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The effect of acute administration of statins on coronary microcirculation during the pre-revascularization period in patients with myocardial infraction

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ABSTRACT

The beneficial effects of statin pretreatment as well as of staccato reperfusion (SR) on myocardium have been demonstrated in patients undergoing cardiac interventions. In this study, we compared the effects of the acute statin administration prior to percutaneous coronary intervention (PCI) with the effects of staccato or abrupt reperfusion on coronary microcirculation in patients with myocardial infarction (MI).
Methods: We randomly assigned 47 patients who had ST-elevation or non-ST-elevation MI 48 h prior to PCI, into three groups: staccato reperfusion (consisting of 6 periods of 10-s balloon inflation/deflation) plus statin therapy (SRSG), statin therapy plus abrupt reperfusion (SG), and abrupt reperfusion alone (ARG). Myocardial contrast echocardiography (MCE) was performed to assess the blood volume (A), velocity (β) and flow ($A \times \beta$) of the segments associated with the PCI-treated artery the day following intervention and 30 days after. LV end-diastolic (EDV) and systolic volumes (ESVs), wall motion score index (WMSI) were evaluated.
Results: Compared to ARG, SRSG and SG resulted in a greater improvement in A, β and $A \times \beta$ ($F = 20.6$, $p < 0.001$ for A, $F = 3.5$, $p = 0.03$ for β and $F = 11.3$, $p < 0.001$ for $A \times \beta$ for the overall effect of intervention) as well as a greater decrease of WMSI, EDV and ESV ($p < 0.01$) one month post-PCI. The changes of all echocardiography markers were greater in SRSG than SG ($p < 0.01$). The % changes in ESV correlated with the corresponding % changes in MCE indices in SRSG and SG ($p < 0.05$).
Conclusion: The acute statin administration prior to reperfusion either alone or in synergy with staccato reperfusion ameliorates coronary microcirculatory dysfunction in patients with myocardial infarction

1. Introduction

Beneficial effects of statin pretreatment on myocardial function have already been demonstrated in a number of studies on patients undergoing cardiac interventions [1–3].

Besides, several studies confirmed the clinical benefit of statins in terms of reduced mortality and morbidity among patients undergoing coronary by pass surgery [4,5] or among patients with acute coronary syndrome (ACS) who were on statins at the time of the event [6]. The lipid-lowering action of statins might explain most of the beneficial effects of long-term statin use [7]. However, the clinical benefit of statin treatment on cardiac cell function appears to be also rapid and rather independent of the reduction of circulating lipid levels, as it is evident within few hours after statin therapy initiation [8,9].

During percutaneous coronary intervention (PCI), the restoration of flow may cause, by a variety of mechanisms, microcirculatory and myocardial injury [10–12]. Several studies have described the mechanisms of protection against post-ischemic reperfusion injury by “conditioning” the heart [13,14]. Accordingly, we have previously reported that in patients with ACS post-conditioning, applied as a staccato reperfusion intervention, improves long-term wall motion score [15] and myocardial microcirculation [16] as assessed by contrast echocardiography.

Myocardial contrast echocardiography (MCE) is a new modality for the evaluation of regional myocardial perfusion and coronary microvascular integrity [17–21]. MCE markers have been closely correlated with myocardial microvascular density and capillary area as assessed by immunohistochemistry in human biopsy specimen [17]. MCE markers of microvascular damage are the best predictors of LV functional recovery after coronary bypass surgery [18] and after acute myocardial infarction (AMI) [19,20].

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The aim of the present study was to test whether acute statin administration prior to reperfusion by coronary angioplasty and stent implantation may affect coronary microcirculation, as assessed by contrast echocardiography, in patients with myocardial infarction.

2. Methods

2.1. Study population & protocol

We recruited 36 patients with STEMI in whom appropriate thrombolytic therapy was given in a hospital without the technical support to perform primary PCI as well as 11 patients with NSTEMI who underwent a PCI within 48 h after the onset of chest pain. None of them was under statin therapy up to the time of the acute ischemic syndrome and had to had only one area at jeopardy treated with revascularization. We excluded patients with acute STEMI undergoing primary PCI, patients with rhythm disorders, those with higher than Killip 2 class during the index event, other heart diseases and chronic inflammatory or other systemic diseases. All patients underwent PCI − stent implantation within 48 h (46 ± 2 h) after admission and were randomly assigned into three groups, as follows; staccato reperfusion plus statin therapy group (SRSG), statin therapy plus abrupt reperfusion group (SG), and abrupt reperfusion group (ARG). In the first two groups statin therapy (40 mg of Rosuvastatin) was started at the admission whereas in the ARG the same statin was started at discharge. The patients were matched for the culprit artery and were randomly assigned as follows: 1 patient for SRSG, 2 patients for SG and 1 patient for ARG. Thus, twelve patients were assigned to the SRSG, 25 to the SG and 12 to the ARG. In the SRSG, the wire was passed across the lesion and the balloon was sequentially inflated at 8 atm, six times of 10 s each, separated by 10 s deflations (total intervention time, 120 s) as previously described [15]. In the ARG and SG, a single, 120-s balloon inflation at 8 atm was applied in the culprit lesion, in order to match the duration of intervention in the SRSG. Then, the balloon was removed and replaced by a new balloon with stent which was placed in the opened lesion. The balloon inflated at 16 atm and the stent was deployed in position.

Conventional echocardiogram and myocardial contrast echocardiography (MCE) were performed the day following angioplasty and repeated 30 days after. Troponin I, creatine kinase (CK) and the myocardial isoenzyme of creatine kinase (CKMB) were monitored at baseline before PCI and at consecutive 8 h intervals during 48 h after intervention.

The study protocol was approved by the Institute's Ethics Committee, and written informed consent was obtained from all patients.

2.2. Echocardiography

Studies were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) phased array ultrasound system. All studies were digitally stored and were analyzed by two blinded observers, using a computerized station (Echopac GE, Horten, Norway).

2.2.1. 2D-echocardiography

Regional wall motion (WM) was semiquantitatively scored according to the recommendations of the American Society of Echocardiography (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and a wall motion score index (WMSI) was calculated by the sum of the score of all segments divided by the total number of segments, using the 17-segment model [16].

Left ventricular end-diastolic volumes (EDVs) and end-systolic volumes (ESVs) were calculated from 4- and 2-chamber views using the modified Simpson biplane method.

2.2.2. MCE acquisition

A second-generation contrast agent (SonoVue, Bracco Inc., Milan, Italy) was administered as i.v. bolus (0.5 cc) over 30 sec and continuous i.v. infusion 0.8–1cc/min. The infusion rate was adjusted until optimal myocardial contrast opacification was achieved. Myocardial contrast echocardiography (MCE) was performed in apical 4-, 3-, and 2-chamber views. MCE images were acquired with the adjusted mechanical index at 0.1, the frame rate at 35 Hz, and the focus at the mitral valve level. Destruction replenishment imaging was used with a transient high mechanical index (1.0) imaging "flash" (for 15–17 frames) to clear myocardial microbubbles; replenishment was then observed over 15 cycles during end expiration. If myocardial microbubble clearance was not complete, another image was acquired after adjustments of flash intensity and duration. The procedure was repeated at least twice for every adequate scan view. Adequate MCE visualization was achieved in 95% of overall LV segments analyzed.

2.2.3. MCE analysis

MCE images were analyzed using the 17-segment model. Segmental regions of interest (ROI) of standard size and shape were manually positioned on end-systolic frames starting in the frame immediately after the flash. The myocardial ROIs were then copied automatically onto all subsequent end-systolic frames but were manually adjusted to carefully avoid overlapping cavity signals during the entire replenishment sequence.

The software package analyses automatically the redistribution of contrast bubbles after high impulse destruction (flash imaging) and calculates the mean acoustic-intensity of each ROI. Time-intensity replenishment curves were generated and were subsequently fitted to the following equation: $y = A \times (1 - \exp^{-\beta \times t})$ using previously published methodology [18,21]. Alpha (A) expresses the maximum signal intensity corresponding to the total microvascular cross sectional area and to peak myocardial blood volume of the ROI. Beta (β) reflects the velocity of microbubble replenishment and expresses the myocardial flow velocity. The product $A \times \beta$ is considered to represent the myocardial flow of the examined myocardial area and thus, changes of this index are thought to indicate changes of the integrity of coronary microcirculation in the absence of a significant epicardial stenosis [16–18,21].

Segments were ascribed to coronary territories: the four apical segments (apex, base-mid anterior wall, base-mid anteroseptum and mid inferior septum) were assigned to the left anterior descending coronary artery (LAD), the base-mid anterolateral and base-mid inferolateral walls were assigned to the left circumflex coronary artery (LCx) and the base-mid inferior wall and base inferior septum were assigned to the right coronary artery (RCA) [21]. On the territorial level, quantitative MCE parameters were defined as feasible if one or more segments were analyzable in each territory.

The mean value of A, β and $A \times \beta$ of all the segments ascribed to the coronary territory of the culprit lesion was calculated in each patient and was used for analysis. The inter- and intra-observer variability for measurement of A was 8.2% and 7.1%, and for β was 8.7% and 7.7%, respectively.

2.3. Statistical analysis

In a pilot study of 15 patients (5 from SRSG, 5 from ARG and 5 from SG), we found that the standard deviation of the change in β and A before and 48-h after PCI was 0.18, 0.17 and 0.17 respectively. We assumed that a 35% increase of the MCE indexes post-PCI compared with baseline in SRSG and SG compared to ARG is