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# Colchicine to prevent sympathetic denervation after acute myocardial infarction: the COLD-MI trial

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**Keywords:**

Colchicine; Heart rate variability; Myocardial infarction; Nuclear imaging; Sympathetic innervation.

# Introduction

Colchicine demonstrated to reduce neutrophil migration, myocardial necrosis,<sup>1</sup> and myocardial denervation in the remote area in mice.<sup>2</sup> In patients, colchicine reduced major cardiovascular events following acute myocardial infarction (AMI) in the Colchicine Cardiovascular Outcomes Trial (COLCOT),<sup>3</sup> especially strokes. Sympathetic innervation is well-established to be particularly frail in cardiac tissue. The aim of this study was to explore the impact of colchicine on myocardial denervation following reperfused AMI patients by assessing the loss of presynaptic adrenaline reuptake function using 123I-metaiodobenzylguanidine single-photon emission computed tomography (123I-MIBG SPECT) imaging.

## Methods

The protocol has been described in detail elsewhere<sup>4</sup>.

The COLD-MI trial was a single-centre, open-label, randomized controlled trial.

Adult patients presenting a first episode of chest pain lasting <12 h and with a diagnosis of ST-elevation myocardial infarction (STEMI) and coronary occlusion on initial angiography were prospectively and consecutively included and randomized to receive either 1 mg colchicine tablets, one per day for 30 days, initiated within 48 h after revascularization or not (1:1 allocation ratio) for 30 days. Follow-up visit was performed at 1 and 6 months after randomization. The trial medication was provided by the in-hospital pharmacy (*Figure 1*).

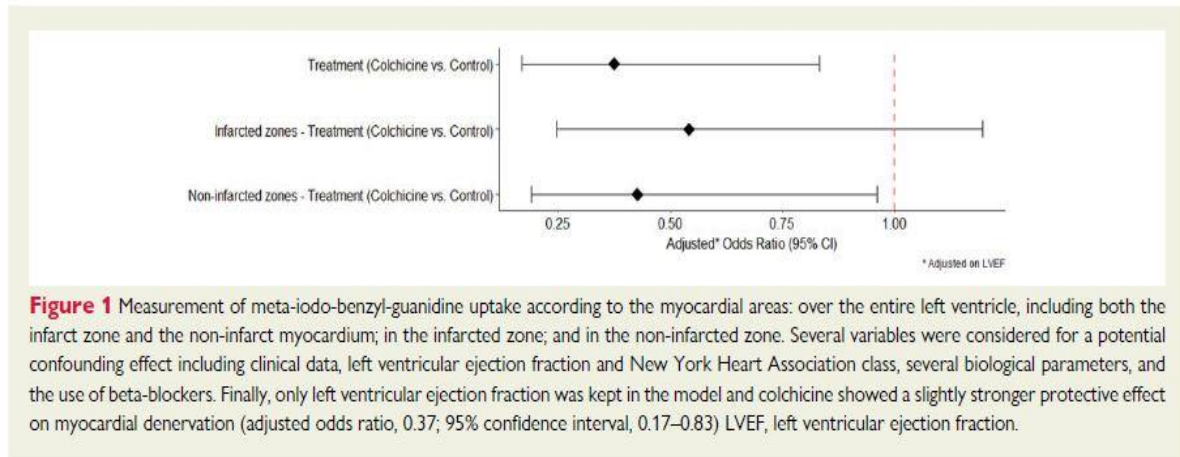
Specific exclusion criteria were as follows:

- any history of myocardial infarction prior to the current episode;
- known contraindication to colchicine (hepatic or renal dysfunction, allergy, co-treatments including macrolides, major digestive disorders, bone marrow aplasia, active chronic inflammatory disease, chronic active infection, cancer, infection, chronic treatments with corticosteroids or non-steroidal anti-inflammatory drugs);
- chronic treatment with colchicine (mainly familial Mediterranean fever).

The primary endpoint was the percentage of myocardial denervation measured by 123I-MIBG SPECT at 6-month follow-up. Secondary endpoints included clinical (e.g. survival, revascularization), imaging (e.g. H/M ratio in planar 123I-MIBG imaging, left ventricular (LV) ejection fraction (EF) on transthoracic echocardiography), and rhythmic [e.g. electrocardiographic parameters, heart rate variability (HRV) analysis, arrhythmias] parameters.

At the 1-month follow-up visit, empty blisters were retrieved to assess patient compliance.

Scintigraphic acquisitions were performed 6 months after randomization. Patients were initially admitted to the nuclear medicine department for a rest myocardial perfusion gated SPECT/CT performed 15 min after intravenous administration of 3.7 MBq/kg of  $^{99m}\text{Tc}$ -tetrofosmin. After an average of 8 days, the patients returned to the nuclear medicine department to receive 400 mg of potassium perchlorate *per os* 1 h before intravenous administration of 185 MBq of  $^{123}\text{I}$ -MIBG. Rest  $^{123}\text{I}$ -MIBG SPECT and planar acquisitions were performed 4 h after administration of the radiotracer.



Scintigraphic data were analysed blinded to the trial arm. The physician in charge of the SPECT interpretation was not aware of the inclusion group and did not meet the patient during the exam. Attenuation corrected rest  $^{99m}\text{Tc}$ -tetrofosmin and  $^{123}\text{I}$ -MIBG bull's eye images were divided into 17 segmental regions. In each segment, resting perfusion or sympathetic innervation is classically quantified (as a percentage) by the ratio between the mean segmental activity (MSA) measured in a segment and the maximum activity measured in the left myocardium (MSA%). Thus, the percentage of necrotic myocardial surface area is estimated by multiplying the number of segments whose MSA% is  $<50\%$  by the mean percentage of myocardial surface area occupied by a segment ( $100/17$ ).

Similarly, the percentage of myocardial surface area denervated is estimated by multiplying the number of segments whose normalized  $\text{MSA}_n\% < 50\%$  by the average percentage of myocardial surface area occupied by a segment. The normalized  $\text{MSA}_n\%$  is calculated by multiplying the MSA% in the  $^{123}\text{I}$ -MIBG bull's eye image by a normalization factor that takes into account the global ventricular uptake of MIBG (H/M ratio).

The protocol was previously described in detail elsewhere.<sup>4</sup> Primary and secondary endpoints were analysed using a modified intention-to-treat approach using complete case analysis. Primary outcome values were compared between arms using a Wilcoxon test, and a multivariate beta regression<sup>5</sup> to adjust for potential confounding effects due to baseline imbalances of participant characteristics between arms. Complementary separate analyses of myocardial denervation in infarcted and non-infarcted zones were performed. More details are available upon reasonable request. Statistical analyses were performed using SAS® 9.4.

# Results

## Study population

Sixty-five patients were screened between December 2020 and September 2021 and 54 patients were enrolled and randomized (27 in each group). Finally, 46 patients with available primary outcome measures were analysed, 25 patients in the colchicine group, and 21 patients in the control group. Briefly, 76% were men, and the mean age was  $58 \pm 9$  years. Six (20%) patients had diabetes mellitus in the colchicine group vs. 1 (4.8%) patient in the control group. The mean ratio of pills really taken by the patients was  $91.91 (\pm 20.66)$  %, evaluated by blister count.

## Impact of colchicine on myocardial denervation after acute myocardial infarction

Myocardial denervation was lower in the colchicine group [median (interquartile range) 59 (29–100) %LV] than in the control group [100 (88–100) %LV]. Unadjusted analysis showed a strong protective effect of colchicine on myocardial denervation [odds ratio (OR), 95% confidence interval (CI) 0.42 (0.19–0.94)].

Colchicine showed a protective effect on myocardial denervation in non-infarcted zones [adjusted OR (95% CI) 0.43 (0.19–0.96)] and tended to have an effect on myocardial denervation in the infarcted zone [adjusted OR (95% CI) 0.54 (0.24–1.20)].

## Secondary outcomes

### Other scintigraphic parameters

H/M ratio was significantly improved in the colchicine group compared with the control group ( $1.55 \pm 0.12$  vs.  $1.46 \pm 0.18$ ,  $P = .04$ ). There was no significant difference in the size of the necrosis ( $P = .22$ ) or LVEF evaluated on SPECT ( $P = .94$ ).

### Other parameters

Electrocardiographic parameters, HRV analysis, and clinical outcomes were not significantly modified by colchicine in our patients. There were no sustained arrhythmias during follow-up. Gastrointestinal side effects were reported in 51.8% of the patients in the colchicine group and 18.5% of the patients in the control group ( $P = .01$ ).

# Discussion

To our knowledge, this is the first study to demonstrate a positive effect of colchicine to reduce cardiac denervation (particularly in the remote areas) in patients after AMI.

This project translates from preclinical study to bedside. Our group already demonstrated that colchicine improved HRV and reduced cardiac sympathetic denervation in the remote areas in a mice model of ischemia-reperfusion.<sup>2</sup>

Meta-iodo-benzyl-guanidine capitation in SPECT reflects the alteration of presynaptic adrenaline reuptake function. It is therefore not denervation in the anatomical sense, but rather a deterioration in one of the functions of myocardial sympathetic neurons induced by an acute ischaemic episode. This is why some patients had 100% denervation in our trial. As a complement, it is common to measure the H/M ratio close to unity on MIBG scintigraphy in patients with heart failure or after an acute coronary syndrome, reflecting a more or less complete absence of MIBG reuptake by myocardial sympathetic neurons.

Here however, a significant increase in gastrointestinal side effects was observed. It might be partly explained by the open-label design but also the higher dose (1 vs. 0.5 mg/day) and the administration within 48 h after AMI (within 30 days after AMI in the COLCOT trial). We failed to demonstrate any effect of colchicine on LVEF or infarct size. This is consistent with the results from the Colchicine for Left Ventricular Remodelling Treatment in Acute Myocardial Infarction trial.<sup>6</sup>

Colchicine is therefore gradually finding its place in the therapeutic arsenal for coronary artery disease, with new light shed on the pathophysiological mechanisms involved in its beneficial effect.

## Declarations

### Disclosure of Interest

Nothing to declare.

### Data Availability

Data will be available upon reasonable request.

### Funding

This work is supported by the Montpellier University Hospital, France.

### Ethical Approval

The protocol was approved by the Ile De France VI Ethics Committee and the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).

## Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT04420624.

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