

Effect of α linolenic acid on cardiovascular risk markers: a systematic review

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Objective: To determine whether dietary supplementation with α linolenic acid (ALA) can modify established and emerging cardiovascular risk markers.

Design: Systematic review and meta-analysis of randomised controlled trials identified by a search of Medline, Embase, Cochrane Controlled Trials Register (CENTRAL), and the *metaRegister* of Controlled Trials (*mRCT*).

Patients: All human studies were reviewed.

Main outcome measures: Changes in concentrations of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglyceride, fibrinogen, and fasting plasma glucose, and changes in body mass index, weight, and systolic and diastolic blood pressure.

Results: 14 studies with minimum treatment duration of four weeks were reviewed. ALA had a significant effect on three of the 32 outcomes examined in these studies. Concentrations of fibrinogen (0.17 $\mu\text{mol/l}$, 95% confidence interval (CI) -0.30 to -0.04 , $p = 0.01$) and fasting plasma glucose (0.20 mmol/l , 95% CI -0.30 to -0.10 , $p < 0.01$) were reduced. There was a small but clinically unimportant decrease in HDL (0.01 mmol/l , 95% CI -0.02 to 0.00 , $p < 0.01$). Treatment with ALA did not significantly modify total cholesterol, triglycerides, weight, body mass index, LDL, diastolic blood pressure, systolic blood pressure, VLDL, and apolipoprotein B.

Conclusions: Although ALA supplementation may cause small decreases in fibrinogen concentrations and fasting plasma glucose, most cardiovascular risk markers do not appear to be affected. Further trials are needed, but dietary supplementation with ALA to reduce cardiovascular disease cannot be recommended.

The cardiovascular benefits of fish oil are now well established,¹ but it is unclear whether α linolenic acid (ALA) confers similar benefits. ALA is a plant ω -3 fatty acid, precursor of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the two main ω -3 polyunsaturated fatty acids found in fish oils.² However, unlike fish oils, ALA is inexpensive to produce and is more palatable than cod liver oil.

Clinical trials of dietary supplementation such as the Lyon diet heart study, in which ALA was a component, suggest that ALA may confer cardiovascular benefits.³ This has led to calls for trials specifically evaluating the effect of substituting oils containing ALA.

We therefore systematically reviewed randomised controlled trials to investigate the impact of ALA on cardiovascular risk markers.

METHODS

We searched Medline, Embase, and the Cochrane Controlled Trials Register (CENTRAL) databases for published studies and the *metaRegister* of Controlled Trials (*mRCT*) for unpublished studies by using the search terms linolenic acid, plant oils, flax, linseed, canola, rapeseed, perilla, juglans, pumpkin, and purslane with a standard search filter to identify randomised controlled trials. We identified additional studies by searching references cited in identified primary studies. We restricted our search to studies of humans and included articles in languages other than English.

Studies were included if they had a control or comparison arm and had either a randomised crossover design (with a washout interval of ≥ 4 weeks) or a parallel group design (with ≥ 4 weeks of intervention). The units of measurement

were converted to the common unit suggested by SI notation. Where crossover studies provided independent data for each intervention period we used data for only the first intervention period. Criteria for assessment of trial quality were the method of randomisation, blinding or objective measurements, loss to follow up, and systematic difference in care between intervention groups. When there was more than one control or ALA comparison group, we pooled results of the similar groups. We analysed subgroups stratified by the ALA dose used and type of control, and by comparing included and excluded trials.

Statistical analysis

Outcomes were changes in total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglyceride, fibrinogen, fasting plasma glucose, body mass index, weight, and systolic and diastolic blood pressures. All data were analysed with Review Manager (version 4.2.3; Update Software, Oxford, UK).

For each trial we calculated the changes in the means between the beginning and the end of each intervention and estimated the standard deviation of the treatment effect. If the standard deviations of change were not provided, we derived them from the 95% confidence intervals or the standard error.

We used a fixed effect meta-analysis model to calculate overall results. When a significant heterogeneity was

Abbreviations: ALA, α linolenic acid; CENTRAL, Cochrane Controlled Trials Register; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high density lipoprotein; LDL, low density lipoprotein; *mRCT*, *metaRegister* of Controlled Trials; VLDL, very low density lipoprotein

observed, we used a random effect model instead. Heterogeneity was determined by χ^2 ($p < 0.10$).

RESULTS

From 2566 references identified (1800 in Medline, 1955 in Embase, and 931 in CENTRAL) we reviewed 46 published clinical studies and one unpublished trial reporting the effects of ALA on cardiovascular risk markers. We excluded 31 of the 47 studies because they were not placebo controlled, provided insufficient information, or had a treatment period of < 4 weeks. We identified 28 outcomes in 16 published papers, reporting 14 studies. Twelve studies, involving 744 subjects, had outcomes in common and were included in the quantitative meta-analysis. Table 1 shows selected characteristics of the included trials.⁴⁻¹⁹

Body weight and blood pressure

Six studies measured body weight and three⁴⁻⁶ reported systolic and diastolic blood pressures. Three reported the body mass index^{4,6,7} and three^{5,8,9} reported weight. Comparisons between ALA and control groups were not significant ($p > 0.05$) for either body weight or blood pressure (table 2).

Cholesterol and triglycerides

Eleven studies⁴⁻¹⁴ with a total of 790 subjects reported changes in total cholesterol and eight studies^{4-9,13,14} reporting triglyceride concentrations enrolled a total of 629 subjects. As significant heterogeneity was evident ($p < 0.05$) a random effect model was used. The pooled mean differences were -0.01 mmol/l for total cholesterol and 0.01 mmol/l for triglycerides (table 2). HDL and LDL cholesterol^{4-10,12,14,16} were studied in a total of 661 and 680 patients, respectively. We also identified two studies that measured VLDL

cholesterol.^{6,14} Heterogeneity between the studies for both HDL cholesterol and VLDL cholesterol were not significant ($p > 0.10$), although heterogeneity was significant ($\chi^2 = 16.38$, $p = 0.06$) for LDL cholesterol. The pooled mean difference in HDL concentrations was -0.01 mmol/l ($p < 0.01$). The effect sizes of LDL and VLDL cholesterol were not significant (table 2).

Glucose and fibrinogen

We identified two studies assessing the effect of ALA on fasting plasma glucose.^{14,15} A fixed effects analysis showed a significant ($p < 0.01$) reduction in the mean difference of 0.20 mmol/l (-0.30 , -0.10 mmol/l). The effect of ALA on fibrinogen was examined in three studies^{4,10,15} with 382 subjects. The pooled mean difference in fibrinogen was a significant ($p = 0.01$) decrease of 0.17 μ mol/l (-0.30 , -0.04 μ mol/l) (fig 1). Heterogeneity between the studies was not significant for both outcomes ($p > 0.10$).

Emerging cardiovascular risk markers

Several changes in plasma markers were reported in only one of the identified studies. The following markers of inflammation were identified in only one study: tumour necrosis factor α , interleukin 6, C reactive protein, cell adhesion molecule 1, vascular cell adhesion molecule 1,^{7,17} and thrombogenic factors such as factor VII, factor XII, von Willebrand factor, thromboxane, lmax, platelet aggregation velocity, plasminogen activator inhibitor 1, tissue plasminogen activator, and D dimer.^{4,5,10,14,18}

Apolipoproteins A and A IV, fatty acids, apolipoprotein B, and Lp(a) lipoprotein were also reported.^{5,14,19} Although the effect of some markers was significant over time, only vascular cell adhesion molecule 1¹⁷ was significantly different between treatments.

Table 1 Randomised controlled trials assessing the effect of ALA on established cardiovascular risk factors and emerging risk markers

| Author | Treatment | Type of intervention | Country | No of subjects | Participants (condition, sex, age group*) | Length of treatment |
|---|---|----------------------|-------------|----------------|---|---------------------|
| Arjmandi <i>et al</i> ^{6†} | Flaxseed, sunflower seed | Breads, muffins | USA | 38 | Hypercholesterolaemic, postmenopausal women, 56.3 years | 6 weeks |
| Bemelmans <i>et al</i> ⁴ | ALA, LA | Margarine | Netherlands | 265 | Cardiovascular risks, men and women, 55 years | 104 weeks |
| Finnegan <i>et al</i> ⁵ | LA, fish oil, ALA | Margarine, capsules | UK | 150 | Moderately hyperlipidaemic, men and women, 53 years | 6 months |
| Finnegan <i>et al</i> ¹⁵ | LA, fish oil, ALA | Margarine, capsules | UK | 150 | Moderately hyperlipidaemic, men and women, 53.3 years | 6 months |
| Junker <i>et al</i> ¹⁰ | Olive oil, sunflower oil, rapeseed oil | Margarine, bread | Germany | 69 | Healthy, men and women, 24-27 years | 4 weeks |
| Karvonen <i>et al</i> ¹¹ | Camelina oil, olive oil, rapeseed oil | Oil | Finland | 68 | Hypercholesterolaemic, men and women, 50-53 years | 6 weeks |
| Kestin <i>et al</i> ⁶ | Fish oil, linseed, safflower oil | Emulsion | Australia | 33 | Hypercholesterolaemic, men and women, 45.9 years | 6 weeks |
| Kratz <i>et al</i> ¹² | Olive oil, sunflower oil, rapeseed oil | Margarine, breads | Germany | 58 | Healthy, men and women, 26 years | 4 weeks |
| Kratz <i>et al</i> ¹⁹ | Olive oil, sunflower oil, rapeseed oil | Margarine, breads | Germany | 48 | Healthy, men and women, 25.4 years | 4 weeks |
| Meshcheriakova <i>et al</i> ¹³ | Fish oil, linseed oil, sunflower oil | Diet | Russia | 120 | NIDDM, 54-56 years | 4 weeks |
| Pang <i>et al</i> ⁸ | ALA, LA | Muffins, diet | Australia | 29 | Healthy, men, 24-25 years | 6 weeks |
| Rallidis <i>et al</i> ⁷ | Linseed oil, safflower oil | Oil | Greece | 76 | Dyslipidaemic, men, 51 years | 12 weeks |
| Södergren <i>et al</i> ^{14†} | Rapeseed oil, saturated oil (butter, olive oil) | Fat products | Finland | 19 | Hyperlipidaemic, men and women, 50 years | 4 weeks |
| St Onge <i>et al</i> ^{9*} | Olive oil, functional oil | Meals | Canada | 28 | Overweight, men, 26-61 years | 4 weeks |
| Thies <i>et al</i> ¹⁷ | Placebo, ALA, GLA, ARA, DHA, fish oil | Oil capsules | UK | 46 | Healthy, men and women, 61-66 years | 12 weeks |
| Wensing <i>et al</i> ¹⁸ | Oleic acid, ALA, EPA+DHA | Shortening | Netherlands | 38 | Healthy, men and women, > 60 years | 6 weeks |

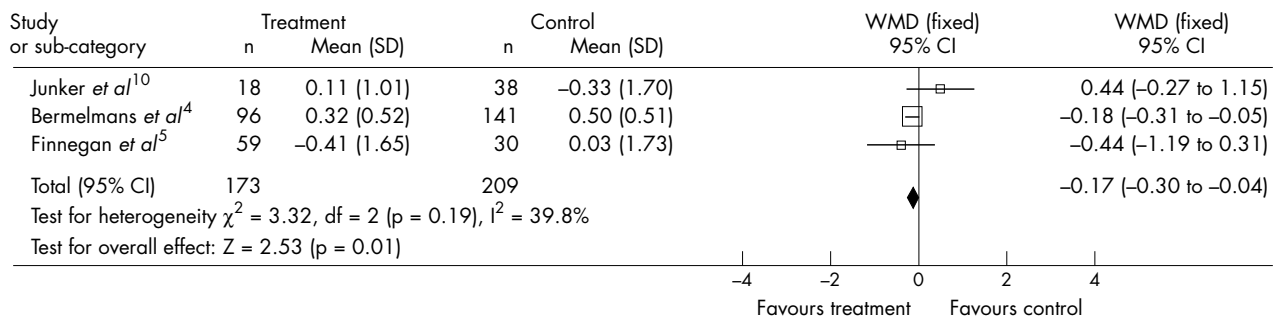
*Age data are means, except in St Onge, where age is given as an interval; †crossover studies.

ALA, α linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ linolenic acid; LA, linolenic acid; NIDDM, non-insulin dependent diabetes mellitus.

Table 2 Summary of the effect of the ALA acid on outcomes

| Outcome | References | No of trials | No of subjects | Effect size (95% CI) | p Value† | $\chi^2‡$ |
|--------------------------------------|------------------|--------------|----------------|------------------------|----------|-----------|
| Total cholesterol (mmol/l) | 4-14 | 11 | 790 | -0.01 (-0.08 to 0.06)* | 0.75 | 19.64 |
| High density lipoprotein (mmol/l) | 4-10, 12, 14, 16 | 10 | 661 | -0.01 (-0.02 to -0.00) | <0.01 | 5.28 |
| Low density lipoprotein (mmol/l) | 4-10, 12, 14, 16 | 10 | 680 | 0.03 (-0.04 to 0.10)* | 0.42 | 16.38 |
| Triglycerides (mmol/l) | 4-9, 13, 14 | 9 | 629 | 0.01 (-0.11 to 0.14)* | 0.83 | 23.36 |
| Weight (kg) | 5, 8, 9 | 3 | 166 | -0.18 (-0.72 to 0.36) | 0.52 | 0.79 |
| Body mass index (kg/m ²) | 4, 6, 7 | 3 | 335 | -0.04 (-0.11 to 0.03) | 0.28 | 1.59 |
| Systolic blood pressure (mm Hg) | 4-6 | 3 | 348 | -0.72 (-2.01 to 0.58) | 0.28 | 1.92 |
| Diastolic blood pressure (mm Hg) | 4-6 | 3 | 348 | -0.17 (-0.82 to 0.48) | 0.61 | 0.11 |
| Fibrinogen (μ mol/l) | 4, 10, 15 | 3 | 382 | -0.17 (-0.30 to -0.04) | 0.01 | 3.32 |
| Fasting plasma glucose (mmol/l) | 14, 15 | 2 | 127 | -0.20 (-0.30 to -0.10) | < 0.01 | 0.11 |
| VLDL cholesterol (mmol/l) | 6, 14 | 2 | 60 | -0.02 (-0.08 to 0.03) | 0.37 | 0.49 |
| Apolipoprotein B (mmol/l) | 14, 15 | 2 | 127 | -0.03 (-0.11 to 0.04) | 0.43 | 2.03 |

*Random effects mode; †p value for effect size; ‡ χ^2 statistic for heterogeneity between trials. CI, confidence interval; VLDL, very low density lipoprotein.

**Figure 1** Size effect of α linolenic acid compared with placebo on fibrinogen concentration. CI, confidence interval; WMD, weighted mean difference.

Subgroup analyses did not show significant differences when analysed by type of placebo or by the dose used of ALA (above and below 5 g/day). Funnel plots for selected outcomes did not provide evidence of publication bias in favour of trials with positive outcomes.

DISCUSSION

This systematic review provides the most reliable assessment yet of whether ALA is associated with established and emerging risk markers for coronary heart disease. Our systematic review indicates that ALA significantly affects fibrinogen and fasting plasma glucose concentrations, decreasing fibrinogen concentrations by 0.17 μ mol/l and fasting glucose by 0.20 mmol/l. No other statistically or clinically significant findings were evident in the quantitatively evaluated cardiovascular risk markers.

A limitation of the meta-analysis was that most trials were small; they did not describe the method of randomisation and not all of them were blinded. For some potential risk markers we were unable to identify two or more studies to allow pooling. We were unable to obtain data from unpublished studies and did not attempt to obtain patient level data. Although we did not adjust statistically for multiple comparisons, the two clinically important differences we observed were highly significant. The subgroup analysis showed no significant difference by either type or dose of placebo; the small dose of olive oil used as a placebo (table 1) is therefore unlikely to have masked any important differences.

On the basis of estimates from a meta-analysis of observational studies, a 2.9 μ mol/l reduction in fibrinogen concentration would lead to a relative risk reduction of 80% in coronary heart disease.²⁰ Therefore, a reduction of 0.17 μ mol/l attributable to ALA would be expected to lead to a reduction of 6% in coronary heart disease. This is a much

smaller reduction than that observed in the Lyon diet heart study, in which patients were randomly assigned to a Mediterranean diet and margarine high in ALA. Fibrinogen is therefore unlikely to mediate a clinically important effect of ALA on cardiovascular risk.

ALA is a metabolic precursor of DHA and EPA and any risk reduction may be mediated through conversion to this fatty acid. However, the metabolic overall conversion rate is low² and varies between the sexes, being higher in women.²¹ Our review suggests that the impact of ALA on decreased cardiovascular risk is unlikely to be mediated through conversion to DHA or EPA, since we noted no changes consistent with increased concentrations of these fatty acids.

Although supplementation with ALA may lead to a small decrease in fibrinogen concentrations and fasting plasma glucose, most established cardiovascular risk factors or emerging risk markers do not appear to be affected. Further trials are needed but on the basis of this meta-analysis, dietary supplementation with ALA to reduce cardiovascular disease cannot be recommended.

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Ethical approval was not required for this study.

REFERENCES

- 1 Bucher HC, Hengstler P, Schindler C, et al. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002;112:298–304.
- 2 Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? *Int J Vitam Nutr Res* 1998;68:159–73.
- 3 De Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. *Circulation* 1999;99:779–85.
- 4 Bemelmans WJ, Broer J, Feskens EJ, et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean alpha-linolenic enriched Groningen dietary intervention (MARGARIN) study. *Am J Clin Nutr* 2002;75:221–7.
- 5 Finnegan YE, Minihane AM, Leigh Firkbank EC, et al. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. *Am J Clin Nutr* 2003;77:783–95.
- 6 Kestin M, Clifton P, Belling GB, et al. n-3 fatty acids of marine origin lower systolic blood pressure and triglycerides but raise LDL cholesterol compared with n-3 and n-6 fatty acids from plants. *Am J Clin Nutr* 1990;51:1028–34.
- 7 Rallidis LS, Paschos G, Liakos GK, et al. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. *Atherosclerosis* 2003;167:237–42.
- 8 Pang D, Allman Farinelli MA, Wong T, et al. Replacement of linoleic acid with alpha-linolenic acid does not alter blood lipids in normolipidaemic men. *Br J Nutr* 1998;80:163–7.
- 9 St Onge MP, Lamarche B, Mauger JF, et al. Consumption of a functional oil rich in phytosterols and medium-chain triglyceride oil improves plasma lipid profiles in men. *J Nutr* 2003;133:1815–20.
- 10 Junker R, Kratz M, Neufeld M, et al. Effects of diets containing olive oil, sunflower oil, or rapeseed oil on the hemostatic system. *Thromb Haemost* 2001;85:280–6.
- 11 Karvonen HM, Aro A, Tapola NS, et al. Effect of alpha-linolenic acid-rich *Camelina sativa* oil on serum fatty acid composition and serum lipids in hypercholesterolemic subjects. *Metabolism* 2002;51:1253–60.
- 12 Kratz M, Cullen P, Kannenberg F, et al. Effects of dietary fatty acids on the composition and oxidizability of low-density lipoprotein. *Eur J Clin Nutr* 2002;56:72–81.
- 13 Meshcheriakova VA, Plotnikova OA, Sharafetdinov K, et al. [Comparative study of effects of diet therapy including eiconol or linseed oil on several parameters of lipid metabolism in patients with type 2 diabetes mellitus]. *Vopr Pitan* 2001;70:28–31.
- 14 Sodergren E, Gustafsson IB, Basu S, et al. A diet containing rapeseed oil-based fats does not increase lipid peroxidation in humans when compared to a diet rich in saturated fatty acids. *Eur J Clin Nutr* 2001;55:922–31.
- 15 Finnegan YE, Howarth D, Minihane AM, et al. Plant and marine derived (n-3) polyunsaturated fatty acids do not affect blood coagulation and fibrinolytic factors in moderately hyperlipidemic humans. *J Nutr* 2003;133:2210–3.
- 16 Arjmandi BH, Khan DA, Juma S, et al. Whole flaxseed consumption lowers serum LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. *Nutr Res* 1998;18:1203–14.
- 17 Thies F, Miles EA, Nebe von Caron G, et al. Influence of dietary supplementation with long-chain n-3 or n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. *Lipids* 2001;36:1183–93.
- 18 Wensing AG, Mensink RP, Hornstra G. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. *Br J Nutr* 1999;82:183–91.
- 19 Kratz M, Wahrburg U, von Eckardstein A, et al. Dietary mono- and polyunsaturated fatty acids similarly increase plasma apolipoprotein A-IV concentrations in healthy men and women. *J Nutr* 2003;133:1821–5.
- 20 Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998;279:1477–82.
- 21 Burdge GC, Wootton SA. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *Br J Nutr* 2002;88:411–20.

IMAGES IN CARDIOLOGY

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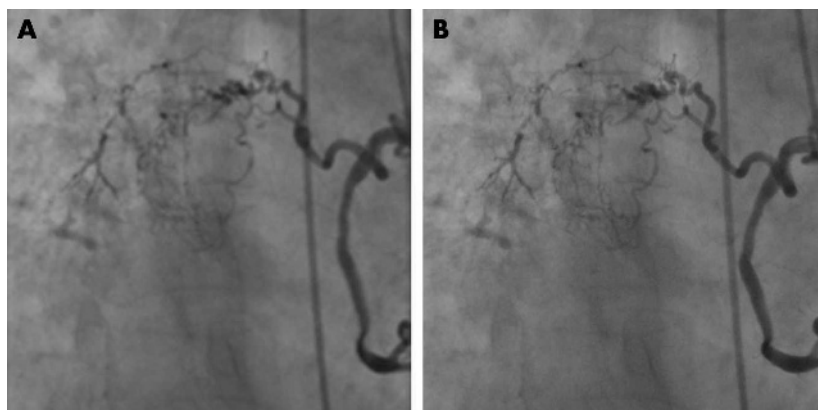
Aberrant right coronary artery collaterals to pulmonary vascular bed

This image shows a right coronary angiogram in a 75 year old woman referred to our chest pain clinic with episodes of chest pain of anginal character, lasting five minutes and relieved by glyceryl trinitrate spray. Her chest pains were initially exertional, but more recently also at rest.

She was an ex-smoker of 18 years with hypercholesterolaemia. She was not diabetic or hypertensive, and never had a stroke. There was no family history of premature coronary heart disease.

On examination, her blood pressure was 102/70 mm Hg, and her pulse was regular at 72 beats per minute. Jugular venous pressure and carotid pulse character were normal. Cardiac apex was undisplaced, heart sounds were normal, and the chest examination normal. The resting ECG showed sinus rhythm and was normal. The chest x ray was normal. Treadmill exercise test was negative for coronary ischaemia but with a submaximal heart rate increment.

Coronary and left ventricular angiography showed normal left ventricular function, and the coronary circulation was free of irregularity and obstruction. The right coronary injection revealed a highly abnormal and unusual large proximal branch which supplied a network of small collateral vessels, which then anastomosed with a sizable segment of pulmonary artery branches in the right upper lobe.



Our clinical suspicion of an acquired collateral circulation between the pericardium and the lung, probably related to previous inflammatory disease and with pericardial–pleural adhesions, was supported by subsequent computed tomographic scanning of the thorax (because of admission for breathlessness one year later) which showed geographic ground glass shadowing and airspace consolidation air bronchograms, consistent with fibrosing alveolitis.

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