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Original article

Postconditioning attenuates early ventricular arrhythmias in patients with high-risk ST-segment elevation myocardial infarction

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ABSTRACT

Background: It has been demonstrated that postconditioning (postcon), brief episodes of ischemia during reperfusion period, in patients with ST-segment elevation myocardial infarction (STEMI) confers protection against ischemia–reperfusion injury and as a result, postcon might reduce infarct size. However, whether postcon may exert its beneficial effect on STEMI patients by reducing the occurrence of early malignant ventricular arrhythmias (VA) is still unknown. The aim of the study was to evaluate the influence of postcon on the presence of VA in early presenters with high-risk STEMI treated with primary coronary intervention (PCI).

Methods: Seventy-five STEMI patients treated with primary PCI within 6 h from symptoms onset were randomly assigned to postcon group ($n = 37$) or conventional PCI group ($n = 38$) in 1:1 ratio. Postcon was performed immediately after restoration of coronary flow as follows: the angioplasty balloon was inflated 4× 1 min with low-pressure inflations, each separated by 1 min of deflation. After that the patients were continuously monitored electrographically for 48 h. The end-point of the study was the occurrence of VA (ventricular fibrillation-VF, sustained ventricular tachycardia-sVT, non-sustained ventricular tachycardia-nsVT) within 48 h after the procedure.

Results: In the postcon group, the occurrence of VAs was significantly lower: VF-3, sVT-0, nsVT-15, i.e. (18 patients – 48.6%) in comparison to control group: VF-2, sVT-4, nsVT-23 (29 patients – 76.3%); $p = 0.013$. The occurrence of accelerated idioventricular rhythm varied insignificantly between both groups (postcon – 45.9% vs control – 34.2%; p = NS).

Conclusions: Postcon may reduce the occurrence of malignant VA in patients with STEMI treated with primary PCI.

Introduction

Timely and effective reperfusion therapy nowadays plays a crucial role in the treatment of patients with ST-elevation myocardial infarction (STEMI) [1]. Early reperfusion with primary percutaneous coronary intervention (PCI) leads to decreased morbidity and mortality, by limiting myocardial necrosis expansion [2]. However paradoxically, while salvaging myocardium from infarction, it may also induce additional myocardial injury and cardiomyocyte death – a phenomenon termed ischemia–reperfusion injury (IRI) [3,4]. The injury to the heart during myocardial reperfusion causes four major types of cardiac dysfunction: myocardial stunning, microvascular obstruction and no-reflow phenomenon, reperfusion arrhythmias, and lethal reperfusion injury [4,5].

It has been demonstrated that postconditioning (postcon), brief interruption of coronary blood flow during reperfusion period, provides protection against IRI [6]. It has been also reported that postcon might reduce infarct size, no-reflow phenomenon, and microvascular obstruction as well as improve left ventricular function in STEMI patients treated with primary PCI [7–12]. However, whether postcon may exert its beneficial effect on STEMI patients by reducing the occurrence of early malignant ventricular arrhythmias (VA) is still unknown.

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The aim of the present study was to evaluate the influence of postcon on the occurrence of VA in early presenters with high-risk STEMI treated with primary PCI.

Methods

Study population

From October 2010 to December 2013 all patients admitted to our department who were eligible for a primary PCI due to STEMI were considered for enrolment on our study, provided they fulfilled the following inclusion criteria: age >18 and <80 years, chest pain >30 min and <6 h (preferably <4 h, <6 h only if chest pain persisted and ST-segment elevations), ST segment elevation >0.1 mV (>0.2 mV in V1–V3) in two contiguous electrocardiogram (ECG) leads, and a thrombolysis in myocardial infarction (TIMI) grade 0 flow in the infarct-related artery. The patients were excluded if they had: previous myocardial infarction, previous coronary artery bypass surgery, cardiogenic shock, cardiac arrest, the presence of collateral flow to the infarcted area as evidenced by a Rentrop score ≥1, known renal impairment (serum creatinine >150 mmol/l), persistent atrial fibrillation, ongoing malignant process, history of gastrointestinal bleeding or stroke, any contraindication for glycoprotein IIb/IIIa inhibitors, and any condition that was considered to interfere with the possibility for the patient to complete the study protocol.

Study design and protocol

This was a prospective, single-center, randomized, controlled, open–label study with blinded evaluation. The study was performed according to the provisions of the 1975 Declaration of Helsinki and good clinical practice. All the participants gave written informed consent for our investigation. The local ethics committee approved the protocol of the study (No. 547/11).

Patients were pretreated with aspirin (300 mg orally), clopidogrel (600 mg orally), and heparin (intravenously at a dose of 60 UI/kg) before PCI. After hospital admission, coronary angiography was performed to identify the culprit lesion and assess TIMI flow in infarct-related artery either antegradely or from collaterals. Coronary angiography was performed by the percutaneous technique using the transradial approach in most cases.

Following angiographic data acquisition, patients were randomized, using 1:1 sequence placed in numbered sealed envelopes, into the control or postcon group. After guidewire placement in the distal part of the vessel, thrombectomy was performed in all patients. In the control group a drug-eluting stent was subsequently implanted with direct technique whenever possible. Postcon was performed by reinflating the balloon at the same location to a pressure 4–6 atm for 60 s starting 1 min after initial reperfusion with thrombectomy. This cycle was then repeated four times. The selection of this ischemia–reperfusion sequence was based on previous experimental and human studies [8,9]. Patients in the control group received no additional intervention during 4 min of reperfusion. The procedure was finished with drug-eluting stent implantation. Glycoprotein IIb/IIIa inhibitors (abciximab) were administered in all patients. All patients were treated with aspirin 75 mg daily lifelong and clopidogrel 75 mg daily for 12 months.

Angiographic analysis

Angiographic assessment was performed independently by two experienced angiographers who were blinded to each other and to the clinical data. It included TIMI flow grade before and after the procedure, myocardial blush grade (MBG), and Rentrop's score of collateral flow [13].

Electrocardiographic monitoring and ECG analysis

All patients were continuously monitored throughout the procedure and after intervention at intensive cardiac care unit (48.4 ± 4.3 h). Multilead and computerized arrhythmia detection system (IntelliVue MP70, Philips, Amsterdam, the Netherlands) was used. All the data were digitally recorded and then analyzed off-line with the use of the equipment software by trained cardiologists. The incidence, length, and time of occurrence of potentially life-threatening arrhythmias, including ventricular tachyarrhythmias such as ventricular fibrillation (VF) and sustained and non-sustained ventricular tachycardia (sVT; nsVT), were studied.

VF was defined as irregular undulations of varying contour and amplitude on the ECG with absent distinct QRS and T waves and hemodynamic compromise requiring defibrillation. sVT was defined as regular wide-complex tachycardia (>110 beats per minute – bpm) of ventricular origin lasting ≥30 s and/or accompanied by hemodynamic compromise requiring electrical cardioversion or anti-arrhythmic therapy. nsVT was defined as regular wide-complex self-limiting tachycardia of at least 3 QRS complexes (RR intervals of <500 ms) and lasting ≤30 s.

Accelerated idioventricular rhythm (AIVR) was defined as ventricular wide-complex rhythm with a rate between 40 and 110 bpm.

Atrial fibrillation was defined as completely irregular atrial rhythm 350–500 bpm (f wave) with irregular ventricular rhythm.

A standard 12-lead ECG tracing was obtained at admission and 30 min after the end of PCI. The sum of ST-segment elevation was measured manually 60 ms after the end of the QRS complex from the leads exploring the infarct area. The resolution of ST segment was calculated as a percentage of the value obtained from basal ECG. A reduction higher than 70% of the initial value was considered significant [14].

Endpoints

The primary endpoint of the study was the combined incidence of VF, sVT, or nsVT. The secondary endpoint was the incidence of AIVR.

Statistical methods

Continuous variables are expressed as mean or median and categorical data are reported as frequencies and percentages. Comparisons between groups were performed using unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous variables and Chi-square or Fisher's exact test for categorical variables. A value of $p < 0.05$ was considered statistically significant.

Considering an expected 20% reduction in the incidence of VAs, we calculated a total sample size of 68 patients to achieve the power of the test of 90%.

Results

From a total of 423 screened patients with STEMI, 121 patients met the initial criteria and had been found eligible for the study, but 26 were subsequently excluded as shown in Fig. 1. The remaining 95 patients underwent randomization to postcon and control groups, but 20 declined participation, which left 75 patients (37 in the postcon group and 38 in the control group). There were no significant differences between groups with regard to baseline demographic, angiographic, and procedural characteristics (Tables 1 and 2). The peak creatine kinase (CK), CK-MB, and troponin I levels were significantly lower in the postcon group (Table 1). This group also showed significantly more frequent occurrence of MBG 3 (30 patients, 81.1%) in

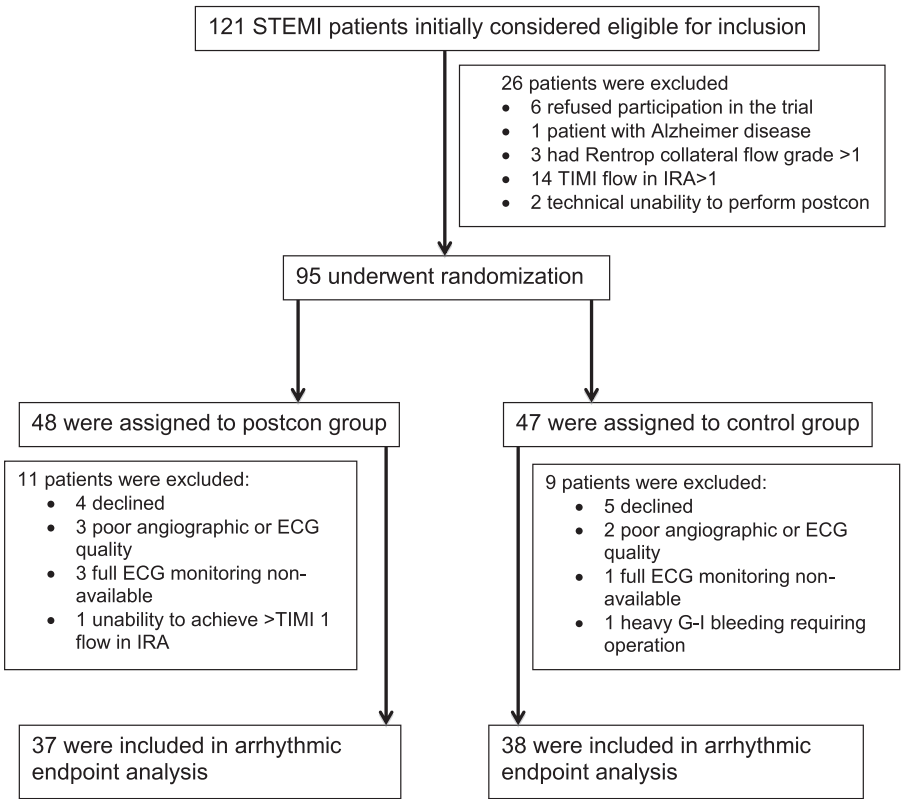

Fig. 1. Patient flow diagram. STEMI, ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction flow grade; IRA, infarct related artery; postcon, postconditioning; ECG, electrocardiography; G-I, gastrointestinal.

comparison with the control group (19 patients, 50%), $p = 0.005$. ST-segment resolution was also significantly more frequent in the postcon group – 33 patients (89.2%) vs 25 patients (65.8%), $p = 0.03$.

The evaluation of arrhythmias

In the postcon group the following VAs were observed: VF – in 3 patients, sVT-0 patients, nsVT-27 episodes in 15 patients, totally

Table 1
Clinical characteristics of study groups.

Characteristics	Postcon $n = 37$	Control group $n = 38$	p
Age (years) ± SD (median)	56.6 ± 10.5 (56)	56.8 ± 9.9 (57)	0.6
Men (%)	25 (67.6)	30 (78.9)	0.27
Body mass index (kg/m^2) ± SD	27.9 ± 4.03 (27.8)	28.1 ± 3.02 (27.6)	0.8
Diabetes mellitus (%)	6 (16.2)	7 (18.4)	0.5
Glycemia on admission (mmol/l) ± SD (median)	8.3 ± 2.7 (7.5)	8.8 ± 4.2 (7.4)	0.9
Obesity (%)	11 (29.7)	11 (28.9)	0.9
Hypertension (%)	19 (51.3)	22 (57.9)	0.6
Family history of angina pectoris (%)	12 (32.4)	9 (23.7)	0.4
Smokers (%)	22 (59.5)	20 (50)	0.6
Symptoms to balloon time (min) ± SD (median)	207.8 ± 82.9 (186)	216.9 ± 91.7 (194)	0.17
Systolic blood pressure on admission (mmHg) ± SD	146.3 ± 20.6	145.8 ± 18.4	0.3
Diastolic blood pressure on admission (mmHg) ± SD	85.3 ± 10.95	86.5 ± 11	0.32
Heart rate on admission (beats per minute) ± SD	73.3 ± 16.2 (76)	71.2 ± 12.4 (68)	0.8
Killip-Kimball Class 1 on admission (%)	35 (94.6)	33 (86.8)	0.25
Multivessel disease (%)	11 (29.7)	17 (44.7)	0.18
Anterior myocardial infarction (%)	11 (29.7)	12 (31.6)	0.9
CK baseline (U/l) (mean ± SD)	176.6 ± 113	233.7 ±162.5	0.075
CK-MB baseline (U/l) (mean ± SD)	30.1 ± 14.4	38.2 ± 30.2	0.08
CK peak (U/l) (mean ± SD)	2328.8 ± 1392.4	3143.2 ± 1352.5	0.003
CK-MB peak (U/l) (mean ± SD)	252.8 ± 196.1	343.1 ± 162	0.01
Troponin I peak (ng/l) (mean ± SD)	68.2 ± 43.1	88.9 ± 34.2	0.03
Ejection fraction (%) (mean ± SD)	50.1 ± 10.4	46.9 ±9.3	0.2
Antiarrhythmic drugs			
β-blockers (%)	33 (89.2)	34 (89.5)	0.63
Amiodarone (%)	5 (15.6)	8 (21)	0.29

SD, standard deviation; CK, creatine kinase.

Table 2
Angiographic characteristics of study groups.

Characteristics	Postcon $n=37$	Control group $n=38$	p
Symptoms-to balloon time (min) ± SD (median)	207.8 ± 82.9 (186)	216.9 ± 91.7 (194)	0.17
Culprit vessel			
LAD (n, %)	11 (29.7)	12 (31.6)	0.86
RCA (n,%)	21 (56.8)	20 (52.6)	0.72
LCx (n, %)	5 (13.5)	6 (15.8)	0.52
Target lesion location			
Proximal (n, %)	22 (59.5)	20 (52.6)	0.55
Mid (n, %)	15 (40.5)	18 (47.4)	0.55
Multivessel disease (n, %)	11 (29.7)	17 (44.7)	0.18
Initial TIMI flow 0 (n, %)	37 (100)	38 (100)	1
Final TIMI flow 3 (n, %)	36 (97.3)	33 (86.8)	0.1
Final TIMI flow 2 (n, %)	1 (97.3)	5 (86.8)	0.12
Reference luminal diameter (mm)	3.4 ± 0.3	3.3 ± 0.3	0.81
Thrombectomy	37 (100)	38 (100)	1

Postcon, postconditioning; LAD, left anterior descending artery; RCA, right coronary artery; LCx, circumflex artery; TIMI, thrombolysis in myocardial infarction flow grade; SD, standard deviation.

the episodes of VAs occurred in 18 patients (48.6%). In the control group: VF was observed in 2 patients, sVT-6 episodes in 4 patients, nsVT-39 episodes in 23 patients, totally the incidence of malignant VAs in control group appeared in 29 patients (76.3%). The difference in the incidence of VAs between postcon group and control group was statistically significant; $p = 0.013$, Fig. 2. The occurrence of AIVR differed non-significantly between both groups – it was observed in 17 patients (45.9%) in postcon group whereas in control group it occurred in 13 patients (34.2%), $p = 0.3$.

Timeframe of the occurrence of VAs is shown in Fig. 3. Generally, the vast majority of incidents of VAs (80% in postcon group and 78.7% in control group) took place during first 12 h after the procedure (Fig. 4).

Atrial fibrillation was observed in only 2 patients (5.4%) in the postcon, and 3 patients (7.9%) in the control group, $p = 0.67$.

The peak CK and CK-MB in patients with arrhythmic events were significantly higher (respectively 2423 ± 1293.2 U/l vs 3053 ± 1341.5 U/l, $p = 0.01$ and 241.7 ± 184.1 U/l vs 353.2 ±164 U/l, $p = 0.009$).

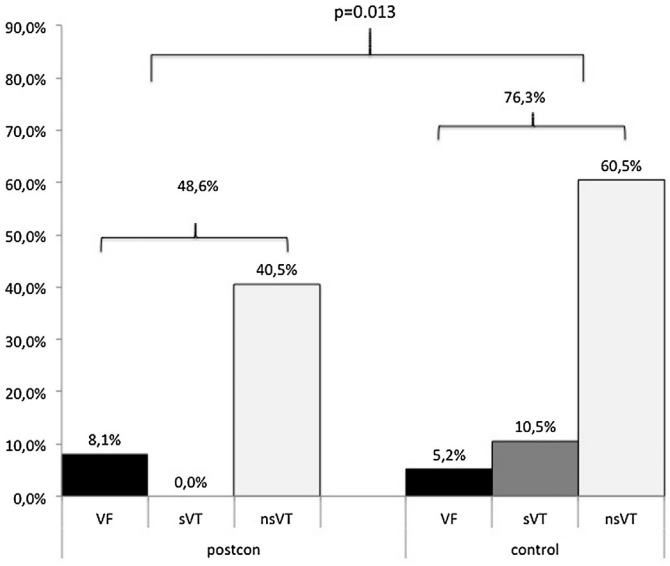

Fig. 2. Ventricular arrhythmia episodes in the postconditioning (postcon) and control groups. VF, ventricular fibrillation; sVT, sustained ventricular tachycardia; nsVT, non-sustained ventricular tachycardia.

Clinical follow-up

One-year follow-up was available for 73 of 75 patients (97.3%). Overall, four patients died – two in control group (cardiac death) and two in postcon group (one – cardiac death and one died because of neoplasm; $p = 0.68$). Recurrent non-fatal myocardial infarction was observed in 4 patients (2 in postcon and 2 in control group, $p = 0.68$). Clinically driven target vessel revascularization was necessary in 6 patients (2 in postcon and 4 in control group, $p = 0.35$).

Discussion

The major finding of the present study is that postcon reduced the occurrence of early malignant arrhythmias in patients with STEMI. According to our best knowledge the present research is the first randomized study evaluating the impact of postcon on the incidence of arrhythmias in humans with STEMI.

Postcon was first described by Zhao et al. who demonstrated in canine hearts that interrupting myocardial reperfusion with three 30-s cycles of left anterior descending artery re-occlusion and reflow prevented IRI and reduced myocardial infarct size by 44% [6]. This therapeutic approach was rapidly translated into clinical setting of primary PCI by Staat et al. [7]. A number of further

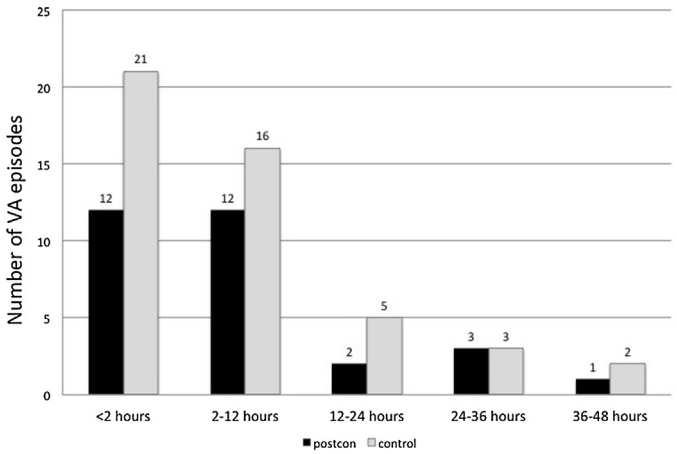

Fig. 3. Time of occurrence of ventricular arrhythmia (VA) episodes during 48 h after the procedure in the postconditioning (postcon) and control groups.

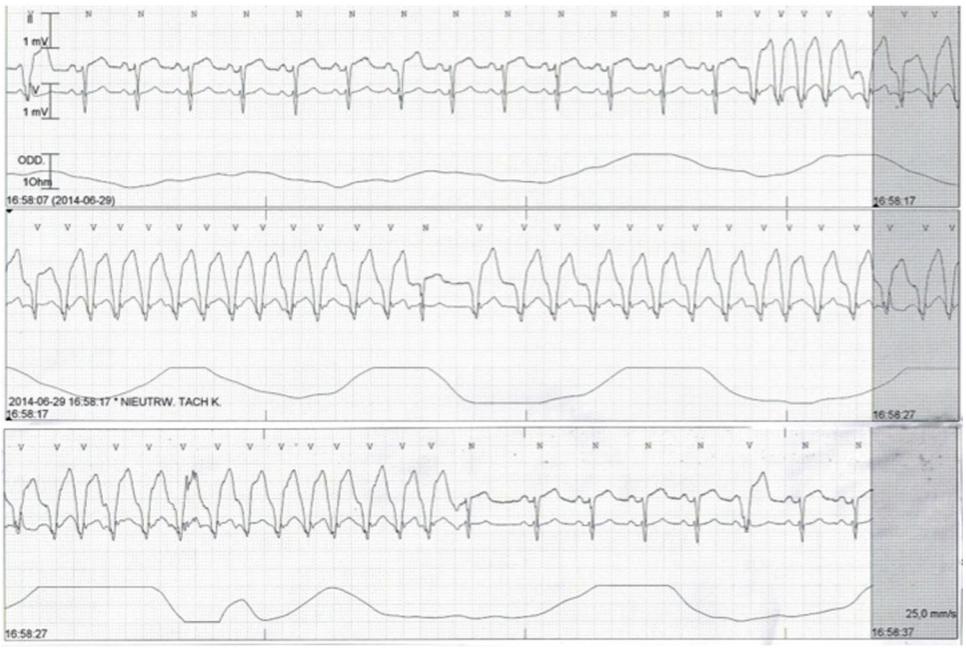

Fig. 4. An example of non-sustained ventricular tachycardia in a 62-year-old patient after anterior wall ST-elevation myocardial infarction treated with primary percutaneous coronary intervention 3 h after symptoms' onset (control group).

studies have confirmed the efficacy of postcon in reperfused STEMI patients including reducing of infarct size, the area of microvascular obstruction, and no-reflow phenomenon, although not all studies were positive [15–19].

A study on animals reported that an intermittent form of reperfusion (postcon) markedly reduced the incidence of reperfusion-induced VF following a 20 min episode of coronary artery occlusion [20]. Several other animal studies support the earlier results of an anti-arrhythmic action of postcon. Galagudza et al. reported that a single 2 min global ischemic episode displaying persistent VF 15 min after reperfusion resulted in defibrillation. This study was performed on isolated rat hearts [21]. Sasaki et al. [22] described the influence of a 5-min global ischemia instituted 1 min after reperfusion to terminate reperfusion arrhythmias in rats, while Kloner et al. reported that a more classical ischemic postcon protocol (4× 20 s) following a 5-min index episode of coronary artery occlusion (insufficient to cause necrosis) performed in a rat in vivo reduced the incidence of VT during reperfusion [23,24]. Our results indicate that postcon attenuates VAs particularly during the first 2 h after the infarct-related artery recanalization (Fig. 3). It means that postcon inhibits mainly reperfusion arrhythmias. The detailed mechanisms of their formation remain unclear. The causes may include heterogeneous recovery of conduction and the refractory period by incomplete reperfusion, reentry, abnormal automaticity, activities triggered by Ca^{2+} overload, and free radicals [25]. Moreover, it has also been reported that radical scavengers can inhibit reperfusion arrhythmias [26]. The mechanisms by which ischemic postcon terminates reperfusion arrhythmia and prevents the recurrence of arrhythmia may involve the correction of electrical homogenization due to reduction of Ca^{2+} overload and free radicals. The details of the mechanisms, however, are still unclear. Pharmacological inhibition studies suggest that the effect in rats is not mediated by adenosine, PI3-kinase, K_{ATP} channels, or mitochondrial permeability transition pore opening. Further study will be necessary to investigate which mechanism is responsible for the antiarrhythmic effects of postcon [27]. Okishige et al. studied the electrophysiological effects of ischemic postcon in a group of 31 patients with acute MI treated with primary PCI [28]. In this observational study the authors found that postcon exhibited significant antiarrhythmic effects which were evaluated by the change in the QT dispersion.

In our study a high prevalence of patients who experienced VAs was observed in both groups (45.9% vs 76.3%). Such a high ratio arrhythmia seems to be considerably higher than in other studies reported in the literature. The incidence of nsVT (monomorphic) in the setting of acute MI is usually reported as being between 1% and 7% of STEMI patients although it may be as high as 75% in patients treated with thrombolysis [29–31]. Cricri et al. observed 7% of life-threatening arrhythmias in patients with STEMI treated with primary PCI [32]. In a study carried out by Ohlow et al. only 4.7% of 510 patients who underwent primary PCI for STEMI developed sustained VAs [33]. The high incidence of VAs in our study is probably due to the fact that we included high-risk patients who presented early with a relatively large area of viable myocardium, which constituted a more pronounced substrate for the development of arrhythmias. In the PAMI trial the delay between onset of symptoms and patients' arrival in the emergency room was shorter in subjects who experienced sustained ventricular tachyarrhythmias in the catheterization laboratory than in those who remained arrhythmia-free [34]. Moreover, in the retrospective cohort study of patients undergoing PCI for STEMI in New York State, patients presenting within 6 h after symptom onset were more likely to experience early, sustained ventricular tachyarrhythmias than those who presented later [35].

Another explanation of such a high prevalence of VAs in our study is probably the fact that in most other studies, only the presence of sVT and VF were assessed.

Opinions on the impact of VAs on clinical outcomes in STEMI patients undergoing PCI remain controversial. In the PAMI trial population, no influence of the occurrence of VF and VT in the cardiac catheterization laboratory during PCI procedure on in-hospital or one-year outcomes was observed; at the same time, mortality seemed to be not at all affected [34]. In contrast, in the APEX AMI trial, the occurrence of VAs during or after PCI was associated with an increased, 90-day mortality in STEMI patients,

irrespective of their underlying baseline risk [36,37]. In the study of Cricri et al., 30-day mortality was significantly higher in patients who had experienced an episode of life-threatening arrhythmia during hospitalization than in those who had not [32].

We believe that postcon method, which is relatively easy to apply in clinical practice, can significantly reduce reperfusion injury including the malignant VAs leading to sudden cardiac death and improve prognosis in STEMI patients. Even the presence of nsVT might be associated with larger area of necrosis and stunned myocardium and lead to the worsening of prognosis. Majidi et al. performed continuous Holter monitoring on patients with anterior STEMI who had TIMI flow grade 3 following primary PCI [38]. Subjects with bursts (defined as >3 ventricular ectopic beats) had higher absolute peak ST segments and more frequent worsening of ST elevation immediately after reperfusion. Furthermore, these investigators showed that these bursts correlated with larger infarct size and lower left ventricular ejection fraction among patients with anterior STEMI with post-primary PCI TIMI flow grade 3 and ST resolution greater than 50% [38]. This hypothesis should be, however, confirmed by further studies.

Study limitations

Undoubtedly, there are some limitations of our study. The primary limitation was the relatively small number of patients. Second, only 22.5% of screened patients were initially included and only 62% of patients meeting the inclusion criteria finally participated in the study. However, because postcon has to be applied within the first minute of reperfusion, it is necessary, in a randomized study such as the present one, to obtain the required informed consent before the angiography is performed, which, consequently, leads to a larger screened population than the potentially angiographic eligible population. The protocol of the study has a considerable impact on the effectiveness of postcon. Therefore, when planning the study we had to make sure to implement an optimal reperfusion therapy. All our patients received glycoprotein IIb/IIIa inhibitors and had infarct-related artery opened using aspiration thrombectomy. Direct stenting was performed whenever possible to avoid microembolization which could grossly deteriorate the beneficial effects of postcon. Such a strict protocol obviously excluded potential participants who had a high risk of bleeding. Despite randomization, as one might expect in a relatively small study, there are some imbalances in the baseline characteristics and procedural outcome between study groups (including baseline CK and CK-MB levels), albeit not statistically significant. However it cannot be excluded that this contributes to the findings.

Another limitation is the fact that estimation of infarcted area was not based on the more advanced methods such as magnetic resonance, echocardiography, or radionuclide imaging, but only on peak CK and CK-MB levels.

Clinical significance (improvement in prognosis) of postcon has not been proven in our study. The study was underpowered to show the potential difference in mortality or in major adverse cardiovascular events.

Conclusions

In conclusion, the results of the present study indicate that postcon can significantly reduce the occurrence of malignant VAs, even though the prognostic value of this phenomenon is still to be investigated. Therefore, further research is necessary to determine the effect of postcon on the appearance of VAs and the clinical outcome.

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Conflict of interest

The authors declare that there is no conflict of interest.

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