3 Atherton DW. Breast feeding and atopic eczema. *Br Med J* 1983;**287**:775-6.
4 Burr ML. Does infant feeding affect the risk of allergy? *Arch Dis Child* 1983; **58**:561-5.
5 Gerrard JW. Allergy in breast fed babies to ingredients in breast milk. *Ann Allergy* 1979;**42**:69-72.
6 Warner JD. Food allergy in fully breast fed infants. *Clin Allergy* 1980;**10**:133-6.
7 Van Asperen PP, Kemp AS, Mellis CM. Immediate food hypersensitivity on first known exposure to the food. *Arch Dis Child* 1983;**58**:253-6.
8 Donnally HH. The question of elimination of foreign protein (egg white) in woman's milk. *J Immunol* 1930;**19**:15-40.
9 Kilshaw PJ, Cant AJ. The passage of maternal dietary protein into human breast milk. *Int Arch Allergy Appl Immunol* 1984;**75**:8-15.
10 Yates VM, Kerr REI, Mackie RM. Early diagnosis of infantile seborrhoeic dermatitis and atopic dermatitis—clinical features. *Br J Dermatol* 1983;**108**:633-8.
11 Kramer MS, Moroz B. Does breast feeding and delayed introduction of solid foods protect against subsequent atopic eczema? *J Pediatr* 1981;**98**:546-50.
12 Taylor B, Wadsworth J, Golding J, Butler N. Breast feeding, eczema, asthma and hayfever. *J Epidemiol Community Health* 1983;**37**:95-9.
13 Hattevig G, Kjellman B, Johansson SGO, Bjorksten B. Clinical symptoms and IgE responses to common food proteins in atopic healthy children. *Clin Allergy* 1984;**14**:551-9.
14 Atherton DJ, Sewell M, Soothill JF, Wells RS, Chilvers CED. A double-blind crossover trial of antigen avoidance diet in atopic eczema. *Lancet* 1978;i:401-3.
15 Ford RPK, Fergusson DM. Egg and cow's milk allergy in children. *Arch Dis Child* 1980;**55**:608-10.
16 Yates VM, Kerr REI, Frier K, Cobb SJ, Mackie RM. Early diagnosis of infantile seborrhoeic dermatitis and atopic dermatitis. Total and specific IgE levels. *Br J Dermatol* 1983;**108**:639-45.
17 Danneus A, Johansson SGO. A follow up study of infants with adverse reactions to cow's milk 1. Serum IgE, skin test reactions and RAST in relation to clinical course. *Acta Paediatr Scand* 1979;**68**:377-82.
18 Taylor B, Fergusson DM, Mahoney GN, Hartley WA, Abbott J. Specific IgA and IgE in childhood asthma, eczema and food allergy. *Clin Allergy* 1982;**12**: 499-505.
19 Hamburger RN. Diagnosis of food allergies and intolerance in the study of prophylaxis and control groups in infants. *Annalés Nestlé* 1984;**42/3**:54-8.
20 Lessof MH, Buisseret PD, Merret J, Merret TG, Wraith DG. Assessing the value of skin prick tests. *Clin Allergy* 1980;**10**:115-20.
21 Michel FB, Bousquet J, Geillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentration and maternal allergy for the prediction of atopic diseases in infancy. *J Allergy Clin Immunol* 1980;**65**:422-30.
22 Mellander L, Carlsson B, Hanson LA. Development of the secretory immune defense (S-IgA and IgM) in newborns and infancy. *Lakaresallskapets Riksstamma, Stockholm, 30 Nov-2 Dec, 1983.* Abstract PE2.
23 Fergusson DM, Horwood LJ, Beautrais AL, Shannon FT, Taylor B. Eczema and infant diet. *Clin Allergy* 1981;**11**:325-31.
24 Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six month's total solid food elimination. *Acta Paediatr Scand* 1983;**72**:411-4.

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Does stopping smoking delay onset of angina after infarction?

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Abstract

This study was designed to determine the relation between stopping smoking and angina after infarction in survivors of an acute coronary attack. The study population comprised 408 men aged under 60 who survived a first attack of unstable angina or myocardial infarction by 28 days and were smoking cigarettes at the time of their attack. These patients were followed up for an average of nine years. Three hundred and eighty four were alive at the one year follow up examination, when the presence or absence of angina together with habits of smoking were recorded. The prevalence of angina at one year was 19·5% in the 241 who had stopped smoking cigarettes compared with 32·2% in those who had continued ($p < 0.01$). Six years later, however, the prevalence of angina after infarction was the same in the two groups.

It is concluded that the onset of angina after infarction can be delayed by stopping smoking cigarettes but that this effect is not maintained in the long term.

Introduction

The greater chance of survival for those who stop smoking cigarettes after a coronary attack is well documented,[1-10] but only one report (with negative findings) mentions explicitly the relation between stopping smoking cigarettes and subsequent angina pectoris.[8] This paper examines this question in a long term follow up study of 408 men who smoked and survived a first attack of unstable angina or myocardial infarction and were entered into the St Vincent's Hospital heart study.

Patients and methods

Between 1 January 1965 and 31 December 1975, 555 consecutive men aged under 60 who survived a first attack of unstable angina or myocardial infarction by at least 28 days were admitted into a long term follow up study. Diagnostic criteria for entry to the study have been previously published.[1] This report concentrates on the 408 (73·4%) of those patients who were smoking one or more cigarettes daily in the three months before their attack. Of these, 81 (19·9%) had a diagnosis of unstable angina.

A uniform programme of rehabilitation and secondary prevention included advice in hospital and at follow up against smoking. Routine drugs such as anticoagulants or β blockers were not used. Follow up data were recorded annually at a special clinic, and 384 of the 408 patients who smoked before the study began were alive at their first ("one year") examination (mean time to examination was 13·8 months). Subsequent long term follow up of these 384 patients was almost complete when this report was written. By the end of 1983, 188 had died and all but nine (2·3%) had their last follow up examination in 1982 or 1983. The mean duration of follow up to death or last examination was 8·3 years (range 0·1-17·7), with an average of 8·1 annual examinations.

In addition to age and the severity of the first attack, baseline characteristics recorded at entry to the study included blood pressure, serum cholesterol concentration, results of a glucose tolerance test, habits of exercise, consumption of cigarettes and alcohol, anginal state before admission, and measurements of height and weight. Only patients with angina for at least three months before their first attack were classified as having angina before infarction. Smoking and anginal state are the two characteristics at follow up reported here. At each examination a smoker who had stopped smoking for at least three months was defined as a "stopped smoker." A high degree of veracity in the stated smoking habits of a sample of these patients has been reported.[11] For both first and follow up examinations the presence or absence of angina pectoris was based on symptoms reported to the investigators.

Statistical techniques included χ^2 and t tests, logistic regression, and an adaptation of the clinical life table of Kaplan and Meier.[12] Significance was determined at a two sided 5% level.

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Results

Of the 384 men who smoked when the study began and survived to attend their first annual follow up examination, 241 (62·8%) had by then stopped smoking. Of these, 47 (19·5%) reported the presence of angina pectoris. The remaining 143 continued to smoke and 46 (32·2%) of them reported the presence of angina; in total 93 (24·2%) patients reported the presence of angina. The prevalence of angina after infarction was reduced by nearly 40% in those who stopped smoking compared with those who continued ($\chi^2=7·85$, df=1, $p<0·01$).

This relation remained significant when potential confounding variables were adjusted for by means of a stepwise logistic regression analysis. Angina at first follow up was the dependent variable, and the 11 first factors mentioned above together with stopping smoking were entered as independent variables. Angina before infarction and serum cholesterol concentration were also independently and significantly associated with angina at one year. A univariate analysis showed that of 95 patients who had angina before infarction, 45 (47·4%) still had angina afterwards, and of 287 who did not have angina before infarction, 48 (16·7%) had it afterwards; data were missing on two patients ($\chi^2=36·4$, df=1, $p<0·0001$). The mean (SE) serum cholesterol concentration in 95 patients who had angina after infarction was 6·97 (0·16) mmol/l (270 (6·18) mg/100 ml) and that in the 291 patients who did not have angina after infarction was 6·55 (0·08) mmol/l (253 (3·09) mg/100 ml) ($t=2·34$, df=382, $p<0·05$). The table shows the joint effect of stopping smoking and angina before infarction on the prevalence of angina at one year. Stopping smoking resulted in an absolute reduction of about 12% in the prevalence of angina at one year irrespective of the presence of angina before infarction.

Prevalence of angina at first annual follow up related to stopping smoking and angina before infarction in 382 survivors of coronary attack

Angina before infarction	Smoking at follow up	Prevalence of angina at one year
Present	Stopped	24/56 (43%)
	Continued	21/39 (54%)
Absent	Stopped	23/183 (13%)
	Continued	25/104 (24%)

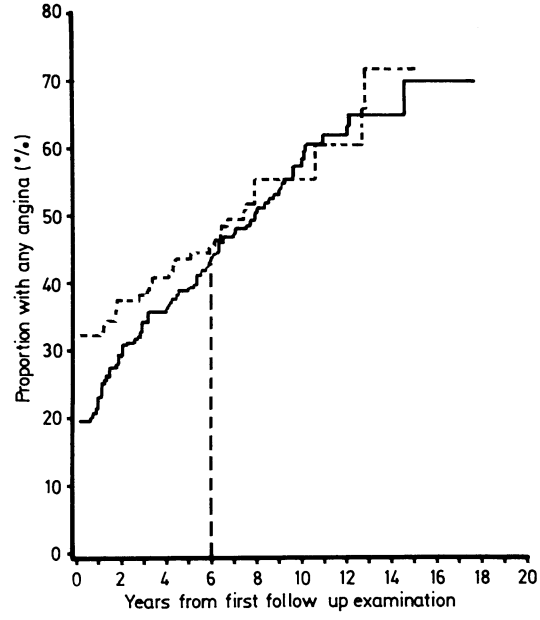
To assess the long term effect of stopping smoking on angina a cumulative score of angina after infarction was calculated for each patient. This was defined as the proportion of follow up examinations at which angina was present. The mean (SE) cumulative score for angina was 47·79 (4·42) in patients with angina before infarction and 25·67 (2·09) in those without angina ($t=4·99$, df=380, $p<0·0001$). The mean (SE) score for angina in patients who stopped smoking was 29·24 (2·37) and in those who continued smoking 34·12 (3·46) ($t=1·20$, df=382, NS).

The fact that stopping smoking, while having a strong influence on immediate angina after infarction, failed to show an effect on long term angina led to further examination. A modified computation of the life table of Kaplan and Meier was applied to the development of angina subsequent to the examination at one year by beginning the life table at the prevalences of angina at one year of 19·5% and 32·2% in the smokers who had stopped and continued, respectively. The figure shows these curves. Deaths were treated as withdrawals from the life table, so that essentially this approach calculated the proportion expected to have experienced angina if there had been no deaths. The figure shows clearly that there was a catch up effect and that after almost six years (seven years from the first attack) angina in the smokers who had continued and stopped was the same. This explains the observed lack of influence of stopping smoking on long term angina. An analysis stratified by the anginal state before infarction showed a similar catch up effect.

Discussion

Two published reports suggest a beneficial effect of stopping smoking on angina in patients with established coronary heart disease. The data from the coronary drug project on 2789 survivors of myocardial infarction are difficult to interpret, however, because of the method used to categorise smoking state.[13] The results of a recent crossover trial on 10 patients with chronic stable angina are only indicative because of the small numbers considered.[14] The only study that examined the question explicitly found no effect in 1023 survivors of myocardial infarction.[8]

This study was carried out to determine the short term and long term effects on subsequent angina of stopping smoking in survivors of a coronary attack who had smoked when the study began. Non-smokers were not included. Long term angina in this paper was based on a cumulative score that was independent of the number of survivors in the groups under comparison. It thus neutralised a potential masking effect caused by the known relation between stopping smoking and mortality—stopped smokers might have reported more angina simply because they lived longer and so had more time to develop it.



Proportion of patients (%) who experienced any angina after infarction subsequent to first annual examination in smokers who stopped (—) and continued (- - - -) (corrected for mortality).

The presence of angina before infarction was strongly related to the prevalence of angina one year after the first attack and to long term angina over the subsequent 17 years. Stopping smoking was independently associated with a 40% reduction in the prevalence of angina at one year but was not related to the score for long term angina. This was explained, however, by an analysis of the proportion of patients who experienced any angina after infarction over time. The results showed that roughly six years after stopping smoking the proportions who had experienced any angina in smokers who had stopped and continued were the same.

The known relation between habitual smoking of cigarettes and increased concentrations of carboxyhaemoglobin, and the observation that raised carboxyhaemoglobin concentrations will aggravate angina that is induced by exercise,[16] lend credence to our findings. We conclude that, in addition to reducing long term mortality and further non-fatal coronary events, a patient who stops smoking after infarction delays the onset of angina pectoris, though the effect is not maintained in the long term.

We thank all the staff, past and present, in the cardiac department of St Vincent's Hospital who have helped in the annual follow up examination of these patients, Mrs Christine Delaney for her excellent typing, and the computer centre, University College, Dublin, for the use of computer facilities.

References

1 Mulcahy R, Hickey N, Graham I, McKenzie G. Factors influencing long-term prognosis in male patients surviving a first coronary attack. *Br Heart J* 1975; **37**:158-65.
2 Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. *Lancet* 1975;i:415-20.
3 Mulcahy R, Hickey N, Graham I, MacAirt J. Factors influencing the 5-year survival rate of men following acute coronary heart disease. *Am Heart J* 1977;**93**:556-9.
4 Sparrow D, Dawber TR, Colton T. The influence of cigarette smoking on prognosis after a first myocardial infarction. *J Chronic Dis* 1978;**31**:425-32.
5 Pohola S, Siltanen P, Romo M, Haapakoshi J. Effect of quitting smoking on the long-term survival after myocardial infarction. *Transactions of the European Society of Cardiology* 1979;**1**:abstract 33.
6 Salonen JT. Stopping smoking and long-term mortality after acute myocardial infarction. *Br Heart J* 1980;**43**:463-9.
7 Vlietstra RE, Kronmal RA, Oberman A. Stopping smoking improves survival in patients with angiographically proven coronary artery disease. *Am J Cardiol* 1982;**49**:984.
8 Aberg A, Bergstrand R, Johansson S, *et al.* Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. *Br Heart J* 1983;**49**:416-22.
9 Daly LE, Mulcahy R, Graham IM, Hickey N. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J* 1983;**287**:324-6.
10 Mulcahy R. Influence of cigarette smoking on morbidity and mortality after myocardial infarction. *Br Heart J* 1983;**49**:410-5.
11 Ronan G, Ruane P, Graham I, Hickey N, Mulcahy R. The reliability of smoking history amongst survivors of myocardial infarction. *Br J Addict* 1981;**76**:425-8.
12 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457-81.
13 Coronary Drug Project Research Group. Cigarette smoking as a risk factor in men with a prior history of myocardial infarction. *J Chronic Dis* 1979;**32**:415-25.
14 Deanfield J, Wright C, Krikler S, Ribeiro P, Fox K. Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med* 1984;**310**:951-4.
15 Hubert HB, Holford TR, Kannel WB. Clinical characteristics and cigarette smoking in relation to prognosis of angina pectoris in Framingham. *Am J Epidemiol* 1982;**115**:231-42.
16 Aronow WF, Cassidy J, Vangrow JS, *et al.* Effects of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. *Circulation* 1974;**50**:340-7.

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SHORT REPORTS

Severe hypocalcaemia and increased serum creatine kinase activity

Serum creatine kinase activity (EC 2.7.3.2) is often requested in the investigation of patients with suspected myocardial infarction or disease of skeletal muscles. Both intramuscular injection and moderate exercise increase serum creatine kinase activity.[1] We studied the association between high serum creatine kinase activity and hypocalcaemia.

Patients, methods, and results

One of our patients (case 1, see table) had a serum creatine kinase activity of over 3000 U/l (mid 95% reference interval 50-230 U/l), which was thought to have been caused by hypocalcaemic convulsions. After treatment with intravenous calcium the patient had no further convulsions, though serum creatine kinase activity remained high, which was surprising as serum creatine kinase has a half life of about 34 hours. When treated with calcitriol the patient's serum calcium concentration gradually returned to normal as did serum creatine kinase activity. This observation led us to study serum creatine kinase activity in other patients. Ten patients with severe hypocalcaemia, eight with hyperphosphataemia but no appreciable hypocalcaemia, and nine with various severe illnesses but normal serum calcium and phosphate concentrations (controls) were studied. No patients had clinically obvious cardiac or skeletal muscle disease.

For each patient serum calcium concentrations and serum creatine kinase activities were determined at least twice on different days in different blood specimens, which were separated promptly and analysed within four hours of collection. Creatine kinase activity and magnesium concentrations were measured by Dupont ACA methods; all other biochemical tests were performed by standard SMAC 1 methods. We corrected serum calcium concentrations using the following formula: corrected serum calcium concentration (mmol/l) = serum calcium concentration (mmol/l) + ((41 − serum albumin concentration (g/l)) × 0·019). The mean normal serum albumin concentration for our population and method was 41 g/l. The table summarises relevant diagnoses and biochemical data.

Two patients (cases 1 and 2) were studied for several weeks. One (case 1) was treated with up to 6 μg calcitriol daily. The other (case 2) was treated with 2 μg calcitriol daily. Serum creatine kinase activities fell as serum calcium concentrations returned to normal. There was an appreciable inverse correlation between serum creatine kinase activity and calcium concentration in these two patients ($r = -0.84$ and -0.96, respectively). In all 28 patients studied there was an inverse correlation between serum creatine kinase activity and serum calcium concentration, which could be linearised by $\log_e$

Summary of biochemical data and principal diagnoses in 28 patients. Values in parentheses are general adult mid-95% reference intervals

Case No	Principal diagnosis	Age (years)	Serum creatine kinase (U/l) (50-230)	Serum calcium (mmol/l) (2·10-2·52)	Serum albumin (g/l) (37-48)	Corrected serum calcium (mmol/l) (2·10-2·52)	Serum phosphate (mmol/l) (0·7-1·4)	Serum creatinine (μmol/l) (50-110)	Serum magnesium (mmol/l) (0·5-0·9)
					Patients with hypocalcaemia				
1	?Idiopathic hypoparathyroidism	61	3100*	1·10	34	1·23	2·1	290	0·85
2	Chronic renal failure	21	9580*	1·15	34	1·28	3·77	1402	1·10
3	Chronic renal failure	32	2840	0·92	37	1·00	2·57	2711	
4	Chronic renal failure	25	803	1·50	38	1·56		803	
5	Chronic renal failure	40	334	1·66	30	1·87	2·16	1211	
6	Chronic renal failure	60	118	1·56	30	1·77	2·32	118	
7	Chronic renal failure	57	230	1·29	30	1·50	2·17	935	
8	?Hypoparathyroidism	20	608	1·23	44	1·17	2·17	60	0·95
9	Thyroidectomy	26	700	1·39	31	1·58	1·15	42	
10	Hypoparathyroidism	35	380	1·67	45	1·60	1·57	93	
11	Rickets	5	208	1·37	46	1·27	1·26	36	
					Patients with hyperphosphataemia and normocalcaemia				
12	Chronic renal failure	60	42	2·40	23	2·74	1·8	363	
13	Chronic renal failure	62	130	2·19	40	2·21	2·1	912	
14	Chronic renal failure	50	190	2·38	35	2·49	3·54	305	
15	Chronic renal failure	55	34	2·05	29	2·26	2·12	464	
16	Chronic renal failure	75	58	2·28	33	2·43	1·60	761	
17	Chronic renal failure	49	26	1·80	26	2·09	2·00	578	
18	Hypertension	48	44	1·91	22	2·27	2·90	812	
19	Systemic lupus erythematosus	23	58	1·90	21	2·27	4·40	304	
					Patients with normocalcaemia and normophosphataemia				
20	Carcinoma of colon	55	20	2·28	35	2·39	1·23	78	
21	Carcinoma of stomach	63	110	2·30	30	2·51	1·18	70	
22	Chronic renal failure	70	36	2·02	19	2·44	0·81	248	
23	Chronic renal failure	61	80	2·15	32	2·32	1·37	1200	
24	Chronic renal failure	65	14	2·04	28	2·29	1·27	247	
25	Chronic renal failure	55	14	2·20	30	2·41	0·94	386	
26	Congestive cardiac failure	66	126	2·49	39	2·53	0·94	142	
27	Diabetes mellitus, septicaemia	56	84	1·68	17	2·14	1·39	199	
28	Nephrotic syndrome	65	26	2·02	20	2·42	1·40	441	

*Electophoretic studies showed increased creatine kinase activity to be exclusively due to the MM (skeletal muscle) isoenzyme.
Conversion: SI to traditional units—Serum calcium: 1 mmol/l ≈ 4 mg/100 ml. Serum creatinine: 1 μmol/l ≈ 0·011 mg/100 ml. Serum magnesium: 1 mmol/l ≈ 2·4 mg/100 ml. Serum phosphate: 1 mmol/l ≈ 3·1 mg/100 ml.