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Out of Hospital Cardiac Arrest Survivors with Inconclusive Coronary Angiogram: Impact of Cardiovascular Magnetic Resonance on Clinical Management and Decision-Making

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Abstract

Background Non-traumatic out of hospital cardiac arrest (OHCA) is the leading cause of death worldwide, mainly due to acute coronary syndromes. Urgent coronary angiography with view to revascularisation is recommended in patients with suspected acute coronary syndrome. Diagnosis and management of patients with inconclusive coronary angiogram (unobstructed coronaries or unidentified culprit lesion) is challenging. We sought to assess the role of Cardiovascular Magnetic Resonance (CMR) in the diagnosis and management of OHCA survivors with an inconclusive coronary angiogram.

Methods and Results This is a retrospective multicentre CMR registry analysis of OHCA survivors with an inconclusive angiogram. Clinical, ECG and multi-modality imaging data were analysed. Clinical impact of CMR was defined as a change in diagnosis or management. Out of 174 OHCA survivors referred for CMR, 110 patients (63%, 84 male, median age 58) had an inconclusive angiogram. CMR identified a pathologic substrate in 76/110 patients (69%): ischemic heart disease was found in 45 (41%) and non-ischemic heart disease in 31 (28%). A structurally normal heart was found in 25 patients (23%) and non-specific findings in 9 (8%). As compared to trans-thoracic echocardiogram, CMR proved to be superior in identifying a pathologic substrate (69% vs 54%, p=0.018). The CMR study carried a clinical impact in 70% of patients, determining a change in diagnosis in 25%, in management in 29% and a change in both in 16%.

Conclusions CMR showed a promising role in the diagnostic work-up of OHCA survivors with inconclusive angiogram and its wider use should be considered.

Introduction

Non-traumatic out of hospital cardiac arrest (OHCA) is the leading cause of death worldwide (1-3) with an estimated incidence of 0.5/1000 person year (4-8). Acute coronary syndromes (ACS) account for more than 2/3 of cases (9-12). According to AHA guidelines, urgent angiography with view to primary percutaneous coronary intervention is a class IB recommendation in patients with resuscitated cardiac arrest whose electrocardiogram (ECG) shows ST elevation (STE) myocardial infarction (MI) (13). Given the high incidence of underlying coronary artery disease (CAD) in this group of patients, European guidelines extended the recommendation to incorporate patients without diagnostic STE, but with high suspicion of on-going infarction (class IIaB) (14). However non-ischemic cardiomyopathy accounts for up to 15% of OHCA (15-19) and a structurally normal heart can be found in up to 10-20% of cases (20-23). While evidence of culprit lesion on angiogram supports acute ischemia as the cause of OHCA, diagnosis and clinical management of OHCA survivors with inconclusive coronary angiogram (either non-identifiable culprit lesion or unobstructed coronary arteries) is challenging. Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique providing accurate diagnosis based on its superior spatial resolution and unique non-invasive tissue characterization.

We sought to assess the additional role and clinical impact of CMR in the diagnosis and management of OHCA survivors with an inconclusive coronary angiogram.

Materials and Methods

The CMR registries from two tertiary Cardiac centres (Bristol, South West of England and Padua, Veneto Region, Italy) were analysed to identify OHCA survivors who underwent urgent coronary angiogram followed by CMR (October 2009-November 2015). The study focused on the analysis of patients with an “inconclusive angiogram”, defined as evidence of stable obstructive CAD (SCAD) with no culprit lesion or unobstructed coronaries (normal coronaries/non-obstructive CAD). Culprit

lesion was defined as obstructive (≥70%) CAD with TIMI 0/1 flow with abrupt closure, or TIMI 2/3 flow with features suggestive of thrombus/ulcerated plaques, ST segment- T wave changes in the corresponding ECG location, and evidence of matching regional wall motion abnormality on left ventriculogram or echocardiogram (24).

CMR

CMR was performed on a 1.5T scanner (Avanto, Siemens Healthcare, Germany) with a protocol including long and short axis cine sequences and post-contrast imaging, performed ten minutes after intravenous administration of 0.1 mmol/Kg of Gadobutrol (Gadovist 1.0 mmol/ml, Bayer-Schering, Berlin, Germany) in identical planes to cine images. Additional sequences for the assessment of myocardial oedema (T2-short tau inversion recovery, T2-STIR) or myocardial ischemia (stress perfusion with 140 to 210 ug/Kg/min adenosine) were performed when indicated, based on clinical and angiographic findings. Ventricular function was assessed with dedicated software (Circle Cardiovascular Imaging, Calgary, Canada), by tracing endo- and epicardial borders on each short axis cine slice in end-diastole and end-systole. All volumes were indexed to body surface area. The localization, extent and distribution pattern of late gadolinium enhancement (LGE) were assessed by using short- and long-axis views and confirmed only if detectable in two orthogonal planes. The pattern of LGE distribution was defined as ischemic, subendocardial or transmural, if involving <50% or ≥50% of wall thickness, respectively, and as mid-wall/epicardial if patchy/spotty intra-mural or sub-epicardial enhancement was detected. The presence of LGE at the right ventricle/left ventricle insertion points, in the absence of other distribution patterns, was defined as non-specific findings, as its diagnostic and prognostic meaning is still unclear.

All the analyses were carried out in accordance with the recommendation of the Society for Cardiovascular Magnetic Resonance (25). The study was reviewed by the local Institutional Research and Innovation Department and in view of the retrospective design, formal ethical approval was waived off. All patients gave written informed consent.

Clinical impact

Clinical, ECG and echocardiographic data were collected and independently analysed by two clinicians blinded to CMR findings. A diagnosis was made based on clinical and imaging data available prior to CMR. According to previously used definitions (26), "clinical impact" of CMR was defined as change in diagnosis, compared to the composite pre-CMR diagnosis, or change in management. A change in management was defined as CMR findings either leading to change in medication, to an invasive procedure (i.e. repeat angiogram, myocardial revascularization, ICD implantation) or to the avoidance of such invasive procedures. Patients with a change both in diagnosis and management were only counted once.

Statistical Analysis

Continuous and categorical variables are expressed as mean±SD or median (IQR), and n (%), respectively. Categorical variables were compared by using the chi-square or Fisher exact test, as appropriate. Continuous data were compared by using the 2-tailed unpaired t test (for normally distributed data sets) or by using the Mann-Whitney U test. Inter-rater agreement for categorical variables was assessed by Cohen's kappa coefficient. A p-value of <0.05 was considered statistically significant. Data were analysed with SPSS® version 23 (IBM®).

Results

Clinical characteristics

Out of 174 consecutive OHCA survivors referred to CMR after coronary angiogram (performed on same day of admission, IQR 0-2 days), 110 patients (63%, 84 male, age 58 years, IQR 46-68) had an inconclusive angiogram and were enrolled in the study: 37 patients (34%) had evidence of SCAD with no culprit lesion and 73 patients (66%) showed unobstructed coronaries. The first registered rhythm was ventricular tachycardia (VT)/ventricular fibrillation (VF) in 104 patients

(95%) and pulseless electrical activity (PEA) in 6 patients (5%). The first ECG was available in 86 patients (78%): non-ST elevation (non-STE) was reported in 68 patients (79%), STE in 18 (21%). SCAD patients with no culprit lesion were more frequently men (p=0.006) and significantly older compared to patients with unobstructed coronaries (p<0.001); risk factors were similar, except for hypertension (p=0.001) and known CAD (p <0.001), which were more frequent among SCAD patients with no culprit lesion. STE was more common among SCAD patients with no culprit (p=0.002). Patients' characteristics are listed in **Table 1**.

CMR findings

Among patients with inconclusive angiogram, CMR was performed within 2 weeks from the index event (median 1.4 weeks, IQR 0.9-2.4, no difference between centres, p=0.588). Time to CMR was significantly shorter among patients with inconclusive angiogram, as compared to patients found to have an acute coronary event on angiogram (p=0.001). Median left ventricular ejection fraction (LVEF) was 57% (IQR 44-64), median indexed left ventricular end-diastolic volume (LViEDV) and end-systolic volume (LViESV) was 87 ml/m^2 (IQR 73-110) and 38 ml/m^2 (IQR 27-56), respectively. LVEF was significantly higher among patients with unobstructed coronaries (p <0.001). Wall motion abnormality was reported in 55 patients (50%), with regional or diffuse pattern in 38 (35%) and 17 patients (15%), respectively (**Table 2**).

On post-contrast sequences LGE was found in 72/110 patients (65%), and it was significantly more common among SCAD patients with no culprit lesion (33/37 vs 39/73, p <0.001). Analysis of LGE distribution pattern showed subendocardial LGE in 15 patients (14%), mid-wall/epicardial in 26 patients (24%), and transmural LGE in 27 patients (25%). More than one distribution pattern was reported in 4 patients (3%). No LGE was found in 38 patients (34%). T2-STIR sequences for myocardial oedema were performed in 58 patients (53%), more frequently in patients with unobstructed coronaries (p=0.001); myocardial oedema was found in 18 patients (31%). Presence of myocardial oedema was not significantly associated with the timing of CMR; however, there was a

trend towards a higher prevalence of myocardial oedema among patients undergoing CMR within one week from index event (p=0.064). There was no difference in prevalence of myocardial oedema between the two groups.

Overall, CMR identified a pathologic substrate in 69% of the population: IHD was the final diagnosis in 45 patients (41%) and non-ischemic heart disease (NIHD) in 31 (28%). Non-specific findings were found in 9 patients (8%) and a structurally normal heart in 25 (23%)(**Table 3**). CMR findings between the two subgroups differed significantly (p<0.001)(**Figure 1 and Supplementary File 1**)

Stable obstructive CAD with no culprit lesion

Thirty-four patients (92%) were found to have IHD, a structurally normal heart (no myocardial oedema, late enhancement or inducible ischemia) was found in 3 (8%). On T2-STIR sequences, performed in 11 patients (30%), myocardial oedema was found in a single coronary artery territory in 5 (45%), helping to localise the culprit lesion. Stress perfusion CMR was performed in 15 patients (41%): inducible ischemia was reported in 10 patients (67%) (single coronary artery territory in 7 patients and multi-vessel territory in 3), 90% of whom received percutaneous/surgical revascularization. A viability study was performed in the remaining 22 (59%) to guide treatment (revascularization/ optimization of medical therapy); CMR showed findings consistent with viable myocardium in 15 patients (68%), of which 12 (80%) underwent revascularization.

Unobstructed coronaries

IHD was diagnosed in 11 patients (15%) and NIHD in 31 (43%), with myocarditis (23%) and DCM (10%) being the most common, followed by congenital and acquired cardiomyopathies (**Table 3**). A structurally normal heart was found in 22 patients (30%) and non-specific findings in 9 (12%)(**Figure 2**). On T2-STIR sequences, performed in 64% of patients, the presence of

myocardial oedema in 13 (28%) identified an acute, reversible, cause of OHCA in 3 IHD patients and in those diagnosed with myocarditis and TTC. LGE was found in 53%.

Comparison between CMR and trans-thoracic echocardiogram

A trans-thoracic echocardiogram (TTE) performed within 1 week from CMR was available in 92 patients (84%). Median LVEF by TTE was lower compared to CMR (50% vs 57%, p <0.001). TTE identified a pathologic substrate in 50/92 patients (54% vs 69% by CMR, p=0.018): the final diagnosis was IHD in 26/92 patients (28%) and NIHD in 24/92 patients (26%). A structurally normal heart was found in 20/92 patients (22%) and non-specific findings (structural and functional abnormalities not attributable to a conclusive diagnosis) in 22 (24%). CMR and TTE provided the same diagnosis in 51/92 patients (55%)(**Table 4**). There was a moderate agreement between CMR and TTE with regards to IHD, which was confirmed on CMR in 22/26 patients (85%)(Cohen's kappa 0.50), and to structurally normal heart, confirmed on CMR in 11/20 patients (55%)(Cohen's kappa 0.43). There was a fair agreement with regards to NIHD, which was confirmed on CMR in 15/24 patients (63%)(Cohen's kappa 0.21); based on tissue characterization CMR identified 7 patients with an ischemic distribution pattern of LGE. CMR provided a diagnosis in 14/22 (64%) patients with non-specific findings on TTE, identifying 6 patients with IHD and 8 patients with NIHD. The ability of CMR to be more definite regarding the underlying cardiac abnormalities was mainly based on LGE.

Clinical impact of CMR

CMR provided a clinical impact in 77/110 patients (70%), leading to change in diagnosis in 27 patients (25%), in management in 32 (29%), and both in diagnosis and management in 18 patients (16%). An entirely new diagnosis was found in 25% of patients, most commonly structurally normal heart (11%) and NIHD (10%). CMR led to an invasive procedure in 32 (29%) patients, namely myocardial revascularization in 21 (19%) and ICD implantation in 11 (10%). Based on

CMR findings, an invasive procedure was avoided in 15 (14%) patients. CMR had greater clinical impact in SCAD patients with no culprit lesion (p=0.002), more frequently experiencing a change in management (86% vs. 25% unobstructed coronaries, p <0.001); a change in diagnosis occurred more frequently among patients with unobstructed coronaries (58% vs. 8% SCAD patients, p <0.001).

Discussion

The main findings of our study were that: 1) 2/3 of OHCA survivors referred to CMR have inconclusive findings on angiogram; 2) CMR identified a pathologic substrate in 69% of the population and a structurally normal heart in 23%; 3) CMR had a clinical impact in more than two thirds of patients.

Acute coronary syndromes account for more than two thirds of OHCA (9-12) mainly secondary to acute coronary thrombosis (26) or ruptured plaque (27), as confirmed by autopsy series. International guidelines recommend urgent angiography in OHCA survivors with STE (13, 14) or whenever there is high suspicion of on-going infarction, irrespective of ECG (14). However, only a minority of cases (30-40%) shows angiographic and clinical evidence of ACS (27), a figure similar to that (37%) in our study. Causes other than acute ischemia are reported in up to 30% of cases (28). When acute ischemia is the obvious cause of OHCA, fewer patients are referred to CMR, mainly to assess the extent of myocardial scarring and the functional significance of bystander CAD. On the other hand, an inconclusive angiogram poses a diagnostic dilemma requiring further investigation, and to our knowledge this is the first study looking at the role and clinical impact of CMR in OHCA survivors with this angiographic finding. Identifying OHCA aetiology is often challenging in the acute setting, as clinical data are often lacking and ECG and echocardiographic interpretation might be affected by resuscitation manoeuvres or external defibrillation (27, 29). However, correct identification of the underlying cause, especially if reversible, plays a determinant role for

appropriate treatment strategy and long-term prognosis. CMR has a well-established diagnostic role, both in the ischemic and non-ischemic scenario, based on its superior tissue characterization properties. In our study, CMR could identify an underlying pathologic substrate in 69% of the population, as compared to 54% by TTE (p=0.018), and this was mainly due to LGE analysis. This superior diagnostic ability carried additional value and clinical impact over TEE in the management of these patients; for example, non-specific findings were more frequently reported by TTE (24% vs 8%), but CMR was able to identify a pathologic substrate in two thirds of them. We found a high prevalence of LGE among OHCA survivors (65%), in keeping with that recently reported by Neilan (71%) in OHCA survivors referred to CMR because of an unclear diagnosis (after clinical and diagnostic assessment) (30). The aim of their study was to identify the role of LGE as an arrhythmic substrate and as a predictor of adverse cardiovascular events. They found that LGE presence and extent are the strongest predictors of adverse arrhythmic outcome, further confirming the relationship between myocardial damage and major arrhythmias, and strengthening the association between tissue characterization and arrhythmic risk, independent of the ejection fraction, as reported by many studies on cardiovascular outcome (31-35). White et al. (36) showed that CMR-based imaging had a pick-up diagnostic rate of 74% in identifying the myocardial substrate of ventricular arrhythmias vs. 51% based on non-CMR imaging (i.e. diagnosis of MI missed in one third of patients on non-CMR imaging). In our study, CMR identified ischemic myocardial damage in 11 patients (15%) with unobstructed coronaries on angiogram; TTE diagnosed IHD in only one of them. Among 88 patients with no label of prior MI, Neilan (30) found ischemic LGE in 49, thus supporting the hypothesis that the presence of LGE in patients with unobstructed coronaries identifies a subgroup of patients at increased risk of arrhythmic events. Compared to Neilan, our study explored the comparative value of CMR vs TTE, as well as the clinical impact of CMR in this patients' cohort.

As already confirmed in different populations, such as in heart failure (26), we found that CMR changed both diagnosis and management in a considerable proportion of OHCA survivors (70%).

Of interest, CMR showed a clinical impact both in patients with unobstructed coronaries, mainly by providing a change in diagnosis, and in SCAD patients with no culprit lesion, mainly by a change in management. An entirely new diagnosis was identified in 25% of cases, mainly based on tissue characterization: a structurally normal heart was found in 11% of patients, based on the absence of LGE, and NIHD was diagnosed in 10%. Stress perfusion CMR has a well-established role not only in detecting CAD and guiding subsequent treatment strategy (37-39), but also in the identification of patients at increased risk of major adverse cardiovascular events (40, 41). Stress perfusion CMR, performed in nearly half of SCAD patients with no culprit lesion, found inducible ischemia in 67% of patients, guiding myocardial revascularization in nearly all of them. It is well-established that CMR has a role, over and above TTE, in re-classifying patients with regards to primary prevention ICD eligibility based on LVEF criteria (42), as it is the gold standard for LV function (43). The ability of CMR to detect reversible myocardial damage could play a role in guiding secondary prevention ICD implantation. In our patient population of OHCA survivors, CMR identified acute reversible myocardial injury (acute myocarditis and acute ischemia), thus avoiding secondary ICD implantation, as per guidelines, in 6% of patients.

Limitations

The main limitation of this study is the retrospective design. However, conducting a prospective trial in OHCA survivors might be difficult due to high mortality rate, variable downtime and consent. Sequences for myocardial oedema were available for analysis in half of the population, thus the clinical impact of oedema analysis might have been higher if performed in all patients. A structurally "normal" heart by TTE and CMR reflects the absence of gross ischemic or non-ischemic underlying conditions, but it cannot exclude ultra-structural abnormalities. Although endomyocardial biopsy is the gold standard to assess myocardial abnormalities, it is an invasive technique, not widely performed clinically and not performed in our patients; therefore some more subtle histological and cellular abnormalities cannot be excluded. With all the above limitations,

this is a real world study that reflects clinical practice in most centres. Our study only analysed the presence of focal fibrosis, although it is increasingly evident that the presence of diffuse fibrosis has a prognostic role, detecting patients at higher risk of fatal arrhythmias (44). The use of the most recent T1 mapping technique might help further understand the pathologic substrate in this group of patients.

Conclusions

Although ACS account for the majority of OHCA, 63% of the survivors in our cohort had an inconclusive angiogram. CMR proved to be superior to TEE in the identification of a pathologic substrate for the event in this cohort (69% vs 54%, p=0.018) and its findings had a clinical impact in 70% of patients, providing a significant change both in diagnosis and in management. CMR showed a promising role in the clinical and diagnostic work-up of OHCA survivors with inconclusive angiogram and its wider use should be considered. Further prospective studies are warranted to confirm these results in a larger population.

Disclosures

Dr Bucciarelli-Ducci is Consultant for Circle Cardiovascular Imaging.

There is no relationship to industry to declare.

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Figure Legends

Figure 1. **CMR findings in OHCA survivors with inconclusive angiogram**

Final CMR findings, according to coronary angiogram data, in OHCA survivors with inconclusive angiogram. Boxes in bold show the final CMR findings in the overall cohort of OHCA survivors with inconclusive angiogram. SCAD, stable coronary artery disease.

Figure 2. CMR findings.

Post-contrast 3 chamber long-axis view showing transmural myocardial infarction (A). Post-contrast 3 chamber long-axis view of a patient with hypertrophic cardiomyopathy (HCM) and replacement fibrosis of the hypertrophied septum (B, arrow). Post-contrast 4 chamber long axis view of a patient with biventricular arrhythmogenic right ventricular cardiomyopathy (ARVC) (C). 3 chamber long axis cine showing prolapse of the posterior mitral leaflet at end-systole (D). Post-contrast short axis view showing epicardial enhancement of the basal lateral wall in a patient with healed myocarditis (E, arrow). Post-contrast short axis view showing non- specific late enhancement of the inferior insertion point (F, arrow).

Supplementary Material

Supplementary File 1. **CMR findings according to coronary angiogram results**

Top panel, no culprit lesion identified on angiogram: ischemic heart disease (IHD) was the most common diagnosis, although CMR identified a structurally normal heart in 8% of patients. Bottom panel, unobstructed coronary arteries: non-ischemic heart disease (NIHD) and structurally normal heart were the most common findings, but CMR identified an ischemic cardiomyopathy in 15% of patients.