Value of Myocardial Defect Size Measured by Thallium-201 SPECT: Results of a Multicenter Trial Comparing Heparin and A New Fibrinolytic Agent

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In a multicenter randomized double-blind trial comparing heparin and a new fibrinolytic agent, anisoylated plasminogen streptokinase activator complex (APSAC), 231 patients presenting with a < 5 hr acute myocardial infarction underwent a contrast angiography (CA) before the end of the first week of admission, and radionuclide cardiac blood-pool imaging and a ^{201}Tl single photon emission computed tomography (SPECT) study before the end of the third week. Left ventricular ejection fraction (LVEF) and a wall motion score (WM) were calculated from CA. LVEF was also obtained from cardiac blood-pool imaging, and defect size (DS) from ^{201}Tl SPECT. Results demonstrated that all parameters were significantly improved in patients treated with APSAC versus heparin (contrast LVEF 53 ± 13 vs. 47 ± 14 $p < 0.01$, WM 9.8 ± 6.5 vs. 13.3 ± 7.9 $p < 0.001$, radionuclide LVEF 43 ± 12 vs. 40 ± 13 $p < 0.05$, DS 14 ± 12 vs. 18 ± 14 $p < 0.05$). When the patients were divided according to infarct site and infarct-related coronary artery patency, it was demonstrated with all four parameters that the beneficial effect of APSAC can be largely explained by the lower incidence of vessel obstruction in this group (37% vs. 77% in the heparin group, $p < 0.001$). It is concluded that (a) when compared with heparin and in the conditions of the trial, APSAC significantly improves the cardiac function and decreases the DS and (b) DS measured by ^{201}Tl SPECT is as valuable a quantitative parameter of therapeutic evaluation as are LVEF and WM.

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Since the appearance of new intracoronary or intravenous fibrinolytic agents, several trials have been designed in order to demonstrate on objective grounds their beneficial effects on cardiac function (*1–6*). In most studies the end-point has been the improvement of the left ventricular ejection fraction (LVEF) measured by contrast or by radionuclide angiography. However, LVEF remains a global indicator of the cardiac function and does not provide detailed information about the presence and site of a myocardial infarction (MI). On the other side since the advent of Thallium-201 (^{201}Tl) single photon emission computed tomography (SPECT), it is possible to visualize a myocardial defect (*7*) and to measure its size (*8–10*). Therefore, when a trial was set to compare the effects of anisoylated plasminogen streptokinase activator complex (APSAC), a new fibrinolytic agent (*11*), against heparin, the results focussed on the four following parameters: LVEF and wall motion measured at contrast angiography (CA), LVEF measured at radionuclide angiography and defect size (DS) measured at ^{201}Tl SPECT. The aims were (a) to detect a possible beneficial effect of APSAC against heparin and (b) to assess the value of ^{201}Tl SPECT against the other procedures in detecting such an effect.

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MATERIALS AND METHODS

Patients Enrollment and Therapy

Between April 1986 and July 1987 the trial was conducted in three university hospitals and 20 community hospitals (see Appendix).

Patient admission was based on the intention to treat principle. Criteria for patient enrollment were age < 70 yr, chest pain of > 20 min and of < 5 hr, persistent after

nitroglycerin therapy, ST segment elevation of > 2 mV in > 2 leads. Exclusion criteria were a previous MI, a coronary artery bypass graft, cardiogenic shock at admission and any contraindication to anti-coagulant or fibrinolytic therapy.

Treatment was selected in a randomized double-blind fashion. The initial dose was 5,000 IU i.v. for heparin and 30 IU i.v. in 3 to 5 min for APSAC. In either case heparin was given at the dose of 500 IU/kg/24 hr after 4 hr. Beta-blockers and calcium-antagonists could not be administered before 6 hr.

Contrast Angiography

CA of the left ventricle and coronary arteries was performed between the second and the seventh day after admission. LVEF was calculated by the Dodge method and a WM score was obtained by the method of Leighton (*12*). Briefly, the left ventricle was divided, relatively to its long axis, into ten upper and ten lower segments. The quality of the WM was graded on a four-point scale, i.e., 0 = normal motion, 1 = mild hypokinesis, 2 = severe hypokinesis, 3 = dyskinesis. The WM score was obtained by summation of the values of the 20 segments. The degree of stenosis and the contrast material perfusion in the infarct-related coronary artery were appreciated visually, resulting in a two-class score, i.e., patent or occluded coronary artery. If indicated, a coronary dilatation was performed.

Thallium-201 Study

Between 15 and 21 days after admission, each patient was referred to the closest university hospital for the scintigraphic studies.

For myocardial scintigraphy the patient was injected, at rest and sitting, with a 1.1 MBq (30 μCi)/kg dose of ^{201}Tl chloride. Ten minutes later a SPECT acquisition was started using a rotating large field-of-view scintillation camera equipped with a low-energy, high resolution collimator. All cameras used in this study were of the same make and model (Gammatome, Sopha Medical, Buc, France). Spectrometry was set with a 25% window over the 69–83 keV x-rays and with a 15% window over the 167 keV gamma-rays of ^{201}Tl. Thirty-two views of 30 sec each were collected during a 180-degree rotation of the camera head between the left posterior and right anterior oblique projections. Each projection was stored as a 64 × 64 matrix in a dedicated computer.

All ^{201}Tl studies were processed in one center, independently by two observers blinded to the patient treatment and to the results of the other tests. Reconstruction of adjacent one-pixel thick transverse sections was performed using a backprojection algorithm with a pure ramp filter (S4000 and Sophy computers, Sopha Medical, Buc, France). A 4-2-1 weighted 18-point three-dimensional smoothing was performed (*13*) and sagittal sections were obtained. DS was measured on the most appropriate series, i.e., the transverse sections for the anterior and lateral infarcts, the sagittal sections for the inferior and posterior infarcts. The limits of the normal myocardium were delineated by thresholding with a line of isoactivity corresponding to 35% of the highest activity in the entire myocardium. The use of this threshold level has been found to be the most appropriate for infarct size measurement by ^{201}Tl SPECT in an animal model (*9*). The limits of the defect were manually drawn by interpolating between its endocardial and epicardial borders (Fig. 1). Normal muscle and defect volumes were calculated by summation of the number of pixels belonging to the normal myocardium and to the defect on all the sections passing through the myocardium. DS was expressed in percent of the entire myocardial volume.

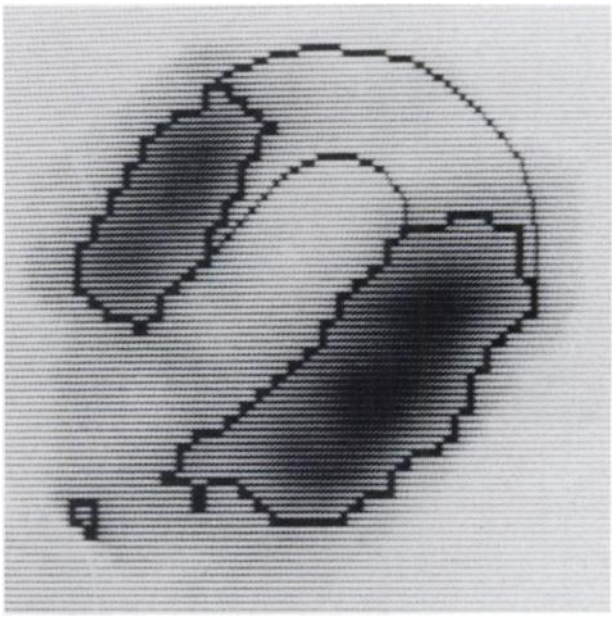

FIGURE 1
Defect size measurement on a ^{201}Tl transverse section: limits of the normal myocardium are delineated by an isocount line and limits of the defect are manually drawn.

Radionuclide Angiography

Immediately after completion of the ^{201}Tl acquisition, each patient was injected with a 74 MBq (20 mCi) dose of technetium-99m human serum albumin or in vitro labeled red blood cells. Gated cardiac blood pool imaging was performed in the left anterior oblique projection and processed in a center different of the ^{201}Tl processing center. A routine semi-automatic method using two left ventricular regions of interest was used for calculation of the LVEF (*14*).

Statistical Analysis

All results were expressed as mean ± s.d. Statistical comparison was done using Student's t-test. All p values were two-tailed.

RESULTS

Patients Population

A total of 231 patients were included in the study. Table 1 shows the baseline characteristics of this population. Lateral and posterior infarctions were grouped with inferior. There was no significant difference between the heparin and APSAC groups, except for the patency of the infarct-related artery (37 vs. 77%, $p < 0.001$). In both groups, seven patients died within three weeks after admission. Of all patients, 209 had contrast angiography, 179 had radionuclide angiography and 182 had a ^{201}Tl study.

TABLE 1
Description of the Overall Patient Population Included in the Trial

Item	Heparin group	APSAC group
Number of patients (pts)	119	112
Anterior MI (pts)	51	45
Inferior MI (pts)	68	67
Time to infusion (min)	189 ± 64	187 ± 61
Age (yr)	56 (38–70)	55 (36–70)
Male (%)	90	93
Coronary dilatation (pts)	7	23*
Patency of infarct-related Artery (%)	37	77†

*$p < 0.05$.
†$p < 0.001$.

Contrast Angiography

Table 2 demonstrates that there was a relative increase of 13% for LVEF ($p < 0.001$) and a relative improvement of 26% for WM ($p < 0.001$) in the APSAC group. The difference was still significant when the patients were separated in anterior and inferior MI. There was only a moderate and nonsignificant improvement in the subgroups containing patients with an obstructed or a patent coronary artery, probably due to the small number of patients in these subgroups.

Globally, the LVEF was significantly lower and the WM higher in the anterior than in the inferior MI (43 ± 15 vs. 54 ± 11, $p < 0.001$ for LVEF, and 16 ± 8 vs. 8 ± 4, $p < 0.001$ for WM).

Radionuclide Studies

Results in Table 3 show that the relative improvement of LVEF in the APSAC group was of 8% ($p < 0.05$). Although there was no significant difference in the other subgroups, the same tendency than with CA could be observed, i.e., LVEF was increased in both the anterior and inferior MI (19% and 4%, respectively) and was only moderately improved in the subgroups of patients with an obstructed or a patent coronary artery.

On ^{201}Tl SPECT, DS was significantly lower in the APSAC group (absolute decrease of four units, relative decrease of 22%, $p < 0.05$). Changes in the subgroups were similar to those observed with radionuclide angiography.

Role of Coronary Artery Patency and Site of Infarct

Table 4 shows that the four studied parameters were significantly better when the infarct-related coronary artery was patent rather than occluded ($p < 0.001$ for each parameter). This remained true in the anterior MI and partly in the inferior ones. The largest differences were observed in the DS (42% improvement vs. 18% for contrast LVEF, 31% for WM and 25% for radionuclide LVEF).

Similarly all four parameters were significantly better in the group of inferior than anterior MI.

Reproducibility of DS Measurement

Intraobserver reproducibility was 0.987 and 0.977 for each observer. The overall interobserver reproducibility was 0.949 (Fig. 2). It was slightly lower with the sagittal sections than with the transverse sections ($r = 0.871$ vs. 0.952, respectively) (Fig. 3). The difference between the two observers was of five units or less in 88% of the studies and in 94% of the transverse sections vs. 82% of the sagittal sections. Overall mean and standard deviation of differences in DS units were 0.2% and 4.0%, respectively.

DISCUSSION

Since the introduction of fibrinolytic agents several attempts have been made in order to detect their possible beneficial effects. Although early reports observed

TABLE 2
Results of the LVEF and WM Measurements Obtained by Contrast Angiography

	Heparin		APSAC		Heparin		APSAC	
	n	LVEF	n	LVEF	n	WM	n	WM
Overall	103	47 ± 14	106	53 ± 13†	101	13.3 ± 7.9	104	9.8 ± 6.5‡
Anterior MI								
All	42	40 ± 16	40	47 ± 14*	42	18.8 ± 8.3	40	13.2 ± 7.9†
Obstructed artery	26	36 ± 16	10	42 ± 10	26	21.6 ± 8.2	10	19.6 ± 6.9
Patent artery	16	47 ± 14	30	49 ± 15	16	14.3 ± 6.3	30	11.1 ± 7.2
Inferior MI								
All	61	52 ± 10	66	56 ± 12*	59	9.3 ± 4.7	64	7.7 ± 4.2*
Obstructed artery	40	50 ± 9	14	52 ± 13	40	9.8 ± 4.2	14	8.0 ± 3.9
Patent artery	21	55 ± 10	52	57 ± 11	19	8.4 ± 5.6	50	7.6 ± 4.4

p Denotes comparison between the heparin and APSAC groups.
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

TABLE 3
Results of the LVEF and DS Measurements Obtained by Radionuclide Studies

	Heparin		APSAC		Heparin		APSAC	
	n	LVEF	n	LVEF	n	DS	n	DS
Overall	89	40 ± 13	90	43 ± 12*	93	18 ± 14	89	14 ± 12*
Anterior MI								
All	39	32 ± 13	38	38 ± 14	40	26 ± 16	35	19 ± 15
Obstructed artery	25	27 ± 10	11	30 ± 11	26	31 ± 16	11	28 ± 17
Patent artery	14	41 ± 13	27	41 ± 14	14	15 ± 12	24	14 ± 12
Inferior MI								
All	50	46 ± 9	52	48 ± 9	53	12 ± 7	54	11 ± 8
Obstructed artery	34	44 ± 10	8	43 ± 14	34	14 ± 7	10	14 ± 12
Patent artery	16	48 ± 7	44	48 ± 7	19	10 ± 7	44	11 ± 7

p Denotes comparison between the heparin and APSAC groups.
* $p < 0.05$.

such a benefit (*1*), several subsequent studies did not show any improvement in the global cardiac function (*2–5*). However, these discrepancies can be explained most of the time by differences in the protocol, mainly in the delay between onset of chest pain and administration of the fibrinolytic agent, or by the small number of patients, which did not allow to reach statistically significant differences in cardiac function. In the present study, a relatively short delay and a large number of patients allowed us to reach a significant difference with all the studied parameters.

The question has been raised as to whether the improvement in left ventricular function following early recanalization could be a result of salvage of myocardium or amelioration in regional function of the noninfarcted segments (*15*). Our study demonstrates by two independent methods, i.e., WM and DS, that the administration of APSAC resulted in a significant degree of myocardial salvage.

In most of the other clinical trials with fibrinolytic agents blood-pool imaging was also utilized to appreciate the global cardiac function but few authors utilized ^{201}Tl scintigraphy. Anderson et al. (*3*) used planar ^{201}Tl imaging. The mean time to randomization was 2.6 hr and ^{201}Tl imaging was obtained after discharge. By a qualitative reading of the scans, they noticed that large defects were present in seven of the 12 surviving control patients and in three of the 16 treated patients ($p < 0.05$). A small defect or more was noticed in ten of the 16 treated and in only three of the 12 controls ($p < 0.05$). These result, like ours, are at variance with those of Ritchie et al. (*16*). In their series of 100 patients who underwent ^{201}Tl SPECT, DS was 19.4 ± 12.8% (n=52) for the streptokinase group and 19.6 ± 11.8% (n=48) for the control group. Interestingly, these values are similar to the values of our heparin group, i.e., 18 ± 14%. The absence of effect of the fibrinolytic therapy in their study could possibly be due to the mean time from onset of chest pain and randomization, which was 276 min vs. 189 min in our study.

It has been reported in a recent study that the global left ventricular function measured by CA improves after

TABLE 4
Effects of Coronary Artery Patency and Site of MI

	Contrast angiography				Scintigraphy			
	n	LVEF	n	WM	n	LVEF	n	DS
Obstructed artery	90	45 ± 14	90	14.0 ± 8.2	78	36 ± 13	81	21 ± 15
Patent artery	119	53 ± 14‡	115	9.6 ± 6.1‡	101	45 ± 11‡	101	12 ± 9‡
Anterior MI								
Obstructed artery	36	38 ± 15	36	21.1 ± 7.8	41	28 ± 10	37	30 ± 16
Patent artery	46	48 ± 15‡	46	12.2 ± 7.0‡	36	41 ± 13‡	38	15 ± 12‡
Inferior MI								
Obstructed artery	54	51 ± 10	54	9.3 ± 4.1	42	44 ± 11	44	14 ± 8
Patent artery	73	56 ± 11†	69	7.8 ± 4.7	60	48 ± 7‡	63	10 ± 7*

p Denotes comparison between obstructed and patent coronary artery.
* $p < 0.05$.
† $p < 0.01$
‡ $p < 0.001$.

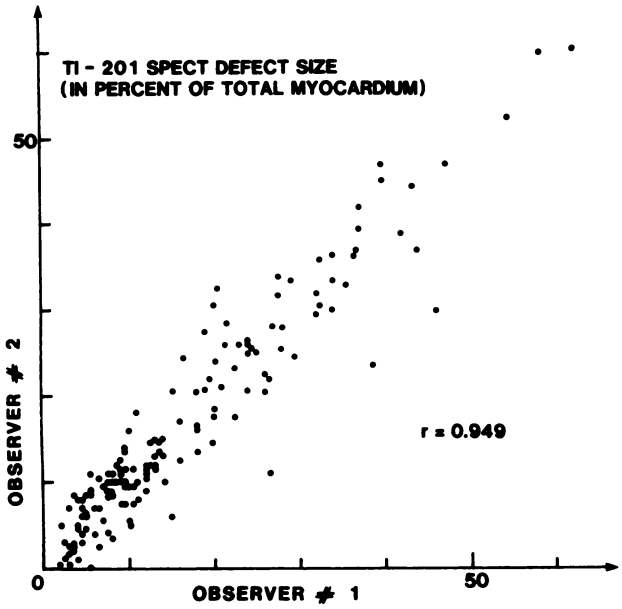

FIGURE 2
Reproducibility of defect size measurement between two observers.

an inferior myocardial infarction (*17*). This is in accordance with our results although in our study the differences were not significant for the scintigraphic parameters.

Although ^{201}Tl DS was determined by a manual method, its reproducibility compared well with that of the other techniques. For instance the mean and s.d. of differences of an automatic edge-detection method for scintigraphic LVEF calculation were reported to be 0.8% and 4.3% respectively (*1*), which is close to our 0.2% and 4.0%. However it must be noticed that a 4.0% variability in DS, which overall mean value was 16%, represents more than a 4.3% variability in LVEF, which mean value was 60%.

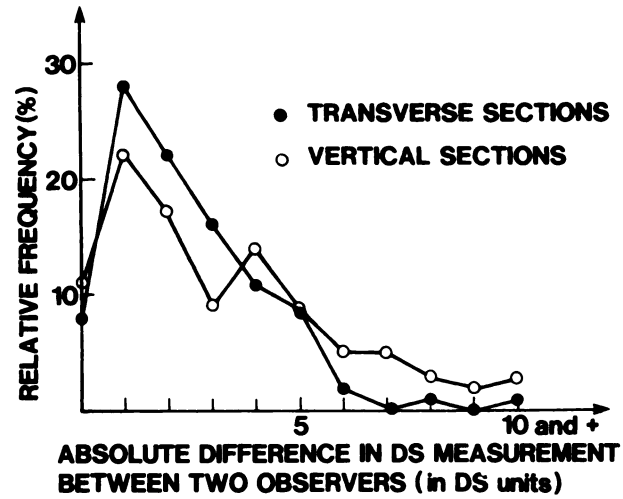

FIGURE 3
Differences in defect size measured on ^{201}Tl SPECT transverse and sagittal sections by two observers.

Some limitations of the method can hardly be overcome. Due to the lack of ^{201}Tl uptake by the infarcted myocardium, the limits of the defect can only be guessed by the operator. This is rather straightforward when the defect is small and surrounded by normal tissue. However, a very large or a peripheral defect, for instance on the posteroinferior wall, can hardly be outlined since in the former the actual curvature of the cardiac wall is unknown and in the latter the far limits of the defect falls in a tissue that does not normally take up ^{201}Tl. In these conditions, the knowledge of the shape of the normal left ventricular myocardium, as well as some experience in drawing the missing part of the wall, are necessary. Interestingly in our study the difference between the two observers was not systematically larger in the large infarcts. Among the reasons for choosing to use planes that are perpendicular or parallel to the long axis of the body rather than of the heart, are that doing so bypasses (a) the additional smoothing resulting from a rotation, and (b) the subjective choice of the long axis by the operator. Also using the long axis of the heart would change the way the basal part of the myocardium is displayed. On the sagittal sections that were used in our study, the posterobasal wall was always adjacent to a part of the anterior and septal walls, resulting in a pattern that was easy to recognize in the normal myocardium and leading to a rather straightforward estimation of a possible posterior defect. On reoriented short axis sections, because of the shortness of the muscular septum as compared with the lateral and inferior walls, the basal sections would show mostly the posterobasal and inferolateral walls, resulting in an empty image in case of MI in this territory. Delineating a defect is seldom possible in these conditions. On reoriented long axis sections an inferolateral defect would also be difficult to delineate because the sections on which it should be seen would not contain enough tissue with normal activity.

It is now widely recognized that ^{201}Tl SPECT is highly sensitive and specific in the diagnosis of MI and coronary artery disease. However it had not been recognized that it can provide quantitative results such as for instance the LVEF of cardiac blood-pool imaging. Results of this study demonstrate that through the DS, ^{201}Tl SPECT do provide quantitative results that not only offer the possibility to discriminate between the effects of two pharmaceutical agents such as LVEF does, but also that still allow a highly sensitive diagnosis of MI and directly show its site.

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