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Long-term (10 years) prognostic value of a normal thallium-201 myocardial exercise scintigraphy in patients with coronary artery disease documented by angiography

D. Pavin, J. Delonca, M. Siegenthaler, M. Doat, W. Rutishauser and A. Righetti

Cardiology Center, University Hospital, Geneva, Switzerland

In order to assess the prognostic significance of normal exercise thallium-210 myocardial scintigraphy in patients with documented coronary artery disease, we studied the incidence of cardiac death and non-fatal myocardial infarction in 69 symptomatic patients without prior Q wave myocardial infarction, who demonstrated one or more significant coronary lesions (stenosis ≥70%) on an angiogram performed within 3 months of scintigraphy (Group 1). These patients were compared to a second group of 136 patients with an abnormal exercise scintigram, defined by the presence of reversible defect(s) and angiographically proven coronary artery disease (Group 2), and to a third group of 102 patients with normal exercise scintigraphy without significant coronary lesions (stenosis ≤30%) or with normal coronary angiography (Group 3).

In contrast to coronary lesions observed in Group 2, patients in Group 1 presented more frequently with single-vessel disease (83% vs 35%, $P<0{\cdot}0001$) and with more distal lesions (55% vs 23%, $P<0{\cdot}0001$). Over a mean follow-up period of 8·6 years, one fatal and eight non-fatal cases of myocardial infarction were observed in Group 1. The majority of patients in Group 1 were treated medically: only 24 (35%) underwent myocardial revascularization, usually by coronary angioplasty. There was no significant difference in the incidence of combined major cardiac events (cardiac death, non-fatal myocardial infarction) in patients with normal exercise scintigraphy, with or without documented coronary artery disease (Groups 1 and 3), while the incidence was higher in Group 2. However, while the mortality remained very low in Group 1, the incidence of non-fatal myocardial infarction was not different from that of Group 2, where most patients underwent revascularization procedures.

In conclusion, patients with coronary artery disease and a normal exercise thallium-201 myocardial scintigram usually have mild coronary lesions (single-vessel disease, distal location) and good long-term prognosis, with a low incidence of cardiac death.
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Key Words: Thallium-201 myocardial scintigraphy, coronary angiography, prognosis.

Introduction

Thallium-201 myocardial perfusion imaging, following exercise testing or dipyridamole infusion, has become a well established diagnostic tool in coronary artery disease. It is also useful to evaluate the prognosis of the disease, especially in cases with abnormal scintigrams. Factors indicating poor prognosis include the presence of large reversible defects, left ventricular dilatation and an increase in pulmonary uptake[1].

The short-term prognostic value of a normal myocardial scintigram, following either exercise or dipyridamole, has been evaluated in patients with suspected coronary artery disease, and found to be very good[1–5]. Only two recent studies have evaluated patients with documented coronary artery disease and have reached the same conclusion[6,7]. However, long-term prognosis was assessed only once[8].

We investigated the long-term evolution of symptomatic patients with angiographically documented coronary artery disease and a normal exercise thallium-201 scintigraphy. Baseline characteristics and the occurrence of cardiac events during follow-up of this group of patients were compared to a second group of patients with angiographically documented coronary disease but an abnormal myocardial scintigram, and to a third group of patients with normal scintigraphy and no evidence of significant coronary lesions by angiography.

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Correspondence: A. Righetti, MD, FESC, Cardiology University Hospital, 1211 Geneva, Switzerland.

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Methods

Patients

From the pool of over 6000 patients who underwent thallium-201 myocardial scintigraphy in our institution between June 1978 and June 1990, we retrospectively selected those with a normal exercise scintigram, i.e. without any perfusion defect, reversible or not, and coronary artery disease demonstrated by coronary angiography and performed within 3 months (before or after) of the myocardial perfusion imaging. Patients with dilated cardiomyopathy, valvular heart disease, prior Q wave myocardial infarction detected by routine electrocardiogram, recent (<3 months) acute coronary episode (unstable angina or non-Q wave myocardial infarction) or a history of coronary revascularization procedures with either angioplasty or bypass grafting were excluded from the study.

This group of 69 patients (Group 1) was compared with two other groups selected in a similar way, from the same database using the same exclusion criteria, based on the results of exercise scintigraphy and coronary angiography.

Group 2 included 136 patients with angiographically documented coronary artery disease and abnormal scintigraphy, with one or more partially or completely reversible perfusion defects suggestive of myocardial ischaemia, combined or not with one or more permanent defects. Patients with permanent perfusion defects only, were not included, as the significance of such defects is not clear in the absence of late redistribution or re-injection. Indeed, they may be related to an area of infarction, to severe ischaemia or even, in some cases, to an artefact caused by tissue attenuation.

Group 3 included 102 patients who had no evidence of significant angiographic coronary lesions (stenosis $\leq$30%) and normal exercise scintigraphy.

Patients in Groups 2 and 3 were recruited consecutively between June 1978 and December 1985 and belong to a cohort of patients followed regularly by our Laboratory until June 1989.

Exercise scintigraphy

Our method has already been described elsewhere[9]. In summary, myocardial imaging was performed after maximal or symptom-limited exercise in the supine position on a bicycle ergometer, with the workload increased by 25 watts every 2 min. Antianginal medications were not usually discontinued. Positive electrocardiogram criteria were defined by the standard 1 mm or more horizontal or downsloping ST-segment depression or by more than 2 mm in cases of upsloping ST-segment depression, lasting at least 80 ms after the J point. Thallium-201-chloride (1·5–2·0 mCi) were infused intravenously at the peak of exercise. Planar scintigrams were obtained in the three standard projections (anterior, 45° left anterior oblique and left lateral) following exercise and the redistribution images were obtained 4 h later. Myocardial scintigrams were analysed visually (qualitative analysis) and with the help of computer software (quantitative analysis) as previously described[9]. Scintigrams were divided into five segments (anterior, septal, apical, inferior and posterior) to allow definition of the location and number of perfusion defects.

Coronary angiography

All patients underwent coronary angiography (mostly biplane) within 3 months of the exercise scintigraphy and during that period no patient suffered a major coronary event (unstable angina, myocardial infarction, angioplasty or by-pass grafting). Catheterization was performed with the standard Judkins technique and the films were reviewed by two independent physicians. Coronary artery disease was defined by the presence of at least one significant luminal narrowing ($\geq$70% visually assessed) of the three major coronary vessels or their main branches.

For each patient, it was possible to indicate the exact stenosis location: (1) proximal lesions included lesions of the left main coronary artery, lesions of the left anterior descending artery before the first septal or the first diagonal branch, lesions of the common circumflex artery and lesions of the right coronary artery before the crux; (2) distal lesions included lesions of the left anterior descending artery after the first septal or the first diagonal branch, lesions of the main diagonal artery, lesions of the circumflex artery or of its marginal branches and lesions of the retroventricular or posterior descending arteries. If either the circulation of the circumflex or right coronary artery was not dominant, any lesion was regarded as distal, irrespective of its location. The most proximal lesion defined the score for each of the three main vessels and a lesion of the left main coronary artery was equal to two proximal lesions (left anterior descending artery and circumflex).

Data concerning the collateral circulation were collected in 66 out of 69 patients with normal scintigraphy. The three remaining patients underwent coronary angiograms in another hospital and the report did not mention the presence or absence of a collateral circulation.

Coronary artery disease was not considered angiographically significant if the angiograms were normal or only showed slight parietal irregularities or vessel narrowing which did not exceed 30% of the diameter.

The left ventricular ejection fraction was calculated using the Dodge method from the left ventricular angiogram obtained by biplane or the right anterior oblique view.

Follow-up

All patients or a family member were contacted by 'phone and requested to complete a standard medical

Table 1 ***Clinical, ergometric and scintigraphic data in the three groups of patients***

	Group 2 Tl-201 (+) Coro (+) (n=136)		Group 1 Tl-201 (−) Coro (+) (n=69)		Group 3 Tl-201 (−) Coro (−) (n=102)
Baseline characteristics:					
Mean age (years)	53 ± 8	ns	55 ± 9	****	47 ± 11
Gender (male %)	92	***	74	ns	68
Diabetes mellitus	12 (9%)	ns	9 (13%)	ns	7 (7%)
β-blockers	77 (57%)	****	19 (28%)	ns	26 (25%)
Nitrates	85 (62%)	*	28 (41%)	ns	32 (31%)
Non-Q wave myocardial infarction	25 (18%)	ns	12 (17%)	****	1 (1%)
Typical angina	119 (87%)	****	32 (46%)	ns	49 (48%)
Ergometric data					
Peak workload (Watts)	95 ± 28	**	107 ± 34	ns	113 ± 36
Age-predicted maximum heart rate (%)	70 ± 11	****	79 ± 13	ns	80 ± 14
Double product	21 000 ± 5500	****	26 200 ± 5700	ns	26 900 ± 6600
Chest pain	70 (51%)	****	7 (10%)	ns	9 (9%)
ST-segment depression	96 (71%)	****	12 (17%)	ns	17 (17%)
Scintigraphic data					
Transient perfusion defect(s)	2·3 ± 0·9		o		0
Permanent perfusion defect(s)	0·2 ± 0·5		0		0

Tl-201=thallium-201 exercise scintigraphy normal (−) or abnormal (+); Coro=coronary arteriography normal (−) or abnormal (+). ns=p non-significant; $*P<0{\cdot}005$; $**P<0{\cdot}001$; $***P<0{\cdot}0005$; $****P<0{\cdot}0001$.

oral questionnaire. In case an ischaemic event had occurred, or when a patient was hospitalized, the patient's physician was contacted and requested to confirm the diagnosis for each event and to provide relevant discharge summaries and other objective documentation. Deaths were interpreted as cardiac (sudden or non-sudden) or non-cardiac, based on evaluation of hospitalization autopsy and family interview data. Sudden cardiac death was considered when occurring within 1 h of the onset of symptoms. Myocardial infarction was verified by hospital documents and the diagnosis based on accepted criteria of characteristic chest pain, electrocardiographic and enzyme changes.

Group 1 patients were followed-up until May 1994. For Groups 2 and 3, the follow-up data were collected to June 1989. Follow-up data were obtained for all patients, except for two in Group 1 and four in each of the other two groups.

Statistical analysis

Numerical data are expressed as mean ± 1 SD or as percentages. Clinical parameters were compared among groups with either an unpaired t-test for the comparison of averages or with a Chi^2 test for the comparison of proportions.

Cardiac events during follow-up include cardiac death and non-fatal myocardial infarction. The analysis was based on the Kaplan–Meier method with comparisons made of: (1) combined major cardiac events (cardiac death or non-fatal myocardial infarction): only the first event was taken into account; (2) cardiac death only; (3) non-fatal myocardial infarction only. In cases of recurrent myocardial infarction, only the first event was taken into account.

All patients, even those with missing follow-up data, were included in the construction and analysis of the Kaplan–Meier curves. The curves were compared 2 by 2: first, patients with documented coronary artery disease, with or without normal scintigrams, and second, patients with normal scintigraphy, with or without angiographically documented coronary artery disease. The statistical analysis took into account the complete follow-up period (up to 10 years) using the Mantel–Cox Log Rank test, which gives the same weight to all the points of the curve. A test reached statistical significant when the P value was lower than 0·05.

Results

Clinical, ergometric and scintigraphic data

Clinical, ergometric and scintigraphic data are presented in Table 1. Patients with normal scintigrams, with or without documented coronary artery disease had similar symptoms, antianginal drug consumption and ergometric data. However, patients with angiographically documented coronary artery disease were older and more frequently had a history of non-Q wave myocardial infarction. However, patients with an abnormal angiogram and an abnormal scintigram more frequently had anginal attacks and therefore a higher consumption of anti-anginal drugs than patients with a normal scintigraphy. They also had a higher incidence of positive exercise tests, which accounts for the statistically significant lower value of the parameters related to the intensity of exercise.

If, by definition, all patients with abnormal scintigraphy had at least one transient perfusion defect

Table 2 Angiographic data of patients with significant coronary artery disease, depending on the normal or abnormal result of the Tl-201 exercise scintigraphy

	Significant coronary stenosis (≥70%)		
	Tl-201 normal (n=69)		Tl-201 abnormal (n=136)
LVEF (%)	67 ± 9	*	64 ± 10
Coronary lesions:			
LMCA or 3-vessel disease	3 (4%)	***	40 (29%)
2-vessel disease	9 (13%)	**	48 (35%)
1-vessel disease	57 (83%)	***	48 (35%)
Number of diseased vessels	1·2 ± 0·5	***	1·9 ± 0·8
Location of lesions:			
LMCA	0		7 (3%)
LAD	37 (44%)	ns	96 (38%)
Cx	19 (23%)	ns	72 (28%)
RCA	28 (33%)	ns	79 (31%)
Proximal lesion	36 (45%)	***	196 (77%)
Distal lesion	44 (55%)	***	58 (23%)

Cx=circumflex artery; LAD=left anterior descending artery; LMCA=left main coronary artery: LVEF=left ventricular ejection fraction.
RCA=right coronary artery.
ns=*P* non-significant; **P*<0·05; ***P*<0·005; ****P*<0·0001.

(2·3 ± 0·9 per patient on average), few patients had a concomitant permanent perfusion defect (0·2 ± 0·5 per patient on average). This low incidence can probably be explained by the exclusion of patients with a history of Q-wave myocardial infarction, despite a history of non-Q wave myocardial infarction in 18% of cases.

Patients in Group 3 had a normal ejection fraction which was not significantly different from patients in Group 1 (68 ± 7% vs 67 ± 9%, *P*=ns). In Group 3, most patients had normal angiograms (74 patients: 71%), while 30 patients (29%) had minimal lesions (stenosis ≤30%).

Angiographic data

Comparison of angiographic data for patients with coronary artery disease appears in Table 2. Left ventricular ejection fraction, although slightly lower in patients with abnormal scintigraphy, remained normal for most of these patients: only one patient presenting with severe three-vessel disease had an ejection fraction below 40% vs no ejection fraction below 40% in patients with normal scintigrams.

Contrary to patients with an abnormal scintigraphy, those with normal scintigraphy had one-vessel disease in 83% of cases, with lesions affecting distal segments or minor branches. The distribution between the three main coronary vessels was comparable. However, lesions of the left anterior descending artery were more often located and isolated on a diagonal branch in patients with normal scintigraphy compared to patients with abnormal perfusion imaging (11 of 37=30% vs eight of 96=8%, *P*<0·005). In addition, when taking into account lesions of the left anterior descending artery only (excluding lesions of a diagonal branch), proximal lesions were more frequent in patients with abnormal scintigrams (65 of 88=74% vs 11 of 26=30%, *P*<0·005). The presence of a collateral circulation was observed in 12 of 66 documented cases: in 10 patients with single-vessel disease and in two patients with two-vessel disease where it was only supplying one of the two vessels.

Follow-up

The mean follow-up was 103 ± 43 months in Group 1, 90 ± 32 months in Group 2 and 105 ± 25 months in Group 3.

In Group 2, there were eight non-cardiac deaths (five from cancer, one from cerebral haemorrhage, one following surgery for an aneurysm of the abdominal aorta and one from sepsis), and 21 cardiac deaths (13 sudden deaths, two myocardial infarctions and six during or following cardiac revascularization procedures). Seventeen patients had at least one non-fatal myocardial infarction. Only one patient had two events: a non-fatal myocardial infarction followed after a few weeks by sudden death. In this group, 90 patients (68%) underwent at least one myocardial revascularization procedure (81 coronary bypass grafts vs nine angioplasties), mostly within the first 6 months after the scintigraphy (63 patients). The first revascularization procedure was essentially bypass grafting (81 vs nine angioplasties), and non-fatal myocardial infarction was not in evidence during these procedures.

In Group 1, there was no non-cardiac and one cardiac death after myocardial infarction. However, eight patients had a non-fatal myocardial infarction. Most patients were treated medically and only 24 (35%) underwent a myocardial revascularization procedure (eight coronary bypass grafts vs 16 angioplasties), within

***Table 3** Characteristics of patients with documented coronary artery disease and a normal scintigraphy who presented a major cardiac event*

Patient	Age (years)	Gender	Angina	nQ MI	% PMHR	Watts	Ex. ECG	N Ves.	Vessel	Revasc.	Cardiac events	
											Date (months)	Type
1	65	M	+	−	74	100	−	1	Diag.	—	1	MI
2	54	M	+	−	90	125	−	1	LAD	—	4	MI
3	60	F	+	−	96	75	−	2	LAD+RCA	CABG	5	MI
4	56	M	−	+	88	125	−	1	LAD	PTCA	10	MI
5	56	M	−	−	80	175	−	1	Diag.	—	11	MI
6	41	M	+	−	78	125	−	2	LAD+RCA	CABG	20	CD
7	61	M	+	−	66	75	−	1	Cx	—	59	MI
8	38	M	−	−	88	150	−	1	LAD	PTCA	80	MI
9	58	F	+	−	69	50	+	1	RCA	—	111	MI

CABG=coronary artery bypass graft; CD=cardiac death; Cx=circumflex artery; Diag.=principal diagonal branch; Ex. ECG=exercise ECG: +=ST-segment depression; LAD=left anterior descending artery; MI=non-fatal myocardial; nQ MI=non-Q wave myocardial infarction; N Ves =number of diseased vessels; PMHR=age-predicted maximal heart rate; PTCA=percutaneous transluminal coronary angioplasty; Revasc.=revascularization procedure; Watts=peak workload during exercise stress test.

the first 6 months of the scintigraphy for half of them (12 of 24); no secondary non-fatal myocardial infarction related to the procedure was observed. The characteristics of patients who had a major cardiac event are presented in Table 3. Ergometric data were similar to those of patients without a major cardiac event. Six out of nine patients had typical angina and five patients had left anterior descending artery lesions located on the proximal segment in four cases. In four patients, a major cardiac event occurred despite myocardial revascularization. More than half of the events (5/9) occurred during the first year following the exercise scintigraphy.

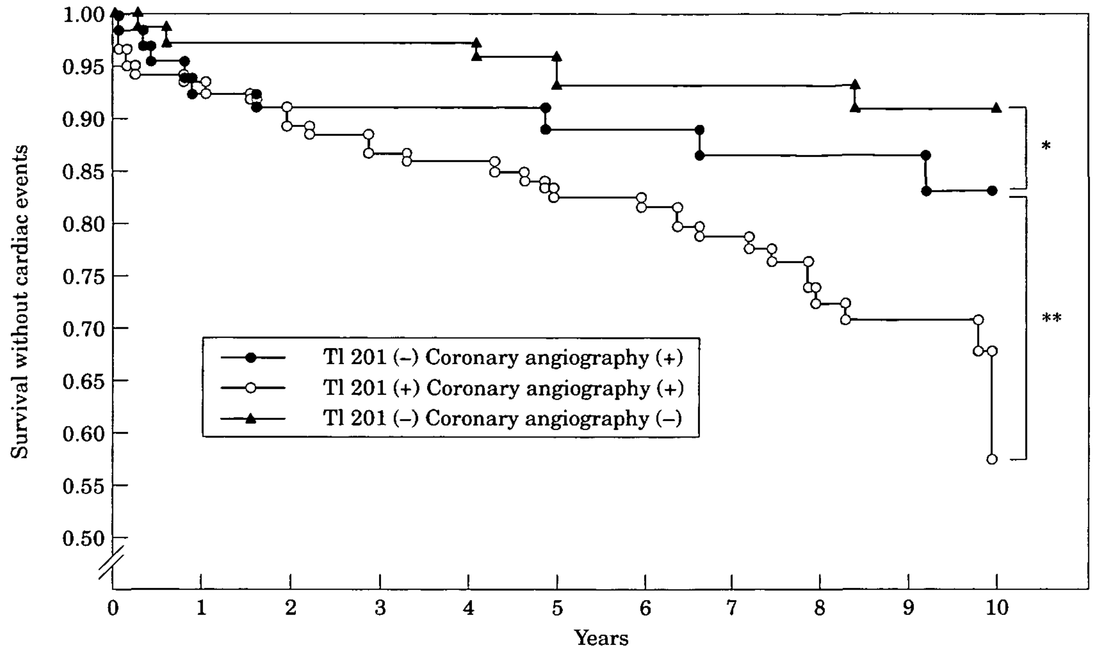
In Group 3, there were three non-cardiac deaths (two from cancer and one from stroke), two sudden deaths and four non-fatal myocardial infarctions (which occurred several years later). Three of the six patients with a major cardiac event had a strictly normal angiogram, and five of them underwent coronary bypass surgery during the follow-up.

Comparisons between the follow-up data of the three groups appear in Figs 1 to 3. Patients in Group 1 had a lower incidence of combined major cardiac events (cardiac death or non-fatal myocardial infarction) than patients in Group 2. Indeed, the survival rate without cardiac death or myocardial infarction was 83% after 10 years in Group 1 vs 58% in Group 2 (Fig. 1). This was the consequence of low cardiac mortality in Group 1, which was in fact comparable to the cardiac mortality rate in Group 3 (Fig. 2). Most cardiac events in Group 1 were non-fatal myocardial infarction (15% at 10 years), and it must be noted that their incidence was not statistically different in Groups 1 or 2.

Discussion

Our study underlines the good long-term prognostic value of thallium-201 myocardial perfusion imaging, especially in terms of cardiac death, in patients with documented coronary artery disease but no prior history of Q-wave myocardial infarction.

The analysis of published data on exercise or dipyridamole scintigraphy yields very low rates of major cardiac events (cardiac death or myocardial infarction), averaging about 1% per year[1–7]. All these studies are retrospective, and most of them used planar scintigraphy, although similar results have been reported with computed tomography[4,5,7]. They included mostly patients with suspected coronary artery disease, without documented coronary angiograms. Therefore, the real prevalence of coronary artery disease remains uncertain in these studies. Only two studies, published recently, report results obtained in patients with normal exercise scintigraphy and documented coronary artery disease[6,7]. Brown and Rowen[6] evaluated 75 patients with a mean age of 59 years: 39 patients (52%) had single-vessel disease, 21 (28%) had two-vessel disease and 15 (20%) had three-vessel disease. During a mean follow-up of 2 years, only one clinical event occurred (one non-fatal myocardial infarction). However, there is no mention of the incidence of revascularization procedures, if any, during that period. Fattah *et al.*[7] reported the follow-up during a period of 32 months on average of 97 patients with a mean age of 60 years: 52 patients (54%) had single-vessel disease, 30 (31%) had two-vessel disease and 15 (15%) had three-vessel disease. Three major cardiac events occurred (two cardiac deaths and one non-fatal myocardial infarction), and 21 patients underwent myocardial revascularization by either angioplasty or bypass grafting because of the worsening of their symptoms. It must be noted that the threshold defining a significant coronary stenosis was 50% in those two studies, which might explain the rather high frequency of multivessel disease. Indeed, the prognosis of patients with moderate stenosis (50–70%) seems better than the prognosis those with more severe lesions (>75%)[10]. This could put into perspective the conclusions of Brown and Rowen and of Fattah *et al.*



—●—	69	62	61	61	58	48	44	34	32	25	24
—○—	136	124	121	114	112	107	101	77	53	35	20
—▲—	102	95	95	95	95	93	91	89	69	46	28

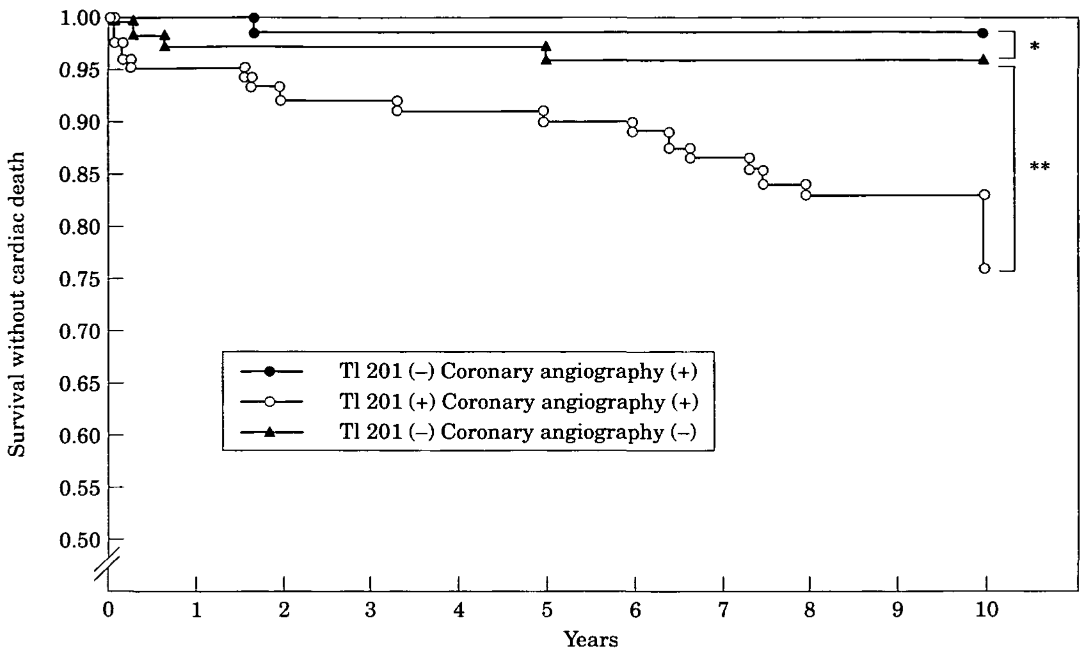
Figure 1 **Incidence of major cardiac events (cardiac death and non-fatal myocardial infarction) in the 3 groups (Kaplan—Meier curves). TI-201 = thallium-201 scintigraphy: normal (–) or abnormal (+). Coronary angiography (–) = angiographically normal or insignificantly narrowed (stenosis <30%) coronary arteries. Coronary angiography (+) = significant coronary artery stenosis (>70%). Mantel's chi-square: *3·33 (*P*=ns); **5·13 (*P*<0·05).**

Our study is one of the very few which evaluated the long-term prognosis of normal perfusion imaging (mean follow-up: 8·6 years), and our results confirm previously published data by showing the good prognostic significance of normal scintigraphy in patients with documented coronary artery disease. In fact, only one other study assessed the long-term prognosis of normal perfusion imaging[8], in 309 patients (mean age 53 years) with suspected coronary artery disease. Over the follow-up period of 9 to 11 years, 18 patients died with a low number of cardiac deaths (3), yielding an overall mortality of 6% and a cardiac mortality of 1%. However, these results are to be taken with caution because of: (1) the lack of information concerning the indication for the thallium-201 scintigraphy (and therefore the real prevalence of coronary artery disease), and (2) the number of patients (21) lost during follow-up.

In our study, the good long-term prognosis of patients with documented coronary artery disease and normal scintigraphy is mainly due to the very low cardiac mortality, which is comparable to the cardiac mortality in a population of patients without coronary artery disease or with minor coronary lesions. Indeed, patients with minor coronary lesions appear to have a low incidence of cardiac death (2–2·7%) during long-term (7 to 10 years) follow-up[11–13]. The event which seems to occur most frequently in that group of patients is non-fatal myocardial infarction (7·5–10% after 10 years)[11,12].

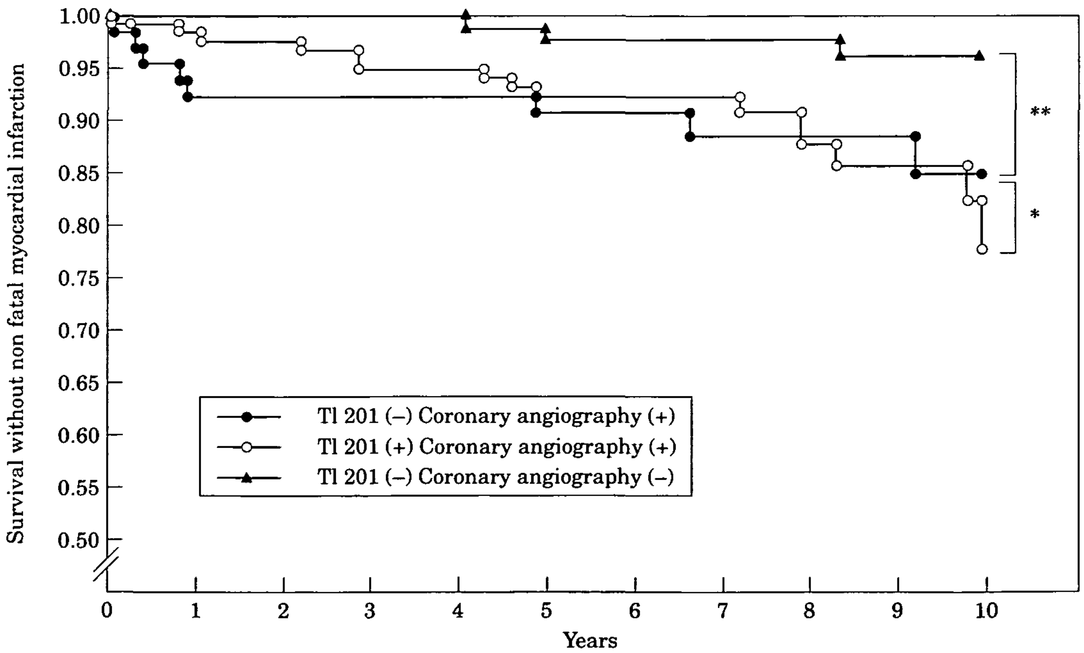
Contrary to other published data, the incidence of non-fatal myocardial infarction is higher in our study (12% for a mean follow-up of more than 8 years), which can be explained by our selected population of patients with documented coronary artery disease. However, this incidence remains lower than the result reported in the literature for medically treated patients, which suggests an incidence of non fatal myocardial infarction just below 3% per year[14].

The incidence of non-fatal myocardial infarction was similar in patients with documented coronary artery disease, whatever the result of the scintigraphy and despite the fact that coronary artery disease appeared to be more severe in patients with abnormal scintigraphy. Koss *et al.* also reported a similar rate of non-fatal myocardial infarction in 515 patients with suspected coronary artery disease and a mean follow-up of 3 years (1·3% vs 1·4% in patients with an abnormal and a normal scintigraphy respectively), although the incidence of myocardial infarction was rather low[15]. Three explanations can be given for these results. Firstly, it is difficult to anticipate the occurrence of myocardial infarction which is probably connected to the presence of atherosclerosis and not to its severity. If plaque disruption followed by platelet deposition triggers



—●—	69	67	66	66	63	56	50	40	36	28	27
—○—	136	126	124	120	119	117	111	86	62	40	23
—▲—	102	95	95	95	95	94	93	90	68	47	28

Figure 2 **Incidence of cardiac deaths in the three groups (Kaplan–Meier curves). Mantel's chi-square: *0·37 (*P*=ns); **9·99 (*P*<0·005).**



—●—	69	62	61	61	58	48	44	34	32	25	24
—○—	136	124	121	114	112	107	101	77	53	35	20
—▲—	102	95	95	95	95	93	91	88	68	46	28

Figure 3 **Incidence of non-fatal myocardial in the three groups (Kaplan–Meier curves). Mantel's chi-square: *0·05 (*P*=ns); **6·13 (*P*<0·005).**

coronary thrombosis and is the cause of most acute coronary events, it is difficult to predict in clinical practice. In the Lipid Research Coronary Prevention Trial[16] where patients with asymptomatic hypercholesterolaemia were followed for 7 to 10 years, a positive treadmill test (and the extent of it) allowed patients with a high mortality risk to be selected. However, the incidence of non-fatal myocardial infarction was similar in patients with or without a positive treadmill test, whatever its extent. In addition, the degree of coronary stenosis does not seem to influence the risk of myocardial infarction. Indeed, Little *et al.* reported that in a population of patients with acute myocardial infarction the culprit artery had a narrowing smaller than 50% at prior angiography in 66% of cases, and smaller than 70% in 97% of cases[17]. Secondly, the incidence of cardiac death increases while the incidence of non-fatal myocardial infarction decreases with the progression of coronary lesions[18]. Myocardial perfusion imaging appears to detect patients with more severe coronary artery disease, in whom the risk of mortality is higher than the risk of morbidity. Thirdly, most coronary artery disease patients with abnormal scintigraphy underwent myocardial revascularization, which confers a better protection against myocardial infarction than medical treatment alone in symptomatic patients with three-vessel disease, especially in cases of proximal or left anterior descending artery lesions[19]. This was indeed the case in many of our patients with abnormal scintigraphy.

Independently of left ventricular function, which has a well-established prognostic value, the good prognostic value of normal scintigraphy, in terms of cardiac death, can be compared to the good prognosis of coronary artery disease patients with no exercise-induced ischaemia, detected by either an electrocardiogram[20] or an exercise radionuclide coronary angiography[21,22], even in cases of three-vessel disease.

In fact, the amount of myocardium at risk, where ischaemia can be detected, appears to be the major prognostic factor. In coronary artery disease patients, a normal scintigram is highly suggestive of either lesions of limited extension, usually located distally on marginal branches, or of a functional collateral circulation. In our study, most of the coronary artery disease in patients with normal scintigraphy had single-vessel disease (83%). In a review of the literature, Kotler and Diamond found a sensitivity for the diagnostic value of thallium-201 scintigraphy of 78% for the detection of single-vessel disease vs 89% and 92% for the detection of two- or three-vessel disease[23]. Moreover, lesions are usually distal and few are located on the proximal segment of the left anterior descending artery. In patients with single-vessel disease treated medically, the proximal or distal location of the lesion only influences the prognosis in cases of a proximal lesion of the left anterior descending artery, where survival at 5 years is 90% vs 98% when the left anterior descending artery lesion is located distally[24]. In cases of multivessel disease, proximal left anterior descending artery lesions are also notorious for influencing the prognosis, and the European Coronary Surgery Study showed a significant benefit for the surgical management of such patients[25].

Finally, the presence of a collateral circulation was found in 18% of our patients. These collaterals were probably functional because, despite the occlusion or sub-occlusion of the coronary vessel, none of the patients had an extensive myocardial infarction, as evidenced by the absence of a Q wave on the electrocardiogram, a good global left ventricular function and normal scintigraphy. Although the role of a collateral circulation has been the source of past controversies, it can probably prevent myocardial infarction or at least limit its size, preserving left ventricular function and therefore improving survival[26,27].

Limitations of the study

(1) Our study was retrospective, which can introduce certain biases, and especially a selection bias, as all our patients had symptoms which prompted coronary angiography; (2) coronary lesions were quantified visually, but they were assessed by at least two independent experienced cardiologists which reflects common clinical practice. In addition, unlike other published data, and in particular the only two studies which assessed the prognostic value of normal scintigraphy in patients with documented coronary artery disease, our threshold to define a significant lesion was 70%; (3) We did not study the natural history of coronary artery disease, as most coronary artery disease patients with abnormal scintigraphy underwent an early revascularization procedure. However, these were appropriate, well-established therapeutic interventions in extensive lesions with proven myocardial ischaemia. In contrast to other studies, all patients who underwent early revascularization were included in our analysis. We believe that to have left them out would have introduced a greater selection bias, because it would increase the number of medically treated patients denied revascularization because of severe and extensive coronary artery disease. However, few coronary artery disease patients with normal scintigraphy underwent myocardial revascularization and they represent our main study group; (4) Although there was an overlap between recruitment and follow-up periods, there was a temporal shift between the group of coronary patients with normal scintigraphy and the other groups. Thus, different therapeutic approaches that may have influenced the outcome of patients have been used. Since thrombolytic therapy and use of aspirin have been demonstrated to improve prognosis in patients with myocardial infarction (and also in patients with chronic stable angina who take aspirin), it introduces a selection bias in favour of Group 1 patients. However, the majority of these patients were recruited before the general use of these therapies towards the end of the 1980s and 6/9 cardiac events occurred before 1986. Conversely, revascularization procedures were all available during the period of the study, even if the indication and techniques of angioplasty changed

rapidly; (5) The surgical mortality may seem high in these patients, given their good global left ventricular function, and despite coronary artery disease, abnormal scintigraphy and bypass grafting, but some patients underwent a second operation during the long follow-up.

Conclusion

Our study suggests that normal thallium-201 scintigraphy yields a good long-term prognosis, especially in terms of cardiac mortality, in symptomatic patients with stable angina pectoris and documented coronary artery disease, undergoing symptom-limited exercise tests. In such patients, coronary lesions are often limited and distal, with sometimes the presence of a collateral circulation. If the incidence of non-fatal myocardial infarction remains low in this population, the risk is not negligible, and so is the evolution of coronary atherosclerosis in general. Coronary angiography can be proposed in patients who remain symptomatic despite medical treatment, but should not be performed routinely.

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