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Original article

Presence and site-matching of ischemia at stress-scintigraphy or contrast stress-echo in individuals developing myocardial infarction within 3 months: does stenosis severity matter?

Carmine Siniscalchi[1], *Claudio Reverberi*[1], *Nicola Gaibazzi*[1]

[1] Parma University Hospital, Parma, Italy

Summary. *Background and aim:* Individuals with ischemia during cardiac stress-test (cST) have a high risk of developing myocardial infarction (MI), but the pathophysiologic mechanism has never been clarified. It is thought that non flow-limiting coronary plaques (FLP) cause more often MI than FLP, but this is in contradiction with the predictive value of cST. We investigated the correspondence between reversible ischemia and location of subsequent MI, since functional assessment *shortly* before MI could clarify whether the culprit plaque is a FLP or not. *Methods:* From 4505 MI and 4959 cST -2017 contrast perfusion stress-echo (cDipSE) and 2942 scintigraphy (SPECT)- performed from 2007 to 2011- 25 patients fulfilling criteria (<3 months between cST and subsequent MI, angiography within 72 hours of symptoms onset and no revascularization between cST and MI) were extracted and data matched. Reversible perfusion defects were considered the endpoint to define a positive cST. *Results:* Reversible perfusion defects on cST were found in 84% of patients (21/25) and 80% (20/25) had matched defects; 95% (20/21) of patients demonstrating a reversible defect had a subsequent MI in the same territory. *Conclusion:* Our data suggest that when cST-MI time is shortened, and plaque progression bias consequently minimized, most MI (80%) develop in the coronary territory where reversible perfusion defects were detected shortly before. These data encourage reconsidering FLP as main determinant of MI. (www.actabiomedica.it)

Key words: myocardial infarction, reversible ischemia, contrast stress-echocardiography, SPECT, acute coronary syndrome pathophysiology

Background

It is recognized that individuals who demonstrate significant reversible ischemia during a cardiac stress-test (cST) have the highest risk of developing future acute coronary syndromes, but the mechanism through which this happens has never been clarified. It is thought that mild and non flow-limiting coronary plaques (NFLP) cause myocardial infarction (MI) most frequently but this is clearly in contradiction with the high predictive value of stress testing, which is intrinsically able to detect only flow-limiting plaques (FLP) (1-3), This poorly acknowledged paradox or "missing link" through which cST results predict subsequent MI may recognize 2 explanations, although neither has ever been proved. The first "mainstream" hypothesis, suggested by some angiographic (1-3) and angioscopic (4) studies, is that the presence of FLP associates with a significant number of pancoronary, potentially "vulnerable" NFLP; in this case patients with a FLP detected by a positive cST would develop MI due to their diffusely associated NFLP. An alternative theory is that the FLP is *in itself* the specific culprit of the subsequent MI, as it is suggested by most recent,

prospective fractional flow reserve studies and recent COURAGE trial angiographic analysis, which proved that only the revascularization of FLP is capable of reducing future MI (5,6) and that most culprit lesions are >50% at angiogram before subsequent MI (7,8); these data suggest that FLP itself is usually the culprit of subsequent MI in patients with a positive antecedent cST. We aimed to describe whether or not there is correspondence between the coronary territory with reversible ischemia and the location of a subsequent MI, since this may indirectly suggest the mechanism (Figure 1 and 2) through which cST predicts subse-

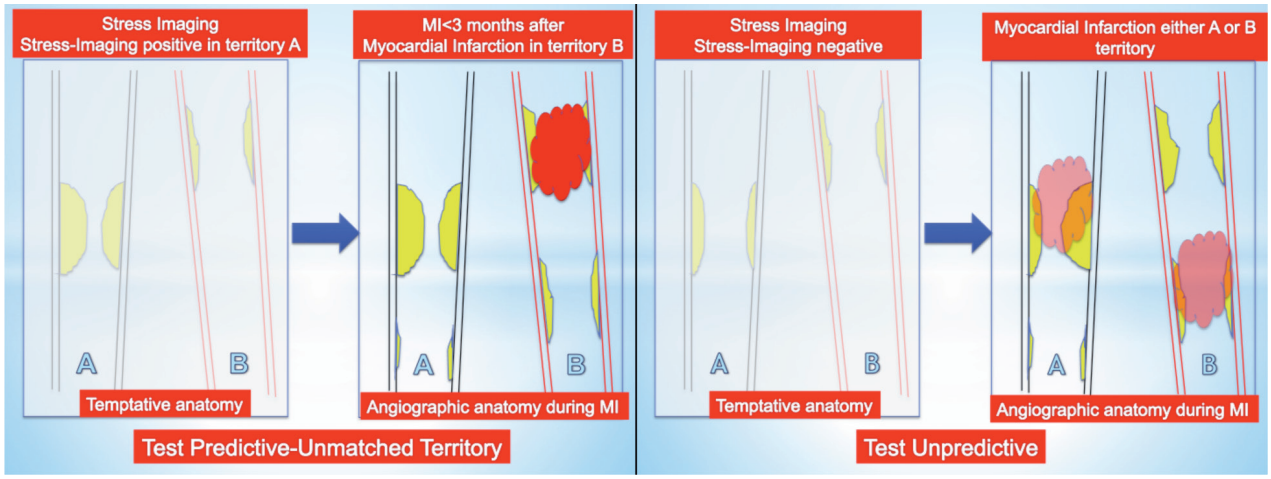

Figure 1. UNMATCHED cases. Stress test predictive of a subsequent MI, which anyway develops in a different coronary territory compared to the one with reversible ischemia (left) or, alternatively, it is not predictive at all of the subsequent MI (normal test) (right). These cases lend support to the theory that since the coronary tree has simply more non flow-limiting plaques, when a flow-limiting one is first detected, most often the MI culprit plaque is a non flow-limiting one, undetectable by any stress-test

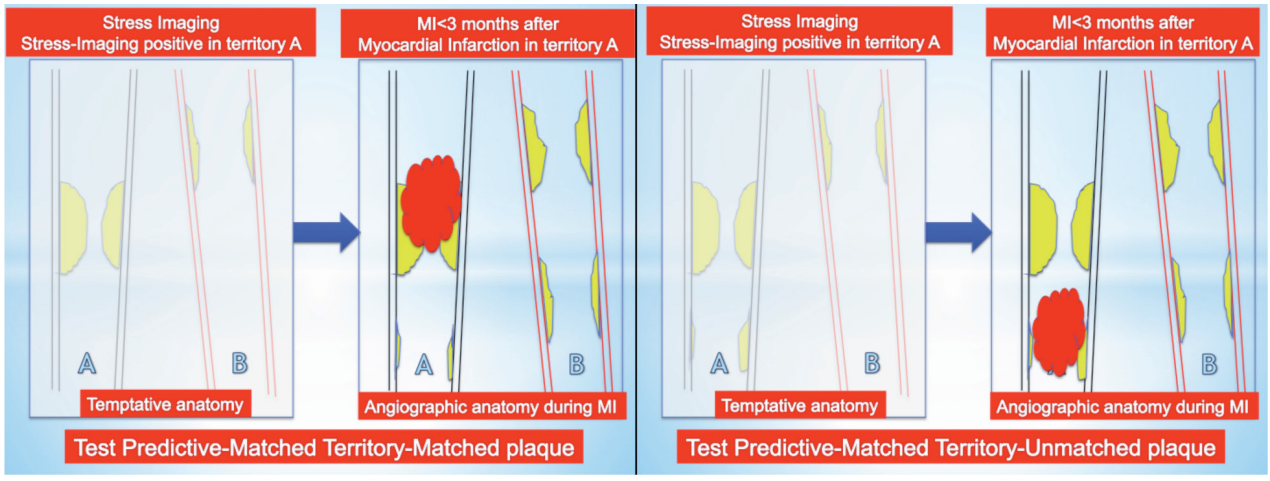

Figure 2. MATCHED cases: Stress test is predictive of a subsequent MI and there is also territory match; culprit plaque of MI may either be the flow-limiting one previously detected by cST (left), or not (right). Prevalence of MATCHED cases would support the theory that MI culprit plaques are mostly the flow-limiting ones detected by cSTs, although the mechanism described on the right remains a theoretical possibility. Still, since mild non flow-limiting plaques are known to affect all the 3 coronaries, MATCHED cases strongly support the theory of flow-limiting plaques being directly the culprit: in fact, if the mild plaques were the culprit, MI would likely happen also in the other territories, different from the ischemic territory at previous stress-test

quent MI. Differently from all previous such studies (9-13), a very short time window (<3 months) between cST and subsequent MI was selected in the current study, so that the confounding of unpredictable, heterogeneous progression of coronary plaques during short periods of time was minimized (14,15).

Methods

Patients' selection

Our hospital (tertiary referral center) electronic database was screened for all patients discharged with MI diagnosis between January 2007 and December 2011, indifferently ST-elevation (STEMI) or non-ST elevation (NSTEMI), who underwent diagnostic catheterization (and revascularization if appropriate) <72hours after chest pain onset; MI with normal coronary arteries were excluded. Then, we retrospectively searched patients satisfying the abovementioned criteria in our stress-SPECT and contrast dipyridamole stress-echo (cDipSE) databases to identify the minority of them who had undergone either provocative test <3 months before their subsequent MI. Patients who underwent a coronary revascularization procedure between cST and the occurrence of the subsequent MI were excluded. Cases satisfying all criteria were reviewed in depth to double-check they were true MI (and not a milder coronary syndrome), according to symptoms, ECG and both cardiac enzymes (troponin I and CK-MB) temporal release. For patients finally satisfying all selection criteria, the results of their cST and coronary angiogram at the time of MI were analyzed and the culprit lesion territory (as defined by the interventional cardiologist in charge) matched with the provocative test results, in particular regarding the presence of reversible perfusion defects.

Stress imaging

Imaging stress tests retrospectively considered in our study were: a) contrast high-dose dipyridamole (0.84 mg/kg) stress-echocardiograms (cDipSE), representing our routine stress-echo protocol which incorporates myocardial perfusion analysis by the flash-replenishment technique and b) 1-day rest/stress gated-scintigraphy (SPECT) using technetium-99m sestamibi, in conjunction with either treadmill exercise (Bruce protocol) or pharmacologic stress (dipyridamole 0.56 mg/kg/4min) for patients who could not exercise to at least 80% of predicted maximal heart rate. Qualitative or semiquantitative visual interpretation was routinely performed by the physician in charge both for wall motion (WM) and perfusion (MP), both for echocardiography and SPECT. Defects were classified as "reversible", reflecting ischemia, or "irreversible/fixed", reflecting prior infarction. Details of the cDipSE protocol are reported elsewhere (16). The left ventricular apex, anteroseptal, distal septum, and anterior walls were assigned to the left anterior descending coronary artery, the lateral wall to the left circumflex, and the inferior wall and basal septum to the right coronary artery (or retrospectively to the left circumflex in case of left dominance shown at coronary angiography at the time of subsequent MI). Continuous variables are described as mean ± SD, and categorical data are expressed as proportions. The study complied with the Declaration of Helsinki and was approved by Institutional Research Board of the Parma University hospital.

Results

Selection of patients

We first screened 4505 patients who were admitted to our medical center and discharged with a diagnosis of acute MI between 2007 and 2011; from those we excluded 92 patients who were discharged as MI with normal coronary arteries, then, we cross-searched our stress imaging database in the same 2007-2011 period (4959 tests), comprising 2017 cDipSE and 2942 SPECT studies. After excluding a) MI patients who, for any reason, did not undergo coronary angiography within 72 hours of chest pain onset, b) who had no imaging cST within prior 3 months or c) who satisfied all the previous criteria but underwent a revascularization procedure between cST and subsequent MI event, we could finally include 25 patients in the analysis (Figure 3).

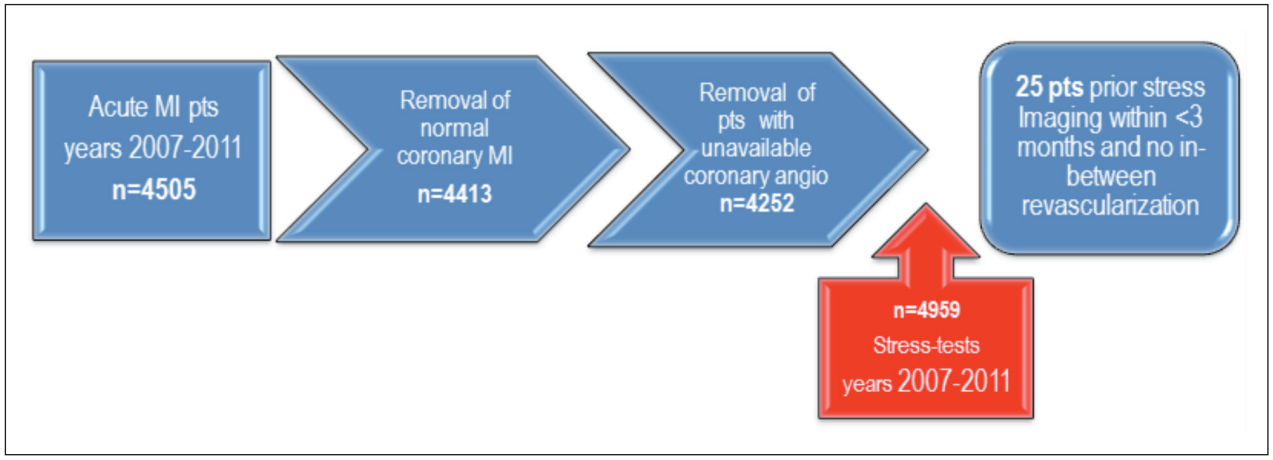

Figure 3. Retrospective selection process of patients to be included in the final analysis. MI, myocardial infarction

Patients' characteristics

Previous medical history, clinical characteristics, MI site and stress imaging results in this population are listed in Table 1. Most patients were males (88%) and more than half had a prior MI or coronary revascularization. All 25 patients underwent primary PCI during their acute MI hospital admission; MI were NSTEMI in 22 and STEMI in 3 patients.

Stress-test vs. MI matching

Among the 25 patients the mean time interval between cST and subsequent MI was 55 days (range 13-

Table 1. Clinical characteristics and stress-imaging findings in 25 selected patients

Age, ys±SD	71±8
Gender M/F	22/3
Stress-test to MI time, days±SD	55±24
range	13-86
Patient history,	
Previous myocardial infarction	16 (64%)
Previous revascularization	17 (68%)
Infarct-related coronary artery	
Left anterior descending artery	13 (52%)
Circumflex coronary artery	6 (24%)
Right coronary artery	6 (24%)
Stress-imaging results (reversible perfusion defects)	
Pts with positive stress-imaging (either modality)	21/25 (84%)
Pts with positive cDipSE	14/14 (100%)
Pts with positive stress-SPECT	9/13 (69%)
Site Matching between stress-imaging and subsequent MI	
Pts with reversible matched defect (any cST)	20/25 (80%)
cDipSE with reversible matched defect	12/14 (86%)
Stress-SPECT with reversible matched defect	10/13 (77%)

Data presented are mean value ±SD or number (%) of patients. Two patients had both cDipSE and SPECT studies (concordantly positive for reversible and matched defects in both cases), so that number of tests (n=27) is higher than the number of patients (n=25). MI, acute myocardial infarction, cDipSE, contrast perfusion stress-echo; SPECT, stress gated myocardial scintigraphy

86 days), 14 underwent cDipSE and 11 stress-SPECT (7 exercise and 4 dipyridamole). Eighty-four percent of patients (21/25) had reversible perfusion defects on cST and 80% (20/25) had matched perfusion defects. Four patients (24%) had cST without reversible perfusion defects; consequently, 95% of patients (20 out of 21) in whom a reversible defect was previously detected had a MI in the very same coronary territory. If wall motion only was assessed during cDipSE, and not myocardial perfusion, sensitivity for MI prediction would significantly diminish, with only 6/14 tests resulting positive for a reversible wall motion abnormality; 8 out of the 14 cDipSE tests were in fact positive for reversible perfusion only (normal wall motion behavior).

Discussion

This retrospective study, not differently from few recent prospective, multicenter studies (5-8), suggests that FLP, defined as plaques able to provoke stress perfusion defects, may cause MI more frequently than NFLP in patients with a recent positive cST. If a MI develops in a patient with positive cST because of a NFLP associated with FLP, it should not take place mostly in the same coronary territory where reversible ischemia (i.e. FLP) was previously identified, due to the high probability that those mild "yellow" NFLP are scattered through the entire coronary tree (Fig 1); on the contrary, if the detected FLP is directly the culprit for subsequent MI, matching between reversible ischemia territory and the territory of future MI should prevail (Fig 2). This second theory is clearly suggested by our study: 80% of the 25 patients who performed a cST <3 months before developed a MI in the same coronary territory in which the reversible perfusion defect was previously detected (matched defect) and 95% of the 21 patients who demonstrated a prior abnormal cST developed a MI in the same territory identified by the reversible perfusion defects.

Discrepancy with previous studies

Both recent and less recent data show that angiographic progression of coronary artery plaques from less than obstructive lesions (<50% diameter stenosis) to potentially flow-limiting (>50%) occurs in at least 20% of individuals ("progressors") in a 6-7 month time frame (14,15). Several studies comparable to the current (1-3,9-13,17,18) were performed, mostly in the last decades of the 20th century and used either prior angiography or prior stress-imaging data (all SPECT but 1 stress-echo study) to predict following MI; most came to the conclusion that the majority of MI are caused by plaques which, at the moment of prior index test or angiography are NFLP (<70% or <50% depending on the specific study) and generally hypothesized this happens because those plaques outnumber FLP. Anyway, FLP are known to be more prone to cause MI on an individual plaque basis than NFLP (3,17, 5-8). Unfortunately, due to the inherent difficulties in this type of research, all such previous studies were forced to use data with very long time intervals between the "baseline" index test (angiographic, SPECT or stress-echo) and the subsequent MI, all studies reporting on MI events taking place several months to several years after the index angiography or cST. The current study, although not the first trying to correlate cST results with the location of subsequent MI, is the first reducing per-protocol the examined interval down to <3 months, by so doing heavily reducing the confounding bias, due to the potentially rapid, unpredictable and heterogenous progression of coronary plaques (14,15). It should be noted that all previous studies found a considerable higher match between location of cST ischemia and subsequent MI when splitting cases in a subset with shorter cST to MI time, compared with longer times.

The current is also the first such study including cDipSE as a stress-imaging modality, a very sensitive method to detect intermediate, though potentially flow-limiting, plaques (16). As expected, most patients (8 out of 14) with a positive cDipSE study who had a subsequent MI had a positive test for perfusion defects only, with normal wall motion behavior: this is not only justified by the higher sensitivity of perfusion imaging compared to wall motion, but also because this subset of patients does not fulfill current guidelines for revascularization as of yet, due to wall motion behavior being considered the main ischemia marker during stress-echo, so that most patients in this category were not revascularized after their cST and could be included in the study, differently form the ones with

wall motion abnormalities also, who usually undergo prompt revascularization. The need to exclude patients who had a revascularization procedure between a positive cST and subsequent MI (today the vast majority of such patients) makes it very difficult to recruit a higher number of patients in a single-centre study, particularly when selecting such very short time between cST and MI.

Study limitations

The current study is single-centre and retrospective, the number of cases is limited and a selection bias towards including patients not undergoing prompt revascularization after a positive cST is inherently present; anyway this selection bias is consistently reduced compared to similar studies, thanks to the reduction of cST-MI time to < 3 months, with a mean time resulting <2 months; this is often within the waiting time for patients undergoing elective coronary angiography and it is likely that most of these (stable) patients were simply waiting for their planned angiography, not classified with urgency priority. We felt unreasonable reporting too many clinical data in such a retrospective study, for example symptoms leading to the cST in each patient, that would need extrapolation from electronic charts, often unreliable for subjective data such as symptoms characterization.

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Correspondence:
Nicola Gaibazzi MD PhD
Parma University Hospital
Via Gramsci, 14 - 43100 Parma-Italy
E-mail: ngaibazzi@gmail.com