Adverse left ventricular remodelling after acute myocardial infarction: is there a simple treatment that really works?

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This editorial refers to ‘Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: the TIPTOP trial’, by G. Cesarino et al., on page 184

Acute myocardial infarction (AMI), with its accompanying adverse sequelae, remains one of the most common causes of morbidity and mortality in the world. Following AMI and secondary to the loss of functional myocardium, the heart undergoes adaptive responses in an attempt to maintain the same cardiac output. The physical changes to the heart that occur as a result of these responses is termed remodelling. This remodelling begins immediately after AMI and may continue for a lifetime. While this adaptive remodelling may be beneficial in the short term, over time it becomes deleterious, leading eventually to congestive heart failure.

The physiology of remodelling includes infarct expansion, chamber dilatation, ventricular hypertrophy, scar formation, neurohormonal responses, cytokine activation, and oxidative stress (Figure 1). The basic cellular mechanisms behind these changes include cardiomyocyte hypertrophy and death, inflammation, alterations of collagen matrix, and microvascular rarefaction. To overcome the adverse effects of post-infarct remodelling, scientists have attempted to use an understanding of the basic physiology to develop effective targeted pharmacological treatments for its prevention. Many of these proposed treatments, including adenosine, nicorandil, nitroprusside, and atrial natriuretic peptide and statins, have been administered simultaneously with reperfusion therapy. Others, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone inhibitors, renin inhibitors, nicorandil, beta-blockers, and statins, have been administered chronically with the intent to affect the chronic phase of left ventricular remodelling positively. Attempts have also been made to overcome or reverse some of the adverse effects of long-term post-infarct remodelling by growing new viable functional myocardium through various forms of stem cell transfer. However, despite many large randomized clinical trials, only modest benefits have thus far been identified with any of these proposed therapies, even though often expensive and long-term treatment strategies were required.

In the results of the ‘Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: the TIPTOP trial’, Cerisano et al. have proposed a short-term, inexpensive, easily administered, potentially very safe and effective, adjunctive therapy for the prevention of post-infarct adverse left ventricular remodelling: doxycycline. Their proposal to use doxycycline came from an understanding of one of the important early mechanisms of remodelling: extracellular collagen matrix damage which is often triggered by the post-infarct inflammatory activation of matrix metalloproteinases (MMPs). For example, increased MMP-2 levels have been implicated in post-infarct remodelling as well as ischaemia–reperfusion injury. Indeed, in addition to its participation in extracellular matrix remodelling, enhanced MMP-2 activity has been associated with direct cardiac dysfunction which possibly results from proteolytic degradation of intracardiomycocyte targets, including troponin I and myosin light chain-1. Doxycycline, an antibiotic long used for the treatment of all kinds of infectious diseases, also has well documented inhibitory effects on a variety of MMPs. It also has an excellent safety profile and is inexpensive.

To begin the investigation of doxycycline for the prevention of post-infarct remodelling, the investigators chose a high risk study population, patients with recent ST-segment elevation myocardial infarction (STEMI) and significant left ventricular dysfunction, thus guaranteeing a high rate of left ventricular remodelling during 6 months of follow-up. The doxycycline dosing regimen chosen (100 mg orally every 12 h for 7 days) was well within usual standards for antibiotic dosing, and was adequate to provide optimal MMP inhibition, which is often possible even with sub-antibiotic doxycycline dosage levels.

The primary endpoint of the study was the percentage change from baseline to 6 months in the echocardiographic left ventricular end-diastolic volume index (LVEDVi). In order to isolate the impact of doxycycline to an effect on left ventricular remodelling,
rather than vessel patency, they limited enrolment to only those patients with successful primary reperfusion. They also documented continued infarct-related coronary arterial patency by performing 6-month follow-up coronary arteriography on as many patients as possible (85%). Additionally, in order to verify the independence of the treatment effect on left ventricular remodelling from final infarct size and severity, they performed 6-month SPECT (single photon emission computed tomography) imaging.

The 110 patient study reached a positive 6-month primary end-point with only a 0.4% increase in LVEDVi in the 55 patients assigned to doxycycline compared with a 13.4% increase in the control patients \((P = 0.012)\). Perhaps equally impressively, although not powered for clinical endpoints, at the end of 6 months, the study also reported a statistically significant 50% reduction in the composite of death, MI, congestive heart failure, and stroke, with the majority of the effect differential occurring with fatal and non-fatal heart failure. Although this impressive clinical result will require validation in large adequately powered placebo-controlled randomized clinical trials, the positive correlation between the results of changes in LVEDVi and clinical outcomes is certainly encouraging.

Although this study was well designed and executed, there are significant limitations that should be noted. For some reason, the trial was designed as an open label study. It seems it could have easily been placebo controlled. Even though the primary endpoint was evaluated by a blinded off-site independent Core Lab, the fact that the investigators caring for the patients knew which arm the patients were randomized to could have affected their care in a variety of ways that could have had an impact on the outcome. Additionally, in this small randomized trial, not all baseline characteristics were evenly matched. Specifically there were more women and diabetics in the control than in the treatment group. Whether these disparities may have adversely affected the outcome of the control arm is not known. Finally, besides its anti-inflammatory and MMP inhibitory properties, doxycycline is also a potent and effective antibiotic. Whether some of its positive effect on left ventricular remodelling occurred because of its antimicrobial action on a co-existing infectious agent, such as Chlamydia pneumoniae, is not known.

In conclusion, with so many sophisticated and costly attempts to minimize the adverse effects of post-infarct remodelling providing only limited benefit, is it possible that a simple, inexpensive, short-term course of doxycycline may really help? With these promising results reported from the TIPTOP trial, it certainly seems justifiable to find out through another large, randomized, double-blind, placebo-controlled treatment trial.

Conflict of interest: none declared.

References
Cardiogenic shock from acute ST-segment elevation myocardial infarction induced by severe multivessel coronary vasospasm

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A 43-year-old woman was brought to the emergency room after acute onset chest pain and dizziness developed while at rest. She developed excruciating chest pain followed by drop of systolic blood pressure to 67 mmHg. Cardiothoracic examination revealed bilateral diffuse moist rales. An 18-lead electrocardiogram showed ST-segment elevation in leads II, III, aVF, and V3R through V5. Initial assessment of the patient suggested the possibility of cardiogenic shock from right ventricular infarction complicating acute inferior myocardial infarction. Because of the profound haemodynamic instability, the patient was immediately transferred for cardiac catheterization. Urgent coronary angiography revealed diffuse and extensive stenoses of the left anterior descending artery and the left circumflex artery (Panels A and B, Supplementary material online, Videos S1 and S2), as well as severe and diffuse stenosis of the right coronary artery (Panel C, Supplementary material online, Video S3). An intra-aortic balloon pump was used to provide haemodynamic support.

After a 12-day hospital stay, repeat coronary angiography surprisingly revealed complete resolution of all stenoses (Panels D, E, and F, Supplementary material online, Videos S4, S5, and S6). After excluding pheochromocytoma, the patient was discharged home 4 days later on a regimen of nimodipine 30 mg three times daily, diltiazem 30 mg four times daily, and perindopril 2 mg once daily. A 4-month follow-up survey indicated that the patient had fully recovered.

This case highlights the importance of identifying possible vasospasm for a variety of clinical manifestations of acute coronary syndrome. The patient was originally diagnosed and treated for acute ST-segment elevation myocardial infarction based on clinical presentations and angiographic finding of severe coronary stenosis. Thus, excluding the possibility of vasospasm is mandatory for every angiographic coronary lesion regardless of the severity of stenosis, even if spasm is not clinically suspected.

Supplementary material is available at European Heart Journal online.

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