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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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groups, however it should be noted that in the doxycycline-group there was a greater incidence of hypertension, HFP pattern, left anterior descending (LAD) disease, and lower troponin I peak values.

2.2. Left ventricular filling pattern on admission and relationship with pro-Brian natriuretic peptide

The echo-Doppler mitral inflow velocities recorded on admission allowed to classify 19 patients as NFP pattern, and 2 patients as HFP pattern, respectively. For the remaining 52 patients with inconclusive mitral inflow velocities, the further assessment of E/E′ or E/Vp ratio allowed to reclassify 37 patients in the NFP group and 15 in the HFP group, respectively. The time course of plasma pro-brain natriuretic peptide (BNP) release was available in 82% of these patients. Of note, the patients in which E/E′ and E/Vp met the cutoff threshold for HFP showed higher values of baseline pro- BNP than their counterparts (2870 pg/mL ± 2833 vs. 1105 pg/mL ± 1505, $p = 0.01$) despite similar values of baseline LVEF (38% ± 7 vs. 39% ± 7, $p = 0{,}82$), and troponin I peak (263 μg/L ± 209 vs. 247 μg/L ± 188, $p = 0.94$), respectively.

2.3. Early changes in LV filling pattern, volumes and ejection fraction in the two study groups

Serial changes in LV filling pattern from baseline to pre-discharge in the two study groups are detailed in Fig. 1. From baseline to pre-discharge, the LV filling changed from HFP to NFP pattern in 91% of patients in the doxycycline-group, and in 67% of those in the control-group, respectively. Conversely, LV filling changed from NFP to HFP pattern in 11% of patients in the doxycycline-group, and in 37% of those in the control-group, respectively. Overall, a pre-discharge HFP pattern was present in 11% of patients in the doxycycline group and in 36% of patients in the control group, respectively ($p = 0.025$).

The modifications in LV filling pattern were accompanied by a significant increase in LV volumes in the control-group compared to the doxycycline-group (Δ LVEDVi: 10 ml/m^2 [from −1 to 15 ml/m^2] vs. 1 ml/m^2 [from −4 to 9 ml/m^2], $p = 0.014$; Δ LVESVi: 4 ml/m^2 [from −2 to 12 ml/m^2] vs. 0,4 ml/m^2 [from −4 to 6 ml/m^2], $p = 0.043$). The LVEF increased in the doxycycline-group while decreased in the control-group. This difference was not significant, however (3% [from −3 to 9%] vs. −1% [from −6 to 7%], $p = 0.183$).

2.4. Independent predictors of pre-discharge high filling pressure pattern

The univariate and multivariate regression analyses were performed to identify independent predictors of pre-discharge HFP pattern (Table 2). In addition to the baseline clinical, echocardiographic, angiographic, procedural, and therapeutic characteristics, we evaluated the peak of troponine I, as estimate of initial infarct size, and echocardiographic (LV volumes and LVEF changes from baseline to pre-discharge) and neurohormonal (pre-discharge plasma pro-BNP values) indexes which reflect a concomitant early LV remodeling process. The significant variables in the univariate analysis were entered in the multivariate model. The troponine I peak values ($p = 0.026$), doxycycline therapy ($p = 0.033$), and baseline to pre-discharge LVEF changes ($p = 0.044$) were found to be independently associated with pre-discharge HFP pattern.

2.5. Relationship between pre-discharge LV filling pressure pattern and 6-month echocardiographic findings

One patient in the control group with pre-discharge HFP died for heart failure in the first month after index myocardial infarction, and another patient refused to complete the echocardiographic follow-up. Thus the 6-month echocardiographic follow-up was available in 71 of 73 patients.

From baseline to 6 months, LV volumes decreased, and LVEF increased in patients with pre-discharge NFP pattern ($n = 56$) compared to their counterpart ($n = 17$), respectively (Δ LVEDVi: 0.5 ml/m^2 [from −5 to 9 ml/m^2] vs.7 ml/m^2 [from −17 to 14 ml/m^2], $p = 0.08$; Δ LVESVi: −4 ml/m^2 [from −11 to 1 ml/m^2] vs.1.5 ml/m^2 [from −7.5 to 12 ml/m^2], $p = 0.03$; Δ LVEF: 11% [from 5 to 19%] vs. 4% [from −4 to 12%], $p = 0.04$), (Fig. 2). Patients with pre-discharge NFP pattern

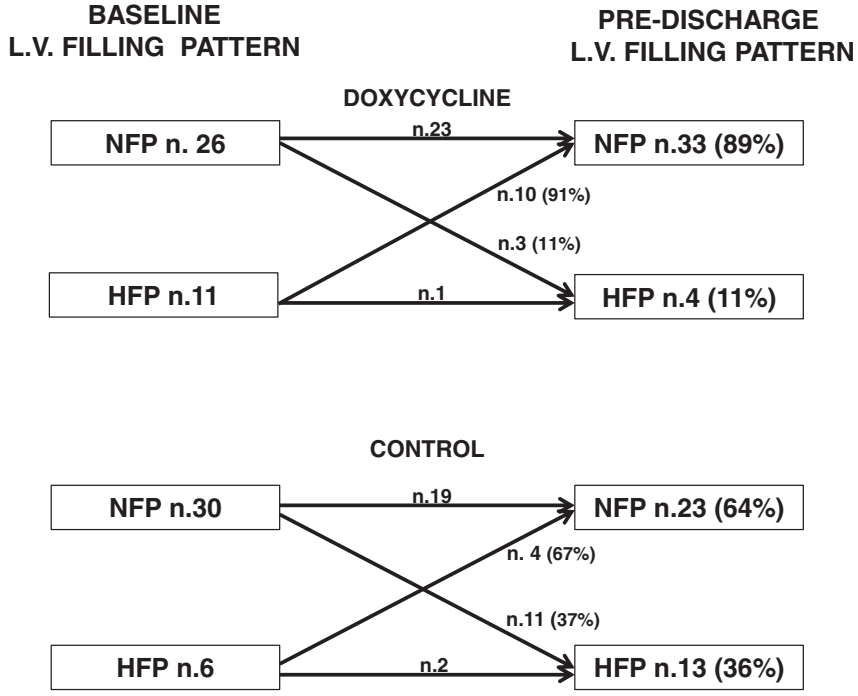

Fig. 1. Early changes in LV filling pattern in the two study groups. From baseline to pre-discharge, in the doxycycline-group was observed a more favorable modification of LV filling pattern compared to control-group. So that, a pre-discharge HFP was present in a significantly higher percentage of patients of control-group than doxycycline-group, respectively (36% vs. 11%, $p = 0.025$).

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Table 2
Independent predictors of high filling pressure at pre-discharge.

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
Baseline clinical findings	B	Exp(B)	95% CI	p	B	Exp(B)	95% CI	p
Age, years	0,04	1,04	0,989–1104	0.114				
Sex male, (%)	−1,42	2,42	0,077–0,763	0.015	−3.966	0,02	0,000–3318	0.132
BSA, (kg/m^2)	−5.01	0,01	0,000–0275	0.008	−1953	0,142	0,000–4434	0.712
Heart rate, (bpm)	0,00	1,00	0,968–1041	0.852				
Systolic blood pressure, (mm Hg)	0,00	1,00	0,980–1016	0.832				
Diabetes, (%)	−0.23	1,26	0,363–4619	0.729				
Dyslipidaemia, (%)	−1.17	0,84	0,237–2985	0.789				
Hypertension, (%)	−0.29	0,75	0,251–2256	0.611				
Total ischemic time, (min)	0,002	1002	0,999–1005	0.193				
Baseline echocardiographic findings								
Baseline LVEDVi, (mL/m^2)	−0.02	0,98	0,937–1029	0.445				
Baseline LVESVi, (mL/m^2)	−0.02	0,98	0,919–1036	0.423				
Baseline LVEF, (%)	0,00	1,00	0,924–1091	0.925				
Angiographic and procedural findings								
IRA TIMI flow grade <2 pre-PCI, (%)	−1,03	0,36	0,092–1390	0.138				
Multivessel disease, (%)	−0.02	0,98	0,478–1995	0.948				
Stent length, (mm)	−0.03	0,97	0,919–1030	0.347				
Procedural time, (min)	0,02	1,03	0,997–1054	0.087				
Pharmacological therapy								
Abciximab, (%)	−0.86	0,43	0,065–2779	0.371				
Beta-adrenergic blocker, (%)	−0.25	0,78	0,182–3300	0.735				
ACE inhibitor/ARB antagonist, (%)	−1.55	4,73	1282–17,44	0.023	0,542	1,72	0,064–46,19	0.747
Mineral-receptor-antagonist, (%)	1,17	3,22	0,986–10,515	0.053				
Loop diuretics, (%)	0,48	1,61	0,542–4806	0.390				
Doxycycline, (%)	−1.54	0,21	0,062–0,742	0.015	−5113	0,01	0,000–0,666	0.033
Enzymatic infarct size								
Troponine I peak, (μg/L)	0,01	1,01	1002–1008	0.000	0,009	1,01	1001–1017	0.026
Pre-discharge findings								
Pre-discharge pro-BNP, (pg/mL)	0,00	1,00	1000–1001	0.004	0,001	1,00	1000–1002	0.120
Baseline-pre-discharge LVEDVi changes, (mm)	0,06	1059	1000–1122	0.051	−0.092	0,912	0,741–1123	0.367
Baseline-pre-discharge LVEF changes, (mm)	−0.08	0,92	0,885–0,995	0.036	−0.255	0,775	0,604–0,994	0.044

Abbreviations as in Table 1.

also showed a lower, but not significant prevalence of 6 months HFP pattern compared to patients with pre-discharge HFP pattern (11% vs. 25%, $p = 0.217$).

Remarkably, the favorable remodeling that we observed in patients with pre-discharge NFP occurred regardless of the LV filling pattern present at baseline assessment. Indeed, the 14 patients with LV filling pattern changes from HFP to NFP from baseline to pre-discharge showed a similar 6-month evolutionary changes in LV volumes in comparison to the 42 patients with NFP pattern at baseline as well as at pre-discharge assessment (Δ LVEDVi: −3 ml/m^2 [from −12 to 8 ml/m^2] vs. 1 ml/m^2 [from −4 to 9 ml/m^2], $p = 0.10$; Δ LVESVi: −7 ml/m^2 [from −15 to 1 ml/m^2] vs. −3 ml/m^2 [from −10 to 1 ml/m^2], $p = 0.24$). The LVEF changes paralleled those of the LV volumes (Δ LVEF: 13% [from 3 to 17%] vs. 11% [from 5 to 19%], $p = 0.62$).

2.6. Relationship between plasma MMPs/TIMPs, therapy and LV filling pressure pattern

The baseline plasma MMPs/TIMPs were not different between the two treatment groups (see Appendix B of the Supplementary Data). However, several significant differences between the 2 study groups were found, according to the baseline echocardiographic pattern of LV filling pressures (see Appendix C of the Supplementary Data). Nominally, control-patients in HFP-pattern-group showed a significant increase in MMP-7/TIMP-3 at

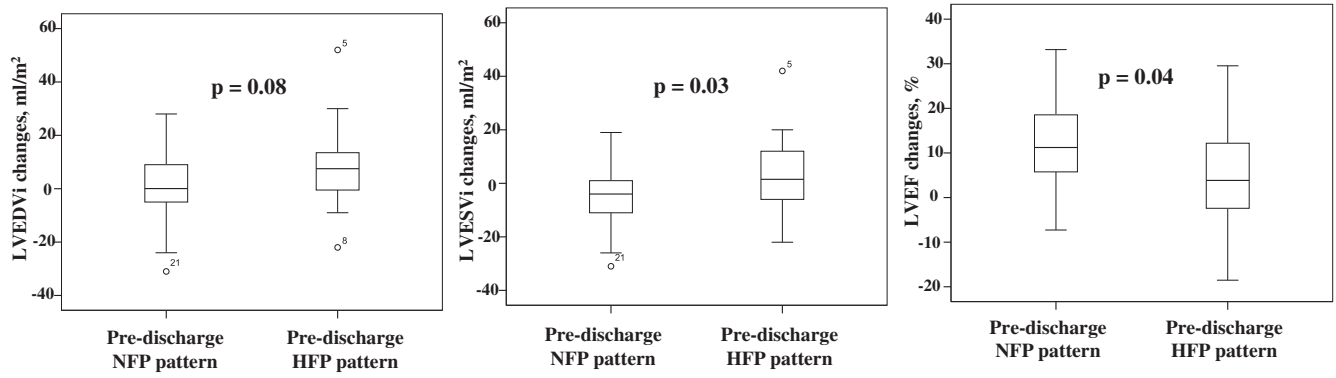

Fig. 2. Relationship between pre-discharge LV filling pressure pattern and 6-month echocardiographic findings. Changes from baseline to 6-month of LV volumes and ejection fraction in patients with pre-discharge HFP pattern (n. = 17) and in those with NFP pattern (n. = 56), respectively. The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line in the middle represents the 50th percentile. The whiskers (the lines that extend out the top and bottom of the box) represent the highest and lowest values.

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24 h, MMP-7/TIMP-1, -2, -3 and -4 at pre-discharge and MMP-7/TIMP-1, -2 and -3 at 6 month follow-up, respectively. On the contrary, 1-month MMP-9/TIMP-1 and -4 ratios, and MMP-8/TIMP-4 ratio significantly increased in doxycycline-group than control-group.

3. Discussion

The unique and significant findings from this study are twofold. First, a short-time treatment with doxycycline, initiated early after mechanical reperfusion in patients with STEMI and LV dysfunction, is associated with a significant improvement in LV filling pattern on echocardiographic assessment from hospital admission to pre-discharge. Importantly, this relationship was independent of the enzymatic infarct size, and concomitant LV remodeling process. Second, compared to patients with pre-discharge HFP, patients with pre-discharge NFP pattern showed less 6-month LV remodeling and, importantly, this occurred regardless of baseline LV filling pattern.

The ECM plays a major role in post-myocardial infarct remodeling [21]. Increased MMPs activation (such as MMP-1, -2, -3, -8, -9 and -14) is a well-accepted pathway leading to early ECM damage and LV remodeling [21]. The inhibition of MMPs by synthetic inhibitors has been shown to be able to reduce post-infarction adverse remodeling in animals [22–25], but not in humans [26].

For the first time, the TIPTOP study [7] has demonstrated that a timely short-term therapy with doxycycline in patients with acute STEMI and LV dysfunction significantly reduces the adverse LV remodeling for comparable definite infarct size. This effect may be due to an up-regulation doxycycline-related of tissue inhibitor of MMP-2 in the first days post myocardial infarction [12]. Moreover, doxycycline possesses cytoprotective effects that are likely secondary to its capacity to act as anti-inflammatory, anti-apoptotic, reactive oxygen species scavenger, as well as MMPs inhibitor [10].

The current analysis of the TIPTOP study opens new perspectives on mechanisms through which doxycycline may determine its favorable action in STEMI patients. In fact, doxycycline therapy was associated with a favorable dynamic behavior of the LV filling during the hospital stage of acute STEMI, resulting in a significantly lower percentage of pre-discharge HFP compared to the control group.

There is no doubt that pharmacological MMP inhibition can favorably alter the course of post-myocardial infarction remodeling in term of LV volumes and function [27]. For example, in the experimental models of AMI in the rat [10] and mice [28], the treatment with broad spectrum inhibitors of MMPs (PD-166793) and doxycycline, respectively, significantly decreased LV dilation 14 days after index infarction, and yielded parallel reduction of LV end-diastolic pressure.

Because of its design, this study was unable to demonstrate any cause-effect relationships, but only correlations, which, however, allow for some interesting hypotheses. First, in control-patients with baseline HFP pattern, the early time-course of MMPs/TIMPs profile was dominated by sustained higher plasma MMP-7/TIMPs ratios than in doxycycline-patients. In adult sheep model of myocardial infarction, MMP-7 deficiency has been related to an improvement of remodeling process after localized delivery of biocomposite materials into infarcted myocardium [29]. Then again, MMP-7 has a large proteolytic portfolio [30] that can modify ECM composition and, consequently, LV architecture, and systolic and diastolic function. Our results suggest this possibility, at least in the clinical setting of STEMI and elevated LV filling pressures. Second, at 1-month follow-up doxycycline-patients with HFP pattern showed higher MMP9/TIMP-1 and -4 and MMP-8/TIMP-4 ratios than control-patients with HFP pattern. Although an early increase of MMP-9 and -8 has been related to adverse LV remodeling [9], in a later phase of myocardial infarction this same proteolytic activity can mediate wound healing [31] and preserve LV systolic function [32]. Consistently, an early short-term MMPs inhibition after experimental myocardial infarction confers a beneficial effect, while a prolonged MMPs inhibition is associated with an adverse LV remodeling [33]. Third, the MMPs/TIMPs ratios changes we observed between the two study-groups, only occurred in patients with baseline HFP pattern. Likely, in the low-risk patients with acute STEMI, such as those with NFP pattern, the powerful salvaging capacity of primary PCI with routine use of modern anti-thrombotic drugs overwhelms the benefits of additional pharmacological cardioprotective strategies, which could otherwise show benefit in patients known to be at higher risk, such as those with HFP pattern.

However, it is interesting to note that in the present study doxycycline was directly associated to a pre-discharge NFP pattern also after controlling for indexes of early concurrent LV remodeling process, namely the LVEDVi and LVEF. Thus, the question arises whether other actions different than ECM modulation can contribute to the relationship between doxycycline and diastolic function early after STEMI. Ali and Coll [15] showed both in rat and human myocardium that MMP-2 colocalizes with titin, and that cleavage of titin in rat hearts subjected to I/R injury was prevented by a selective MMP inhibitor (ONO-4817). Thus, this study highlights an interesting link between the two components responsible for myocardial stiffness: the ECM (also known to be degraded by MMPs including MMP-2) and titin filaments inside the cardiomyocyte. Metalloproteinase-2 is responsible also for the degradation of troponin I [13] and myosin light chain [14] after I/R injury, and doxycycline has been shown to inhibit both [13,14]. In our study, we did not observe significant differences in MMP-2 plasma levels according to doxycycline therapy. However, since we measured the plasma MMP concentration, we cannot exclude that doxycycline may have modulated post-translation MMP activity [34]. Anyway, the protective effect of doxycycline on titin is currently only an intriguing and plausible hypothesis.

In the present study we have observed a pre-discharge HFP pattern in 23% of patients. This finding is in agreement with previous reports in which HFP, as assessed by Doppler transmitral flow profile and/or by a short DT, ranged from 13 to 26% in non-selected patients with AMI treated with medical therapy [35–37], and occurred in ≈20% of 3396 patients included in the most recent MeRGE study [2]. Importantly, in the MeRGE study it was associated with a 3-fold increase in risk of death, with a considerably greater power than any previous study [2]. Our patients with pre-discharge NFP have a better outcome at 6-month follow-up in terms of LV remodeling compared to patients with HFP. Also this result is in agreement with previous reports [3–5], and likely provide the critical linkage between HFP and poor clinical outcome after AMI. Since the favorable outcome associated with the pre-discharge NFP pattern occurs regardless of baseline LV filling pattern, the pre-discharge period appear a good time-point for an effective assessment of diastolic function in survivors of the acute phase of a myocardial infarction.

The present analysis is subject to several limitations. The first is the lack of simultaneous hemodynamic measurement obtained with Eco-Doppler examination. The non-invasive evaluation of LV filling might be problematic to differentiate normal from pseudonormal transmitral velocity pattern. However, both E' and Vp have been shown to be reliable in detecting a pseudonormal LV filling pattern, especially in patients with LV systolic dysfunction such as our patients. An E/E′ ratio > 15 as well as an E/Vp ratio ≥ 2.5 not only predict high filling pressures with reasonable accuracy [19,20], but they have also shown to be highly predictive of a poor prognosis after AMI [38,39]. A further support of the reliability of these indexes in classifying the proper LV filling pattern arises from the fact that our patients with E/E′ ratio > 15 or E/Vp ≥ 2.5 had significantly higher values of pro-BNP respect to their counterparts [40,41], despite similar values of enzymatic infarct size and LV systolic function. Second, given the small sample size, LV filling pattern was evaluated using a binary approach, namely NFP/HFP. Therefore, HFP-group comprises patients with Echo-Doppler findings indicative of both pseudonormal and restrictive filling pattern. However, this fact might be irrelevant from a clinical point of view since both patterns have shown an unfavorable prognosis post AMI than patient without echo-Doppler findings of HFP [2]. Third, we only analyzed selected MMPs and therefore our analysis may have oversimplified the complex interplay of MMPs and TIMPs [42]. Finally, this is a post hoc analysis of a small randomized trial and the results can be considered only hypothesis generating.

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The relationship between doxycycline and post-myocardial infarct remodeling must be confirmed by double-blind study via MRI and Echo-Doppler modalities. Obviously, the impact of doxycycline on long-term clinical outcomes should be further assessed in the future with more highly powered studies.

4. Conclusions

In patients treated by primary PCI for a first STEMI with LV dysfunction, timely, short-term therapy with doxycycline can favorably modulate LV diastolic filling pattern during the early stage of index myocardial infarction. This may be one of the mechanisms by which doxycycline has been shown to have a favorable effect in addition to standard-of-care therapy for STEMI. To date, a major unresolved question is how to manage optimally patients with abnormal LV filling. Doxycycline can be an exciting opportunity.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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