Original article

Colchicine added to standard therapy further reduces fibrosis in pigs with myocardial infarction

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Background The anti-inflammatory drug colchicine improves the outcome of patients with myocardial infarction (MI). As an intense inflammatory and fibrotic response after MI may lead to scar expansion and left ventricular (LV) remodeling, the clinical benefit of colchicine could be related to a positive effect on the infarct scar and LV remodeling.

Methods Pigs underwent left anterior descending artery occlusion through an angioplasty balloon for 90 min and were then randomized into two groups: standard therapy [ACE inhibitor, beta blocker, mineralocorticoid receptor antagonist (MRA), aspirin] plus colchicine ($n = 14$) or standard therapy alone ($n = 13$). The pigs were treated for 30 days and underwent two cardiac magnetic resonance (CMR) scans at 72 h and 30 days. The pigs were then sacrificed the day after the second CMR. The primary efficacy end point was the extent of fibrosis in the infarct zone (calculated on eight samples from this zone and averaged).

Results In the hearts explanted after 31 days, pigs in the colchicine group had less fibrosis in the infarct zone than the other animals [41.6% (20.4–51.0) vs. 57.4% (42.9–66.5); $P = 0.022$]. There was a trend toward a higher myocardial salvage index (MSI; an index of the efficacy of revascularization) in pigs on colchicine ($P = 0.054$). Conversely, changes in LV volumes, ejection fraction and mass did not differ between groups.

Conclusion Colchicine therapy for 1 month after reperfused MI further reduces myocardial fibrosis when added to standard therapy, while it does not have additional effects on LV remodeling.

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Keywords: colchicine, myocardial infarction, remodeling, scar

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Background

Despite significant advances in the treatment of myocardial infarction (MI), the risk of developing heart failure after MI is still high: for example, one in four individuals aged at least 75 years will develop heart failure within 5 years after a first MI.[1] Some of these patients will develop heart failure with preserved ejection fraction (HFpEF), which is becoming increasingly common even after an MI.[2] Other patients will experience left ventricular (LV) remodeling, which is characterized by scar expansion, a change to a more spherical LV shape, and a final decline in LV systolic function.[3] LV remodeling is promoted by an intense inflammatory and fibrotic response to MI.[4,5] Therefore, an anti-inflammatory drug could potentially prevent heart failure development after MI.

Colchicine is an anti-inflammatory drug that has been used for decades for the prevention of acute inflammatory flares in gout and familial Mediterranean fever. In recent years, clinical trials have demonstrated its potential in several cardiovascular conditions. Colchicine is taken up by leucocytes, binds to tubulin and interferes with microtubular function; this ultimately affects the expression of cytokines and interleukins, and the neutrophil functions.[6] The prognostic benefit of colchicine in patients with acute coronary syndrome (ACS) is controversial. In the Colchicine in Patients with Acute Coronary Syndrome (COPS) trial, the addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months and was associated with a higher rate of mortality.[7] Conversely, in the Colchicine Cardiovascular

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Outcomes Trial (COLCOT), colchicine improved cardiovascular outcomes in patients with a recent MI.[8] The trial COlchicine for Left VEntricular Remodeling Treatment in Acute Myocardial Infarction (COVERT-MI) specifically investigated the effects of colchicine at the time of reperfusion and for 5 days on MI size and LV remodeling over 3 months, and did not find any significant difference.[9] We reappraised the effects of colchicine after MI in a preclinical model closely recapitulating the features of human patients with reperfused MI, including full neurohormonal antagonism. In this model, colchicine therapy was started when the inflammatory response to MI was maximal and it was given for a whole month. The effects of the colchicine were investigated through serial cardiovascular magnetic resonance (CMR) scans and an analysis of myocardial tissue.

Methods

Experimental groups

The animal study was conducted from November 2021 to August 2022. It was approved by the local Animal Experimentation Unit Ethical Committee and Government Authorities (Junta de Extremadura), and complied with guidelines concerning the use of animals in research and teaching as defined by the Guide for the Care and Use of Laboratory Animals.[10] All procedures were performed at the *Centro de Cirugía de Mínima Invasión Jesús Usón* in Cáceres (Spain). In 4-month-old pigs (Landrace X LargeWhite, 50% males, weight 35–40 kg), MI was induced by occluding the left anterior descending (LAD) artery through an angioplasty balloon for 90 min.[11] Pigs surviving MI induction were randomized in a 1 : 1 ratio to two groups:

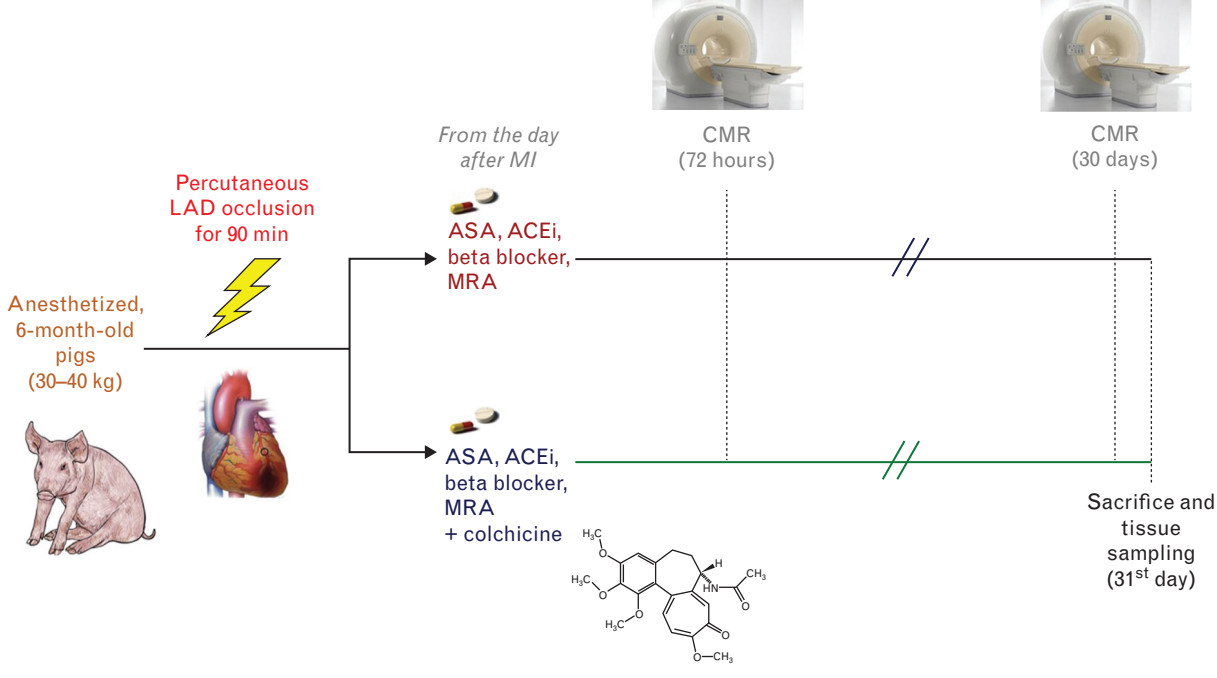
(1) control group ($n = 14$): MI induction and reperfusion, standard therapy (see the following);
(2) colchicine group ($n = 13$): MI induction and reperfusion, standard therapy plus colchicine.

The pigs underwent a first CMR scan 72 h after MI induction, and another CMR at day 30. The pigs were then sacrificed the day after the second CMR examination (Fig. 1). The primary end point was fibrosis extent in the infarct zone (see the following). Secondary end points were late gadolinium enhancement (LGE) at 30 days (as absolute mass or as a percentage over the LV mass), myocardial salvage index (MSI; see below), and percentage changes in LV end-diastolic volume, ejection fraction and mass.

Sample size calculation

By estimating a moderate effect of colchicine on the primary end point, the total sample size was calculated as 26 (0.5 effect size, 5% significance level and 80% power). By assuming a mortality rate of 7% during the acute phase of MI, based on prior data from our animal

Fig. 1



Study design. ACEi, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; CMR, cardiovascular magnetic resonance; LAD, left anterior descending; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist.

laboratory, the total number of pigs to undergo MI induction was calculated as 28.

Induction of myocardial infarction

The MI was induced through a percutaneous approach using the femoral arterial access, under full anesthesia (see the following). The pigs received a 5000-IU unfractionated heparin dose. After selective catheterization of the LAD artery and positioning of an angioplasty guide (0.014″ Balance Middleweight guide wire; Abbott Laboratories, Illinois, USA) in the distal segment of the LAD artery, an angioplasty balloon (Maverick monorail angioplasty balloon; Boston Scientific Scimed, Maple Grove, Minnesota, USA) was inflated just after the origin of the first diagonal artery, completely occluding the LAD. After 90 min, the balloon was deflated and a coronary angiography was performed to check vessel patency and establish the Thrombolysis In Myocardial Infarction grade, from 0 (no perfusion) to 3 (normal flow, which fills the distal coronary bed completely).

Anesthesia protocols

Pigs did not eat solid food for 12 h before MI induction. Pigs received intramuscular ketamine (15 mg/kg) and diazepam (0.4 mg/kg). After 10 min, anesthesia was induced by intravenous propofol 1% (3 mg/kg). Pigs were then intubated with endotracheal tubes. Maintenance anesthesia was achieved through sevoflurane with an end-tidal concentration of 1.8–2%. Pigs were connected to a ventilatory circuit with an initial fresh gas flow (FGF) of 3 l/min. Intra-operatory analgesia was achieved through an association of intravenous ketorolac/tramadol (1 and 2 mg/kg, respectively) at the beginning of the procedure, followed by a continuous infusion of remifentanil (0.15–0.18 μg/kg/h). Before coronary occlusion, a bolus of 1 mg/kg of lidocaine 2% was given. To achieve postoperative analgesia, intramuscular buprenorphine at a dose of 10 μg/kg/12 h for 1 day and a transdermic patch of fentanyl (25 μg/h) was applied.

Before the CMR scan, pigs received intramuscular ketamine (15 mg/kg) and diazepam (0.4 mg/kg). After 10 min, anesthesia induction was performed by intravenous propofol 1% (3 mg/kg). Maintenance anesthesia was achieved through continuous propofol infusion at the rate of 8–12 mg/kg/h. Pigs were mechanically ventilated with 100% oxygen.

Therapies

After the MI procedure, all pigs were given a loading dose of aspirin (250 mg intravenously), followed by a maintenance dose (100 mg orally daily) for the entire study duration. From the day after MI induction, all pigs received therapy with an angiotensin-converting enzyme inhibitor, a beta blocker and a mineralocorticoid receptor antagonist (MRA). The drugs were given orally by mixing powders with chow, with the following doses: captopril, 0.8 mg/kg daily[12]; bisoprolol, starting dose 0.125 mg/kg, increased by 0.125 mg/kg daily for the following 3 days until reaching a maintenance dose of 0.5 mg/kg daily[13]; spironolactone: 0.8 mg/kg daily.[14] Colchicine was administered orally at a dose of 0.025 mg/kg every 12 h, starting from the first postoperative day. In the absence of data from the literature, the daily dose (0.050 mg/kg) was chosen as half the toxic dose in humans (0.1 mg/kg).[15]

Cardiac remodeling was evaluated over 30 days, in agreement with previous studies.[16,17] Pigs were euthanized on the 31st day after the procedure.

Cardiac magnetic resonance

The CMR scans at 72 h and 30 days were performed on a 1.5 T machine (Intera 1.5 T, Philips Medical Systems, The Netherlands). All images were acquired through algorithms for ECG gating. The examinations were performed and interpreted by experienced operators in a blinded fashion. LV ejection fraction (LVEF), LV mass, LV end-diastolic and end-systolic volumes indexed for body surface area were calculated through specific software for image analysis (IntelliSpace Portal, Philips Medical Systems, Best, The Netherlands). Myocardial edema was assessed at 72 h only through T2-weighed, triple inversion recovery fast spin-echo sequences. Infarct size was computed from short-axis images acquired 5–15 min after the injection of 0.2 mmol/kg of a gadolinium-based contrast agent (Gadobutrol Gadovist 1.1 mmol/l, Bayer Schering Pharma AG) using a breath-hold 3D gradient-echo inversion-recovery sequence. Central dark zones within the area of hyperenhancement were included in the calculations. MSI is an index of the efficacy of coronary revascularization. Myocardial salvage (MS) was quantified by the difference between the area at risk (zone of myocardial edema at 72 h) and final infarct size (LGE area at 30 days), and MSI was calculated as the percentage of myocardial salvage over the area at risk.[18]

Tissue sampling and histological analyses

Animals were euthanized on day 31 through a pentobarbital sodium overdose (200 mg/kg, intravenously; Dolethal, Vetoquinol E.V.S.A). After mid-sternotomy, excised hearts were washed in saline-buffered solution to remove any residual blood, then sliced transversely into three 1–1.5 cm sections from artery ligation to the apex. Tissue transverse samples of about 5 mm were obtained from both the infarct zone (i.e. scar area in the anterior LV free wall) and from the remote zone (posterior LV free wall) of each section. The specimens were fixed in 10% buffered formalin and embedded in paraffin, or snap-frozen in OCT for histological and immunofluorescence evaluations, respectively.

The histological analysis was performed by experienced operators (D.M.F. and C.G.M.) blinded to treatment allocation. Masson's trichrome, Picrosirius red and lectin stainings were performed on 3 μm-thick paraffin sections. The extent of fibrosis was evaluated on eight samples from the infarct zone in the basal and mid-cavity segments of the LV, stained with Masson's trichrome. The extent of fibrosis (expressed as percentage of fibrosis area on the total section area) was quantified through the Image J software, and the average extent from the eight samples was calculated. In all samples, the presence of collagen types I and III was analyzed in four random fields on an adjacent section stained with Picrosirius red, viewed under polarized light in a DMI6000B microscope (Leica, Wetzlar, Germany), and quantified using Image-Pro Plus software (6.2.1 version; Media Cybernetics, Inc., Rockville, USA).

Statistical analysis

Normal distribution was checked through the Shapiro–Wilk test. All continuous variables were nonnormally distributed and were then expressed as median and interquartile range. The Wilcoxon signed-rank test was used to compare CMR findings at 72 h and 30 days within the same group. Comparisons between groups were performed through the Mann–Whitney *U* test. Statistical analysis was performed using IBM SPSS Statistics (version 22, 2013).

Results

Fourteen pigs were randomized to the colchicine group and 13 to the standard therapy group. The percentages of male animals (57 vs. 46%, respectively) did not differ significantly ($P = 0.577$). All pigs underwent coronary occlusion and reperfusion; in all cases, a normal antegrade epicardial flow was observed following reperfusion [Thrombolysis In Myocardial Infarction grade 3 (TIMI-3)]. The area of ischemia (either irreversible or reversible) was quite large, with median LGE areas at 72 h corresponding to about 20% of the LV mass. Still, all animals survived and repeated the CMR at 30 days. LGE extent decreased from 72 h to 30 days in both groups, following edema resolution. Final LGE mass tended to be lower in pigs on colchicine (Table 1). There was also a trend toward a higher MSI in pigs in the colchicine group [39.1% (31.3–68.8) vs. 29.3% (9.4–41.6); $P = 0.054$] (Fig. 2).

In the hearts explanted at day 31, pigs in the colchicine group had less fibrosis in the infarct zone than the other animals [41.6% (20.4–51.0) vs. 57.4% (42.9–66.5); $P = 0.022$] (Fig. 2). Furthermore, pigs in the colchicine group had less collagen type I in the infarct zone and a lower ratio between collagen types I and III. Conversely, the amount of collagen type III in the infarct zone and of collagen types I and III in the remote myocardium did not differ significantly (Table 2).

On the 72-h scan, pigs in both groups had LV systolic dysfunction, with a median LVEF of 29% (23–32) in the colchicine plus standard therapy group vs. 30% (23–33) in the standard therapy group. LVEF remained depressed at 30 days [31% (25–34) vs. 25% (22–31), respectively]. LV volumes, EF and mass did not differ significantly between the two groups at 72 h and 30 days, with just a trend toward lower LV end-systolic volume index (LVESVi) and higher LVEF in the colchicine group at 30 days (Table 3). LV end-diastolic volume index (LVEDVi) increased significantly in both treatment groups (Table 3), and both absolute and percentage changes in LVEDVi did not change significantly between groups ($P = 0.720$ and 0.830, respectively). LV mass index (LVMI) increased significantly only in pigs on standard therapy (Table 3).

Colchicine therapy was well tolerated, with no report of gastrointestinal disturbances.

Discussion

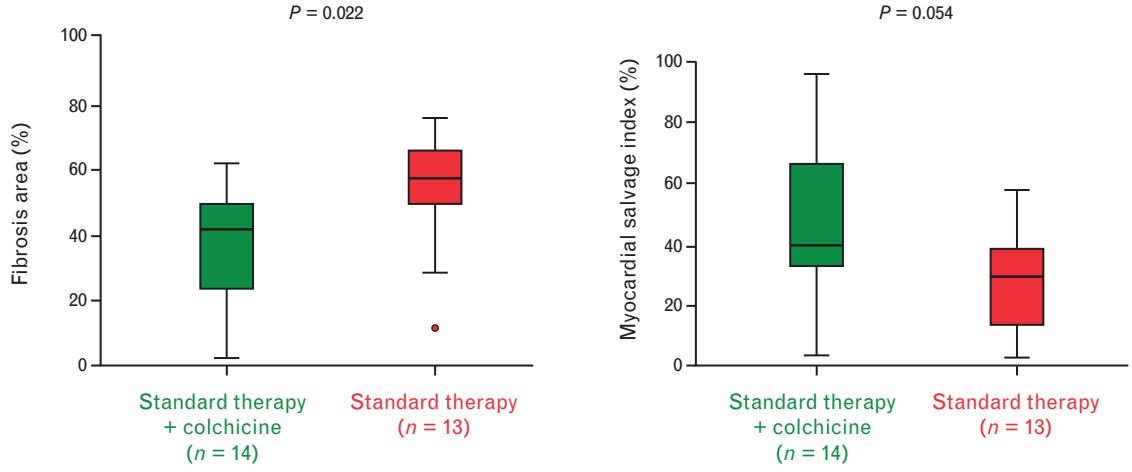
We evaluated for the first time the efficacy of colchicine in a pig model of reperfused MI. Importantly, colchicine was investigated on top of standard therapy for MI, including an MRA. Percutaneous occlusion of the LAD for 90 min produced a large area of LV ischemia, with LGE extent at 72 h (including both necrotic and still reversibly injured myocardium) spanning for about one-fifth of the LV; LGE extent was also similar in the two groups. Pigs displayed

Table 1 Cardiovascular magnetic resonance-based tissue characterization

	72 h CMR			30-day CMR		*P* (30-day vs. 72 h CMR)	
	Edema (g)	LGE mass (g)	LGE mass (% of LV mass)	LGE mass (g)	LGE mass (% of LV mass)	LGE mass (g)	LGE mass (% of LV mass)
Standard therapy plus colchicine	12.0 (10.8–15.5)	15.2 (13.3–18.0)	18.8 (16.1–24.6)	8.6 (6.0–11.4)	10.3 (5.9–12.0)	**0.001**	**0.001**
Standard therapy	15.0 (12.0–19.0)	18.0 (15.7–19.7)	23.4 (17.6–25.8)	9.7 (8.7–11.6)	11.3 (8.8–13.5)	**0.001**	**0.001**
P (same time points)	0.159	0.094	0.302	0.076	0.202		

The amount of edema was visually evaluated on T2-weighted short-axis acquisitions at 72 h. LGE extent was compared at the same time points (72 h and 30 days) between the two groups, and between the 30-day and 72-h scans in each group. CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular. Significant *P* values are highlighted in bold.

Fig. 2



Effects of colchicine on the area of fibrosis (left) and myocardial salvage index (right).

also a severe systolic dysfunction, with median LVEF of about 30% in both groups (i.e. about half of reference values of 59 ± 8%).[19] All the pigs survived during the entire follow-up period despite the extensive MI. We report that pigs receiving colchicine for 1 month tended to have a greater MSI (i.e. a better recovery from ischemic injury, without progression to myocardial necrosis). In the infarcted area, pigs on colchicine had also less fibrosis as well as less collagen type I, which forms thick, stiff and long fibrils that drastically reduce tissue compliance.[20] The positive effects on scar development and composition are reasonably due to the blunting of tissue inflammation by colchicine, particularly during the acute and subacute phases of MI. These effects did not translate into different patterns of LV remodeling. Nonetheless, changes from 72 h to 30 days were quite limited, with a slight LV dilation and no further decline in LVEF.

After an MI, an important inflammatory response starts in the minutes after reperfusion and peaks in the first days after reperfusion.[5,21,22] Inflammatory cells such as neutrophils, followed by monocytes and macrophages, rapidly infiltrate the injured myocardium with abundant proinflammatory cytokine secretions that may cause additional damage to the myocardium.[21] These inflammatory processes have been identified as key mediators of reperfusion injury in ST-segment–elevation MI (STEMI).[22] The anti-inflammatory approaches tested to reduce this acute inflammatory injury have yielded disappointing results, except for the finding that colchicine therapy reduces the incidence of cardiovascular events over a median of 19.5 months in patients with a recent MI.[8] Based on these findings, the Food and Drugs Administration has recently approved colchicine as the first anti-inflammatory agent reducing the risk of cardiovascular events in patients with established atherosclerotic cardiovascular disease (https://us.agephapharma.com/blog/2023/06/20/us-fda-approves-first-anti-inflammatory-drug-for-cardiovascular-disease/). Importantly, the end point included many elements (such as recurrent MI or stroke) that may reflect the stabilization of atherosclerotic plaques, rather than positive effects on the infarct scar or the remote myocardium; this would be in agreement with the prognostic benefit of colchicine in patients with chronic coronary syndrome (https://us.agephapharma.com/blog/2023/06/20/us-fda-approves-first-anti-inflammatory-drug-for-cardiovascular-disease/). The evolution of scar size and LV remodeling in patients receiving colchicine vs. placebo were not specifically investigated in COLCOT.[8]

A pilot study was designed to assess the efficacy of colchicine treatment in reducing infarct size among

Table 2 Collagen types in the infarct zone and remote myocardium

		Colchicine plus standard therapy	Standard therapy alone	*P*
Infarct zone	Collagen type I (%)	1.07 (0.38–2.32)	2.43 (1.46–3.27)	**0.043**
	Collagen type III (%)	10.39 (7.26–13.38)	12.31 (10.56–13.74)	0.076
	Type I–III ratio	0.10 (0.06–0.09)	0.19 (0.11–0.24)	**0.022**
Remote myocardium	Collagen type I (%)	0.07 (0.06–0.09)	0.06 (0.05–0.10)	0.841
	Collagen type III (%)	0.15 (0.13–0.20)	0.08 (0.04–0.17)	0.076

Table 3 Left ventricular volumes, ejection fraction and mass

	72 h CMR				30-day CMR				30-day vs. 72-h CMR			
	LVEDVi (ml/m²)	LVESVi (ml/m²)	LVEF (%)	LVMI (g/m²)	LVEDVi (ml/m²)	LVESVi (ml/m²)	LVEF (%)	LVMI (g/m²)	*P* LVEDVi	*P* LVESVi	*P* LVEF	*P* LVMI
Colchicine + standard therapy	83.7 (67.9–89.5)	59.2 (46.2–68.0)	29 (23–32)	88.6 (84.7–98.5)	97.6 (73.9–107.8)	70.3 (49.7–78.0)	31 (25–34)	92.0 (85.3–101.3)	**0.022**	0.084	0.254	0.875
Standard therapy	81.4 (67.0–99.2)	58.2 (43.5–76.2)	30 (23–33)	88.1 (83.7–107.9)	102.7 (87.0–103.6)	81.5 (65.9–92.1)	25 (22–31)	95.5 (82.6–103.6)	**0.005**	0.064	0.674	**0.011**
P (same time points, between-group differences)	0.458	0.402	0.583	0.259	0.220	0.085	0.076	0.867				

CMR, cardiovascular magnetic resonance; LVEDVi, left ventricular end-diastolic volume index; LVEF, LV ejection fraction; LVESVi, LV end-systolic volume index; LVMI, LV mass index.

patients with STEMI undergoing primary percutaneous intervention.[23] Colchicine was administered at a starting dose of 2 mg and continuing with 0.5 mg twice daily for 5 days. The study reported up to a 50% reduction in the infarct size, assessed through both cardiac biomarkers release and imaging parameters. Although CMR with LGE was only collected in a subset of participants, the infarct size indexed for body surface area was 18.3 vs. 23.2 ml/1.73 m^2 ($P = 0.019$) in the colchicine and placebo arms, respectively.[23] The COVERT-MI trial focused instead on the effects of colchicine therapy on the heart, and did not find any significant difference in infarct size at 5 days or 3 months, or LV remodeling over 3 months.[9] In this trial, colchicine was given with an oral bolus of 2 mg followed by 0.5 mg twice daily during 5 days. In our study, colchicine was given starting from the day after MI induction, that is, from 20 to 24 h later. Inflammation was then modulated following the very acute phase of MI, but when the inflammatory response was still intense and before the start of the anti-inflammatory reparative phase (days 4–7), which is characterized by the suppression, resolution and containment of the initial pro-inflammatory response.[24] We opted for colchicine administration for 1 month based on the positive results of long-term colchicine therapy in COLCOT[8] and the hypothesis that modulating the persistent or chronic inflammatory response to MI may provide therapeutic targets for preventing adverse LV remodeling following MI.[24] However, despite the longer duration of colchicine therapy compared with the COVERT-MI trial,[9] our results align with those of previous studies showing no significant differences in terms of LV mass with LGE at both 72 h and 30 days.

The evaluation of the modifications in inflammatory biomarkers following colchicine therapy in ACS is beyond the scope of this study but is another possible topic for future research. The On-admission Low-dose Colchicine in Addition to Atorvastatin to Reduce Inflammation in Acute Coronary Syndrome (COLOR-ACS) trial has been planned to assess the safety and efficacy of short-term colchicine (1 mg of loading dose continued by 0.5 mg daily until discharge) combined with atorvastatin (80 mg) among patients with non-STEMI after 30 days. Based on previous evidence, patients receiving colchicine are expected to manifest reduced levels of inflammatory biomarkers (e.g. C-reactive protein).[25] Another point of main interest includes the safety and tolerability of colchicine.[26] Several studies demonstrated an increased incidence of gastrointestinal symptoms (e.g. diarrhea, nausea, abdominal pain) and myalgias in patients treated with colchicine.[27] However, gastrointestinal adverse events may be prevented at lower doses (0.5 mg/die) of the drug.[28]

Several limitations must be acknowledged to this hypothesis-generating study. First and foremost, the colchicine

dose regimen was chosen arbitrarily and was quite high (in terms of dose per weight) for human patients. For example, for a 70-kg man, it would have been 3.5 mg/die that is seven times the dose adopted in humans in the COLCOT trial.[8] On the other hand, tissue effects of colchicine depend on the dose administered, intestinal absorption and the drug half-life in pigs. The lack of gastrointestinal toxicity tends to exclude that circulating colchicine levels were very high. Unfortunately, colchicine pharmacodynamics were not investigated. Furthermore, pigs did not receive dual antiplatelet therapy, which is a standard treatment in human patients with MI, and colchicine was not evaluated on top of statin therapy, which could have had a critical impact on the inflammation burden and colchicine's effects. These differences in the treatment regimen between the animal model and clinical practice could potentially limit the generalizability of the findings. Additionally, the MI size was possibly too large to represent what is usually seen in clinical practice. Inflammatory infiltrates were expected to be very limited after 1 month from the MI, regardless of treatment but were not specifically investigated. The CMR scan did not include acquisitions for strain analysis or cardiac tagging, which would have enabled a more granular assessment of global and regional systolic function of the LV. Finally, we did not evaluate the impact of colchicine therapy on the arrhythmic burden through a wearable or implantable ECG monitoring device, although the positive effects of colchicine therapy on the infarct scar could translate into a lower burden of ventricular arrhythmias.

In summary, colchicine treatment for 1 month in a pig model of reperfused STEMI has additive effects to standard therapy in reducing myocardial fibrosis in the infarcted myocardium, while it does not have a beneficial effect on LV remodeling.

Conflicts of interest

There are no conflicts of interest.

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