



HAL
open science

Life-threatening arrhythmias in anterior ST-segment elevation myocardial infarction patients treated by percutaneous coronary intervention: adverse impact of morphine

François Sauer, Laurence Jesel, Benjamin Marchandot, François Derimay, Thomas Bochaton, Camille Amaz, François Roubille, Guillaume Cayla, Gilles Rioufol, David Garcia-Dorado, et al.

► To cite this version:

François Sauer, Laurence Jesel, Benjamin Marchandot, François Derimay, Thomas Bochaton, et al.. Life-threatening arrhythmias in anterior ST-segment elevation myocardial infarction patients treated by percutaneous coronary intervention: adverse impact of morphine. *European Heart Journal: Acute Cardiovascular Care*, 2020, 10.1093/ehjacc/zuaa005 . hal-03153469

HAL Id: hal-03153469

<https://hal.science/hal-03153469>

Submitted on 26 Feb 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Life-threatening arrhythmias in anterior ST-segment elevation myocardial infarction patients treated by percutaneous coronary intervention: adverse impact of morphine

François Sauer¹, Laurence Jesel^{1,2}, Benjamin Marchandot¹, François Derimay³, Thomas Bochaton³, Camille Amaz⁴, François Roubille⁵, Guillaume Cayla⁶, Gilles Rioufol³, David Garcia-Dorado⁷, Marc Claeys⁸, Denis Angoulvant⁹, Eric Bonnefoy-Cudraz³, Patrice Guérin¹⁰, Annie Trinh¹, Kensuke Matsushita^{1,2}, Patrick Ohlmann¹, Claire Jossan⁴, Nathan Mewton^{3,4}, Michel Ovize^{3,4}, and Olivier Morel^{1,2*}

¹Université de Strasbourg, Pôle d'Activité Médico-Chirurgicale Cardio-Vasculaire, Nouvel Hôpital Civil, Centre Hospitalier Universitaire, BP 426, 67091 Strasbourg, France; ²UMR 1260 INSERM Nanomédecine Régénérative Université de Strasbourg, Strasbourg, France; ³Hopital Cardiovasculaire Louis Pradel, Hospices Civils de Lyon, Lyon, France; ⁴Centre d'Investigation Clinique de Lyon, CIC 1407, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France; ⁵Hôpitaux Universitaires de Montpellier, Montpellier, France; ⁶Hôpital de Nîmes, Nîmes, France; ⁷Hospital Universitaire Vall d'Hebron, Barcelona, Spain; ⁸University Hospital Antwerp, Edegem, Belgium; ⁹Centre Hospitalier Regional Universitaire de Tours, Tours, France; and ¹⁰Hôpitaux Universitaires de Nantes, Nantes, France

Aims

Important controversies remain concerning the determinants of life-threatening arrhythmias during ST-segment elevation myocardial infarction (STEMI) and their impact on late adverse events. This study sought to investigate which factors might facilitate ventricular tachycardia (VT) and ventricular fibrillation (VF), in a homogeneous population of anterior STEMI patients defined by abrupt left anterior descending coronary artery (LAD) occlusion and no collateral flow.

Methods and results

The 967 patients, who entered into the CIRCUS (Does Cyclosporine ImpRove Clinical oUtcome in ST elevation myocardial infarction patients) study, were assessed for further analysis. Acute VT/VF was defined as VT (run of tachycardia >30 s either self-terminated or requiring electrical/pharmacological cardioversion) or VF documented by electrocardiogram or cardiac monitoring, during transportation to the cathlab or initial hospitalization. VT/VF was documented in 136 patients (14.1%). Patients with VT/VF were younger and had shorter time from symptom onset to hospital arrival. Site of LAD occlusion, thrombus burden, area at risk, pre-percutaneous coronary intervention Thrombolysis in Myocardial Infarction flow, and ST-segment resolution were similar to that of patients without VT/VF. There was no impact of VT/VF on left ventricular remodelling or clinical outcomes. By multivariate analysis, the use of morphine (odds ratio 1.71; 95% confidence interval (1.13–2.60); $P = 0.012$) was the sole independent predictor of VT/VF occurrence.

Conclusions

In STEMI patients with LAD occlusion, our findings support the view that morphine could favour severe ventricular arrhythmias.

Keywords

Ventricular tachycardia • Ventricular fibrillation • Acute coronary syndromes • Morphine

Introduction

Important controversies remain concerning the determinants of life-threatening arrhythmias [sustained ventricular tachycardia or ventricular fibrillation (VT/VF)] during ST-segment elevation myocardial infarction (STEMI) and their impact on late adverse events. Lack of ischaemic preconditioning, age of <60 years, enhanced inflammatory response, reduced door to balloon time, magnitude of ST-segment elevation,¹ infarct size, increased Killip class, and subsequent left ventricular (LV) dysfunction are described as possible determinants of VT/VF at the acute phase.^{2–5} Whereas acute phase ventricular tachyarrhythmias have been evidenced as a marker of early in-hospital death, early VT/VF did not appear to substantially alter post-discharge mortality.^{6,7} Many flaws, such as the enrolment of different types of myocardial infarction (anterior vs other locations), various initial Thrombolysis in Myocardial Infarction (TIMI) flow or the lack of visible collateral flow evaluation have up to now preclude a precise analysis of VT/VF determinants and their prognosis impact in STEMI.

In the present study, we sought to characterize the predictors of VT/VF in a homogeneous population of anterior STEMI patients characterized by abrupt left anterior descending coronary artery (LAD) occlusion and without collateral flow. Secondary objective was to clarify the impact of VT/VF on LV remodelling and cardiovascular outcome.

Methods

CIRCUS trial

The subjects in the present study were recruited from the CIRCUS trial database.^{8,9} In brief, the CIRCUS trial was an international prospective multicentre randomized double-blind placebo-controlled clinical trial conducted between April 2011 and February 2014 that evaluated the efficacy of cyclosporine to prevent reperfusion injury in an anterior STEMI population. The CIRCUS trial did not show any significant effect of cyclosporine on clinical outcomes. Approval for the present study was obtained from ethics committees in the relevant countries and all patients provided written informed consent prior to inclusion in the CIRCUS trial. To be eligible for enrolment in the present study, patients had to be ≥ 18 years of age, present within 12 h after the onset of acute coronary syndrome symptoms, show ST-segment elevation ≥ 2 mm in at least two anterior leads and be referred for primary percutaneous coronary intervention (PPCI). The culprit coronary artery was the LAD with a TIMI flow grade of 0 or 1 at the time of coronary angiography. Complete inclusion and exclusion criteria, study design and the primary results have already been reported elsewhere.^{8,9} Randomization with stratification according to study centre was performed after the initial coronary angiography to ensure that (i) LAD was occluded (TIMI 0/1) and (ii) no collateral flow existed (Rentrop 2 and 3 for the region at risk were excluded).

Patients underwent PPCI according to standard guidelines. The indication of morphine administration was analgesia in patients with ongoing chest pain unresponsive to nitrates. Morphine was given in a non-randomized fashion as required by emergency teams en route to the cathlab or by interventional cardiologists in the cathlab and prior to the occurrence of VT/VF.

The use of thrombus aspiration, bare metal or drug-eluting stents, and glycoprotein IIb/IIIa inhibitors was left to the discretion of the treating physician. Acute phase VT/VF was defined as VT (runs of VT of > 30 s which was either self-terminated or required electrical/pharmacological cardioversion due to haemodynamic instability) or VF documented by

electrocardiogram or cardiac monitoring during transportation to the cathlab or during the initial hospitalization. Precise timing of VT/VF was not available, but VT/VF occurrence was further discriminated between early (<24 h) and late (>24 h) VT/VF.

Study endpoints

Patients underwent echocardiography during the initial hospitalization and again after 1 year. The LV ejection fraction (LVEF) was estimated by the Simpson method, as were LV end-diastolic volume (LVEDV) and LV end-systolic volume. Absolute remodelling was defined as the relative increase in LVEDV between baseline and 1 year. Adverse LV remodelling was defined as a $\geq 15\%$ increase in LVEDV [i.e. (LVEDV at 1 year - initial LVEDV)/initial LVEDV $> 15\%$]. Clinical outcomes were recorded prospectively at 1 year and were a composite of all-cause death and heart failure worsening during initial hospitalization or rehospitalization for heart failure. All clinical events were adjudicated by an events validation committee whose members were unaware of the study group assignment.

Statistical analysis

All statistical analyses were *post hoc* analyses and were not pre-specified in the original CIRCUS statistical analysis plan. Quantitative variables were expressed as mean \pm standard deviation. Categorical variables were expressed as numbers (percentage). Bivariate comparisons were made using Student's t-test for continuous variables or Wilcoxon test when assumptions were not validated. χ^2 tests (or Fischer's exact test when the expected cell frequency was < 5) were used for categorical variables. Predictors of VT/VF were evaluated by using logistic-mixed-effect regression that included centre as a random effect. A multivariable mixed logistic model was estimated, including centre as random effect and all univariate analysis at $P < 0.10$ as fixed effects. When appropriate, log transformation was performed prior to regression to achieve normality. Survival curves were constructed using the Kaplan–Meier method. Comparison between groups was conducted using the log-rank test. Statistical testing was done at the two-tailed a level of 0.05. Data were analysed using the R statistical software version 3.3.3.

Results

Of the 967 patients included in this study, VT/VF was documented in 136 patients (14.1%). Seventeen patients presented VF, 113 VT, and 6 patients VT and VF. Among the VF sub-group ($n = 23$), 18/23 events (78.3%) occurred during the first 24 h (Day 1) and 5/23 (21.7%) between Day 1 and Day 8. In the VT subgroup ($n = 119$), 66/119 (55.5%) events occurred during the first 24 h (Day 1) and 53/119 (44.5%) between Day 1 and Day 8. Baseline characteristics, pre-hospital management, and angiographic data stratified by the presence or absence of VT/VF are summarized in [Tables 1](#) and [2](#). Patients with VT/VF were younger, were less likely to have previous coronary artery disease treated by percutaneous coronary intervention (PCI), had higher diastolic blood pressure and had shorter symptom onset to hospital arrival times. Site of LAD occlusion, thrombus burden, area at risk, pre-PCI TIMI Flow grade, maximal ST elevation, and ST-segment resolution were equivalent between the two subsets. No differences in heart rate and arterial blood pressure could be evidenced at baseline and 3–6 h post-PCI ([Table 3](#)). Baseline medications did not differ significantly between groups except for a more frequent use of morphine and GPIIb/IIIa in the VT/VF group ([Table 2](#)). A total of 552 (57.2%) patients received morphine at first medical contact in the CIRCUS trial.

Table 1 Baseline characteristics

	Study population (n = 967)	No VT/VF (n = 831)	VT/VF (n = 136)	P-value
Age (years)	59.9 ± 12.9	60.4 ± 12.9	57 ± 12.8	0.005
Male sex, no./total no. (%)	794/967 (82.1%)	676/831 (81.3%)	118/136 (86.8%)	0.159
BMI (kg/m ²)	26.9 ± 4.2	26.9 ± 4.3	26.8 ± 3.7	0.922
DBP (mmHg)	83.2 ± 16.6	82.7 ± 16.3	86 ± 18	0.049
SBP (mmHg)	134.2 ± 24.2	134 ± 24	135.5 ± 25.4	0.511
Heart rate (b.p.m.)	78.7 ± 16.2	78.7 ± 16.3	78.6 ± 15.5	0.939
Killip class at admission, no./total no. (%)				0.806
I	750/858 (87.4%)	647/738 (87.7%)	103/120 (85.8%)	
II	85/858 (9.9%)	72/738 (9.8%)	13/120 (10.8%)	
III	16/858 (1.9%)	13/738 (1.8%)	3/120 (2.5%)	
IV	7/858 (0.8%)	6/738 (0.8%)	1/120 (0.8%)	
Current smoking, no./total no. (%)	409/967 (42.3%)	347/831 (41.8%)	62/136 (45.6%)	0.456
Hypertension, no./total no. (%)	359/967 (37.1%)	317/831 (38.1%)	42/136 (30.9%)	0.126
Diabetes mellitus, no./total no. (%)	123/967 (12.7%)	113/831 (13.6%)	10/136 (7.4%)	0.059
Dyslipidaemia, no./total no. (%)	372/967 (38.5%)	315/831 (37.9%)	57/136 (41.9%)	0.427
Previous myocardial infarc- tion, no./total no. (%)	54/967 (5.6%)	46/831 (5.5%)	8/136 (5.9%)	0.999
Previous coronary artery disease treated with PCI, no./total no. (%)	51/63 (81%)	46/54 (85.2%)	5/9 (55.6%)	0.026
Previous heart failure, no./total no. (%)	6/967 (0.6%)	6/831 (0.7%)	0/136 (0%)	0.999
GFR, no./total no. (%)				0.329
Stage 1	494/880 (56.1%)	420/760 (55.3%)	74/120 (61.7%)	
Stage 2	270/880 (30.7%)	240/760 (31.6%)	30/120 (25%)	
Stage 3–5	116/880 (13.2%)	100/760 (13.2%)	16/120 (13.3%)	

We don't have information on chronic kidney disease.

In hospital management, together with discharge cardiac medications are displayed in [Table 4](#). As expected, a longer length of stay was evidenced in patients who experienced VT/VF.

Adverse events, echocardiographic endpoints, and VT/VF

The impact of VT/VF on primary and secondary endpoints is given in [Table 5](#). At 1-year follow-up, death from any cause, cardiac death, major adverse cardiac event (MACE), recurrent myocardial infarction, and heart failure did not differ significantly between groups. The occurrence of the composite outcome of death from any cause or heart failure event was not significantly different according to VT/VF ([Figure 1](#)). Similarly, remodelling was similar in the two groups [VT/VF⁺: 55/112 (49.1%) vs VT/VF⁻: 288/641 (44.9%); $P=0.474$; [Table 5](#)].

Comparison between early and delayed VT/VF

Because pathophysiological mechanisms may vary between early and delayed VT/VF, patients were stratified according to the onset of VT/VF. Baseline characteristics, prehospital management, angiographic data, in hospital management, primary and MACE in patients with acute (≤ 24 h) or delayed (>24 h) VT/VF are given in [Supplementary material online, Tables S1–S4](#) and [Figure 1](#). No differences between total ischaemic time, area at risk, segment ST resolution, post-PCI-LVEF, and 1 year LVEF could be evidenced.

Determinants of VT/VF

To identify potential determinants of VT/VF, multivariate logistic analyses were performed ([Table 6](#)). The use of morphine [odds ratio 1.71; 95% confidence interval (1.13–2.60); $P=0.012$] was identified as

Table 2 Pre-hospital management and angiographic data

	Study population (n = 967)	No VT/VF (n = 831)	VT/VF (n = 136)	P-value
Time from symptom onset to hospital arrival (h)	3.4 ± 3	3.5 ± 3.1	3 ± 2.6	0.009
Time from hospital arrival to treatment administration (h)	1 ± 1.5	1 ± 1.6	1 ± 1.1	0.319
Total ischaemic time				
Duration (h)	4.5 ± 3	4.5 ± 3	4 ± 2.8	0.067
Distribution, no.(%)				0.345
<2 h	96/877 (10.9%)	81/747 (10.8%)	15/130 (11.5%)	
2–6 h	612/877 (69.8%)	516/747 (69.1%)	96/130 (73.8%)	
>6 h	169/877 (19.3%)	150/747 (20.1%)	19/130 (14.6%)	
Medication from first medical care to PCI, no./total no. (%)				
Heparin	794/965 (82.3%)	679/829 (81.9%)	115/136 (84.6%)	0.529
Glycoprotein IIb/IIIa inhibitor	366/965 (37.9%)	303/829 (36.6%)	63/136 (46.3%)	0.037
Loading dose of P2Y12 inhibitor	861/965 (89.2%)	739/829 (89.1%)	122/136 (89.7%)	0.963
Aspirin	896/965 (92.8%)	769/829 (92.8%)	127/136 (93.4%)	0.936
Morphine	552/965 (57.2%)	456/829 (55%)	96/136 (70.6%)	0.001
Cyclosporine	474/967 (49%)	412/831 (49.6%)	62/136 (45.6%)	0.440
Site of occlusion in left anterior descending artery, no./total no. (%)				0.871
Proximal or main left artery	415/967 (42.9%)	358/831 (43.1%)	57/136 (41.9%)	
Medial or distal segment or diagonal branch	552/967 (57.1%)	473/831 (56.9%)	79/136 (58.1%)	
Vessel disease, no./total no. (%)				0.668
One	610/967 (63.1%)	523/831 (62.9%)	87/136 (64%)	
Two	248/967 (25.6%)	210/831 (25.3%)	38/136 (27.9%)	
Three	106/967 (11%)	95/831 (11.4%)	11/136 (8.1%)	
Thrombus burden ≥3, no./total no. (%)	625/928 (67.3%)	528/795 (66.4%)	97/133 (72.9%)	0.166
Area at risk (%)	36.3 ± 8.5	36.4 ± 8.5	35.7 ± 8.8	0.895
TIMI flow grade before PCI, no./total no. (%)				0.522
0	752/927 (81.1%)	640/794 (80.6%)	112/133 (84.2%)	
1	110/927 (11.9%)	99/794 (12.5%)	11/133 (8.3%)	
2	48/927 (5.2%)	40/794 (5%)	8/133 (6%)	
3	17/927 (1.8%)	15/794 (1.9%)	2/133 (1.5%)	
Thrombus aspiration, no./total no. (%)	734/967 (75.9%)	626/831 (75.3%)	108/136 (79.4%)	0.356
Direct stenting, no./total no. (%)	551/927 (59.4%)	476/794 (59.9%)	75/133 (56.4%)	0.498
Stenting, no./total no. (%)	854/967 (88.3%)	734/831 (88.3%)	120/136 (88.2%)	0.999
No reflow observed on angiography, no./total no. (%)	55/967 (5.7%)	47/831 (5.7%)	8/136 (5.9%)	0.999
TIMI flow grade after PCI, no./total no. (%)				0.468
0	13/951 (1.4%)	12/818 (1.5%)	1/133 (0.8%)	
1	10/951 (1.1%)	9/818 (1.1%)	1/133 (0.8%)	
2	58/951 (6.1%)	46/818 (5.6%)	12/133 (9%)	
3	870/951 (91.5%)	751/818 (91.8%)	119/133 (89.5%)	
Maximal ST elevation before PCI (mm)	5.4 ± 2.7	5.3 ± 2.7	5.8 ± 3	0.098
Maximal ST elevation at discharge (mm)	1.9 ± 1.2	1.9 ± 1.2	1.9 ± 1.2	0.580
ST-segment resolution > 70% (at discharge), no./total no. (%)	331/812 (40.8%)	280/697 (40.2%)	51/115 (44.3%)	0.458

We don't have information on stent diameter and length, BMS, DES, and cumulative ST elevation.

Table 3 Haemodynamic characteristics 3-6 after PCI

	Study population (n = 967)	No VT/VF (n = 831)	VT/VF (n = 136)	P-value
DBP (mmHg)	66.5 ± 11.2	66.5 ± 11.2	66.2 ± 11.4	0.758
SBP (mmHg)	107.5 ± 15.3	107.8 ± 15.3	105.5 ± 15.3	0.117
Heart rate (b.p.m.)	75.8 ± 14.3	75.9 ± 14.3	75.5 ± 13.9	0.803

Table 4 In hospital management

	Study population (n = 967)	No VT/VF (n = 831)	VT/VF (n = 136)	P-value
Killip class ≥ 2 at 6 h post-PCI, no./total no. (%)	84/762 (11%)	71/648 (11%)	13/114 (11.4%)	0.999
IABP, no./total no. (%)	23/926 (2.5%)	22/796 (2.8%)	1/130 (0.8%)	0.233
Non-invasive positive pressure ventilation, no./total no. (%)	45/920 (4.9%)	40/790 (5.1%)	5/130 (3.8%)	0.665
Intravenous diuretics, no./total no. (%)	97/385 (25.2%)	82/320 (25.6%)	15/65 (23.1%)	0.784
Inotropic agents, no./total no. (%)	32/381 (8.4%)	27/316 (8.5%)	5/65 (7.7%)	0.999
Average length of stay (day)	7 ± 6	6.8 ± 5.8	8.1 ± 7.3	0.001
AAP, no./total no. (%)				
Aspirin	933/954 (97.8%)	801/819 (97.8%)	132/135 (97.8%)	0.999
P2Y12	899/954 (94.2%)	771/819 (94.1%)	128/135 (94.8%)	0.910
Beta-blockers	879/954 (92.1%)	749/819 (91.5%)	130/135 (96.3%)	0.078
Statins	913/954 (95.7%)	782/819 (95.5%)	131/135 (97%)	0.500
ACE inhibitors or ARBs	853/954 (89.4%)	728/819 (88.9%)	125/135 (92.6%)	0.252
Calcium channel blockers (CCB)	25/954 (2.6%)	22/819 (2.7%)	3/135 (2.2%)	0.999
Nitrates	125/954 (13.1%)	109/819 (13.3%)	16/135 (11.9%)	0.743

We don't have information on diurectics, soludactone/eplerenone.

the sole predictor of VT/VF occurrence (Figure 2). In contrast, no impact of baseline LVEF, total ischaemic time, ST-segment resolution and inflammation, as assessed by leukocytes levels measurement on VT/VF could be evidenced.

Discussion

The salient results of the present study are as follows: (i) the use of morphine, a non-selective opioid agonist, was an independent predictor of VT/VF occurrence; (ii) VT/VF occurred in a sizeable proportion of anterior STEMI patients with abrupt LAD occlusion and lack of collateral flow (14.1%); and (iii) VT/VF occurrence was not predictive of late adverse events including all-cause death, MACE, recurrent myocardial infarction, and LV remodelling.

Impact of morphine on severe ventricular arrhythmias

The association between VT/VF and the use of morphine was unexpected and has, to our knowledge, not been described in STEMI patients. Unbearable chest pain, acute pulmonary oedema, or pain

related to cardiopulmonary resuscitation and defibrillation are common causes of morphine administration in STEMI patients. Because these conditions are usually associated with a more severe presentation, one could not exclude that the association between morphine and VT/VF could solely constitute a bias. However, this hypothesis appears unlikely since Killip class as a marker of pulmonary oedema or systolic blood pressure and heart rate as markers of sympathetic activation were equivalent among groups. Moreover, we have verified that no morphine administration was given after VT/VF occurrence.

Although the study was not designed to provide mechanistic insights, several hypotheses could be raised. We cannot exclude that the use of morphine has a pro-arrhythmogenic effect *per se*. Although morphine is commonly described as mainly a μ -opioid receptor agonist, interactions between δ and κ -receptor opioid receptor subtype have been reported in animal studies.¹⁰ In swine, experimental data have demonstrated that κ -opioid receptor activation is pro-arrhythmogenic and exacerbated ischaemia-induced arrhythmias in a model of myocardial infarction induced by LAD occlusion. Some experiments have demonstrated that preconditioning with a selective δ opioid agonist did not decrease infarct size but

Table 5 Primary and secondary endpoint—MACE

	Study population (n = 967)	No VT/VF (n = 831)	VT/VF (n = 136)	P-value
Primary endpoint, no./total no. (%)				
Primary composite outcome	475 (49.1%)	404 (48.6%)	71 (52.2%)	0.494
MACE	236 (24.4%)	205 (24.7%)	31 (22.8%)	0.716
Death from any cause	53 (5.5%)	48 (5.8%)	5 (3.7%)	0.427
Cardiovascular death	47 (4.9%)	43 (5.2%)	4 (2.9%)	0.364
Recurrent myocardial infarction	28 (2.9%)	23 (2.8%)	5 (3.7%)	0.578
Stroke	20 (2.1%)	17 (2%)	3 (2.2%)	0.753
Heart failure	180 (18.6%)	156 (18.8%)	24 (17.6%)	0.846
Cardiogenic shock	50 (5.2%)	43 (5.2%)	7 (5.1%)	0.999
Unstable angina	23 (2.4%)	22 (2.6%)	1 (0.7%)	0.234
Secondary endpoint				
Biological data				
Leukocyte H0 (10 ⁹ per L)	12.2 ± 6.3	12.1 ± 6.5	12.5 ± 4.3	0.198
Leukocyte peak (10 ⁹ per L)	12.7 ± 6.1	12.7 ± 6.3	13.1 ± 4	0.060
BNP 3–6 h after PCI (ng/L)	406.8 ± 968.1	411.9 ± 1000.3	357.8 ± 591.7	0.901
Echocardiography				
Post-PCI EF (%)	47.4 ± 10	47.5 ± 10	47.1 ± 9.8	0.632
Post-PCI EDV (mL/m ²)	105 ± 30.3	104.3 ± 30.3	108.9 ± 30.2	0.099
Post-PCI ESV (mL/m ²)	55.8 ± 23.2	55.5 ± 23.6	57.6 ± 20.4	0.111
EF at 1 year (%)	51.9 ± 10.8	52 ± 10.8	51.6 ± 10.6	0.533
EDV (1 year) (mL/m ²)	121.4 ± 41.8	120.4 ± 41.7	127 ± 41.9	0.071
ESV (1 year) (mL/m ²)	61.2 ± 32.2	60.5 ± 32.2	65.1 ± 32.1	0.057
LV remodelling, no./total no. (%)	343/753 (45.6%)	288/641 (44.9%)	55/112 (49.1%)	0.474

We don't have information on CRP H0, CRP peak, BNP peak, and BNP 1 year.

increased ischaemia-induced arrhythmia.¹¹ Up to now, important controversies remain concerning the ability of morphine preconditioning to induce heart protection against ischaemia–reperfusion injury. In isolated cardiomyocytes, morphine has been demonstrated to mimic preconditioning through K⁺-dependent ATP channels opening. In rabbits, morphine reduced infarct size only when supra-clinical doses were used (3 mg/kg). In rats, administration of 3 mg/kg of morphine 10 min before permanent LAD occlusion enhanced infarct size.¹² In contrast, in human, when given in addition to remote ischaemic preconditioning, the use of morphine (5 mg 5 min before first balloon inflation) was associated with greater percentage of ST-segment resolution and lower troponin peak levels.¹³

Morphine interacts with P2Y₁₂ inhibitors pharmacokinetic during STEMI. A previous report by Hobl *et al.*¹⁴ has demonstrated that morphine decreases clopidogrel concentrations and effects. In the large ATLANTIC trial (pre-hospital administration of ticagrelor in STEMI), patients who did not receive morphine had a significant improvement of ST-segment resolution.¹⁵ *Post hoc* analysis has demonstrated that morphine administration was associated with delayed

onset of action of various P2Y₁₂ inhibitors including ticagrelor that could favour the thrombotic burden and subsequent embolization when PCI would be performed.¹⁶ Accordingly, in the RAPID (Rapid Activity of Platelet Inhibitor Drugs) trial, morphine use was evidenced as an independent predictor of high residual platelet reactivity.¹⁷ In line with this view, recent study by de Waha's *et al.*¹⁸ has shown that IV morphine administration prior to PCI in patients with STEMI was independently associated with suboptimal reperfusion success and larger infarct size assessed by magnetic resonance imaging. Another recent report has underlined that pre-PCI morphine analgesia induces a prothrombotic state associated with reduced reperfusion rate and greater infarct size.¹⁹ This effect was also demonstrated with other opioids such as fentanyl, which delays platelet inhibition.²⁰ In the CIRCUS study, although the use of morphine was not randomized, no significant impact of morphine on ST resolution, enzymatic infarct size, or adverse LV remodelling could be demonstrated.²¹ Altogether, our findings support the view that morphine has no favourable impact on ischaemic preconditioning in anterior STEMI patients but could be associated with the ventricular arrhythmic burden.

Kaplan-Meier Curves for composite outcome of death from any cause or heart failure event, according to VT/VF

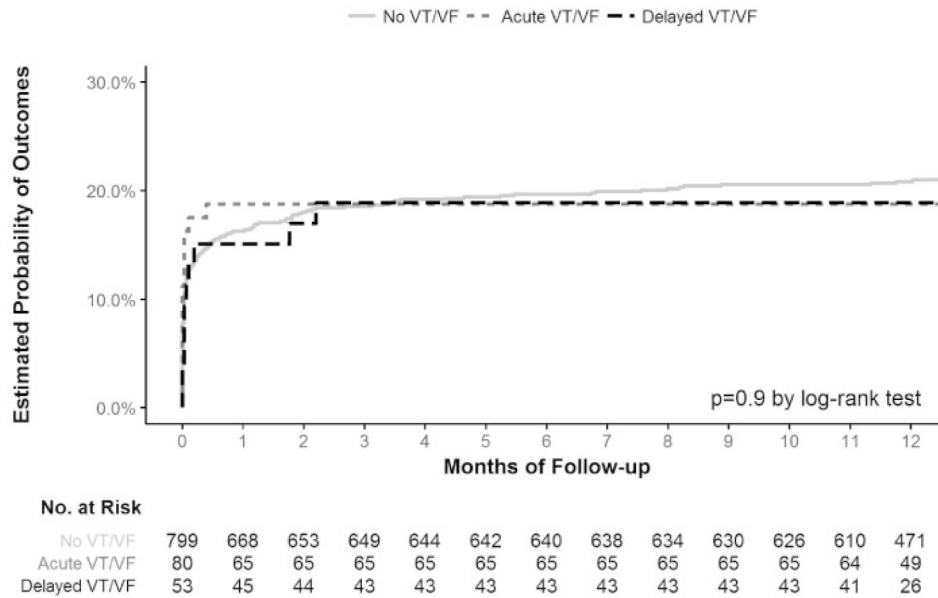


Figure 1 Kaplan–Meier curves for composite outcome of death from any cause or heart failure event, according to ventricular tachycardia/ventricular fibrillation.

Impact of VT/VF on cardiovascular outcome and LV remodelling

Previous studies have suggested that in patients with acute coronary syndromes, both early and late ventricular tachyarrhythmias portended an adverse prognosis. In a recent report drawn from a sizeable Israeli population, patients with early ventricular tachyarrhythmia (<48 h) had an increased risk of early in-hospital death but not post-discharge mortality.⁷ Conversely, patients with late ventricular tachyarrhythmia (>48 h) had larger myocardial infarction, more severe LVEF impairment and increased early and late mortality (1 year) rates with respect to patients without VT/VF or patients with early VT/VF.

Another recent *post hoc* analysis from the HORIZONS-AMI trial has emphasized the view that pre-PCI VT/VF has no impact on early mortality but was strongly associated with increased 3-year rates of death and stent thrombosis, as a possible consequence of reduced LVEF.²² In that setting, the finding that early VT/VF was associated with an adverse late prognosis might suggest that the underlying electrophysiology substrate rather than the acute arrhythmic events *per se* was responsible for increased rates of death.²² In contrast, in our homogeneous population, no impact of VT/VF on 1-year clinical outcomes could be evidenced and this, independently of the time occurrence: either early (<24 h) or late (>24 h) VT/VF. Moreover, our data did not substantiate the view that delayed VT/VF could be associated with larger myocardial impairment.

Frequency of VT/VF in anterior STEMI

In the present study, the frequency of VT/VF is much higher (14.1%) than previously reported (3.8–5.2%).⁷ LAD coronary artery, anterior

wall myocardial infarction, sum of ST-segment elevation were previously identified to be more common in patients with ventricular arrhythmias, as a possible consequence of larger infarct, more severe ischaemic burden, ventricular dysfunction or heart failure.^{1–5} Challenging this paradigm, no clear relationship between the occurrence of VT/VF and either total ischaemic time, area at risk, or post-PPCI LVEF could be established in our study population. In contrast, infarct size tended to be greater in the VT/VF group (data not shown). By design, the CIRCUS trial has enrolled high-risk patients characterized by no visible collaterals, complete occlusion of the culprit coronary artery at the time of admission and a large myocardial area at risk.

For instance, when analysis was performed on STEMI patients with LAD occlusion and Final TIMI 3 flow, ventricular arrhythmia burst could be detected in a very large proportion of the patients (51%).²¹

Study limitations

Limitations inherent to the retrospective nature of our study must be acknowledged. First, although analyses were conducted in a prospective and homogenous anterior STEMI population, these analyses were not prespecified in the CIRCUS protocol and should therefore be considered as *post hoc* analysis. Second, the trial was not stratified on morphine use and dose of morphine along with corresponding analgic pain scale evaluation were not recorded. Of note, cyclosporine was equally administered amongst two groups removing potential bias from further analysis and even though the CIRCUS trial showed no overall better clinical outcomes for the cyclosporine group. Third, the delivery of external cardioversion during VF may lead to increase cardiac enzyme levels and may have led to an artefactual

Table 6 Predictors of VT/VF

	Binomial logistic regression analysis				Multinomial logistic regression analysis			
	Univariate analysis		Multivariate analysis		Acute		Delayed	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.98 (0.97–1)	0.012	0.99 (0.97–1.0)	0.100	0.98 (0.96–1.0)	0.023	0.99 (0.97–1.02)	0.534
Male sex	1.66 (0.96–2.87)	0.068	1.49 (0.85–2.61)	0.162	1.11 (0.58–2.13)	0.761	1.79 (0.74–4.31)	0.193
Current smoking	1.21 (0.83–1.76)	0.329						
Hypertension	0.73 (0.49–1.1)	0.13						
Diabetes mellitus	0.53 (0.26–1.06)	0.071	0.61 (0.30–1.23)	0.170	0.60 (0.25–1.44)	0.256	0.52 (0.18–1.48)	0.221
Dyslipidaemia	1 (0.68–1.49)	0.988						
BMI	1.01 (0.96–1.05)	0.766						
Previous myocardial infarction	1.29 (0.58–2.89)	0.532						
Post-PCI EF	1 (0.98–1.02)	0.782						
Total ischaemic time	0.93 (0.85–1.01)	0.066						
Medial or distal segment or diagonal branch	0.98 (0.67–1.45)	0.937						
3-vessel disease	0.6 (0.31–1.18)	0.141						
Killip class ≥ 2 at 6 h post-PCI	0.81 (0.41–1.6)	0.544						
TIMI flow grade before PCI (ref. 0)								
1	0.56 (0.29–1.12)	0.1						
2	1.13 (0.5–2.54)	0.773						
3	1.14 (0.25–5.25)	0.864						
TIMI flow grade after PCI (ref. 0)								
1	2.08 (0.11–40.73)	0.628						
2	3.48 (0.37–32.41)	0.274						
3	2.32 (0.27–19.64)	0.44						
Thrombus aspiration	1.34 (0.82–2.2)	0.243						
Stenting	0.88 (0.48–1.6)	0.676						
ST-segment resolution $>70\%$ (at discharge)	1.24 (0.81–1.89)	0.321						
Leukocyte H0	1 (0.98–1.03)	0.756						
Time from symptom onset to hospital arrival	0.94 (0.88–1.01)	0.078						
Morphine	1.77 (1.17–2.68)	0.007	1.71 (1.13–2.60)	0.012	2.24 (1.33–3.76)	0.002	1.58 (0.89–2.79)	0.019
Glycoprotein IIb/IIIa inhibitor	1.10 (0.73–1.66)	0.643						

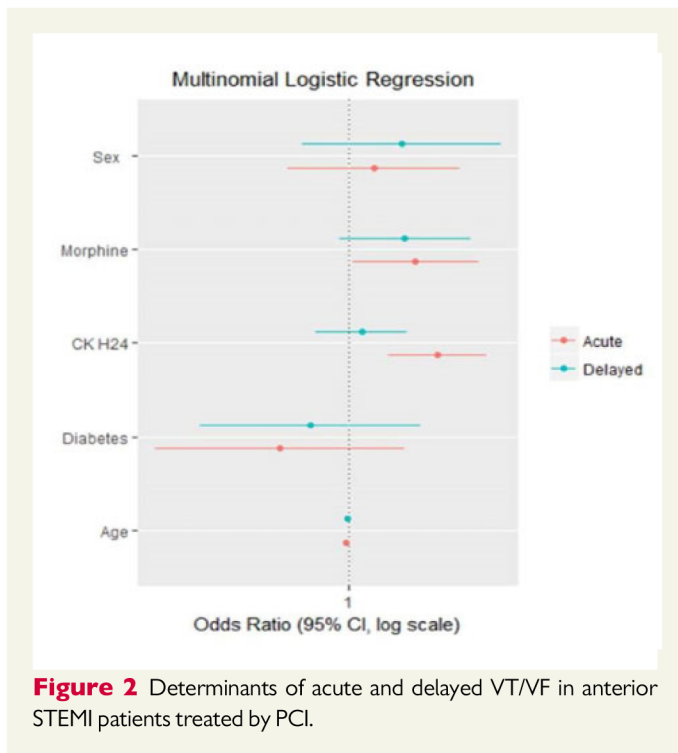
overestimation of enzymatic infarct size. Finally, in this retrospective analysis, the precise timing of arrhythmic events with respect to the achievement of reperfusion (before or after PCI) could not be defined. We fully recognize that arrhythmic events occurring before reperfusion could represent a distinct pathophysiological pattern. However, because optimal reperfusion by PCI (achievement of TIMI 3 flow) did not always translate into optimal myocardial perfusion (absence of no reflow phenomenon), early and delayed VT/VF were stratified according to their onset (≤ 24 h) and not according to the end of the PCI procedure.

A total of 552 (57.2%) patients received morphine at first medical contact in the CIRCUS trial. We recognize that this proportion is higher than previously reported (around 30%).²² According to ACCF/AHA and ESC guidelines, intravenous morphine is generally recommended in STEMI patients when chest pain is unresponsive to nitrates. Whereas no definite explanations could be

provided, we believe that the specific inclusion criteria of the CIRCUS trial have led to the enrolment of 'painful' patients. Specifically, the enrolment was limited to (i) patients with a total occlusion of the LAD and (ii) without any collateral flow. Unfortunately, data regarding morphine doses were not available in the CIRCUS database. Owing to these numerous limitations, the link between morphine and VT/VF burden should only be considered as 'hypothesis generating'.

Conclusion

VT/VF occurred in a sizeable proportion (14.1%) of anterior STEMI patients with abrupt LAD occlusion and lack of collateral flow. Ventricular arrhythmia within 48 h in acute anterior myocardial infarction was more frequent in patients treated by morphine. No



relationship between VT/VF occurrence and late adverse events could be established.

Funding

This work was supported by the RHU MARVELOUS (ANR-16-RHUS-0009) of l'Université Claude Bernard Lyon 1 (UCBL), within the programme 'Investissements d'Avenir' operated by the French National Research Agency (ANR) and by GERCA (Groupe pour l'Enseignement, la Recherche cardiologique en Alsace).

Conflict of interest: none declared.

References

- Demidova MM, Carlson J, Erlinge D, Platonov PG. Predictors of ventricular fibrillation at reperfusion in patients with acute ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol* 2015;**115**: 417–422.
- Jabbari R, Engstrøm T, Glinge C, Risgaard B, Jabbari J, Winkel BG, Terkelsen CJ, Tilsted HH, Jensen LO, Hougaard M, Chiuvé SE, Pedersen F, Svendsen JH, Haunsø S, Albert CM, Tfelt-Hansen J. Incidence and risk factors of ventricular fibrillation before primary angioplasty in patients with first ST-elevation myocardial infarction: a nationwide study in Denmark. *J Am Heart Assoc* 2015;**4**:e001399.
- Gheeraert PJ, De Buyzere ML, Taeymans YM, Gillebert TC, Henriques JP, De Backer G, De Bacquer D. Risk factors for primary ventricular fibrillation during acute myocardial infarction: a systematic review and meta-analysis. *Eur Heart J* 2006;**27**:2499–2510.
- Majidi M, Kosinski AS, Al-Khatib SM, Smolders L, Cristea E, Lansky AJ, Stone GW, Mehran R, Gibbons RJ, Crijns HJ, Wellens HJ, Gorgels AP, Krucoff MW. Implications of ventricular arrhythmia "bursts" with normal epicardial flow,

myocardial blush, and ST-segment recovery in anterior ST-elevation myocardial infarction reperfusion: a biosignature of direct myocellular injury "downstream of downstream". *Eur Heart J Acute Cardiovasc Care* 2015;**4**:51–59.

- Majidi M, Kosinski AS, Al-Khatib SM, Lemmert ME, Smolders L, van Weert A, Reiber JH, Tzivoni D, Bär FW, Wellens HJ, Gorgels AP, Krucoff MW. Reperfusion ventricular arrhythmia 'bursts' predict larger infarct size despite TIMI 3 flow restoration with primary angioplasty for anterior ST-elevation myocardial infarction. *Eur Heart J* 2009;**30**:757–764.
- Masuda M, Nakatani D, Hikoso S, Suna S, Usami M, Matsumoto S, Kitamura T, Minamiguchi H, Okuyama Y, Uematsu M, Yamada T, Iwakura K, Hamasaki T, Sakata Y, Sato H, Nanto S, Hori M, Komuro I, Sakata Y; OACIS investigators. Clinical impact of ventricular tachycardia and/or fibrillation during the acute phase of acute myocardial infarction on in-hospital and 5-year mortality rates in the percutaneous coronary intervention era. *Circ J* 2016;**80**:1539–1547.
- Orvin K, Eisen A, Goldenberg I, Gottlieb S, Kornowski R, Matetzky S, Golovchiner G, Kuznietz J, Gavriolov-Yusim N, Segev A, Strasberg B, Haim M. Outcome of contemporary acute coronary syndrome complicated by ventricular tachyarrhythmias. *Europace* 2016;**18**:219–226.
- Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guérin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice MC, Ider O, Dubois-Randé JL, Untersee T, Le Breton H, Béard T, Blanchard D, Grollier G, Malquart V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med* 2015;**373**:1021–1031.
- Mewton N, Cung TT, Morel O, Cayla G, Bonnefoy-Cudraz E, Rioufol G, Angoulvant D, Guerin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, Morice MC, Monassier JP, Ider O, Dubois-Randé JL, Untersee T, Lebreton H, Beard T, Blanchard D, Grollier G, Malquart V, Staat P, Sudre A, Hansson MJ, Elmer E, Boussaha I, Jossan C, Torner A, Claeys M, Garcia-Dorado D, Ovize M; CIRCUS Study Investigators. Rationale and design of the Cyclosporine to ImpRove Clinical oUtcome in ST-elevation myocardial infarction patients (the CIRCUS trial). *Am Heart J* 2015;**169**:758–766.e6.
- Coles JA Jr., Sigg DC, Iazzo PA. Role of kappa-opioid receptor activation in pharmacological preconditioning of swine. *Am J Physiol Heart Circ Physiol* 2003;**284**:H2091–H2099.
- Sigg DC, Coles JA Jr, Oeltgen PR, Iazzo PA. Role of delta-opioid receptor agonists on infarct size reduction in swine. *Am J Physiol Heart Circ Physiol* 2002;**282**: H1953–H1960.
- Markiewicz W, Finberg JP, Lichtig C. Morphine increases myocardial infarction size in rats. *Anesth Analg* 1982;**61**:843–846.
- Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardioprotective role of remote ischemic preconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv* 2010;**3**:49–55.
- Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2014;**63**:630–635.
- Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chetibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;**371**:1016–1027.
- Silvain J, Storey RF, Cayla G, Esteve JB, Dillinger JG, Rousseau H, Tsatsaris A, Baradat C, Salhi N, Hamm CW, Lapostolle F, Lassen JF, Collet JP, Ten Berg JM, Van't Hof AW, Montalescot G. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost* 2016;**116**: 369–378.
- Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013;**61**:1601–1606.
- de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G, Thiele H. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. *Clin Res Cardiol* 2015;**104**:727–734.

19. Farag M, Spinhakis N, Srinivasan M, Sullivan K, Wellsted D, Gorog DA. Morphine analgesia pre-PPCI is associated with prothrombotic state, reduced spontaneous reperfusion and greater infarct size. *Thromb Haemost* 2018;**118**: 601–612.
20. McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, Keramati AR, Goli RR, Gratton TP, Brinker JA, Chacko M, Hwang CW, Johnston PV, Miller JM, Trost JC, Herzog WR, Blumenthal RS, Thiemann DR, Resar JR, Schulman SP. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: the PACIFY Randomized Clinical Trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl). *Circulation* 2018;**137**:307–309.
21. Bonin M, Mewton N, Roubille F, Morel O, Cayla G, Angoulvant D, Elbaz M, Claeys MJ, Garcia-Dorado D, Giraud C, Rioufol G, Jossan C, Ovize M, Guerin P; CIRCUS Study Investigators. Effect and safety of morphine use in acute anterior ST-segment elevation myocardial infarction. *J Am Heart Assoc* 2018;**7**: e006833.
22. Kosmidou I, Embacher M, McAndrew T, Dizon JM, Mehran R, Ben-Yehuda O, Mintz GS, Stone GW. Early ventricular tachycardia or fibrillation in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention and impact on mortality and stent thrombosis (from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Trial). *Am J Cardiol* 2017;**120**:1755–1760.