 (16%)
Current Smoker	n/N (%)	37/92 (40%)
Hypertension	n/N (%)	54/108 (50%)
Hypercholesterolemia	n/N (%)	54/108 (50%)
Renal Disease	n/N (%)	8/112 (7%)
Vessel features		
Lesions treated	Mean (SD)	1.49 (0.92)
Target Vessels	N	184
LMS	n/N (%)	10/184 (5%)
LAD prox	n/N (%)	49/184 (27%)
LAD other	n/N (%)	48/184 (26%)
RCA	n/N (%)	48/184 (26%)
LCX	n/N (%)	29/184 (16%)
Target Lesions	N	197

Abbreviations: N : total number of patients (or of vessels) for whom the information on each baseline characteristic is available; n : absolute number of patients (or of vessels) that display a specific characteristic; SD : standard deviation; MI : myocardial infarction; CABG : coronary artery by-pass graft operation; PCI : percutaneous coronary intervention; LMS : left main stem; LAD : left anterior descending; LCx : left circumflex; RCA : right coronary artery; prox : proximal.

died before 30 days, 9 (18%) did so within the first 24 hours after PCI. The level of risk fell rapidly with time, with only 30% of deaths occurring after the end of the first week.

Patient demographics and medical history

Patient gender was not associated with mortality (p=0.520), but age was highly correlated with mortality (p=0.021), with increasing age giving a greater risk. By considering age as a categorical variable transformed into decade bands it was apparent that this relationship was simple, exhibiting a gentle linear trend, thus making it appropriate to consider age as a continuous variable in further models. There were no differences in mortality (p=0.762) according to which hospital performed the PCI. We found evidence of an effect on mortality for a history of MI (p=0.026) but not for diabetes (p=0.564), seasonality (p=0.248) or any trend across the 7 years of the study (p=0.400).

Indication and urgency of PCI

The indication for PCI showed no correlation with mortality (p=0.573) while the impact of the level of urgency (p=0.155) was only weak. Cardiogenic shock, however, was highly correlated with mortality (p=0.007) and demonstrated a high level of significance with an odds ratio for death at 30 days of 3.4 [1.4-8.1; 95% CI]. The admission route (from within the centre, direct to or *via* an inter-hospital transfer), was not significant (p=0.724), nor was the distinction between ST elevation and depression in the presenting ECG (p=0.511).

Angiographic and procedural characteristics

TIMI flow in the culprit artery: Reduced pre-procedural flow (TIMI<3) was associated with increased mortality (p=0.020); the association remained significant even at different binary cut-offs but became insignificant in multivariate analysis.

Culprit vessel: We found that no individual culprit vessel was associated with greater risk of death at 30 days (p=0.770). We also found no evidence that the total number of vessels attempted had an impact on mortality (p=0.216).

Extent of coronary artery disease (CAD) – number of diseased vessels: At a 50% threshold for coronary artery stenosis severity there is a significant association between the number of diseased coronary arteries and mortality (p=0.038). The number of coronary arteries with a stenosis >70% was an even stronger significant predictor of risk (p=0.003) even when age, previous MI and cardiogenic shock were included as covariates.

There was a reduction in the significance of age as a risk factor for mortality when we included the number of diseased vessels in the analysis, probably due to the biologically plausible strong correlation between age and the extent of CAD (p=0.012; Spearman correlation).

Extent of revascularization: We found that incomplete revascularisation was associated with a significantly higher risk of death (p<0.001). To check this for robustness we added, first, the number of vessels attempted, then the total number of diseased vessels as additional covariates but still found a high level of significance (p<0.001 and p=0.007 respectively) for incomplete revascularisation as a predictor of death at 30 days. In a final test we chose the most conservative scenario, by including the number of diseased vessels as a factor (rather than a covariate), but still found a significant association (p=0.014). The odds ratio for death in the presence of incomplete revascularisation was 7.0 [1.5-33.1; 95% CI].

We tested all subsequent variables in the presence of age, previous MI, cardiogenic shock and extent of revascularisation as background variables. The detailed LR output is presented in the supplementary material available on-line.

Effectiveness of PCI

Having the PCI classified as 'successful' is only weakly linked with reduced mortality (p=0.093) in the LR. When analysed in isolation it appears highly significant, but much of the effect is due to the presence of the other factors. Despite the impact of these prior factors post-procedural TIMI flow is highly relevant (p=0.012).

Timing and delays in treatment: The time between onset of symptoms and PCI (whether or not we include the outcome of the PCI in our calculation (p=0.911 and 0.964 respectively)), the time spent in hospital prior to PCI (p=0.965 & 0.768), the duration of PCI (p=0.280 & 0.635) or the time between PCI and discharge (p=0.420 & 0.175) had no impact on mortality at 30 days.

Key variables

After working through all possible variables, we were left with a small subset (cardiogenic shock, extent of revascularisation and post-PCI IRA flow) that remain consistently and strongly associated with mortality, regardless of the composition of the model (Table 2). When tested in concert the p-values assigned to them

Table 2: Variables correlated with mortality at 30 days (by logistic regression).

Variable Name	p-value	Odds Ratio for death [95% CI]
Cardiogenic shock	0.008	4.552 (1.495,13.680)
Incomplete revascularisation	<0.001	7.554 (2.521,22.581)
Limited flow in IRA post-op	0.011	9.788 (1.679,57.044)

are 0.008, 0.000 and 0.011 respectively. Previous MI was also close to the threshold for significance (P=0.079).

Discussion

We identified a strong association between incomplete revascularisation and increased mortality, with cardiogenic shock at presentation and <TIMI 3 flow in the IRA post-procedurally also strongly associated with increased mortality. We found that 30-day mortality was high at 43% and tended to occur mainly in the 1st week after PCI, while the presence or absence of ST-segment elevation (STE) on the presenting ECG did not affect 30-day mortality.

Although the recent advent of PPCI has led to an increased interest in developing evidence-based protocols of cath lab access for OOHCA survivors, it is striking how little data is available on the PCI outcomes of comatose OOHCA survivors, the specific patient population that we report here.

In a recent publication [2] there is no distinction made between comatose and conscious OOHCA survivors, nor is there such a distinction reported in a Turkish study from October 2018 [3].

The most recent (December 2018) paper on OOHCA survivors of STEMI that we could find included only conscious patients [4], while the BCIS Dataset (2016) gives a prevalence of 'emergency ventilated PCI' between 0.5%–4% across the UK but does not distinguish between PPCI and PCI for NSTEMI or other indications [5]. We think that, as resuscitation protocols evolve and the prevalence of successful CP with immediate post OOHCA resumption of spontaneous circulation (ROSC) increases [6], it is essential we gather data on comatose survivors who reach the cath lab, in order to develop specific interventional protocols in such patients.

Our study is the 3rd largest series to date reporting comatose patients who had emergency PCI following OOHCA. Of the 41 studies reviewed in the European Consensus Statement [7], 7 included more patients than ours, and of these, only two included comatose patients.

After some progress in the long-standing debate on full *vs.* IRA-only revascularisation at the time of PPCI, the recent CULPRIT-SHOCK results [8] reconfigured the debate again [9]. Three pivotal randomised studies had demonstrated the benefit of full revascularisation, albeit with an inconsistent effect on mortality. In CvLPRIT [10] the superiority of complete revascularisation was driven by reduction in all components of composite primary end point, while PRAMI [11] was stopped early due to a significant reduction in MI and refractory angina in the complete revascularisation group. In DANAMI-3-PRIMULTI, the advantage of the 'complete' group was driven by a reduction in ischaemia-driven revascularization [12]. However, in CULPRIT-SHOCK [8], 'among patients with acute myocardial infarction and cardiogenic shock, the risk of death or renal-replacement therapy at 30 days was lower with culprit-lesion-only PCI than with immediate multivessel PCI, and mortality did not differ significantly between the two groups at 1 year of follow-up'.

IRA patency before PPCI has been identified as a predictor of one-year mortality in the PPCI context [13], but it did not associate with survival in multivariate analysis in our patient population. A recent French registry documented pre-procedural IRA patency in one third of patients with STEMI, more often in those who had prasugrel or ticagrelor before angiography, and in those who had sought help early. Intriguingly, there was higher IRA patency with increasing time delays from qualifying ECG to angiography, which suggests a role for spontaneous recanalization [14]. Post-procedural IRA TIMI flow grade has been identified as a strong predictor of outcomes after PPCI [15] and our data confirm this finding.

While the benefits of immediate PPCI in STEMI are clearly established, the evidence is contradictory. In RIDDLE-NSTEMI, for instance, an immediate invasive strategy in NSTEMI patients was associated with lower rates of death or new MI compared with a delayed invasive strategy at 30 days and at one year [16]. In the more recent VERDICT trial, however, in spite of a numerical trend favouring early PCI, the occurrence of the composite primary end-point was not reduced by early (<12h) access to PCI [17]. (https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.037152). Our patients (with STEMI and NSTEMI alike) were, by virtue of

their presentation with OOHCA, a cohort with the highest risk of MACE, so finding that PCI benefits regardless of the presence or absence of ST elevation is biologically plausible. We hypothesize that the benefit of revascularisation is so high in this extreme-risk group that it may overcome the progressive worsening of outcomes seen with delaying intervention.

Limitations of the Study

The data was based on registry data and the results should be interpreted in this context. We considered all cause death and did not distinguish cardiac from non-cardiac causes of death. There were some incomplete data, inherent issues with clinical registry data, including patchy documentation of left ventricular ejection fraction (LVEF). Although LVEF is a powerful predictor of outcomes, it is likely to correlate to, or even be determined by, factors that we found to influence 30-day mortality, such as extent of revascularisation and shock at presentation, so we do not think its addition would have changed our conclusions significantly.

Conclusions

Mortality at 30 days following emergency PCI in comatose survivors of OOHCA is higher in patients who do not have full revascularisation, are older, have low TIMI flow scores after PCI, or present in cardiogenic shock. Mortality was not different between STEMI and NSTEMI. Emergency PCI should strongly be considered in the management of all comatose victims of OOHCA in whom a non-cardiac cause has been excluded.

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