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Clinical paper

Coronary angiography findings in patients with shock-resistant ventricular fibrillation cardiac arrest

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Abstract

Introduction: Shock-resistant ventricular fibrillation (VF) poses a therapeutic challenge during out-of-hospital cardiac arrest (OHCA). For these patients, new treatment strategies are under active investigation, yet underlying trigger(s) and substrate(s) have been poorly characterised, and evidence on coronary angiography (CAG) data is often limited to studies without a control group.

Methods: In our OHCA-registry, we studied CAG-findings in OHCA-patients with VF who underwent CAG after hospital arrival. We compared baseline demographics, arrest characteristics, CAG-findings and outcomes between patients with VF that was shock-resistant (defined as >3 shocks) or not shock-resistant (≤3 shocks).

Results: Baseline demographics, arrest location, bystander resuscitation and AED-use did not differ between 105 patients with and 196 patients without shock-resistant VF. Shock-resistant VF-patients required more shocks, with higher proportions endotracheal intubation, mechanical CPR, amiodaron and epinephrine. In both groups, significant coronary artery disease (≥1 stenosis >70%) was highly prevalent (78% vs. 77%, $p = 0.76$). Acute coronary occlusions (ACOs) were more prevalent in shock-resistant VF-patients (41% vs. 26%, $p = 0.006$). Chronic total occlusions did not differ between groups (29% vs. 33%, $p = 0.47$). There was an association between increasing numbers of shocks and a higher likelihood of ACO. Shock-resistant VF-patients had lower proportions 24-h survival (75% vs. 93%, $p < 0.001$) and survival to discharge (61% vs. 78%, $p = 0.002$).

Conclusion: In this cohort of OHCA-patients with VF and CAG after transport, acute coronary occlusions were more prevalent in patients with shock-resistant VF compared to VF that was not shock-resistant, and their clinical outcome was worse. Confirmative studies are warranted for this potentially reversible therapeutic target.

Keywords: Cardiac arrest, Ventricular fibrillation, Resuscitation, Coronary angiography

Introduction

Ventricular fibrillation (VF) is frequently observed as initial rhythm in out-of-hospital cardiac arrest (OHCA).[1] An important subset of these patients have VF that is resistant to multiple defibrillation attempts, i.e. VF that persists or recurs despite shock delivery. This so-called shock-resistant VF is most commonly defined as requiring >3 shocks.[2–4] These patients with prolonged arrest duration are at high risk of mortality and poor neurologic outcome, and have gained increasing interest in recent years.[5,6]

A wide range of treatment strategies has been studied for shock-resistant VF, ranging from experimental studies to a pilot randomised trial on dual sequential defibrillation and a large randomised trial on amiodarone.[4,7,8] Recently, more invasive protocols such as early coronary angiography and extra-corporeal life support have gained attention.[2,9–11] As of yet, only the use of anti-arrhythmic drugs has been incorporated in cardiopulmonary resuscitation (CPR) guidelines as routine treatment.[12] However, despite the growing interest in the optimal therapeutic strategy for these patients, the underlying myocardial substrate has scarcely been described. Importantly, detailed analyses on underlying etiology may reveal potential therapeutic targets.

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One recently published study investigated a treatment strategy with immediate coronary angiography (CAG) in patients with VF that was refractory to ≥3 shocks without intermittent return of spontaneous circulation (ROSC).[2] This study revealed that significant coronary artery disease (CAD) was present in 82% of the patients with refractory VF, with acute thrombotic lesions in 64%. However, that study was limited in patient numbers (n = 55) and there was no description of CAG-findings in a control group.

Given the high prevalence of coronary artery disease in VF-patients in general, additional study is warranted to identify coronary substrate that is specific for shock-resistant VF.[13–15] Such analyses may provide impetus for further study on treatment specifically targeted towards this substrate, which in turn may contribute to improved outcomes in these high-risk patients. Therefore, we studied coronary angiography findings in cardiac arrest patients with VF that was shock-resistant vs. VF that was not shock-resistant.

Methods

Patient population

We studied patients from the Nijmegen area OHCA-cohort (Gelderland-Zuid, the Netherlands).[16] We included patients ≥18 years with a non-traumatic OHCA and a shockable first observed rhythm (defined as either an ECG-confirmed initial rhythm of VF or pulseless ventricular tachycardia, or a shockable rhythm as indicated by the automated external defibrillator [AED] if the first shock was administered by the AED), resuscitated between 1 January 2013 and 1 July 2018, transported to our tertiary hospital and undergoing CAG. Appreciating the non-interventional study design, written informed consent was not necessary to obtain (Dutch Act on Medical Research involving Human Subjects).[17]

Emergency medical services

Gelderland-Zuid (population 530,000 residents, 1040 square kilometers) includes (sub)urban and rural areas. The emergency medical service (EMS) system is activated by calling 112. Paramedics will give instructions to the caller to initiate CPR, and usually two ambulances are dispatched to the OHCA-location. Ambulances are staffed by a driver and a paramedic, who is professionally trained to perform advanced life support. CPR was performed according to the prevailing European Resuscitation Council guidelines at the time of the OHCA.[12]

Data acquisition

Baseline characteristics and outcome data were collected using EMS-records, hospital records and data from municipal registries, following Utstein style definitions.[18]

Coronary angiography

A dedicated angiography committee (1 senior, 1 fellow interventional cardiologist) reviewed all CAG-images specifically for research purposes, using a predefined template including the angiographic parameters of interest.[19,20] A random sample of 20% of all evaluated CAGs was used to calculate inter-observer agreement. In concordance with previous studies, a kappa of >0.80 was used as a cut-off to decide whether the initial evaluations would be used for final reporting, or if a systematic evaluation of all CAGs by a third reader would be required.[21]

It was hospital policy to perform CAG in all patients with VF that regained ROSC and had no contraindication for CAG, but the final decision to perform CAG was left to the discretion of the treating physician. From January 2017 we participated in the Coronary Angiography after Cardiac Arrest (COACT) trial, in which patients with ROSC after shockable cardiac arrest without ST-elevation were randomised to immediate or delayed CAG.[15] Patients that were randomised in the COACT study were also included in the present study.

In accordance with previous studies we used the following definitions:

- Significant stenosis: stenosis >70%.[2]
- Significant coronary artery disease: at least one stenosis >70%.[2]
- Acute coronary occlusion: a presumably new obstructive lesion (i.e. the ability to pass a guidewire easily through the occlusion if angioplasty was attempted) with TIMI 0-I flow.[14,20]
- Chronic total occlusion (CTO): complete occlusion of one of the main coronary artery branches, deemed >3 months old.[22]

Study groups

Patients were categorised as having either shock-resistant VF or VF that was not shock-resistant. In line with previous studies and an American Heart Association consensus document, we used a cut-off of >3 shocks.[2,3] Patients with >3 shocks were categorised as shock-resistant VF, whereas patients with VF requiring ≤3 shocks were categorised as patients with VF that was not shock-resistant. For this categorisation, both AED and EMS shocks were taken into account.[4]

Outcome measure

Primary outcome measures were CAG-findings as described above. Secondarily, we calculated the proportions of ROSC, 24-h survival and survival to discharge.

Statistical analysis

Categorical data were expressed as frequencies (percentages) and compared using Chi-squared tests. Continuous data were tested for normal distribution and reported as means (standard deviations) or medians (interquartile ranges) and compared using student t-tests or Mann-Whitney U tests, whichever appropriate. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS (Version 25, IBM Corp., USA).

Results

Entire patient population

Baseline and arrest characteristics

During the study period, 571 patients were transported to our hospital with OHCA. A total of 301 patients was included in the present analysis, with exclusion mainly related to presentation with a non-shockable rhythm (Supplement 1).

The majority was male (82%) and median age was 63 (53–70) years (Table 1). Of all arrests, 58% occurred at a public location, 88% was witnessed, of which 8% by the EMS. Bystander CPR was performed in 79% of the non EMS-witnessed cases. AED use before EMS-arrival occurred in 54% of the patients. For the entire

Table 1 – Clinical and baseline variables.

	Overall	Shock-resistant VF		p-value
		Yes (>3 shocks) (n = 105)	No (≤3 shocks) (n = 196)	
Male	246 (82%)	89 (85%)	157 (80%)	0.32
Age	63 (53–70)	63 (54–71)	63 (53–70)	0.72
Prior MI (n = 288)	66 (23%)	23 (24%)	43 (23%)	0.82
Previous cardiac disease	125 (43%)	43 (43%)	82 (43%)	0.88
Arrest characteristics				
Public location	166 (58%)	56 (54%)	110 (60%)	0.32
Witnessed	249 (88%)	89 (86%)	160 (88%)	0.62
Bystander	226 (80%)	83 (81%)	143 (79%)	0.53
EMS	23 (8%)	6 (6%)	17 (9%)	
Bystander CPR*	215 (79%)	75 (78%)	140 (80%)	0.72
AED used before EMS arrival*	151 (54%)	57 (57%)	94 (52%)	0.42
EMS response time (min)	7 (5–10)	9 (5–15)	6 (5–10)	0.08
Shocks by EMS	220 (73%)	98 (93%)	122 (62%)	<0.001
Total nr of shocks	2 (1–4)	5 (4–8)	2 (1–2)	<0.001
Autopulse used	45 (16%)	27 (28%)	18 (10%)	<0.001
Endotracheal intubation	166 (60%)	68 (72%)	98 (54%)	0.006
Patients receiving amiodarone	96 (33%)	70 (70%)	26 (15%)	<0.001
Patients receiving epinephrine	120 (42%)	74 (74%)	46 (25%)	<0.001
ST-elevation on ECG	170 (60%)	66 (71%)	104 (55%)	0.009

Clinical and baseline characteristics in patients with shock-resistant vs. non-shock-resistant VF. * Of all cases not witnessed by the EMS. VF = Ventricular fibrillation, MI = Myocardial infarction; CPR = Cardiopulmonary resuscitation; AED = Automated external defibrillator; EMS = Emergency medical services; ECG = Electrocardiogram; ROSC = Return of spontaneous circulation.

study population, the median total number of shocks was 2 (1–4) shocks.

Coronary angiography findings

The blinded secondary review resulted in an inter-observer agreement of 93% for acute coronary occlusion, of 93% for no acute coronary occlusion and a kappa of 0.83. Given this high level of agreement, we report on the CAG-reviews of the first observer in all cases.

Of all patients, 77% had significant coronary artery disease, with 40% of all patients having 1-vessel disease and 37% having ≥2-vessel disease (Table 2). An acute coronary occlusion was present in 31% of all patients. The localization of these acute occlusions can be found in Table 2. Of all patients, 31% had a chronic total occlusion (CTO), of which the localization can be found in Table 2.

Outcomes

Of all patients, 83% was transported with sustained ROSC, 87% survived for at least 24 h and 72% survived to hospital discharge.

Comparisons between study groups

Of all patients, 105 (35%) received >3 shocks and were thus classified as shock-resistant VF, while the remaining 196 (65%) patients were classified as patients with VF that was not shock-resistant.

Baseline and arrest characteristics

Baseline demographics did not differ between the two groups (Table 1). There were no differences in arrest location, bystander CPR and AED use. Patients with shock-resistant VF more often received shocks by the EMS, more often underwent endotracheal intubation, and more frequently received epinephrine and amiodarone. There was a significantly higher proportion of ST-segment elevation on the post-arrest ECG among patients with shock-resistant VF (71% vs. 55%, p = 0.009).

Coronary angiography findings

Comparisons between both study groups are shown in Table 2. The proportion with immediate CAG (i.e. immediately after admission) was high, and significantly higher in patients with than without shock-resistant VF (97% vs. 89%, p = 0.02).

There was no difference in the occurrence of significant CAD between the two groups (78% vs. 77%, p = 0.76).

An acute coronary occlusion occurred significantly more often in patients with compared to those without shock-resistant VF (41% vs. 26%, p = 0.006). There was a statistically significant association between the number of shocks and the proportion of patients with an acute coronary occlusion (Fig. 1). There was a trend towards a higher proportion of acute occlusions in the LAD and a significantly higher proportion of acute occlusions in the RCA in patients with shock-resistant VF.

There was no difference in the occurrence of CTOs between patients with vs. without shock-resistant VF (29% vs. 33%, p = 0.47), and a trend towards a higher proportion of patients undergoing PCI in the shock-resistant VF group (63% vs. 53%, p = 0.09). Lesions in patients undergoing PCI are described in Supplement 2.

Outcomes

Proportions of sustained ROSC, 24-h survival and survival to discharge were lower in patients with compared to patients without shock-resistant VF (Fig. 2).

Table 2 – Coronary angiography data.

	Overall	Shock-resistant VF		p-value
		Yes (>3 shocks) (n = 105)	No (≤3 shocks) (n = 196)	
Immediate CAG	277 (92%)	102 (97%)	175 (89%)	0.02
Coronary angiography without ROSC	12 (4%)	9 (9%)	3 (2%)	0.004
Re-arrest in the cath-lab	15 (5%)	8 (8%)	7 (4%)	0.12
Coronary artery disease				
Significant CAD	232 (77%)	82 (78%)	150 (77%)	0.76
1 vessel	119 (40%)	50 (48%)	69 (35%)	0.17
2 vessel	64 (21%)	19 (18%)	45 (23%)	
3 vessel	49 (16%)	13 (12%)	36 (18%)	
Location of significant stenosis				
LM	21 (7%)	6 (6%)	15 (8%)	0.53
LAD	142 (47%)	49 (47%)	93 (47%)	0.90
RCx	115 (38%)	33 (31%)	82 (42%)	0.08
RCA	132 (44%)	44 (42%)	88 (45%)	0.67
Acute coronary occlusions				
≥1 ACO	93 (31%)	43 (41%)	50 (26%)	0.006
ACO LAD	47 (16%)	22 (21%)	25 (13%)	0.06
ACO RCx	27 (9%)	9 (9%)	18 (9%)	0.86
ACO RCA	26 (9%)	15 (14%)	11 (6%)	0.01
Chronic total occlusion				
≥1 CTO	94 (31%)	30 (29%)	64 (33%)	0.47
CTO LAD	22 (7%)	4 (4%)	18 (9%)	0.09
CTO RCx	38 (13%)	11 (11%)	27 (14%)	0.42
CTO RCA	68 (23%)	23 (22%)	45 (23%)	0.85
Percutaneous coronary intervention				
≥1 lesion treated with PCI	169 (56%)	66 (63%)	103 (53%)	0.09
LM	12 (4%)	5 (5%)	7 (4%)	0.62
LAD	83 (28%)	33 (31%)	50 (26%)	0.27
RCx	50 (17%)	18 (17%)	32 (16%)	0.86
RCA	56 (19%)	24 (23%)	32 (16%)	0.15

Coronary angiography data in patients with shock-resistant vs. non-shock-resistant VF. VF = Ventricular fibrillation; CAG = Coronary angiography; ROSC = Return of spontaneous circulation; CAD = Coronary artery disease; LM = Left main; LAD = Left anterior descending artery; RCx = Ramus circumflex; RCA = Right coronary artery; ACO = Acute coronary occlusion; CTO = Chronic total occlusion; PCI = Percutaneous coronary intervention.

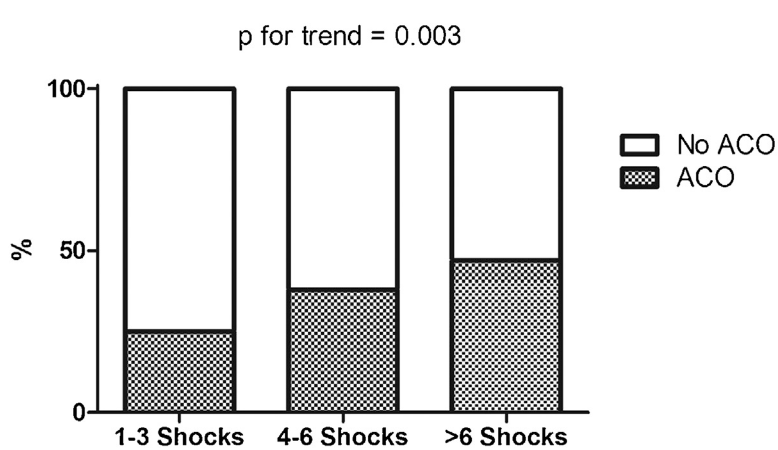

Fig. 1 – The association between number of shocks and occurrence of an acute coronary occlusion.
Figure demonstrating the association between number of shocks and occurrence of an ACO. ACO = Acute coronary occlusion.

Discussion

We compared coronary angiography findings between cardiac arrest patients with VF that was shock-resistant (>3 shocks) and patients with VF that was not shock-resistant (≤3 shocks), and found that significant coronary artery disease was present in >75% of patients in both groups. Notably, we found 1.5 times as many acute coronary occlusions among shock-resistant VF-patients and a significant association between the number of shocks and the proportion of acute

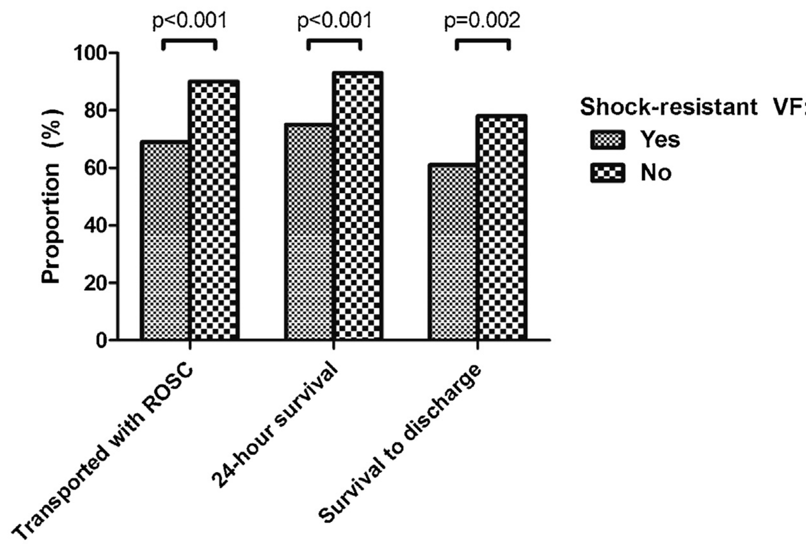

Fig. 2 – Outcomes in patients with and without shock-resistant VF**.**
Outcomes in shock-resistant vs. non-shock-resistant VF. These are all patients that were transported to the hospital. VF = Ventricular fibrillation, ROSC = Return of spontaneous circulation.

coronary occlusions. Outcomes were also poorer in case of shock-resistant VF. Larger registries that confirm our angiographic and clinical outcome data could provide impetus randomised controlled studies on the potential benefit of an early invasive approach in patients with shock-resistant VF.

Coronary angiography findings

We found significant CAD ($\geq$1 stenosis >70%) in 78% of patients with shock-resistant VF, which is comparable to findings reported in a previous study with 55 patients with VF refractory to >3 shocks, without intermittent ROSC.[2] However, as in that report a control group without refractory VF was lacking, it was unclear whether those findings were exclusive to VF requiring multiple shocks, particularly given the high prevalence of CAD in VF-patients in general.[13–15,23]

We now demonstrate that significant CAD is also often present in VF that is not shock-resistant (77%). The extent of CAD, in terms of number of vessels affected, was also similar between both groups. We did, however, find a higher proportion of acute coronary occlusions in the group of patients with shock-resistant VF. This is in line with the fact that we also found more ST-elevation in this group, as ST-elevation is a strong predictor for ACO.[24] Our observations could indicate that an ACO in itself may be a trigger or a sustaining substrate of shock-resistant VF.

It could also be hypothesised that an ACO triggers VF, and that VF becomes shock-resistant in case of a persisting acute occlusion, while VF that is not shock-resistant occurs in case of reperfusion before CAG. Studies on primary PCI show that reperfusion before PCI occurs in 15–30% of patients.[25] Our findings also corroborate with animal studies, which show that VF induced by a persistent acute coronary occlusion on average requires more shocks before regaining ROSC than VF without persistent coronary occlusion.[26,27]

In terms of PCI-performance, Table 1 shows that there is a significant difference in acute coronary occlusions but not in the proportion of patients undergoing a PCI, implying that there are relatively many patients without shock-resistant VF group with lesions that are not persistently occluded, but in whom PCI has been performed.

Regarding the infarct related artery, acute occlusion of the RCA was significantly more frequent in case of shock-resistant VF. Based on mechanistic studies, there is a complex interplay between the extent of ischemia, the presence of prior infarction, genetic predisposition and conduction disturbances in the initiation of ventricular arrhythmias.[28–30] As for CTOs, data in OHCA-patients is scarce.[31] Our findings indicate no association between CTO and shock-resistant VF. It should be noted that patients with CTO form a heterogeneous group, where in some the CTO is related to prior infarction, whereas in others there may be no signs of myocardial scar. Importantly, previous studies did not specifically study the role of CTOs in shock-resistant VF, and to our knowledge we describe the first study on CAG-findings in this patient category with a control group without shock-resistant VF.

Baselines, arrest characteristics and outcomes

Baseline characteristics and key prognostic arrest characteristics (e.g. public location, bystander CPR, AED use) did not differ between both study groups. This provides additional support to the hypothesis that the underlying substrate is a major contributing factor to the shock-resistancy of VF. To further explore this, we studied and confirmed the association between increasing numbers of required defibrillation attempts and a higher likelihood of an acute coronary occlusion (Fig. 1).

We found a trend towards a longer response time in shock-resistant VF-patients, which might have contributed to VF becoming shock-resistant, given the association between longer VF-duration and lower shock success.[5,6] In an exploratory post-hoc logistic regression analysis we corrected for response time, and the association of an acute coronary occlusion with shock-resistant VF remained significant (adjusted odds ratio 2.20, p = 0.045). However, this analysis should be considered hypothesis generating as our study was not designed to identify predictors of shock-resistant VF.

In the current cohort, overall survival is high, which could have several reasons. First, we selected only VF-patients transported to the hospital and undergoing routine CAG. In a previous report from our registry, we studied all, non-selected OHCA-cases and found survival to discharge rate of 15%.[32] Importantly, the present data corroborate with previous studies using similar inclusion criteria.[33,34] Second, we defined shock-resistant VF according to the number of defibrillation shocks, in line with previous studies.[35] As such, included patients may have had intermittent organised rhythm or output between shocks. Other studies, such as Yannopoulos et al., exclusively focused on patients with refractory VF without intermittent ROSC, with poorer outcomes.[2,11] Third, we found a markedly high proportion of bystander AED-use, which is common in the Dutch setting.[36] In the Netherlands, AED-use has been widely advertised and we previously reported on rising numbers of AED-use and survival in our region.[16]

Implications

The high proportion of acute coronary occlusions in shock-resistant VF implies that these may be a trigger or substrate for difficult-to-defibrillate VF. In the context of these findings, and the current possibilities of transport with mechanical resuscitation and extracorporeal membrane oxygenation programs, our data support future initiatives to investigate the impact of immediate catheterization in patients with shock-resistant VF.[3,9,11] Two recently published randomised trials (COACT and PEARL) found that early CAG is not beneficial for patients without ST-elevation and without ongoing resuscitation. The present study focusses on all VF-patients transported to the hospital and undergoing CAG, regardless of the ECG-pattern and whether or not ROSC is reached before CAG, and can therefore be interpreted as complementary to COACT and PEARL.[15,37] Our findings implicate that the need for multiple shocks might indicate a high likelihood of acute coronary occlusion. Whether or not such patients benefit from early invasive strategies is an interesting topic for further study. Prerequisite for future intervention studies is that our angiographic and clinical outcomes are corroborated by additional studies. Importantly, pevious reports indeed demonstrated favorable outcomes in case of early transportation to the cath-lab in patients with refractory VF, both in observational as well as in pilot randomised studies.[2,11]

The downside of an early-invasive strategy for shock-resistant VF is that several shocks have to be awaited before deciding to transport the patient, as the patient only then fulfils the criteria for shock-resistant VF. Longer VF- duration is associated with worse outcomes.[5,6] Thus, it would be helpful to either predict the chance of VF becoming shock-resistant, or identify a coronary occlusion earlier, i.e. at the moment of arrival at the patient. With regard to the former, we found no baseline characteristics associated with shock-resistant VF, which precludes predicting of the occurrence of shock-resistant VF using such characteristics. Regarding the latter, experimental studies suggest that there may be a role for analysis of the morphology of the VF-waveform itself in early identification of acute coronary occlusions.[38] Animal and human studies demonstrate that the VF-signal is markedly altered in case of an underlying coronary occlusion.[27,34] This should be investigated further, preferably using prospective studies, which are currently lacking.

Limitations

As stated, we used a cut-off of >3 shocks for defining shock-resistant VF, in accordance with the scientific statement of the American Heart Association and previous studies.[2,3] This does not necessarily mean that VF has actually persisted through all shocks as we cannot exclude the possibility of intermittent return of organised rhythm and VF-recurrence. This is a problem frequently encountered in studies on VF requiring multiple shocks, as defibrillator read-out is not routinely performed.[35] This hampers comparing (outcome) data between different cohorts. Future studies should aim for a more uniform methodology to define shock-resistant VF, as we previously demonstrated that the type of VF (recurrent or persisting) may impact patient outcomes.[39]

Although selection bias cannot be excluded, during the study period it was hospital policy to perform immediate CAG in all resuscitated VF patients that regained ROSC. Arguments not to perform catheterization are shown in Supplement 2: no ROSC at any point during CPR was the main reason (67%). Exclusion of the 8% with delayed (i.e. not immediately after presentation at the emergency room, but still during the same hospital admission) CAG did not alter the results, as can be seen in Supplement 3. Importantly, the present study was designed to assess CAG-findings and not to provide in-depth analyses on outcome. As such, those findings should be considered hypothesis generating.

Conclusions

In VF-cardiac arrest patients transported to our hospital and undergoing coronary angiography, we found significantly more acute coronary occlusions in case VF was shock-resistant (>3 shocks) compared to when VF was not shock-resistant (≤3 shocks). Shock-resistant VF-patients had adverse outcome. Larger confirmative registries are warranted and the collective evidence may provide impetus for randomised controlled trials on the potential benefit of an early invasive approach in patients with shock-resistant VF.

Disclosures

Niels van Royen received research grants from Abbott, Biotronik, AstraZeneca and Philips, and professional fees from Abbott, Microport, Amgen and Medtronic. Peter Damman has received consultancy fees from Philips and Abbott, and research grants from Philips and AstraZeneca. Marleen van Wely has received proctor fees from Zoll Medical. The other authors have no conflicts of interest to declare

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Conflicts of interest

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CRediT authorship contribution statement

J Nas, **JL Bonnes**, **T ten Cate**, **MA Brouwer:** Conception and design. **J Nas**, **J Thannhauser**, **EGJA van Dijk**, **C Verkroost**, **P Damman**, **M van Wely**, **T ten Cate**, **MA Brouwer:** Collection and assembly of data. **J Nas**, **J Thannhauser**, **RJ van Geuns**, **N van Royen**, **MJ de Boer**, **JL Bonnes**, **T ten Cate**, **MA Brouwer:** Analysis and interpretation of data. **J Nas**, **T ten Cate**, **MA Brouwer:** Drafting of the manuscript. **J Thannhauser**, **EGJA van Dijk**, **C Verkroost**, **P Damman**, **M van Wely**, **RJ van Geuns**, **N van Royen**, **MJ de Boer**, **JL Bonnes:** Critical revising.

Final approval of the manuscript

All authors mentioned above.

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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.2021.05.006.

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