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ORIGINAL ARTICLE

Prognostic implications of post-stress ejection fraction decrease detected by gated SPECT in the absence of stress-induced perfusion abnormalities

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Abstract
Purpose The prognostic meaning of a post-stress ejection fraction (EF) decrease detected by perfusion gated SPECT is still unclear. We therefore followed up patients with post-stress EF decrease in the absence of stress-induced perfusion abnormalities.
Methods We prospectively enrolled 57 consecutive patients with post-stress EF drop ≥5 EF units and summed difference score (SDS)≤1. They were followed up for more than 1 year and their outcome was compared with a group of sex- and age-matched controls with the same SDS but without EF decrease.
Results During follow-up there were 13 events (1 cardiac death, 1 non-fatal myocardial infarction, 1 congestive heart failure and 10 late revascularizations). In the control group we registered six events. There was a significant difference ($p<0.0001$) between the event-free survival curves of the two groups.
Conclusion The event rate of patients with post-stress EF decrease≥5 EF units is relatively high and is significantly worse than that of a control group of patients with similarly normal SDS but without EF changes. Therefore, a post-stress EF decrease without stress-induced perfusion abnormalities should be cautiously interpreted.

Keywords Gated SPECT · Left ventricular ejection fraction · Myocardial perfusion · Prognosis

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Introduction

According to the model of myocardial stunning, stress-induced ischaemia may cause wall motion abnormalities or a decrease in the left ventricular (LV) ejection fraction (EF) that may be detected by comparing resting and post-stress gated single photon emission computed tomography (SPECT) [1]. For this reason, the presence of a post-stress EF decrease has been indicated as an additional sign of coronary artery disease (CAD) severity, like increased tracer lung uptake or transient ischaemic dilatation, which are known to have an adverse prognostic meaning [2–6]. However, a recent study has demonstrated that the post-stress EF decrease in patients with inducible ischaemia is usually negligible and that only a very limited percentage of ischaemic patients have a really significant EF decrease [7]. This would imply that the value of this finding is poor, also because of the simultaneous presence of clear ischaemic perfusion defects [7]. On the other hand, in patients submitted to dual gated SPECT studies a remarkable post-stress EF decrease can be sometimes detected in the presence of a normal or near-normal perfusion pattern. It is therefore unclear whether an EF drop in the absence of stress-induced perfusion defects is just a casual finding or should be more cautiously regarded as an expression of underlying coronary artery disease, with potential prognostic implications. To clarify this issue we performed a follow-up study of patients that presented without inducible ischaemia but with a post-stress EF drop and we compared their outcome with a control group of sex- and age-matched patients similarly without inducible ischaemia but with unchanged EF.

Materials and methods

Patient population

This is a prospective observational study based on the patient population that underwent stress-resting myocardial perfusion gated SPECT in our laboratory for the standard clinical indications between May 2004 and May 2008. The patients were prospectively included in the follow-up registry if they showed a ≥5 EF units decrease in post-stress images without stress-inducible ischaemia (as below defined) [6, 8]. Because the meaning of the EF drop was still under investigation, it was our policy to avoid indicating it in the clinical report. They were compared with a sex- and age-matched control group of patients without stress-inducible ischaemia retrospectively selected from our data base of the year 2007, which had been previously revised for an internal quality assessment.

Stress myocardial perfusion protocol

Patients underwent either symptom-limited exercise with a bicycle ergometer or pharmacological stress with dipyridamole infusion. Exercise was terminated when any of the following endpoints was reached: typical anginal pain, horizontal ST segment depression exceeding 1.0 mm in the presence of chest pain or 3.0 mm in the absence of pain, life-threatening arrhythmias or leg fatigue. The dosage of dipyridamole was 0.56 mg/kg body weight over 4 min. The protocol included the acquisition of a post-stress scan approximately 30 min after the injection of sestamibi. The rest gated SPECT was acquired 1 h after tracer injection using a separate day protocol.

Gated SPECT

Gated SPECT was acquired after ^{99m}Tc-sestamibi injection (740 MBq), using a dual-head camera (SKYlight, Philips Medical Systems, Milpitas, CA, USA) equipped with high-resolution collimators, 180° rotation arc, 32 projections, 60 s/projection, 8 frames/heart cycle, no arrhythmia rejection and 64×64 matrices. The studies were reconstructed using filtered backprojection without attenuation or scatter correction and realigned along the heart axis. Image evaluation was performed blindly by an experienced observer, who was unaware of patient's data. The LV was divided into 17 segments and the tracer uptake was classified using a 5-point scoring scheme (0=normal, 1=mildly reduced, 2=moderately reduced, 3=severely reduced and 4=absent uptake) [9]. The summed rest score (SRS) and the summed stress score (SSS) were obtained by adding the scores of the 17 segments in resting and stress images, respectively. The summed difference score (SDS) represents the difference between the stress and resting scores [9]. Inducible ischaemia was classified as mild (2–5), moderate (6 –7) and severe (>7) [8]. For the purpose of the study only patients with SDS=0 or =1 were selected. The measurement of LV end-diastolic and end-systolic volume and EF was performed by the QGS program (Cedars-Sinai Medical Center, Los Angeles, CA, USA) [10]. Volumetric data were corrected for body surface area and expressed as indexes. The same program automatically calculated the transient ischaemic dilation (TID) as well.

Patient follow-up

Patients were followed up by review of hospital records and by telephone contact with the patient, relatives or referring physician. An investigator who was unaware of perfusion imaging results collected follow-up data. The mean follow-up period was 22±9 months. The evaluated events were cardiac death, non-fatal myocardial infarction, congestive heart failure requiring hospitalization and coronary revascularization >60 days after index gated SPECT.

Statistical analysis

Values are presented as mean value±standard deviation (SD). In the case of scores, the median and the interquartile range are indicated. Continuous variables were compared with Student's t test for unpaired samples or with the Mann-Whitney U test as appropriate. The comparisons of proportions were made using either the Fisher exact test or the chi-square test with Yates' correction as appropriate. Event-free survival curves were constructed using the Kaplan-Meier method and were compared with the log-rank test. A probability value of $p<0.05$ was considered statistically significant.

Results

General findings

During the indicated time interval, 60 patients fulfilled the selection criteria. Of them, three were lost to follow-up because they could not be reached at their initial address. Therefore, the final patient population included 57 patients (24 women, mean age 67.3±10 years). The indications for myocardial perfusion imaging (MPI) were: (1) diagnosis of coronary artery disease in patients with intermediate pre-test probability (20 patients), (2) worsening of anginal symptoms in chronic coronary artery disease or evaluation of anginal symptoms in prior myocardial infarction (8 patients), (3) evaluation of chest pain in previous revascularization (21 patients) and (4) evaluation prior to major

non-cardiac surgery (8 patients). The stress test used was exercise in 36 and dipyridamole in 21 patients.

The control group included 57 sex- and age-matched patients (23 women, mean age 67.2±9.4 years). As shown in Table 1, the control group was comparable with the study group in terms of risk factor profile, previous clinical history, indication for perfusion imaging and type of stress testing.

Gated SPECT findings

In the study group, the resting gated SPECT was normal in 41 patients and abnormal in 10, with a median SRS of 0 (0–0). The resting EF was 63±10%. In stress gated SPECT, the SSS was 0 in 41 patients and ≥1 in 16, with a median of 0 (0–0.5). The post-stress EF was 55±10%. The delta EF was −8±3%. The TID was 1.06±0.13. Table 2 compares the gated SPECT findings of the study group with those of the control group. In particular, no significant difference in the other stress parameters with prognostic relevance was registered. There was a trend to a higher rate of anginal symptoms (28 vs 12%, $p=0.06$) and of patients with post-stress EF<50% (28 vs 12%, $p=0.06$) in the cases versus the control group.

Follow-up data

During follow-up among the patients with EF drop there were one cardiac death, one non-fatal myocardial infarction, one congestive heart failure and ten delayed revascularizations: four coronary artery bypass grafting (CABG) and six percutaneous coronary interventions (PCI). Conversely, in the control group we registered one non-fatal myocardial infarction followed by revascularization (CABG) and five delayed revascularizations (one CABG and four PCI). Figure 1 compares the survival curves in the patients with EF drop versus the controls, showing a highly significant difference ($p<0.0001$) between the two groups in terms of event-free survival. Conversely, there was no difference if the whole patient population was stratified on the basis of the type of stress test and of the presence of resting EF <50%. If the patients were divided into those with versus those without post-stress EF < 50%, there was a borderline significant difference in the event-free survival group in favour of the latter group ($p<0.05$).

Discussion

Results of the present study

The main result of the present study is that in a patient population selected on the basis of the finding of a post-stress decrease in gated SPECT EF≥5 EF units, but without inducible ischaemia, there was a relatively high rate of cardiac events. In particular, there was a significantly higher rate of events than in an age- and sex-matched control group of patients without detectable inducible ischaemia and with unchanged EF after stress.

Table 1 Clinical characteristics of the patient population

	EF drop (n=57)	No EF drop (n=57)	p
Age, years, mean±SD	67.3±10	67.2±9.4	NS
Female sex, n (%)	24 (42)	23 (40)	NS
Family history of CAD, n (%)	35 (61)	33 (58)	NS
Systemic hypertension, n (%)	51 (89)	45 (79)	NS
Hypercholesterolaemia (total cholesterol>200 mg/dl), n (%)	33 (58)	33 (58)	NS
History of smoking, n (%)	35 (61)	31 (54)	NS
Diabetes mellitus, n (%)	21 (37)	15 (26)	NS
Prior coronary artery bypass grafting, n (%)	5 (9)	5 (9)	NS
Prior percutaneous coronary intervention, n (%)	16 (28)	17 (30)	NS
Recent coronary angiography			
One-vessel disease, n (%)	5 (9)	4 (7)	NS
Multi-vessel disease, n (%)	14 (25)	9 (16)	NS
Indication for stress MPI			
Diagnosis of suspected CAD, n (%)	20 (35)	24 (42)	NS
Evaluation in known CAD, prior infarction, n (%)	8 (14)	7 (12)	NS
Evaluation in prior revascularization, n (%)	21 (37)	17 (32)	NS
Evaluation before major non-cardiac surgery, n (%)	8 (14)	9 (16)	NS
Pharmacological stress, n (%)	21 (37)	21 (37)	NS

Table 2 Gated SPECT findings

	EF drop (n=57)	No EF drop (n=57)	p
Maximal exercise workload (W), mean±SD	90±24	92±26	NS
Maximal heart rate (bpm), mean±SD	122±26	127±26	NS
Peak systolic blood pressure (mmHg), mean±SD	182±30	185±30	NS
Peak diastolic blood pressure (mmHg), mean±SD	96±14	92±12	NS
Rate-pressure product, mean±SD	22,590±7,009	23,867±7,333	NS
Typical angina, n (%)	16 (28%)	7 (12%)	= 0.06
Ischaemic electrocardiographic changes, n (%)	12 (21%)	8 (14%)	NS
SRS, median (interquartile range)	0 (0–0)	0 (0–0)	NS
SSS, median (interquartile range)	0 (0–0.5)	0 (0–0.5)	NS
SDS, median (interquartile range)	0 (0–0)	0 (0–0)	NS
Resting EF, mean±SD	63±10%	60±11%	NS
Resting EF<50%, n (%)	6 (11%)	9 (16%)	NS
Resting end-diastolic volume index (ml/m^2), mean±SD	46±14	47±17	NS
Resting end-systolic volume index (ml/m^2), mean±SD	19±11	21±14	NS
Post-stress EF, mean±SD	55±10%	62±11%	< 0.005
Post-stress EF<50%, n (%)	16 (28%)	7 (12%)	= 0.06
Delta EF, mean±SD	−8±3%	1.6±2%	< 0.00001
TID, mean±SD	1.06±0.13	0.93±0.12	< 0.00001

Comparison with previous studies

To the best of our knowledge, there are no other studies that specifically examined the outcome of patients with post-stress EF decrease in the absence of perfusion abnormalities. Several prior reports indicated that patients with normal or near-normal stress perfusion have an excellent prognosis [11–16]. According to all these studies, the outcome of patients with normal perfusion is excellent, and the same is true for those with very mild perfusion abnormalities. Indeed, in our control group, the event rates (1.5% for hard events and 9% for soft events) appear higher than those reported in the literature, but this difference can be explained by the features of our cohort, which showed a quite severe risk factor profile and included a large proportion of patients with known coronary artery disease, and by the fact that we focused our selection criteria on the normality of SDS as an expression of stress-induced perfusion changes and not on the absence of perfusion abnormalities altogether. It is therefore even more intriguing that in our patient population with EF drop the event rate appears to be significantly higher than in controls, with an incidence of 5% for hard events and of 17.5% for soft events. These values appear at least comparable and possibly superior to those previously reported for patients with mild to moderate perfusion abnormalities [8, 17, 18].

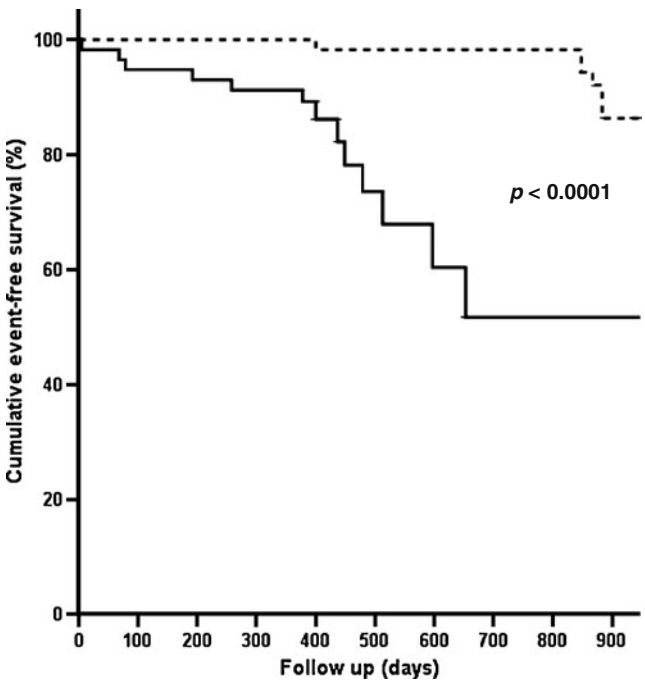

Fig. 1 Event-free survival curves for the patients with (*solid line*) versus those without (*dashed line*) EF drop≥5 EF units

Clinical implications

Similarly to increased lung uptake and TID, the presence of a major EF drop after stress is commonly considered as a sign of severe coronary artery disease, but the meaning of a borderline post-stress EF decrease has been recently questioned [1, 2, 4, 6, 7]. Conversely, our results indicate that the prognosis of patients with this finding and without inducible ischaemia is significantly worse than in compa-

rable patients with the same perfusion pattern but with stable EF. This would imply that a clear EF decrease even though registered in the absence of inducible perfusion defects should be considered as a potential indirect sign of coronary artery disease and prompt further investigations or at least a more attentive clinical follow-up. It must be noted that the resting EF was unable to identify the patients with higher probability of events. Conversely, the finding of a post-stress EF<50% selected a high-risk group as well, but the difference between the event-free survival curves was clearly lower than in the case of EF drop. However, there is a relationship between the presence of EF drop and of abnormal post-stress EF. In practical terms, both findings suggest that the statement that post-stress and resting EF values may be considered equivalent is not always true.

Mechanisms of EF decrease

As already mentioned, post-ischaemic stunning explains the occurrence of functional abnormalities in patients that underwent exercise stress testing. The presence of multivessel coronary artery disease with ischaemia in more than one territory could justify the lack of detectable perfusion defects together with global functional impairment in these subjects. However, it is noteworthy that these findings have been registered also in patients that underwent vasodilator instead of physical stress. It was already known that functional changes may be observed and have diagnostic value in the setting of vasodilator stress as well as after exercise [4, 5]. Furthermore, recent data based on the EF calculated using gated PET after adenosine or dipyridamole infusion support the concept that abnormalities in stress-induced functional response may play an important diagnostic role even in the instance of vasodilator stimulation [19, 20]. These observations suggest that in the patients with EF drop true diffuse ischaemia without regional perfusion inhomogeneities could occur, leading to transient functional impairment.

Study limitations

The limitations of the present study must be considered. First of all the patient population of this exploratory study is quite small, and its results must be regarded as preliminary and should be confirmed in a prospective study on a wider cohort. The population from which we enrolled our patients was unselected and the type of stress testing was not the same in all patients. This offers the advantage that our study cohort is close to common practice, but, together with the fact that the study protocol did not include coronary angiography as reference standard, prevents an exact definition of the mechanisms that cause the EF changes. Indeed, other factors than disseminate and severe coronary artery disease leading to diffuse ischaemia as above hypothesized, such as coronary microvascular dysfunction in hypertensive heart disease or diabetic microangiopathy, could have played a role in determining the decrease in EF after stress. The relatively high rate of hypertensive and diabetic patients in our series, although not significantly different than that in the control group, could justify this hypothesis. We did not perform any arrhythmia rejection and therefore we cannot exclude that transient rhythm disturbances during the acquisition could have influenced the EF calculation. However, previous data indicate that the influence of arrhythmia rejection on the functional parameters derived from gated SPECT is limited [21]. Because we adopted a relatively low threshold for classifying the EF response as abnormal, the gated SPECT reproducibility is a major issue. However, both literature data and our prior direct experience indicate that in general the reproducibility of gated SPECT is high enough to make the 5% cutoff clinically reliable [6, 22–24].

Conclusion

Our results indicate that the event rate of a patient population without inducible ischaemia selected on the basis of a post-stress EF decrease≥5 EF units is relatively high as compared to that of patients with similar perfusion but without EF drop. Therefore, the finding of a clear post-stress EF decrease, even though registered in the absence of stress-induced perfusion abnormalities, should be attentively evaluated and cautiously interpreted taking into account the individual patient's clinical context.

Conflicts of interest None.

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