Use of ^{99m}Tc-sestamibi gated SPECT to assess the influence of anterograde flow before primary coronary angioplasty on tissue salvage and functional recovery in acute myocardial infarction

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Abstract. *Purpose:* Preserved thrombolysis in myocardial infarction (TIMI) flow before percutaneous coronary intervention (PCI) in acute myocardial infarction is related to improved outcome. Gated single-photon emission computed tomography (SPECT) allows the simultaneous assessment of left ventricular perfusion and function. We evaluated the initial risk area and subsequent evolution of perfusion and function according to TIMI flow before successful primary PCI. *Methods:* In 36 patients, treated with abciximab, primary PCI and stenting, ^{99m}Tc-sestamibi was injected before PCI and gated SPECT acquired thereafter. Gated SPECT was repeated 7 and 30 days later. Perfusion defect, wall motion score index, left ventricular ejection fraction and volumes were examined. *Results:* Before PCI, 14 patients (group A) showed TIMI flow 2–3 and 22 (group B) TIMI flow 0–1, but no differences in clinical variables, initial risk area, wall motion score, ejection fraction or volumes. Perfusion defect was smaller in group A at 7 (9%±11% vs 19%±14%, $p<0.02$) and 30 days (7%±7% vs 16%±12%, $p<0.02$) and the salvage index was higher at 30 days (77%±22% vs 55%±28%, $p<0.02$). Wall motion score was lower in group A at 30 days ($p<0.05$). Ejection fraction significantly improved in both groups at 7 and 30 days. End-diastolic volume showed a trend towards a reduction in group A, whilst it was significantly increased in group B. Conversely, end-systolic volume was significantly decreased in group A but remained unchanged in group B. *Conclusion:* In the setting of optimal myocardial reperfusion for myocardial infarction, preserved TIMI flow before PCI does not limit the initial risk area but it does improve myocardial salvage and functional recovery.

Keywords: Abciximab – Angioplasty – Myocardial infarction – Scintigraphy

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Introduction

Myocardial salvage is the main mechanism by which patients with acute myocardial infarction benefit from reperfusion therapy, either thrombolysis or primary percutaneous coronary intervention (PCI), in terms of functional recovery and clinical outcome. ^{99m}Tc-sestamibi perfusion scintigraphy is considered a most reliable method to detect myocardial salvage after reperfusion therapy [1–5]. Nowadays, perfusion imaging is performed using gated single-photon emission computed tomography (SPECT), and thus allows the simultaneous assessment of regional and global left ventricular function. This method represents a suitable tool to assess changes over time in both myocardial perfusion and left ventricular function in infarct patients [6–8]. Retrospective studies suggest that the presence of spontaneous anterograde flow before reperfusion therapy in acute myocardial infarction improves left ventricular functional recovery and patient outcome [9–11]. Data from the early 1990s suggested that in the presence of preserved flow before primary PCI there is a trend towards a smaller initial risk area, and myocardial salvage is significantly greater [12]. Since then, major advances in primary PCI,

including coronary stenting and glycoprotein IIb/IIIa receptor inhibitor (such as abciximab) administration, have been introduced. The relationship between thrombolysis in myocardial infarction (TIMI) flow before primary PCI, extent of initial risk area, subsequent myocardial salvage and functional recovery is not completely defined in the setting of the currently used techniques [13]. In this study, we used gated SPECT to examine the changes in myocardial perfusion and left ventricular function after successful primary PCI, performed with abciximab administration and coronary stenting, taking into account the TIMI flow observed in the infarct-related artery before mechanical revascularisation.

Materials and methods

Patient population

We prospectively evaluated 44 patients with first myocardial infarction referred to our catheterisation laboratory for primary angioplasty within 6 h of symptom onset, who received ^{99m}Tc-sestamibi injection before mechanical recanalisation. Infarct diagnosis was based on typical chest pain lasting for >30 min associated with >0.1 mV ST segment elevation in at least two contiguous electrocardiographic leads. Exclusion criteria were: (1) history of previous myocardial infarction or other heart disease; (2) presence of atrial fibrillation. The patient population was divided into two groups according to the TIMI flow before primary angioplasty: TIMI flow 2–3 (group A, *n*=15) and TIMI flow 0–1 (group B, *n*=29). Eight patients were excluded from the analysis for the following reasons: clinical instability precluding the acquisition of myocardial scintigraphy at admission (*n*=3 of group B); suboptimal mechanical recanalisation with TIMI flow 2 after primary angioplasty (*n*=1 of group A and *n*=3 of group B); incomplete scintigraphic data (*n*=1 of group B; patient died before 30 days' evaluation). Thus, the final study group included 36 patients who underwent successful primary PCI.

Study protocol

At admission, all patients received aspirin (500 mg), heparin (bolus of 60 U/kg body weight, up to a maximum of 5,000 U, followed by a continuous infusion of 7 U/kg per hour), clopidogrel (300 mg) and abciximab (bolus of 0.25 mg/kg body weight followed by a continuous infusion of 0.125 µg/kg per minute, up to a maximum of 10 µg/min, for 12 h). Then, patients were transferred to the catheterisation laboratory, where ^{99m}Tc-sestamibi [1,110 MBq (30 mCi)] was injected. Immediately after tracer injection, patients underwent selective coronary angiography and primary PCI. Gated SPECT was acquired within 6 h of tracer injection to assess the extent and severity of the initial perfusion defect, wall motion score, left ventricular ejection fraction and volumes. Subsequently, patients underwent baseline resting gated SPECT at 7 and 30 days of index infarction to assess the changes in the extent and severity of myocardial perfusion defect, left ventricular wall motion, ejection fraction and volumes. All patients gave informed consent to participation in the study, which was approved by the Ethics Committee of our institutions.

Coronary angiography and mechanical revascularisation

Selective coronary angiography was performed in multiple projections before mechanical reperfusion. Immediately after diagnostic angiography, PCI was performed using standard material. The TIMI flow in the infarct-related vessel before and after coronary angioplasty was graded visually by consensus of two blinded experienced angiographers. TIMI grade 3 coronary flow in the treated vessel with a residual stenosis <20% was considered indicative of successful angioplasty [14].

Gated SPECT

Scintigraphic images were acquired using a dual-head gamma camera (ADAC Vertex, Milpitas, CA, USA) equipped with high-resolution collimators and with a 15% window centred on the 140-keV photopeak of ^{99m}Tc. SPECT was performed in step-and-shoot mode, with 32 projections over a 180° elliptical orbit, matrix size 64×64, 45 s/projection, 8 frames/cardiac cycle. The studies were reconstructed using filtered back-projection without attenuation or scatter correction and realigned along the heart axis. The left ventricle was divided into 16 segments [15]. Regional wall motion was assessed visually by consensus of two blinded experienced observers and scored using a four-point scale (1=normal, 2=hypokinesis; 3=akinesis; 4=dyskinesis) [16]. Previous data indicated a good reproducibility of these evaluations in our laboratory [17]. Segments that showed tracer uptake less than 30% of peak uptake were deemed unsuitable for regional functional analysis and were considered by definition to be akinetic [18]. The left ventricular wall motion score index was calculated as the sum of the single segment scores divided by 16. Segment functional recovery after revascularisation was defined on the basis of a decrease by ≥1 grade in wall motion score at follow-up [16]. However, a change from dyskinesia to akinesia was not considered to be significant [19]. Gated SPECT processing and calculation of ejection fraction were performed by an automated and validated method [6]. Perfusion defect extent was assessed on the polar map displays using a threshold method and expressed as percentage of the left ventricular wall [4, 5, 8]. The following parameters were calculated: the initial perfusion defect (area at risk) and the infarct size at 7 and at 30 days. The difference between area at risk and infarct size provided the extent of myocardial salvage. The salvage index was calculated as the ratio between myocardial salvage and area at risk [4, 5].

Statistical analysis

Results are expressed as mean ± standard deviation. The comparisons within groups were made with the Wilcoxon paired rank test or the Friedman non-parametric analysis of variance (ANOVA), as appropriate. The comparisons between groups were made with the Mann-Whitney *U* test. The comparison of proportions was made using Fisher's exact test. The correlations between ejection fraction and perfusion defect were calculated using Pearson's correlation coefficient. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the STATISTICA 4.5 software program.

Results

Before PCI, 14 patients (group A) showed a TIMI flow of >1 in the infarct-related vessel (TIMI flow 3 in nine

Table 1. Comparison of clinical and angiographic characteristics between patients with (group A) and patients without (group B) anterograde flow of the infarct-related vessel before primary PCI

	Group A (n=14)	Group B (n=22)	p value
Mean age (yr)	64±12	62±11	NS
Men (n, %)	13 (93)	16 (73)	NS
Hypertension (n, %)	6 (43)	7 (32)	NS
Diabetes mellitus (n, %)	2 (14)	5 (23)	NS
Hypercholesterolaemia (n, %)	5 (36)	11 (50)	NS
Current smoker (n, %)	9 (64)	10 (45)	NS
Time from symptom onset to:			
Admission (min)	152±106	138±109	NS
Mechanical reperfusion (min)	227±108	211±118	NS
Multivessel disease (n, %)	5 (36)	10 (45)	NS
Myocardial infarct territory (n, %)			
Left anterior descending artery	7 (50)	6 (27)	NS
Left circumflex artery	1 (7)	4 (18)	NS
Right coronary artery	6 (43)	12 (55)	NS
Coronary stenting (n, %)	14 (100)	22 (100)	NS

and TIMI flow 2 in five) while 22 patients (group B) had no anterograde flow. There were no significant differences in baseline clinical and angiographic findings between the two groups (Table 1). Group A showed a higher degree of ST segment elevation resolution at 60 min of recanalisation (84%±26% vs 64%±25%, p<0.02) and a lower creatine kinase peak (1,413±1,260 vs 2,859±2,042 IU, p<0.03). At the time of the 30-day follow-up, no patient had evidence of re-infarction, stress-induced ischaemia (stress gated SPECT was performed in 25 patients) or restenosis of the culprit vessel (control angiography was performed in the remaining 11 patients).

Myocardial perfusion imaging

The area at risk ranged from 8% to 50% in group A (28%±14%) and from 11% to 59% in group B (33%±14%), and was not significantly different between the two groups (Table 2). The salvage index was clearly higher in group A at 7 days, and the difference became significant (p<0.02) at 30 days. Therefore, in spite of a similar trend towards a significant decrease in perfusion defect in the two groups (ANOVA chi-square 22.3, p<0.00001 and 38.9, p<0.000001, respectively, in groups A and B), the infarct size was smaller in group A patients at 7 days (9%±11% vs 19%±14%, p<0.02) and at 30 days (7%±7% vs 16%±12%, p<0.02) (Fig. 1).

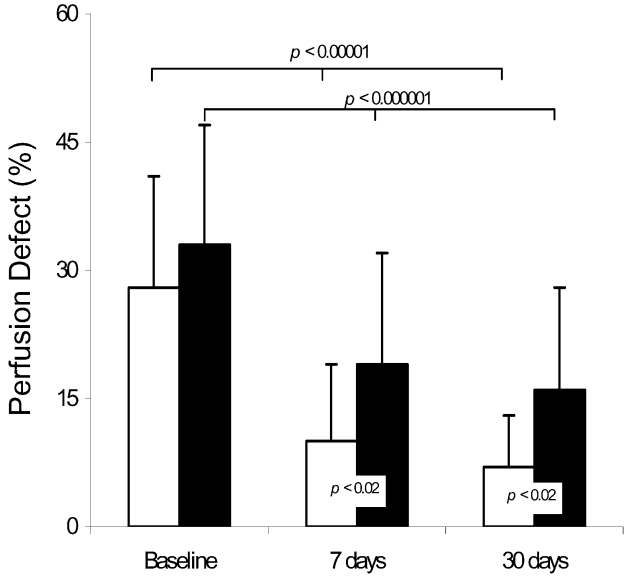

Fig. 1. Histogram showing the perfusion defect expressed in percent of left ventricular wall at admission (initial risk area before PCI = baseline) and during follow-up. Patients with preserved TIMI flow before PCI (group A) are indicated by *white bars*, and those without (group B) by *black bars*

Left ventricular function

In the admission gated SPECT, the infarct zone included 89 asynergic segments out of 224 in group A and 147 out of 352 in group B (NS), without a significant difference in the wall motion score index of the infarct zone between the two groups. At 7 days, functional recovery was observed in 52/89 (58%) asynergic segments in group A and in 49/147 (33%) in group B (p<0.0005). Also, the proportion of segmental functional recovery at 30 days was higher in group A than in group B (78% vs 71%), but the difference was not statistically significant. The wall motion score index improved significantly in both groups (ANOVA chi-square 25, p<0.000001 and 31, p<0.000001, respectively, in groups A and B), but was significantly lower in group A at 30 days (p<0.05) (Table 3). Significant correlations were found between

Table 2. Comparison of perfusion data between patients with (group A) and patients without (group B) anterograde flow of the infarct-related vessel before primary PCI

Patients	Risk area (%)	Defect at 7 days (%)	Defect at 30 days (%)	Salvage index at 7 days	Salvage index at 30 days
Group A					
1	26	1	1	0.96	0.96
2	24	1	2	0.96	0.96
3	18	1	4	0.94	0.78
4	48	22	14	0.54	0.71
5	50	26	23	0.48	0.54
6	16	16	9	0	0.44
7	39	1	1	0.97	0.97
8	12	1	2	0.91	0.83
9	23	6	4	0.74	0.83
10	13	9	8	0.31	0.38
11	38	9	2	0.76	0.95
12	29	1	1	0.97	0.97
13	41	32	21	0.22	0.49
14	8	0	0	0.38	1
Mean±SD	28±14	9±11*	7±7**	65±33	77±22***
Group B					
15	33	11	11	0.67	0.67
16	19	0	0	1	1
17	11	3	3	0.73	0.73
18	43	12	3	0.72	0.93
19	30	25	23	0.16	0.23
20	28	9	5	0.68	0.82
21	43	21	15	0.51	0.65
22	59	46	33	0.22	0.44
23	28	11	8	0.61	0.71
24	44	23	19	0.48	0.57
25	24	12	6	0.50	0.75
26	19	12	12	0.37	0.37
27	22	5	5	0.77	0.77
28	45	25	23	0.44	0.49
29	24	17	21	0.30	0.13
30	27	26	20	0.37	0.26
31	40	26	10	0.35	0.75
32	20	18	18	0.10	0.10
33	21	6	2	0.71	0.91
34	58	56	44	0.03	0.20
35	57	33	38	0.42	0.32
36	38	28	26	0.26	0.31
Mean±SD	33±14	19±14*	16±12**	47±25	55±28***

*p<0.02; **p<0.02; ***p<0.02

risk area and ejection fraction at admission (r=–0.72; p<0.00001) and between infarct size and ejection fraction at 7 (r=–0.53, p<0.001) and 30 days (r=–0.50; p<0.003). An improvement in ejection fraction was observed in both groups (ANOVA chi-square 26.1, p<0.000001 and 20.5, p<0.00005, respectively, in groups A and B; Fig. 2). As regards LV volumes, the end-diastolic volume decreased from admission to 30 days in group A, but the change was not significant; in contrast, there was a significant increase in end-diastolic volume in group B (ANOVA chi-square 8.7, p<0.02; Fig. 3). The end-systolic volume decreased significantly in group A (ANOVA chi-square 11.6, p<0.005), but remained unchanged in group B (Fig. 4).

Discussion

Retrospective studies have shown that in acute myocardial infarction, spontaneous anterograde flow (TIMI

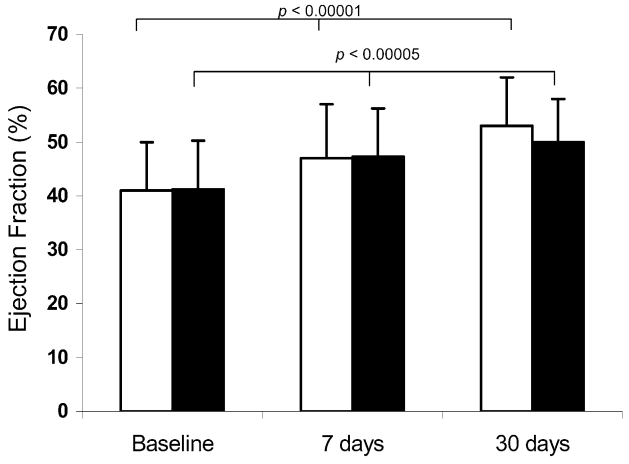

Fig. 2. Left ventricular ejection fraction at admission (= baseline) and during follow-up. Same symbols as in Fig. 1

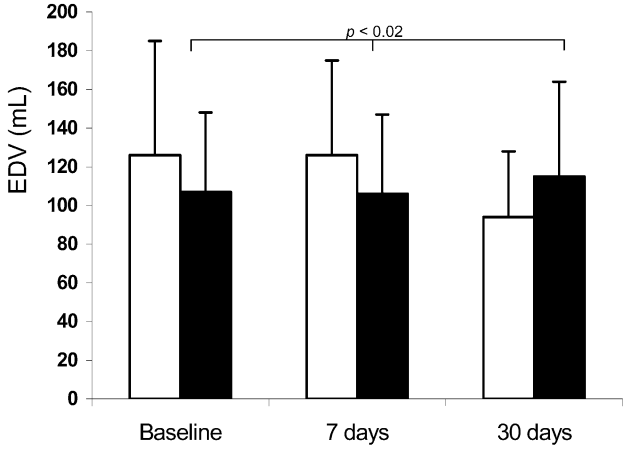

Fig. 3. Left ventricular end-diastolic volume (*EDV*) at admission (= baseline) and during follow-up. Same symbols as in Fig. 1

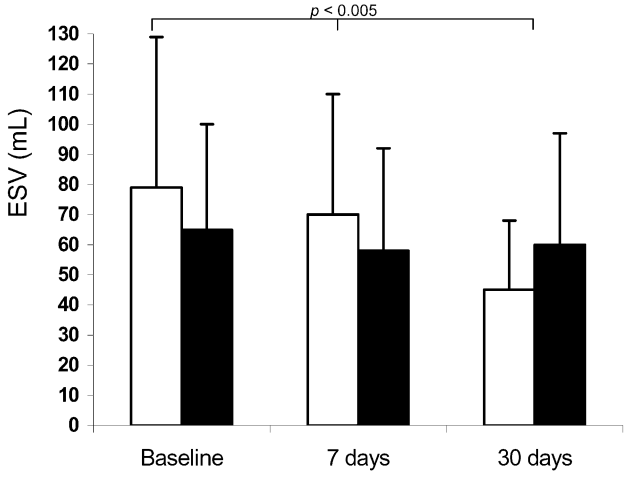

Fig. 4. Left ventricular end-systolic volume (*ESV*) at admission (= baseline) and during follow-up. Same symbols as in Fig. 1

flow >1) before reperfusion therapy improves left ventricular function recovery and patient outcome [9–11]. However, the exact mechanisms that mediate this favourable effect are still uncertain. In the early 1990s, Clements et al. demonstrated that a preserved TIMI flow (grade 1–3) was related to a smaller initial risk area and to a greater effectiveness of primary PCI in terms of myocardial salvage and limitation of the final infarct size [12]. In that study, a TIMI grade 2 or 3 was present in just 9/60 patients (15%). In our series, a TIMI grade 2 or 3 was observed in 15/43 patients (35%), possibly because of the adjunctive pharmacological treatment with abciximab, as demonstrated in the ADMIRAL study [20]. Accordingly, we used a more demanding definition of preserved flow, including grades 2 and 3 only. In this setting, the area at risk was not significantly smaller in patients with versus those without preserved anterograde flow at admission. On the other hand, the salvage index was significantly higher in patients with TIMI flow >1 before primary PCI, who also had a significantly smaller infarct size at 30 days. It could be concluded that preserved flow plays a favourable role in obtaining more extensive myocardial salvage. The more effective myocardial reperfusion was also documented by the significantly earlier ST segment elevation resolution and by the lower creatine kinase peak observed in patients with anterograde flow before PCI. These findings are in agreement with those of other recent studies, which, using different methods, verified myocardial reperfusion in infarct patients treated with primary PCI [14, 21].

As expected, the reduction in the perfusion defect was followed by the functional recovery of the infarct zone, which we could evaluate directly from perfusion imaging using gated SPECT. The use of gated SPECT to assess left ventricular function from perfusion data is the innovative methodological contribution of this study. Although area at risk and final infarct size are considered reliable surrogate end-points for studies comparing different treatment strategies in acute myocardial infarction [22], the prognostic implications of left ventricular ejection fraction and left ventricular volumes are well known [23–25]. Gated SPECT could be particularly advantageous for this kind of study, given that it allows reproducible assessment of both perfusion and functional changes [2–5, 16, 17, 26]. To our knowledge, this is one of the first studies to consider the value of repeated perfusion scans in the setting of acute myocardial infarction in conjunction with the additional contribution of repeated measurements of the left ventricular ejection fraction.

According to our data, a trend towards improvement in left ventricular function was observed in both groups, but the single parameter that became significantly different between the two groups was the wall motion score index, which was significantly lower in group A than in group B at 30 days. However, the analysis of left ventricular volume changes showed that in group A there was a

Table 3. Comparison of functional data between patients with (group A) and patients without (group B) anterograde flow of the infarct-related vessel before primary PCI

Patients	WMSI			LVEF (%)			LVEDV (ml)			LVESV (ml)		
	Adm	7 days	30 days	Adm	7 days	30 days	Adm	7 days	30 days	Adm	7 days	30 days
Group A												
1	2	1	1	40	58	58	80	105	116	48	44	48
2	1.68	1.31	1.06	54	65	68	73	86	94	33	31	35
3	1.56	1.12	1	42	44	52	142	159	75	82	90	32
4	2.37	1.43	1.43	32	42	48	144	119	72	98	69	38
5	2.37	2.06	2.12	25	42	43	189	174	186	142	101	106
6	1.37	1.31	1.25	46	47	52	93	93	60	50	49	29
7	2	1.93	1	44	46	55	95	83	86	51	45	39
8	1.25	1.06	1.06	51	55	55	120	114	71	56	52	32
9	1.5	1.43	1	40	42	67	96	116	89	57	67	40
10	1.43	1.37	1.12	35	39	42	142	149	124	91	91	72
11	1.93	1.31	1.12	26	29	39	285	255	108	210	210	65
12	1.18	1.06	1.06	49	62	62	66	51	52	34	19	20
13	2.31	2.06	1.93	36	39	44	167	137	73	107	83	41
14	1.25	1	1	53	53	58	76	126	115	36	59	49
Mean±SD	1.7±0.4	1.4±0.4	1.2±0.4*	41±9	47±10	53±9	126±19	126±49	94±34	79±50	70±40	45±23
Group B												
15	1.44	1.19	1	30	52	54	118	60	46	83	32	22
16	1.12	1	1	53	35	54	88	88	88	42	42	32
17	1.37	1.37	1.12	48	51	48	74	80	120	39	34	55
18	1.75	1.12	1.12	33	60	65	107	81	102	71	53	47
19	1.75	1.75	1.75	50	56	57	140	139	163	67	65	84
20	1.37	1.25	1.12	47	43	63	77	106	111	41	35	38
21	2.25	1.62	1.18	45	52	55	110	100	98	57	34	42
22	2.25	2.18	1.62	36	43	52	62	85	74	40	49	27
23	1.5	1.5	1.12	49	63	60	45	42	45	23	20	20
24	2	1.87	1.62	39	53	51	97	107	120	60	61	58
25	1.43	1.5	1.43	54	49	49	69	63	77	31	23	31
26	1.37	1.25	1.06	49	51	50	135	136	169	75	65	83
27	1.87	1.37	1.18	39	50	47	117	114	118	71	58	60
28	1.75	1.62	1.25	35	44	44	137	89	90	75	43	42
29	1.43	1.43	1.43	40	46	48	96	115	132	57	53	70
30	1.37	1.37	1.25	42	45	44	114	103	111	66	58	62
31	1.93	1.37	1.5	33	45	43	89	101	128	59	54	67
32	1.43	1.43	1.31	45	29	34	95	88	107	47	41	60
33	1.37	1.37	1.12	46	24	29	74	96	76	39	53	44
34	2.68	2.43	2	21	43	59	175	215	216	138	153	143
35	2.75	2.75	1.56	23	52	54	225	213	250	173	162	177
36	2.06	2	1.68	39	35	54	111	111	108	68	60	44
Mean±SD	1.7±0.4	1.6±0.4	1.3±0.3*	41±9	47±9	50±9	107±41	106±41	115±49	65±35	58±34	60±37

Adm, admission; LV, left ventricle; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; WMSI, wall motion score index

*$p<0.05$

trend towards a decrease in both the end-diastolic and the end-systolic volume, which reached statistical significance for the latter parameter. Conversely, in group B there was a significant increase in end-diastolic volume from admission to 30-day follow up, whilst the end-systolic volume remained unchanged. Therefore, whilst group A had a favourable volumetric evolution, group B showed a trend to left ventricular remodelling.

The results of this study must be evaluated with caution because of its limitations. As already mentioned, the small patient population is a most important limitation. This also prevented analysis of possible differences related to the TIMI grade in cases of preserved flow. Ideally, patients with TIMI grade 2 should be examined separately from those with grade 3. Unfortunately, the number of group A patients was too small to allow such

a separate evaluation. Similarly, we had no control group of patients who had not been submitted to revascularisation, and thus we were unable to delineate the natural history of an acute myocardial infarction as assessed by repeated gated SPECT studies. However, a large number of studies have already demonstrated the effectiveness of primary PCI in patients admitted early after symptom onset, and thus ethical considerations precluded denial of this treatment just to evaluate the natural course of gated SPECT changes. No prognostic data were available in our series and therefore we were unable to establish whether the higher degree of myocardial salvage and the better recovery of the patients with preserved flow before primary PCI also implied a more favourable clinical outcome. Naturally, the general limitations of gated SPECT for the evaluation of left ventricular function must be considered [27]. The inverse relationship between infarct size and left ventricular ejection fraction on the basis of a single gated SPECT study has recently been demonstrated, but not in the setting of acute myocardial infarction [28]. It must also be considered that the admission ejection fraction was measured after PCI and therefore some degree of very early improvement could already have been present (although this is quite unlikely), and might have affected the relationship with the perfusion defect size that was present at the time of tracer injection. Furthermore, an influence of myocardial stunning or subendocardial ischaemia in producing an apparent decrease in tracer uptake through the partial volume effect cannot be excluded [29]. It must be borne in mind, however, that gated SPECT was always acquired after a resting injection in our series, and that other data suggest that gating does not have a major influence on the infarct size assessment [30]. Finally, the difficulty in defining the regional wall motion by gated SPECT in segments with very low tracer uptake must be considered, although prior data suggest that it is very unlikely that these segments will include a significant amount of viable tissue and hence have a preserved wall motion [18].

In conclusion, our data, obtained using a single imaging modality, i.e. perfusion gated SPECT, suggest that in the setting of optimal myocardial reperfusion, preserved anterograde flow before primary PCI plays a favourable role in terms of myocardial salvage. Moreover, we observed a more favourable trend towards left ventricular ejection fraction increase and left ventricular volume decrease in patients with preserved TIMI flow compared with the other patients. Further studies on wider patient populations are needed to confirm these preliminary observations and to analyse fully their clinical and prognostic implications, particularly with regard to different TIMI grades of preserved flow.

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