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Early changes of left ventricular filling pattern after reperfused ST-elevation myocardial infarction and doxycycline therapy: Insights from the *TIPTOP* trial☆

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ABSTRACT

Aim: Metalloproteinases inhibition by doxycycline reduces cardiac protein degradation at extracellular and intracellular level in the experimental model ischemia/reperfusion injury. Since both extracellular cardiac matrix and titin filaments inside the cardiomyocyte are responsible for the myocardial stiffness, we hypothesized that doxycycline could favorably act on left ventricular (LV) filling pressures in patients after reperfused acute ST-elevation myocardial infarction (STEMI).

Methods and results: Seventy-three of 110 patients of the TIPTOP trial underwent a 2D-Echo-Doppler on admission, and at pre-discharge and at 6-month after a primary PCI for STEMI and LV dysfunction. From admission to pre-discharge, LV filling changed from a high filling pressure (HFP) to a normal filling pressure (NFP) pattern in 91% of the doxycycline-group, and in 67% of the control-group. Conversely, 1% of the doxycycline-group, and 37% of the control-group changed the LV filling from NFP to HFP pattern. Overall, a pre-discharge HFP pattern was present in 4 patients (11%) of the doxycycline-group and in 13 patients (36%) of the control-group ($p = 0.025$). The evaluation of metalloproteinases and their tissue inhibitors plasma concentrations provide possible favorable action of doxycycline. On the multivariate analyses, troponine I peak ($p = 0.026$), doxycycline ($p = 0.033$), and on admission to pre-discharge LVEF changes ($p = 0.044$) were found to be associated with pre-discharge HFP pattern. Independently of their baseline LV filling behavior, the 6-month remodeling was less in patients with pre-discharge NFP pattern than in patients with HFP pattern.

Conclusions: In patients with STEMI and LV dysfunction doxycycline can favorably modulate the LV filling pattern early after primary PCI.

Doppler echocardiography has provided a rapid, feasible, and simple noninvasive method of assessing left ventricular (LV) filling in various cardiac diseases in which diastolic abnormalities have been observed [1]. In this context, a growing body of clinical evidence have indicated that the presence of echocardiographic indexes of elevated LV filling pressures, as a marker of LV diastolic dysfunction, predicts a poor prognosis early after acute myocardial infarction (AMI) [2], despite pharmacological [3] or mechanical reperfusion [4,5] and independently of systolic function [2]. Thus, a major unresolved question is how to optimally manage AMI patients having advanced LV diastolic dysfunction [6].

For the first time in the clinical setting, the TIPTOP (Early Short-term Doxycycline Therapy In Patients with Acute Myocardial Infarction and Left Ventricular Dysfunction to Prevent The Ominous Progression to Adverse Remodeling) trial [7] demonstrated that a timely, short-term therapy with doxycycline is safe and able to induce a significant decrease in LV dilation in patients successfully treated with primary percutaneous coronary intervention (pPCI) for a first ST-elevation AMI (STEMI) and LV dysfunction. Several pleiotropic properties of

Abbreviations: STEMI, ST-elevation myocardial infarction; MMPs, mealloproteinases; NFP, normal filling pressure; HFP, high filling pressure; *E*-wave, transmitral early peak velocity; A-wave, transmitral late peak velocity; DT, deceleration time of transmitral early peak velocity; E', early peak velocity on the septal side of the mitral annulus; Vp, left ventricular flow propagation velocity during early filling; LVEDVi, left ventricular end diastolic volume index; LVESVi, left ventricular end systolic volume index; LVEF, left ventricular ejection fraction; ECM, extracellular cardiac matrix; PCI, percutaneous coronary intervention.

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doxycycline [8] mainly related to its ability to act as a matrix metalloproteinases (MMPs) inhibitor at the level of extracellular collagen matrix (ECM) [9] could explain this favorable anti-remodeling effect observed in the experimental [10,11] and clinical [12] setting. Metalloproteinases activation can also occur intracellularly in heart subjected to ischemia/reperfusion (I/R), and it is responsible for the degradation of sarcomeric proteins including titin [13–15], thus contributing to cardiomyocytes injury under oxidative stress. Accordingly, MMPs inhibition by doxycycline prevents acute stunning in isolated rat-hearts subjected to I/R injury [13,14] and mimics the MMP-2 inhibition and infarct size reduction found with ischemic post-conditioning [16]. Since both ECM and titin filaments inside the cardiomyocyte are two important components responsible for the myocardial stiffness, it is possible to hypothesize that doxycycline, through its MMPs-inhibitor action, has a favorable effect on diastolic LV filling.

Thus, we set out to analyze the time course of changes in the LV filling pattern during the acute stage of STEMI treated with doxycycline in the TIPTOP trial.

1. Methods

1.1. Study design, patients and procedures

The TIPTOP study design has been already descripted in detail [7]. In brief, TIPTOP trial is a prospective, phase-2, single-centre, randomized, open-label controlled trial in which 110 patients older than 18 years with acute STEMI and LV ejection fraction (LVEF) < 40% were randomly assigned in a 1:1 ratio to receive doxycycline or standard care. All patients were treated with primary PCI, including stenting of the infarct-related artery (IRA), and received medical therapy for STEMI and LV dysfunction in accordance with standard and recommended practice. Doxycycline (Bassado; Pfizer Italia s.r.l.) was administered at 100 mg oral dose immediately after primary PCI and then every 12 h for 7 days. The antimicrobial dose we used ensures plasma levels of doxycycline similar to those obtained with higher doses used in the experimental model where the doxycycline has been proved effective in inhibiting MMPs and preventing abdominal aortic aneurysm [17] and post-infarction LV remodeling [10,11]. The pre-defined primary endpoint of the TIPTOP trial was the percent change from baseline to 6 months in echocardiographic LV end-diastolic volume index (LVEDVi). Thus, two-dimensional and Doppler echocardiographic examinations (2D-Echo-Doppler) at baseline (immediately after primary PCI) and at 6 months were performed. DICOM standardized images were recorded and stored on digital media, and sent to an independent, blinded, off-site core laboratory for analysis. The study plan also included: i) ^{99m}Tc-sestamibi-gated single-photon emission computed tomography (SPECT) to evaluate the final infarct size and severity at 6-month follow-up and ii) a coronary angiography at 6 months for the evaluation of IRA patency. Local ethical committee approved the study protocol, and informed written consent was obtained from the subjects. Doxycycline was provided directly from the local hospital, and the manufacturer had no role in the study.

For the present study we analyzed 73 of 110 patients of the TIPTOP trial, specifically those for which a 2D Echo-Doppler assessment including diastolic function was available also at pre-discharge (average 6 ± 3 days), a not pre-specified time-point of echocardiographic evaluation of the TIPTOP [7], as well as at baseline and six-month follow-up. Patients in the present sub-study had similar clinical characteristics to those included in the main trial (see Appendix A of the Supplementary Data). Both the main trial and the present sub-study were conducted in accordance with the Declaration of Helsinki.

1.2. Echocardiographic analyses

Two-D Echo-Doppler studies were performed with a commercially available imaging systems (Philips IE-33, Amsterdam, The Netherlands), and the following measurements were obtained according to established criteria [1,18]: i) LV volumes and ejection fraction, ii) peak of early (E) and late (A) transmitral velocities and *E*-wave deceleration time (DT), iii) peak of early (E′) septal mitral annulus velocities and iiii) LV flow propagation velocity during early filling (Vp). According to the protocol of the main study [7], LV dysfunction was defined as an LVEF <40%, as calculated by the on-site operator at the first echo examination in the coronary care unit immediately after primary PCI. Consistent with the current guidelines [1] on patients with LV systolic dysfunction (such as our patients), we defined a high filling pressure (HFP) pattern an E/A ratio ≥2, and a normal filling pressure (NFP) pattern an E/A ratio ≤0,8 and E < 50 cm/s, respectively. For patients that fall in between, HFP was confirmed in presence of an E/E′ ratio >15 [19] or an E/Vp ratio ≥2,5 [20].

1.3. Statistical analyses

Discrete data were summarized as frequencies, whereas continuous data were summarized as mean ± SD or median and interquartile range, when appropriate. Differences in baseline characteristics between the two study groups were analyzed using the x^2 test or Fisher's exact test for categorical variables, and the unpaired and paired, 2-tailed Student's *t*-test or Mann-Whitney test for continuous variables. Univariable and multivariable logistic regression analyses were performed to evaluate the independent contributions of pre-discharge HFP pattern. Over that baseline clinical and therapeutic variables, the changes from baseline to pre-discharge of LVEDVi, LVEF and pro-BNP release at pre-discharge were also tested in view of the possible interaction between the LV filling pattern and the concomitant LV remodeling process. The variables tested in the univariate model were listed in Table 2. For the significant variables on univariate analysis (*p*-value <0.05), multicollinearity was assessed using collinearity diagnostics. The variance inflation factors showed no significant collinearity among these covariates (<2.0). Variables with a *p*-value <0.05 at univariable model, were entered into the multivariable model. All tests were two-sided, and a *p*-value <0.05 was considered statistically significant. Analyses were performed with SPSS software, version 19 (IBM Corp, Somers, NY).

2. Results

2.1. Study patients

The baseline clinical, echocardiographic, angiographic/procedural and therapeutic characteristics, of the two study groups are shown in Table 1. There were no significant differences between the two study

Table 1
Baseline clinical and procedural characteristics of the two study groups.

	Doxycycline group (n.37)	Control group (n. 36)
Clinical findings		
Age, years	72 [62–79]	71 [60–75]
Male sex, (%)	70	72
BAS, (kg/m^2)	1,85 ± 0,2	1,82 ± 0,1
Heart rate, (b.p.m)	77 ± 16	79 ± 13
Systolic blood pressure, (mm Hg)	130 [110–150]	130 [111–150]
Diabetes, (%)	21	19
Dyslipidaemia, (%)	30	22
Hypertension, (%)	54	39
Symptoms to door time, (min)	145 [89–229]	137 [90–315]
Pro-BNP, (pg/mL)	575 [173–2195]	648 [175–3177]
Troponine I peak, (μg/ml)	196 ± 177	277 ± 192
Echo-color-Doppler findings		
E-wave peak, (cm/s)	64 ± 20	64 ± 19
A-wave peak, (cm/s)	81 ± 18	78 ± 21
EA ratio	0,8 ± 0,5	0,9 ± 0,4
DT, (ms)	194 ± 60	191 ± 52
Septal E′-wave peak, (cm/s)	7 ± 3	7 ± 2
Vp, (cm/s)	30 [25–42]	33 [21–48]
High filling pressures pattern, (%)	30	17
LVEDVi, (mL/m^2)	47 [41–57]	47 [40–61]
LVESVi, (mL/m^2)	31 [24–35]	31 [23–37]
LVEF, (%)	39 [32–44]	37 [33–43]
Angiographic and procedural findings		
Left anterior descending artery, (%)	94	89
IRA TIMI flow grade <2 pre-PCI, (%)	68	67
Multivessel disease, (%)	44	49
IRA stenting, (%)	100	100
Number of stents	1,3 ± 0,6	1,4 ± 0,6
Stent length, (mm)	20 [16–31]	20 [16–27]
IRA TIMI flow grade 3 post-PCI, (%)	100	100
Procedural time, (min)	27 [20–41]	28 [21–35]
Pharmacological therapy		
Aspirin, (%)	94	98
Thienopyridine, (%)	100	100
Abciximab, (%)	87	95
Statin, (%)	100	100
Beta-adrenergic blocker, (%)	94	83
ACE inhibitor/ARB antagonist, (%)	75	86
Mineral-receptor-antagonist, (%)	19	28
Loop diuretic, (%)	40	47

BAS denotes body surface area, BNP, brain natriuretic peptide, E-wave, peak early ventricular filling velocity, A-wave, peak late ventricular filling velocity, DT, deceleration time of early filling velocity, E′ early diastolic peak velocity on the septal side of the mitral annulus, Vp, flow propagation velocity during early filling, LVEDVI, left ventricular end diastolic volume index, LVESVi, left ventricular end systolic volume index, LVEF, left ventricular ejection fraction, IRA, infarct-related artery, TIMI, thrombolysis in myocardial infarction, ACE, angiotensin-converting-enzyme, ARB, angiotensin II receptor blockers. Values are expressed as mean ± SD, or median [IQ range] or number (%).

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